

OVERVIEW

Skin, the largest organ in the body, is the major direct interface between the environment and the internal organs. Its components, an **epidermis**, **epidermal derivatives** (hair, glands, nails), and **dermis**, act as a protective barrier and at the same time serve as a critical means of communication between the external and internal environments.

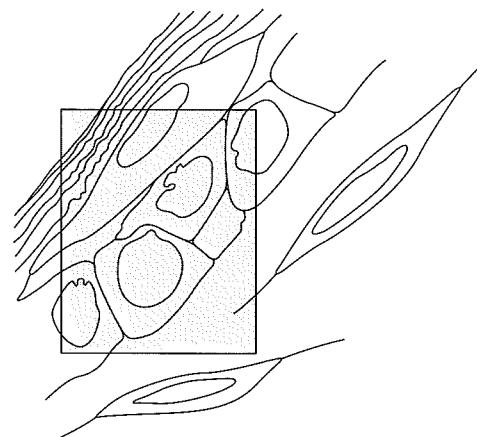
The **epidermis** (E, bracket, micrograph) is a stratified squamous epithelium composed primarily of **keratinocytes** that undergo differentiation that culminates in a surface layer of dead cells packed with the protein keratin. Keratin provides the characteristic strength and inertness to the epidermis. As the keratinocytes mature and move closer to the skin surface, sequential expression (often in pairs) of genes within a family controlling keratin synthesis results in changes in the composition, size, organization, and quantity of keratin within the cell.

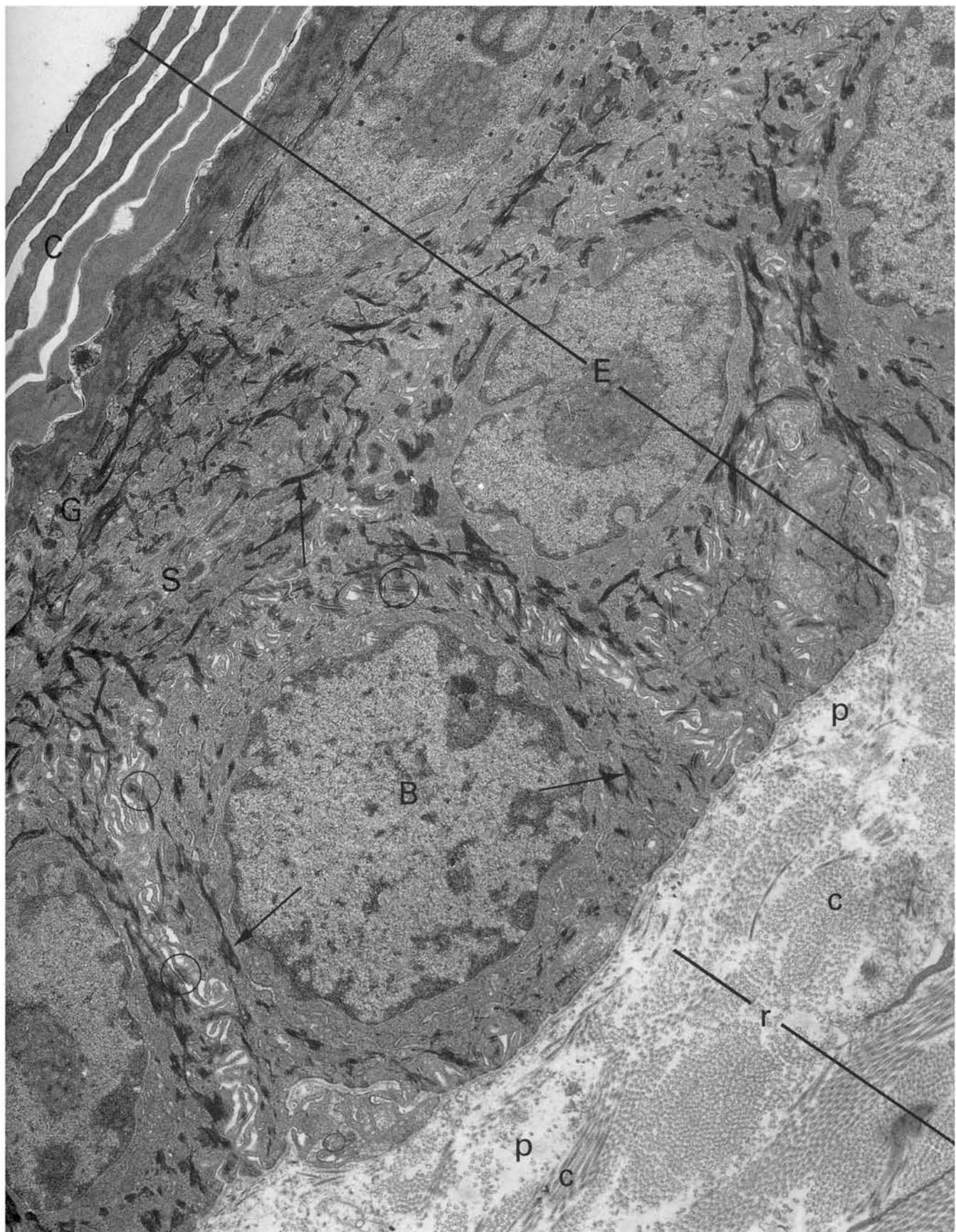
The **layers of the epidermis** are most easily defined by the changes that occur in keratin as differentiation proceeds. Stem cells in the stratum basalis (B, micrograph) and cells in the next stage of differentiation in the stratum spinosum (S, micrograph) synthesize keratin in the form of tonofilaments (arrows, micrograph). These filaments and their associated desmosomes (circles, micrograph) maintain the structural integrity of the epidermis. With age, the tonofilaments cross-link to form granules in the stratum granulosum (G, micrograph). In the final stages of differentiation, organelles are completely replaced with mature keratin that fills the highly ordered cells of the stratum corneum (C, micrograph). As cells are added from the bottom, other cells are lost or desquamated from the surface. Thus, optimal epidermal thickness is maintained. The progression from division to desquamation normally occurs in one month.

The switch from basal cell mitosis to the beginning of programmed cell death occurs when keratinocytes detach from the basal lamina. Fibronectin, a prominent component of basal lamina, can regulate the terminal differentiation of keratinocytes.

Keratinocytes provide a framework that houses other cell types. Together, these cells carry out functions including protection of underlying tissue (from desiccation, foreign invasion, physical trauma, and UV irradiation), sensation, and the formation of a vitamin D precursor.

The **dermis** consists of a thin layer of loose connective tissue (papillary layer; p, micrograph) directly under the epidermis, and a deeper, thicker layer of dense irregular connective tissue (reticular layer; r, bracket, micrograph). The **papillary layer** (unusually thin in this micrograph) is the major region of cellular traffic associated with immune and inflammatory reactions. The **reticular layer**, recognized by dense masses of collagen (c, micrograph), provides strength and elasticity, is a conduit for nerves and the larger blood vessels, and, along with the hypodermis, houses the basal portions of hairs and the secretory regions of glands. Secretions of fibroblasts, the hallmark cell of loose and dense connective tissue, include not only the extracellular components of these tissues but also factors necessary for the normal division and differentiation of the epidermis. A codependency between dermis and epidermis operates at many levels.





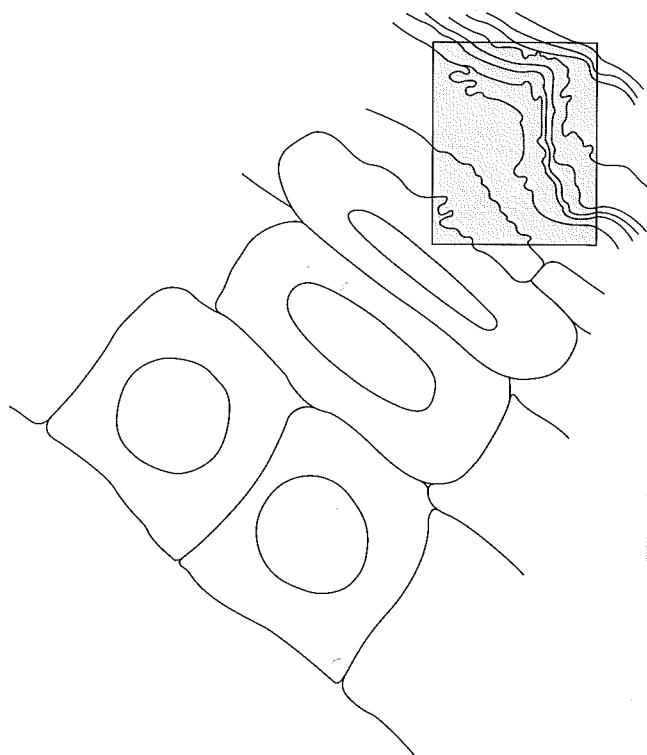
EPIDERMIS: Stratum Granulosum

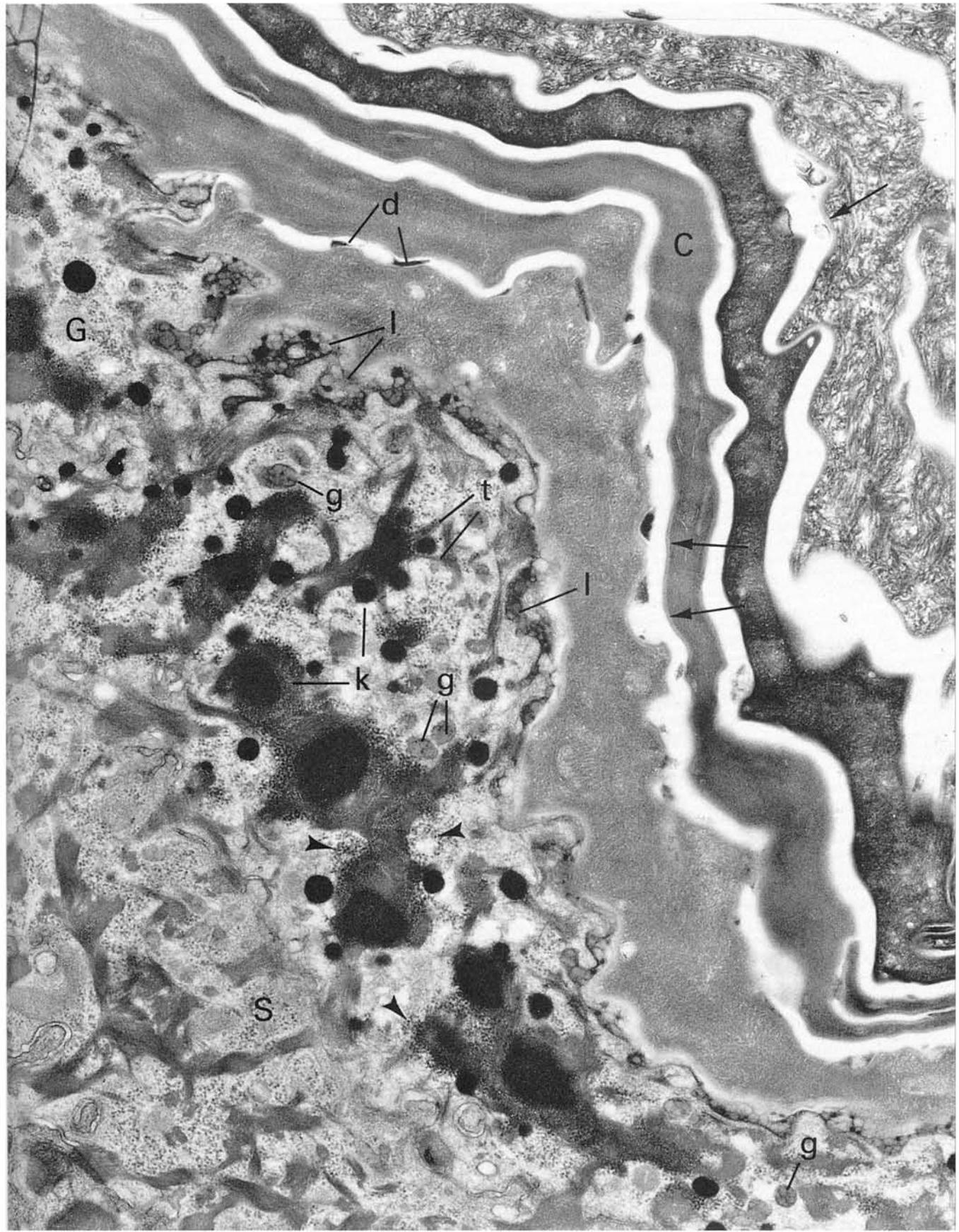
Critical events in the differentiation of the keratinocyte occur in the **stratum granulosum** (G, micrograph). The extent of these changes is clearly appreciated by comparing the structure of the relatively undifferentiated precursor cells in the stratum spinosum (S, micrograph) to the fully differentiated product, the stratum corneum cells (C, micrograph).

The stratum granulosum is named for the presence of nonmembrane-bound **keratohyalin granules** (k, micrograph) that appear in conjunction with the tonofilaments (t, micrograph). These granules contain the protein **filaggrin**, which cross-links tonofilaments as keratin takes on a new form. Many of the ribosomes (arrowheads, micrograph) in the granulosum cells are concentrated around these granules and may be involved in the synthesis of filaggrin. The patchy occurrence of ribosomes reflects an overall alteration in the cytoplasm as these cells differentiate and lose many organelles, including nuclei. Even after the cells have lost their transcription ability changes in the keratin continue to occur (e.g., new disulfide cross-links, interaction with matrix proteins, molecular size changes) that are reflected by distinct ultrastructural changes during progression from the stratum granulosum outward (micrograph).

Some of the events related to cell death in the stratum granulosum begin to take place in the stratum spinosum. In the stratum spinosum the evenly dispersed ribosomes, in addition to supporting all of the metabolic events of this active cell, direct the synthesis of proteins that are essential to differentiation into the stratum granulosum, including the enzyme **transglutaminase** and the structural protein **involucrin**. As the spinosum cells differentiate into granulosum cells, calcium levels rise and activate transglutaminase. Once activated, transglutaminase cross-links involucrin to the inner leaf of the cell membrane, creating an impermeable barrier that isolates each cell from nutrients and accelerates cell death. The thickness of the involucrin envelope can be appreciated in certain areas (arrows, micrograph) in the stratum corneum.

Before being sealed and isolated from the environment, the cells of the stratum granulosum release a lipid secretion that occupies the spaces between corneum cells, providing cohesion and creating the permeability barrier of skin. Lipid can be seen in the cytoplasm as granules called **membrane-coating granules** (g, micrograph). After secretion lipid (l, micrograph) accumulates in the space between the stratum granulosum and the stratum corneum. The removal of sulfate from cholesterol sulfate, an important mortar component, is a necessary prerequisite for desquamation. Desquamation also depends upon the progressive loss of desmosomes, which are reduced to remnants (d, micrograph) in the stratum corneum.





EPIDERMIS: Melanocyte

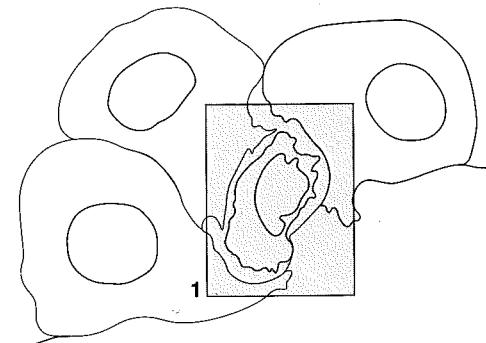
Dividing keratinocytes in the stratum basalis are vulnerable to mutation caused by exposure to short-wavelength UV radiation. A cap of melanin granules over the nucleus of these cells protects against chromosome damage by absorbing the potentially destructive radiation.

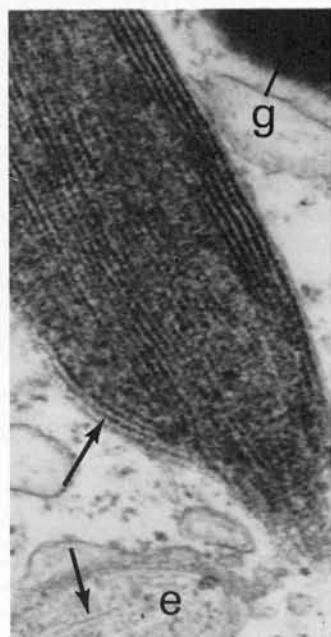
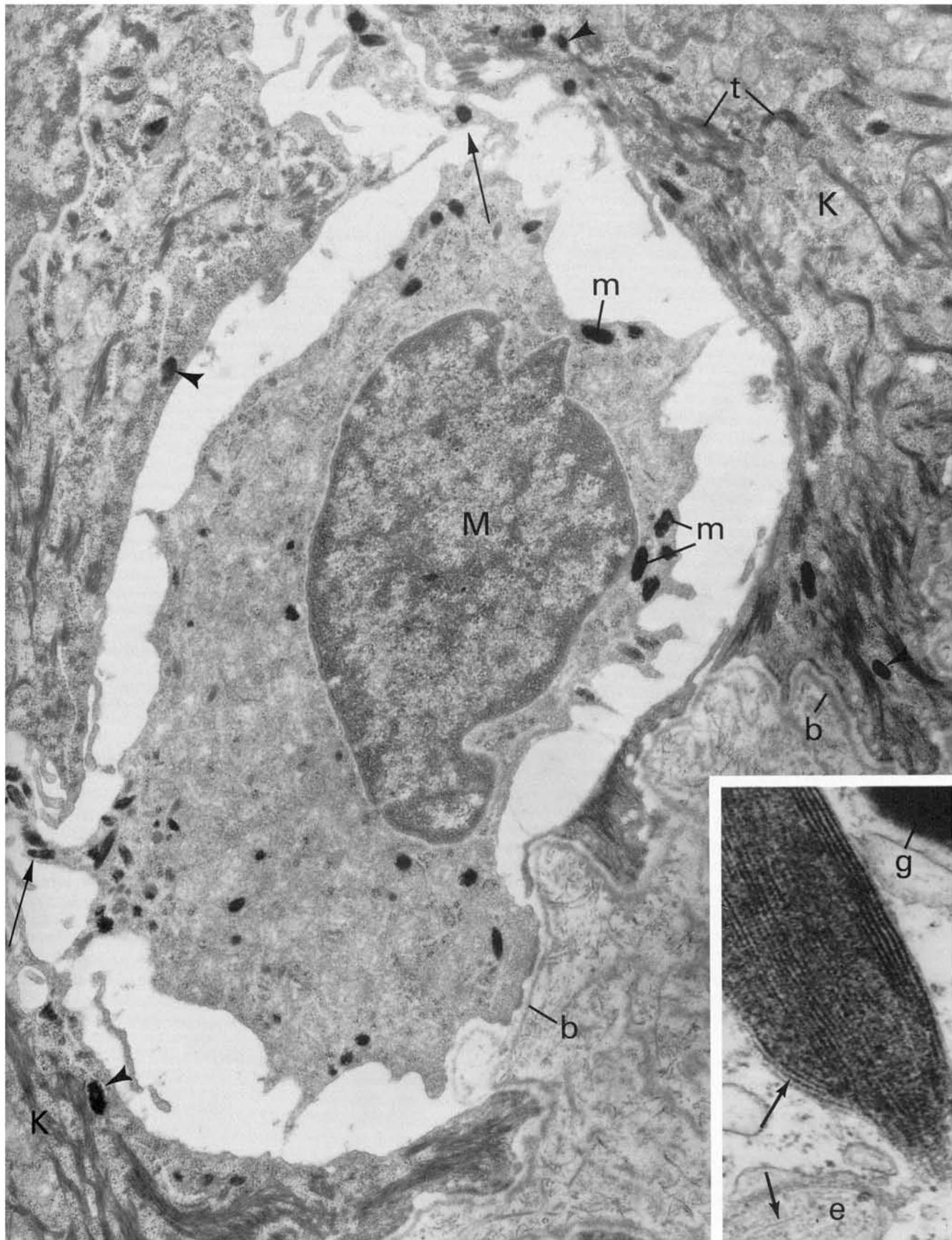
Melanin is produced by **melanocytes** (M, micrograph 1) that migrate from the neural crest to the epidermis during fetal development. Melanocytes enter the epidermis and remain attached to the basal lamina (b, micrograph 1), where they occupy regions between basal keratinocytes (K, micrograph 1). Melanocytes are easily recognized by (1) their tendency to separate from keratinocytes during tissue preparation, since these two cell types are not attached by desmosomes, and (2) the absence of tonofilaments (t, micrograph 1), which are obvious in keratinocytes. In contrast to keratinocytes, which move away from the basal lamina as they divide and differentiate, melanocytes maintain their position among the stem keratinocytes.

Melanin is synthesized within melanosomes (m, micrograph 1). Coated vesicles originating from the Golgi concentrate **tyrosinase**, the critical enzyme necessary for three steps in the single pathway to melanin formation. The coated vesicles become melanosomes as tyrosinase's substrates (tyrosine, 3,4-dihydroxyphenylalanine or dopa, and 5,6-dihydroxyindole) become available and the reactions take place to form melanin. Special melanosome matrix proteins provide a lamellar scaffolding (arrows, inset, courtesy of Dr. A. Breathnach) that aids in the spatial organization of the biochemical pathway associated with melanin formation. The protein framework that can be seen in the early melanosomes (e, inset) is obscured in mature granules (g, inset).

Melanosomes are donated to surrounding keratinocytes by the melanocytes that produce them. Melanosomes move to and concentrate within thin melanocyte processes (arrows, micrograph). The most common mechanism of intercellular transfer is phagocytosis of these processes by keratinocytes. The keratinocytes adjacent to the melanocyte in micrograph 1 have taken up several melanosomes (arrowheads). Most of the melanosomes within the keratinocyte cytoplasm will be moved to form a cap over the nucleus. Each melanocyte "feeds" a defined number of keratinocytes, and this number varies in different regions of the body. One melanocyte can feed as many as 36. Melanocytes do divide normally during routine turnover; however a set ratio is consistently maintained. A change in the ratio characteristic for a given region is an indication of a proliferative condition, either nonmalignant moles or malignant melanoma. In the absence of melanin, as in the albino condition, DNA is not protected from UV radiation and there is an increased incidence of DNA damage and epidermal cancer.

Differences in skin color are not related to differences in the number of melanocytes, but rather to the amount of melanin per cell, reflected by the size or number of melanosomes. The darkening of skin color associated with tanning initially involves a change in the configuration of existing melanin, but can subsequently involve increased synthesis. With prolonged sun exposure, both melanin structure and synthesis are altered, reducing the protection of DNA.





EPIDERMIS: Merkel Cell

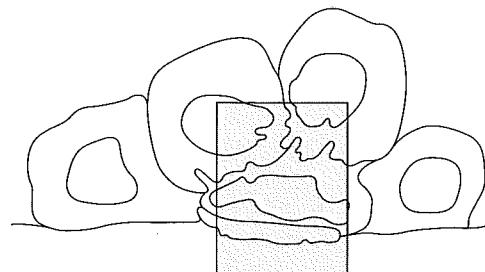
In addition to its obvious protective role, skin is a major sensory organ. Afferent neurons carry sensation to the central nervous system, where the information is processed. The sensory endings of these neurons terminate in both epidermis and dermis and also below the skin in the hypodermis. They are either naked (i.e., free) or associated with other cells that encase them (as in Pacinian, Krause, Ruffini's and Meissner's corpuscles) or, more simply, abut them (as with Merkel cells).

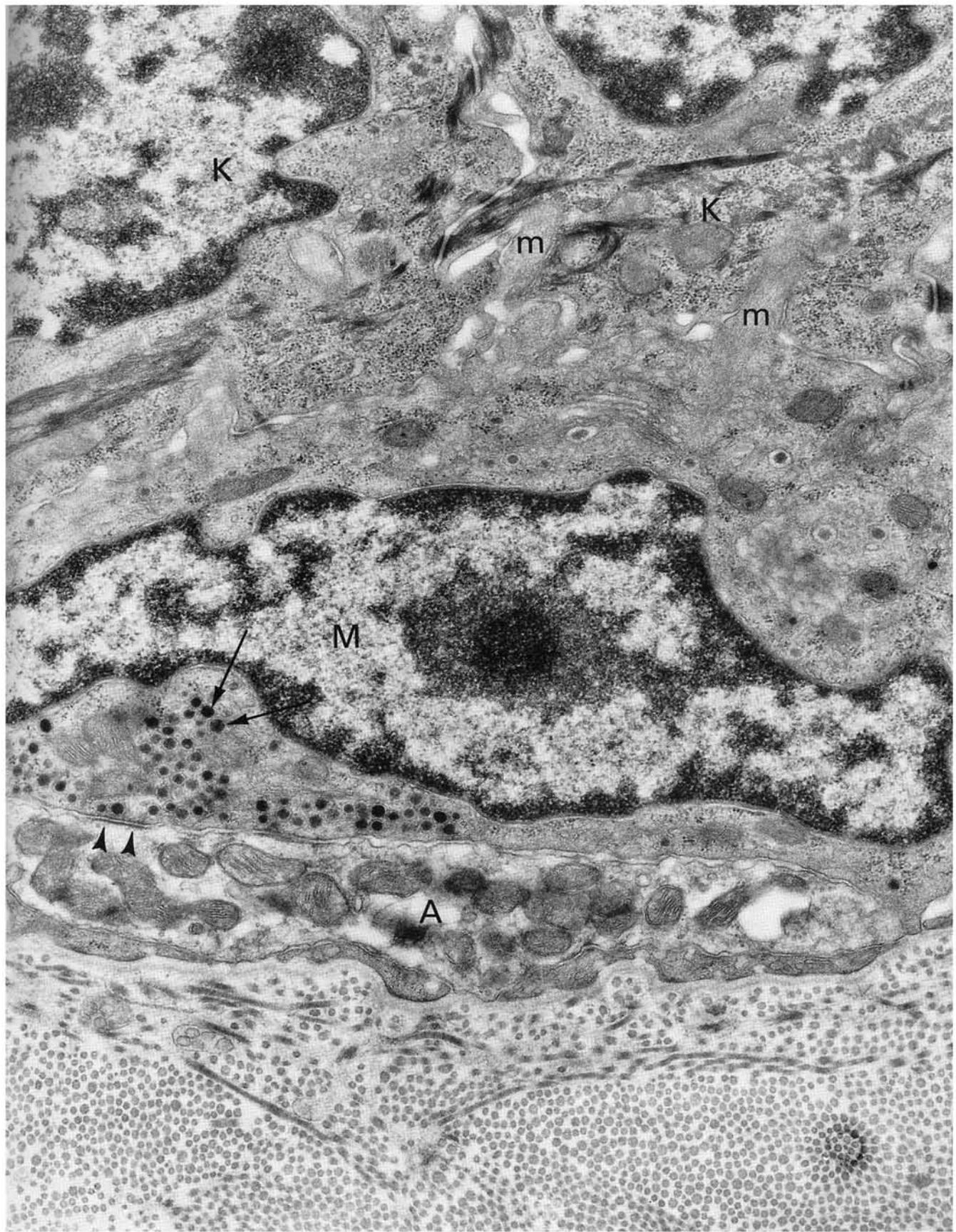
Sensory modalities, including pain, temperature, and touch, are sometimes matched with a particular structure. The **Merkel cell–neuron complex** in the micrograph is a mechanoreceptor localized within the epidermis, found predominantly in the most sensitive areas such as the lips and fingertips. Each Merkel cell (M, micrograph) rests in a cuplike depression formed by the terminal ending of its associated axon (A, micrograph).

Merkel cells have a structure characteristic of transducer sensory cells that act as intermediates between an initial stimulus and the neuron impulse. They contain: (1) **microvilli** (m, micrograph) seen projecting into depressions in adjacent keratinocytes (K, micrograph); (2) **granules** (arrows, micrograph) that contain peptides that are known neurotransmitters; and (3) **synapses** with their associated neurons (arrowheads in the micrograph indicate a possible synaptic region). Based on this overall ultrastructure, it is often proposed that the Merkel cell is a mechanoreceptor in which deformation of the microvilli causes granule release at the synapse and activation of the underlying neuron. However, electrophysiological studies have demonstrated that chemical synapse activity in Merkel cells is too slow to account for the generation of afferent impulses. In addition, the neuron ending itself is capable of responding directly as a mechanoreceptor.

There is evidence to suggest that even though the Merkel cell may not be the primary transducer, it can modify the neuron's response by affecting the threshold of response. In all of the other skin receptors, associated cells (and extracellular material) often modify the afferent nerve response but do not act as transducers of incoming messages as do classical receptor cells in other sensory modalities such as taste, vision, and hearing.

Merkel cells may also (1) provide essential metabolic support for the associated neuron (note the large numbers of mitochondria in the neuron, a characteristic of afferent as well as efferent nerve terminals); (2) be a “target” essential to the movement of neurons into the epidermis during development and nerve regeneration following injury; and (3) have effects associated with the release of neuropeptides, which, in addition to acting locally as synaptic transmitters, have far-reaching effects on autonomic nerves, blood vessels, and inflammatory cells.





EPIDERMAL DERIVATIVES: Eccrine Sweat Glands

The surface of the epidermis is bathed with secretions released from eccrine (watery-serous secretion), sebaceous (lipid secretion), and apocrine (carbohydrate-rich secretion) glands. Of these, **eccrine sweat glands** (micrographs) are the most numerous and functionally significant. They help maintain homeostasis by their role in electrolyte balance, excretion, and thermoregulation.

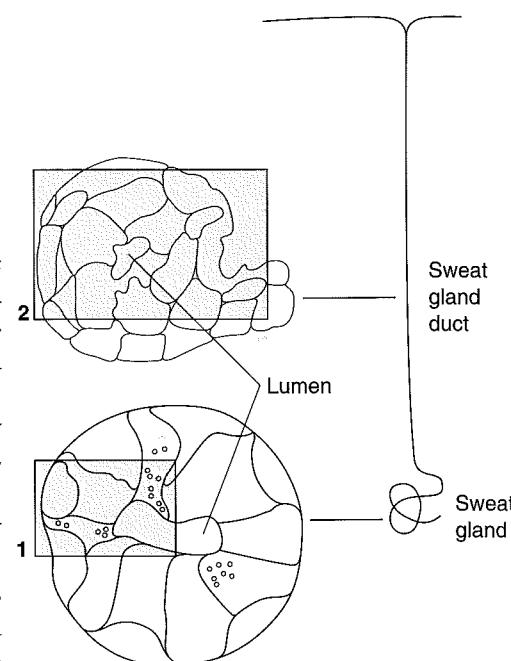
The **secretory portion** (micrograph 1) of eccrine glands is found in the dermis (or hypodermis) at the end of a simple coiled tubular **duct** (micrograph 2). The major components of the secretion, ions (primarily sodium chloride) and water, are produced by “**clear**” cells (C, micrograph 1). Movement of NaCl across the cell into the lumen is driven by sodium/potassium exchange pumps located in the highly infolded basolateral membranes (arrowheads, micrograph 1). Water follows passively. Energy required for pumping activity is provided by mitochondria (m, micrograph 1).

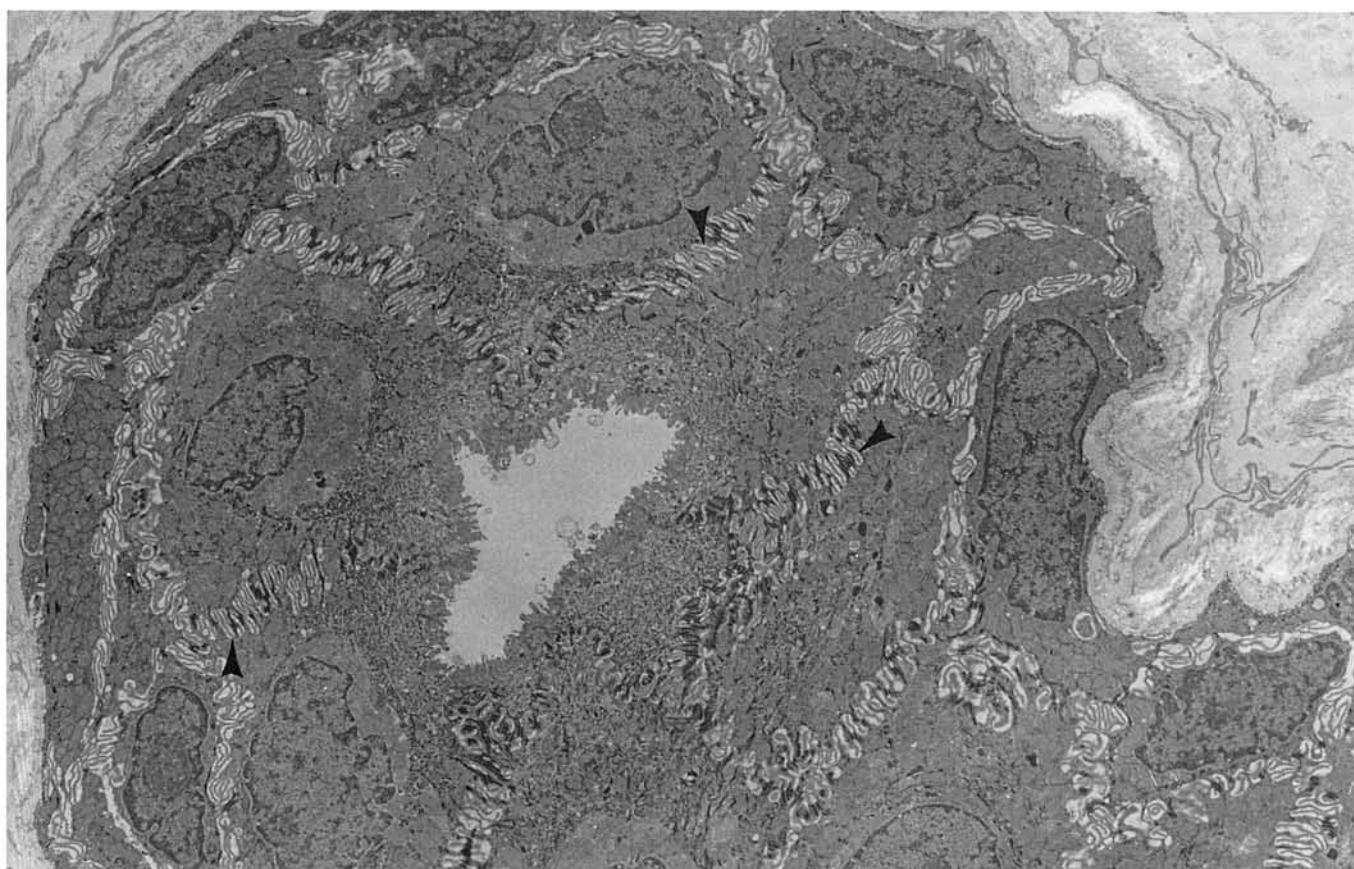
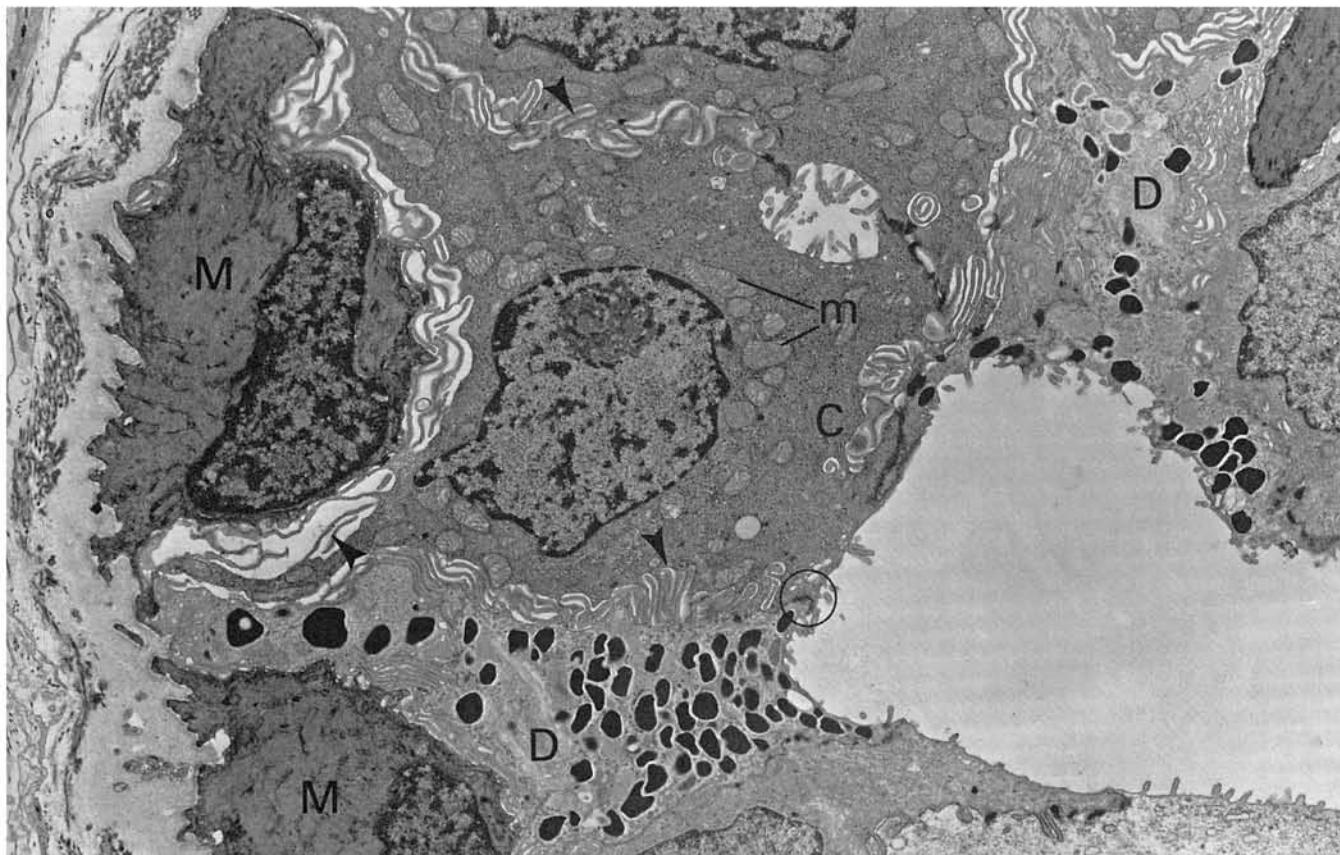
The primary secretion released from the clear cells is isotonic with plasma. As it moves through the duct, sodium and chloride are reabsorbed by the lining cells in order to conserve these essential electrolytes. Sodium/potassium pumps in the highly infolded basolateral membranes (arrowheads, micrograph 2) of both cell layers of the duct move sodium out of the cell into the interstitium. Chloride follows passively through special channels in the membrane. Since the ductal lining cells are not as permeable to water as the secretory cells, the removal of ions from the lumen results in a final sweat that is hypotonic. Evaporation of this watery sweat acts to dissipate body heat, a significant mechanism of thermoregulation. Each individual has approximately 2 million eccrine sweat glands, situated in skin of nearly all regions.

Cystic fibrosis is a fatal disease related to a single gene defect affecting the chloride channel. The reduced chloride permeability in the sweat gland ducts in individuals with this disease results in increased levels of NaCl in sweat, a characteristic frequently used as a diagnostic tool. A similar ion imbalance in respiratory epithelium leads to a thick, sticky mucus secretion, infection, and a subsequent life-threatening blockage of airways.

Dark cells (D, micrograph 1), named for their dense granules, are an integral part of the simple epithelium of the secretory portion, attached to the clear cells by junctional complexes (circle, micrograph 1). The granules contain glyccoproteins that are released into the sweat gland lumen by exocytosis. Epidermal growth factor, a component of sweat, appears to be stored in the dark cell granules and may be involved in regulating the function of gland epithelial and **myoepithelial cells** (M, micrograph 1). Myoepithelial cells contract, as in other locations, to facilitate the expulsion of secretion.

The secretory cells make other significant contributions to the final secretion, including IgA (from plasma cells), which moves across the dark cells, and urea (from plasma), which moves across the clear cells. Eccrine glands share with the kidneys the role of urea excretion; elevated urea concentrations in sweat can suggest kidney failure.





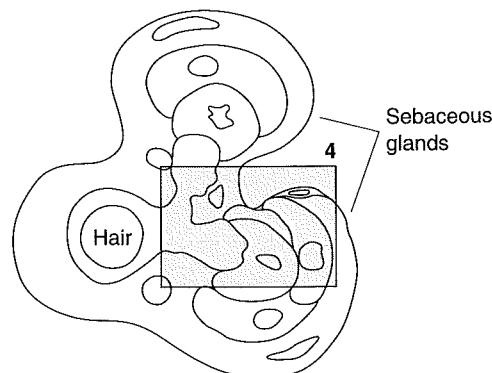
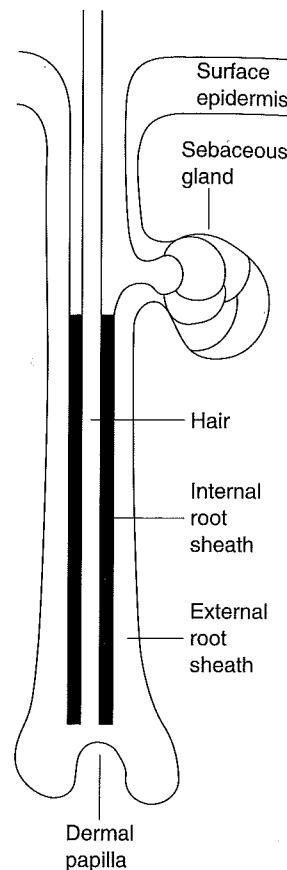
EPIDERMAL DERIVATIVES: Hair and Sebaceous Glands

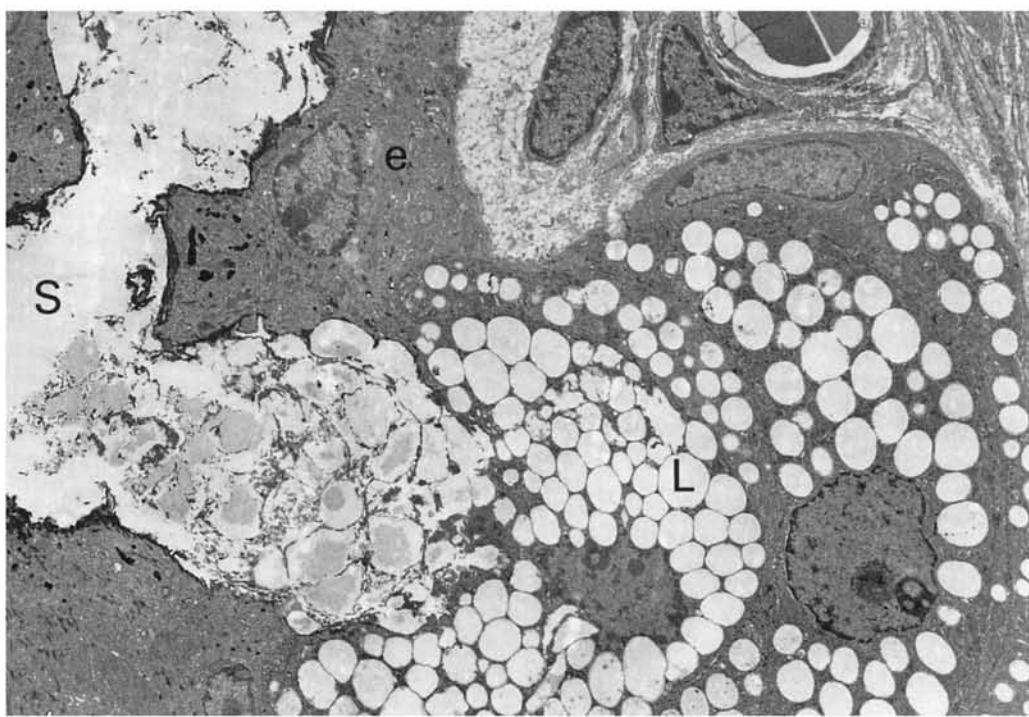
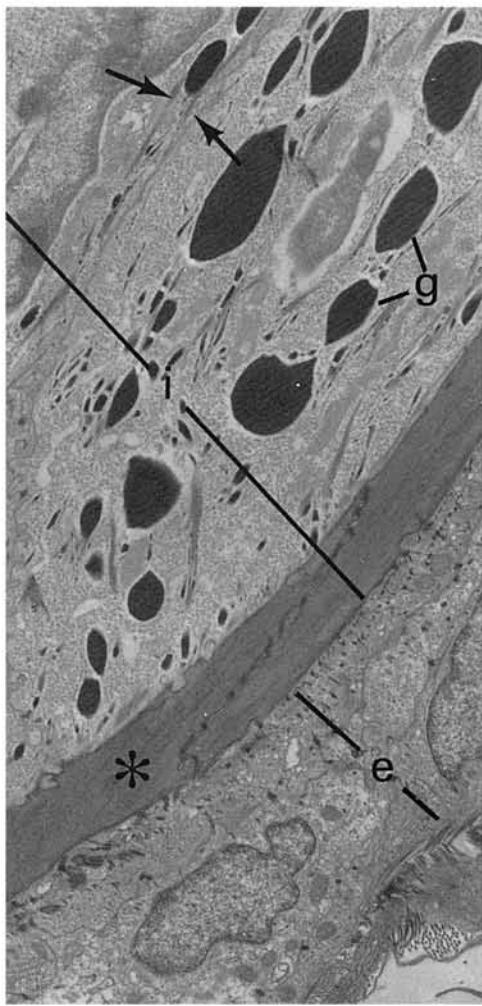
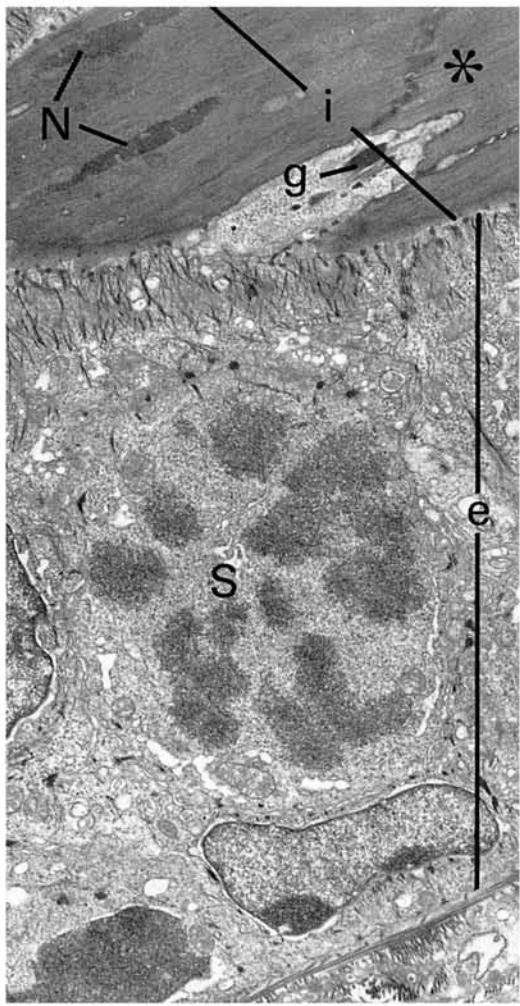
The micrographs illustrate the surface of hair (scanning electron micrograph 1), the surrounding sheaths (micrographs 2 and 3), and a sebaceous gland (micrograph 4). The adjacent diagram provides orientation to the relationship between these structures. An external root sheath grows down from and is continuous with the stratum basalis and spinosum of the surface epidermis. This sheath contains the stem cells that give rise to the hair, an internal root sheath, and sebaceous and apocrine glands. The hair and internal root sheath grow upward together associated by interlocking plates (surface plates of hair seen on micrograph 1) until the internal root sheath ends at the level of the sebaceous glands.

The external root sheath (e) is seen in micrographs 2, 3, and 4. The stem cells (S, micrograph 2) within the sheath, like stem cells in the gastrointestinal tract, have one of the most rapid mitotic cycles in the body, with the potential to replace damaged epidermis quickly and effectively. Two cell layers of the internal root sheath (i) are evident in micrographs 2 and 3. In both of these micrographs the outer layer (asterisk) is completely keratinized (except for two remaining nuclei, N, in micrograph 2), while the inner layer, in an earlier stage of differentiation, still contains granules (g). The granules, like keratohyalin granules of epidermis, are closely associated with keratin filaments (arrows, micrograph 3), are not membrane bound, and have been shown to contain the filament-linking protein filaggrin. At the point where the internal sheath degenerates, the space (S, micrograph 4) surrounding the hair becomes filled with the secretion of sebaceous glands.

The keratinocytes of the hair cortex and covering cuticle are packed with keratin filaments that are particularly insoluble, unreactive, and contain more disulfide bonds than does "soft" keratin. Formation of this "hard" keratin does not involve a keratohyalin granule stage, and the cells do not undergo regular desquamation. Hairs grow until the end of a growth cycle, after which the entire hair is replaced. On the scalp, hairs are replaced every two to six years. Adjacent hairs are in different phases of the cycle, so the dynamics of hair replacement is not obvious.

The development of sebaceous and apocrine glands is typically coupled to the development of hairs. **Sebaceous glands** secrete sebum, which contains fatty acids and is rich in squalene and wax esters, lipids not formed by the surface epidermis itself. As the gland cells differentiate, they increase in size and become packed with lipid droplets (L, micrograph 4). At their final stage of development they rupture and become the secretion. Sebaceous secretion contributes to the lipid coating of the epidermis and may act as a lubricant, but whether it has any added effect in preventing water loss over and above lipids produced by the surface epidermis is questionable. Sebaceous glands (like apocrine glands and certain types of hairs) undergo maximum development in response to rising androgen levels at puberty.





DERMIS: Papillary Layer

The **papillary layer** of the dermis is located directly under the epidermis (E, micrograph) and attached to it via a basement membrane (b, micrograph). A number of different types of cells are found within the loose connective tissue of the papillary layer, many of which migrate within the highly hydrated glycosaminoglycans synthesized by local **fibroblasts** (F, micrograph). Collagen (c, micrograph), another major secretory product of fibroblasts, is obvious, but considerably less concentrated here than in the underlying reticular dermis.

The papillary dermis houses an extensive network of **capillaries** (C, micrograph) that provide nutrition to the avascular epidermis. These small blood vessels are also the source of defense molecules and cells, including **lymphocytes** (L, micrograph). Some of the lymphocytes present in the connective tissue migrate into the epidermis, where, in conjunction with keratinocytes and epidermal macrophages known as Langerhans cells, they mount a specific epidermal immune response.

The amount of blood flowing through papillary capillaries is finely controlled and functions as one of the most important mechanisms of body temperature regulation. When the external temperature drops, body heat is conserved by reducing blood flow through these capillaries. Conversely, when the temperature rises, heat is lost through the epidermis via an increase in superficial blood flow. The arteriovenous shunts that adjust this flow are located in the papillary/reticular junction.

The thin, fenestrated wall of the capillary in the upper half of the micrograph differs in permeability from the thicker wall of the capillary below. The permeability of all types of papillary capillaries is influenced by both normal and abnormal events. Vasoactive substances, such as histamine released from **mast cells** (M, micrograph) as a part of a normal defense mechanism, increase vessel permeability. Dermal mast cells respond in the classic IgE-allergen manner, and also respond directly to neuropeptides released from neurons and Merkel cells. Permeability also increases when vessels are damaged, for example, as a result of immune diseases such as psoriasis or as a result of excess UV irradiation. The familiar blistering associated with sunburns is a consequence of plasma leaking through damaged capillaries and accumulating directly under the epidermis.

The thickness and composition of the dermis differs dramatically at different sites of the body. The presence of **skeletal muscle** (Mu, micrograph) is unique to regions where skin movement is under voluntary control, such as the face. The myelinated **nerve fibers** (N, micrograph) surrounded by Schwann cells (S, micrograph) may be those innervating the skeletal muscle, or they may be afferent fibers that originate from encapsulated touch receptors, Meissner's corpuscles. The bracketed region appears to be a glancing section through a Meissner's corpuscle.

