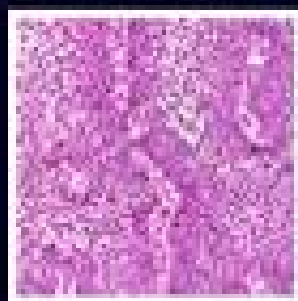
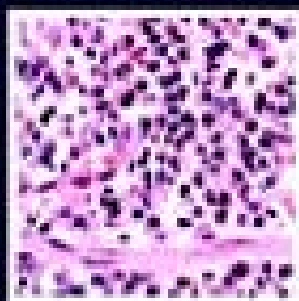
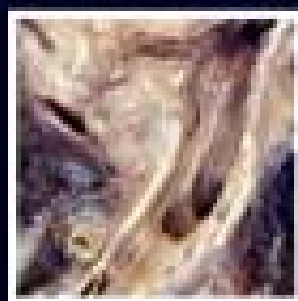
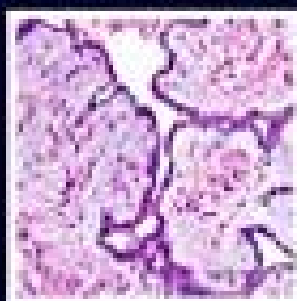


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ROSAI AND ACKERMAN'S

# SURGICAL PATHOLOGY

*Eleventh Edition*

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# Preface

It is a daunting task to continue the incredible tradition of Drs. Rosai and Ackerman's work on this monumental surgical pathology textbook. No single pathologist is capable of tackling the complexities of modern surgical pathology, as the depth and breadth of knowledge required to write such a comprehensive textbook grows with each passing year. In light of this, we decided that a team approach was necessary to uphold the excellent tradition of this textbook and, hence, the 11th edition of *Rosai and Ackerman's Surgical Pathology* was born. The four of us were truly humbled to be invited to continue this tradition, as were our colleagues who joined the team. It was clear to us from the inception that our goal was to maintain Dr. Rosai's style and singular voice as best we could. We are hopeful the reader will notice a continuity of style with the previous editions. Nevertheless, it is impossible to emulate Dr. Rosai's unique voice as the only surgical pathologist in the world who could write multiple editions of this textbook.

The previous edition of *Rosai and Ackerman's Surgical Pathology* was published in 2011. Much has changed in surgical pathology since then, including identification of new entities, reappraisal of older entities, and increasingly sophisticated ancillary techniques, including immunohistochemistry and molecular diagnostics as tools commonly applied in the everyday practice of surgical pathology. We recognized the need for additional help from a number of expert colleagues in different areas of surgical pathology; we are truly grateful to the many authors who have contributed their time and energy to this project. As eloquently stated by Dr. Rosai in the preface of

the 10th edition, "A constant attempt has been made to preserve as much as possible the pragmatic flavor initially given to this work by its peerless begetter, Dr. Lauren V. Ackerman."

Each of us is truly grateful to the countless staff pathologists, pathology residents, and fellows at each of our respective institutions who have helped us complete this textbook. We would like to thank Drs. Rahul Jawale, Lani Clinton, Youran Zou, Ryan Berry, Sara Hawes, Hannah Goyne, Ankur Sangoi, Christopher Przybycin, and Amy McKenney for their superb assistance with reviewing and proofreading the text. We would also like to sincerely thank Ms. Kathleen Ranney and Ms. Beth Minors for their outstanding administrative assistance—none of this work would be possible without them. Finally, we would like to thank Ms. Asmita Shirali for her efforts in representing the group of editors.

Most of all, we would like to thank Dr. Juan Rosai for allowing us the opportunity to follow in his enormous footsteps. It goes without saying that Dr. Rosai has been and remains one of the legendary giants of the field of surgical pathology, and it is our greatest professional honor to be able to carry on his tradition in the form of the 11th edition of *Rosai and Ackerman's Surgical Pathology*.

**John R. Goldblum, MD**  
**Laura W. Lamps, MD**  
**Jesse K. McKenney, MD**  
**Jeffrey L. Myers, MD**



# Preface

## to the First Edition

This book can be only an introduction to the vast field of surgical pathology: the pathology of the living. It does not pretend to replace in any way the textbooks to general pathology, its purpose being merely to supplement them, assuming that the reader has a background in or access to those texts. The contents are not as complete as they might be because emphasis has been placed on the common rather than the rare lesions and are, to a great extent, based on the author's personal experiences. This book has been written for the medical student as well as for those physicians who are daily intimately concerned with surgical pathology. This must of necessity include not only the surgeon and the pathologist, but also those physicians in other fields who are affected by its decisions, such as the radiologist and the internist. Gross pathology has been stressed throughout with an attempt to correlate the gross findings with the clinical observations. The many illustrations have been selected as typical of the various surgical conditions, although in a few instances the author has been unable to resist showing some of the more interesting rare lesions he has encountered. Concluding each chapter there is a bibliography listing those references which are not only relatively recent and readily available, but also those which will lead the reader to a more detailed knowledge of the subject.

Dr Zola K Cooper, Assistant Professor of Pathology and Surgical Pathology, has written one of the sections on Skin, and Dr David E Smith, Assistant Professor of Pathology and Surgical Pathology, has written the chapter on Central Nervous System. Both of these members of the Department are particularly well qualified for their respective roles because of their background and present responsibilities in these fields. Their efforts on my behalf are most gratefully acknowledged.

Many members of the Surgical Staff at Barnes Hospital have given much help both knowingly and unwittingly. I am particularly grateful

to Dr Charles L Eckert, Associate Professor of Surgery, for letting me bother him rather constantly with my questions and for giving freely of his experience. Dr Richard Johnson, who succeeded me as Pathologist at the Ellis Fischel State Cancer Hospital, agreeably made available all the material there, and Dr Franz Leidler, Pathologist at the Veterans Hospital, has been most cooperative.

Thanks must be given to Dr HR McCarroll, Assistant Professor of Orthopedics, for constructively criticizing the chapter on Bone and Joint, and to Dr California Waldron for helping me with the chapters related to the Oral Cavity. Among other faculty friends and colleagues who were especially helpful, I would like to mention Dr Carl E Lischer, Dr Eugene M Bricker, Dr Heinz Haffner, Dr Thomas H Burford, Dr Carl A Moyer, Dr Evarts A Graham, Dr Robert Elman, Dr Edward H Reinhard, Dr J Albert Key, Dr Glover H Copher, Dr Margaret G Smith, and Dr Robert A Moore. Mr Cramer K Lewis, of our Department of Illustration, has been very patient with my demands, and his efforts and skill have been invaluable. Miss Marion Murphy, in charge of our Medical Library, and her associates gave untiringly of their time.

Because of recent advances in anesthesia, antibiotics, and pre- and postoperative care, modern surgery permits the radical excision of portions or all of various organs. There is a need today for contemplative surgeons, men with a rich background in the fundamental sciences, whether chemistry, physiology, or pathology. The modern surgeon should not ask himself, "Can I get away with this operation?" but rather, "What does the future hold for this patient?" It is hoped that this book may contribute in some small fashion toward the acquisition of this attitude.

Lauren V Ackerman MD  
St. Louis, Missouri, 1953

# Introduction: The Legacies of Dr. Lauren V. Ackerman and Dr. Juan Rosai

Jesse K. McKenney

1

*Excellence is an art won by training and habituation. We do not act rightly because we have virtue or excellence, but we rather have those because we have acted rightly. We are what we repeatedly do. Excellence, then, is not an act but a habit.*

—Aristotle

The continuous success of this book since the first edition appeared in 1953 is a testament to the incredible careers of Dr. Lauren Ackerman and Dr. Juan Rosai and their unrelenting pursuit for excellence. We find it fitting to begin this 11th edition with their personal stories, so that younger generations will understand the magnitude of their impact on our field of surgical pathology.

## Lauren V. Ackerman, MD



Dr. Lauren Ackerman was born in Auburn, New York in 1905. After completing studies at Hamilton College in 1927 and a year of work as an engineer, he entered medical school at the University of Rochester where he received his degree in 1932. At the recommendation of his medical school mentor, Dr. George Whipple, he traveled to the West Coast and completed training in internal medicine at the University of California, San Francisco (a decision that certainly had great influence on his approach to surgical pathology). After working as an Assistant Professor of Medicine focusing on pulmonary

disease and autopsy correlation, Dr. Ackerman decided to pursue pathology. From 1936 to 1939 he was a pathology resident at Pondville Hospital in Wrentham, MA, where he studied under the legendary Dr. Shields Warren and developed his lifelong interest in tumor pathology.

In 1940, Dr. Ackerman became the Director of Laboratories at Ellis Fischel State Cancer Hospital in Columbia, MO. With the combination of his clinical background in internal medicine, his growing experience with tumor histology, and a commitment for nothing short of excellence, he helped to shape a model cancer hospital. During this time, he wrote his groundbreaking oncology textbook, with co-author Dr. Juan del Regato, *Cancer: Diagnosis and Treatment*, which served as the premier reference for a generation of oncologists through multiple editions. It was also during his time in Columbia that he described verrucous carcinoma, based on correlation with the unexpected local clinical aggressiveness of the tumor that seemed incongruous with the bland histologic features.

In 1948, Dr. Ackerman was recruited to Washington University in St. Louis as pathologist-in-chief at Barnes Hospital where he spent the next 25 years. During this phase of his career, his influence on other pathologists was enormous. He played a major role in the evolution of surgical pathology into a field that was focused on the clinical implications of histologic findings with regard to prognosis and therapy. Dr. Juan Rosai reminisced on his first experience with an Ackerman case conference; he thought he had entered the wrong room because of the thorough discussion of clinical history and imaging studies that was taking place. Dr. Ackerman codified his approach to the practice of surgical pathology in 1953 with publication of the first edition of this book, *Surgical Pathology*, which greatly increased the worldwide reach of his teaching and has had long-lasting impact on the evolution and current strength of our discipline. In 1973, Dr. Ackerman moved to the Department of Pathology of SUNY at Stony Brook, where he continued to practice pathology for 20 more years until his death at the age of 88.

During his career spanning over 50 years, Dr. Ackerman received enumerable awards for his professional contributions, including the Janeway Medal from the American Radium Society (1970), the Fred W. Stewart Award of the Memorial Sloan Kettering Cancer Center (1986), and the Gold-Headed Cane from the American Association of Pathologists and Bacteriologists (1987). In 1990, the new Surgical Pathology Laboratory at Washington University was dedicated in honor of Lauren V. Ackerman, MD, and, at that time, he also received the Distinguished Service Award from Washington University. In

1992, he received the Prix de Paris Award in recognition of his work at the Institut Gustave-Roussy in Villejuif.

One would be remiss discussing Dr. Ackerman without paying homage to his wit, which “by report” sometimes bordered on irreverent or even abrasive. During one particular dinner, he was given the task of choosing the table’s wine, which he certainly enjoyed. After being told that the restaurant did not have either of the first two bottles of wine he requested, he asked for “the list of wines you actually have... not the list of wines you wish you had.” On another occasion, after witnessing a young trainee order a “scotch and coke,” he noted “I bet you like Tchaikovsky.” One can only imagine his response to an improperly handled gross specimen.

Despite all of Dr. Ackerman’s accomplishments, his most impressive legacy may be the lasting influence of surgical pathologists he trained. At the time of his death, Dr. Leon Sokoloff, professor emeritus of pathology and orthopedics at Stony Brook said, “He, more than anyone else, changed the character of anatomical pathology by directing the focus toward surgical pathology.” The fact that so many leaders in academic surgical pathology emerged from Washington University is a testament to his mentorship and ability to inspire. His emphasis on the ideal that care of the patient be the driving force in surgical pathology continues on. It is unlikely that any practicing surgical pathologist today has not been trained or influenced by one of Ackerman’s disciples.

## Juan Rosai, MD



Giovanni “Juan” Rosai was born in Poppi, Italy (a small town in Tuscany) in 1940 and emigrated to Argentina with his parents at the age of eight. He attended the School of Medicine at the University of Buenos Aires where he met his first mentor in pathology, Dr. Eduardo Lascano. At the time of his graduation, the Hospital Regional Mar del Plata had just opened with the first formal residency programs in Argentina. Dr. Rosai became their only pathology resident, and he handled every surgical case and autopsy under the tutelage of

Dr. Lascano, who had also moved to the new facility. At the time that a complex political situation ended the existence of the teaching hospital, Dr. Rosai met Dr. Lauren Ackerman, who was giving a talk at a medical conference in Buenos Aires. That meeting led to an acceptance of a residency with Dr. Ackerman at the Washington University in St. Louis, where Dr. Rosai completed training and remained as faculty until 1974. Dr. Rosai subsequently led several departments of pathology in the United States, first as: Director of Anatomic Pathology at the University of Minnesota (1974–1985), Director of Anatomic Pathology at Yale University (1985–1991), and Chairman of Pathology at Memorial Sloan Kettering (1991–1999). After a 35-year career in the United States, Dr. Rosai returned to Italy to serve as Chair of Pathology at the Cancer Institute of Milan.

Throughout his career, Dr. Rosai has made enumerable contributions to the field of pathology. His landmark descriptions of distinct entities include Rosai-Dorfman disease (sinus histiocytosis with massive lymphadenopathy), desmoplastic small round cell tumor, sclerosing angiomatoid nodular transformation of the spleen, and spindle epithelial tumor with thymus-like differentiation of the thyroid (SETTLE). To date, he has published over 400 articles, as well as 52 books, book chapters, and monographs. He served as editor in chief for the third series of the AFIP Fascicles and was the founding editor in chief of *The International Journal of Surgical Pathology*. He personally authored two of the third series AFIP Fascicles: *Tumors of the Thymus* and *Tumors of the Thyroid Gland* and edited a book on the history of surgical pathology in America, *Guiding the Surgeon’s Hand*. A recent educational milestone was the creation of *The Juan Rosai Collection of Surgical Pathology Seminars*, an open online resource that includes digital images of the original slides and an annotated discussion representing nearly 1500 seminars and over 18,000 individual cases. Of course, one of Dr. Rosai’s most renowned contributions has been the authorship of *Rosai and Ackerman’s Surgical Pathology*, which he took over for Dr. Ackerman in 1981. Handling this task as a single author will probably stand as one of the monumental accomplishments of modern surgical pathology education and is a feat that we are quite sure will never be duplicated. *In this 11th edition our goal is to preserve what we can of his voice and influence, while acknowledging that there is no one among us who could singlehandedly create this work.*

Dr. Rosai has received numerous professional awards and honors over his career. These include Doctorate Honoris Causa from the University of Bologna (Italy), the University of Santiago de Compostela (Spain), the National University of Cordoba (Argentina), and the University of Ioannina (Greece). He is a Life Trustee of the American Board of Pathology and served for many years creating the Anatomic Pathology examination. His lifetime of service to the United States and Canadian Academy of Pathology (USCAP) and the International Academy of Pathology (IAP) has been acknowledged with the Maude Abbot Lectureship (USCAP 1995), the Distinguished Pathologist Award (USCAP 2010), and the Golden Medal Award (IAP 2011). Other recognition includes an Honorary Membership in the Royal College of Pathologists (England 2001) and the Fred Waldorf Stewart Award of the Memorial Sloan Kettering Cancer Center (New York 2006).

Personal stories can tell measures about a person’s abilities, and Dr. Rosai’s many trainees over the years all describe in near identical detail an otherworldly consult sign-out experience. On a typical day, as an unusual consult case was reviewed under the microscope (which could be from anywhere on the body), Dr. Rosai would ask someone to pull a specific box of slides off of the wall and another to retrieve a specific file folder containing manuscripts and notes. Of course, the lesions represented by the slides within the box were identical to the case under discussion and the folder contained relevant

articles and personal thoughts. For those with a love of surgical pathology, one cannot imagine a more magical and enlightening experience.

Dr. Rosai is known by many from the hundreds of educational lectures given over his career. His lectures often include philosophical discussions about current tumor classification with an admixture of historical antecedents that clarify the evolution of a specific topic. Of course, he is also masterful at presenting key diagnostic features and pitfalls for everyday practice. The delivery of these lectures is difficult to describe on the written page, but his wit and grace (combined with his incredible depth of knowledge) create a dynamic live experience that is seldom duplicated in surgical pathology

conferences. His lectures still create an anticipatory buzz wherever he is speaking.

Today, Dr. Rosai maintains an active diagnostic surgical pathology consultation practice in Milan, Italy at the International Center of Oncologic Pathology Consultations of the Centro Diagnostico Italiano and also serves as a consultant surgical pathologist for ARUP laboratories in Salt Lake City, Utah. His academic activities continue as evidenced by his contributions to four new manuscripts in 2016, covering thyroid and neuroendocrine neoplasia. Dr. Rosai is one of the most distinguished surgical pathologists of the 20th century for his incredible (and unmatched) breadth and depth of knowledge, service to the field, and his remarkable ability to make us all better pathologists.

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# 2

# Dermatoses

Steven D. Billings

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## Introduction to Dermatopathology

The entities described in this section are a select group taken from the large number of diseases that affect the skin. They have been chosen to encompass the types of non-neoplastic material generally seen in surgical pathology laboratories. Many of the infrequently biopsied, histologically nonspecific, and rare dermatoses are excluded. Their characteristics are described in texts devoted wholly to dermatopathology and in the dermatologic literature.<sup>1-12</sup>

The fact that isolated histopathologic analysis has distinct limitations becomes more evident in the evaluation of the reactive processes associated with diseases of the skin than in most other organs. It is imperative that the clinical differential diagnosis be correlated with the gross and microscopic observations to render a clinically meaningful diagnosis.<sup>13</sup>

Skin biopsies are often small and have minimal gross changes. Ideally, the lesion should be examined by the pathologist on the patient, but, in lieu of this, an accurate clinical description and differential diagnosis should accompany each biopsy. With the ease

of digital photography, the inclusion of a clinical image can be extremely useful in the interpretation of the biopsy findings. All biopsies should be taken from grossly characteristic areas. It is a waste of time and money to biopsy ruptured bullae, secondarily infected or heavily scratched areas, or the incipient or involuting lesion. Multiple biopsies may be advisable when the lesions present differing forms and stages. In diseases in which the expected changes are quantitative rather than qualitative (i.e. hyperkeratosis, acanthosis, increase in dermal thickness), the evaluation of these changes is best made by taking a punch biopsy also of clinically normal skin nearby, which represents the best possible control. Formalin, 10% buffered, is an adequate and widely available fixative. Bouin and Zenker fixatives may be used but have no unique merits. Incisional and punch biopsies can be kept from curling during fixation by placing them on a piece of file card prior to immersion. When the specimen is 0.3 mm or less in diameter, it is best processed into paraffin in one piece. It may then be sampled at various levels in the block. This prevents loss of tissue during the facing-up of the

## Abstract

This chapter focuses on inflammatory diseases, infectious diseases, and miscellaneous disorders of the skin. For inflammatory disorders of the skin, the entities are classified according to reaction patterns. Entities with significant epidermal change are categorized into spongiotic, psoriasiform, and interface patterns. For entities without significant epidermal change, they are classified into perivascular, nodular and diffuse, palisading granulomatous, and sclerosing patterns. Panniculitis is subdivided into septal and lobular patterns, and bullous disease is divided into subepidermal and intraepidermal bullous dermatoses. Infections are categorized by nature of the infectious agent. At the end of the chapter is a group of miscellaneous disorders that are not easily classified in the aforementioned groups.

## Keywords

Spongiotic dermatitis,  
psoriasiform dermatitis,  
interface dermatitis,  
perivascular dermatitis,  
nodular and diffuse dermatoses,  
palisading granulomatous dermatitis,  
scleroderma/morphea,  
panniculitis,  
vesiculobullous disease,  
infection,  
pyoderma gangrenosum

block and allows more adequate sampling. These technical niceties prevent delays, mishaps, and some mistakes.

## Normal Anatomy

The skin or integument is a complex organ with many functions and with three main anatomic components: epidermis and skin adnexa, melanocytic system, and dermis and subcutis.<sup>14–17</sup>

The epidermis is a stratified squamous epithelium that differentiates to form the outer protective layer of keratin. It is composed of keratinocytes arranged in four layers: basal, squamous (prickle, malpighian), granular, and cornified (horny). The basal cells are the mitotically active cells that give rise to all other keratinocytes; they contain low-molecular-weight keratin and are separated from the dermis by a continuous basal layer, to which they are attached by hemidesmosomes. The basal membrane is a complex antigenic structure that plays an important role in many cutaneous diseases.<sup>18</sup> The dermoepidermal junction is thrown into undulating folds of interlocking ridges of epidermis (rete ridges) and dermal papillae. Thus the undersurface of the epidermis seen in whole mounts presents an anastomosing and reticulated pattern of ridges and valleys. The pattern and size of these ridges vary from area to area. With age, they diminish in size, and the dermoepidermal junction becomes flattened.

The squamous layer is composed of several layers of cells, which become larger, more flattened, and more eosinophilic as they approach the surface. This correlates with the intracytoplasmic accumulation of filaments, which are the precursors of keratin, and a diminution of ribosomes. Some cells in the squamous layer exhibit a clear, vacuolated cytoplasm (sometimes resulting in nuclear indentation), which should not be confused with melanocytes or Paget cells. Melanocytes and Paget cells, unlike vacuolated keratinocytes, have cytoplasm clinging to their nuclei. When the cells are separated, as a result of fixation and dehydration or intercellular edema, these areas of attachment are seen via the light microscope as fine spiny (“intercellular”) bridges, with a dot-like structure at their center (Bizzozero nodule), representing the desmosome. The epidermal cells are not a syncytium, and true intercellular bridges do not exist. Destruction of these attachments causes the cells to lose their cohesion. This process, termed acantholysis, is seen in pemphigus vulgaris and related diseases. The granular layer is composed of one to three layers of flattened cells containing keratohyaline granules. These coarse, intensely basophilic granules are rich in histidine and represent the precursors of the protein filaggrin, which is responsible for the aggregation of keratin filaments. The cornified layer contains multiple layers of polyhedral cells that have lost their nuclei and that are arranged in a basket-weave pattern (except for the acral regions, in which this layer is thick and compact). The skin from the palms and soles features an additional layer—the stratum lucidum—located between the granular and the cornified layers and appearing as a homogeneous eosinophilic zone.

The major proteins of basal keratinocytes are keratins 5 and 14, which form an extensive network of 10-nm cytoskeletal filaments. As keratinocytes differentiate, they downregulate this pair of keratins and switch on expression of other pairs, the nature of which is dependent on the site. In the epidermis, terminally differentiated keratinocytes express keratins 1 and 10.

The keratinization cycle usually takes 30–45 days. Many dermatoses result in alterations in the pattern and speed of this process. Abnormal keratinization may be manifest by hyperkeratosis, in which the stratum corneum is thickened, usually in association with a more prominent granular layer, or by parakeratosis, in which the cells of the stratum corneum retain their nuclei and the granular layer is diminished or absent.

Certain descriptive terms are applied to alterations in the pattern of the epidermis. It may become *atrophic* or thinned with age or disease. It may be thickened, and as it proliferates the rete ridges extend deeper into the dermis, a process known as *acanthosis*. Outward overgrowth of the epidermis accompanied by elongation of the dermal papillae is *papillomatosis*. A degenerative process in which the basal cells become vacuolated, separated, and disorganized is called *liquefactive* or *hydropic degeneration*. Various combinations of these changes are seen in the dermatoses, and this descriptive jargon allows succinct communication.

In addition to keratinocytes, the normal epidermis contains melanocytes, Langerhans cells, and Merkel cells. Melanocytes are described in more detail in the chapter on cutaneous neoplasms. Langerhans cells are bone marrow–derived dendritic cells whose function is to present antigens to immunologically competent T cells. They are scattered throughout the upper part of the squamous layer and are difficult to identify in routinely stained sections. Ultrastructurally, they have a characteristic organelle—the Birbeck granule—a rod-shaped structure with zipper-like striations and sometimes a bulbous end. Immunohistochemically, they express CD1a, langerin, and S-100 protein; they have receptor sites for the Fc portion of the immunoglobulin G (IgG) molecule and the third component of complement.<sup>15</sup>

Merkel cells, also extremely difficult to identify in hematoxylin and eosin (H&E) sections and even with special stains, are concentrated in the glabrous skin of the digits, lips, outer root sheath of hair follicles, and tactile hair disks. Ultrastructurally, they contain cytoplasmic dense core (neurosecretory-type) granules, often arranged beneath the cell membrane or located within unmyelinated neurites. Spinous processes projecting from the cytoplasm anchor these cells to adjacent keratinocytes. Immunohistochemically, Merkel cells are reactive for neuron-specific enolase (NSE), neurofilaments, keratin (including CK20), chromogranin, and synaptophysin.<sup>15,19,20</sup>

The skin adnexa are represented by the hair follicles, sebaceous glands, sweat (eccrine) glands, and apocrine glands. The hair follicle, sebaceous gland, erector pili muscle, and (in certain regions) the apocrine gland constitute a functional complex known as the *pilar unit*.

The hair follicle is responsible for the formation of hair, a cyclic process that proceeds in three phases: *anagen* or growing phase, *catagen* or involuting phase, and *telogen* or resting phase. The mitotically active cells of the hair follicles lining the dermal papilla are the matrix (generative) cells. These cells give rise to the hair shaft and the *inner root sheath*. The outer layer of the latter structure is surrounded by a layer of large clear (glycogen-rich) cells known as the *outer root sheath*. At the level of the isthmus, these cells undergo an abrupt type of keratinization, which occurs without the interposition of a granular layer; this is referred to as *trichilemmal keratinization* and, by extension, the layer itself is known as the *trichilemmal sheath*. By contrast, the keratinization in the infundibular portion of the follicle is similar to that of the adjacent epidermis. It is not unusual to find *Demodex* folliculorum mites, clumps of *Staphylococcus epidermidis*, and yeasts of *Malassezia* (formerly *Pityrosporum*) inside the pilar infundibulum.

The sebaceous glands are lobulated structures containing an outer layer of germinative cells that, as they differentiate, move toward the inside and accumulate intracytoplasmic lipid droplets. These result in a typical multivacuolated appearance, with multiple indentations of the centrally located nucleus. The excretory duct of the sebaceous glands opens into the infundibulum of the hair follicle.

*Sweat glands* are of three types: *eccrine* (responsible for thermoregulation and therefore the only “true” sweat glands), *apocrine*, and *mixed* (apoeccrine glands). Eccrine sweat glands are tubular structures with a secretory and an excretory portion. The secretory coil, located

in the deep dermis or sometimes in the subcutis, is composed of secretory cells (further divided into clear and dark cells) and myoepithelial cells. The excretory portion is composed of a dermal (straight) and an intraepidermal (spiral) portion, the latter also known as the *acrosyringium*.

Although the apocrine glands are concentrated in the axillae, groin, and perineum, they also occur in small numbers on the face and elsewhere. Like eccrine glands, they have a secretory and an excretory component. It is the former that gives them their highly characteristic appearance. The cells have an abundant acidophilic cytoplasm, which may contain lipid, iron, and lipofuscin.

Immunohistochemically, the various epithelial components of eccrine and apocrine glands stain for carcinoembryonic antigen (CEA), epithelial membrane antigen (EMA), keratin, S-100 protein, the enzyme carbonic anhydrase, ferritin, secretory immunoglobulin, and pregnancy-specific  $\beta$ -I-glycoprotein (SPI). In addition, apocrine glands express the marker known as gross cystic disease fluid protein (GCDFP)-15.<sup>21</sup> The myoepithelial cells stain for actin, calponin, caldesmon, S-100 protein, and Sox10.<sup>21-28</sup>

The epidermal adnexa are seldom the sites of primary changes. However, diagnostic changes do occur: heterotopias as in nevus sebaceous of Jadassohn, in which apocrine glands are found in the scalp; pigmentation of eccrine gland basement membranes in argyria and hemochromatosis; atrophy, as in scleroderma; duct obstruction with subsequent retention, as in the various forms of miliaria; and deposition of aggregates of granules of mucoprotein in the eccrine gland cells in myxedematous patients.

The dermis is a connective tissue structure composed of collagen and elastic fibers bathed in ground substance and containing adnexal structures, vessels, and nerves. It is divided into two layers: adventitial and reticular. The adventitial dermis comprises the superficial layer located immediately beneath the epidermis—the papillary dermis—and that located around adnexal structures—the periadnexal dermis.<sup>15</sup>

The *adventitial dermis* is largely composed of a delicate network of collagen fibers (mainly type I, with a scattering of type III or “reticulin” fibers), whereas the *reticular dermis* is made up of thick bundles of type I collagen intermixed with thick elastic fibers.

The thickness of the dermis varies considerably from area to area; it is particularly thick in the back, a feature that is sometimes misinterpreted as being abnormal in biopsies.

The subcutaneous tissue (subcutis) is composed of lobules of mature adipose tissue separated by thin bands of connective tissue interlobular septa. The dermal blood vessels are divided into a deep plexus (located in the reticular dermis) and a superficial plexus (located in the papillary dermis), with communicating vessels in between. From the superficial vascular plexus, capillary loops extend into the dermal papillae. The acral skin contains specialized arteriovenous anastomoses—the *Sucquet-Hoyer canals*—surrounded by a row of modified smooth muscle—the *glomus cells*—which have a round shape, clear cytoplasm, and well-defined cytoplasmic borders. The lymphatics of the skin are also divided into a deep and a superficial plexus.

Specialized nerve end organs present in the skin are the *Wagner-Meissner corpuscles* (with a tactile function; mainly located in the papillary dermis of the palms and soles) and *Pacinian corpuscles* (sensitive to pressure; mainly located in the deep dermis and subcutis of weight-bearing areas). With age, and more so in areas exposed to sunlight, the collagen and elastica undergo structural and tinctorial changes called *solar (actinic) elastosis*. These changes should not be attributed to some suspect disease and should be distinguished from pathologic connective tissue changes, such as increased dermal mucin deposition.

The dermis is the site of inflammatory reactions. In normal skin, a few fibroblasts, macrophages, mast cells, lymphocytes, and dermal

dendrocytes are present. The latter represent a population of mononuclear dendritic cells located in the papillary and upper reticular dermis and are thought to function as antigen-presenting cells. They express the coagulation factor XIIIa (also known as fibrin stabilizing factor) and are known to increase in number in a large number of inflammatory and neoplastic disorders.<sup>29</sup>

The perivascular and periadnexal spaces and the papillary layer of the dermis are the usual sites in which inflammatory cells aggregate. Certain dermatoses, such as lichen planus and chronic discoid lupus erythematosus, have distinct patterns of inflammatory reaction. Others, such as urticaria pigmentosa, have a specific cellular population. Changes in the nerves, visible in sections stained with H&E, are infrequent but when present are of note (see section on [leprosy](#)).

## Inflammatory Dermatoses

As previously mentioned, a thorough and detailed discussion of inflammatory dermatoses is beyond the scope of this text and the reader should seek texts devoted to dermatopathology for a complete discussion of inflammatory diseases of the skin. Nevertheless, biopsies of inflammatory diseases are still encountered with relative frequency by surgical pathologists. Therefore some familiarity with these entities is necessary. Approaching inflammatory dermatoses based on the pattern of inflammation is a rational approach that results in more refined diagnoses. Multiple different patterns exist. For the purposes of this text, a simplified approach will be used. Broadly speaking, the inflammatory reaction patterns can be divided into five groups: (1) dermatoses with significant epidermal changes, (2) dermatoses with dermal inflammation without significant epidermal change, (3) sclerosing diseases, (4) panniculitis, and (5) immunobullous/vesiculobullous disease. These will be discussed in turn. There are also a variety of diseases with specific etiologies (e.g. infections) and miscellaneous disorders that will be described separately at the end of the chapter.

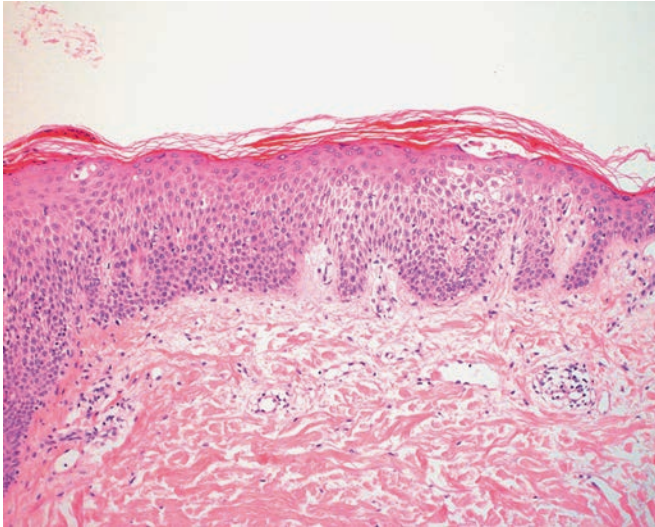
### Inflammatory Dermatoses With Epidermal Change

There are three primary patterns within this group: spongiotic, psoriasiform, and interface dermatitis. Spongiotic dermatitis is characterized by the accumulation of edema fluid within the epidermis, resulting in the epidermal keratinocytes being pulled apart by hydrostatic forces. The psoriasiform pattern is characterized by epidermal acanthosis (hyperplasia) without significant spongiosis. There is often overlap between these patterns. The interface pattern is characterized by a dermal infiltrate, either lichenoid or perivascular, that is associated with damage to the epidermis along the dermoepidermal junction with basal vacuolization and dyskeratotic keratinocytes. Select entities within these groups will be discussed.

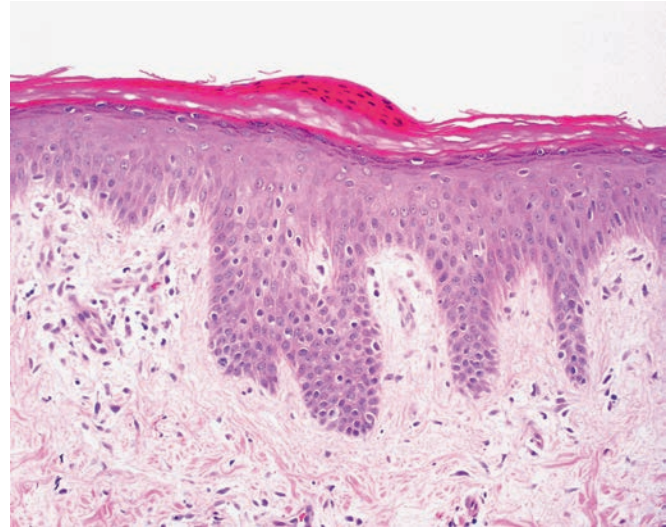
### Spongiotic Dermatitis

Spongiotic dermatitis is a reaction pattern that is most commonly seen in the clinical spectrum of eczematous dermatitis, including allergic contact dermatitis, nummular dermatitis, atopic dermatitis, dyshidrotic eczema, stasis dermatitis, and eczematous drug reactions. All of these dermatoses are characterized by the presence of intraepidermal edema (spongiosis). Histologically, these entities resemble one another and differentiating them relies on knowledge of the clinical presentation rather than histologic features in most cases. That being said, this group of clinical disorders is frequently biopsied and have common histologic features.<sup>29</sup>

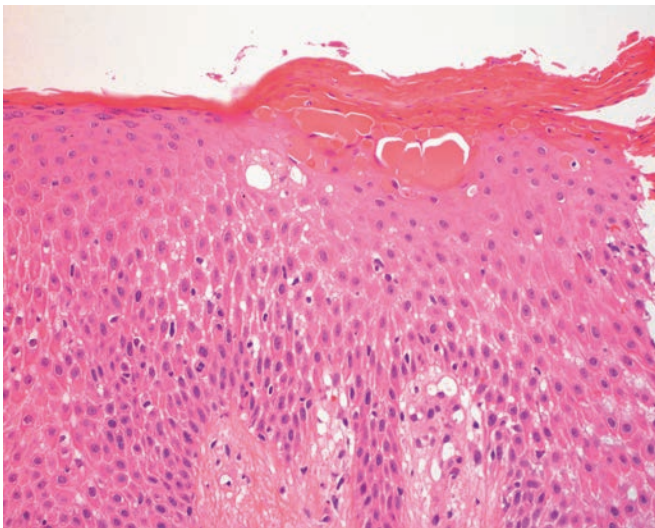




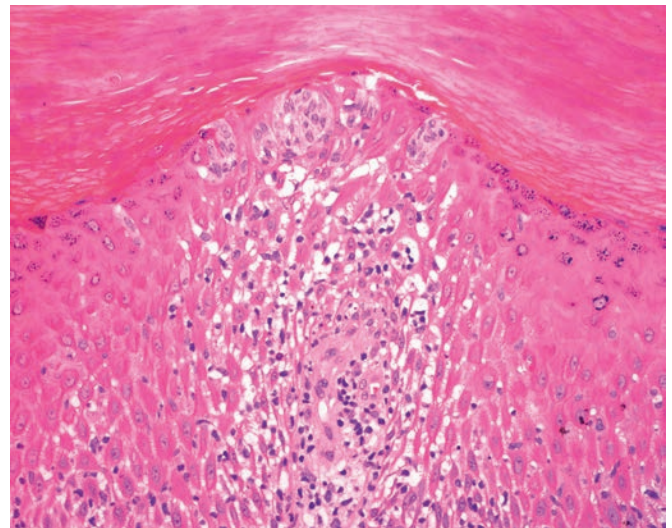
**Figure 2.1 Acute Spongiotic Dermatitis.** The stratum corneum is largely normal, and there is intraepidermal edema (*spongiosis*) and a superficial perivascular inflammatory infiltrate.



**Figure 2.3 Chronic Spongiotic Dermatitis.** There is compact hyperkeratosis, a thickened granular layer, minimal spongiosis, and a sparse perivascular infiltrate.



**Figure 2.2 Subacute Spongiotic Dermatitis.** The epidermis is acanthotic and spongiotic with overlying parakeratosis.



**Figure 2.4 Langerhans Cell Microabscess.** Intraepidermal collections of Langerhans cells are often found in allergic contact dermatitis.

The histologic features are somewhat dependent on when the biopsy is taken during the disease process. The range of histologic features can be divided into three phases, although one should recognize that these phases exist along a continuum. In *acute spongiotic dermatitis*, there is accumulation of edema fluid in the epidermis, sometimes with spongiotic microvesicle formation. The stratum corneum often retains its normal basket-weave configuration or may have some focal parakeratosis. Acanthosis is absent or mild. Within the dermis there is a variable superficial perivascular infiltrate of lymphocytes often admixed with eosinophils (Fig. 2.1). In the *subacute* form, there is associated parakeratosis, often with a diminished granular layer, acanthosis of the epidermis, variable spongiosis, and a similar superficial perivascular dermal inflammatory infiltrate (Fig. 2.2). In the *chronic* phase, there is often compact hyperkeratosis, a thickened granular layer, acanthosis, minimal spongiosis, and mild superficial inflammatory infiltrate (Fig. 2.3). The subacute and chronic phases can have significant histologic overlap with entities in the psoriasisform dermatitis category. In addition to

spongiosis, there is variable parakeratosis, hyperkeratosis, and irregular acanthosis.

### Allergic Contact Dermatitis

Allergic contact dermatitis is a common entity that is biopsied with some frequency. Typical examples of common allergens include detergents, nickel, and plants, such as poison ivy, but a whole host of potential allergens exist. Microscopically, it is a spongiotic dermatitis that is indistinguishable from other forms of spongiotic dermatitis. Some cases have Langerhans cell microabscesses in the epidermis (Fig. 2.4). This is a clue to possible allergic contact dermatitis but is not entirely specific.

### Nummular Dermatitis

Nummular dermatitis presents as round to oval plaques, commonly on the extremities. Clinically, it may get confused with psoriasis.

Microscopically, most cases show features of subacute spongiotic dermatitis. Clues that help to distinguish it from psoriasis include serum in the parakeratotic scale, epidermal spongiosis, and, when present, eosinophils in the dermal infiltrate.

### Atopic Dermatitis

This is a chronic eczematous dermatitis that runs in families and is associated with allergic rhinitis and asthma. It is infrequently biopsied and typically shows features of a subacute to chronic spongiotic dermatitis.

### Dyshidrotic Eczema

Also called pompholyx, this is a recurrent dermatitis that affects the hands and feet, and many are in actuality an allergic contact dermatitis. Clinically, it often has a vesicular appearance. Microscopically, it resembles a typical spongiotic dermatitis. Spongiotic microvesicles are relatively common. It is important to exclude a dermatophyte infection, especially in lesions from the feet.

### Eczematous Drug Reactions

A small subset of drug eruptions may be eczematous in nature. Histologically, they are not distinguishable from other forms of spongiotic dermatitis. Rather correlation with onset related to a medication is required.

### Summary

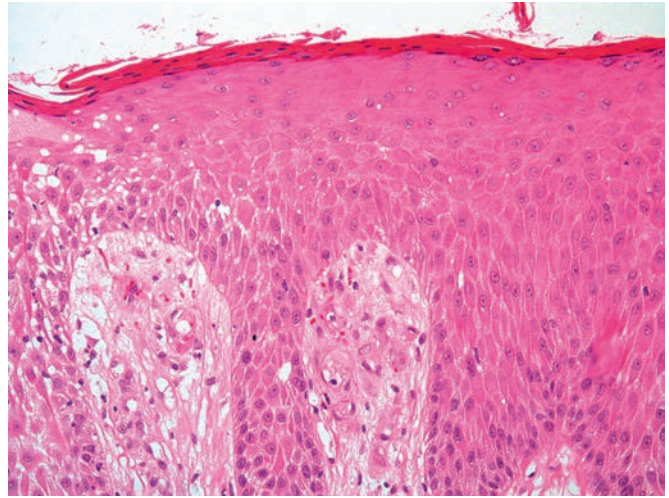
As a general rule, pathologists can render only a descriptive diagnosis of spongiotic dermatitis because the histologic features themselves are not specific. That being said, it is important to exclude more specific diagnoses, such as psoriasis and dermatophyte infection, which can have overlapping features and are discussed later. If information is known about the clinical presentation, a more specific diagnosis can be suggested in a comment.

### Stasis Dermatitis

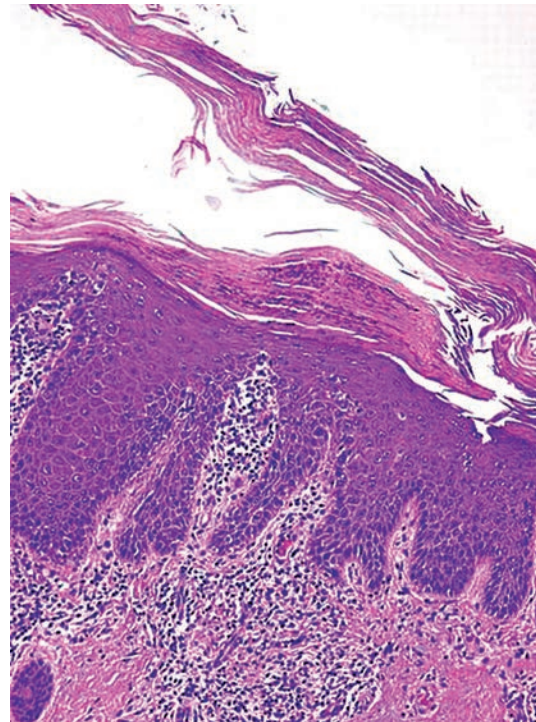
A more distinct form of dermatitis that can have either a spongiotic or psoriasiform pattern is stasis dermatitis. Stasis dermatitis occurs on the lower legs of older and/or obese patients. Often it is bilateral but sometimes presents as an isolated lesion that can mimic a neoplasm clinically.<sup>30</sup> Microscopically, it is associated with variable acanthosis and spongiosis. The key feature is the presence of a lobular proliferation of relatively thick-walled blood vessels in the papillary dermis (Fig. 2.5). Frequently there are extravasated erythrocytes and siderophages. In longstanding cases there may be significant dermal fibrosis with an associated fibroblastic proliferation, called *acroangiodermatitis*, a condition that can superficially mimic Kaposi sarcoma.<sup>30</sup> It should be remembered that other forms of eczematous dermatitis, such as contact dermatitis, can be superimposed on patients with underlying stasis change.

### Psoriasiform Dermatitis

The most common entities in this group include psoriasis and lichen simplex chronicus/prurigo nodularis. This group is characterized by prominent epidermal hyperplasia. That being said, there may be considerable overlap with subacute to chronic spongiotic dermatitis, which also is associated with epidermal hyperplasia. In that regard, placing subacute to chronic spongiotic dermatitis in the spongiotic pattern is somewhat arbitrary.



**Figure 2.5 Stasis Dermatitis.** Within the superficial dermis there is a lobular proliferation of relatively thick-walled vessels with hemorrhage and overlying spongiosis in the epidermis.



**Figure 2.6 Typical Appearance of Psoriasis.** Note the engorgement of papillae and Munro microabscesses.

### Psoriasis

Psoriasis is one of the more common dermatoses. Estimates of its incidence vary between 0.5% and 1.5% of the population.<sup>31</sup> In its most common form, *psoriasis vulgaris*, it is a chronic, bilaterally symmetric, nonpruritic lesion formed by erythematous plaques covered by fine silvery scales.<sup>32-34</sup> Typically, it involves the extensor surfaces, such as the elbows, knees, back, and scalp. Generalized lesions also occur. The morphologic characteristics are those of uniform acanthosis of the epidermis with prominent parakeratosis and attenuation of the epidermis overlying the dermal papillae, a feature known as “suprapapillary thinning” (Fig. 2.6). Within the

parakeratosis and sometimes the epidermis, there are collections of neutrophils. Within the dermal papillae, the capillaries are dilated and tortuous. There is also a polymorphic inflammatory infiltrate composed of lymphocytes, macrophages, and neutrophils.<sup>35</sup> Psoriasis may also be induced by tumor necrosis factor- $\alpha$  inhibitors, typically in the setting of inflammatory bowel disease.<sup>35</sup> In our experience, drug-induced psoriasis in this setting often has eosinophils, in contrast to conventional psoriasis in which eosinophils are typically absent. Eosinophils are usually absent with the exception of drug-induced forms of psoriasis, usually secondary to tumor necrosis factor- $\alpha$  inhibitors. The hyperproliferation appears to be caused by overexpression of cytokines (e.g. tumor necrosis factor- $\alpha$ , interferon gamma, and various interleukins), as well as chemokines and chemokine receptors (e.g. CCL2, CCL3, CCL4, CXCL1, CXCL8), suggesting a Th1 disorder.<sup>36,37</sup>

Other variants of psoriasis lack the prototypical uniform hyperplasia but will be discussed in this section. *Pustular psoriasis* is a variant in which the subcorneal abscesses are particularly prominent.<sup>31,32,36,38</sup> In pustular psoriasis, there is less prominent epidermal hyperplasia. *Guttate psoriasis* is a special type of psoriasis that is characterized by a rapid onset of small papules and plaques, typically after an antecedent streptococcal pharyngitis. It lacks the epidermal hyperplasia, and the granular layer is often retained. It is characterized by discrete mounds of parakeratosis with collections of neutrophils overlying the epidermis (Fig. 2.7).<sup>38</sup>

The differential diagnosis of psoriasis typically centers on subacute forms of spongiotic dermatitis, usually nummular. In contrast to spongiotic dermatitis, the epidermis in psoriasis is more uniformly acanthotic and the parakeratosis is “dry,” lacking the serum present in the overlying crust scale in spongiotic dermatitis. Psoriasis also typically lacks eosinophils (with the exception noted previously), which are frequently present in spongiotic dermatitis. Dermatophyte infections can have similarity to psoriasis. Both have collections of neutrophils in the parakeratosis, but dermatophyte infections usually lack the uniform acanthosis and may have eosinophils in the infiltrate. A periodic acid-Schiff (PAS) or Gomori methenamine silver (GMS) stain can help with this differential diagnosis. *Pityriasis rubra pilaris* is a rare disorder that can closely resemble

psoriasis with a similar pattern of acanthosis and parakeratosis. However, collections of neutrophils in the parakeratotic scale are not seen. Finally, partially treated psoriasis may lack some of the typical histologic features. The presence of dilated and tortuous papillary dermal blood vessels can be a clue in partially treated psoriasis. As in all inflammatory dermatoses, clinical correlation is essential.

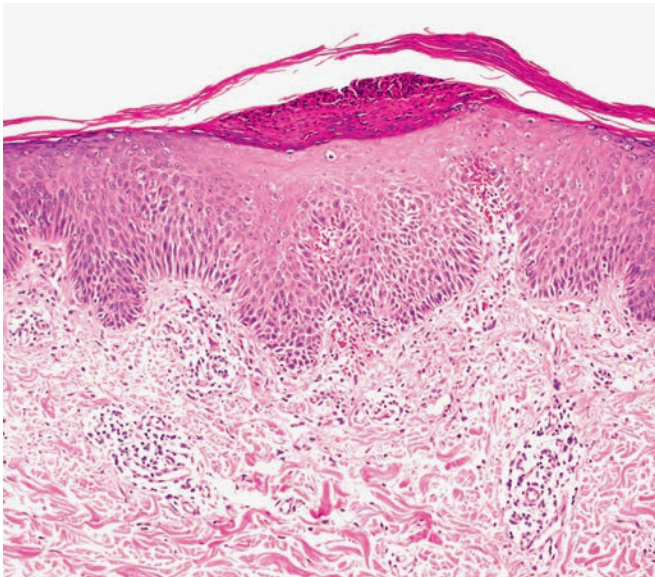
### Lichen Simplex Chronicus and Prurigo Nodularis

*Lichen simplex chronicus* and *prurigo nodularis*, sometimes clinically referred to as neurodermatitis, are ends of a spectrum of a dermatosis that are the result of persistent excoriation rather than inflammation. They are often seen in patients with medical conditions that result in pruritus (e.g. renal failure) and in a subset of patients with psychiatric disorders.<sup>39</sup> They present as plaques (lichen simplex chronicus) or nodules (prurigo nodularis). The clinical location is a clue to the diagnosis in that lesions are only seen in areas that can be readily reached. This condition is most commonly encountered on the extremities, abdomen, genitalia, and scalp, but they may present at any easily accessible location on the body. Lichen simplex chronicus involving perianal and genital skin is often biopsied with a clinical diagnosis of lichen sclerosus. These disorders can also be seen as a complication of a chronic eczematous process, such as a persistent contact dermatitis (see earlier).

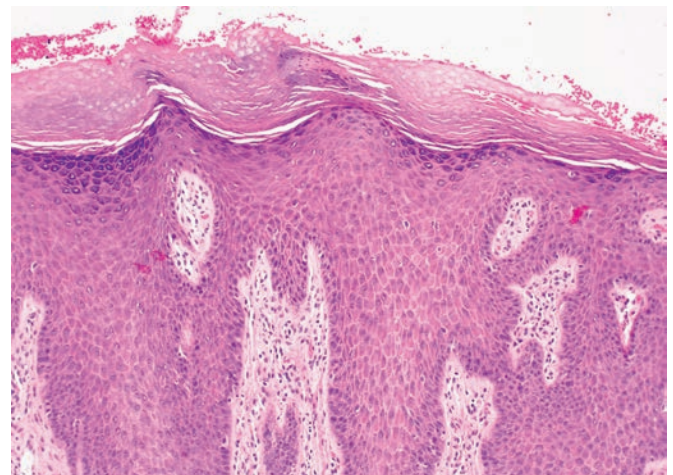
Microscopically, they demonstrate marked acanthosis of the epidermis, marked hyperkeratosis, a thickened granular layer, and vertical fibrosis of the papillary dermal collagen (Fig. 2.8).<sup>40</sup> Occasional cases may show pseudoepitheliomatous hyperplasia or focal parakeratosis. Typically, there is little inflammation unless it is superimposed on an underlying chronic eczematous process.

### Interface Dermatitis

Interface dermatitis is characterized by basal vacuolization and dyskeratosis. The presence of dyskeratotic keratinocytes is important, as some cases of spongiotic dermatitis have basilar spongiosis that mimics vacuolar change. Broadly speaking, interface dermatitis can be grouped in two patterns: lichenoid and perivascular, although entities within this group may have overlapping features.



**Figure 2.7** Guttate Psoriasis. Note the discrete mound of parakeratosis with overlying collections of neutrophils.



**Figure 2.8** Lichen Simplex Chronicus. There is compact hyperkeratosis overlying an acanthotic epidermis with a thickened granular layer. Vertically oriented, thickened collagen bundles are present in the superficial dermis.

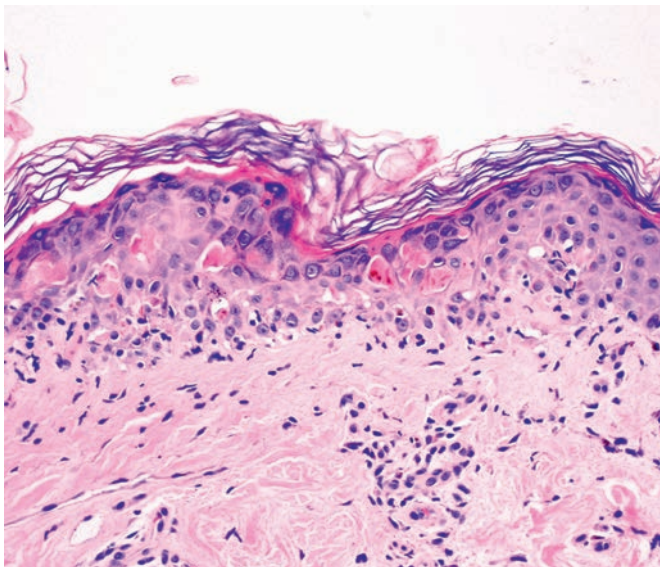
### Interface Dermatitis With Perivascular Pattern

#### *Erythema Multiforme, Stevens-Johnson Syndrome, and Toxic Epidermal Necrosis*

This group of disorders forms of spectrum of dermatoses that are histologically similar. Specific diagnosis requires knowledge of the clinical presentation.<sup>41,42</sup> *Erythema multiforme* is a self-limiting episodic eruption that usually affects acral surfaces and oral mucosa of young adults. It is associated with herpes simplex virus and *Mycoplasma* infections, as well as a variety of medications.<sup>41,42</sup>

*Stevens-Johnson syndrome* and *toxic epidermal necrolysis* involve both mucosa and epidermis. By definition, Stevens-Johnson syndrome affects  $\leq 10\%$  of the total body surface area and toxic epidermal necrolysis  $\geq 30\%$  of the body surface area, leaving an intermediate category between the two ends of the spectrum. Both Stevens-Johnson syndrome and toxic epidermal necrolysis are almost invariably triggered by adverse reactions to medications. They are considered true emergencies, and there is an associated mortality rate ranging from 10% to 40%. Recognition of Stevens-Johnson syndrome and toxic epidermal necrolysis is therefore critical because these patients may need to be managed in specialized burn units.

Microscopically, all of these entities show similar features. There is interface change characterized by basal vacuolization of the epidermis and frequent necrotic keratinocytes at all levels of the epidermis with exocytosis of lymphocytes into the overlying epidermis (Fig. 2.9).<sup>43</sup> In some cases there is complete necrosis of the epidermis. There is typically a relatively sparse to mild superficial perivascular lymphocytic infiltrate that may contain a few eosinophils.<sup>44</sup> The infiltrate is typically disproportionately mild compared with the amount of epidermal damage. Reactive epidermal changes, such as acanthosis, parakeratosis, and hyperkeratosis, are notably absent, and this absence is a clue to differentiating this group from other dermatoses with interface change. Some cases may have a bullous appearance due to detachment of the epidermis secondary to the marked interface change.<sup>45</sup>



**Figure 2.9 Erythema Multiforme.** There is interface change with basal vacuolization, numerous dyskeratotic keratinocytes, and a sparse perivascular infiltrate.

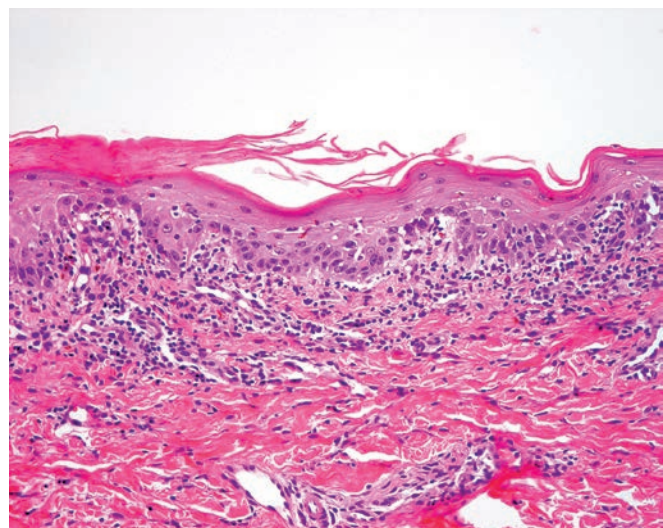
### Graft-Versus-Host Disease

*Graft-versus-host disease* is an important cause of morbidity and mortality following bone marrow transplantation. The acute form is characterized microscopically by vacuolization of the basal layer, spongiosis, and individual cell necrosis, associated with mononuclear cell infiltration of the upper dermis (Fig. 2.10).<sup>46,47</sup> Sometimes these epidermal changes occur in the absence of an inflammatory infiltrate.<sup>47</sup> The amount of inflammation seems to be the most important prognostic determinant.<sup>48</sup> This has been quantitated through the Lerner grading system, which has a high degree of interobserver concordance,<sup>49</sup> but which is of limited use in predicting the likelihood of a skin rash progressing to a clinically more significant disease.<sup>50</sup> In this system, grade 1 acute graft-versus-host disease is characterized by basal vacuolization with a superficial perivascular lymphocytic infiltrate without dyskeratotic keratinocytes. Grade 2 has the features of grade 1 graft-versus-host disease but with dyskeratotic keratinocytes and satellite cell necrosis. Grade 3 is associated with cleft formation between the epidermis and dermis, and grade 4 is characterized by complete loss of the epidermis. In general, most cases of acute graft-versus-host disease are grade 2.

The chronic form of graft-versus-host disease has been divided into a predominantly lichenoid form and sclerodermoid form.<sup>51,52</sup> In lichenoid chronic graft-versus-host disease the epidermis shows thickening of the granular layer like lichen planus, but the inflammatory infiltrate is usually less dense. The sclerodermoid form is essentially indistinguishable from scleroderma/morphea with marked sclerosis of dermal collagen.

### Lupus Erythematosus

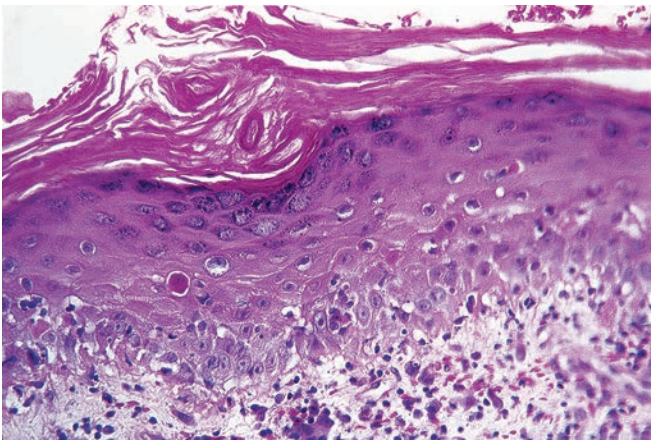
Cutaneous lupus erythematosus can be divided into the chronic/discoid, acute/systemic, and subacute forms.<sup>53-55</sup> *Chronic discoid lupus erythematosus* is a relatively common condition with a distinct preference for women, presenting as delimited erythematous to hyperkeratotic to atrophic patches and plaques on the face, neck, scalp, and, less frequently, the arms and trunk (Fig. 2.11). *Systemic lupus erythematosus* is an immune-mediated disease caused by antibodies to homologous and heterologous DNA. It manifests a protean symptomatology usually characterized by fatigue, fever, arthritis, various cutaneous lesions of which the erythematous bimalar



**Figure 2.10** Microscopic changes of acute graft-versus-host reaction.



**Figure 2.11** Extensive facial lesions of chronic discoid lupus erythematosus.



**Figure 2.12** Lesion of chronic discoid lupus erythematosus showing hyperkeratosis and interface change with hydropic degeneration along basal layer.

“butterfly” blush is most common, signs of renal involvement, lymphadenopathy, and panseritis. Sunlight may cause exacerbations. *Subacute lupus erythematosus* usually presents as plaques, often annular, on sun-exposed skin of the extremities and trunk. The face is usually spared. Histologically, there is overlap between the subtypes. They all have basal vacuolization with interface change and scattered dyskeratotic cells associated with a superficial or superficial and deep perivascular lymphocytic infiltrate with increased dermal mucin. In the discoid form there is often follicular plugging, epidermal atrophy, a thickened basement membrane, and periadnexal inflammation (Fig. 2.12).<sup>55-58</sup> Eosinophils are absent, and their presence argues against the diagnosis.<sup>59</sup> *Tumid lupus erythematosus* is a form of chronic lupus erythematosus without interface change and may represent the same process that has also been termed *Jessner lymphocytic infiltration of the skin*.<sup>58</sup> Clusters of CD123-positive plasmacytoid dendritic cells are present in lupus erythematosus and their presence can support the diagnosis.<sup>60</sup>

Direct immunofluorescence will show the presence of immunoglobulins (usually IgG and IgM) and so-called membrane attack

complex (C5b, C6, C7, C8, and C9) in approximately 90% of specimens obtained from clinically involved skin of patients with either systemic or chronic discoid lupus erythematosus.<sup>61,62</sup> The deposition consists of coalescing clumps along the dermoepidermal junction, resulting in the formation of an irregular band (so-called *lupus band test*), a finding that is not entirely specific for this entity.<sup>63</sup> Clinically uninvolved areas will show deposition of immunoglobulins in approximately half of the patients with systemic lupus erythematosus but no deposition of the membrane attack complex.<sup>61,64</sup> Direct immunofluorescence may be helpful in selected cases but is generally not necessary to establish the diagnosis. Histologic examination and correlation with clinical history usually allows accurate diagnosis.

## Dermatomyositis

Dermatomyositis is an inflammatory disorder affecting skeletal muscle and skin, characterized clinically by proximal, symmetric muscle weakness, and cutaneous lesions. There are cutaneous forms without muscle involvement, termed dermatomyositis sine myositis. Microscopically, the skin changes may be those of a nonspecific chronic dermatitis or may acquire features very similar to those of systemic lupus erythematosus, although typically with less inflammation.<sup>65,66</sup> By immunofluorescence, features favoring dermatomyositis over lupus erythematosus are a negative “lupus band test” and deposition of C5b-q (the membrane attack complex of complement).<sup>64</sup> Biopsies of the afflicted muscles show distinct myositis with necrosis of myofibers, fragmentation, phagocytosis, and some sarcolemmal nuclear proliferation. In the later stages, fibrosis, fat infiltration, and fascicular atrophy appear.<sup>67,68</sup>

Much has been written about the incidence or coincidence of adenocarcinoma with dermatomyositis.<sup>69-71</sup> A review of the literature carried out by Williams many years ago found that 15% of dermatomyositis patients had neoplasms of the stomach, breast, ovary, lung, or colon. Remissions of the dermatomyositis have occurred following resection of the neoplasm.<sup>71</sup> Therefore careful investigation of adults with dermatomyositis for undetected carcinoma is certainly worthwhile. However, in the majority none will be found.

## Interface Dermatitis With Lichenoid Pattern

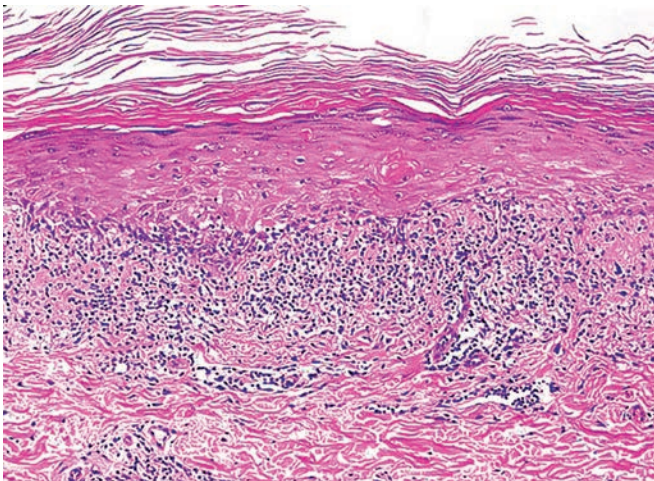
### *Lichen Planus*

Lichen planus is a pruritic, violaceous, subacute to chronic, papulosquamous dermatitis of unknown etiology (Fig. 2.13).<sup>72-74</sup> It usually involves the flexor surfaces of the arms and the legs, but it may be found in many other sites. Lesions may be confined to the oral mucosa, or they may precede or accompany the skin changes.<sup>75</sup> Histologically, the well-developed lesions are rather distinct (Fig. 2.14). The epidermis is hyperkeratotic, the granular layer is prominent, and the hyperplastic epithelium forms irregular sawtooth acanthotic pegs. Within the dermis there is a dense band-like (lichenoid) lymphocytic infiltrate that may contain a few eosinophils and histiocytes. Dyskeratotic keratinocytes, also referred to as *Civatte bodies*, are often seen in the basal layer and sometimes also in the upper dermis and malpighian layer. On occasion, subepidermal cleavage occurs with the formation of bullae. In oral lichen planus, there is may be parakeratosis, subtle formation of keratohyaline granules. Prominent hyperkeratosis and hypergranulosis are absent in *oral lichen planus*. Histologically, the dyskeratotic cells and absence of atypia in oral lichen planus assists in distinguishing it from dysplasia (see Chapter 4). Clinicopathologic variants of lichen planus include bullous, pemphigoid, hypertrophic, atrophic, and follicular (lichen planopilaris) forms.<sup>76-79</sup>

A morphologic pattern akin to that of lichen planus and designated as lichenoid dermatitis, lichenoid tissue reaction or



**Figure 2.13** Clinical Appearance of Lichen Planus Affecting the Dorsum of the Hand. One of the lesions has been biopsied.

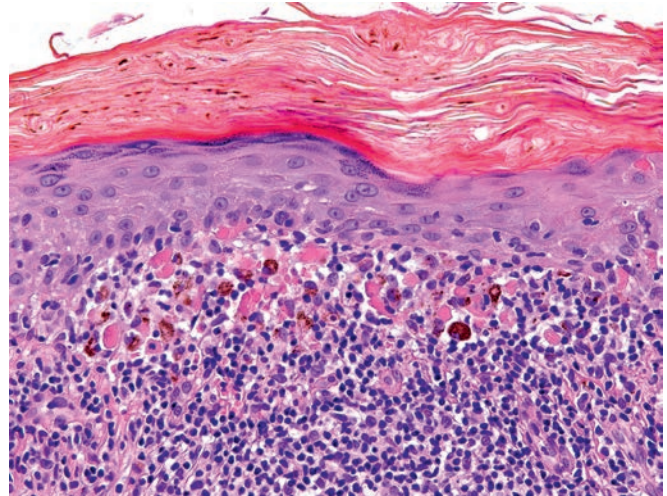


**Figure 2.14** Microscopic Appearance of Lichen Planus. There is orthotopic hyperkeratosis, hypergranulosis, basal vacuolization, and a band-like inflammatory infiltrate with melanophages.

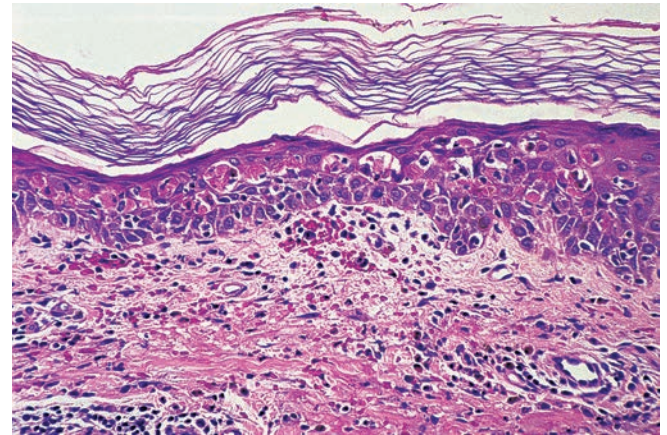
interface dermatitis can be seen in a variety of conditions, including lichenoid drug eruptions (see later), lichenoid actinic keratosis, benign lichenoid keratosis, solitary lichen planus, lupus erythematosus, acute graft-versus-host reaction, and several other conditions.<sup>80-87</sup> A lichenoid reaction is the rule in regressing melanoma (a notorious pitfall) and can also be seen in the epidermis overlying a dermatofibroma.<sup>88,89</sup>

#### Lichenoid Drug Eruption

Lichenoid drug eruptions present as widespread papular eruptions. A variety of agents can trigger lichenoid drug eruptions, including common agents, such as thiazide diuretics. The eruption can develop soon after ingestion of the drug or weeks after.



**Figure 2.15** Lichenoid Tissue Reaction. Lichenoid drug reactions resemble lichen planus, but typically have parakeratosis, which is usually absent in lichen planus. (Courtesy of Dr Fabio Facchetti, Brescia, Italy.)



**Figure 2.16** Fixed Drug Eruption. The infiltrate is rich in eosinophils and is accompanied by necrotic keratinocytes.

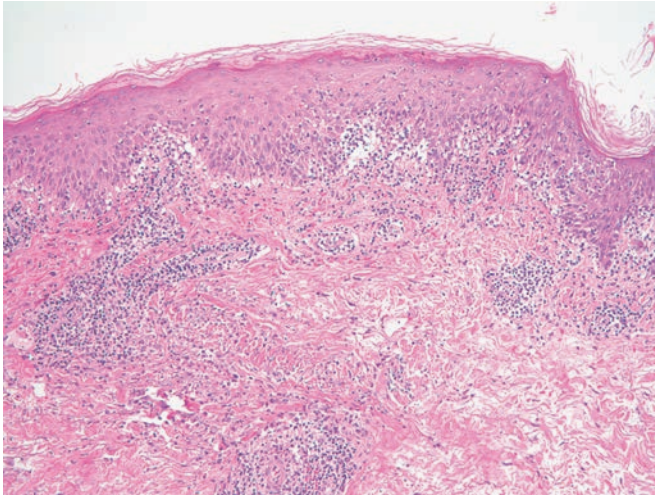
Microscopically, lichenoid drug eruptions are very similar to lichen planus. There is a lichenoid lymphocytic infiltrate with prominent epidermal damage. The epidermis has a thickened granular layer. The presence of parakeratosis and conspicuous eosinophils help to distinguish lichenoid drug eruption from lichen planus (Fig. 2.15).<sup>80,87</sup>

#### Fixed Drug Eruption

Fixed drug eruption is an unusual localized type of adverse medication reaction that recurs in the same location on subsequent exposures.<sup>90-93</sup> Microscopically, it is an interface dermatitis with a lichenoid or perivascular infiltrate and basal vacuolization with dyskeratotic keratinocytes (Fig. 2.16). The overlying stratum corneum usually has a normal basket-weave configuration but may have some parakeratosis. The infiltrate contains lymphocytes, histiocytes, and eosinophils. Melanophages are frequently present.

#### Pityriasis Lichenoides

Pityriasis lichenoides occurs in two clinical forms: *pityriasis lichenoides acuta et varioliformis acuta* (PLEVA; also known as *Mucha-Habermann disease*) and *pityriasis lichenoides chronica* (PLC).<sup>94-97</sup> The etiology is uncertain but may be related to a hypersensitivity reaction to various



**Figure 2.17** Pityriasis Lichenoides Et Varioliformis Acuta. There is interface change with basal vacuolization and a superficial and deep lymphocytic infiltrate with papillary dermal hemorrhage.

infectious agents or drugs.<sup>98-100</sup> It has also been associated with autoimmune disease. PLEVA is associated with the appearance of numerous, small papules that ulcerate and heal, leaving behind smallpox-like (varioliformis) scars. The eruption is predominately on the extremities but may also involve the trunk and buttocks. In PLC the eruption is characterized by brownish-red papules that typically do not result in scarring. Some patients may have overlapping features of both PLEVA and PLC.

Histologically, pityriasis lichenoides shows overlapping features of a lichenoid interface dermatitis and a perivascular interface dermatitis.<sup>101,102</sup> The features somewhat depend on the timing of the biopsy during the evolution of the disease. In fully developed, nonulcerated lesions of PLEVA, there is a superficial perivascular to lichenoid infiltrate with an accompanying wedge-shaped perivascular infiltrate extending into the underlying dermis. There is interface change with basal vacuolization, dyskeratosis, and papillary dermal hemorrhage (Fig. 2.17). The hemorrhage is likely due to a lymphocytic vasculitis, and vasculitic changes can sometimes be seen. In addition to interface change, the epidermis is spongiotic with parakeratosis-prominent exocytosis of lymphocytes and often exocytosis of erythrocytes. Although some authors prefer to classify this as a lymphocytic vasculitis, considering it in the family of interface dermatitis is prudent given the more consistent histologic findings of interface damage. In older lesions, the epidermis may be completely ulcerated. From a pathologic standpoint, ulcerated lesions are histologically nonspecific. Early lesions may show considerably less interface and epidermal change. PLC is similar to PLEVA but with less pronounced histologic features.<sup>102</sup> There is less interface damage, less inflammation, and little to no hemorrhage. Again, a given patient may have lesions that histologically span the spectrum of both PLEVA and PLC.

The differential diagnosis includes other interface dermatitides, as outlined previously. PLEVA has a distinct clinical presentation, which aids in its diagnosis. PLEVA also typically has extravasation of erythrocytes, which is not a conspicuous feature of the aforementioned entities. The presence of spongiosis helps to distinguish it from chronic interface dermatitides, such as lupus erythematosus. Lichen planus and lichenoid drug eruptions have a lichenoid pattern without a deeper perivascular extension. Graft-versus-host disease has much less inflammation. As with all inflammatory diseases, knowledge of the clinical presentation is very helpful.

However, one entity may have a very similar clinical presentation to PLEVA: lymphomatoid papulosis (LYP).<sup>103-106</sup> LYP is actually considered an indolent T-cell lymphoma. There are multiple different histologic types, ranging from type A to E.<sup>107-111</sup> Types A, B, and C are the classic forms. Type A can show considerable histologic overlap with PLEVA but also has numerous large, atypical CD30<sup>+</sup> lymphocytes that are not seen in PLEVA admixed within the infiltrate. Type B LYP resembles mycosis fungoides microscopically. Type C histologically resembles cutaneous anaplastic large cell lymphoma, with sheets of large atypical, CD30<sup>+</sup> lymphocytes. The primary way to differentiate types B and C LYP from their mimics is knowledge of the clinical history of waxing and waning papulonecrotic lesions.

## Inflammatory Dermatoses With Dermal but Not Epidermal Change

This section will encompass a wide variety of entities and by necessity is somewhat superficial, mostly concentrating on more common dermatoses. The patterns discussed will include perivascular, nodular and diffuse, palisading granulomatous and sclerosing dermatoses.

### Perivascular Dermatoses

This pattern is typified by an inflammatory infiltrate that is predominantly in a perivascular distribution. Some entities in this pattern will have overlapping features with the nodular and diffuse pattern. This further highlights how inflammatory diseases and their patterns are on a biologic continuum that we by necessity categorize as discrete entities.

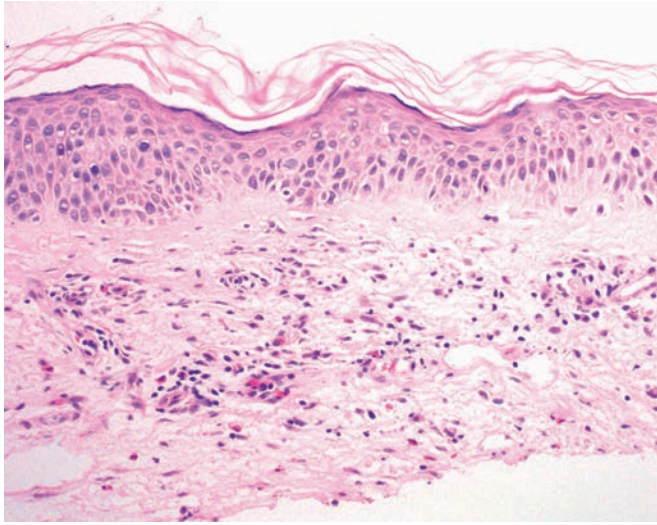
### Dermal Hypersensitivity Reactions

Dermal hypersensitivity reaction is a somewhat wastebasket term that encompasses a variety of entities, most commonly morbilliform drug eruptions, urticaria, and arthropod bite reactions. Although clinically distinct, these entities may be histologically indistinguishable. Morbilliform drug eruptions tend to be widespread, erythematous maculopapular eruptions associated with ingestion of a new medication, although sometime it may take weeks after initiation of a new medication, complicating the clinicopathologic correlation. Urticaria, or hives, classically presents as transient wheals that resolve in 24 hours, although occasionally they may be more persistent. Arthropod bite reactions may present as solitary lesions or numerous papules.

*Morbilliform drug eruptions* are the most common type of adverse medication reaction.<sup>112</sup> They are usually characterized by a mild superficial or superficial and deep, perivascular mixed inflammatory infiltrate of lymphocytes with a few eosinophils (Fig. 2.18). Some cases may show mild basal vacuolization, therefore overlapping with the interface pattern. *Urticaria* is almost identical with a mild perivascular infiltrate of lymphocytes, eosinophils, and sometimes neutrophils.<sup>113,114</sup> In urticaria, there may also be margination of neutrophils in the vascular lumens. In chronic cases, there may be subtle vascular damage resulting in urticarial vasculitis.<sup>113,115</sup> *Arthropod bite reactions* have a similar pattern of inflammation with eosinophils but typically a denser inflammatory infiltrate (Fig. 2.19). In the setting of underlying hematologic malignancies, such as chronic lymphocytic leukemia, reactions to arthropod assaults can be quite pronounced.<sup>116</sup>

### Vasculitis

There is a large group of cutaneous diseases in which the basic alteration is an inflammatory change in the wall of the dermal and/



**Figure 2.18 Morbilliform Drug Eruption.** The epidermis is relatively normal. Within the dermis there is a mild perivascular infiltrate of lymphocytes and eosinophils.

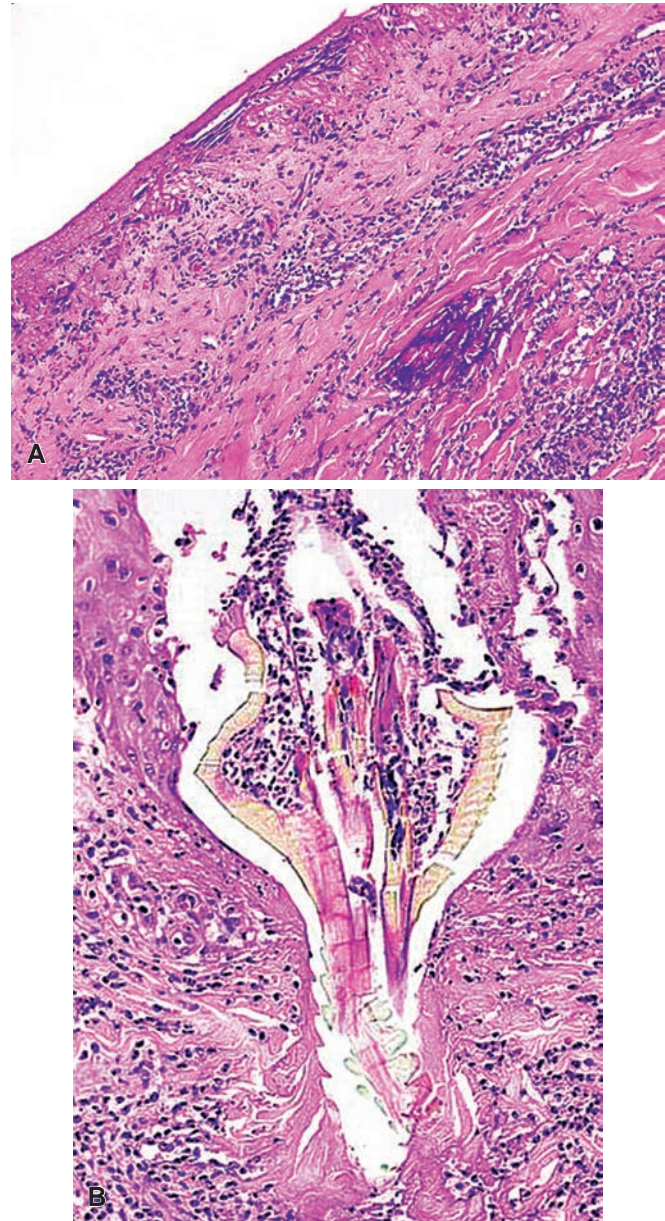
or subcutaneous vessels (i.e. a vasculitis).<sup>117–120</sup> The mechanism is in all likelihood immune mediated for the majority of them, through the action of immune complexes.<sup>121,122</sup> The disease can be restricted to the skin or also involve internal organs; if limited to the skin, it may be generalized or localized to a single focus.<sup>123</sup> The vessels involved may be the capillaries of the papillary dermis, arterioles, and venules of the deep dermis and subcutaneous tissue, or deep-seated medium-sized vessels. Erythrocytes extravasation is a constant feature.

The inflammatory infiltrate can be predominantly neutrophilic (usually accompanied by leukocytoclasia), lymphocytic, eosinophilic, or granulomatous.<sup>124,125</sup> Necrotizing changes (usually of fibrinoid type) of the vessel wall may be present or absent. Secondary changes in the overlying epidermis and in the sweat glands are frequent.<sup>126</sup> Direct immunofluorescence often shows granular deposits of immunoglobulins, complement, and fibrin in and about vessel walls, although with the exception of Henoch-Schönlein purpura, direct immunofluorescence plays little role in the diagnosis.<sup>127,128</sup>

Taking into account all of the foregoing features, morphologic classifications of cutaneous vasculitides have been proposed that correlate well with a variety of clinical conditions.<sup>125,129–131</sup>

*Leukocytoclastic* (neutrophilic, allergic) *vasculitis* is a neutrophilic vasculitis of small vessels accompanied by fibrinoid necrosis and leukocytoclasia (Fig. 2.20).<sup>125</sup> It usually presents as purpuric palpable lesions, most commonly on the lower part of the legs. Systemic involvement, particularly of the kidneys, is frequently found in the form known as Henoch-Schönlein purpura (IgA vasculitis).<sup>128,132</sup> *Henoch-Schönlein purpura* resembles conventional leukocytoclastic vasculitis but on direct immunofluorescence has prominent perivascular deposits of IgA and variable deposits of complement C3. Other distinct subtypes of leukocytoclastic vasculitis are those associated with chronic idiopathic urticaria, hypocomplementemia, and essential mixed cryoglobulinemia.<sup>133,134</sup> The presence of systemic disease is more likely when the vasculitis extends deeply into the reticular dermis or subcutaneous fat,<sup>135</sup> but in general the morphologic features of the systemic and the purely cutaneous form are the same.<sup>136–138</sup>

Etiologic agents include infections, foreign proteins, chemicals, drugs, and a variety of diseases. Some patients with acute leukemia



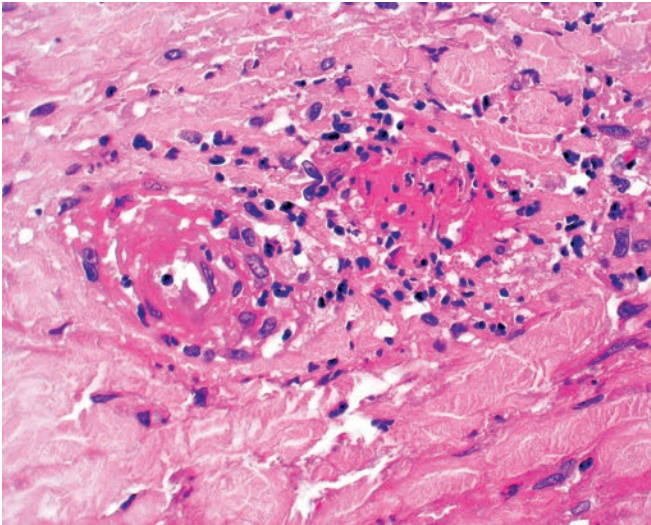
**Figure 2.19 Arthropod Bite.** **A**, Heavy inflammatory dermal infiltrate around necrotic focus. **B**, Section of the arthropod. (Courtesy of Dr Raffaele Gianotti, Milan, Italy.)

develop cutaneous vasculitis, the suggestion having been made that the vascular injury is mediated by the leukemic blasts.<sup>139</sup>

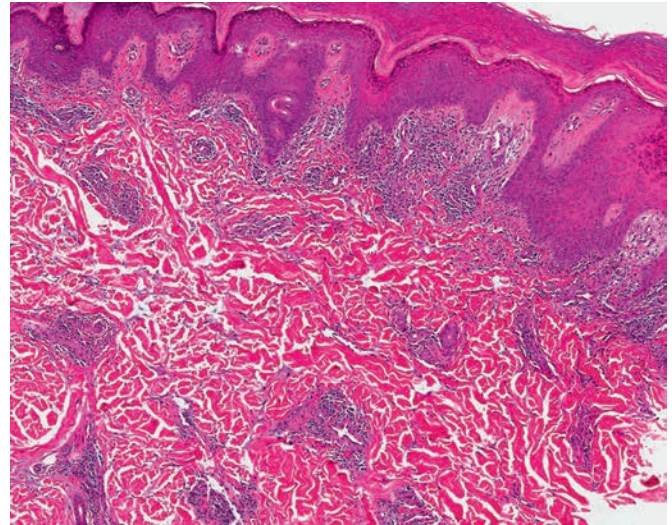
Involvement of larger vessels, often accompanied by necrotizing changes, is seen in allergic granulomatosis of Churg and Strauss, polyarteritis nodosa (systemic or limited to the skin), giant cell arteritis, and granulomatosis polyangiitis (formerly Wegener granulomatosis).<sup>140–143</sup> Prominent vascular involvement without necrotizing changes is also seen in the cutaneous lesions of lymphomatoid granulomatosis, a form of B-cell lymphoma.<sup>144,145</sup> Angiodestruction can be seen in type E LYP.<sup>110</sup>

Other entities associated with vascular injury that do not fit in the category of leukocytoclastic vasculitis include pigmented purpuric dermatosis, perniosis, malignant atrophic papulosis, and segmented hyalinizing vasculitis (atrophie blanche of Milian).

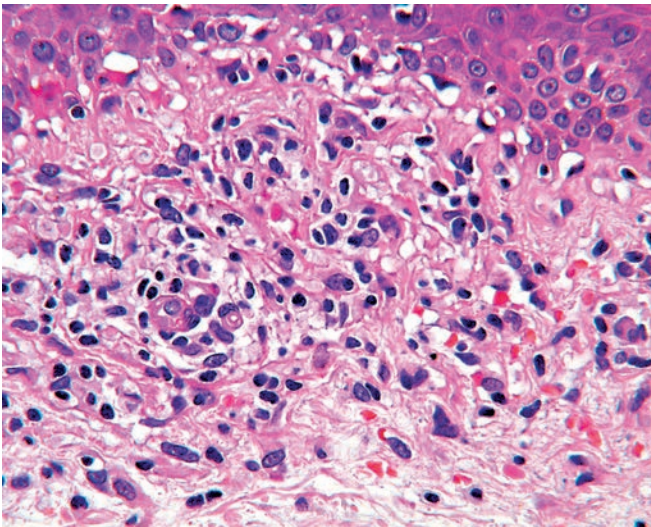




**Figure 2.20** Acute Necrotizing Changes in Leukocytoclastic Vasculitis.



**Figure 2.22** Perniosis is characterized by a superficial and deep perivascular lymphocytic vasculitis.



**Figure 2.21** Chronic Non-Necrotizing Vasculitis in Pigmented Purpuric Dermatitis.

### Pigmented Purpuric Dermatitis

Pigmented purpuric dermatosis has a variety of clinical forms, the most common of which is *Schamberg disease*. Schamberg disease most commonly presents in men and is characterized by asymptomatic, bilateral purpura and petechiae, most commonly involving the lower extremities. Clinically, it may be confused with leukocytoclastic vasculitis but lacks the indurated nature of the lesions seen in leukocytoclastic vasculitis. Microscopically, it consists of a superficial perivascular infiltrate of lymphocytes with extravasated erythrocytes and sometimes siderophages (Fig. 2.21).<sup>146,147</sup> The vessels can show endothelial swelling, and the condition is considered by some a form of lymphocytic vasculitis, although fibrinoid necrosis of vessels is not seen.

### Perniosis/Chilblains

Perniosis usually occurs in cold, damp weather and most commonly presents as painful, erythematous nodules on the fingers or toes. It

is a form of lymphocytic vasculitis. Microscopically, there is a superficial and deep perivascular and periecrine lymphocytic infiltrate (Fig. 2.22). The vessels often demonstrate fibrinoid change that has been described as having a fluffy appearance. Papillary dermal edema is often marked.<sup>148,149</sup>

### Malignant Atrophic Papulosis (Degos Disease)

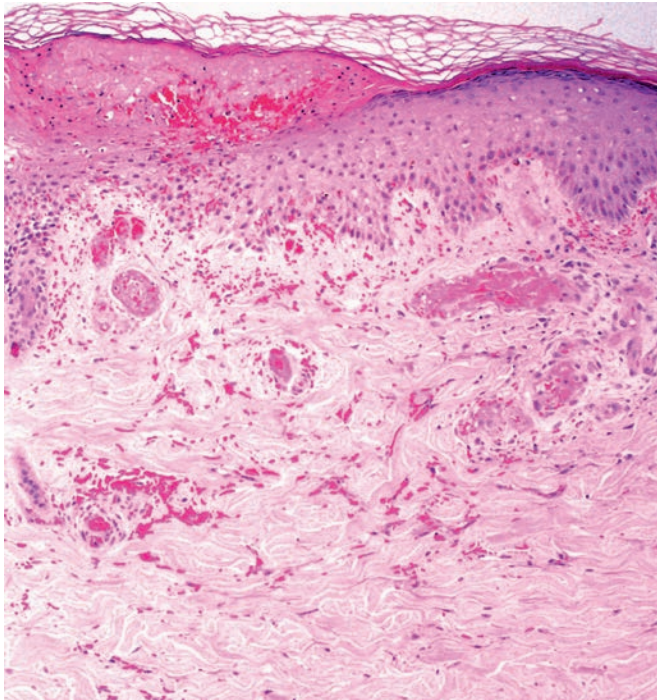
This disorder usually occurs in young adult men and is characterized by papules and patches with a central, depressed white area surrounded by an erythematous rim. It has been associated with lupus erythematosus and may represent a reaction pattern rather than a distinct entity. Microscopically, the main change is an ischemic, wedge-shaped infarct of the skin resulting from intimal proliferation of a deep-seated arteriole with or without a lymphocytic infiltrate.<sup>150-152</sup>

### Atrophie Blanche

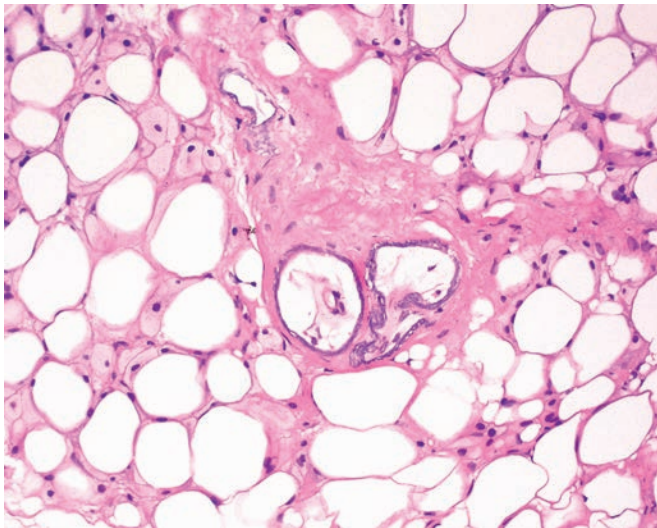
In atrophie blanche (segmented hyalinizing vasculitis) the dermal capillaries show focal endothelial proliferation, marked thickening of the wall by PAS-positive eosinophilic hyaline material, and eventually occlusion of the lumen by a fibrin thrombus (Fig. 2.23).<sup>153,154</sup> This condition has been associated with a variety of hypercoagulable states, and the presence of numerous thrombosed vessels should prompt the pathologist to recommend an appropriate evaluation to exclude those possibilities.

### Calciophylaxis

Calciophylaxis usually presents in patients with chronic renal failure as bilateral, painful ulcers involving the thighs. Involvement of the breasts, buttocks, and penis has also been described. This is a medical emergency with a mortality rate greater than 50%.<sup>155-157</sup> Histologically, most of the findings are in the subcutis. Therefore it is important that any diagnostic biopsy be of adequate depth. Calciophylaxis is characterized by calcium deposition in small- to medium-sized arterioles, associated with thrombosis and extensive fat necrosis of the subcutis (Fig. 2.24). The calcium deposits are usually evident in routine H&E sections, but von Kossa stains may be useful in selected cases. Vascular thrombosis of vessels in the overlying dermis may also be seen.



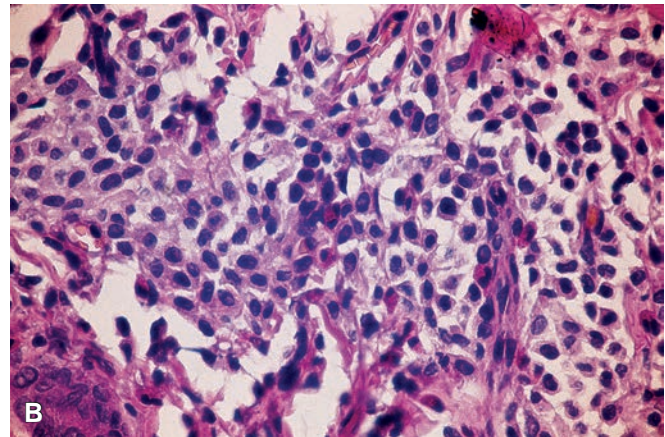
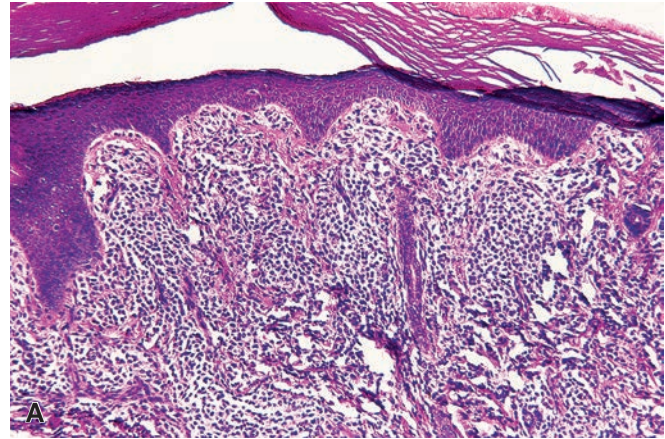
**Figure 2.23** Atrophie blanche is characterized by intravascular fibrin thrombi without a true vasculitis.



**Figure 2.24** Calciphylaxis. There is calcium deposition affecting vessels in the subcutis and associated fat necrosis.

## Mastocytosis

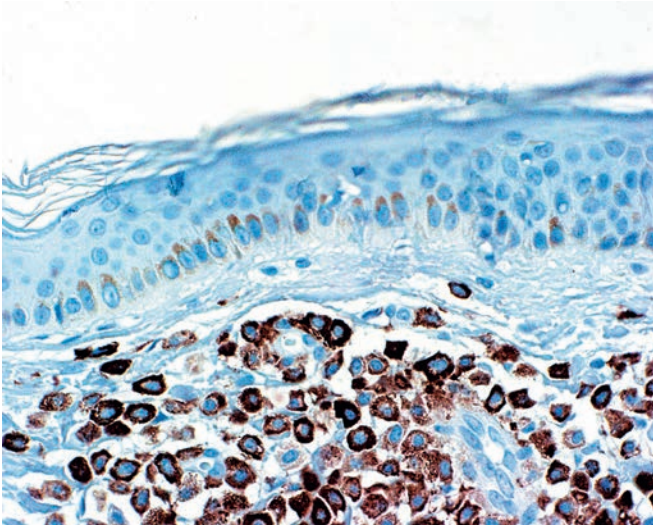
Mastocytosis of the skin can manifest in the form of *urticaria pigmentosa*, (solitary) *mastocytoma*, *diffuse and erythrodermic cutaneous mastocytosis*, and *telangiectasia macularis eruptiva perstans*.<sup>158–161</sup> Urticaria pigmentosa, accounting for approximately 80% of cutaneous mastocytosis, usually has its onset during childhood in the form of multiple brown macules.<sup>158,162</sup> On occasion, it makes its first appearance in adults.<sup>162</sup> The brown macules may be diffusely distributed or, less frequently, may be single.<sup>160,163</sup> When the lesions are stroked, the skin urticates because of the release of histamine.



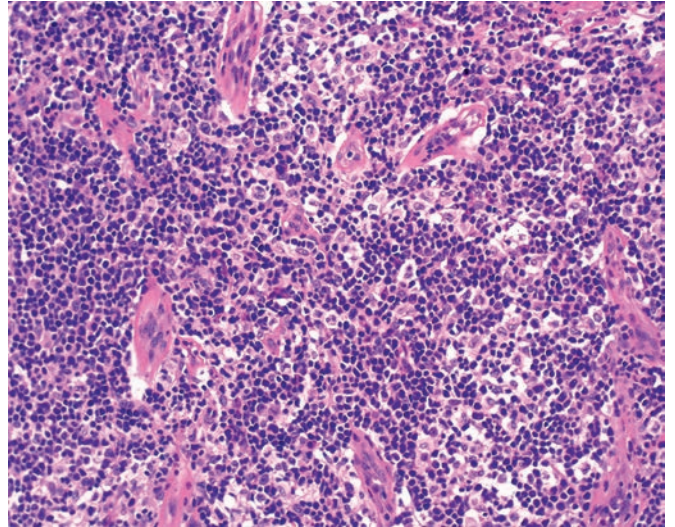
**Figure 2.25** Urticaria Pigmentosa. **A**, Diffuse dermal infiltrate of mast cells admixed with eosinophils. **B**, High-power view of the infiltrate. (Courtesy of Dr Raffaele Gianotti, Milan, Italy.)

Systemic mastocytosis accounts for approximately 20% of cases and may have involvement of the spleen, liver, bone marrow, and lymph nodes, with or without cutaneous lesions.<sup>164,165</sup> Most behave in an indolent fashion, but aggressive forms with a malignant clinical course, including mast cell leukemia, do occur. In general, it is not possible on morphologic grounds to distinguish urticaria pigmentosa with systemic involvement from that having skin disease only,<sup>166</sup> but expression of CD2 or CD25 on mast cells is more common in patients with systemic disease.<sup>167</sup> Aberrant expression of CD30 is also associated with more aggressive disease.<sup>168</sup>

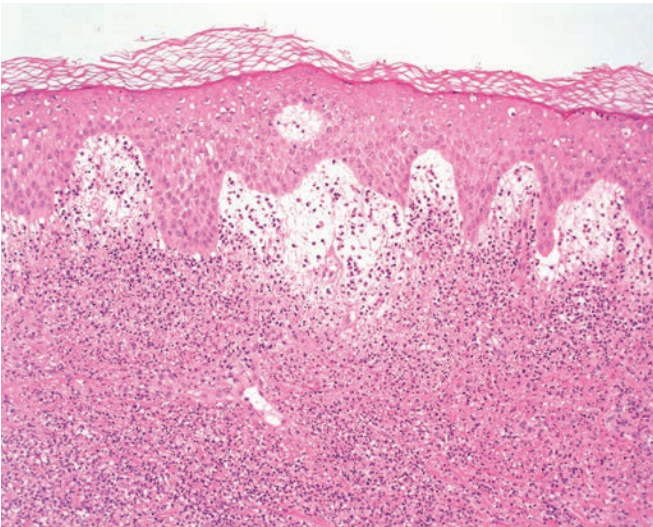
The diagnosis of mastocytosis in a skin biopsy can be easily missed unless the cytologic features of mast cells in sections stained with H&E are remembered (Fig. 2.25).<sup>169</sup> Some of the cells have large, pale nuclei, distinct cytoplasmic boundaries, and a faintly granular cytoplasm. Others are elongated and closely simulate fibroblasts or perithelial cells. Mast cells can be highlighted with toluidine blue, Giemsa, or Leder cytochemical stains. They can also be highlighted with immunohistochemical stains for tryptase, calretinin, and CD117 (c-kit) (Fig. 2.26).<sup>170–173</sup> The mast cells are often admixed with eosinophils, a feature that may induce confusion with Langerhans cell histiocytosis, but the latter often has involvement of the epidermis and is positive for S100 protein, langerin, and CD1a. Mutations of KIT have been documented in a significant proportion of cases.<sup>174,175</sup> Therefore patients with systemic disease may respond to treatment with imatinib mesylate.<sup>176,177</sup>



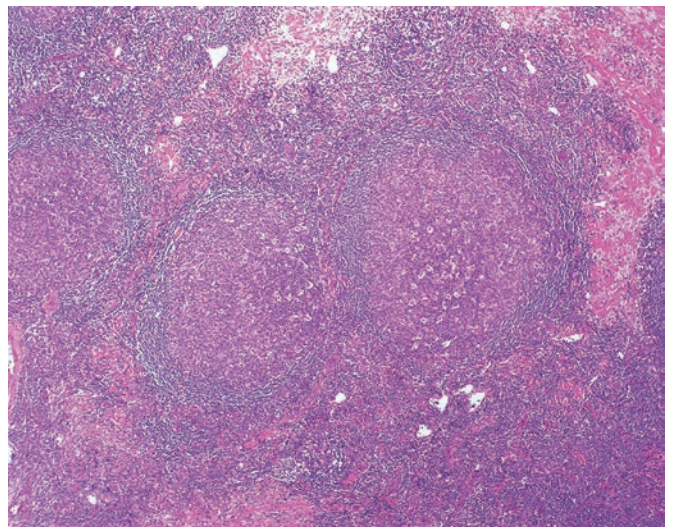
**Figure 2.26** Urticaria Pigmentosa. Immunohistochemical demonstration of mast cells with tryptase.



**Figure 2.28** Cutaneous B-Lymphoid Hyperplasia. Dense infiltrate of reactive lymphocytes and histiocytes. Variable number of eosinophils or plasma cells may be present.



**Figure 2.27** Sweet Syndrome. Diffuse dermal infiltrate of neutrophils with leukocytoclasia but without vasculitis.



**Figure 2.29** Cutaneous B-Lymphoid Hyperplasia. Reactive germinal centers with frequent tingible body macrophages may be present.

## Nodular and Diffuse Dermatoses

Entities in this reaction pattern involve the dermis that is not concentrated around vessels. In selected entities there can be histologic overlap with perivascular inflammatory dermatoses.

### Acute Febrile Neutrophilic Dermatitis (Sweet Syndrome)

*Acute febrile neutrophilic dermatitis*, most commonly referred to as *Sweet syndrome*, is characterized by acute onset of fever, leukocytosis, arthralgias, and erythematous plaques that often involve the extremities and face. It is most common in middle-aged women, but any age group can be affected.<sup>178</sup> It can be associated with underlying inflammatory bowel disease, connective tissue disease, infection, and, in a small subset, malignancies, usually hematologic malignancies but also solid tumors.<sup>178,179</sup> Microscopically, there is a dense infiltrate of neutrophils in a nodular to sheet-like pattern (Fig. 2.27).

Leukocytoclasia is common, but vascular damage is not a feature, distinguishing it from leukocytoclastic vasculitis, described previously.<sup>180,181</sup> There may be prominent dermal edema, sometimes giving rise to a bullous appearance to the process.<sup>182</sup>

### B-Cutaneous Lymphoid Hyperplasia

B-cutaneous lymphoid hyperplasia, also known as *lymphocytoma cutis* and *pseudolymphoma*, most commonly presents in the head and neck as solitary erythematous to violaceous plaques or nodules in adults.<sup>183</sup> Although most cases are idiopathic, such triggering agents as arthropod bites, *Borrelia* infections, drugs, and jewelry have all been implicated.<sup>184,185</sup>

Histologic examination reveals a nodular to sheet-like lymphoid proliferation that can mimic a B-cell lymphoma (Fig. 2.28). Lymphoid follicles with reactive germinal centers containing centroblasts, centrocytes, and tingible body macrophages may be present (Fig. 2.29).<sup>186-188</sup> These are surrounded by a proliferation of small reactive



**Figure 2.30** Clinical Appearance of Granuloma Faciale. The lesion appears as thickened purplish patches.

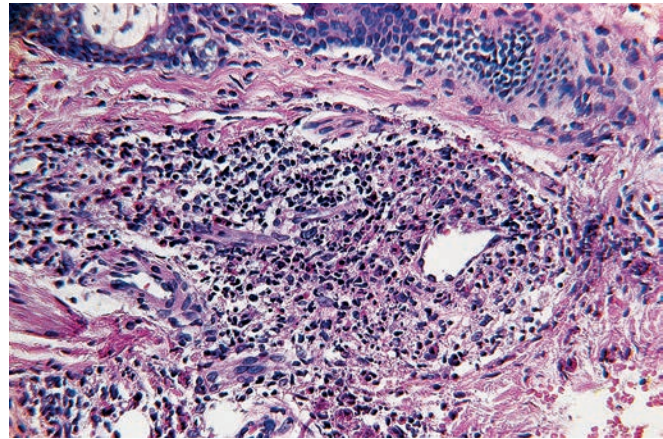
T-cells. The B-cells in the lymphoid follicles can be highlighted by stains for CD20, bcl-6, and CD10. The interfollicular cells are largely negative for these markers. Stains for CD21 will highlight an intact dendritic network in the germinal centers.

The main differential diagnosis includes cutaneous marginal zone lymphoma and cutaneous follicle center lymphoma, which are discussed in more detail in the chapter on cutaneous neoplasms. Briefly, in cutaneous marginal zone lymphoma there is a sheet-like proliferation of monocytoid B cells with variable numbers of monotypic plasma cells in the interfollicular zone. The monocytoid B cells disrupt reactive follicles, resulting in expansion of the follicular dendritic network. The neoplastic B cells may also have aberrant CD43 expression. In primary cutaneous follicle center lymphoma, the germinal centers are more monomorphous with few to no tingible body macrophages.

### Granuloma Faciale

*Granuloma faciale* typically presents on the face of adults as a thickened, purplish brownish patch, which clinically may be confused with infected nevus, tumor, or sarcoid (Fig. 2.30).<sup>189</sup> For this reason, it is often excised or biopsied, and acquaintance with its histologic appearance is helpful. The generally unaltered epidermis is separated from the zone of dermal inflammation by a narrow band of uninvolved dermis. The inflammatory reaction is nodular to sheet-like and formed by lymphocytes, histiocytes, neutrophils, and often large numbers of eosinophils. The infiltrate is frequently prominent, and there is overlap with entities with a nodular or diffuse pattern of inflammation, such as acute febrile neutrophilic dermatosis and arthropod bite reactions. It is considered a chronic vasculitis, and in early lesions evidence of a leukocytoclastic vasculitis may be present (Fig. 2.31).<sup>190</sup> It has been suggested that eosinophilic angiocentric fibrosis of the larynx and other portions of the sinonasal tract is the mucosal equivalent of cutaneous granuloma faciale. Indeed, they look very similar microscopically and can coexist.<sup>191</sup>

*Erythema elevatum diutinum* shares some morphologic features with granuloma faciale and is thought to be pathogenetically related



**Figure 2.31** Vascular changes in granuloma faciale.

to it.<sup>192,193</sup> It generally presents in systemically ill patients as bilaterally symmetrical plaques, papules, or nodules, often over the dorsa of joints. Microscopically, it initially presents as a leukocytoclastic vasculitis and later resolves with storiform or concentric fibrosis that imparts a more diffuse pattern to the inflammatory process.<sup>194</sup> In contrast to granuloma faciale, eosinophils are scanty or absent. Sometimes the disease has a nodular quality that mimics a neoplastic process.<sup>195</sup>

### Sarcoidosis

Sarcoidosis can present as an acute self-limiting disease, chronic cutaneous disease, or systemic disease that also involves lymph nodes and viscera. The clinical manifestations of cutaneous sarcoidosis are multifarious, earning the disease a site among the “great imitators in medicine.”<sup>196,197</sup> Clinically, the cutaneous manifestations of the disease vary a great deal from case to case. The lesions can be single or multiple and can range from macules to large plaques and nodules.<sup>196–199</sup>

Microscopically, the dermis is infiltrated by nests and clusters of noncaseating epithelioid granulomas almost devoid of associated inflammatory cells (Fig. 2.32). In particular, Langhans giant cells are scarce. The often-mentioned asteroid bodies, seen in giant cells, and the calcified Schaumann bodies are uncommon and nonspecific.

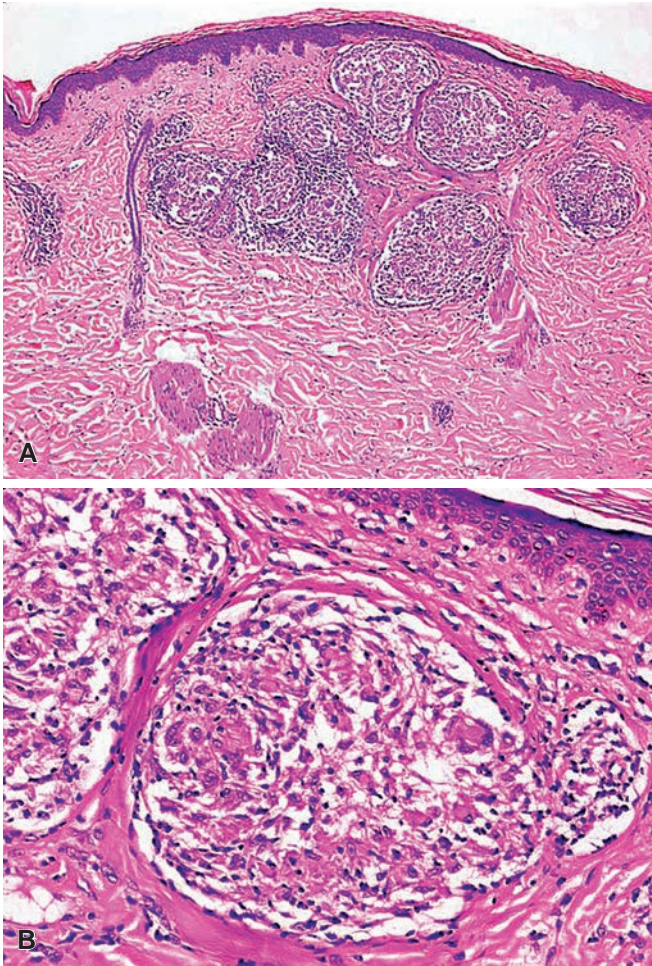
Sarcoidosis is a diagnosis of exclusion, inasmuch as granulomas with an identical microscopic appearance can also appear in the skin in a variety of infectious diseases, including tuberculosis, atypical mycobacteriosis, and syphilis; as a reaction to zirconium, beryllium, and tattoos; and as a secondary change in malignant lymphoma. Therefore, at a minimum, stains for infectious organisms should be performed the first time a biopsy from a given patient with possible sarcoidosis is encountered.

### Palisading Granulomatous Disease

This group of disorders is characterized by a histiocytic infiltrate that surrounds zones of altered collagen. Granuloma annulare and necrobiosis lipoidica are the prototypical examples in this category.

### Granuloma Annulare

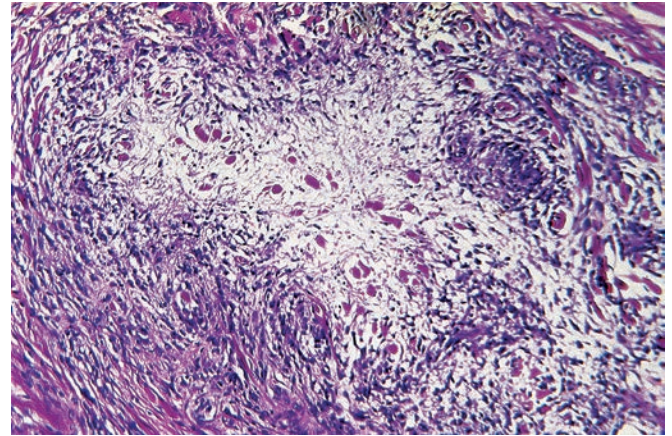
*Granuloma annulare* occurs most frequently on the dorsum of the hands and arms as circinate or grouped clusters of pink nodules with slight central depressions (Fig. 2.33). Occasionally, the disease



**Figure 2.32** A and B, Low- and Higher-Power Views of Cutaneous Sarcoidosis.



**Figure 2.33** Clinical Appearance of Multiple Lesions of Granuloma Annulare of Dorsum of Hand.



**Figure 2.34** Typical Lesion of Granuloma Annulare, With Palisading of Histiocytes Around “Necrobiotic Collagen” Center.

is generalized.<sup>200</sup> Associated systemic diseases are present only exceptionally.<sup>201,202</sup> Histologically, the key component of the lesion is the so-called necrobiotic or palisading granuloma.<sup>203</sup> This is characterized by a well-demarcated zone of disintegrating extracellular material with the appearance of collagen mixed with dermal mucin and cellular debris that is found in the mid-dermis surrounded by a cuff of radially oriented fibroblasts mixed with lymphocytes and histiocytes (Fig. 2.34). Occasional foreign body giant cells and foci of vasculitis may be found. In many lesions the palisading granuloma is not as well developed and has a more interstitial pattern.<sup>204</sup> Multiple sections may be necessary to arrive at a specific diagnosis in this setting.

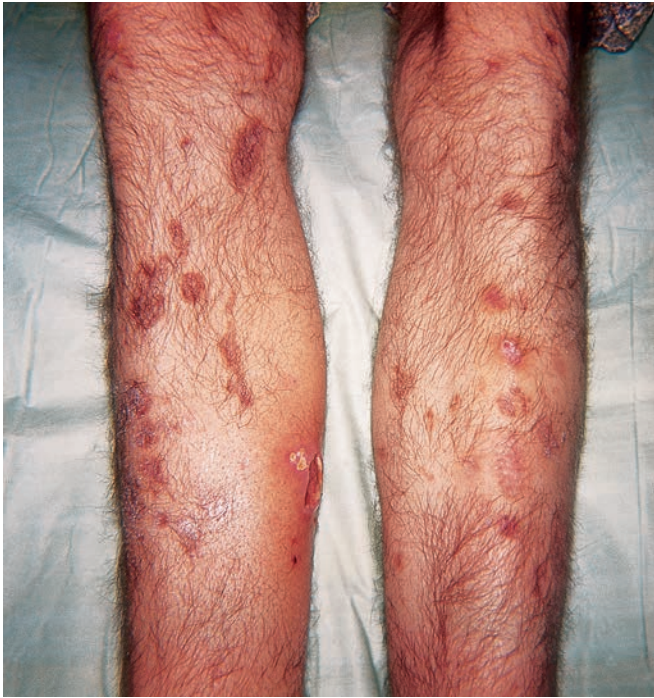
Immunohistochemically, the “histiocytes” of granuloma annulare stain for vimentin and lysozyme but not for other histiocytic markers, such as HAM-56 or KP-1 (CD68).<sup>205</sup> Ultrastructural studies have shown a prominent component of degenerated elastic (rather than collagen) fibers.<sup>206</sup> Isolated, large, rather deep, necrobiotic collagen granulomas are sometimes seen on the extremities or occiput in children<sup>204</sup> and sometimes in adults.<sup>207,208</sup> They have been referred to as deep, subcutaneous, or giant granuloma annulare and as pseudorheumatoid nodule.<sup>209,210</sup>

An entity histologically similar to granuloma annulare that occurs on heavily sun-damaged skin has been designated as *O'Brien actinic granuloma*, *Miescher granuloma*, and *annular elastolytic giant cell granuloma*.<sup>211,212</sup> Histologically it is almost identical to conventional granuloma annulare and is considered by some to represent the same disease, just occurring in sun-damaged skin. The presence of elastic fibers in the giant cells, as seen by light and electron microscopy, is one of its most important distinguishing features.<sup>213–215</sup>

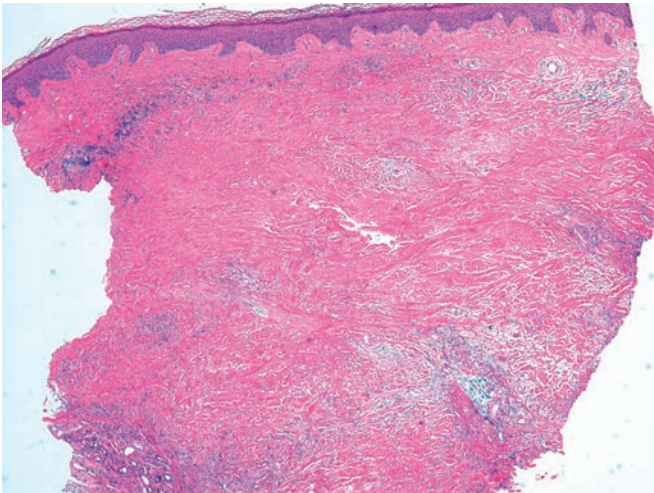
The subcutaneous nodules of rheumatoid arthritis and rheumatic fever share with granuloma annulare the presence of the necrobiotic collagen granuloma, but the combination of clinical and microscopic features usually allows an easy distinction.<sup>209,216</sup> Rheumatoid nodules are usually deeper and the central zone of the palisading granuloma contains fibrin rather than dermal mucin.

### Necrobiosis Lipoidica

*Necrobiosis lipoidica* typically presents as atrophic, yellow, depressed plaques involving the lower legs (Fig. 2.35).<sup>217,218</sup> Necrobiosis lipoidica is associated with diabetes mellitus and hypothyroidism, but the association with underlying endocrine disorder is less frequent than originally thought.<sup>219</sup> Although most cases involve the legs, presentation outside this location may occur.<sup>219–221</sup> Microscopically,

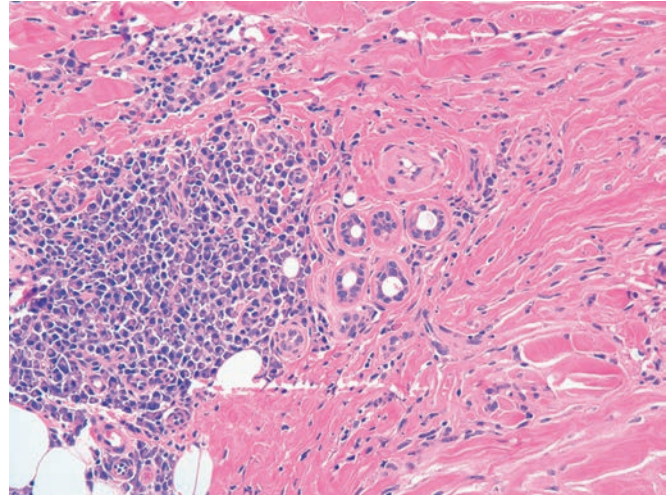


**Figure 2.35** Clinical Appearance of Lesions of Necrobiosis Lipoidica.



**Figure 2.36** Necrobiosis Lipoidica. Tiered arrangement of inflammatory cells and altered collagen.

ill-defined areas of disintegrating dermal collagen are seen surrounded by a lymphohistiocytic infiltrate, often arranged in a tiered or layered pattern (Fig. 2.36).<sup>220,221</sup> This has been likened to the appearance of a layer cake or bacon. Lymphoid aggregates with plasma cells are typical (Fig. 2.37). Thickening of the blood vessel wall is usually prominent. It may also have a deeper component with the features of septal panniculitis. Granuloma annulare tends to have a more circumscribed pattern of palisading granulomas and plasma cells are typically absent in granuloma annulare. In addition, in contrast with granuloma annulare, stains for mucin and immunoreactivity for lysozyme tend to be negative, although these stains are not generally necessary to distinguish these entities.<sup>222</sup> The differential diagnosis also includes *necrobiotic xanthogranuloma*, a disease occurring in the head, neck, and trunk of patients in association with paraproteinemia.<sup>223</sup>



**Figure 2.37** Necrobiosis lipoidica usually has lymphoplasmacytic aggregates.

## Sclerosing Disorders

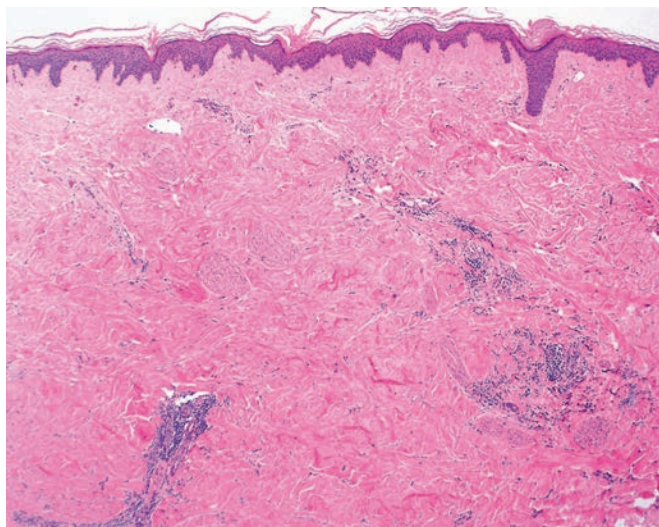
This group of disorders is characterized by dermal sclerosis, usually with comparatively little inflammation. Included in this group are scleroderma/morphea, eosinophilic fasciitis, and lichen sclerosus.

### Scleroderma/Morphea

Scleroderma is manifest in two distinct forms: *localized scleroderma*, or morphea, and *systemic scleroderma*, in which the skin, particularly of the face, the upper trunk, hands, and arms (acrosclerosis), the esophagus, the heart, and the lungs are diseased.<sup>224–226</sup> Most patients are adults, but the disease can also present in childhood.<sup>227,228</sup> Morphea is the most common form of scleroderma in childhood.<sup>229</sup> Sometimes, visceral disease typical of systemic scleroderma occurs in the absence of cutaneous involvement. A few cases of morphea have been associated with generalized or systemic disease.

The dominant microscopic change in scleroderma is an increase in the amount of collagen, which is morphologically, ultrastructurally, and biochemically unremarkable.<sup>230,231</sup> The relative proportions and distribution of type I and type III collagens are also closely similar to those found in the normal dermis.<sup>232</sup> The histologic appearance is that of enlarged, swollen collagen fibers with a decrease in the normal spacing between the collagen bundles of the reticular dermis (Fig. 2.38). The sclerosis may extend in depth to encircle the secretory coils of the eccrine sweat glands. Concomitantly, the epidermis becomes atrophic. Varying amounts of a mild lymphoplasmacytic infiltrate may be seen in the dermis. In well-developed lesions, the infiltrate may be absent or present at the leading deep edge of the sclerotic change. Early lesions may have little collagen change and a superficial and deep perivascular lymphoplasmacytic infiltrate, suggesting that the fibrosis may represent a secondary phenomenon.<sup>233,234</sup> One should not mistake the normally relatively thick collagen bundles of the back for scleroderma. The collagen bundles of the back will still have retained spaces between the fibers. Dystrophic calcification may occur in scleroderma, and in some patients the dominant patterns is that of acrosclerosis preceded by, or associated with, Raynaud phenomenon.

Scleroderma is usually distinguishable from lichen sclerosus (discussed in more detail later) by the depth of dermal involvement, but in some cases coexisting features of lichen sclerosus



**Figure 2.38 Scleroderma.** Thickened collagen bundles with decreased spaces between the collagen bundles of the reticular dermis.

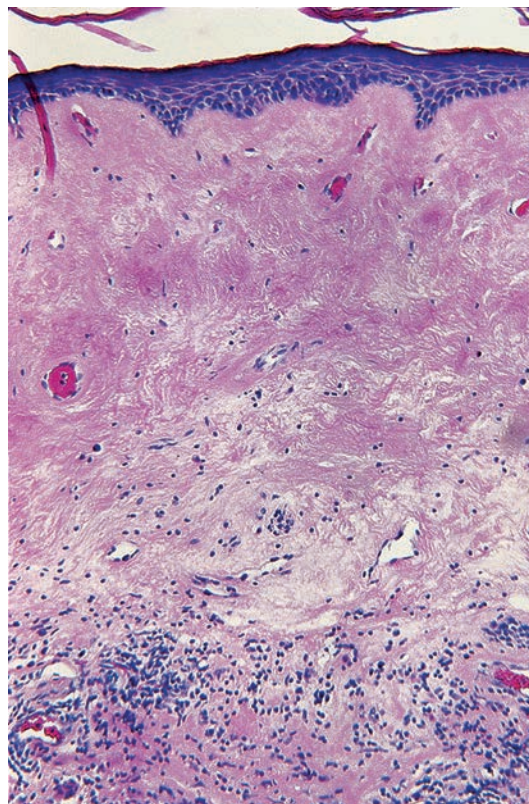
may be present and the diseases may represent a spectrum.<sup>235</sup> Scleroderma should also be differentiated from eosinophilic fasciitis (see later).

### Eosinophilic Fasciitis

Eosinophilic fasciitis (Shulman disease) is characterized clinically by swelling, tenderness, and stiffness of an extremity, often involving the lower forearm and sometimes associated with carpal tunnel syndrome and peripheral eosinophilia.<sup>235-239</sup> The most important difference between scleroderma and eosinophilic fasciitis on histologic grounds is that in the latter condition there is marked inflammation and thickening of the deep fascia (with or without eosinophils), whereas in scleroderma this structure tends to show minimal or no abnormalities.

### Lichen Sclerosus

Lichen sclerosus, also called *lichen sclerosus et atrophicus*, occurs most often on the anogenital areas, upper trunk and neck, and flexor surface of the wrist. When this disease is located in the vulva or glans penis, it is also designated as *kraurosis* and *balanitis xerotica obliterans*, respectively. The disease occurs most commonly in women, often at or around menopause, but it can also be seen in children and young adults.<sup>240</sup> The lesions present as white papules and plaques with a wrinkly surface. Patients have an increased risk of development of high-grade squamous intraepithelial lesions of the differentiated or simplex type, and squamous cell carcinoma in the affected sites, but the risk is relatively low (<10%). The etiology is unknown, but there is a strong association with autoimmune disorders and a link with HLA DQ7.<sup>241</sup> The microscopic features vary depending on the timing of the biopsy. Early lesions may demonstrate an interface dermatitis that can mimic lichen planus.<sup>242</sup> More established lesions have the characteristic edematous, homogenization of the papillary dermis with atrophy of the overlying epidermis (Fig. 2.39). A variable perivascular to lichenoid lymphocytic infiltrate is frequently at the leading edge of the dermal change. Varying degrees of non-necrotizing vasculitis may be seen.<sup>243</sup> As previously mentioned, lichen sclerosus should be distinguished from scleroderma/morphea, although the two diseases may coexist and distinction may not always be possible.<sup>234,244</sup>



**Figure 2.39 Lichen Sclerosus.**

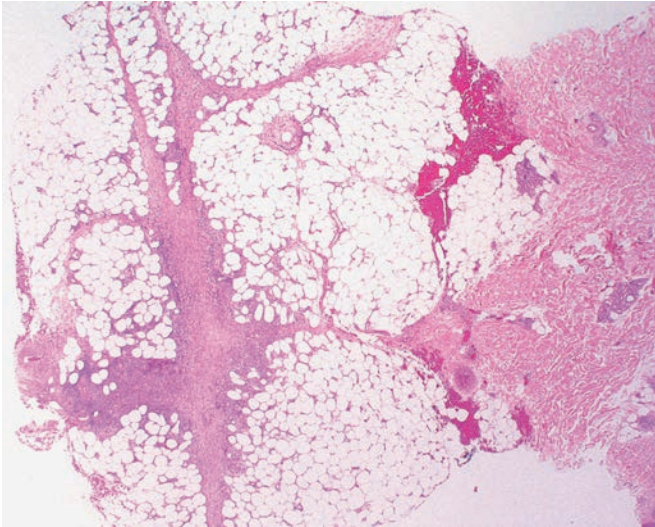
### Panniculitis

Panniculitis exists in a predominantly septal or lobular pattern, although there is considerable histologic overlap in both of these patterns. It is important to examine the biopsy at low magnification to assess for where the predominant pattern of inflammation/alteration of the subcutis is present. Erythema nodosum is the prototypical septal panniculitis, whereas nodular vasculitis is the prototypical lobular panniculitis.

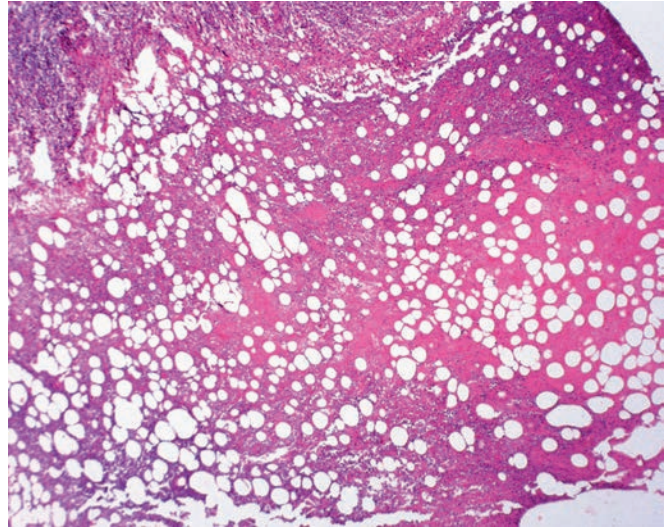
### Erythema Nodosum

*Erythema nodosum* is the most common form of primary panniculitis, accounting for approximately 70%–80% of cases of panniculitis. The lesions present as painful, red, subcutaneous nodules on the anterior surface of the legs.<sup>245</sup> Typically, they involute within a few days or weeks, leaving slightly depressed pigmented areas. They do not ulcerate, as do the lesions of erythema induratum. It seems certain that the pathogenesis is immune mediated, but the precise mechanism is unknown.<sup>246</sup> In an old series of a British population with erythema nodosum, 45% of the patients had antecedent streptococcal infections, 6% had tuberculosis, 36% had sarcoid, and 13% had a variety of lesions.<sup>247</sup> Several other infectious agents can be involved.<sup>248</sup> Some cases are associated with chronic ulcerative colitis and others with Behçet syndrome.<sup>249-253</sup> In the endemic areas of the United States, coccidioidomycosis is a common antecedent.

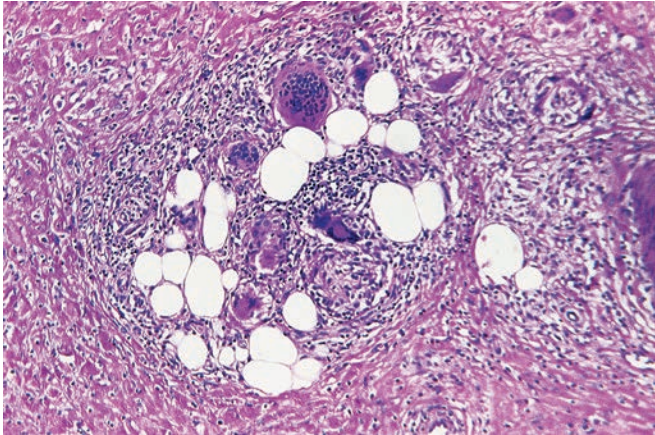
Histologically, the junction of the dermis and the subcutis is inflamed. An inflammatory infiltrate extends along the fibrous septa between the fat and about the vessels of the dermis (Fig. 2.40). There is usually spillover into the adjacent lobules, but it is concentrated at the periphery. The composition of the inflammatory infiltrate



**Figure 2.40 Erythema Nodosum.** The inflammation predominantly affects the subcutaneous septae.



**Figure 2.42 Nodular Vasculitis/Erythema Induratum.** The inflammation predominantly affects the subcutaneous lobule.

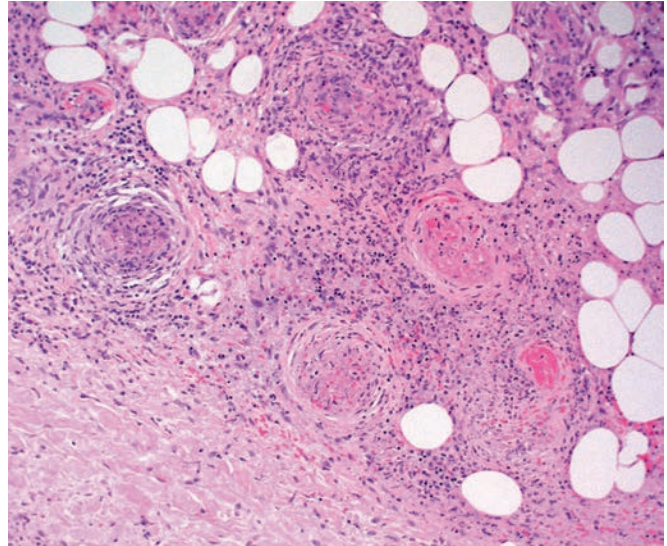


**Figure 2.41 Panniculitis With Scattered Multinucleated Giant Cells in Erythema Nodosum.**

depends largely on the age of the lesion. It may be predominantly neutrophilic, lymphocytic, or histiocytic, with isolated giant cells or noncaseating granulomas (Fig. 2.41).<sup>245,254–256</sup> A characteristic lesion seen in the early stages of the disease is represented by a cluster of small histiocytes radially arranged around a central cleft (Miescher radial granuloma).<sup>255</sup>

### Nodular Vasculitis/Erythema Induratum

Both terms are used for the same condition. This condition usually presents on the calves of young to middle-aged women.<sup>257</sup> They present as painful violaceous nodules that may be complicated by ulceration. Some cases represent a manifestation of underlying tuberculosis (Bazin disease) and is a form of tuberculin hypersensitivity.<sup>258</sup> Acid-fast bacilli are not seen in special stains, but mycobacterial DNA has been found in these lesions by polymerase chain reaction (PCR) by some authors but not by others.<sup>259</sup> In the United States, most cases of erythema induratum are idiopathic and are not related to underlying tuberculosis. The etiopathogenesis of this disease and its relation to tuberculosis remain controversial.



**Figure 2.43 Vasculitis in Nodular Vasculitis.**

Nodular vasculitis/erythema induratum is predominantly a lobular panniculitis, although some septal involvement may also be seen (Fig. 2.42). The inflammatory infiltrate is variably composed of lymphocytes, histiocytes, and neutrophils. Granulomas may be present. In most cases there is an associated leukocytoclastic vasculitis involving medium-sized vessels of the septum or lobule (Fig. 2.43).<sup>257</sup> The differential diagnosis includes erythema nodosum and infection. Erythema nodosum has a distinctly different clinical presentation, lacks the vasculitis, and is predominantly a septal panniculitis. Infectious processes usually lack the associated vasculitis, but infectious stains should be used if there is a question of infection.

### Lipodermatosclerosis

Lipodermatosclerosis, or sclerosing panniculitis, is a type of panniculitis that is the result of chronic venous insufficiency. It occurs in elderly or morbidly obese patients and presents as woody



induration of the lower legs.<sup>260,261</sup> Microscopically, unlike other panniculitides, it is relatively noninflammatory. There is lobular alteration of the fat, with hyalinization, microcyst formation, and membranocystic fat necrosis that has been compared with the appearance of frost on a windowpane (Fig. 2.44). The septa are

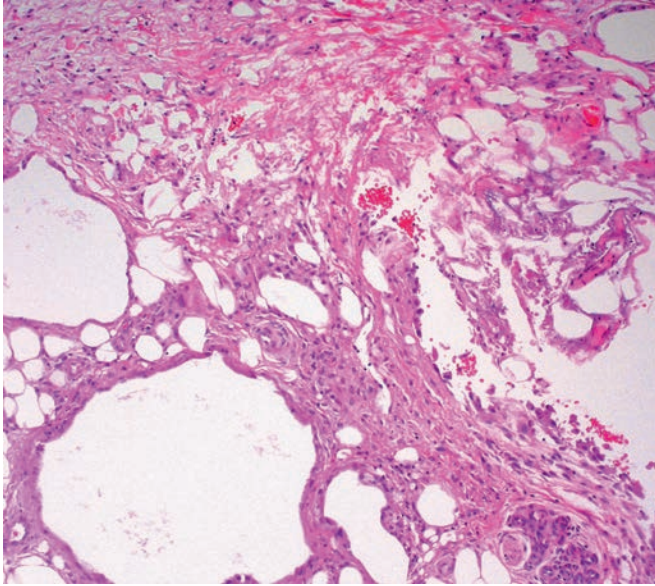


Figure 2.44 Membranocystic Fat Necrosis of Lipodermatosclerosis.

typically spared. The overlying dermis usually shows evidence of stasis change. It may also be seen as a result of vascular compromise due to radiation therapy.<sup>261</sup>

## Vesiculobullous Diseases

The key morphologic features in the microscopic evaluation of vesiculobullous lesions are the level of the plane of separation and the type of cellular change seen, particularly the presence or absence of acantholysis—as masterfully described in the classic monograph by Lever<sup>262</sup> (Table 2.1), now supplemented by their immunofluorescent pattern (Table 2.2). Vesicles and bullae (large vesicles) are divided according to their location into subepidermal and intraepidermal, which in turn may be suprabasal or subcorneal. In making this distinction, one should be aware that a bulla that was originally subepidermal can become intraepidermal because of regrowth of epithelium across its base, a process that can be very rapid. Actually, large intraepidermal bullae unassociated with acantholytic changes should be suspected of being healed subepidermal bullae. Biopsying early lesions (<24 hours old) minimizes this problem. Biopsies for complimentary direct immunofluorescence studies should be perilesional and submitted in Michel's solution rather than formalin. A complete discussion of the wide range of bullous dermatoses is beyond the scope of this text, but selected entities will be emphasized.

### Subepidermal Bullous Disease

Subepidermal bullous dermatoses include a wide range of entities, including *bullous pemphigoid*, *cicatricial pemphigoid*, *epidermolysis bullosa*

Table 2.1 Grouping of cutaneous bullous diseases according to the location and mechanism of formation of the bullae

INTRAEPIDERMAL	SUBEPIDERMAL
<p><b>Subcorneal/Glandular</b></p> <p>Miliaria crystalline Staphylococcal scalded skin syndrome Pemphigus foliaceus and variants Bullous impetigo IgA pemphigus Subcorneal pustular dermatosis Erythema toxicum neonatorum Transient neonatal pustular melanosis Acropustulosis of infancy</p> <p><b>Spinous</b></p> <p>Spongiotic dermatitis Friction blister (may extend into dermis) Miliaria rubra Incontinentia pigmenti IgA pemphigus Epidermolytic hyperkeratosis Hailey-Hailey disease</p> <p><b>Suprabasal</b></p> <p>Pemphigus vulgaris and variants Paraneoplastic pemphigus Darier disease</p>	<p><b>Basal Keratinocyte Necrosis, Cytologic, or Damage</b></p> <p>Epidermolysis bullosa simplex Thermal injury (some) Erythema multiforme Herpes gestationis</p> <p><b>Epidermal Basement Membrane Zone Destruction or Disruption</b></p> <p>Lamina lucida Bullous pemphigoid Cicatricial pemphigoid Herpes gestationis Dermatitis herpetiformis Linear IgA dermatosis Epidermolysis bullosa acquisita Porphyria cutanea tarda Epidermolysis bullosa letalis (junctional) Suction blister Thermal injury (some) Sublamina densa Cicatricial pemphigoid Linear IgA dermatosis Epidermolysis bullosa dystrophica Epidermolysis bullosa acquisita Bullous systemic lupus erythematosus Dermal Penicillamine-induced blisters (iatrogenic)</p>

Ig, Immunoglobulin.

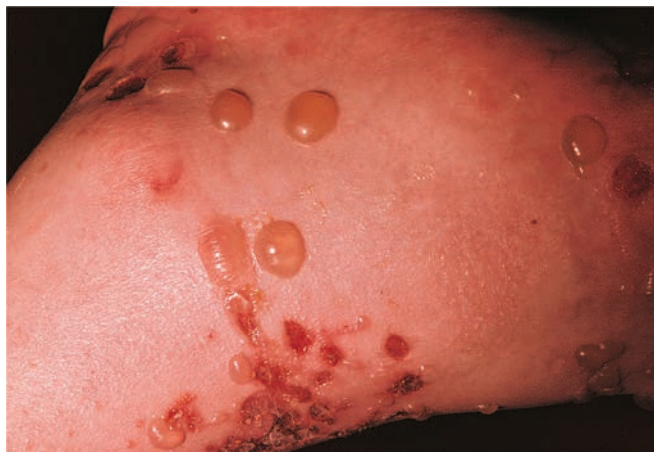
**Table 2.2** Usual immunofluorescence patterns in the various types of vesicobullous dermatoses.\*

DERMATOSIS	PRINCIPAL IMMUNOREACTANT	LOCATION	PATTERN
Pemphigus			
All types except below	IgG	ISR	Lace-like
IgA type	IgA	ISR	Lace-like
Paraneoplastic type	IgG C3, IgG C3, IgG	ISR EBMZ EBMZ	Lace-like Linear Granular
Bullous pemphigoid	C3, IgG	EBMZ	Linear
Cicatricial pemphigoid	C3, IgG	EBMZ	Linear
Herpes gestationis	C3	EBMZ	Linear
Epidermolysis bullosa acquisita	C3, IgG	EBMZ	Linear
Bullous systemic lupus erythematosus	C3, IgG C3, IgG	EBMZ EBMZ	Linear Granular
Dermatitis herpetiformis	IgA	EBMZ	Granular
Linear IgA dermatosis	IgA	EBMZ	Linear
Erythema multiforme	C3, IgM C3, IgM	EBMZ Vessels	Granular Granular

\*It should be noted that immunoglobulins other than those listed above may also be present, although less commonly and less intensely. EBMZ, Epidermal basement membrane zone; Ig, immunoglobulin; ISR, intercellular squamous region.



**Figure 2.45** Clinical Lesions of Dermatitis Herpetiformis. Note the small size of the vesicles and their symmetric distribution.



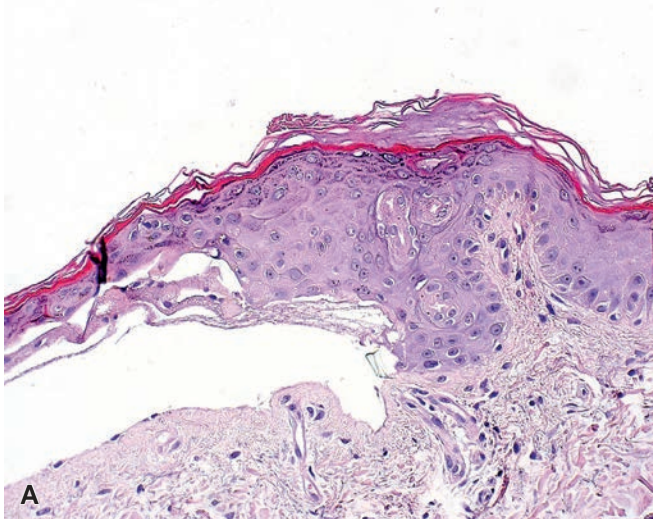
**Figure 2.46** Clinical Appearance of Bullous Pemphigoid. Large bullae are present, some of which have ruptured.

*dermatitis herpetiformis*, and *porphyria cutanea tarda* (Figs. 2.45 and 2.46).<sup>263</sup> They can also be seen as a secondary event in any dermatosis associated with liquefactive degeneration of the basal layer, such as lupus erythematosus, erythema multiforme, scleroderma, and lichen planus (see earlier).<sup>264</sup>

Microscopically, a distinction between these various subepidermal processes is not always possible; however, careful evaluation of a set of criteria as seen in routinely stained sections results in a high level of concordance with the clinical diagnosis (see Tables 2.1 and 2.2).<sup>265</sup>

### Bullous Pemphigoid

A number of clinical forms exist. The most common form, *generalized cutaneous pemphigoid*, presents as tense blisters involving the skin of older patients.<sup>265,266</sup> In a minority, there may also be mucosal involvement.<sup>267</sup> The most consistent histologic features of bullous pemphigoid is a subepidermal blister above the basement membrane that contains numerous inflammatory cells, including frequent eosinophils, in the blister cavity (Fig. 2.47). Direct immunofluorescence on specimens submitted in Michel's solution will reveal linear deposition of



**Figure 2.47** **A**, Bullous pemphigoid. A net separation is present between the epidermis and dermis, with protrusion of dermal papillae into the bulla. The inflammatory infiltrate is very scanty. **B**, Immunostaining for type IV collagen shows that the basement membrane is at the base of the bulla. (Courtesy Dr Fabio Facchetti, Brescia, Italy.)

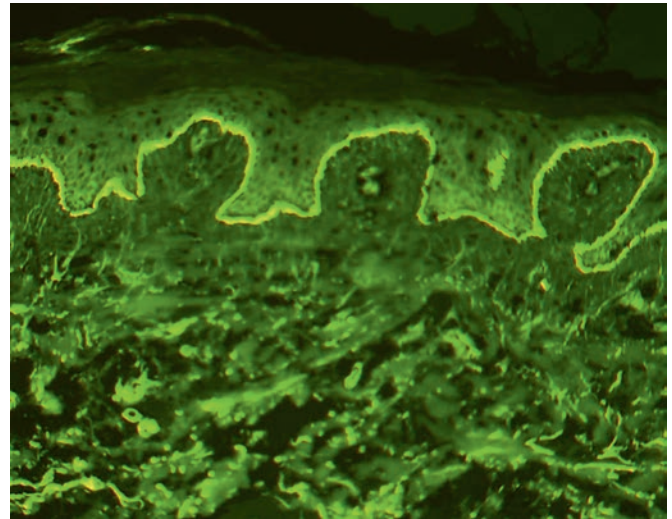
complement C3 and usually IgG along the basement membrane zone (Fig. 2.48).

### Cicatricial Pemphigoid (Mucous Membrane Pemphigoid)

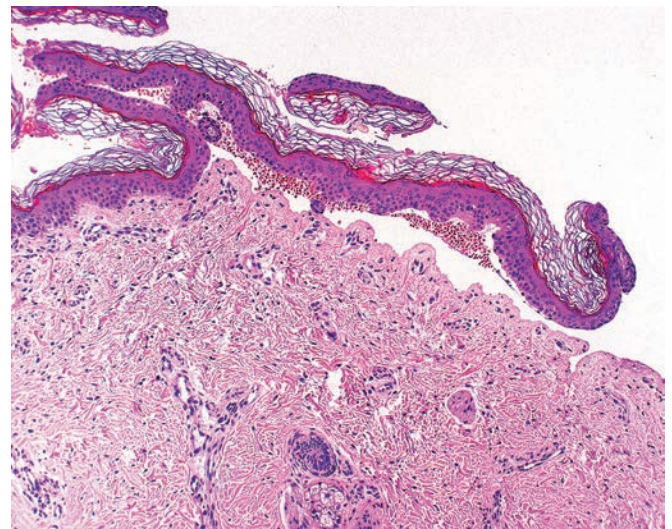
This rare form of pemphigoid involves ocular and oral mucosa and is often associated with scarring, especially ocular lesions.<sup>266,267</sup> Involvement of genital mucosa is relatively common in female patients with this condition. Histologically, they can be indistinguishable from generalized cutaneous pemphigoid, but the inflammatory infiltrate is often much less intense. In older or recurrent lesions, an underlying scar is often present. Direct immunofluorescence is similar to bullous pemphigoid, although IgA deposits may also be seen in a minority of cases.

### Epidermolysis Bullosa Acquisita

There are multiple different variants and only the classical variant will be discussed.<sup>268-272</sup> Patients present with marked skin fragility



**Figure 2.48** Linear deposition of complement C3 in bullous pemphigoid.



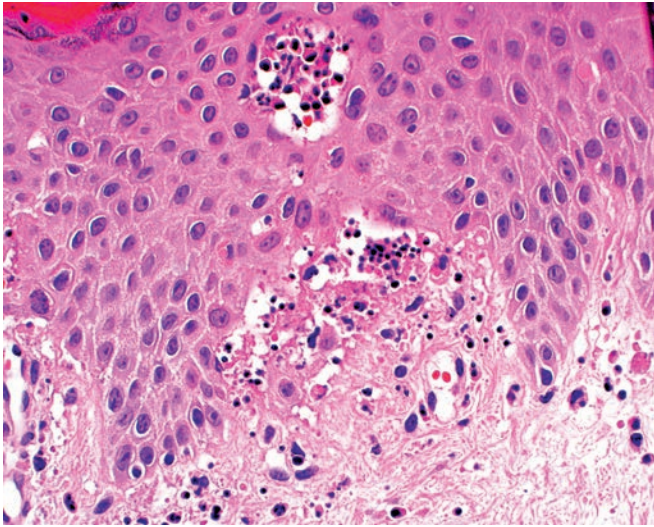
**Figure 2.49** Clean subepidermal bulla of epidermolysis bullosa.

at sites prone to trauma, such as the hands. Patients easily develop blisters and erosions, and milia are frequently present.

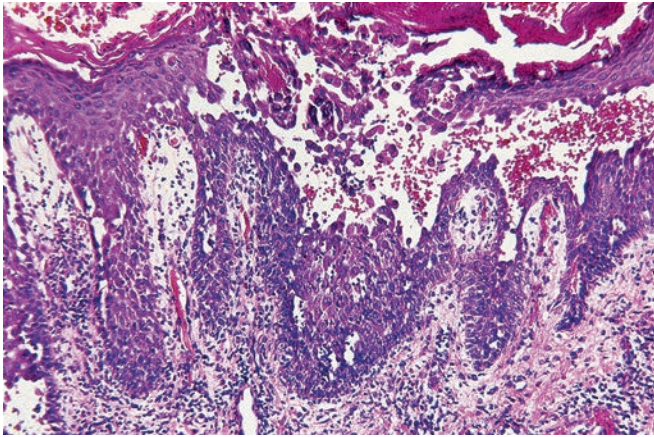
Microscopically, cell-poor subepidermal blisters are characteristic, although occasional cases will show some inflammatory cells in the blister cavity (Fig. 2.49). By direct immunofluorescence, linear deposits of IgG and complement C3 are present, similar to pemphigoid. Salt-split skin preparations examined with direct immunofluorescence will demonstrate the immune deposits on the floor of the blister in epidermolysis bullosa acquisita rather than the roof of the blister in pemphigoid.<sup>272</sup>

### Dermatitis Herpetiformis

*Dermatitis herpetiformis* usually presents in young adults as an intensely pruritic papulovesicular eruption often on extensor surfaces. Clinically, it is closely related to celiac disease. Histologically, the most useful criterion for the diagnosis of dermatitis herpetiformis is the presence of papillary microabscesses forming a multilocular subepidermal bulla (Fig. 2.50).<sup>273</sup> Direct immunofluorescence demonstrates granular deposits of IgA along the basement membrane zone that are typically



**Figure 2.50** Typical appearance of early lesion of dermatitis herpetiformis.



**Figure 2.51** Pemphigus Vulgaris. The bulla is in a suprabasal location.

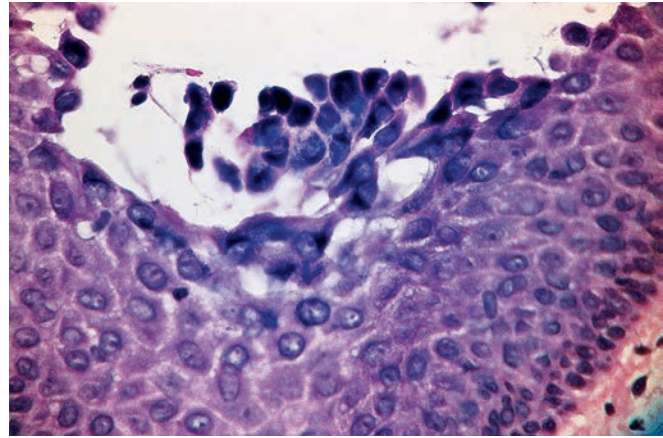
more intense in the dermal papillae. *Linear IgA disease* can be histologically and clinically indistinguishable from dermatitis herpetiformis.<sup>274</sup> Like dermatitis herpetiformis, it is characterized by subepidermal blisters with neutrophils along the dermoepidermal junction. It differs by having a linear pattern of IgA deposition along the dermoepidermal junction. Linear IgA bullous dermatosis is frequently triggered by adverse drug reactions.<sup>274</sup>

### Intraepidermal Bullous Disease

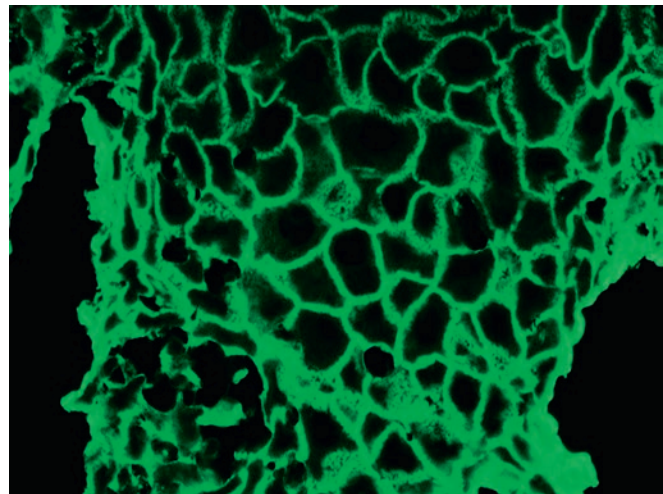
Intraepidermal bullous dermatoses are characterized by acantholysis and intraepidermal blisters. These disorders include a variety of conditions, including the pemphigus group (pemphigus vulgaris, pemphigus vegetans, pemphigus foliaceus and pemphigus erythematosus), Darier disease, Hailey-Hailey disease, and Grover disease.

### Pemphigus

The pemphigus group consists of a variety of related diseases. In *pemphigus vulgaris* and *vegetans*, the pattern of acantholysis results in a cleavage plane just above the basal layer (Fig. 2.51), whereas in *pemphigus foliaceus* and *pemphigus erythematosus* the split is in or



**Figure 2.52** Pemphigus Erythematosus. The acantholytic cells are in a superficial location.



**Figure 2.53** Immunofluorescent Demonstration of Anti-Pemphigus Vulgaris Antibody.

just below the granular layer (Fig. 2.52).<sup>262,275-277</sup> Indirect immunofluorescent stains performed with sera of patients with pemphigus demonstrate the presence of antiepithelial autoantibodies in most cases, although the test may be negative in the early stages (Fig. 2.53).<sup>278,279</sup> In addition, IgG and complement C3 can be detected in more than 90% of cases in the epidermal intercellular spaces by a direct immunofluorescence technique.<sup>280</sup> These autoantibodies directed against desmogleins play an important role in the pathogenesis of pemphigus.<sup>281-286</sup> Some cases of pemphigus are seen in association with internal organ malignancies (paraneoplastic pemphigus).<sup>286-288</sup> A statistically increased incidence of internal malignancies has been observed in patients with pemphigus, in addition to the well-known association between pemphigus and thymoma.<sup>288</sup>

Acantholysis can be seen in several other dermatologic conditions, such as *familial benign pemphigus* or *Hailey-Hailey disease* (often located in inguinal folds and clinically resembling candidiasis and condylomas),<sup>289</sup> viral vesicles, the pemphigus-like lesions induced by D-penicillamine,<sup>290</sup> actinic keratosis, and the type of squamous cell carcinoma arising from it (adenoid or pseudoglandular), *Darier disease*, *warty dyskeratoma*, and *transient acantholytic dermatosis* (*Grover disease*). The latter is characterized by transient edematous and

excoriated papules and vesicles located predominantly on the trunk, thought to be the result of the combined action of heat and sweating.<sup>291–293</sup> According to Chalet et al. the most important clue to the diagnosis is the association of acantholysis and spongiosis.<sup>293</sup> In addition, focal acantholytic dyskeratotic changes (sometimes limited to a single rete ridge) totally devoid of clinical significance can be found in association with a variety of localized lesions, such as dermatofibroma, basal cell carcinoma, melanocytic nevus, and malignant melanoma.<sup>294,295</sup>

In subcorneal pustular dermatosis, the vesicles are just beneath the keratin layer, as they are in *impetigo contagiosa*.<sup>296,297</sup> Another subcorneal vesicular lesion that has been mistaken clinically for junctional nevus is the blood blister, in which the erythrocytes are trapped beneath the thick stratum corneum of the toes or fingers. This has been termed talon noir and is commonly seen in athletes.<sup>298</sup>

## Infections

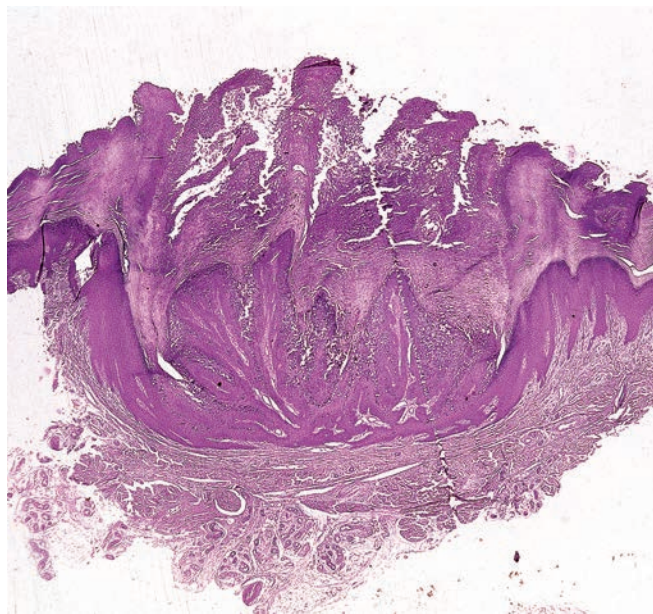
### Viral Diseases

The viral lesions of skin most commonly seen histologically are warts and condylomas. Molluscum contagiosum and herpesvirus infections are also commonly biopsied.

### Warts

Warts are cutaneous (and sometimes mucosal) lesions caused by one of the several human papilloma viruses (HPVs), papovavirus.<sup>299–301</sup> Several variants of warts occur, depending primarily on the HPV subtype, but also on the anatomic features of the region.<sup>302–304</sup> *Verruca vulgaris* (generally associated with HPV-2) usually occurs on the hands as an elevated, hard, rough, flesh-colored lesion. The top may be peeled off, leaving a pink granular surface. *Verruca plantaris* occurs on the sole of the foot, is covered by a callus, and is often painful. *Verruca plana* (usually associated with HPV-10) is, as its name indicates, a flatter lesion usually seen in crops or clusters on the face and hands. Flat warts disseminated throughout the body are a feature of the genetically determined *epidermodysplasia verruciformis*.<sup>305,306</sup> *Condyloma acuminatum* or “venereal wart” (usually caused by HPV-6 and HPV-11) occurs around the anus and vulva, on the glans penis, and sometimes in other mucosal membranes, such as the oral cavity. Genital warts with increased risk for developing dysplasia and subsequent carcinoma are predominantly caused by HPV-16 and HPV-18.

The histologic characteristics of these lesions are those of focal epidermal hyperplasia manifested by hyperkeratosis and parakeratosis, varying degrees of acanthosis, and (except for *verruca plana*) papillomatosis (Fig. 2.54). A trichilemmal type of keratinization may be present.<sup>307</sup> Distinct vacuolization of the cells in the upper portion of the malpighian layer is a feature in early lesions; some of these abnormal cells have large cytoplasmic eosinophilic aggregates. Smaller vacuolated cells with pyknotic nuclei may also be seen in the lower portions of the thickened stratum corneum. In *condyloma acuminatum*, acanthosis may be florid, and tangential cuts can show isolated nests of squamous cells surrounded by inflamed dermis. Care should be taken not to overdiagnose such lesions as squamous cell carcinoma. Older verrucae may not show the microscopic changes that allow their recognition; they may appear simply as papillomas or keratoses. Flat warts undergoing involution exhibit marked mononuclear dermal and intraepidermal inflammation associated with degenerative epidermal changes.<sup>308,309</sup> The viral nuclear inclusions are basophilic, Feulgen positive, and DNase resistant. They can be demonstrated immunohistochemically and with in situ



**Figure 2.54 Verruca Vulgaris.** The lesion is cup-shaped and highly keratotic.

hybridization techniques.<sup>310</sup> The eosinophilic cytoplasmic masses are not made of viral material but rather represent accumulations of tonofilaments.

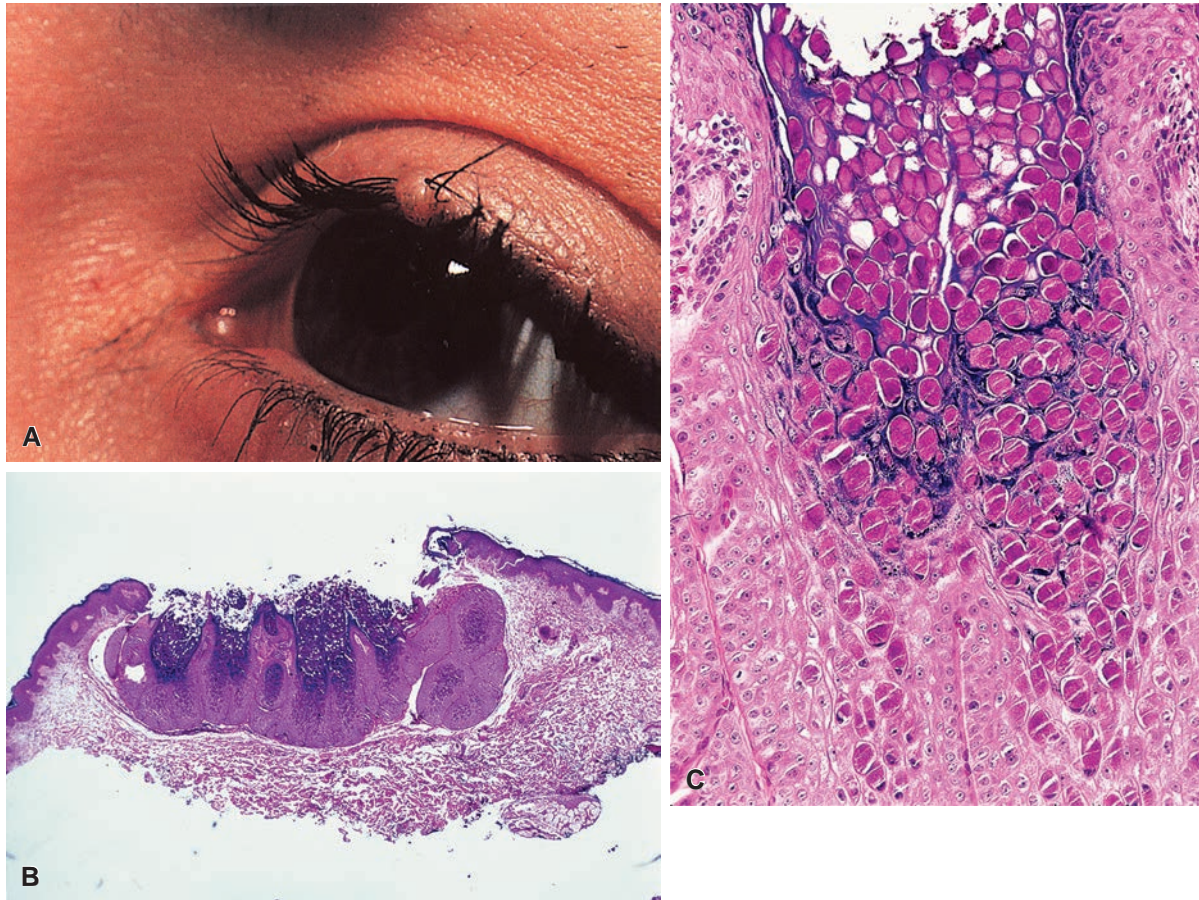
Occasionally, benign or malignant skin tumors and tumor-like conditions of various types (e.g. seborrheic keratosis, squamous cell carcinoma in situ [Bowen disease], and invasive squamous cell carcinoma) are seen superimposed on HPV-induced lesions, suggesting a causal relationship.<sup>311–313</sup> In our experience, this is most common in elderly and immunocompromised patients (e.g. solid organ transplant patients). Epidermodysplasia verruciformis is another example.<sup>314,315</sup> Changes in keratin expression occur in the keratinocytes as a result of the viral infection, and further changes develop when a neoplastic process supervenes.<sup>315,316</sup>

### Molluscum Contagiosum

Molluscum contagiosum is a skin disease produced by a *Molluscipoxvirus*, a virus specific to humans, present worldwide, and passed by direct skin to skin contact.<sup>317,318</sup> It occurs often in young individuals and may even be congenital.<sup>319,320</sup> Clinically, it is characterized by small, firm, usually multiple nodules that, when fully developed, have central cores from which white keratinous material can be expressed (Fig. 2.55). The microscopic picture is characteristic. The dermis is indented by a sharply delimited and lobulated mass of proliferating epithelium. As the cells differentiate within the mass, their cytoplasm gradually is filled by a faintly granular eosinophilic inclusion that displaces the nucleus and enlarges the cells (see Fig. 2.55). These molluscum bodies are formed of viral particles that are similar in size and mode of formation to the poxviruses.<sup>321</sup> Inflammation in the surrounding dermis is intense, sometimes in the form of an abscess<sup>322</sup> and sometimes in the form of a pleomorphic T-cell infiltrate that can simulate a lymphomatous/leukemic process.<sup>323,324</sup> Metaplastic ossification has been occasionally observed.<sup>325</sup>

### Herpes Virus

Herpes zoster is a painful disease caused by the same virus that causes chickenpox (varicella). It may vary from relatively benign



**Figure 2.55 Molluscum Contagiosum.** **A**, Clinical appearance of lesion located in eyelid. **B**, Low-power view of cup-shaped lesion. **C**, High-power view showing numerous molluscum bodies. (**A** courtesy Dr Carlos Ramos, Belleville, Illinois.)

pruritic lesions on the trunk, usually unilateral and in the distribution of a single dermatome, to severe involvement of the first division of the trigeminal nerve with herpetic keratitis and corneal ulceration.<sup>326,327</sup> Postherpetic neuralgia is the unpleasant sequela. Patients with leukemia and malignant lymphoma are particularly prone to develop herpes zoster infection.<sup>328</sup>

Oral and genital herpes are typically caused by herpes simplex virus 1 (HSV1) and HSV2, respectively, although either virus can be found in either location. Infection with both HSV1 and HSV2 results in recurrent, painful blistering eruptions.

The histopathologic features of varicella–herpes zoster are essentially identical to herpes simplex lesions, although it has been suggested that the lesions of zoster have a more prominent inflammatory infiltrate than herpes simplex lesions.<sup>329</sup> In both conditions, there are intradermal blisters with acantholysis and multinucleated keratinocytes with the characteristic intranuclear steel gray viral inclusions with peripheral margination of nuclear chromatin (Fig. 2.56). In some cases the dermal lymphocytic infiltrate can be of an intensity and atypia such as to simulate a malignant lymphoma.<sup>330</sup>

## Bacterial Diseases

### Folliculitis

The term folliculitis refers to an inflammatory process distributed around hair follicles and involving the follicular opening or adjacent

perifollicular skin.<sup>331</sup> A fair number of cases are drug induced.<sup>332</sup> They have been divided microscopically into the following:

#### 1. Infectious

Superficial (usually suppurative): resulting from fungi, bacteria, syphilis, or viruses

Deep (usually granulomatous): resulting from fungi or bacteria

#### 2. Noninfectious

Superficial (usually suppurative): acne vulgaris, rosacea, follicular mucinosis, steroid induced, etc.

Deep (usually granulomatous): acne vulgaris (conglobate and keloidal forms), perforating forms, etc.

Spongiotic: Fox-Fordyce disease, atopic dermatitis, pruritic folliculitis of pregnancy

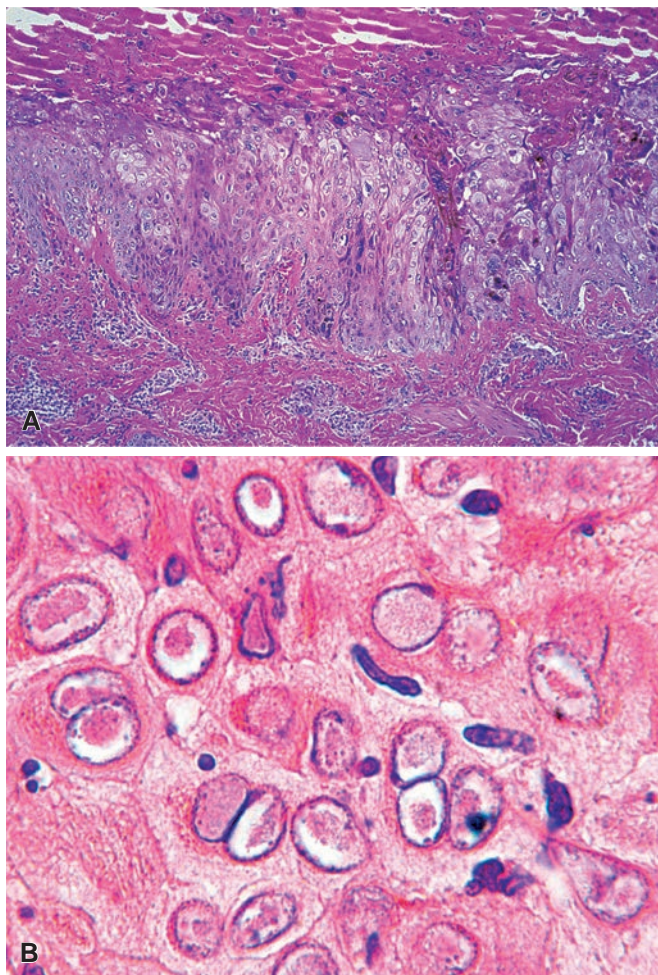
#### 3. Perifolliculitis

Predominantly lymphocytic: lichen planopilaris, pityriasis rubra pilaris, rosacea, etc.

Predominantly granulomatous: perioral dermatitis, rosacea, etc.

*Demodex* mites are more frequent in inflamed follicles than in normal ones, but it is not clear whether they play an etiologic role.<sup>333</sup>

*Eosinophilic folliculitis*, as seen in adults and infants, is usually a human immunodeficiency virus (HIV)-related dermatosis.<sup>334,335</sup> The



**Figure 2.56** **A**, Medium-power image of herpes simplex infection. **B**, High-power image of herpes simplex infection demonstrating large intranuclear inclusions.

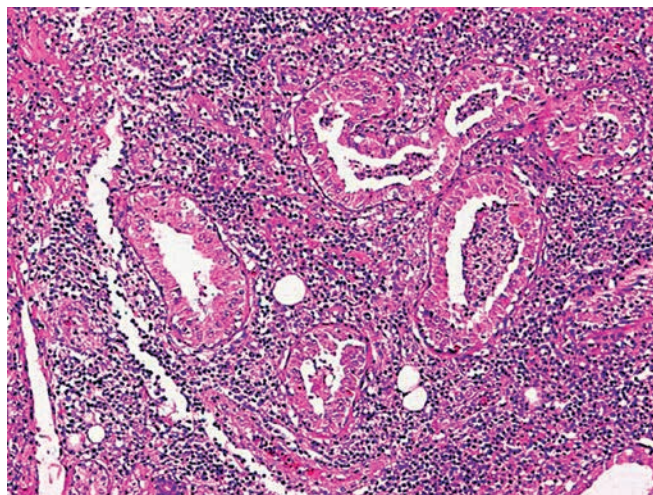
term *pseudolymphomatous folliculitis* has been proposed for a skin lesion usually located in the face and characterized histologically by a dense lymphocytic infiltrate of mixed nature centered around hair follicles, with infiltration of the follicular epithelium.<sup>336</sup> The suggestion has been made that some cases diagnosed as solitary sclerotic fibroma of the skin may be the end stage of a folliculitis.<sup>337</sup>

### Hidradenitis Suppurativa

*Hidradenitis suppurativa* is caused by bacterial infection in and about apocrine glands, usually in the axilla but occasionally involving the perineum or vulva (Fig. 2.57).<sup>338</sup> Anaerobic organisms are the most important pathogens. Abscesses, sinuses, and perianal fistulas occur with subsequent scarring.<sup>339</sup> The process tends toward chronicity, and in refractory cases excision of the involved skin may be required.<sup>340</sup> The follicles into which the apocrine glands open are plugged by keratin and infection develops following stasis. At present, hidradenitis suppurativa is considered a disease of follicular occlusion (acne inversa) rather than a primary inflammatory/infectious process of apocrine glands.<sup>341,342</sup>

### Tuberculosis and Atypical Mycobacteriosis

Cutaneous tuberculosis is an uncommon disease in the United States, although its incidence is on the rise.<sup>343</sup> It has various clinical and



**Figure 2.57** **Hidradenitis Suppurativa.** A heavy neutrophilic infiltrate is present around apocrine glands and in their dilated lumina. (Courtesy of Dr Raffaele Gianotti, Milano, Italy.)



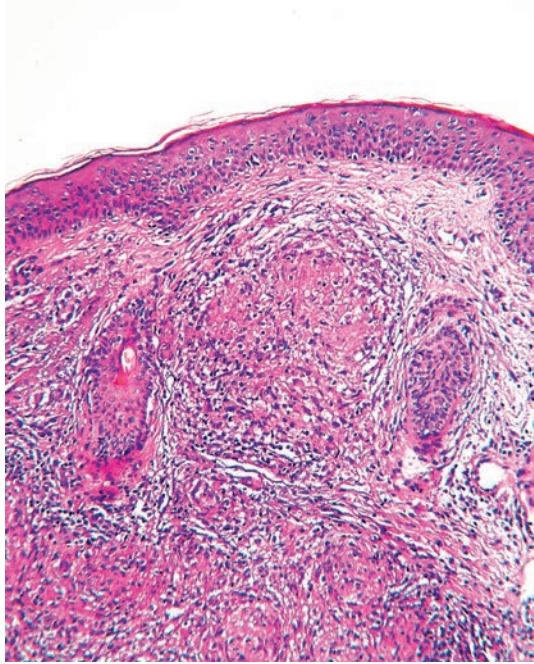
**Figure 2.58** **Clinical Appearance of Lupus Vulgaris.** The lesion presents in the form of an irregularly shaped red patch with elevated borders.

morphologic forms depending on the mode of entry and whether it is a primary or secondary infection.<sup>343,344</sup>

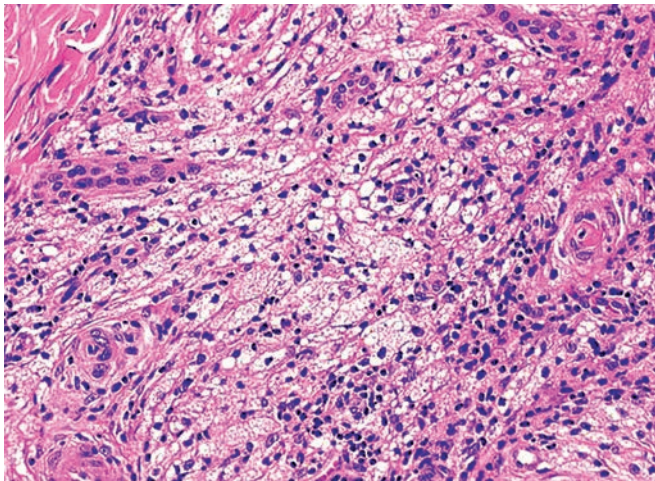
*Lupus vulgaris* is a reactivation type of tuberculosis. It generally involves the face, and the lesions are formed of red patches in which small, firm nodules reside (Fig. 2.58).<sup>345</sup> When pressed with a glass slide (diascopy), these nodules have a pale tan color. Microscopically, non-necrotic (sarcoid-like) and—less commonly—necrotic granulomas are found in the dermis (Fig. 2.59). Acid-fast bacilli are difficult to demonstrate but may be found. Cultures are recommended. The organisms can also be demonstrated with PCR methods.<sup>346</sup> Ulceration of the skin may occur. In longstanding cases, frank squamous cell carcinoma may arise from these lesions.

*Papulonecrotic tuberculid* is a skin lesion associated with tuberculosis but typically devoid of organisms; it is seen in both adults and children and is characterized microscopically by dermal necrosis, a poorly formed granulomatous infiltrate, vasculitis, and edema.<sup>347,348</sup> Rarely, the vasculitis is in the form of a nodular granulomatous phlebitis.<sup>349</sup>

Atypical mycobacteriosis can also affect the skin and result in a variety of lesions, including ulceration, abscesses, granulomas, diffuse histiocytic reactions, panniculitis, and rheumatoid-like nodules.<sup>350–353</sup>



**Figure 2.59 Tuberculosis of Skin (Lupus Vulgaris).** Well-formed granulomas with necrotic centers are present in the dermis.

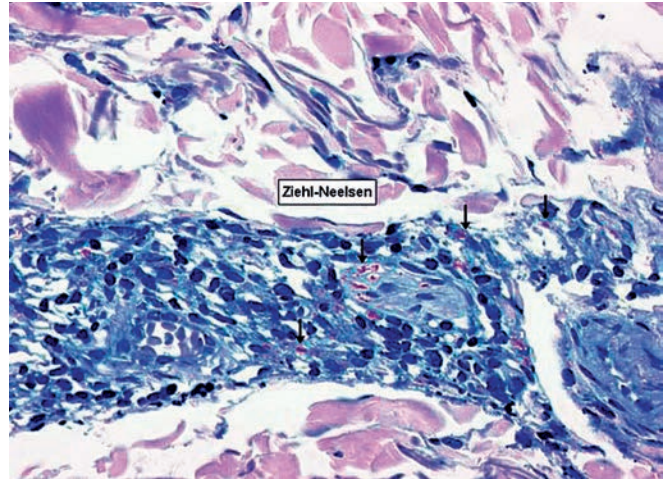


**Figure 2.60 Lepromatous Leprosy.** Large collections of foamy macrophages (*Virchow cells*) infiltrate the dermis.

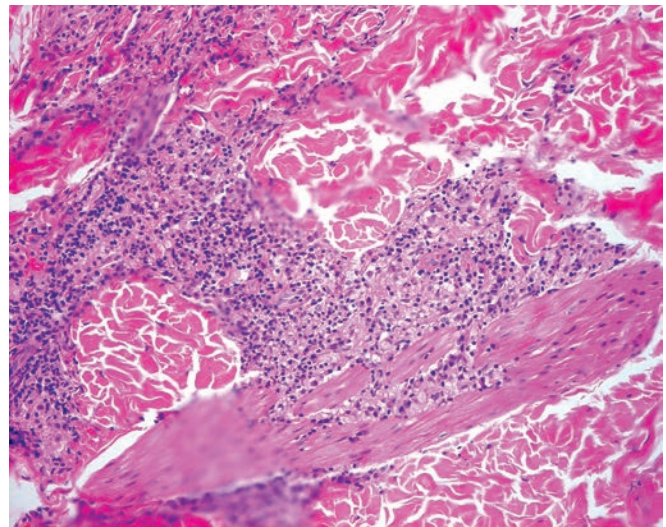
*Mycobacterium kansasii*, *M. marinum*, and *M. ulcerans* are the organisms most commonly implicated.<sup>350-353</sup> Infection with atypical mycobacteria should be considered whenever routine bacterial cultures are negative.

## Leprosy

In most regions of the United States, leprosy, or Hansen disease, is a rarity. However, an increased number of cases have been seen during as the result of the influx of immigrants from Asia and other regions of the world in which the disease is still endemic. Therefore the pathologist should consider it in the differential diagnosis of dermal granulomas and histiocytic tumors. In *lepromatous* and *dimorphic leprosy* the lepra or Virchow cells, filled with acid-fast bacilli, are plentiful (Figs. 2.60 and 2.61), whereas in *tuberculoid* and



**Figure 2.61** Acid-fast stain shows leprosy organisms (*arrows*) in a perineurial inflammatory infiltrate. (Courtesy of Dr Raffaele Gianotti, Milan, Italy.)



**Figure 2.62** Infiltration of the Arrectores Pili Muscle by Inflammatory Cells. This is a diagnostic clue for the diagnosis of leprosy.

*indeterminate leprosy*, bacilli are very scanty.<sup>354</sup> As for tuberculosis, a PCR-based diagnosis of leprosy is now available.<sup>355</sup> A diagnosis of leprosy should be suspected whenever the granulomas or the lymphocytic infiltration is located in and around the cutaneous nerves or when seen infiltrating and destroying arrectores pili muscle (Fig. 2.62).<sup>354,356</sup> Histoid leprosy (a bad term) is regarded by most workers as a variant of lepromatous leprosy which follows resistance to dapsone therapy.<sup>357</sup> It presents clinically as sudden eruptions of dome-shaped nodules that can simulate keratoacanthomas or cutaneous metastases.<sup>358</sup> Microscopically, the dermis shows sheets of round to spindle-shaped histiocytes, with a pattern resembling benign fibrous histiocytoma.

## Syphilis

The cutaneous lesions of secondary syphilis are of the maculopapular type and can be confused clinically with drug eruption, lichen planus, psoriasis, and other dermatoses (Fig. 2.63). Secondary syphilis can also present in the form of moth-eaten alopecia.<sup>359</sup> The microscopic



appearance can be nonspecific, especially in the macular lesions. The late papular lesions are more likely to exhibit the distinctive microscopic appearance of a dense perivascular or diffuse lichenoid infiltrate predominantly or almost exclusively composed of plasma cells (Fig. 2.64).<sup>360</sup> Noncaseating granulomas may also be present. The blood vessels characteristically show marked endothelial swelling and often proliferation. The cutaneous lesions of syphilis occurring in HIV-infected individuals do not differ significantly at the microscopic level from those seen in immunocompetent persons.<sup>361</sup>

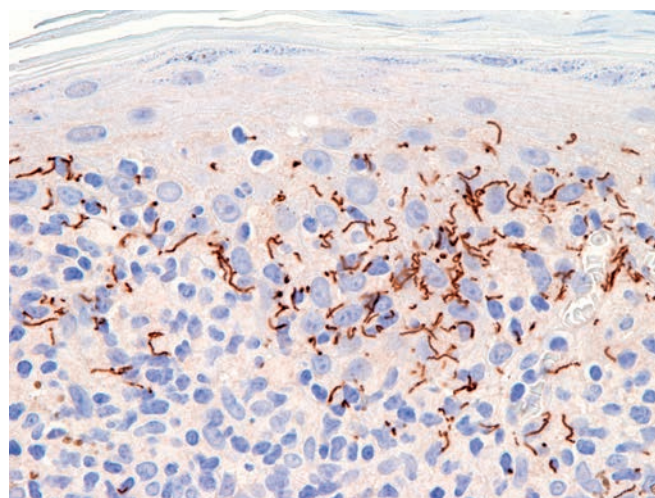


**Figure 2.63** Palmar Lesions of Secondary Syphilis.

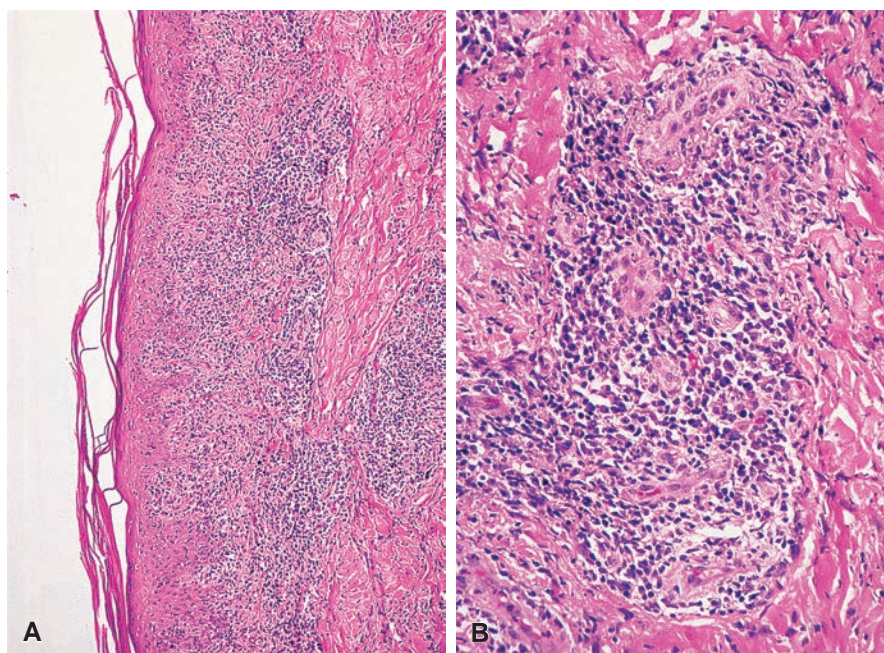
Although the organisms can be detected by Steiner silver stains, immunohistochemistry is a significantly more sensitive and superior technique (Fig. 2.65).<sup>362</sup> Of interest, in primary syphilis, the spirochetes show a mixed epitheliotropic and vasculotropic pattern, whereas in secondary syphilis, the spirochetes are almost confined to lower levels of the epidermis in an intercellular distribution.<sup>363</sup> PCR methods to detect *Treponema pallidum* in biopsies and biologic fluid is also available.<sup>364</sup>

### Lyme Disease

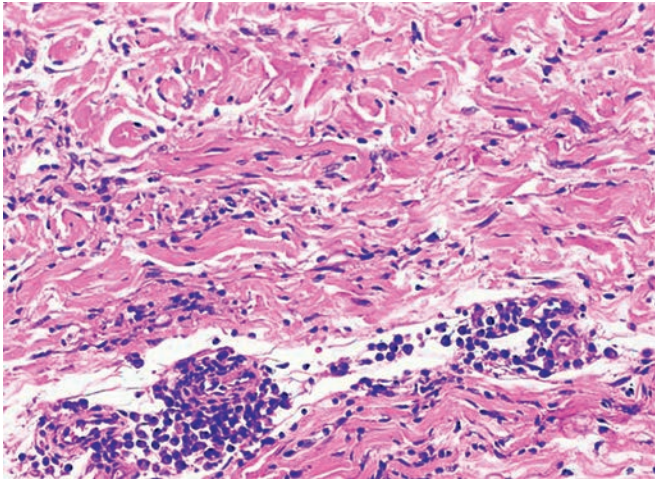
Lyme disease, a multisystem disorder caused by the spirochete *Borrelia burgdorferi*, is most commonly transmitted to humans by a tick



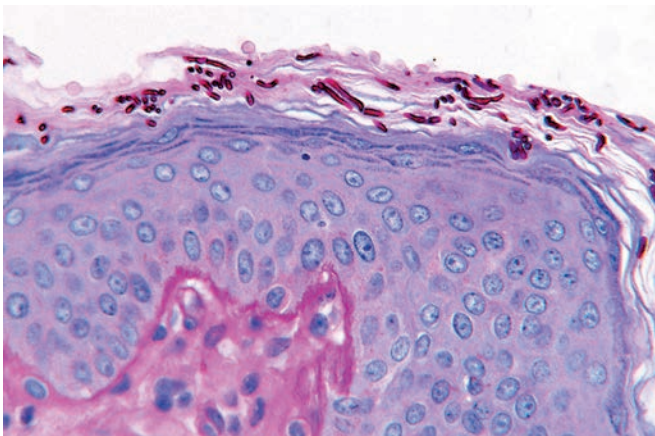
**Figure 2.65** Numerous *Treponema* organisms are seen in this immunostain in a case of secondary syphilis. (Courtesy of Dr Fabio Facchetti, Brescia, Italy.)



**Figure 2.64** Secondary Syphilis. **A**, Low-power view showing a dense infiltrate predominantly affecting the upper dermis. **B**, High-power view showing markedly hyperplastic blood vessels surrounded by a lymphoplasmacytic infiltrate.



**Figure 2.66** Lyme Disease. A perivascular infiltrate of lymphocytes and plasma cells is seen in the dermis.



**Figure 2.67** Dermatophytosis due to *Trichophyton*, demonstrated by periodic acid-Schiff stain.

bite.<sup>365,366</sup> It may be manifest in the skin as *erythema chronicum migrans* (currently regarded as pathognomonic of the disease), *acrodermatitis chronica atrophicans*, and *cutaneous lymphoid hyperplasia* ("borreliolymphocytoma").<sup>367-371</sup> In the early stages the predominant microscopic finding is a superficial and deep perivascular infiltrate largely composed of lymphocytes but also containing plasma cells and/or eosinophils (Fig. 2.66). Spirochetes can be demonstrated with the Warthin-Starry silver stain.<sup>372</sup> The organisms have also been detected by PCR in synovial fluid.<sup>373</sup> Other organs that may be involved by Lyme disease in addition to skin include the heart, joints, and nervous system.

It has been suggested that some cases of morphea, lichen sclerosus et atrophicus, anetoderma, and atrophoderma of Pasini and Pierini may also be caused by borreliolymphocytoma, but this remains controversial.<sup>374,375</sup>

## Fungal Diseases

### Tinea (Dermatophytoses)

In the dermatophytoses, the fungal spores and hyphae are found in the stratum corneum and in or about hair shafts (Fig. 2.67).<sup>376</sup> Mild epidermal changes, such as focal intercellular edema and varying



**Figure 2.68** Clinical Appearance of North American Blastomycosis.

amounts of dermal inflammation, may be seen. The fungal elements are readily seen in sections stained by the PAS or GMS methods. Occasionally, atypical clinical forms of tinea are biopsied, and the fungi are readily missed if not sought. Bacterial folliculitis and perifolliculitis may be superimposed on tinea of the scalp and beard. These lesions are known as *kerion celsi* and *sycosis barbae*, respectively, and may, on occasion, be mistaken for infected tumors. Histologically, cellulitis, abscesses, pseudoepitheliomatous hyperplasia, and a few fungi in the hair follicles and adjacent tissues are seen. A related disorder is *Majocchi granuloma (nodular granulomatous perifolliculitis)*, in which inflammation of dermal and subcutaneous tissue by dermatophytes is present; *Trichophyton rubrum* is the organism most commonly involved.<sup>377</sup>

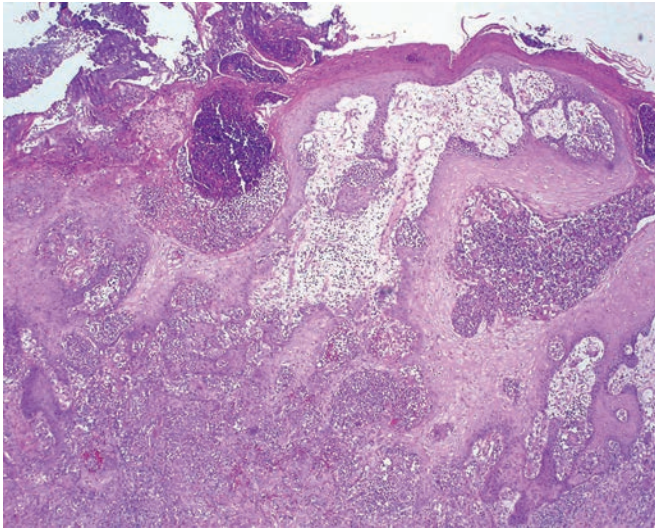
It should be kept in mind that dermatophytes can be found superimposed on an inflammatory (pyoderma, scabies) or neoplastic lesion of the skin.<sup>378</sup> We have seen cases of mycosis fungoides that were missed originally because the atypical dermal lymphoid infiltrate was attributed to the fungi seen in the horny layer.

### North American Blastomycosis

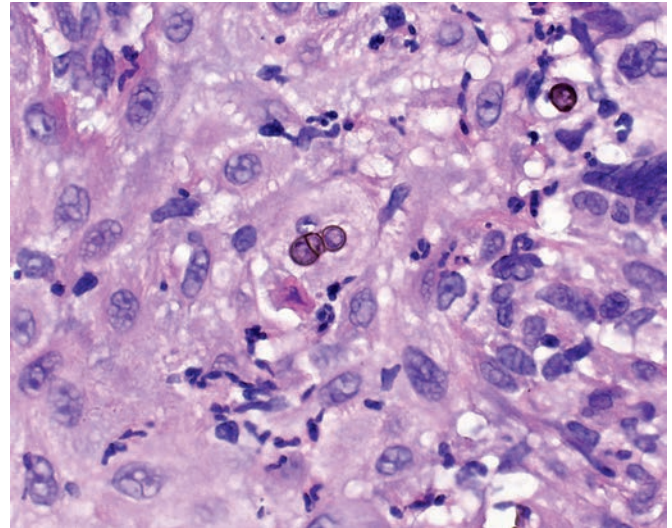
Isolated cutaneous blastomycosis is an uncommon lesion. Usually the skin lesion is secondary to pulmonary involvement, which may be subclinical.<sup>379</sup> Overall, approximately 20% of patients with blastomycosis have cutaneous lesions.<sup>380</sup> The causative organism, *Blastomyces dermatitidis*, is a spheric, double-contoured  $12 \mu\text{m} \pm 4 \mu\text{m}$  yeast. It reproduces by budding, and this characteristic allows its identification in sections. The skin lesions are slowly enlarging verrucous plaques in which numerous small abscesses are present (Fig. 2.68).<sup>380</sup> Microscopically, they are characterized by marked pseudoepitheliomatous hyperplasia and a mixed granulomatous and acute polymorphonuclear infiltrate (Fig. 2.69).<sup>380</sup> The accompanying pseudoepitheliomatous hyperplasia may cause diagnostic confusion with squamous cell carcinoma. The organism is generally found in giant cells. Smears and cultures are recommended diagnostic adjuncts (Fig. 2.70).

### Chromoblastomycosis

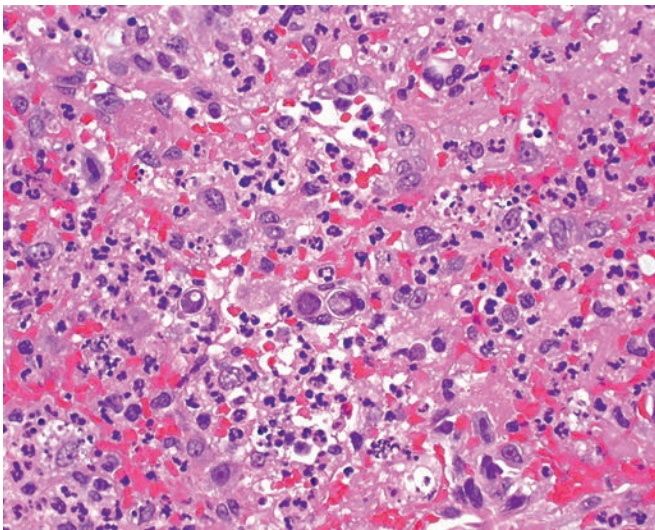
*Chromoblastomycosis* is an indolent cutaneous disease with a verrucous or nodular gross appearance, often misdiagnosed clinically as carcinoma and therefore excised.<sup>381-383</sup> It is an occupation-related disease, mainly affecting individuals in tropical and temperate regions.<sup>383</sup> Hematogenous dissemination occurs very rarely.<sup>384</sup> The spores are



**Figure 2.69 Blastomycosis.** Pseudoepitheliomatous hyperplasia and dense neutrophilic infiltrate.



**Figure 2.71 Chromoblastomycosis.** Pigmented septate organisms.



**Figure 2.70 Blastomycosis.** Budding yeast with thick refractile cell walls.

brown, hence their name, and the tissue reaction is similar to that seen in blastomycosis (Fig. 2.71). These fungi, closely related species of *Phialophora*, *Fonsecaea* and *Cladosporium*, multiply by cross wall formation and splitting. Their color, cross walls, and lack of budding distinguish them from *B. dermatitidis*. Sometimes, fungi with an identical appearance are found in subcutaneous abscesses.<sup>385</sup>

## Miscellaneous Disorders

### Foreign Body Reaction

Silica, talc, exogenous lipids, zirconium, beryllium, and aluminum induce granulomatous reactions within the dermis.<sup>386-389</sup> Residual particles of talc, silica, and lipids are demonstrable in tissue by routine or polariscopic microscopy. Beryllium, previously a component of the phosphorus in fluorescent lights, induces a distinct necrotizing and granulomatous reaction. Aluminum, used for vaccination and allergen desensitization, can induce a variety of changes

in the injection site, including fat necrosis, panniculitis, prominent lymphoid follicle formation, and perifollicular lymphoid infiltrate. A clue to the diagnosis is the finding of histiocytes with a violaceous granular cytoplasm.<sup>390</sup>

### Pyoderma Gangrenosum

Pyoderma gangrenosum is associated with a systemic disorder (such as inflammatory bowel disease) in approximately half of the cases.<sup>391,392</sup> It begins with an acute-phase necrotic pustule or furuncle and can evolve to a large and deep necrotic ulcer with a violaceous border and a surrounding halo of erythema.<sup>392</sup> Most lesions are found on the extremities. The majority are deeply seated, but they can also be superficial and vegetant.<sup>393</sup> Microscopically, the changes are those of hemorrhagic necrosis with abscess formation in the early stage and represented by a heavy infiltrate of lymphocytes and plasma cells in the late stage. Marked epidermal hyperplasia can be seen at the edges. The pathogenesis is probably immune mediated. Histologically, pyoderma gangrenosum does not have specific features but requires clinical correlation for diagnosis.

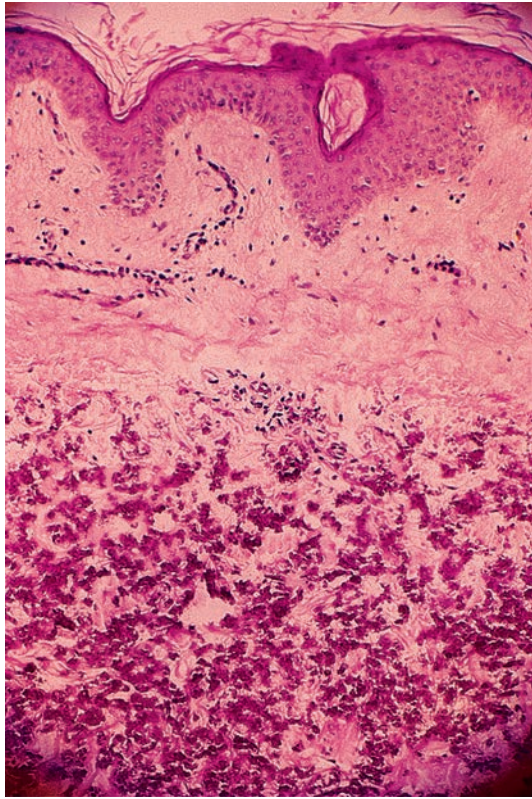
### Elastosis Perforans

*Elastosis perforans* (serpiginosa) typically involves the back of the neck in adolescent boys.<sup>394</sup> Microscopically, clumps and strands of abnormally coarse elastic fibers penetrate the epidermis and produce a focal epidermal hyperplasia.<sup>395,396</sup> The altered elastica in the papillary dermis is easily missed and recognition usually requires elastic tissue stains.

Elastosis perforans needs to be distinguished from other perforating dermatoses, such as *reactive perforating collagenosis*, *perforating folliculitis*, and *Kyrle disease*.<sup>397-400</sup> The nosologic identity of the latter two disorders and their relationship to each other remains controversial. A high proportion of them are seen in patients with chronic renal failure (in hemodialysis) or diabetes mellitus.<sup>401,402</sup>

### Pseudoxanthoma Elasticum

The dermal changes in *pseudoxanthoma elasticum* are manifestations of a heritable disease also having ocular and vascular lesions resulting from degeneration of elastic fibers and due to mutations of the



**Figure 2.72** Pseudoxanthoma Elasticum.

*ABCC/MRP6* gene (which codes for an ATP-binding protein).<sup>403–405</sup> Angioid streaks in the retina and degenerative changes in arteries leading to occlusion or rupture are described.<sup>406</sup> Yellow streaks and plaques of the skin, particularly in areas of creases, such as the neck, axillae, and groin, account for the name pseudoxanthoma. Histologically, the mid and lower dermis contains clumps and strands of altered, basophilic connective tissue that stain intensely with aldehyde fuchsin and Verhoeff elastic tissue stain (Fig. 2.72). The basophilic staining quality of the elastic material is due to dystrophic calcification of the fibers.

### Cutaneous Mucinosis

*Pretibial myxedema* is characterized by sometimes large nodular lesions that occur on the legs of patients who are or have been thyrotoxic.<sup>407</sup> When particularly extreme, the disease has been referred to as *elephantiasis*.<sup>408</sup> The accumulation of mucopolysaccharides in the dermis is similar to that in the orbital tissues, which is caused by excess thyroid-stimulating hormone (TSH) secretion by the pituitary gland. Histologically, the dermal collagen is separated by aggregates of faintly basophilic material that stains with Mayer mucicarmine, Hale colloidal iron, and PAS (diastase resistant).

Other conditions associated with the deposition of large amounts of acid mucopolysaccharides in the dermis are the generalized myxedema of hypothyroidism, papular mucinosis (lichen myxedematosus), myxoid cyst, cutaneous focal mucinosis, and follicular mucinosis.<sup>409–418</sup> The latter condition is a reaction pattern of follicular epithelium that is particularly prominent in alopecia mucinosa but that can also be seen in a variety of other diseases, including mycosis fungoides.<sup>419</sup> Morphologically, the idiopathic and mycosis fungoides-related forms of the disease are similar; follow-up studies on patients with the idiopathic form have shown little or no progression toward



**Figure 2.73** Clinical Appearance of Darier Disease. The lesion typically affects the back and presents in the form of reticulated keratotic lesions.

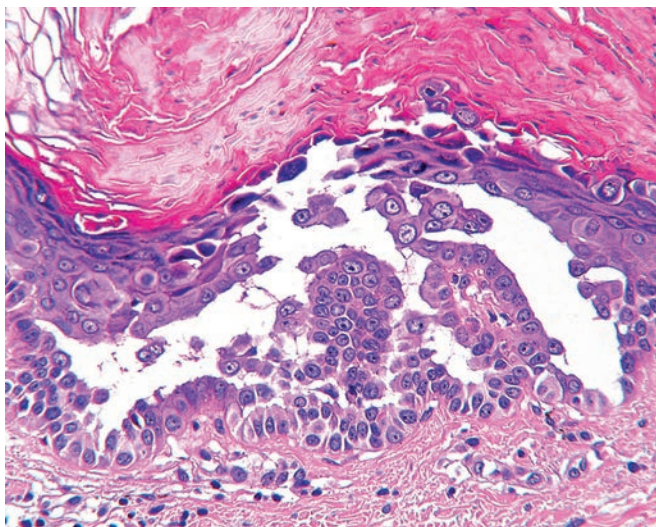
mycosis fungoides, despite the presence in some cases of a clonal T-cell population.<sup>419</sup> *Cutaneous myxomas* (superficial angiomyxomas) are an important component of Carney complex, which also includes cardiac myxomas, spotty hyperpigmentation, and endocrine hyperactivity.<sup>420</sup>

### Acanthosis Nigricans

Acanthosis nigricans manifests clinically as brown, velvety plaques most often found in the axillae, back of the neck, and other flexural areas. Two major forms exist, one associated with internal malignant neoplasms (particularly of the gastrointestinal tract) and the other with a heterogeneous group of disorders having as common denominator the presence of tissue resistance to insulin.<sup>421–424</sup> The latter form includes diabetes, obesity, and Cushing syndrome. Microscopically, the changes are similar in both types and are characterized by papillomatosis and hyperkeratosis (rather than by acanthosis and hyperpigmentation, as suggested by the name). In the cases associated with malignancy, the disease may be the result of production of epidermal growth factors by the tumor cells.<sup>425,426</sup>

### Darier Disease

Although Darier disease has bullous features, it is not an autoimmune inflammatory bullous dermatosis. Darier disease is an uncommon genodermatosis caused by germline mutation of the *ATP2A2* gene.<sup>427,428</sup> It usually presents with a symmetrical distribution of keratotic reddish-brown papules over the seborrheic areas of the body (Fig. 2.73). Unilateral and localized variants have been described.<sup>429</sup> Microscopically, the skin lesions are characterized by suprabasal



**Figure 2.74** Darier Disease.

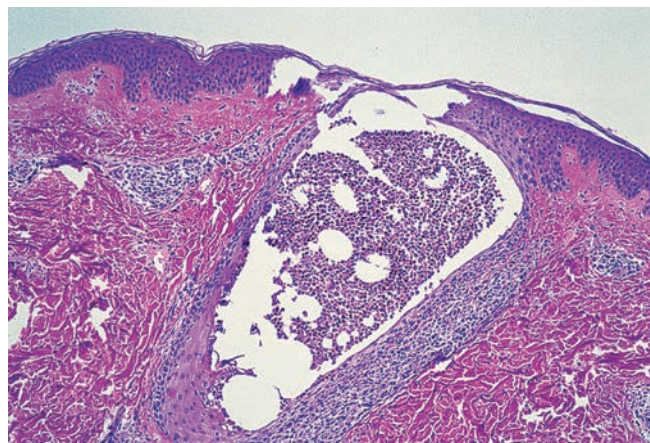
clefts in which acantholytic cells called grains are found (Fig. 2.74).<sup>430</sup> The dermal papillae covered by a layer of basal cells form small villi at the base of the lesion. In addition, within the epidermis, large individually dyskeratotic cells called *corps ronds* are found. When the lesions are closely spaced, the skin assumes a verrucous appearance. The back is the most common site of involvement. The oral mucosa and hairless skin may be involved, showing that the disease is not limited to the hair follicle, as suggested by the synonym keratosis follicularis. *Warty dyskeratoma*, an isolated follicular lesion, is histologically similar but unrelated to Darier disease.

### Dermatoses in HIV-Infected Patients

HIV-infected patients may develop a large variety of skin diseases, ranging from inconspicuous macular rashes to Kaposi sarcoma, the latter being the condition that contributed in the mid-1980s to the recognition of this immune deficiency syndrome.<sup>431-434</sup>

Non-neoplastic skin manifestations of HIV infection include the following:

1. Maculopapular eruptions. In acute HIV disease, approximately one-fourth of patients develop a maculopapular erythematous eruption in the trunk that may extend to involve the extremities. Microscopically, there is a nonspecific perivascular collection of lymphocytes and histiocytes in the upper dermis, sometimes associated with small papulovesicular foci with necrotic keratinocytes and a few neutrophils.<sup>435,436</sup>
2. Papular pruritic eruptions. These lesions, which may develop after the acute HIV phase, have a tendency for waxing and waning and can occur anywhere in the body. Microscopically, there is a superficial and mid-dermal perivascular lymphocytic dermatitis, often featuring eosinophils, acanthosis, and parakeratosis.<sup>437</sup>
3. Vasculitis. A few cases of leukocytoclastic vasculitis have been reported. Some have been said to be the direct result of



**Figure 2.75** Eosinophilic Folliculitis in a Human Immunodeficiency Virus-Infected Patient.

HIV infection<sup>438</sup> and others of cytomegalovirus (CMV) infection.<sup>439</sup>

4. Folliculitis and syringitis. The clinical observation has been made that full-blown AIDS is often preceded by some manifestation of folliculitis.<sup>440</sup> Microscopically, the usual appearance is that of a mixed perifollicular chronic inflammatory infiltrate, sometimes associated with follicle rupture. In some cases the inflammation has a prominent eosinophilic component (HIV-associated eosinophilic folliculitis) (Fig. 2.75).<sup>441</sup> Herpetic syringitis (i.e. inflammation of the acrosyringium of the sweat glands) has been described, sometimes accompanied by squamous syringometaplasia.<sup>442</sup>
5. Seborrheic dermatitis. This common complication of HIV infection differs from that seen in immunocompetent individuals in that it tends to involve the trunk and extremities and is clinically more severe.<sup>443,444</sup> Microscopically, the changes depend on the stage of the lesion and are qualitatively similar to those seen in the usual form of the disease.
6. Psoriasis.
7. Drug reaction.
8. Parasitic (scabies), fungal (cryptococcosis, histoplasmosis, dermatophytosis), and bacterial (mycobacteriosis, syphilis, bacillary angiomatosis) infections.
9. Viral infections (other than these already mentioned). Herpes simplex occurs in approximately 20% of HIV-infected patients, usually in the form of a painful ulcer in the perianal or perioral regions (see Fig. 2.56).<sup>445</sup> Varicella-herpes zoster infection can be severe and widespread, sometimes with involvement of numerous dermatomes.<sup>446,447</sup> CMV may be detected in ulcerative lesions at mucocutaneous junctions. Other viral infections include measles,<sup>448</sup> molluscum contagiosum, oral hairy leukoplakia, and HPV-induced lesions (such as anal warts and Bowenoid papulosis).<sup>449</sup>
10. Papular neutrophilic xanthoma. This HIV-associated lesion is characterized by collections of foamy macrophages, extracellular nuclear dust, and hyaline necrosis of collagen fibers.<sup>450</sup>

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# Tumors and Tumorlike Conditions of the Skin

# 3

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The skin is, contrary to the ubiquitous simplistic concept, a remarkably heterogeneous organ. The nodular lesions (hamartomatous, reactive, and neoplastic) that occur in the skin are more numerous than those produced by any other organ. For example, the eccrine sweat gland alone gives rise to 10 or more histologically distinct adenomas. This diversity, combined with a body of descriptive data (clinical, histologic, histochemical, immunohistochemical, and ultrastructural) amassed over the past century and dispersed in varying literatures, produces confusion, chiefly in the area of nomenclature. Within the

limits inherent in a textbook that covers a breadth of surgical pathology specialties, it is impossible to pursue finite segmentation, interesting and accurate as it may be. The more common lesions will be discussed in some detail and pertinent references provided for the rare lesions.

Most of the mesenchymal tumors that may involve the dermis are discussed in the chapter on soft tissues. Only those showing exclusive or preferential involvement of the skin are included in this chapter.

**Abstract**

This chapter focuses on cutaneous tumors and tumorlike conditions of the skin. Epidermal tumors, adnexal tumors, melanocytic tumors, neuroendocrine tumors, cutaneous soft tissue tumors, and lymphoproliferative/hematopoietic lesions will be covered.

**Keywords**

Seborrheic keratosis,  
squamous cell carcinoma,  
basal cell carcinoma,  
adnexal tumor,  
melanocytic nevus,  
melanoma,  
Merkel cell carcinoma,  
dermatofibrosarcoma protuberans,  
atypical fibroxanthoma,  
lymphoma

## Epidermis

### Seborrheic Keratosis

*Seborrheic keratoses* are common, benign, pigmented, predominantly basal keratinocytic proliferations occurring chiefly on the trunk of adults. They may be single or multiple. The sudden appearance of, or increase in the number and size of, seborrheic keratoses in association with internal malignant disease is known as the *Leser-Trélat sign*.<sup>1</sup>

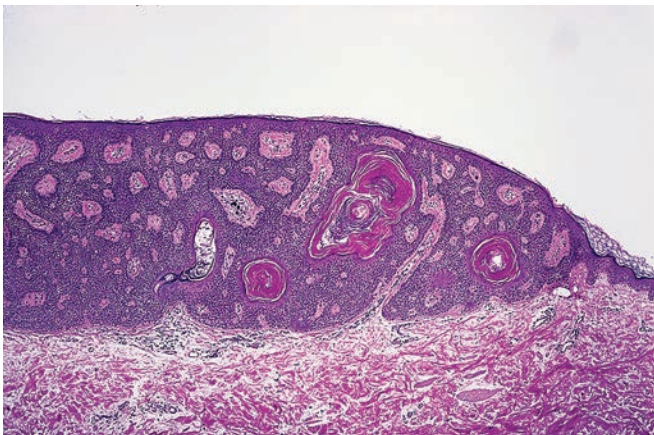
Grossly, the lesions of seborrheic keratosis protrude above the surface of the skin, are soft, and vary in color from tan to black. The single, heavily pigmented seborrheic keratoses may be confused clinically with malignant melanoma.

Microscopically, the number of epidermal basal cells is greatly increased, presumably as a result of a maturation defect. The acanthotic pattern is the most frequent, in which a thick layer of basal cells is seen interspersed with pseudohorn cysts (Fig. 3.1). Some of these cells contain melanin, as the result of transfer from neighboring melanocytes. Other microscopic variants of seborrheic keratosis are the *hyperkeratotic*, *adenoid*, *acantholytic*,<sup>2</sup> and *desmoplastic*. The latter may simulate invasive squamous cell carcinoma.<sup>3</sup> *Psoriasisform keratosis* is a recently described condition combining features of seborrheic keratosis and psoriasis, the true nature of which still needs to be determined.<sup>4,5</sup>

Immunohistochemically, the keratinocytes of seborrheic keratosis invariably express low-molecular-weight keratin but often exhibit a deficiency of the high-molecular-weight keratins.<sup>6,7</sup>

In *irritated seborrheic keratosis*, squamous metaplasia is pronounced, often in the form of so-called squamous eddies. This phenomenon, presumably arising from the acrotrichia, should not be overdiagnosed as basosquamous carcinoma.<sup>8</sup> It does not seem to be related to human papilloma virus (HPV).<sup>9</sup> Instead, HPV can be identified in the seborrheic keratosis-like lesions of patients with *epidermodysplasia verruciformis*<sup>10,11</sup> and in those exhibiting bowenoid changes.<sup>12,13</sup> The latter should probably be interpreted as condylomas rather than as true seborrheic keratoses.<sup>14</sup>

Malignant skin neoplasms of various types (particularly basal cell carcinoma) may be seen contiguous or adjacent to lesions of seborrheic keratosis.<sup>15</sup> Seborrheic keratoses are genetically stable but frequently have mutations in a variety of oncogenes in the *FGFR3-RAS-mitogen-activated protein kinase (MAPK)* pathway but not tumor suppressor genes.<sup>16</sup>



**Figure 3.1** Seborrheic keratosis with mild pigmentation in the skin of a senior pathologist. Pseudohorn cysts are evident.

### Benign Lichenoid Keratosis

*Benign lichenoid keratosis* (lichenoid keratosis, lichen planus–like keratosis) presents as a solitary lesion, most commonly on the trunk or extremities of middle-aged and older patients. Clinically, they are often confused with basal cell carcinomas. Microscopically, the epidermis is acanthotic with hyperkeratosis and a thickened granular layer in association with a dense lichenoid lymphocytic infiltrate with interface change reminiscent of lichen planus.<sup>17</sup>

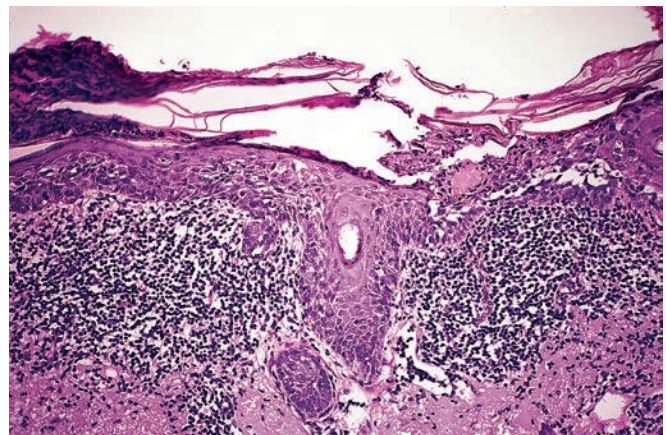
### Acrochordon

Acrochordon is the preferred name for a common and inconsequential skin lesion also known as fibroepithelial papilloma, fibroepithelial polyp, fibroma molle, and skin tag. As these various names indicate, it is a polypoid lesion composed of varying amounts of stroma covered by a papillomatous epidermis. A clue to the diagnosis is the absence of adnexal structures in the underlying dermis.

A distinctive variant of this exophytic fibroepithelial process is represented by the *acquired (digital) fibrokeratoma*, characterized by collagenous protrusions covered by hyperkeratotic epidermis, usually occurring around interphalangeal joints but sometimes in other sites.<sup>18</sup>

### Actinic Keratosis

In that portion of the epidermis exposed to sunlight, chiefly that of the near ultraviolet (UV) spectrum, a sequence of atrophic, hyperplastic, and eventually dysplastic changes known as actinic keratosis may develop.<sup>19</sup> The term “senile” keratosis, often used as a synonym, is inappropriate. An increased incidence of these changes has been found in renal transplant recipients, particularly in the lip region.<sup>20</sup> Histologically, actinic keratoses involve the interfollicular epidermis, sparing the follicular apparatus and the intraepidermal portion of the sweat duct, as demonstrated in the classic article by Pinkus.<sup>21</sup> The stratum corneum is replaced by a parakeratotic scale. Excessive production and accumulation of this scale lead to the formation of cutaneous horns. The granular layer is generally absent except at and about the follicular orifices. The malpighian layer shows disorderly maturation, as well as individually dysplastic and dyskeratotic cells (Fig. 3.2). Morphologic variations on the theme of actinic keratosis include basaloid proliferations resembling early basal cell carcinomas, changes along the dermoepidermal junction resembling lichen planus



**Figure 3.2** Actinic Keratosis. Note the hyperparakeratosis, moderate malpighian atypia, and dermal inflammatory infiltrate.