Primer of Dermatopathology

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Little, Brown and Company
Boston/Toronto

First Edition

Library of Congress Catalog Card No. 83-80293

ISBN 0-316-37216-1

Printed in the United States of America

HAL

Preface

Looking at a skin biopsy under the microscope can be a bewildering and frustrating experience for inexperienced dermatology and pathology residents and practioners alike. This book was conceived from that frustration. When Dan Burnes was rotating through dermatopathology as a dermatology resident at the Massachusetts General Hospital, he frequently complained that there should be a logical and systematic way to look at and evaluate a skin biopsy. The textbooks available at that time were all traditionally organized by pathogenesis, which was useful only if you knew the answer in advance. Challenged by the problem, Dan sat down and outlined dermatopathologic disorders according to (1) their location in the skin—from the stratum corneum to the panniculus—and (2) "reaction patterns" of disease. The latter organization he had learned from Martin Mihm, who had learned it from Wally Clark, who learned it from heaven knows whom. Encouraged by Dr. Thomas Fitzpatrick, who loves a logical approach to disease, Dan's outline was filled in and expanded, and line drawings and photographs were added. Many revisions later, *Primer of Dermatopathology* became a functional entity.

We deliberately called this book a primer to identify its purpose. It is an introduction to dermatopathology, an expanded outline of diseases according to the anatomic location and the pattern of changes observed. It attempts to simplify and clarify a complex situation in order to get people involved in making a (differential) diagnosis from a piece of tissue on a slide.

This book includes most of the diseases seen by dermatology or pathology residents during their years of training. It is not, however, all-inclusive, and for completeness, the reader should have ready access to at least one (inclusive) major textbook, such as those written by Walter Lever, James Graham and Elson Helwig, and, for inflammatory disorders, that of A. Bernard Ackerman.

A.F.H.
T.H.K.
D.C.B.
M.C.M.

Acknowledgments

It is impossible to adequately thank everyone who contributed to *Primer of Dermatopathology*; however, certain people must be mentioned. We voice our appreciation to Dr. Thomas B. Fitzpatrick, Department of Dermatology, Harvard Medical School; Dr. Irwin M. Freedberg, Department of Dermatology, New York University School of Medicine; Dr. Thomas T. Provost and Dr. Evan R. Farmer, Department of Dermatology, The Johns Hopkins University, School of Medicine; and Dr. Harold F. Dvorak, Department of Pathology, Harvard Medical School. Their continued encouragement and gentle prodding kept the project going. Appreciation is also extended to Otto Coontz for his beautiful drawings, to Ben Bronstein of the Massachusetts General Hospital Dermatopathology Unit, and to the dermatology residents at Johns Hopkins, who reviewed the manuscript in its various stages of evolution and offered constructive criticism and helpful suggestions.

We owe special thanks to Marletta Winston, Linda Pottillo, Denise Fritter, and Bonnie Weissfeld, who patiently turned illegible squiggles into final copy. We are ever grateful to histology technologists such as Norma King and Obdula Morales, who maintain such standards that our work at the microscope is not only possible but esthetically delightful. The photomicrographs in this primer were made possible by Beth Israel Hospital Photographic Services, the Massachusetts General Hospital Pathology Photography Laboratory, Steven Halpern of the Tufts University Medical School Department of Pathology, and Rita Ann Monahan of the Beth Israel Hospital Department of Pathology.

Finally, we acknowledge our debt to patients, residents, and associates, from whom we learn daily.

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Guide to the Use of this Book

Primer of Dermatopathology is designed to assist dermatologists and pathologists (in training or in practice) in the microscopic diagnosis of skin disease. By emphasizing a systematic approach to the examination of a skin biopsy, we hope to enable even the relatively uninitiated individual to locate and identify the abnormal histologic features present in a given lesion and to establish either a diagnosis or a differential diagnosis.

To use this book most effectively, we recommend an initial reading of the introductory section. The normal histology of the skin is briefly reviewed, and the illustrated glossary provides an introduction to common pathologic alterations (parakeratosis, basal vacuolation, etc.) and to the terminology used in dermatopathology.

A skin biopsy should be examined first with the unaided eye and then with the lowest-power objective on the microscope. Simple appreciation of the *type* of biopsy submitted can give valuable insight into the questions being asked by the referring physician. For example, trephine (punch) biopsies are usually obtained from inflammatory lesions while shave biopsies and elliptical excisions are usually from neoplastic lesions. Inked margins indicate the surgeon's concern about the extension of a malignant tumor.

While still using low power, identify the anatomic site of the major pathologic change (i.e., the epidermis, basement membrane zone, dermis, appendages, or panniculus), turn to that section of the book, and note the chapter headings. At higher power, determine the predominant abnormality and match it with the corresponding chapter. Some chapters (e.g., Chapter 21, Cysts in the Dermis) will require perusal of the entire contents to generate a diagnosis, while others (e.g., Chapter 8, Disorders of the Melanocyte) are further subdivided. For example, examination of a skin biopsy reveals that the most prominent change is a perivascular infiltrate in the reticular dermis. Turn to Part IV (Reticular Dermis), Chapter 14 (Predominantly Perivascular Infiltrate). To further classify the lesion, determine the cellular composition of the infiltrate and whether there is vascular damage or thrombosis. Accordingly, a subdivision can be selected and a differential diagnosis generated. Histologic differential diagnoses are given in the right-hand column. The differential diagnoses of specific histologic findings, such as Pautrier microabscesses or hypogranulosis, are also in the right-hand column but are boxed for emphasis.

Skin biopsies, especially when taken from inflammatory lesions, often show histologic changes in more than one anatomic area. A lesion of lupus erythematosus, for example, may exhibit epidermal atrophy, basal vacuolation, and a perivascular mononuclear cell infiltrate. The diagnosis may be established by looking at any one of those features in Chapter 7 (Atrophic Processes of the Epidermis), Chapter 9 (Vacuolation of the Basement Membrane Zone), or Chapter 14 (Predominantly Perivascular Infiltrate).

Characteristic histologic features of the individual disorders are enumerated in the text and illustrated wherever possible with schematic drawings and/or photomicrographs. The most important or distinguishing histologic features are emphasized with bold type.

Suggested readings are given at the end of each chapter to provide additional information to the curious and inquiring student of dermatopathology.

Contents

Part I

Introduction

1. Normal Histology of the Skin
2. Glossary

Chapter 1

Normal Histology of the Skin

A basic knowledge of cutaneous histology is easily attained by a systematic approach. The skin can be considered by anatomic levels: epidermis, dermoepidermal junction, dermis, and subcutis (Fig. 1-1). Traversing the dermis and subcutis are the peripheral branches of the vascular and nervous systems as well as the epidermal appendages (pilosebaceous, apocrine, and eccrine units). Regional variations in the skin account for marked differences in epidermal thickness, dermal thickness, elastic fiber content, and the presence or absence of hair follicles and sebaceous, apocrine, or eccrine glands.

Epidermis

The epidermis is composed of four types of cells—keratinocytes, melanocytes, Langerhans cells, and Merkel cells. These cells vary markedly in structure, function, and place of origin. *Keratinocytes* comprise the major cell population of the epidermis (80%). Keratinocytes are subclassified by their location in the epidermis (Fig. 1-2). The *basal layer* (stratum basale) consists of a single layer of cuboidal cells located next to the dermoepidermal junction. These cells have a relatively large nuclear-cytoplasmic ratio and slightly basophilic cytoplasm. The *spinous layer* (stratum spinosum), named for its prominent intercellular connections, which allegedly resemble spines, is located above the basal layer. Usually several cells thick, the spinous layer consists of polygonal cells, which exhibit cytoplasmic eosinophilia reflecting increased keratinization. The *granular layer* (stratum granulosum) is one to five cells thick, and consists of flattened cells with coarse, deeply basophilic cytoplasmic granules. These are called *keratohyaline granules.* The *cornified layer* (stratum corneum), the most superficial layer of the epidermis, is composed of extremely flattened, anucleate keratinocytes arranged in a pattern sometimes described as "basketweave." The cornified layer appears dense and thickened on surfaces subject to friction, such as the palms and soles. Keratinocytes—particularly basal cells—also may contain small, brown pigment (melanin) granules. The degree of epidermal melanization varies with genetic and environmental factors.

Melanocytes have a variable appearance, which sometimes makes definitive identification difficult in routine hematoxylin-eosin (H&E) stained sections. Melanocytes are located in the basal layer and usually appear as cuboidal cells with clear cytoplasm and eccentrically placed, crescent-shaped nuclei. The function of these neural crest–derived cells is to synthesize melanin, which is then transferred to adjacent keratinocytes via dendritic projections. Pigment production in these cells and their true dendritic shape are infrequently appreciated without special stains. The ratio of melanocytes to basal cells is 1:4 to 1:9 and varies with anatomic location on the body (but not with race).

Langerhans cells have an appearance similar to that of melanocytes but are located at any level of the epidermis. Reliable identification can be made with gold chloride–stained sections or by electron microscopy. Ultrastructural cytoplasmic organelles called *Birbeck granules* (said to resemble tennis rackets) are characteristic of Langerhans cells. Langerhans cells have many features of monocytes and macrophages and probably migrate to the skin from the bone marrow.

Merkel cells, located in the basal layer, are also difficult to visualize in hematoxylin-eosin stained sections. They are identified by distinctive ultrastructural membrane-bound granules similar to those found in neuroendocrine tissues. The function of Merkel cells is not understood.

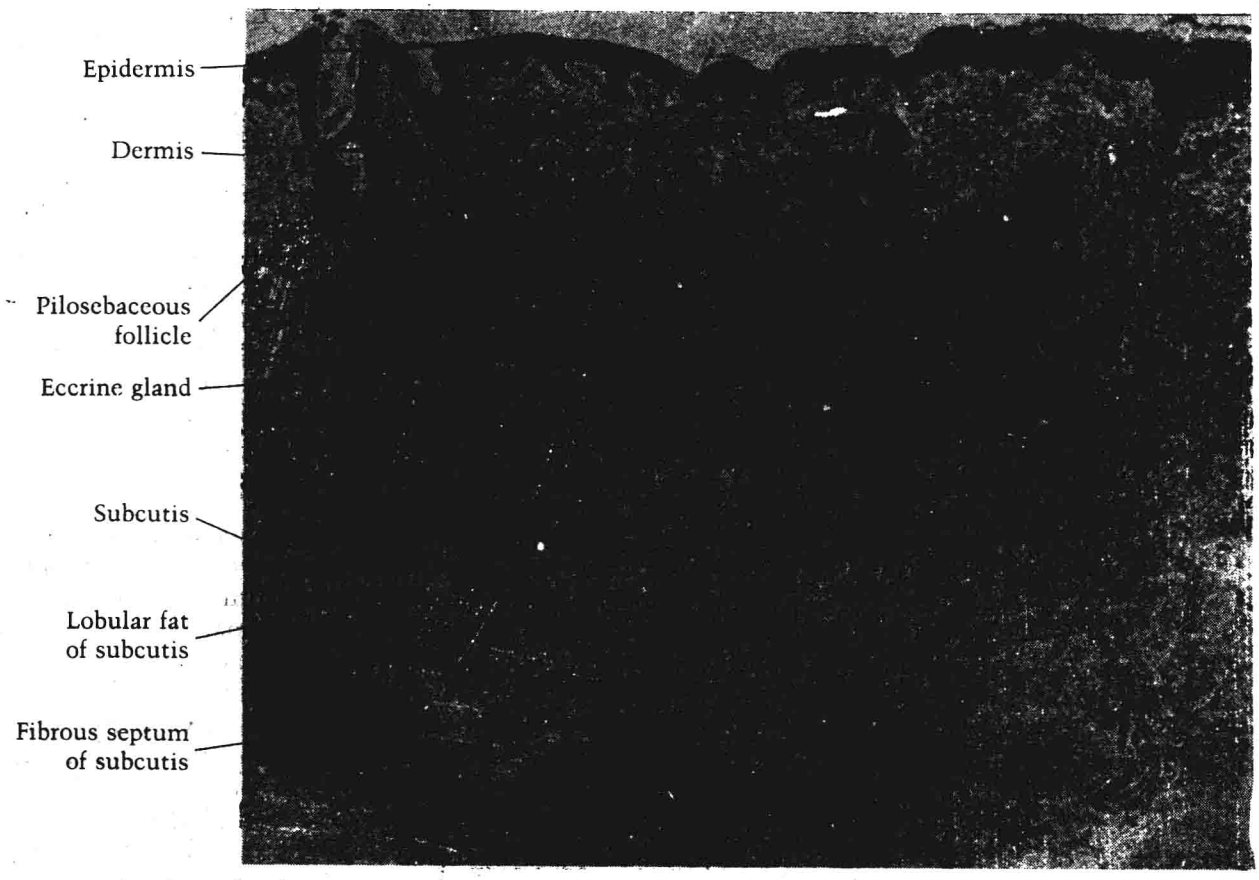

Fig. 1-1. *The skin. The three anatomic layers of the skin are the epidermis, dermis, and subcutis. The epidermal appendages, including pilosebaceous follicles and eccrine glands, extend into the dermis. The subcutis is subdivided into lobular and septal areas. (approximately ×64)*

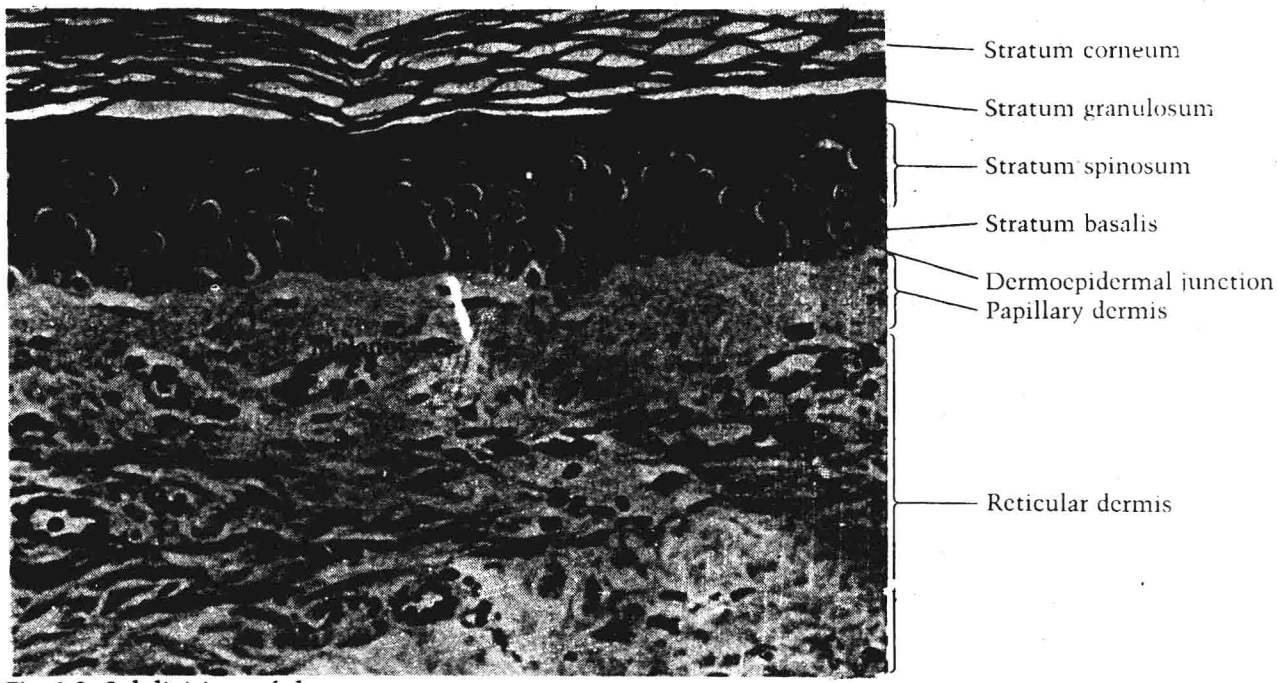

Fig. 1-2. *Subdivisions of the epidermis and dermis. (×256)*

Dermoepidermal Junction

The dermoepidermal junction in hematoxylin-eosin stained sections appears as a fine (1–2 μm) band of slightly condensed eosinophilic material (Fig. 1-2). This basement membrane zone consists of a glycoprotein matrix in which are embedded collagen, reticulin, and elastic fibers. Periodic acid Schiff (PAS) stain highlights this area. The basement membrane zone continues around all the epidermal appendages.

The lower border of the epidermis on most parts of the body has numerous undulating downward projections called *rete ridges* (when seen in three dimensions, these form a netlike, or rete, pattern). The corresponding and interdigitating upward elevations of the dermis are called *dermal papillae.*

Dermis

The dermis is divided into two parts: a thin superficial portion known as the *papillary dermis* and a wider, deep area known as the *reticular dermis* (Fig. 1-2). Both the papillary and reticular dermis contain collagen, reticulin, and elastic fibers embedded within a matrix of glycoproteins. Collagen, the major component of the dermis, is readily visualized in hematoxylin-eosin stained sections as eosinophilic fibers of regular diameter which are gathered into bundles of varying size. Collagen fibers are birefringent in polarized light. Reticulin fibers are small, possibly young, collagen fibers and are best visualized with special reticulin stains. Elastic fibers are wavy, eosinophilic, and slightly refractile, and they vary markedly in their diameter and length. They are easily visualized with stains such as the Verhoeff–van Giesen. The glycoprotein matrix of the dermis cannot be visualized in hematoxylin-eosin stained sections. In certain pathologic states characterized by excessive production of acid mucopolysaccharides, these materials can be identified by alcian blue stain.

The papillary dermis is recognized microscopically as a thin (40–100 μm) zone of connective tissue located below the dermoepidermal junction and above the reticular dermis. The small collagen bundles of the papillary dermis are easily distinguished from the larger collagen bundles of the reticular dermis. The papillary dermis surrounds all the appendageal structures as they plunge downward into the dermis and subcutis. This periadnexal papillary dermis is called the *adventitial* (outermost) *dermis.*

The reticular (netlike) dermis is easily distinguished from the papillary dermis by the presence of large (12–25 μm) collagen bundles. These bundles, which appear to be oriented in every possible plane, are mingled with reticulin and elastic fibers to form a closely knit net.

Subcutis

The subcutis (panniculus adiposus, subcutaneous fat) is composed of lobules of lipocytes separated by fibrous connective-tissue septa. The thickness of the subcutis varies with the sex and nutritional status of the individual and with anatomic location. Vessels, nerves, and appendages pass into and through the subcutis. Below the subcutis, muscle and/or fascia can be found.

Vessels: Arteriovenous and Lymphatic

The arteriovenous framework of the skin can be visualized as follows. Arteries traverse the septa of the subcutis and form a *deep plexus* in the region of the junction of the subcutis and dermis. From this deep plexus, smaller arteries pass upward to the junction of the reticular and papillary dermis, where they form the *superficial plexus.* From these arterioles, capillary-venules form superficial vascular loops, which ascend into and descend from the dermal papillae. Capillary-venules are so named because the flow of blood may be arterial to venous or vice versa. The venous return in the skin follows a reverse, and frequently more variable, course. The arteriovenous system of the skin, therefore, consists of deep and superficial plexuses with communicating vessels and, most distally, capillary venular loops (Fig. 1-3).

Given this framework, note that considerable regional variation exists with regard to the density and caliber of these vessels. Furthermore, there are numerous arteriovenous shunts, particularly on distal extremities. These arteriovenous shunts are controlled by *glomus cells,* abundantly innervated by adrenergic fibers. Glomus cells are

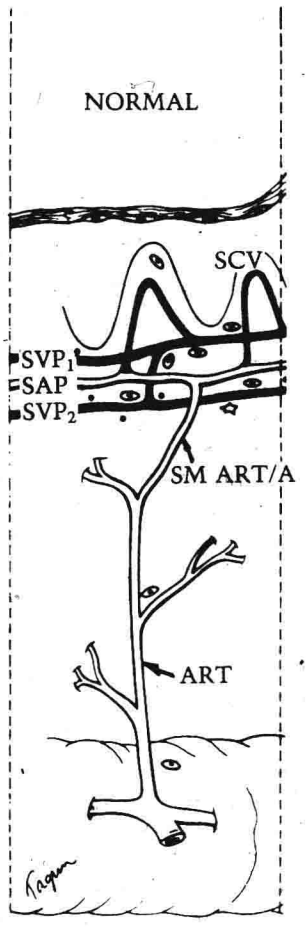

Fig. **1-3.** *Arteriovenous system. ART, artery; SM ART/A, small artery/arteriole; SAP, superficial arterial plexus; SCV, superficial capillary venule; SVP_1 and SVP_2, components of superficial venular plexus. (Reprinted with permission from M. C. Mihm., et al.,* J. Invest. Dermatol. *67:306, 1976. Copyright © 1976, The Williams & Wilkins Co., Baltimore.)*

recognized by their round nuclei, polygonal shape, and tendency to group around vessels (Fig. 1-4).

The microscopic structure of cutaneous vessels is similar to that of visceral vessels. Surrounding a lumen, endothelial cells rest on a PAS-positive basement membrane zone, which in turn is surrounded by smooth muscle cells, pericytes, and/or connective tissue. The latter layers vary with the size and type of vessel.

Mast cells in varying numbers (up to five per sectioned vessel) are present almost always about superficial vessels and to a lesser extent throughout the dermis. In hematoxylin-eosin stained sections, mast cells have densely basophilic nuclei and opaque, violet cytoplasm. Their characteristic and identifying cytoplasmic granules are metachromatic blue-purple when stained with Giemsa.

The lymphatics of the skin consist of a blind-ended vascular system that flows from the superficial dermis to the subcutis and then more centrally. The most distal tributaries in the papillary dermis are lined by endothelial cells without a basal lamina. The thicker-walled, more proximal portions of the system contain valves. Thin walls and valves are the features that distinguish lymphatics from other vessels. Probably because they are collapsed, lymphatic channels are observed infrequently in the skin of normal individuals.

Nerves

The cutaneous nerves comprise a system of nerve plexuses and branches that roughly parallels the vascular system. Cutaneous nerves function in sensory (afferent) and autonomic (efferent) modes. Sensory impulses, generated from encapsulated (Meissner and Vater-Pacini corpuscles) and nonencapsulated ("end organs" ramifying about hair follicles and in dermal papillae and ending in Merkel cell–neurite complexes) receptors, pass to the dorsal root ganglia and centrally. By a presumed process of summation and integration there is perception of particular sensations described as touch, pressure, temperature, pain, itch, and location. Motor impulses, which in the skin are autonomic, originate in the sympathetic nervous system and pass to glomus bodies and smooth muscles of vessels (affecting peripheral flow), to hair follicle–associated smooth muscle (causing gooseflesh), and to apocrine and eccrine glands (causing sweating).

In hematoxylin-eosin stained sections, sensory fibers cannot be distinguished from autonomic fibers, and one appreciates little more than small nerve branches and Meissner and Vater-Pacini corpuscles. Nerve branches have the same structure as elsewhere in the peripheral nervous system. Larger nerves of the subcutis exhibit epineurium, perineurium, and endoneurium (Fig. 1-5). Small nerve branches in the superficial dermis lack these layers. Individual nerve fibers with Schwann cells measure 3 to 5 μm in diameter. The small size of these fibers helps one to distinguish them from smooth muscle. Meissner corpuscles are said to play a role in mediation of the sensation of touch. Located in the dermal papillae, each of these encapsulated ellipsoid structures (20–50 μm) has the appearance of string wound about a spindle (Fig. 1-6). The Vater-Pacini corpuscles, which mediate the sensation of pressure, are located in the subcutis, each appearing as a large (up to 1 mm) oval encapsulated body with a distinctive internal structure of concentric lamellae (Fig. 1-7). Vater-Pacini bodies are most numerous on the palms and soles.

Special stains are necessary to demonstrate nonencapsulated receptors and autonomic innervation.

Fig. **1-4.** *Glomus body. Numerous glomus cells surround arteriovenous anastomoses. Glomus bodies are numerous in nailfolds, toes, fingerpads, and the pinnae. (×256)*

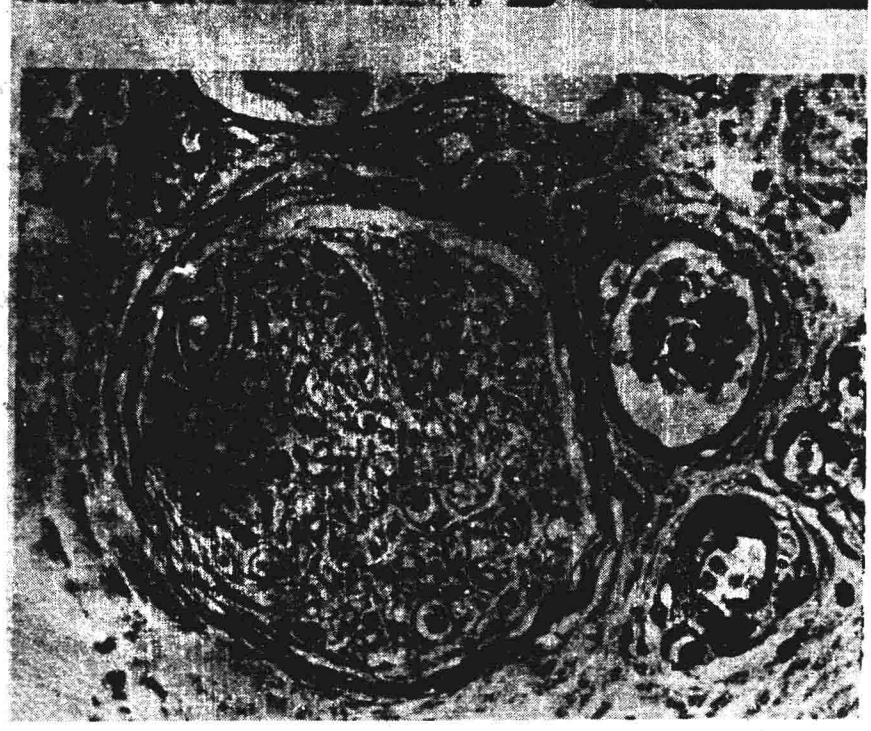

Fig. **1-5.** *Peripheral nerve. A thin fibrous capsule, the perineurium, surrounds the bundle of myelinated nerve axons.* **Endoneurium** *refers to the delicate collagen fibers surrounding nerve trunks within the perineurium. Schwann cell nuclei can be identified, but nerve axons are difficult to visualize. Two capillaries also are present in this field. (×640)*

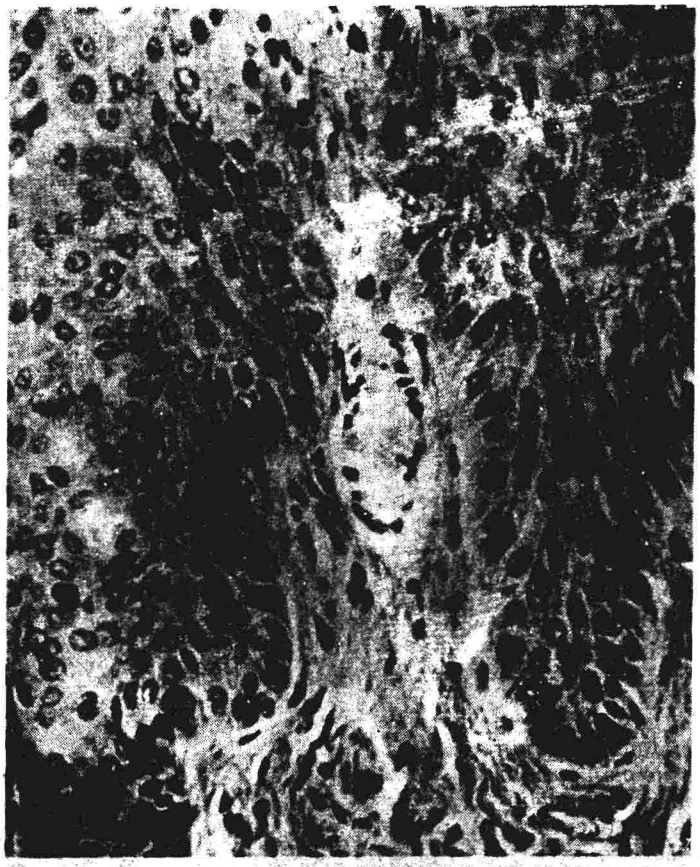

Fig. **1-6.** *Meissner corpuscle. Tucked within the dermal papilla, this neuroreceptor resembles a ball of string wound about a spindle. Portions of an intraepidermal eccrine duct are present at left. (×400)*

Fig. **1-7.** *Pacinian corpuscles. The rounded forms of these concentric lamellated structures in the subcutis are characteristic. (×64)*