SIXTH EDITION

1197 Illustrations

ANDREWS'
DISEASES OF THE SKIN

CLINICAL DERMATOLOGY

BY

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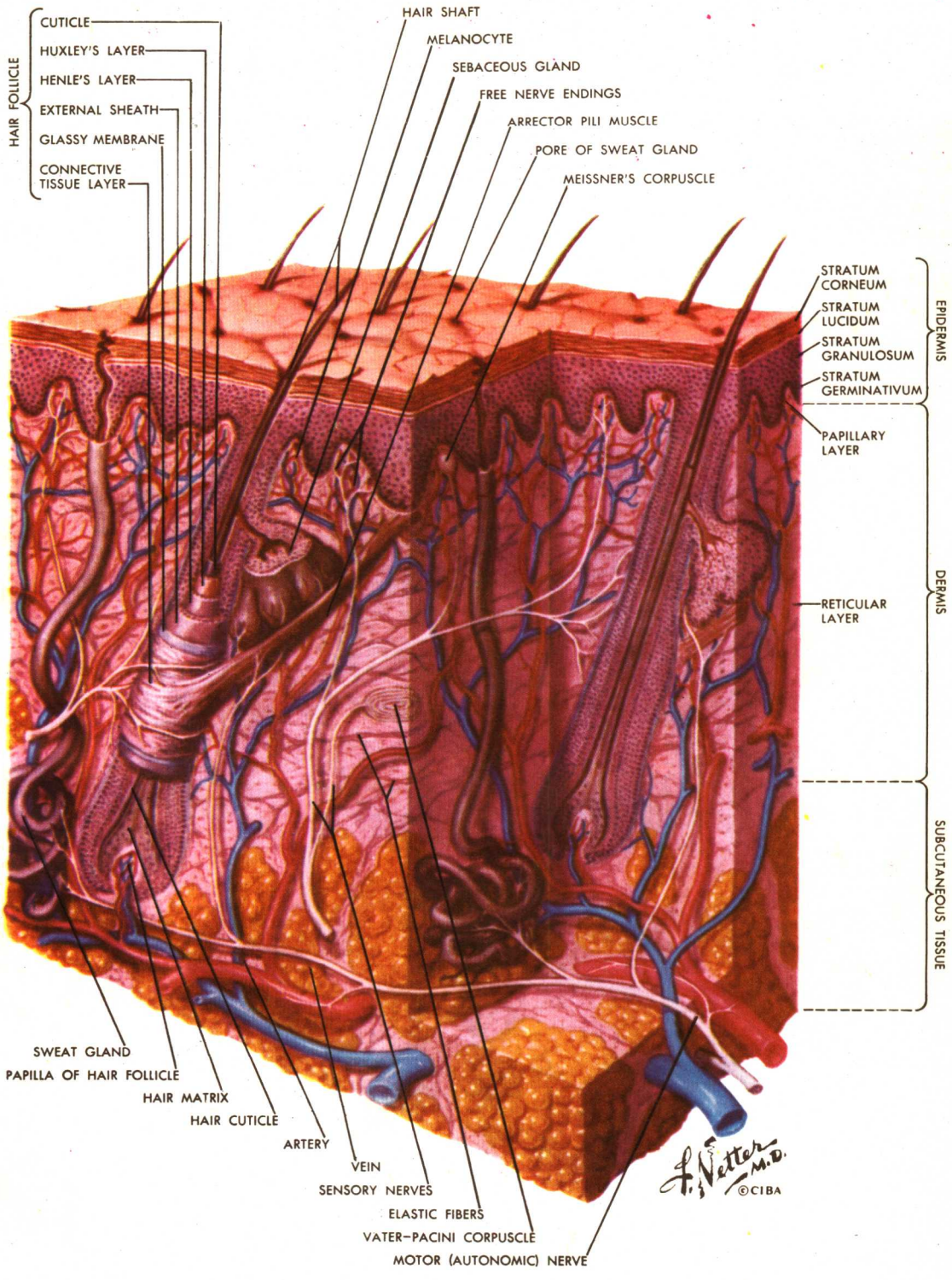
HAIR FOLLICLE
CUTICLE
HUXLEY'S LAYER
HENLE'S LAYER
EXTERNAL SHEATH
GLASSY MEMBRANE
CONNECTIVE TISSUE LAYER
HAIR SHAFT
MELANOCYTE
SEBACEOUS GLAND
FREE NERVE ENDINGS
ARRECTOR PILI MUSCLE
PORE OF SWEAT GLAND
MEISSNER'S CORPUSCLE
STRATUM CORNEUM
STRATUM LUCIDUM
STRATUM GRANULOSUM
STRATUM GERMINATIVUM
EPIDERMIS
PAPILLARY LAYER
RETICULAR LAYER
DERMIS
SUBCUTANEOUS TISSUE
SWEAT GLAND
PAPILLA OF HAIR FOLLICLE
HAIR MATRIX
HAIR CUTICLE
ARTERY
VEIN
SENSORY NERVES
ELASTIC FIBERS
VATER–PACINI CORPUSCLE
MOTOR (AUTONOMIC) NERVE
F. Netter M.D.
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This edition is dedicated to

DOROTHY

the author's wife
whose enduring encouragement, patience
and help
have brought this text to fruition

PREFACE

This preface will begin on a personal note. Throughout preparation of this new edition, I have had the constant support, advice and encouragement of George Clinton Andrews, who for four editions of this work single-handedly carried on a scholarly text of broad scope and meticulous detail. He entrusted its coauthorship to me in its fifth edition and now has reposed in me primary responsibility for this revision and future editions of Diseases of the Skin. I hope that I have been able to discharge effectively the obligation he always felt toward highest accuracy and clinical authority.

This Sixth Edition has been completely rewritten and expanded, with the purpose of constructing a comprehensive text on clinical dermatology. The text, on a larger page format, has increased from 658 to 968 pages, and the number of illustrations from 605 to 1197. Of these, 899 have not appeared in previous editions. Over 250 new dermatologic entities have been added, to make a total of some 1400 diseases of the skin described in this text. The references have been brought completely up to date so that most fall within this past decade. Every attempt was made to maintain the detailed index of previous editions. The index contains nearly 8000 entries.

Most of the dermatologic diseases know no national or hemispheric boundaries. Because of today's increased and rapid international travel, the physician may be confronted with some exotic disease such as tungiasis not only in Equatorial Africa but also in New York City or in Marshfield, Wisconsin. For this reason the chapters on diseases due to animal parasites, hanseniasis and other diseases are now more detailed, and modern treatment methods are emphasized. Today we are concerned with "global dermatology." Moreover, every effort was made to present a comprehensive coverage of clinical dermatology so that the text would be as useful in Timbuktu as in New York City and still remain within the confines of a thousand pages.

The resurgence of syphilis has necessitated the expansion of the chapter on lues. Detailed description of its many clinical forms, the newer serologic tests and the latest treatment have been included.

The chapter on dermatoses due to physical causes has been completely reorganized and is presented in a more concise manner. The chapter on contact dermatitis and eczema has also been completely reorganized to facilitate diagnosis not only by tests but also through more specific clinical descriptions.

Mr. Carl Braestrup has thoroughly revised and brought up to date the chapter on

x-ray physics in dermatology. This chapter and the one on ionizing radiation therapy are again included in this edition so that this useful treatment modality may be used in its proper perspective in modern day therapeutics.

These and many other additions to the text have been supplemented by a comprehensive reference list at the end of each chapter. All references have been carefully chosen as to most recent publication and as to pertinence to the specific subject.

The increased number of illustrations should greatly facilitate diagnosis. The black and white illustrations have been chosen for their clarity and for their ability to depict the inherent changes of a particular dermatosis. For many diseases, not one but several illustrations are used to show slight nuances of diagnostic significance.

The saying, "A good picture is worth ten thousand words," is nowhere more true than in dermatology. It is hoped that the illustrations, many of which have been furnished by our many friends throughout the world, will assist accurate diagnosis of most all dermatoses that may be encountered. In addition to the many excellent photographs contributed by our friends, some are from our private practice and from the Dermatology Department at the Columbia Presbyterian Medical Center, where Mr. William Kramer and Mrs. Ida Nathan produced many of the excellent illustrations for this edition. We are grateful to all.

We also acknowledge with thanks the color frontispiece by Dr. Frank Netter, furnished to us by the Ciba Company from the Ciba Collection of Medical Illustrations.

Throughout the revision of this text many of our friends have sustained us with help and advice in numerous ways. Dr. Sam F. Rosen has again helped in the preparation of this edition as he has in all of the previous editions. Dr. Carl T. Nelson helped in formulating the broad outlines of the text. Special thanks are due for his forbearance in making it possible for the author to devote more time to the preparation of this edition. Drs. Helen and William Curth have made many valuable suggestions and also have helped in reading and correcting galley proofs. Dr. Richard Walzer prepared the new chapter on dermatologic immunology. Dr. Lewis Shapiro made helpful suggestions for the chapter on general anatomy and pathology as well as on other matters concerning histopathology.

Dr. Leonard Harber has given much help in the preparation of the sections on photosensitivity and the porphyrias. Dr. Roger Williams made many important suggestions and corrections in the chapter on diseases due to animal parasites. Dr. Louis Suarez helped with the revision of the discussion of nail diseases. Dr. Leo Schweich helped with the chapter on lupus erythematosus. Dr. Joseph Penner has read all the galley proofs and helped in many phases. We are extremely grateful to all.

The author is also indebted and thankful to Drs. William G. Atwood, Irwin M. Braverman, Charles P. De Feo, Jr., Jack Eisert, Theodore A. Labow, John T. McCarthy, Thomas W. Murrell, Jr., Frederick Reiss, Saul L. Sanders and Marguerita Silver-Hutner for the whole-hearted and enthusiastic help they gave in reading and correcting manuscripts and galley proofs.

Appreciation is expressed to our office staff for the whole-hearted support they have maintained throughout this venture. To Miss Judi Miller and Mrs. Anthony Bustamente special commendation is in order for the excellent work they performed in the typing of the manuscript and index.

By far the most importantly involved person concerned with the preparation of this edition has been Dorothy, my wife, who has devoted her full energies to reading manuscript, suggesting alterations and encouraging continued work even at the time of our greatest personal tragedy. Without her sustained efforts, this edition would not have come to fruition.

To our publishers, the W. B. Saunders Company, we wish to express our gratitude for their wonderful cooperation and endless patience in the preparation of this edition. It would not be amiss to single out and to thank especially Mrs. Charlotte Brick, Mr. Robert B. Rowan, Mr. Albert J. Beringer and Mr. Sam Mink for their gracious and deep involvement in this project.

ANTHONY N. DOMONKOS

CONTENTS

1

CUTANEOUS STRUCTURE AND PATHOLOGY

ANATOMY

The integument is an integral part of the body organism and also has special, independent functions. It is a complex, elastic, fibrous structure that encases all the living tissues and organs of the body. Through the connective tissue, with its numerous blood vessels, nerves and lymphatics, the skin is in close relation with the viscera beneath. It protects these organs by covering them, and by serving as an information station, which enables the organs to adjust to changes in the outer environment. The skin is a barrier against dehydration; it can lower body temperature by the increased evaporation of sweat; it synthesizes keratin, a flexible, durable and resistant protein.

Spread over the integument is a greasy mixture of sebum, sweat, exfoliated epidermal cells and various additives from external sources. This surface film contains amino acids, urea, uric acid, lactic acid, ammonia, triglycerides, free fatty acids, wax alcohols, sterols, phospholipids, pentoses, complex polypeptides and other substances. These materials and the hydrogen ion concentration of this surface film act as defenses against infection, supply lubrication, work as buffering agents and influence hydration of the corneous cells.

The skin consists, in general, of three layers: the epidermis, the corium and the subcutaneous tissue. Their relative thickness and structure vary in the different regions of the body.

EPIDERMIS

Embryonal Epidermis

In the earliest days of fetal life, the epidermis is a single sheet of cells. It becomes a double layer between the fifth and seventh weeks, the periderm being the outer layer and the stratum germinativum being the inner layer. About the twelfth week an intermediate layer appears. Keratinization is seen at about the sixteenth week, and the intermediate layer multiplies itself to become the stratum malpighii. The embryonal stratum germinativum is responsible for the development of all epithelial structures, with the exception of melanocytes and other neural derivatives. This embryonal layer gives rise directly to the basal cell layer, to the eccrine sweat glands and to the primary epithelial germ cells. The latter give rise in turn to the sebaceous glands, to the apocrine sweat glands and to the hair follicles.

Adult Epidermis

The adult human epidermis is composed entirely of cells and has no interstitial supporting material. These cells are keratinocytes (malpighian cells), Langerhans' cells and melanocytes which are elaborated from

the neural crest. These types of genetically independent cells, having very different biologic and biochemical characteristics, nevertheless live in close association in the same tissue. Each maintains itself as a separate unit, not connected by fibers but simply in contact with nearby cells. Together with intraepidermal adnexal units, these cells form a living symbiosis that produces keratin and melanin and functions to protect the body.

Epidermal Layers

The epidermis (also called the cuticle or epithelial layer) is the outermost or surface part of the integument and is stratified squamous epithelium. It protects the more delicate underlying parts from trauma, from chemical irritation, from bacterial invasion and from other external factors. The epidermis may be divided conveniently into layers, beginning with the most exterior: the stratum corneum, or horny layer; the stratum lucidum, seen only on the palms and soles; the pars compacta; the stratum granulosum, or granular layer; the stratum malpighii, rete mucosum or prickle cell layer; and the stratum germinativum, or basal cell layer. Frequently the term stratum malpighii is used to denote both the basal cell and prickle cell layers. Although described in this order, the layers originate in the opposite sequence. The basal cell layer gives origin to all the others.

Study of the healing of surgical wounds and of mitoses in the skin of various animals has shown that mitoses take place throughout the prickle cell layer as well as in the basal cell layer, and that the majority of cells growing over a wound are derived from the prickle cell layer of the old epithelium. A basal cell layer is later formed by modification of these prickle cells. Also, in the healing of wounds, the cells of the outer root sheaths of the hair follicles and those of the sweat gland ducts may change into stratified squamous epithelium.

The appendages of the skin, which are the sebaceous glands, the hair follicles, the sweat glands and the nails are considered to be outgrowths of the epidermis.

The **stratum corneum** or horny layer is the outer or surface division of the epidermis; it is thickest on the palmar and plantar areas and thinnest on the eyelids, prepuce, cheeks, forehead, abdomen and flexor surfaces of the elbows. It is composed of dead epithelial cells that have become horny or keratinized. They are flattened, dry and nonnucleated, usually showing vacuoles. The periphery has become hardened and the

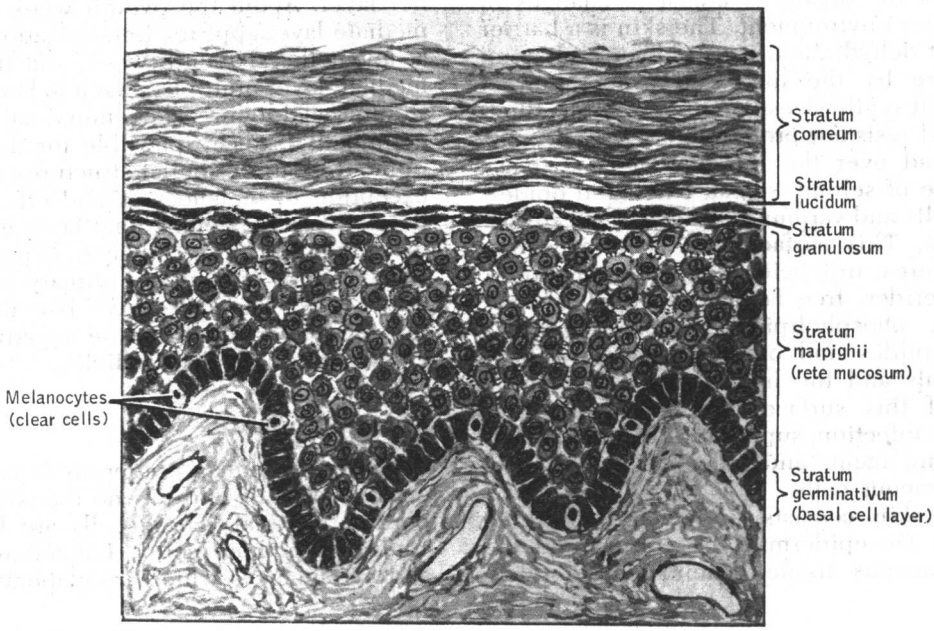

Figure 1-1. Diagrammatic illustration of epidermis. Highly magnified.

prickles have persisted as dried-up spicules of keratin. Cellular outlines are lost and are replaced by keratin. Next to the stratum lucidum there is more cellular structure.

The **stratum granulosum**, or keratohyaline layer, is directly beneath the pars compacta and is composed of one or several strata of flattened, coarsely granular cells, with shrunken protoplasmic fibers and with shriveled nuclei lying in spaces. The stratum granulosum varies in thickness and is most prominent on the palms and soles. The granules are elongated, irregular in shape and consist of keratohyalin. The granular layer is absent in mucous membranes except in the presence of such diseases as leukoplakia, in which keratinization takes place. There is every reason to believe that the granular layer performs an important task in keratinization, but is absent from the nail matrix.

The **stratum malpighii** (rete, squamous cell layer, prickle cell layer, stratum spinosum) is made up of a varying number of rows of polygonal keratinocytes, which are built up like a mosaic. The cells normally undergo mitosis and differ in size according to the thickness and turgescence of the particular region in the epidermis. The protoplasm is spongy, and the nucleus, lying in the center, is large and oval, rarely round. The cells are attached to one another by intercellular mooring granules, which occur at matching points on adjacent cells. These bridges are adherence points known as *desmosomes;* elsewhere the cell membranes are separated by an intercellular space. The basophilic cells of the rete show cytoplasmic fibrils known as *tonofibrils* and terminate in the desmosomes, also known as the *Bizzozero nodes*. The precursor of keratin is laid down in the form of wavy fibrils with branching processes that attach to the mooring granules. These polygonal cells tend to become flattened in the higher layers, and the spaces between them are narrower, and the prickles, though distinct, are shorter than in the deeper cells. The nuclei and protoplasm both remain stainable.

The basal cell layer (stratum germinativum) consists of three types of cells, the basal cell (keratinocyte), the Langerhans' cell and the melanocyte. It is the innermost layer of the epidermis and usually consists of a single row of vertically arranged, regular, columnar cells. These cells gradually undergo mitosis, their function being that of reproduction.

KERATINOCYTES

These cells are derived from the primordial malpighian layer and produce the fibrous protein keratin. This is the principal constituent of the epidermis, the hair, the nails and the organic matrix of tooth enamel. It has been demonstrated that the keratinocytes possess A and B blood group antigens and share with red blood cells the same antibodies that are absorbed selectively in some immune reactions.

The importance of vitamin A in the development of the keratinocyte has been demonstrated by tissue cultures of the ectoderm of the chick embryo. Epidermis normally contains little or no glycogen, but under certain circumstances glycogen may appear in rather large amounts. Fetal epidermis, with incomplete keratinization, has abundant glycogen. Glycogen is present in the outer root sheath of active hair follicles, and after injuries to the epidermis, the presence of glycogen may indicate an increase in the rate of cellular metabolism.

Each basal cell or keratinocyte has a dark-staining oval nucleus and a small amount of basophilic cytoplasm enclosed by an undulant nuclear membrane. These keratinocytes produce all the other cells of the stratified epidermis. They are stem cells (progenitors) and are capable of differentiation into other epidermal cells. These keratinizing cells are united at the desmosomes. The cytoplasm of the basal cells contains granular and rod-shaped *mitochondria* and the Golgi apparatus (bodies) present in all living cells. The bodies resemble erythrocytes with fuzzy edges and are piled up like stacks of poker chips. They appear to produce a vesiclelike substance that drifts to the cell border where it becomes a part of the cell membrane. Free ribosomes, endoplasmic reticulum, RNA particles and pinocytic particles are also found in the basal cell cytoplasm. Frequently melanin granules form a nuclear cap over the distal half of the nucleus. Basal cells normally become prickle cells, although both have "prickles."

The prickle cells, which are also keratinocytes, are usually larger than the basal cells and are polyhedral in shape. They tend to flatten in the upper layers.

The nucleus is round or oval. The cytoplasm is composed of two zones. The inner zone is scarcely visible in ordinary stains and contains several mitochondria and the Golgi

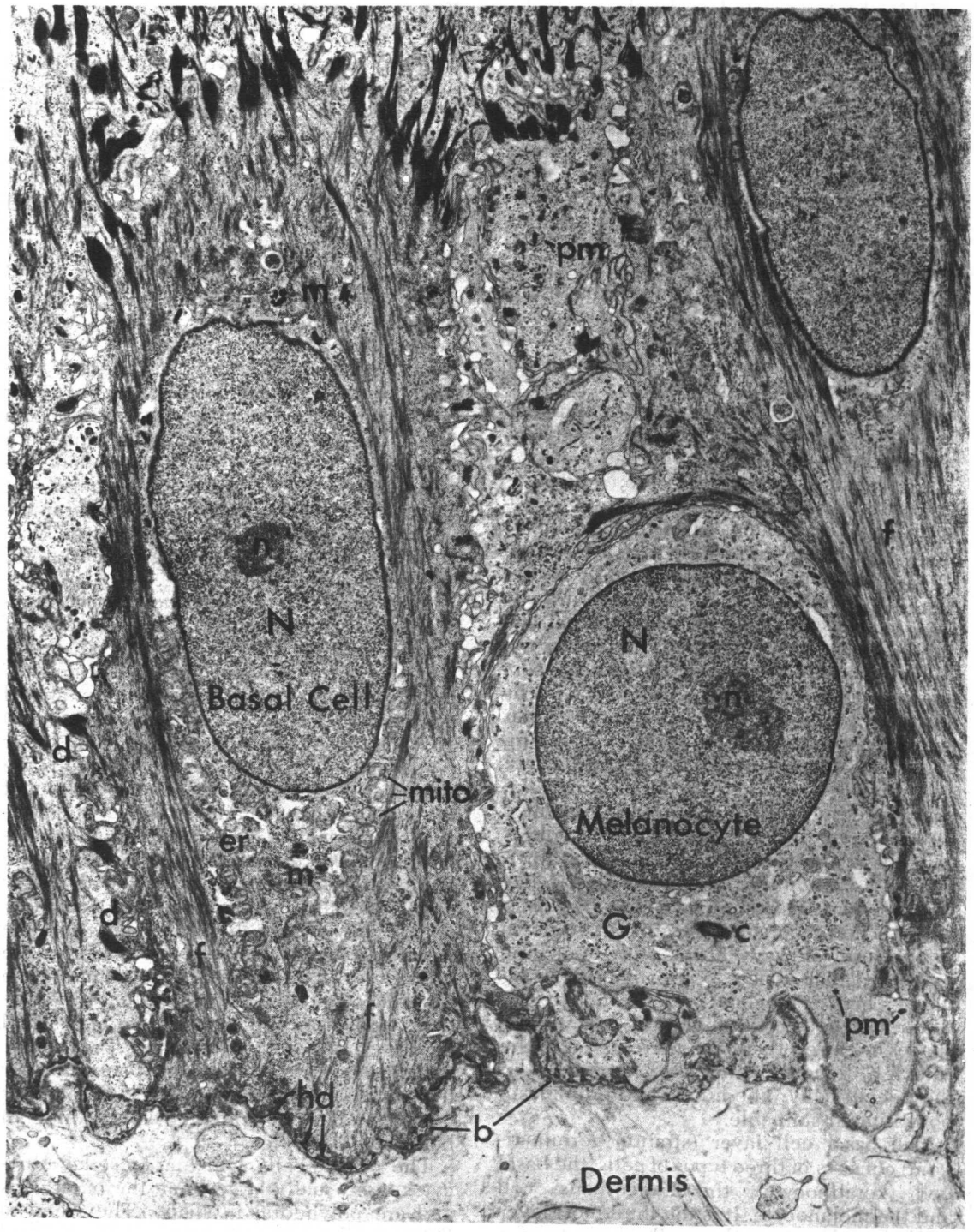

Figure 1-2. A pair of cells from the basal cell layer of human epidermis labeled basal cell (on the left) and melanocyte (on the right). (× 8300.) (Courtesy of Dr. G. F. Odland.) Labeled structures are as follows:

b basal lamina
c centriole
d desmosome
er rough endoplasmic reticulum
f tonofilaments
G Golgi vesicles and saccules
hd hemidesmosome
m melanosome
mito mitochondria
N nucleus
n nucleolus
pm premelanosome

net. The outer zone is denser and contains tonofibrils. These are fibrils that traverse the cell and tend to form a basketlike net around the nucleus.

Prickle cells and cells of the adnexa may revert to basal cells. This is illustrated in the healing of wounds, in which there is a normal transformation of one type of epidermal cell into another.

Keratinization. Various kinds of keratin are formed from the cytoplasmic filaments known as tonofibrils contained in the epidermal cells, starting in the basal cell layer and thereafter being transformed into keratin in the granular layer. There is a constant displacement of the cells from the basal cell layers to successively higher levels by the formation of new cells. Keratin is elaborated in the cytoplasm as it migrates toward the surface until the metabolically active cytoplasm is displaced. Bloom and Fawcett refer to this as *cytomorphosis.* Epidermal cell renewal in the human epidermis has been estimated by Epstein and Maibach to be 13 to 18 days. The desmosomes are altered structurally and undergo thickening.

Keratinization is closely related to the sulfhydryl content of the epidermis. In the malpighian layer, especially in the stratum germinativum, there is a concentration of sulfhydryl groups, seen particularly in the basal cytoplasmic processes, the intercellular bridges and the desmosomes. Sulfhydryl groups are also found in the stratum corneum. Keratin has a complex composition and is not a specific substance; the term may denote either a fibrous or an amorphous protein. In the past a soft and a hard protein were usually specified. Because of its vagueness the term "keratin" is now being abandoned.

Keratinization occurs in the differentiating basal cell, producing through orderly processes cytoplasmic fibrils, membrane coating granules, keratohyalin, a coated envelope of plasma membrane and a horny matrix. As water is lost, the horny matrix, rich in sulfur, is formed.

Melanocytes

These are derived from the neural crest and migrate to the epidermis through the mesenchyme during early embryonic life, coming to rest in the stratum germinativum. Here they assume a dendritic form and can be recognized as clear cells by the ordinary hematoxylin-eosin stain. The melanocytes reach the epidermis before the hair follicles form, and the growing hair follicles push some of these cells down with them. Melanocytes and Langerhans' cells are the dendritic cells in the epidermis. They multiply by mitosis, have no desmosomes and are located near the basement membrane of the epidermis. In transit to the epidermis some melanocytes remain in the dermis, where they have no known function.

The nucleus is bounded by a double nuclear membrane. A nucleolus is present, as well as endoplasmic reticulum, mitochondria in abundance, Golgi apparatus and pinocytic vesicles. The dendrites extend between the epidermal cells and play an important role in the transfer of pigment to keratinocytes. Mature melanin granules may be seen on many dendritic processes.

The formation of pigment granules is said to begin in the Golgi apparatus. The granules become elongated to form aggregates of fibrils on a matrix. This is the *premelanosome.* The deposition of melanin upon the premelanosome forms the *melanosome.*

Langerhans' Cells

Dendritic cells resembling melanocytes, found in the upper layers of the malpighian layer, were described by Langerhans. With the gold chloride staining method the cells are stained black and show slender processes, but they do not stain for melanin with dopa. This cell, as well as the melanocyte, lacks desmosomes. However, it contains lysosomes and lipid droplets. Linear structures with striations and rounded ends are found in the Langerhans' cells and are known as *Langerhans' cell granules.* These are distinctive and are not found in the melanocyte nor the keratinocyte.

Zelickson has suggested that the Langerhans' cell may be formed by the division of a melanocyte to produce either a melanocyte or a Langerhans' cell. Its functional significance remains obscure.

Indeterminate Cell

In addition to the melanocyte and Langerhans' cell, Zelickson has called attention to another epidermal dendritic cell, the indeterminate cell which occupies approximately 1 percent of the epidermis. These cells are located in the lowermost stratum of the epi-

dermis. No typical cytoplasmic organelles are present in these cells, a fact which differentiates them from the two other types of dendritic cells. Melanocytes contain melanosomes and Langerhans' cells contain the typical Langerhans' cell granules.

Zelickson suggests that the indeterminate cells represent a form of premelanocyte in which melanin synthesis can be induced, or it may be an effete melanocyte which is no longer active. Still another possibility is that of an undifferentiated cell that may give rise to either type of dendritic cell.

PIGMENTATION

The color of the skin is influenced by the amount of melanin pigmentation, by the degree of vascularity and by carotene. Pigmentation is the greatest in the areolae of the nipples, axillae, scrotum, around the anus, and in the hairs.

The pigment is chiefly melanin, which is found in sections as small yellowish granules of rather uniform size in the basal cells, mostly in the cytoplasm on the distal sides of the nuclei, as if protecting them from outside light. In persons who have a dark complexion the pigment is found also in the more superficial layers of the epidermis.

Melanogenesis occurs in the dendritic melanocytes that are located in the skin, namely in the basal cell layer and in the hair bulb. The formation of melanin granules in the melanocyte may be said to begin with the synthesis of tyrosinase on the ribosomes, from where the secretory product moves to the Golgi vesicle. Here the first stage of melanin granule development occurs with the formation of subunits that polymerize on an underlying structural unit to form the *premelanosome.* From here, in the presence of oxygen and tyrosinase, the tyrosine is converted into melanin. The presence of tyrosinase and melanin in one unit denotes the *melanosome.* It is believed that the actual site of melanin formation is the melanosome. When there is no longer any tyrosinase activity the unit becomes known as a melanosome.

Keratinocytes may contain melanosome complexes that are derived from the melanocytes. Pigment passes to the keratinocytes from the melanocyte by way of the dendritic processes, or by the direct introduction of melanin granules into the keratinocyte. When a melanocyte is surrounded by a number of keratinocytes the entire complex becomes an "epidermal melanin unit." The effect of sunlight on the skin is to produce proliferation of keratinocytes, which induces increased secretion of pigment granules from the melanocytes.

At the **dermoepidermal junction** there is a structure known as the *basement membrane.* This does not stain with hematoxylin-eosin, but does with periodic acid-Schiff (PAS stain), suggesting the presence of neutral polysaccharides. No epidermal or dermal mooring filaments are recognized to cross this membrane. One has to consider the basement membrane within the framework of each epidermal structure, for it is thickest where there is the greatest functional activity and shows in the vitreous membrane of the hair follicle, around the sweat glands and below the epidermis.

The nerve networks at the dermoepidermal junction have been beautifully demonstrated. There is a characteristic beaded appearance to the terminal rami. In some instances, according to Winkelmann, a terminal syncytium appears to be present. It has been proposed that this is a distinct nerve ending of one axon only.

DERMIS

The dermis, also known as the corium, derma or cutis vera, is a dense fibrous layer beneath the epidermis which gives strength and elasticity to the skin. It consists of connective tissue composed of two different fibers—the collagenous and elastic fibers.

The dermis contains and supports the blood vessels, lymph vessels, glandular structures, hair follicles, muscle elements, prolongations of the fatty tissue, and the nerves with terminal organs of touch and sensation.

PAPILLAE

The entire surface of the dermis is beset with numerous conical papillae. This stratum is called the *papillary layer* of the dermis, whereas the deep stratum is termed the *reticular layer.* The papillae, in which are terminal capillaries and sensory nerve endings, are fingerlike projections of the corium that dovetail with the overlying epidermis. They are arranged in rows of varying