Andrews'

DISEASES OF THE SKIN

CLINICAL DERMATOLOGY

Seventh Edition

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PREFACE

Eleven years ago, in 1970, Anthony N. Domonkos virtually rewrote Andrews' *Diseases of the Skin* for its sixth edition. Over four years ago, in 1977, he invited me to help him update it for this seventh edition. During these seven years he had been collecting new material and upgrading and adding illustrations. Andrews, who had taken no part in the preparation of the sixth edition in his retirement, died at his home in Florida in December, 1978.

Together, Domonkos and I had worked our way through Chapter 20, and the first 12 chapters had been set in type, when—on February 19, 1979—he succumbed unexpectedly to the latest exacerbation of the chronic illness that had plagued him for the past seven years.

It was a tragically premature end to a brilliant career. He was only 66. He had been elected president of the American Dermatological Association only ten months before, and in two more months he would have presided over its ninety-eighth annual meeting. More importantly, in another year or two he would have held in his hand the first copy of our new book.

In April, two months later, Colonel Richard B. Odom, Chief of Dermatology at Letterman Army Medical Center since 1973, agreed to join me in finishing the revision from Chapter 13 on. He participated so effectively that in June he was invited to be coauthor. The expertise he has brought to the project as director of a three-year residency training program has been invaluable.

Despite the many changes that have been made in Andrews' original text since its first edition in 1930, the book has been maintained through six editions as a compact, concise, single volume essentially single-authored, clinically oriented working text for desk-top rather than library use by students, interns and residents, internists, family practitioners, pediatricians, and indeed all physicians, including dermatologists. The increasing conciseness that reduced it from 1,091 pages in the first edition to 658 in the fifth has been maintained, though new diseases and new pictures expanded it to 1,027 pages in the sixth edition and almost 1,200 pages in this one.

Very few major changes have been made in this seventh edition. We would have liked to reorganize the text along more strictly etiologic lines, but this would have required considerable sacrifice of the strong clinical orientation that has always been one of the book's most appealing characteristics. Several disorders now believed by many to be variants of psoriasis were moved into the chapter on that disease. A few diseases now known to be caused by bacteria were moved into the appropriate chapter. The chapter on roentgen ray physics, written by Carl B. Braestrup in every previous edition, was reduced to a few paragraphs in the chapter on radiation therapy, in keeping with the greatly diminished importance of this subject in modern dermatologic practice.

Many new diseases have been added: transient acantholytic dermatosis; mucocutaneous lymph node syndrome; lymphomatoid papulosis and lymphomatoid granulomatosis; focal dermal hypoplasia; sinus histiocytosis with massive lymphadenopathy; trichothiodystrophy; and many others. Many diseases have been reclassified: melanomas, lipoproteinemias, ichthyoses, and disorders of elastic tissue, for example. Many new treatments and changes in the perceived usefulness or risks of old treatments will be found in this edition. A new view of the nature and pathogenesis of neurotic pruritus is presented. The considerable emphasis placed by Domonkos in the sixth edition on the relative safety of repository corticosteroids as compared with oral prednisone for prolonged systemic corticosteroid therapy has not been diminished.

What is said in the text is in large part what the best-informed dermatologists have said, in meetings or in published articles or books, during the past decade. Where it differs from that, which is not often, it reflects the experience of the authors.

The references at the ends of the chapters do not include most of those that appeared in the sixth edition, except for some that can be considered classic or that have not been superseded by more recent reports. Even most of those older references still referred to in the text have been regretfully deleted to save space. The reader who is frustrated by this can readily find them in the sixth edition, of course.

We trust that physicians in all specialties will find this updated and revised seventh edition as useful to them in their practice as its predecessors have been. Nearly every page has been revised, but the emphasis is still on problems of patient care. The opening chapter on the anatomy of the skin has been rewritten by a practicing clinician and dermatopathologist, Dr. David N. Silvers, Associate Clinical Professor of Dermatology and Pathology at Columbia University College of Physicians and Surgeons in New York. He also revised most of the descriptions of histopathology in the text.

We earnestly solicit from our readers any criticisms they have of what we have written to aid us in the next edition. We want to hear from you! We would also welcome illustrations wherever they are lacking or in need of improvement.

Our thanks are given to the many who helped: to our wives, Jeanne Arnold and Ann Odom, for their patience with our preoccupation with the revision; to the former, for listening to the whole book read aloud from page proofs while she held the galley proofs; to Colonel Detlef Klaus Goette, who made it possible for his chief to spend more time on the book; to Dr. Domonkos' daughter, Dita Altman, who helped her father in the photographic darkroom and was helpful in many other ways; to the scores of colleagues who generously shared their clinical photographs with us; to Dr. Samuel F. Rosen, who continued as with every previous edition to provide counsel and contribute ideas and material; to Dr. Domonkos' office staff, who retyped much material including some of the bibliographies; to our editor, Donald H. Abbott, at Saunders; and to George Vilk, who edited the manuscript and performed the herculean task of compiling that indispensable aid, the index.

HARRY L. ARNOLD, JR.
RICHARD B. ODOM

CONTENTS

1

The Skin: Basic Pathophysiology

DAVID N. SILVERS, M.D.

The skin is composed of three layers: **epidermis, dermis,** and **subcutis** or **panniculus** (Fig. 1–1). The epidermis, the outermost layer, is directly contiguous with the environment. It is formed by an ordered arrangement of cells called keratinocytes, whose basic function is to synthesize keratin, a filamentous protein which serves a protective function. The dermis is the middle layer. Its principal constituent is the fiberlike structural protein, collagen. The innermost layer of skin, the subcutis or panniculus, is composed of lobules of lipocytes or fat cells.

Inflammatory conditions of the skin principally affect one of the three skin layers. The clinical manifestations of psoriasis reflect an accelerated proliferation of keratinocytes. Keratinocytes are rapidly transformed into cornified cells, which accumulate on the surface as scale. Allergic reactions to ingested

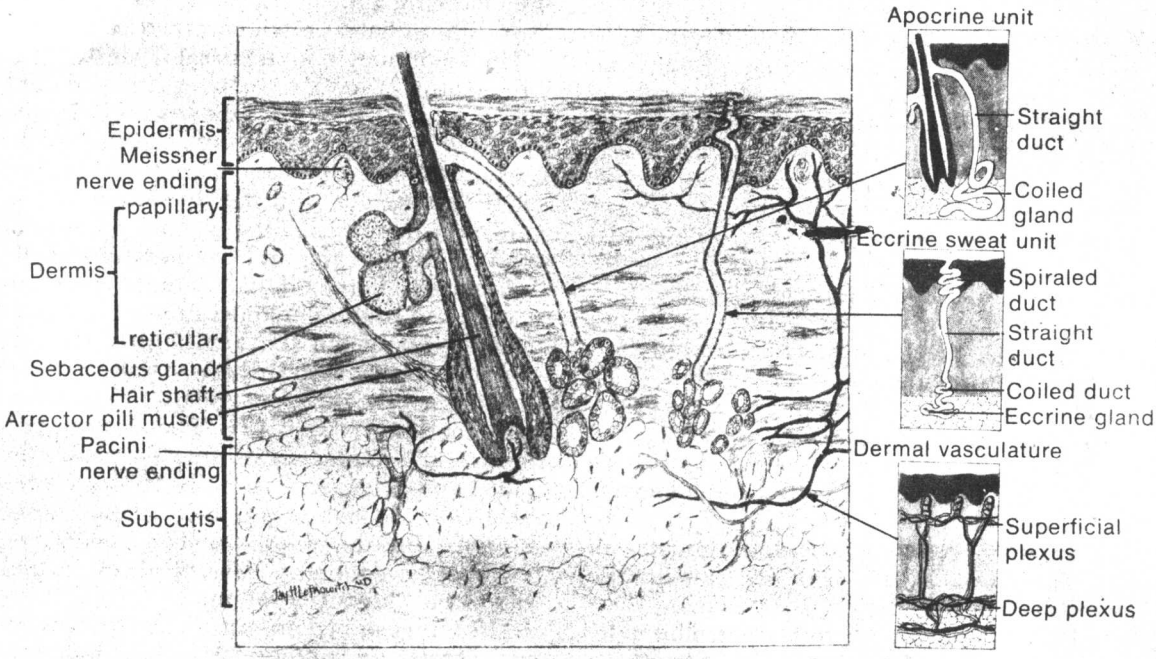

Figure 1–1 Cross section of the skin.

drugs may lead to inflammation in the dermis, by ectasia of blood vessels and the appearance of a variety of white blood cells, which percolate through the collagen bundles. A specific type of inflammation of the subcutaneous fat can result from the release of enzymes into the general circulation secondary to pancreatitis or pancreatic carcinoma. These enzymes lyse fat cells, resulting in the formation of a granulomatous reaction primarily involving the fat lobules.

Benign and malignant neoplasms of the skin, like their inflammatory counterparts, principally involve one of the three anatomic layers. They reflect autonomous proliferation of a specific cell type and are best illustrated when the specific cells of the skin are examined in detail.

All skin sites are composed of these three anatomically distinct layers, although there is considerable regional variation in their relative thickness. The epidermis is thickest on the palms and soles, measuring approximately 1.5 mm. It is very thin on the eyelids, where it measures less than 0.1 mm. The dermis is thickest on the back, where it is 30 to 40 times as thick as the overlying epidermis. The amount of subcutaneous fat is generous on the back and buttocks compared to the nose, where it is indeed meager.

EPIDERMIS

During the first weeks of fetal life, the epidermis consists of a single sheet of contiguous, undifferentiated cells, which subsequently assume the characteristics of keratinocytes. Adnexal structures, particularly pilar and eccrine sweat units, originate during the third month of fetal life as downgrowths from the developing epidermis. Later, apocrine sweat units develop from the upper portion of the follicular epithelium, and sebaceous glands and ducts from the midregion of the follicle. The development of adnexal structures at specific skin sites, like the regional variation in thickness of the three skin layers, is genetically modulated.

The adult epidermis is composed of three basic cell types: **keratinocytes, melanocytes,** and **Langerhans cells** (Fig. 1–2). Two additional types of cells, the **indeterminate cell** and the **Merkel cell,** can occasionally be found within the epidermis. However, their presence may be largely fortuitous. The indeterminate cell, so called because of its rather nondescript appearance, is identified within the epidermis in inflammatory dermatoses, and is probably a displaced lymphocyte which has migrated into the epidermis from the dermis. The Merkel cell, rarely found within the adult epidermis, contains intracytoplasmic neurosecretory-like granules, and, because of its association with terminal neurites, is thought to mediate the sensation of touch. Despite its direct connection to adjacent keratinocytes by desmosomes, specialized attachment plates characteristic of ectodermal-derived cells, Breathnach believes the Merkel cell to be of neural crest origin rather than of either ectodermal or mesenchymal origin.

THE KERATINOCYTE

The keratinocyte, or squamous cell, is the principal cell of the epidermis. It is a cell of ectodermal origin which has the specialized function of producing keratin, a complex filamentous protein that not only forms the surface coat (stratum corneum) of the epidermis but also is the structural protein of hair and nails.

The epidermis may be divided into the following zones beginning with the innermost layer: **basal layer, malpighian** or **prickle layer, granular layer,** and **horny layer,** or **stratum corneum** (Fig. 1–3). These names reflect the changing appearance of the keratinocyte as it differentiates into a cornified cell.

The keratinocyte in the basal layer divides. One daughter cell remains as a so-called "basal cell." The other daughter cell moves in a stepwise fashion through the full thickness of the epidermis and changes as it does so. It flattens out, and the nuclear:cytoplasmic ratio increases. Finally, the nucleus of the cell disappears, and the keratinocyte is then called a horn cell. Just as there is regional variation in the thickness of the three anatomic layers of the skin (epidermis, dermis, and subcutis) so also is there variation in the thickness of the different zones of the epidermis according to skin site. The stratum corneum and granular layers are thickest on the palms and soles, and virtually absent on the more delicate skin of the flexor aspect of the forearms and the abdomen. The basal layer, however, is generally one cell thick regardless of the skin site examined.

The process of keratinization remains incompletely understood. Matoltsy has sug-

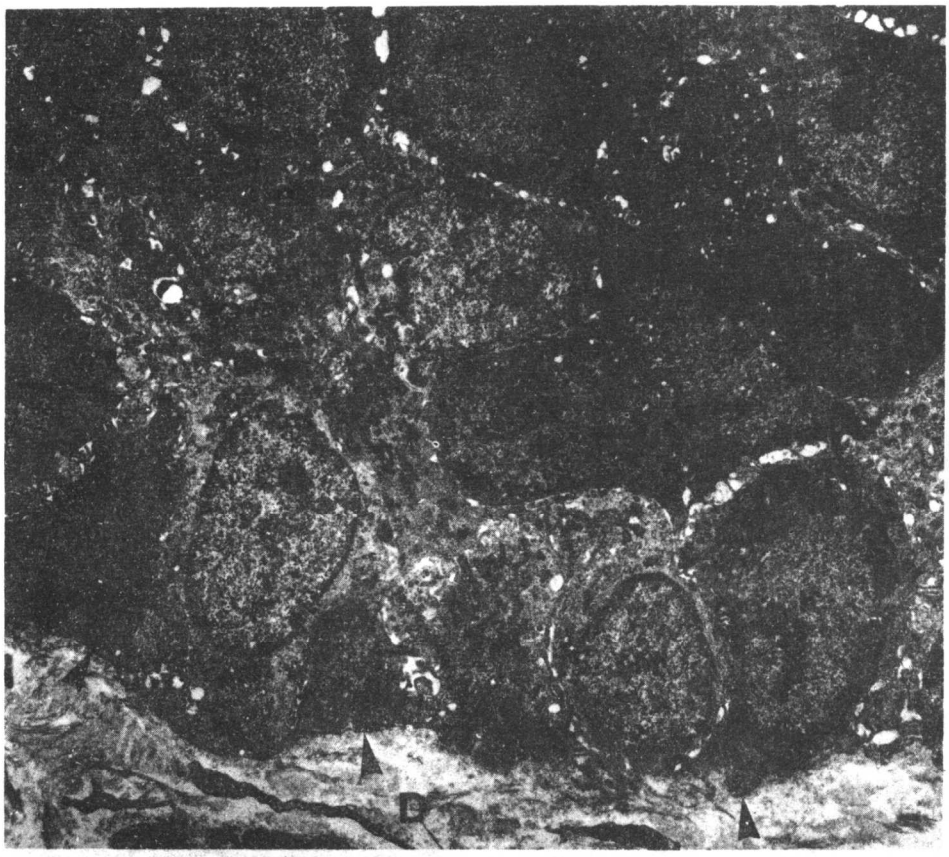

Figure 1–2 Electronmicrograph illustrating the ultrastructural appearance of the three basic cell types of the epidermis and their relationship to one another. The majority of cells are keratinocytes, some of which are labeled (K). Langerhans cells (L) with their characteristic cribriform nuclei are distributed among keratinocytes in the stratum malpighii. Melanocytes (M) are located in the basal layer of the epidermis, which is separated from the dermis (D) by the basement membrane zone (arrows).

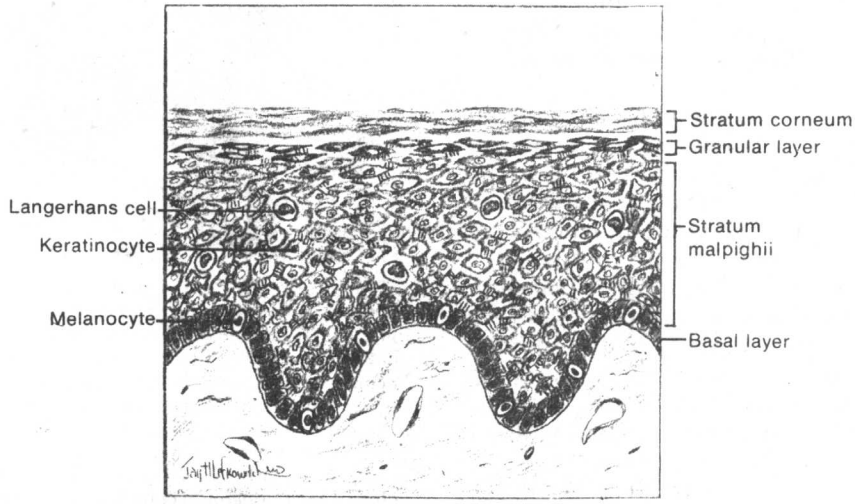

Figure 1–3 The zones of the epidermis.

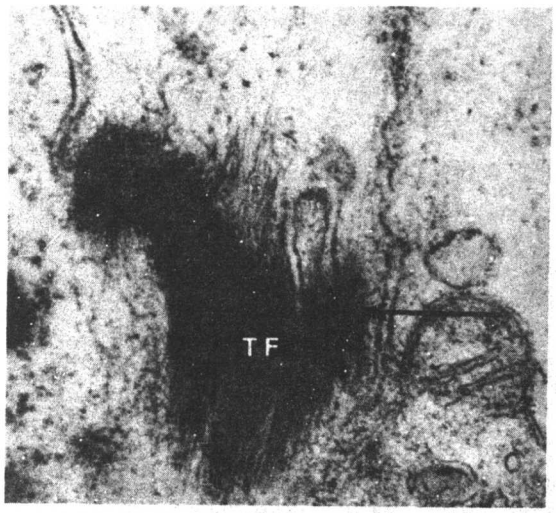

Figure 1–4 Ultrastructural appearance of the desmosome (arrow), the specialized attachment plate between adjacent keratinocytes. Tonofilaments (TF) within the cytoplasm of adjacent keratinocytes converge on the plasma membrane of each cell, where they condense to form an electron-dense zone.

gested that the keratinocyte passes through first a synthetic and then a degradative phase on its way to becoming a horn cell. In the synthetic phase, the keratinocyte accumulates within its cytoplasm filaments composed of a fibrous protein arranged in an alpha-helical pattern. These **tonofilaments** are fashioned into bundles, which converge upon and terminate at the plasma membrane, where they form specialized attachment plates called **desmosomes** (Fig. 1–4). The plasma membranes of adjacent cells are separated by an intercellular space. Electron-microscopic histochemical studies have shown that this interspace contains glycoproteins, which are thought to contribute to cellular cohesion.

Keratinocytes of the granular zone contain, in addition to the filament system, **keratohyaline granules,** composed of amorphous particulate material of high sulfur-protein content. The relationship between tonofilaments and keratohyaline granules is poorly understood. Lamellated organelles called **keratinosomes** are found intracellularly in upper-level keratinocytes and extracellularly at the junction of the granular and horny layers. Their appearance extracellularly coincides with the degradative phase of keratinization, which is characterized by the disappearance of cell organelles and the consolidation of all contents into a mixture of filaments and amorphous materials enveloped by a thickened cell membrane (horn cell of the stratum corneum) (Fig. 1–5).

A variety of skin diseases are manifestations of abnormal keratinization. Psoriasis is characterized by an abnormally rapid transformation of basal cells into horn cells. Instead of the normal so-called transit time of 14 days, it may take only three or four days for a basal cell to become a horn cell. Loss of cohesion of keratinocytes results in the bullous lesions of pemphigus. Desmosomal attachments between keratinocytes are disrupted (acantholysis) and the cells round up and separate from one another. This pathologic process is associated with the presence of circulating antibodies directed at the intercellular space.

THE MELANOCYTE

The melanocyte is the pigment-producing cell of the epidermis. It is derived from the neural crest, and by the eighth week of devel-

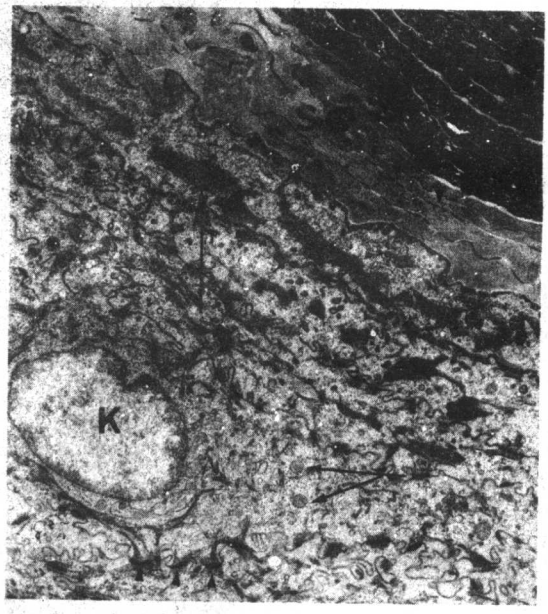

Figure 1–5 The upper portion of the epidermis is illustrated. Keratinocytes (K) are flatter in appearance than those of the lower portion (see Fig. 1–2) and contain keratinosomes (thin arrows). Desmosomes (short arrows) become more obvious as the nuclear/cytoplasmic ratio of the keratinocyte increases. Keratinocytes of the granular layer contain keratohyaline granules (broad, long arrow). The stratum corneum (SC) is composed of horny cells which retain only filaments and amorphous material enveloped by a thickened cell membrane. Horny cells, like other keratinocytes, are connected to one another by desmosomes (short arrows).

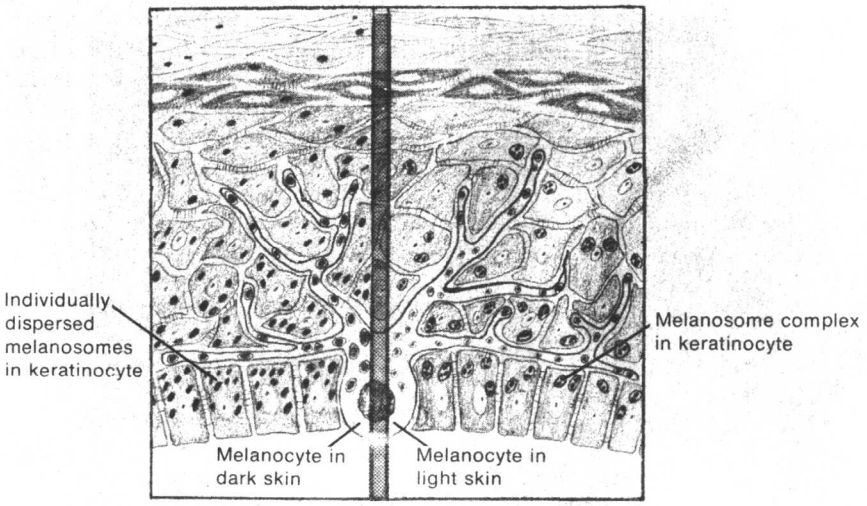

Figure 1–6 The epidermal-melanin unit in light and dark skin.

opment can be found within the fetal epidermis. In normal adult epidermis, melanocytes reside in the basal layer at a frequency of approximately one for every 10 basal keratinocytes. The number of melanocytes in the epidermis is the same regardless of race or color; rather, it is the number and size of the **melanosomes** or pigment granules, continuously synthesized by these melanocytes, which determine racial differences in skin color (Fig. 1–6).

In histologic sections of skin routinely stained by hematoxylin and eosin the melanocyte appears as a "clear" cell in the basal layer of the epidermis. The apparent "halo" is an artefact caused by separation of the melanocyte from adjacent keratinocytes during fixation of the specimen. This occurs because the melanocyte, lacking tonofilaments, cannot form desmosomal attachments with keratinocytes.

The melanocyte is actually a dendritic cell, a feature rarely appreciated at the light microscope level. Ultrastructural and tissue culture studies have demonstrated the octopus-like appearance of the melanocyte. Its dendrites extend for long distances within the epidermis, and any one melanocyte is therefore in contact with a great number of keratinocytes; together they form the so-called **epidermal-melanin unit.**

Although the melanocyte is the pigment factory for the skin, **melanosomes** synthesized there are continuously transferred to adjacent keratinocytes, which serve as reservoirs for pigment in the skin. Melanosomes are synthesized in the Golgi zone of the cell and pass through a series of stages in which the enzyme tyrosinase acts upon melanin precursors to produce the densely pigmented granules. While this is occurring, the melanosome migrates to the tip of a dendrite, where it is transferred to an adjacent keratinocyte by apocopation, a phenomenon in which the keratinocyte phagocytoses the dendrite of the melanocyte.

Melanocytes of dark skin synthesize melanosomes larger than those produced in light skin. The size of the melanosome is the principal factor in determining how the melanosomes will be distributed within the keratinocytes. The larger melanosomes of dark skin are individually dispersed within the cytoplasm of keratinocytes; smaller melanosomes of light skin are packaged in membrane-bound complexes within the keratinocyte (Figs. 1–7 and 1–8). Chronic sun exposure can "trick" the melanocyte into producing larger melanosomes, thereby making the distribution of melanosomes within keratinocytes resemble the pattern seen in dark-skinned individuals.

Areas of leukoderma or "whitening" of skin can be caused by very different phenomena. In **vitiligo,** the affected skin becomes white because of destruction of melanocytes, leading to decrease in their number. This may be temporary or permanent. In **albinism,** the number of melanocytes is normal. However, they are unable to synthesize fully pigmented melanosomes. In the former case, the pigment factory has disappeared; in the lat-

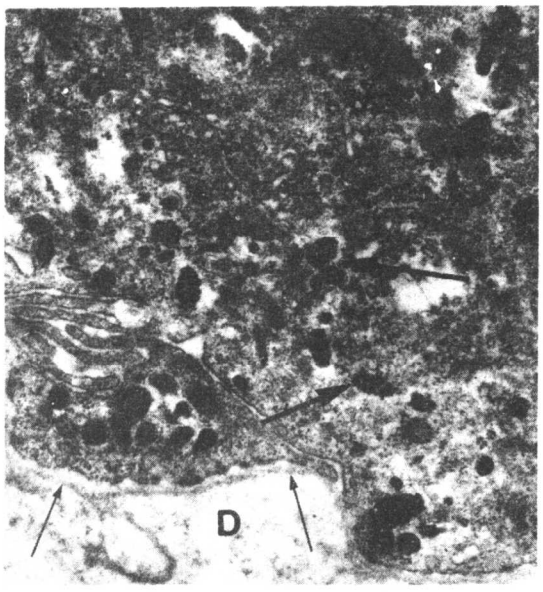

Figure 1–7 Portion of a melanocyte from dark skin illustrating melanosomes (broad arrows) at various stages of development. Basement membrane zone (thin arrows) and dermis (D) are also shown.

ter, the tools for pigment synthesis are faulty.

Local areas of increased pigmentation can be due to a variety of causes. The typical freckle is due to a localized increased production of pigment by a normal number of melanocytes. Nevi are benign proliferations of melanocytes. Melanomas are their malignant counterpart. Frequently, though, skin lesions are not pigmented because of hyperplasia or hyperactivity of melanocytes. Rather, they are colored by pigment within the keratinocyte. The seborrheic keratosis is a common example of such a benign pigmented epithelial neoplasm. An example of a malignant epithelial neoplasm which may be pigmented — but not by an increase in the relative number of melanocytes — is the basal cell carcinoma.

THE LANGERHANS CELL

Langerhans cells are normally found scattered among keratinocytes of the middle region (stratum malpighii) of the epidermis. Like the melanocyte, they are not connected to adjacent keratinocytes by desmosomes. At the light-microscopic level, Langerhans cells are difficult to detect in routinely stained sections. Ultrastructurally they are characterized by a folded nucleus and distinct intracytoplasmic organelles called **Langerhans granules** (Fig. 1–9). These organelles in their fully developed form are rod-shaped with a vacuole at one end, and resemble a tennis racquet.

Langerhans cells can be detected in the fetal epidermis by 14 weeks. Although formerly thought to be "effete" or altered melanocytes, they have been shown by animal studies to be not of neural crest origin and not developmentally related to melanocytes. Langerhans cells can occasionally be found within the dermis. In the histiocytosis-X group of diseases, ultrastructural studies have confirmed that they form the principal cell type of the infiltrate. These observations suggest that the Langerhans cell may be of mesenchymal origin, and, like the indeterminate cell, may merely wander into the epidermis at appropriate times.

Although the function of the Langerhans cell remains controversial, Silberberg has re-

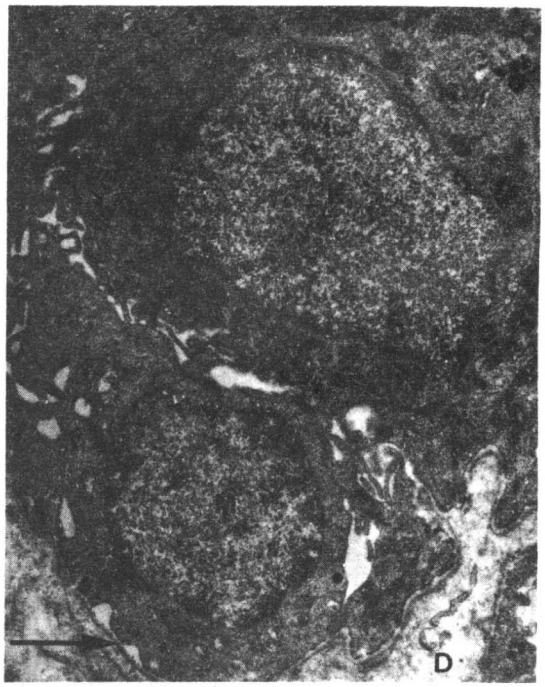

Figure 1–8 The relationship between melanocyte (M) and basal keratinocyte (K) in light skin is illustrated. Melanocytes synthesize melanosomes (pigment granules), which are transferred to keratinocytes where they are contained within membrane-bound "melanosome-complexes" (small arrows). Bundles of tonofilaments (broad, short arrow) identify the cell as a keratinocyte. The basement membrane zone (long arrow) separates epidermis from dermis (D).

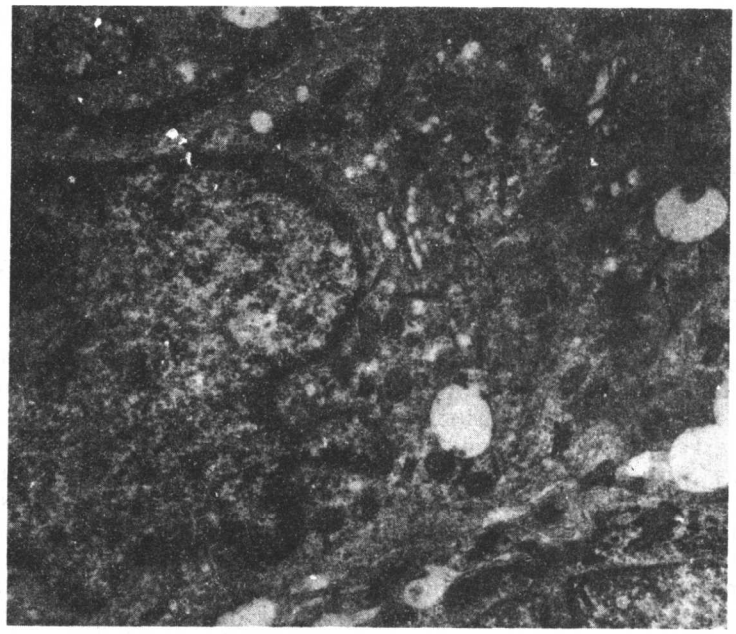

Figure 1–9 Ultrastructural appearance of the Langerhans cell (L). The characteristic intracytoplasmic Langerhans granules have a rod-shaped "handle" (thin arrow) and a saccular "head" (broad arrow). The Langerhans cell is not connected to adjacent keratinocytes (K) by desmosomes.

cently offered convincing evidence that the Langerhans cell may serve a primary role in immune reactions of the delayed hypersensitivity type, specifically, allergic contact dermatitis.

THE EPIDERMAL-DERMAL JUNCTION

The junction of epidermis and dermis is formed by the basement membrane zone (Fig. 1–2). Ultrastructurally, this zone is composed of four components: the **plasma membranes** of the basal cells with their specialized attachment plates (hemidesmosomes); a **clear space,** the intermembranous zone; the **basal lamina;** and the **fibrous components** associated with the basal lamina, including anchoring fibrils, dermal microfibrils, and collagen fibers (Fig. 1–10). At the light-microscope level, the so-called PAS-positive basement membrane is composed solely of the fibrous components, which are of dermal origin. The basal lamina is synthesized by the basal cells of the epidermis.

The basement membrane zone is considered to be a "porous" semipermeable filter, which permits exchange of cells and fluid between the epidermis and dermis. It further serves as a structural support for the epidermis and holds the epidermis and dermis together. Not only is the basement membrane zone to be found close to the surface epi-

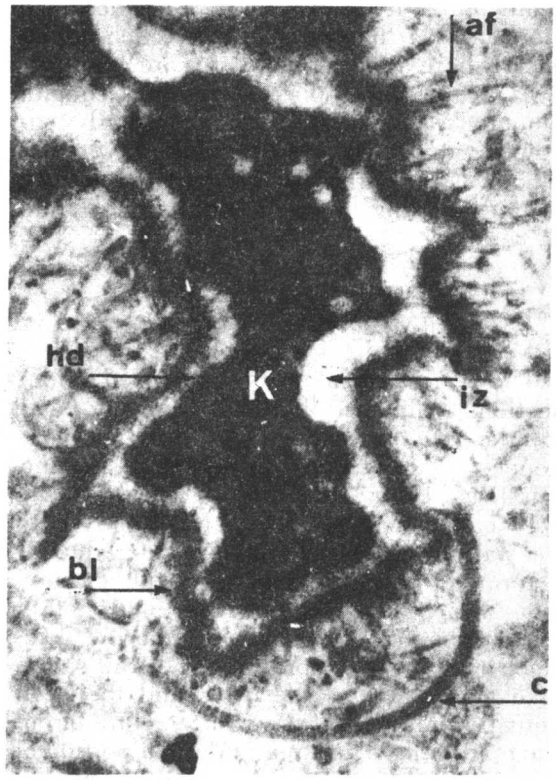

Figure 1–10 Ultrastructural appearance of the basement membrane zone at the junction of epidermis and dermis. The zone comprises four parts: the plasma membrane of basal keratinocytes (K) with their specialized attachment plates, the hemidesmosomes (hd); the clear zone or intermembranous space (iz); the basal lamina (bl); and the dermal fibrous components, including anchoring fibrils (af) and collagen fibers (c).

dermis, but it also serves the same functions for the skin appendages.

EPIDERMAL APPENDAGES (THE ADNEXA)

Eccrine and apocrine glands and ducts and pilosebaceous units constitute the skin adnexa. Embryologically, they originate as downgrowths from the epidermis and are therefore ectodermal in origin. Melanocytes and presumably other cells which are seen in the adult epidermis can be found within the adnexa. While the various adnexal structures serve specific functions, they all can function as "reserve" epidermis.

Re-epithelialization after injury to the surface epidermis occurs principally by virtue of the migration of keratinocytes from the adnexal epithelium along the skin surface. It is not surprising, therefore, that skin sites such as the face or scalp, which contain pilosebaceous units in abundance, re-epithelialize more rapidly than do skin sites such as the back, where adnexa of all types are comparatively scarce. Since those sites which contain numerous adnexa are also abundantly endowed with a rich network of nerves and blood vessels within the surrounding dermis, wound healing in general is more rapid there.

THE ECCRINE SWEAT UNIT

The eccrine sweat unit is composed of four sections which are modified from the basic tubular structure that formed during embryogenesis as a downgrowth of surface epidermis (Fig. 1–1). The *intraepidermal component* of the unit, which opens directly onto the skin surface, is called the **spiraled duct.** It is formed by a discrete aggregate of keratinocytes which ultrastrueturally resemble rather closely the appearance of neighboring keratinocytes of the epidermis. Cornification takes place within the duct, and the horn cells become part of the stratum corneum of the epidermis. The straight dermal portion of the duct is composed of a double layer of cuboidal epithelial cells and is lined by an eosinophilic cuticle on its luminal side.

The secretory acinar portion of the unit, or **coiled gland**, is found within the panniculus near the junction of dermis and subcutis. An inner layer of epithelial cells, the secretory portion of the gland, is surrounded by a layer of flattened myoepithelial cells. The secretory cells are of two types: glycogen-rich, large pale cells and smaller, darker-staining cells. The pale glycogen-rich cells are thought to initiate the formation of sweat. The darker cells may function in a manner similar to that of cells of the dermal duct, which actively reabsorb sodium, thereby modifying sweat from a basically isotonic solution to a hypotonic one by the time it reaches the skin surface. Sweat is similar in composition to plasma, containing all the same electrolytes, though in a more dilute concentration.

Eccrine sweat units are found at virtually all skin sites. They are most abundant on the palms, soles, forehead, and axillae. Secretion of sweat is dependent upon many factors and is mediated by cholinergic innervation. Heat is a prime stimulus to increased sweating, but other physiologic stimuli, including emotional stress, are important as well. Increased sweat production in response to heat is part of the thermoregulatory system of the body: together with increased cutaneous blood flow, it can effectively dissipate excessive body heat. At friction surfaces, such as the palms and soles, eccrine secretion is thought to assist tactile sensibility and improve adhesion.

THE APOCRINE UNIT

Adult apocrine units develop as outgrowths, not of the surface epidermis, but of the infundibular or upper portion of the hair follicle (Fig. 1–1). They are therefore intimately related, at least anatomically, if not functionally, to pilar units. Although immature apocrine units are found covering the entire skin surface of the human fetus, these regress and are absent by term.

The straight excretory portion of the duct, which opens into the infundibular portion of the hair follicle, is composed of a double layer of cuboidal epithelial cells. The coiled secretory gland is located at the junction of the dermis and subcutaneous fat. It is lined by a single layer of cells, which vary in appearance from columnar to cuboidal. This layer of cells is surrounded by a layer of myoepithelial cells.

The apexes of the columnar cells project into the lumen of the gland and in histologic cross-section appear as if they are being ex-

truded (so-called decapitation secretion). However, histologic and ultrastructural studies of apocrine glands in man have confirmed that the apexes of the cells of the gland are not shed during secretion.

The composition of the product of secretion is only partially understood. Protein, carbohydrate, ammonia, lipid, and iron are all found in apocrine secretion. It appears milky and is odorless until it reaches the skin surface, where it is altered by bacteria in such a way as to make it odoriferous.

Apocrine secretion is mediated by adrenergic innervation and by circulating catecholamines of adrenomedullary origin. Excretion, or the propulsion of the secretion through the duct, is episodic, though the actual secretion of the gland is continuous.

Apocrine gland secretion in man serves no known function; in animals it has a protective as well as a sexual function. In some species, it is important in thermoregulation as well.

Although occasionally found in an ectopic location, apocrine units of the human body are generally confined to the following sites: axillae, areolae, the anogenital region, the external auditory canal (ceruminous glands), and the eyelids (glands of Moll). Conditions such as Fox-Fordyce disease and hidradenitis suppurativa, traditionally thought to be apocrine gland dysfunctions, may in fact be related etiologically to the excretory components of the apocrine unit, i.e., the apocrine ducts and their associated pilar units, rather than to any abnormality in apocrine secretion per se.

THE HAIR FOLLICLE

During embryogenesis, mesenchymal cells in the fetal dermis collect immediately below the basal layer of the epidermis. Epidermal buds grow down into the dermis at these sites. The developing follicle forms at an angle to the skin surface and continues its downward growth. At its base, the column of cells widens and surrounds the small collections of mesenchymal cells forming the bulb. The hair is formed from cells just above the bulb, which also give rise to concentric zones of differentiated epithelial cells destined to form the inner and outer root sheaths. Along one side of the follicle, two buds are formed: an upper, which develops into the sebaceous gland, and a lower, which becomes the attachment for the arrector pili muscle. At skin sites destined to have apocrine units, a third epithelial bud develops from the opposite side of the follicle above the level of the sebaceous gland anlage. The uppermost portion of the follicle, which extends from its surface opening to the entrance of the sebaceous duct, is called the **infundibular segment.** The portion of the follicle between the sebaceous duct and the insertion of the arrector pili muscle is the **isthmus.** The **matrix,** or inferior portion, includes the lowermost part of the follicle and the hair bulb.

Hair follicles develop sequentially in rows of three. *Primary* follicles are surrounded by the appearance of two *secondary* follicles; other secondary follicles subsequently develop around the principal units. The density of pilosebaceous units decreases throughout life, mainly because of the poor development of the secondary follicles.

The actual hair shaft, as well as an inner and outer root sheath, develops from the mitotically active undifferentiated cells of the matrix portion of the hair bulb (Fig. 1–11). The sheaths and contained hair are derived from different regions of the bulb, and they form concentric cylindrical layers. The hair shaft and inner root sheath move together as the hair grows toward the surface; the outer root sheath remains fixed in position. The epidermis of the upper part of the follicular canal is contiguous with the outer root sheath and includes the infundibular and isthmus zones of the follicle. This portion of the follicle is permanent; the portion of the follicle between the bulb and the upper limit of the inner root sheath is completely replaced at each new cycle of hair growth.

The rate of hair growth is dependent upon mitotic activity of the cells of the bulb matrix. Hair "form," or cross-sectional shape of the hair, depends upon the arrangement of cells in the bulb. Scalp hair of Caucasians is round; pubic hair, beard hair, and eyelashes are oval. The scalp hair of Negroes is also oval. Curliness of Negro hair is due to this, and to a curvature of the follicle just above the bulb.

Basic hair color is due to the distribution of melanosomes within hair bulb cells, which become the cells of the hair shaft. Melanocytes of the hair bulb synthesize melanosomes and transfer them to the cells of the bulb matrix in a fashion similar to the transfer of melanosomes from melanocytes to keratinocytes in the surface epidermis. Larger melanosomes are found in the hair of Blacks; smaller melanosomes, which are aggregated