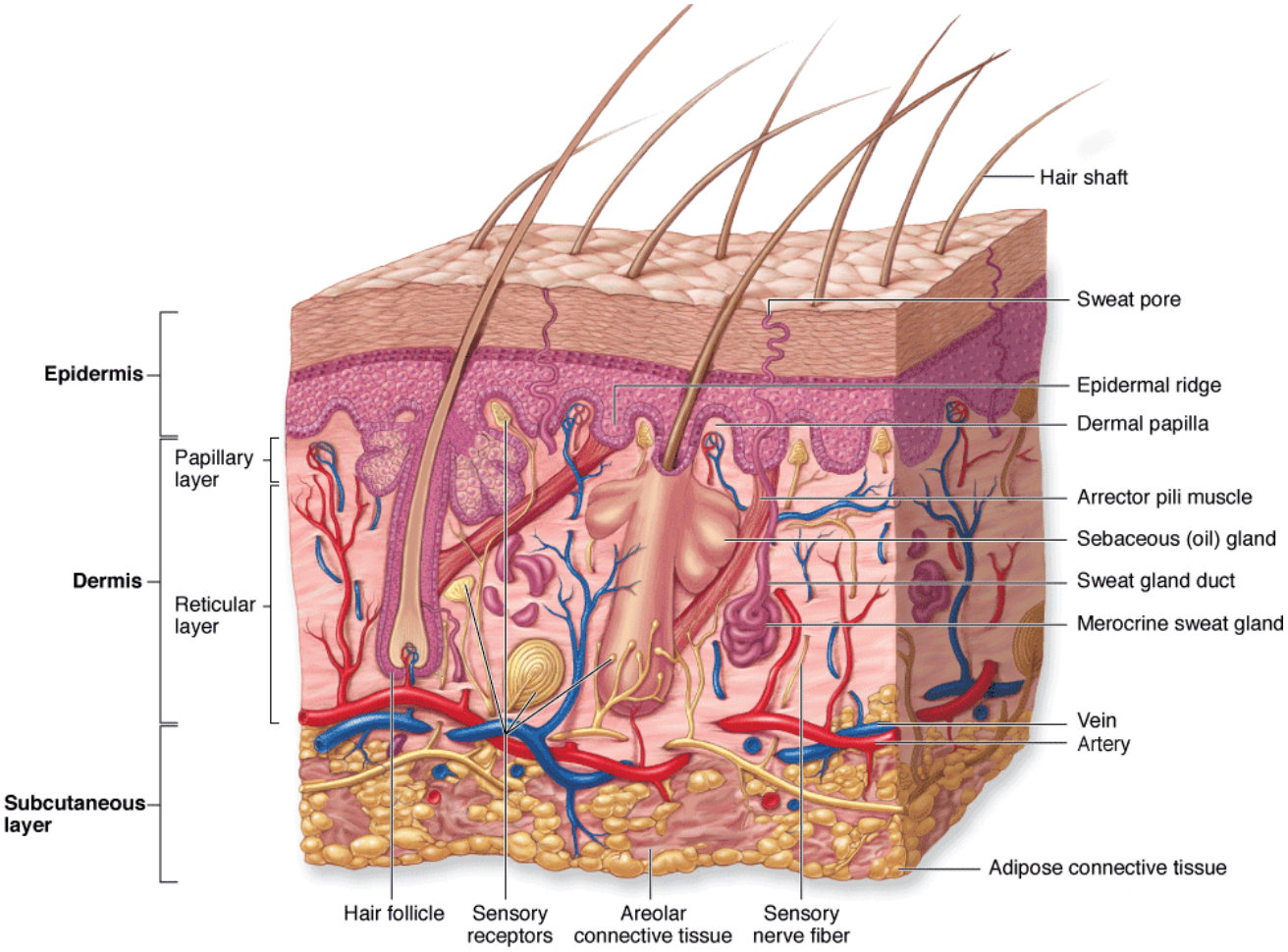
Note: Large images and tables on this page may necessitate printing in landscape mode.

SKIN: INTRODUCTION

The skin is the largest single organ of the body, typically accounting for 15–20% of total body weight and, in adults, presenting 1.5–2 m^2 of surface to the external environment. Also known as the **integument** (L. *integumentum*, covering) or **cutaneous layer**, the skin is composed of the **epidermis,** an epithelial layer of ectodermal origin, and the **dermis,** a layer of mesodermal connective tissue (Figure 18–1). The junction of dermis and epidermis is irregular, and projections of the dermis called **papillae** interdigitate with evaginations of the epidermis known as **epidermal ridges**. Epidermal derivatives include hairs, nails, and sebaceous and sweat glands. Beneath the dermis lies the **subcutaneous tissue** or **hypodermis** (Gr. *hypo,* under, + *derma,* skin), a loose connective tissue that may contain pads of adipocytes. The subcutaneous tissue binds skin loosely to the underlying tissues and corresponds to the superficial fascia of gross anatomy.

Figure 18–1.



Layers and appendages of skin.

Diagram of skin layers shows their interrelationships and the locations of the epidermal appendages (hair follicles, sweat and sebaceous glands), the vasculature, and the major sensory receptors.

The specific functions of the skin fall into several broad categories.

- **Protective**. It provides a physical barrier against thermal and mechanical insults such as frictional forces and against most potential pathogens and other material. Microorganisms that do penetrate skin alert resident lymphocytes and antigen-presenting cells of skin (Figure 14–6) and an immune response is mounted. The dark pigment melanin in epidermis protects cells against ultraviolet radiation. Skin is also a permeability barrier against excessive loss or uptake of water, which has allowed for terrestrial life. Skin's selective permeability allows some lipophilic drugs such as certain steroid hormones and medications to be administered via skin patches.
- **Sensory**. Many types of sensory receptors allow skin to constantly monitor the environment and various mechanoreceptors with specific locations in skin are important for the body's interactions with physical objects.
- **Thermoregulatory**. A constant body temperature is normally more easily maintained thanks to the skin's insulating components (eg, the fatty layer and hair on the head) and its mechanisms for accelerating heat loss (sweat production and a dense superficial microvasculature).
- **Metabolic**. Cells of skin synthesize vitamin D_3, needed in calcium metabolism and proper bone formation, through the local action of UV light on the vitamin's precursor. Excess electrolytes can be removed in sweat and the subcutaneous layer stores a significant amount of energy in the form of fat.
- **Sexual signaling**. Many features of skin, such as pigmentation and hair, are visual indicators of health involved in attraction between the sexes in all vertebrate species, including humans. The effects of sex pheromones produced by the apocrine sweat glands and other glands of skin are also important for this attraction.

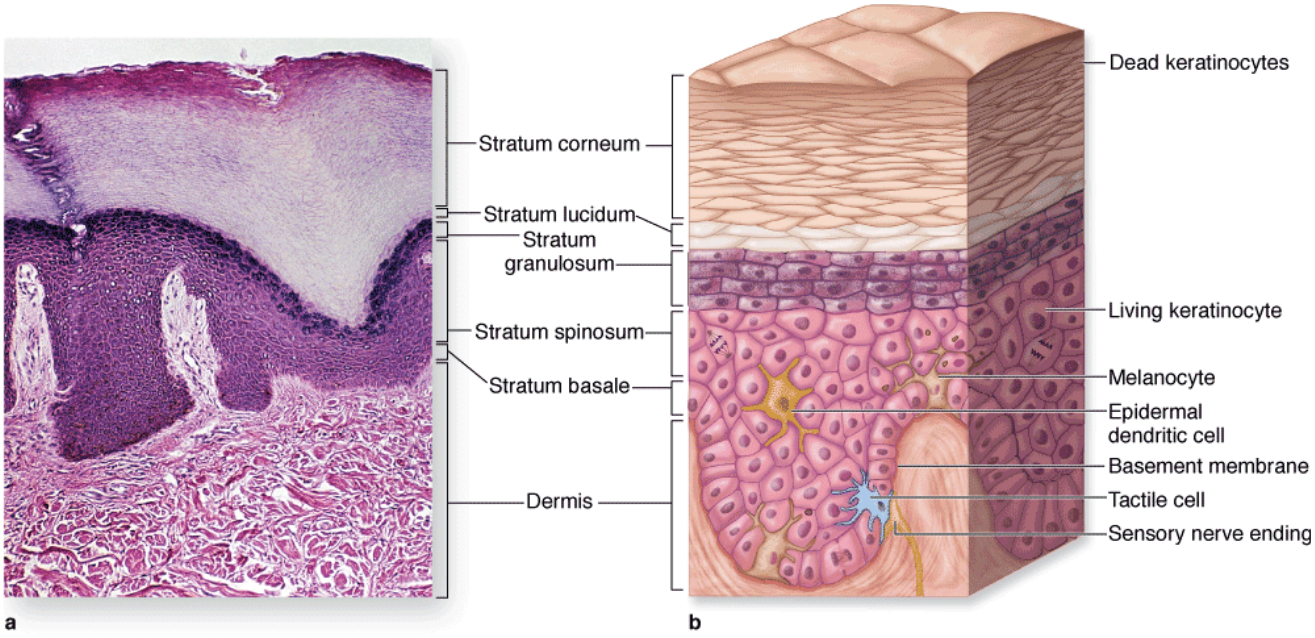
The dermal-epidermal interdigitations are of the peg-and-socket variety in most skin, but occur as well-formed ridges and grooves in the thick skin of the palms and

soles which is more subject to friction. These ridges and the intervening sulci form distinctive patterns unique for each individual, appearing as combinations of loops, arches, and whorls, called dermatoglyphs, also known as fingerprints and footprints. Skin is elastic and can expand rapidly to cover swollen areas and like the gut lining is self-renewing throughout life. In healthy individuals injured skin is repaired rapidly. The molecular basis of skin healing is increasingly well-understood and provides a basis for better understanding of repair and regeneration in other organs.

EPIDERMIS

The epidermis consists mainly of a stratified squamous keratinized epithelium composed of cells called **keratinocytes**. Three less abundant epidermal cell types are also present: pigment-producing **melanocytes**, antigen-presenting **Langerhans cells,** and tactile epithelial cells or **Merkel cells** (Figure 18–2).

Figure 18–2.

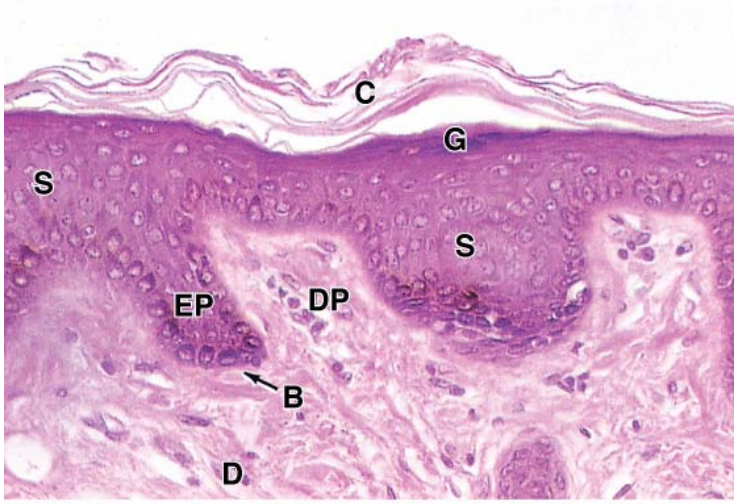


Layers (strata) of epidermis in thick skin.

(a): Micrograph shows the sequence of the epidermal layers in thick skin and the approximate sizes and shape of keratinocytes in these layers. Also shown are the coarse bundles of collagen in the dermis and on the far left, the duct from a sweat gland entering the epidermis from a dermal papilla and coiling to a surface pore through all the strata. X100. H&E. **(b):** Diagram illustrating the sequence of the epidermal layers also indicates the normal locations of three important nonkeratinocyte cells in the epidermis: melanocytes, a dendritic (Langerhans) cell, and a tactile cell.

The epidermis forms the major distinction between **thick skin** (Figure 18–2), found on the palms and soles, and **thin skin** (Figure 18–3) found elsewhere on the body. The designations "thick" and "thin" refer to the thickness of the epidermal layer, which varies from 75 to 150 μm for thin skin and from 400 to 1400 μm (1.4 mm) for thick skin. Total skin thickness (epidermis plus dermis) also varies according to site. For example, skin on the back is about 4 mm thick, whereas that of the scalp is about 1.5 mm thick.

Figure 18–3.



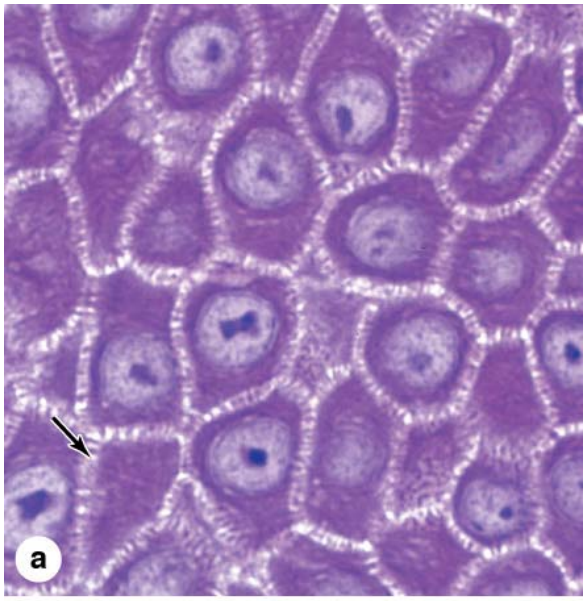
Layers of epidermis in thin skin.

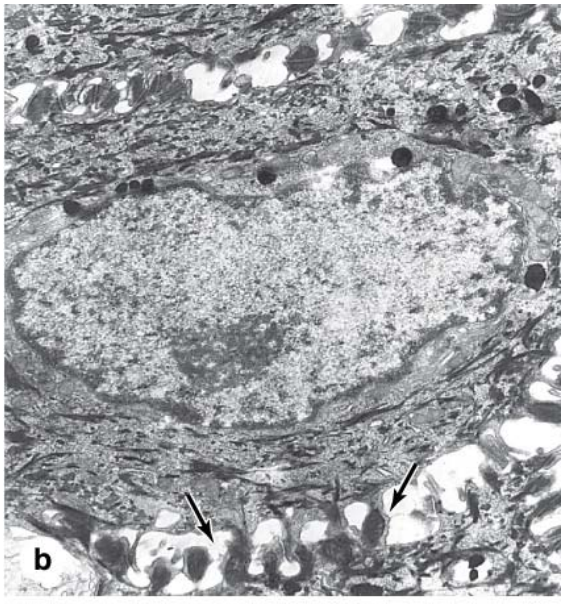
The interface between dermis and epidermis in thin skin is held together firmly by interlocking epidermal pegs (EP) and dermal papillae (DP). The dermis (D) is more cellular and well vascularized than that of thick skin, with elastin and less coarse bundles of collagen. The epidermis usually shows only four layers in thin skin: the one-cell thick stratum basale (B) containing most mitotic cells; the stratum spinosum (S) where synthesis of much keratin and other proteins takes places; the stratum granulosum (G); and the stratum corneum (C), consisting of dead squames composed mostly of keratin. X240. H&E.

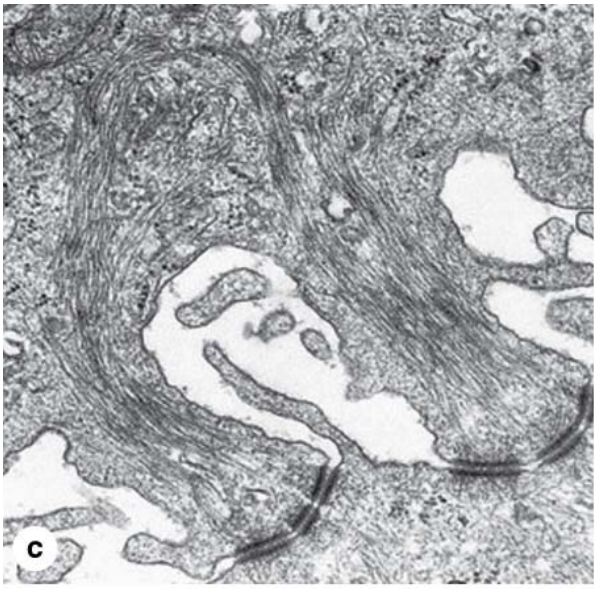
From the dermis outward, the epidermis consists of four layers of keratinocytes, five layers in thick skin (Figure 18–2):

- The **basal layer** (**stratum basale**) is a single layer of basophilic columnar or cuboidal cells on the basement membrane at the dermal-epidermal junction (Figures 18–2 and 18–3). Hemidesmosomes in the basal plasmalemma help bind these cells to the basal lamina and desmosomes bind the cells of this layer together in their lateral and upper surfaces. The stratum basale is characterized by intense mitotic activity and is responsible, in conjunction with the initial portion of the next layer, for constant production of epidermal cells. Although stem cells for keratinocytes are found in the basal layer, a niche for such cells also occurs in a specialized bulge in the hair follicle sheath continuous with the epidermis. The human epidermis is renewed about every 15–30 days, depending on age, the region of the body, and other factors. All keratinocytes in the stratum basale contain intermediate filaments about 10 nm in diameter composed of **keratins**. As the cells progress upward, the amount and types of keratin filaments increase until they represent half the total protein in the outermost layer.
- The **spinous layer** (**stratum spinosum**), normally the thickest epidermal layer (Figures 18–2 and 18–3), consists of polyhedral or slightly flattened cells having central nuclei with nucleoli and cytoplasm actively synthesizing keratin filaments. Just above the basal layer some cells may still divide and this combined zone is sometimes called the stratum germinativum. The keratin filaments form microscopically visible bundles called **tonofibrils** which converge and terminate at the numerous desmosomes, by which the cells are joined together strongly to resist friction. Cytoplasm is drawn into short cellular extensions around the tonofibrils on both sides of each desmosome (and these are elongated if the cells shrink slightly when processed histologically), leading to the appearance of many short spines or prickles at the cell surfaces (Figure 18–4). The epidermis of areas subjected to continuous friction and pressure (such as the soles of the feet) has a thicker stratum spinosum with more abundant tonofibrils and desmosomes.

Figure 18–4.







Keratinocytes of the stratum spinosum.

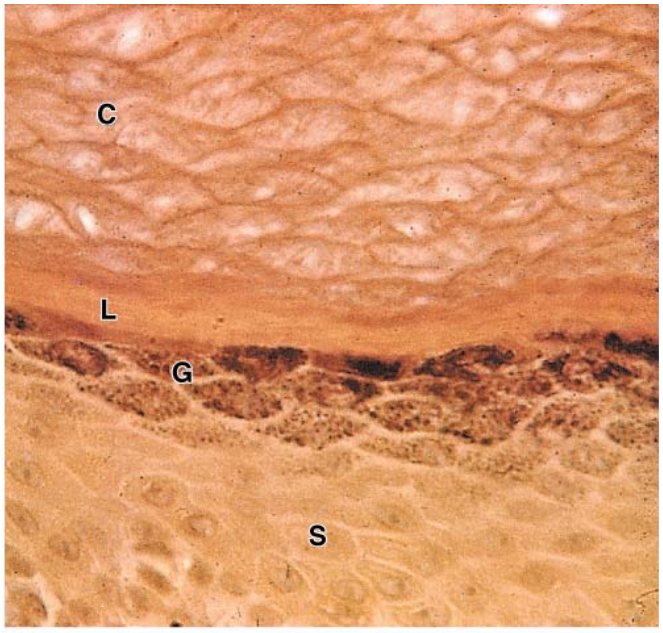
(a): Light micrograph of a section of skin from the sole of the foot (thick skin), showing only the stratum spinosum, highlights cells with numerous, short cytoplasmic projections (arrow). X400. PT. **(b):** TEMs show a single spinous keratinocyte with arrows marking some desmosomes at the projections. X8400. **(c):** Detail of the desmosomes joining two cells showing intermediate filaments associated with desmosomes. Keratinocytes of the stratum spinosum undergo considerable protein synthesis, primarily making keratins which form large bundles called tonofibrils. These terminate at the desmosomes linking the cells (arrows) and form the short cellular extensions characteristic of this layer when the cells shrink slightly. The black granules next to the nucleus are melanin granules. X40,000.

MEDICAL APPLICATION

In adults, one third of all cancers are of the skin. Most of these derive from cells of the basal or spinous layers, producing, respectively, basal cell carcinomas and squamous cell carcinomas. Fortunately both types of tumors can be diagnosed and excised early and consequently are rarely lethal. Skin cancer shows an increased incidence in fair-skinned individuals residing in regions with high amounts of solar radiation.

- The **granular layer (stratum granulosum)** consists of 3–5 layers of flattened polygonal cells undergoing terminal differentiation. Their cytoplasm is filled with intensely basophilic masses (Figures 18–2, 18–3, and 18–5) called **keratohyaline granules.** These structures are not membrane-bound and consist of dense masses of **filaggrin** and other proteins that associate with the keratins of tonofibrils, linking them into large cytoplasmic structures in the important process of **keratinization**. Other characteristic features visible only with the TEM in cells of the granular layer are the membrane-coated **lamellar granules,** small (0.1–0.3 μm) ovoid structures containing many lamellae composed of various lipids. Lamellar granules undergo exocytosis, discharging their contents into the intercellular spaces of the stratum granulosum. There this lipid-rich material produces sheets that envelop the cells, which are now little more than flattened sacs filled with keratins and associated proteins. The layer of lipid envelopes is a major component of the epidermal barrier against the loss of water from skin. Formation of this barrier, which appeared first in reptiles, was one of the important evolutionary events that permitted animals to develop on land. Together, keratinization and production of the lipid-rich layer also have a crucial sealing effect in skin, forming the barrier to penetration by most foreign materials.
- The **stratum lucidum** is only seen in thick skin, where it consists of a thin, translucent layer of extremely flattened eosinophilic cells (Figures 18–1 and 18-5). The nuclei and organelles have been lost and the cytoplasm consists almost only of densely packed keratin filaments embedded in an electron-dense matrix. Desmosomes are still evident between adjacent cells.
- The **stratum corneum** (Figures 18–2 and 18–3) consists of 15–20 layers of flattened, nonnucleated keratinized cells whose cytoplasm is filled with birefringent filamentous keratins. Keratin filaments contain at least six different polypeptides, with molecular mass ranging from 40 to 70 kDa, their composition changing as the epidermal cells differentiate and when the tonofibrils become heavily massed with other proteins from the keratohyaline granules. After keratinization, the cells contain only fibrillar and amorphous proteins with thickened plasma membranes and are called **squames** or horny, cornified cells. These cells are continuously shed at the surface of the stratum corneum.

Figure 18–5.



Stratum granulosum and stratum lucidum: thick skin.

In keratinocytes moving upward from the stratum spinosum (S) differentiation proceeds with the cells becoming filled with numerous large, amorphous masses of protein called keratohyaline granules which are highly basophilic. Cells that contain such granules form a stratum granulosum (G) only three to five cells thick, where keratin filaments are cross-linked with filaggrin and other proteins from these granules to produce tight bundles filling the cytoplasm and flattening the cells. Smaller organelles called lamellar granules undergo exocytosis in this layer, secreting a lipid-rich layer around the cells which makes the epidermis impermeable to water. Together the lipid envelope and the keratin-filled cells determine most of the physical properties of the epidermis. The cells leaving the stratum granulosum, still bound together by desmosomes, undergo terminal differentiation and in thick skin appear as a dense, thin layer called the stratum lucidum (L). The acidic proteins in the granular, basophilic masses are dispersed through the tonofibril bundles, giving the cells of this new layer an eosinophilic, clear appearance. In the most superficial layers, the stratum corneum (C), the cells are fully differentiated and have lost nuclei and cytoplasm. They consist only of flattened, keratinized structures called squames bound by hydrophobic, lipid-rich intercellular cement and at the surface they are worn away (thick skin) or flake off (thin skin). X560. H&E.

MEDICAL APPLICATION

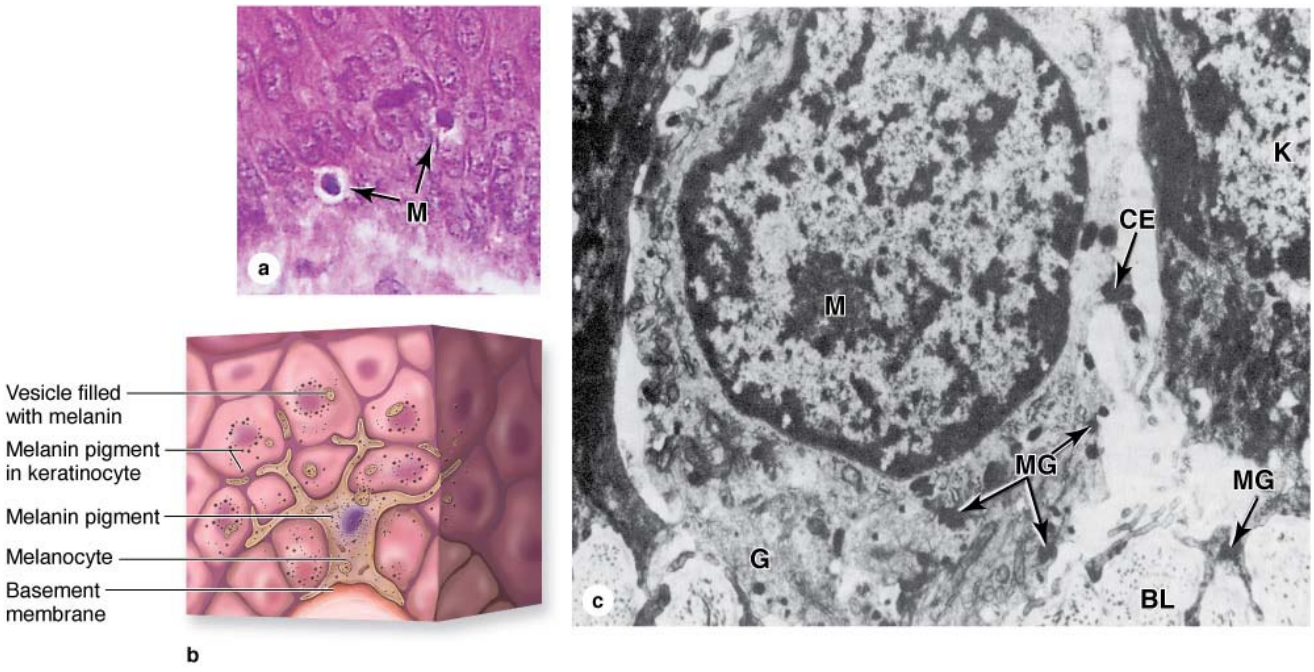
In **psoriasis**, a common skin disease, there is an increase in the number of proliferating cells in the stratum basale and the stratum spinosum as well as a decrease in the cycle time of these cells. This results in greater epidermal thickness and more rapid renewal of epidermis, but also can produce abnormal keratinization with a defective skin barrier.

Melanocytes

The color of the skin is the result of several factors, the most important of which are the keratinocytes' content of **melanin** and **carotene** and the number of blood vessels in the dermis.

Eumelanin is a brownish black pigment produced by the **melanocyte** (Figures 18–6 and 18–7), a specialized cell of the epidermis found among the cells of the basal layer and in the hair follicles. The similar pigment found in red hair is called **pheomelanin** (Gr. *phaios,* dusky, + *melas,* black). Melanocytes are neural crest derivatives which migrate into the developing epidermis' stratum basale, where eventually one melanocyte accumulates for every five or six basal keratinocytes (600–1200/mm^2 of skin). They have rounded cell bodies and form hemidesmosomes with the basal lamina, but no desmosomes with adjacent keratinocytes. Long irregular dendritic extensions from each melanocyte branch into the epidermis, running between the cells of the basal and spinous layers and terminating in invaginations of the neighboring five to ten keratinocytes. Ultrastructurally, a melanocyte is a pale-staining cell with numerous small mitochondria, short cisternae of rough endoplasmic reticulum (RER), and a well-developed Golgi apparatus (Figure 18–6).

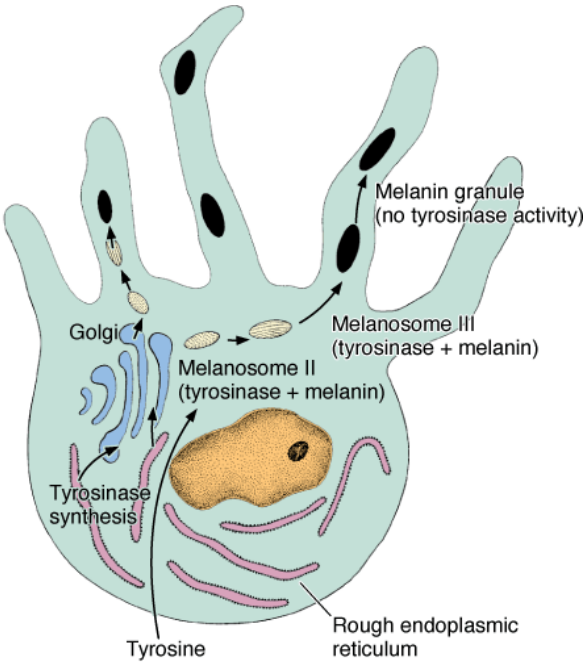
Figure 18–6.

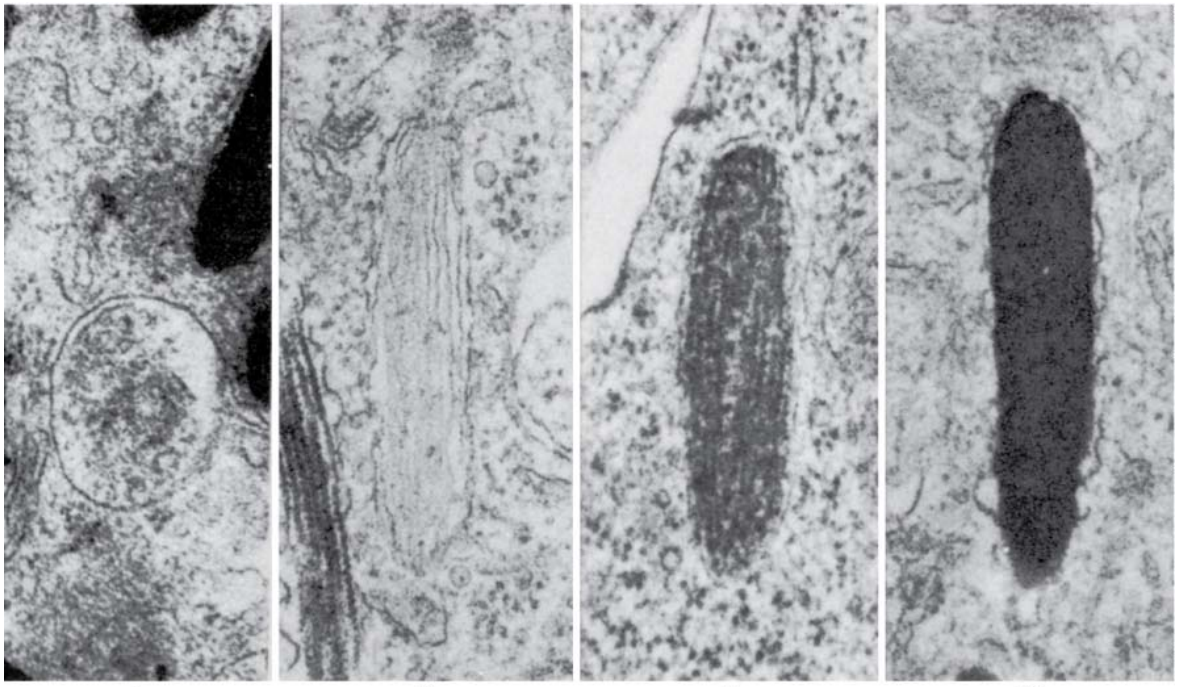


Melanocytes.

(a): Micrograph showing melanocytes (M) in the epidermal basal layer which synthesize melanin granules and transfer them into neighboring keratinocytes of the basal and spinous layers. Typically melanocytes are pale-staining cells on the basement membrane, with lower total melanin content than the keratinocytes. X400. H&E. **(b):** Diagram of a melanocyte. It sends irregular dendritic processes between neighboring keratinocytes for transfer of melanin to those cells. **(c):** Ultrastructurally, a melanocyte is located on the basal lamina (BL) and has well-developed Golgi complexes (G) producing the vesicles in which melanin is synthesized. As they fill, these vesicles become melanin granules (MG), which accumulate at the tips of the dendritic cytoplasmic extensions (CE) before transfer to keratinocytes (K). X14,000.

Figure 18–7.





Melanosome formation.

(Upper part): Diagram of a melanocyte, illustrating the main features of melanin formation. **(Lower part):** Maturation of the granules shown ultrastructurally. Tyrosinase is synthesized in the rough ER, is processed through the Golgi apparatus, and accumulates in vesicles that also have a fine granular matrix of other proteins (stage I melanosomes). Melanin synthesis begins in the ovoid stage II melanosomes, in which the matrix has been organized into parallel filaments on which polymerized melanin is deposited. Melanin accumulates on the matrix, forming a stage III melanosome and finally a mature melanin granule (stage IV) in which melanin completely fills the vesicle. This structure loses its tyrosinase activity and the internal matrix appears completely filled with melanin. The mature granules are ellipsoid, approximately 0.5 by 1 μm in size, and visible by light microscopy. Melanin granules are transported to the tips of the melanocyte's processes and are then transferred to the neighboring keratinocytes of the basal and spinous layers. In keratinocytes the melanin granules are transported to a region near the nucleus, where they accumulate as a supranuclear cap shading the DNA against the harmful effects of UV radiation.

MEDICAL APPLICATION

Malignant melanoma is an invasive tumor of melanocytes. Dividing rapidly, malignantly transformed melanocytes penetrate the basal lamina, enter the dermis, and invade the blood and lymphatic vessels to gain wide distribution throughout the body.

Melanin is synthesized in the melanocyte, with **tyrosinase** playing an important role in the process. Tyrosinase and tyrosinase-related proteins are transmembrane proteins synthesized in the rough ER, which accumulate in vesicles formed in the Golgi complex (Figure 18–7). Tyrosinase activity converts tyrosine first into **3,4-dihydroxyphenylalanine** (**DOPA**), which is then further transformed and polymerized into melanin. This pigment is then linked to a matrix of structural proteins in the vesicles. Melanin accumulates in these vesicles until they form mature granules called **melanosomes**, which are elliptical structures about 1 μm in length.

Once formed, melanin granules are transported via kinesin along microtubules to the actin-rich tips of the melanocyte's dendrites. The associated keratinocytes in both the basal and spinous layers phagocytose the tips of these dendrites and the ingested material fuses with lysosomes. These are transported along keratinocyte microtubules via dynein to the region near the nucleus, where the melanosomes are released. Within each keratinocyte they accumulate as a supranuclear cap which absorbs and scatters sunlight, protecting nuclear DNA from the deleterious effects of UV radiation.

Although melanocytes synthesize melanin, the keratinocytes act as a depot and contain more of this pigment than the cells that make it. One melanocyte plus the keratinocytes into which it transfers melanosomes make up an **epidermal-melanin unit**. The density of such units is similar in all individuals. Melanocytes of people with ancestral origins near the equator, where the need for protection against the sun is greatest, produce melanin granules more rapidly and accumulate them in keratinocytes more abundantly. UV radiation causes keratinocytes to secrete various paracrine factors that stimulate melanocyte activity.

Darkening of the skin (tanning) after exposure to solar radiation (wavelength of 290–320 nm) is the result of a two-step process. First, a physicochemical reaction darkens preexisting melanin. Next, the rates of melanin synthesis in the melanocytes and transfer to keratinocytes accelerate, increasing the amount of this pigment.

MEDICAL APPLICATION

In humans, lack of cortisol from the adrenal cortex causes overproduction of adrenocorticotropic hormone (ACTH), which can increase the pigmentation of the skin. An example of this is **Addison disease**, which is caused by dysfunction of the adrenal glands.

Albinism, a hereditary inability of the melanocytes to synthesize melanin, is caused by the absence of tyrosinase activity or the inability of cells to take up tyrosine. As a result, the skin is not protected from solar radiation by melanin, and there is a greater incidence of basal and squamous cell carcinomas (skin cancers).

The degeneration and disappearance of entire melanocytes causes a patchy loss of pigment in the skin disorder called **vitiligo**.

Dendritic (Langerhans) Cells

Antigen-presenting **dendritic cells** (**Langerhans cells**), which are usually most clearly seen in the spinous layer, represent 2–8% of the epidermal cells. Cytoplasmic processes extend from these dendritic cells between keratinocytes of all the layers, forming a fairly dense network in the epidermis (Figure 14–6). They are bone marrow–derived, blood-borne cells, capable of binding, processing, and presenting antigens to T lymphocytes in the same manner as immune dendritic cells in other organs. Microorganisms cannot penetrate the epidermis without alerting its dendritic cells and triggering an immune response. Langerhans cells, along with more scattered epidermal lymphocytes and similar immune cells in the dermis, make up a major component of the skin's adaptive immunity.

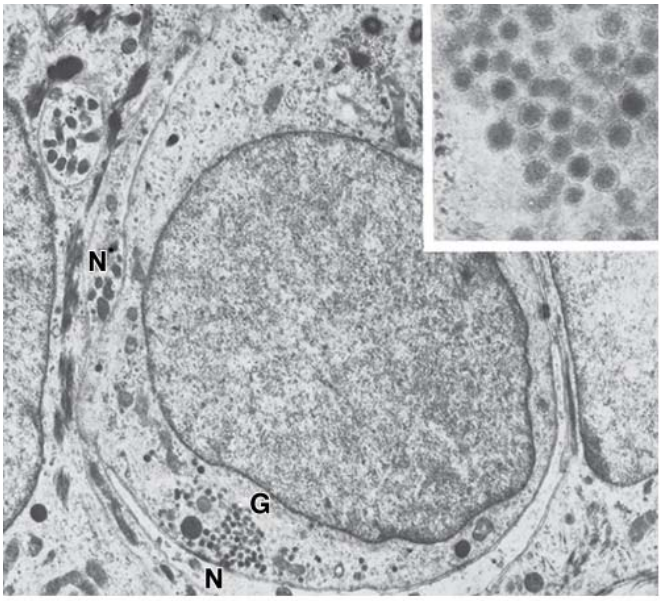
Because of its location the skin is continuously in close contact with many antigenic molecules. Various epidermal features participate in both innate and adaptive immunity (Chapter 14), providing an immunological component to the skin's overall protective function.

Tactile (Merkel) Cells

Epithelial tactile cells (commonly called **Merkel cells**) are mechanoreceptors that resemble pale-staining keratinocytes with keratin filaments in their cytoplasm but few if any melanosomes. Small, Golgi-derived dense-core neurosecretory granules containing peptides like those of neuroendocrine cells are a characteristic feature.

Derived from neural crest cells, Merkel cells are located in the basal epidermal layer (Figure 18–2) in areas of high tactile sensitivity and at the bases of hair follicles. The basolateral surfaces of the cells contact expanded terminal discs of unmyelinated sensory fibers that penetrate the basal lamina (Figure 18–8). Tactile cells have functions related to the diffuse neuroendocrine system (Chapter 20) in addition to their contributions as mechanoreceptors in the sense of touch.

Figure 18–8.



Tactile (Merkel) cell.

Epithelial tactile cells in the basal epidermal layer of skin with high tactile sensitivity are neural crest-derived cells that function as mechanoreceptors. TEM of a tactile cell from the finger epidermis of a 21-week fetus shows a mass of dense-core cytoplasmic granules (G) near the basolateral cell membrane, which is in direct contact with the expanded ending of a nerve (N). X14,000. **Inset:** Granules are similar in morphology and content to the granules of many neuroendocrine cells. X61,500. (Reproduced, with permission from Fitzpatrick TB et al: *Dermatology in General Medicine*. The McGraw-Hill Companies, 2008.)

MEDICAL APPLICATION

Merkel cells are of clinical importance because an uncommon carcinoma derived from them is very aggressive and difficult to treat. Merkel cell carcinoma is 40 times less common than malignant melanoma, but has twice the mortality of that disease.

DERMIS

The **dermis** is the connective tissue (Figures 18–1 and 18–2) that supports the epidermis and binds it to the subcutaneous tissue (hypodermis). The thickness of the dermis varies according to the region of the body, and reaches its maximum of 4 mm on the back. The surface of the dermis is very irregular and has many projections (dermal papillae) that interdigitate with projections (epidermal pegs or ridges) of the epidermis (Figure 18–1). Dermal papillae are more numerous in skin that is subjected to frequent pressure, where they reinforce the dermal-epidermal junction. During embryonic development, the dermal mesenchyme determines the differentiative fate of the overlying epidermis. For example, in mouse experiments, dermis obtained from the fetal foot sole always induces the formation of a thick, heavily keratinized epidermis irrespective of the site of origin of the epidermal cells.

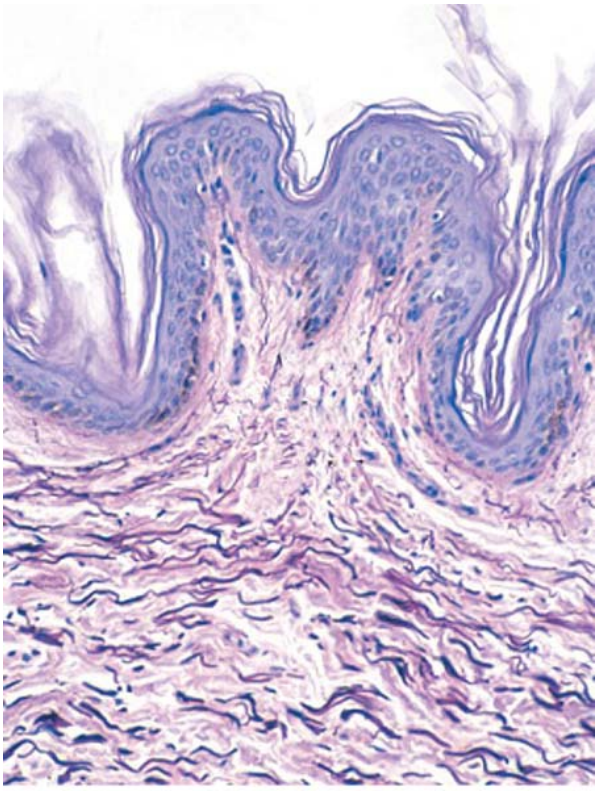
A **basement membrane** is always found between the stratum basale and the papillary layer of the dermis and follows the contour of the interdigitations between these layers. The basement membrane is a composite structure consisting of the **basal lamina** and the **reticular lamina** and can usually be seen with the light microscope. Nutrients for keratinocytes must diffuse into the avascular epidermis from the dermis vasculature through this basement membrane.

MEDICAL APPLICATION

Abnormalities of the dermal-epidermal junction can lead to one type of blistering disorder (**bullous pemphigoid**). Another type of blistering disorder (**pemphigus**) is caused by autoimmune damage to intercellular junctions between keratinocytes.

The dermis contains two layers with rather indistinct boundaries—the outermost papillary layer and the deeper reticular layer (Figure 18–1). The thin **papillary layer**, which constitutes the major part of the dermal papillae, is composed of loose connective tissue, with fibroblasts and other connective tissue cells, such as mast cells and macrophages. Extravasated leukocytes are also seen. From this layer, **anchoring fibrils** of type VII collagen insert into the basal lamina and bind the dermis to the epidermis**.** The **reticular layer** is thicker, composed of irregular dense connective tissue (mainly bundles of type I collagen), and has more fibers and fewer cells than the papillary layer. A network of elastic fibers is also present (Figure 18–9), providing elasticity to the skin. Spaces between the collagen and elastic fibers are filled with proteoglycans rich in dermatan sulfate.

Figure 18–9.



Elastic fibers of dermis.

Section of thin skin stained for elastic fibers shows the extensive distribution of darkly stained elastic fibers among the eosinophilic collagen bundles. In the dermal papillary layer, the diameter of fibers decreases as they approach the epidermis and insert into the basement membrane. X100. Weigert elastic stain.

MEDICAL APPLICATION

With age, collagen fibers thicken and collagen synthesis decreases. Elastic fibers steadily increase in number and thickness, so the elastin content of human skin increases approximately fivefold from fetal to adult life. In old age, extensive cross-linking of collagen fibers, the loss of elastic fibers, and degeneration of these fibers due to excessive exposure to the sun (**solar elastosis**) cause the skin to become more fragile, lose its suppleness, and develop wrinkles.

In several disorders, such as **cutis laxa** and **Ehlers-Danlos syndromes**, there is a considerable increase in skin and ligament extensibility caused by defective collagen-fibril processing.

The dermis is the site of such epidermal derivatives as the hair follicles and glands. There is also a rich supply of nerves in the dermis. The effector nerves to dermal structures are postganglionic fibers of sympathetic ganglia; no parasympathetic innervation is present. Sensory afferent nerve fibers form a network in the papillary dermis and around hair follicles, ending at epithelial tactile cells, at the encapsulated sensory receptors in dermis, and as free (uncovered) nerve endings among cells of the epidermis.

SUBCUTANEOUS TISSUE

The **subcutaneous layer** (Figure 18–1) consists of loose connective tissue that binds the skin loosely to the subjacent organs, making it possible for the skin to slide over them. This layer, also called the hypodermis or superficial fascia, often contains fat cells that vary in number in different regions of the body and vary in size according to nutritional state. An extensive vascular supply in the subcutaneous layer promotes rapid uptake of insulin or drugs injected into this tissue.

VESSELS & SENSORY RECEPTORS

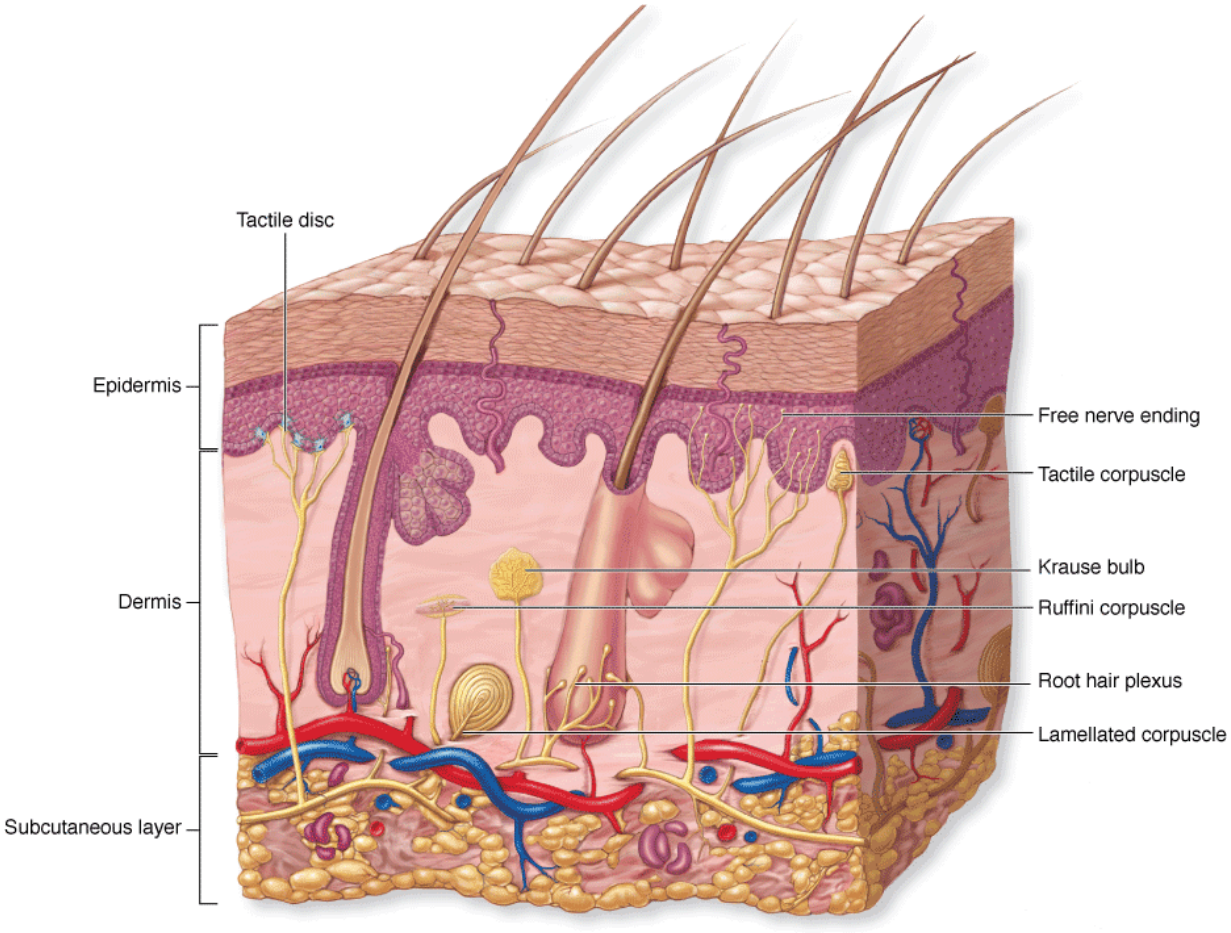
The connective tissue of the skin contains a rich network of blood and lymphatic vessels. Blood vessels that nourish the cells of skin form two major plexuses (Figure 18–1): deep at the interface between hypodermis and dermis, and superficially between the papillary and reticular dermal layers. The latter **subpapillary plexus** sends branches into the dermal papillae and supplies a rich, nutritive capillary network just below the epidermis.

In addition to the nutritive function, dermal vasculature has a thermoregulatory function which involves numerous **arteriovenous anastomoses** or shunts (Chapter 11) located between the two major plexuses. The shunts decrease blood flow in the papillary layer to minimize heat loss in cold conditions and increase this flow to facilitate heat loss when it is hot, thus helping maintain a constant body temperature. Lymphatic vessels begin as closed sacs in the dermal papillae and converge to form two plexuses located with the blood vessels.

With its large surface and external location, the skin functions as an extensive receiver for certain stimuli from the environment. A variety of sensory receptors are present in skin, including both simple nerve endings with no glial or collagenous covering and more complex structures with sensory fibers enclosed by glia and delicate connective tissue capsules (Figure 18–10). The *unencapsulated* receptors include the following:

- **Tactile discs** associated with the epidermal tactile cells (Figure 18–8), which function as receptors for light touch.
- **Free nerve endings** in the papillary dermis and extending into lower epidermal layers, which respond primarily to high and low temperatures, pain, and itching, but also function as tactile receptors.
- **Root hair plexuses**, a web of sensory fibers surrounding the bases of hair follicles in the reticular dermis that detects movements of the hairs.

Figure 18–10.



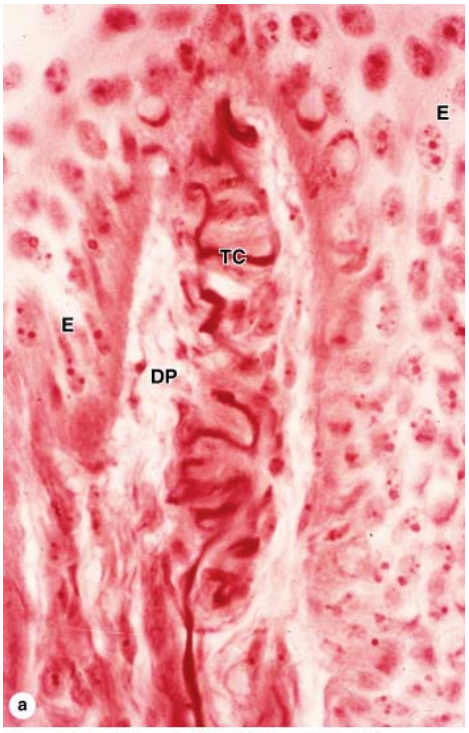
Tactile receptors.

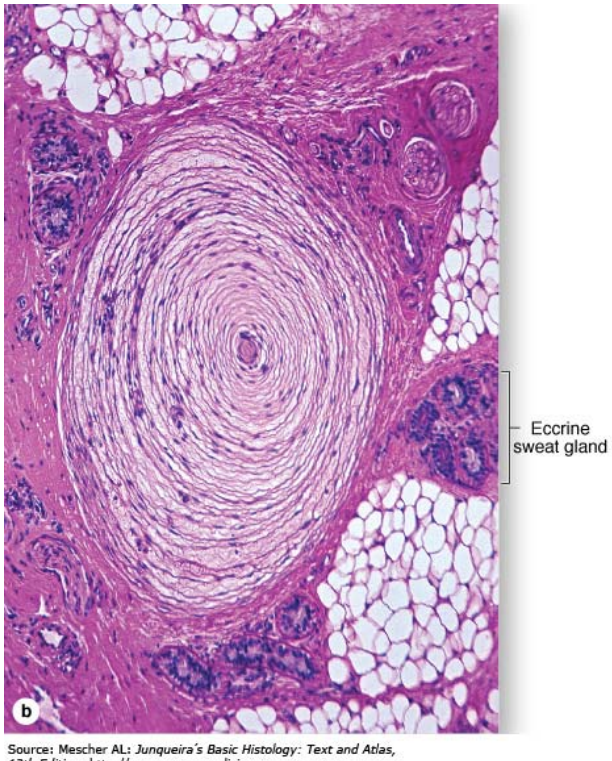
Skin contains several types of sensory receptors, primarily involved in the sense of touch. In the epidermis are free nerve endings and tactile discs on nerve fibers associated with tactile (Merkel) cells of the basal layer. Both have unencapsulated nerve fibers, as does the root hair plexus around the bases of hair follicles in the dermis. They detect light touch or movement of hair, although epidermal free nerve endings also detect pain and temperature extremes. More complex tactile receptors encapsulated with connective tissue layers are all in the dermis and include tactile (Meissner) receptors (light touch), lamellated (Pacinian) corpuscles (pressure and high-frequency vibration), Krause bulbs (pressure and low-frequency vibrations), and Ruffini corpuscles (continuous pressure and tissue distortion). The latter two receptors are less well characterized structurally and functionally.

The following *encapsulated* receptors are tactile mechanoreceptors:

- **Tactile corpuscles** (also called **Meissner corpuscles**) are elliptical structures, about 30–75 μm by 150 μm, perpendicular to the epidermis in the dermal papillae (Figure 18–11a) and papillary layer of the fingertips, palms and soles. They detect light touch.
- **Lamellated (Pacinian) corpuscles** are large oval structures, approximately 0.5 mm by 1 mm, found deep in the reticular dermis or hypodermis, with an outer capsule and 15 to 50 thin, concentric lamellae of flat Schwann-type cells and collagen surrounding a highly branched, unmyelinated axon (Figure 18–11b). Lamellated corpuscles are specialized for sensing coarse touch, pressure (sustained touch), and vibrations, with distortion of the capsule amplifying a mechanical stimulus to the axonal core where an impulse is initiated.
- Krause corpuscles and Ruffini corpuscles are other encapsulated, pressure-sensing mechanoreceptors in dermis, but are more poorly characterized structurally (Figure 18–10).

Figure 18–11.





Tactile and lamellated corpuscles.

Micrographs showing the two most commonly seen sensory receptors of skin. **(a):** Tactile (Meissner) corpuscle. X400. H&E. **(b):** Lamellated (Pacinian) corpuscle. X40. H&E. Tactile corpuscles (TC) are specialized to detect light touch and are frequently located in dermal papillae (DP), very close to the epidermis (E). They are elliptical in shape, approximately 150 μm long, with an outer capsule (from the perineurium) and thin, stacked inner layers of modified Schwann cells, around which course several nerve fibers.

Lamellated corpuscles detect coarse touch or pressure and are much larger oval structures, frequently 1 mm in length, found deep in the reticular dermis near the subcutaneous tissue. Here the outer connective tissue capsule surrounds 15 to 50 thin, concentric layers of modified Schwann cells, each separated by slightly viscous interstitial fluid. Several axons enter one end of the corpuscle and lie in the cylindrical, inner core of the structure. Movement or pressure of this corpuscle from any direction displaces the inner core, leading to a nerve impulse.

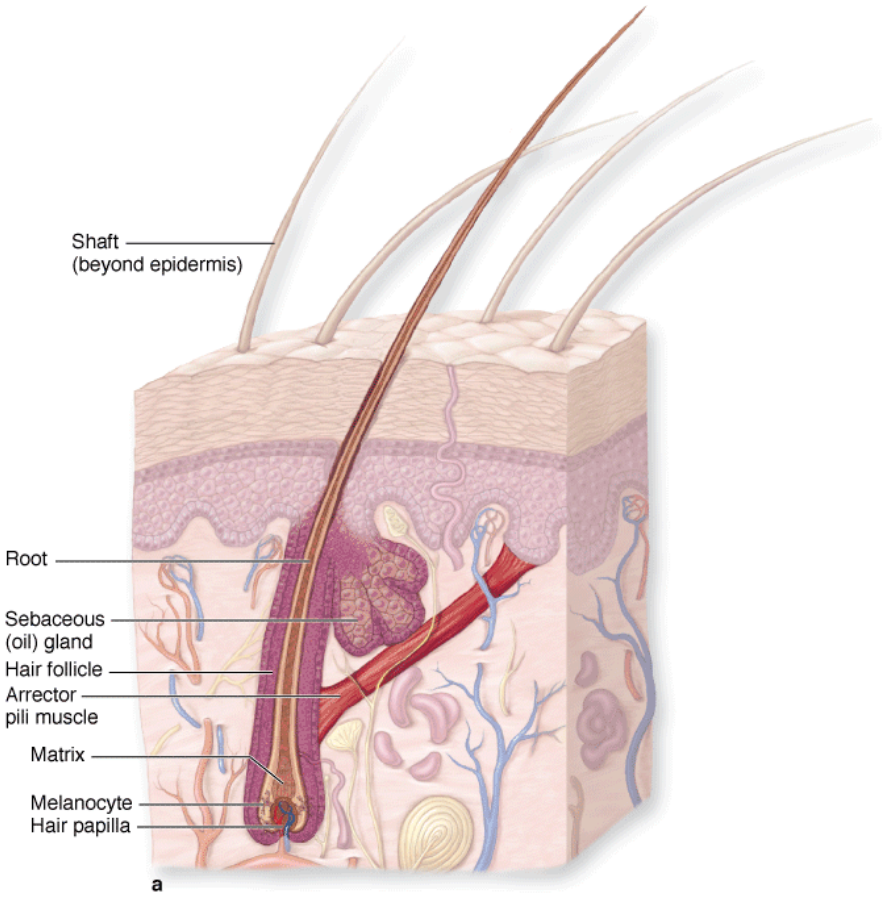
The encapsulated, lamellated mechanoreceptors are also found in the connective tissue of organs located deep in the body, including the wall of the rectum and urinary bladder, where they also produce the sensation of pressure when the surrounding tissue is distorted.

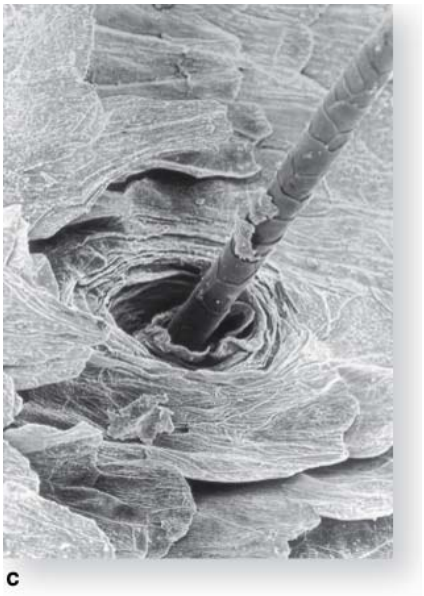
HAIR

Hairs are elongated keratinized structures derived from invaginations of the epidermal epithelium called **hair follicles** (Figure 18–12). The color, size, shape and texture of hairs vary according to age, genetic background, and region of the body. All skin has at least minimal hair except that of the palms, soles, lips, glans penis, clitoris, and labia minora. The face has about 600 hairs/cm^2 and the remainder of the body has about 60/cm^2. Hairs grow discontinuously, with periods of growth followed by periods of rest, and this growth does not occur synchronously in all regions of the body or even in the same area. The duration of the growth and rest periods

also varies according to the region of the body. In the scalp, growth periods (**anagen**) may last for several years, whereas the periods of follicle regression (**catagen**) and inactivity (**telogen**) may together last only 3 to 4 months. Hair growth on the face and pubis is strongly influenced by sex hormones, especially androgens.

Figure 18–12.





Hair.

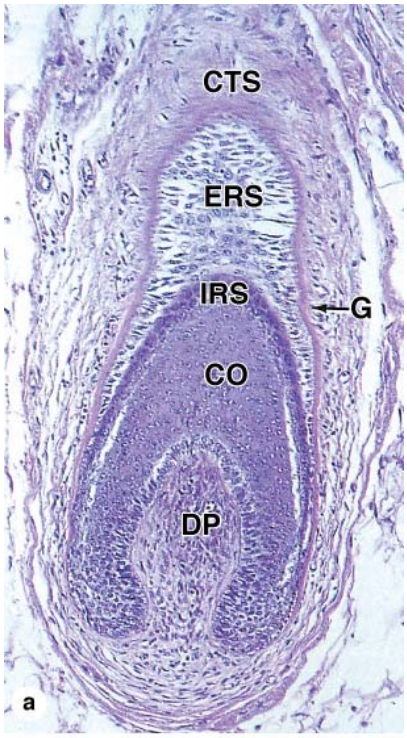
All types of body hair have a similar composition and form in hair follicles derived from the epidermis but extending deep into the dermis. One or more sebaceous glands form from the same epidermal down-growth and the entire structure is referred to as a pilosebaceous unit, which contains a specialized niche with stem cells for keratinocytes of the unit and neighboring epidermis. **(a):** Schematic diagram shows major parts of a hair follicle, including the arrector pili muscle which pulls the hair erect and sebaceous glands which empty into the follicle near the epidermis.

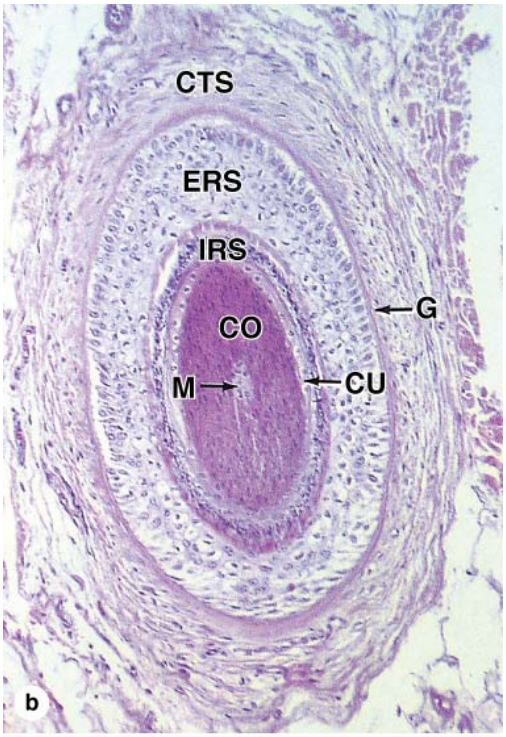
(b): Micrograph shows the medulla and cortex in the root of a hair cut longitudinally and the epithelial and connective tissue sheaths surrounding the growing hair. Both figures show the dermal hair papilla with microvasculature entering the base of the follicle. This nutritive papilla is surrounded by a matrix of epithelial cells similar to those of the stratum germinativum. Cells of the matrix proliferate, take up melanin granules, and undergo keratinization to differentiate as the three concentric layers of the hair. The outermost layer of the hair is the thin cuticle, composed of shingle-like cells. X70 and X180. H&E. **(c):** SEM shows the cuticle on a shaft of hair emerging at the stratum corneum from its follicle. X260.

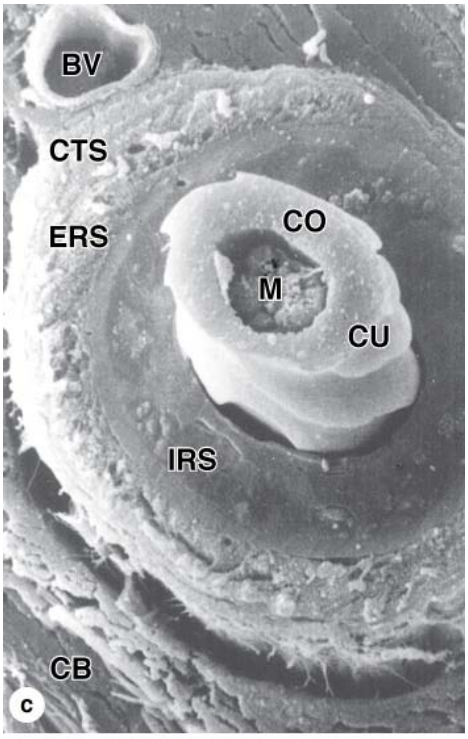
During anagen the hair follicle has a terminal dilatation called a **hair bulb** (Figure 18–12). A **dermal papilla** inserts into the base of the hair bulb and contains a capillary network required to sustain the hair follicle. Loss of this blood flow results in death of the follicle. The epidermal cells covering this dermal papilla form the **hair root** that produces and is continuous with the **hair shaft** protruding beyond the skin surface.

The epithelial cells (keratinocytes) that make up the hair bulb are similar to those in the basal and spinous layers of epidermis. They divide constantly and then undergo keratinization, differentiating into specific cell types. In certain types of thick hairs, the cells of the central region of the root at the apex of the dermal papilla produce large, vacuolated, and moderately keratinized cells that form the **medulla** of the hair (Figures 18–12b and 18–13). Other cells differentiate into heavily keratinized, compactly grouped fusiform cells that form the hair **cortex**. The most peripheral cells produce the hair **cuticle,** a thin layer of heavily keratinized, shingle-like cells covering the cortex (Figures 18–12c and 18–13). Melanocytes in the hair bulb transfer melanin granules into the epithelial cells that will later differentiate to form the hair.

Figure 18–13.







Layers of a hair and its follicle.

(a): The base of a hair follicle sectioned obliquely shows the vascularized dermal papilla (DP) continuous with the surrounding connective tissue sheath (CTS). The papilla is surrounded by the deepest part of the epithelial sheath, which is continuous with both the internal root sheath (IRS) and external root sheath (ERS). Both of these layers are in turn continuous with the stratified epidermis. Just outside the ERS is the glassy membrane (G) which is continuous with the basement membrane of the epidermis. The epithelial cells (keratinocytes) around the papilla proliferate and differentiate as the root of the hair itself. Above the papilla only the cortex (CO) of the hair is clearly seen in this section. X140. H&E. **(b):** A hair root sectioned more transversely shows the same layers of the follicular sheath, but the layers of the hair root are now seen to include the medulla (M), cortex (CO), and cuticle (CU). X140. H&E. **(c):** SEM of a similar specimen gives a different perspective on these layers, including the shingle-like nature of the thin cuticle surface, and the small blood vessel (BV) and collagen bundles (CB) in the surrounding dermis. X2600. (Figure 18–13c, with permission, from W.H. Freeman & Co., Kessel, R.G. and Kardon, R.H., 1979, Tissues and Organs: A Text-Atlas of Scanning Electron Microscopy.)

The outermost cells of the hair bulb are continuous with the epithelial root sheath, in which two layers can be recognized. The **internal root sheath** completely surrounds the initial part of the hair shaft but degenerates above the level of the attached sebaceous glands. The **external root sheath** covers the internal sheath and extends all the way to the epidermis, where it is continuous with the basal and spinous layers.

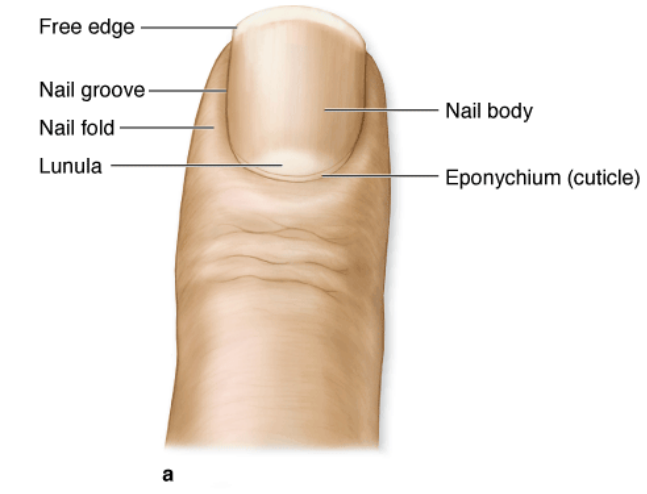
Separating the hair follicle from the dermis is an acellular hyaline layer, the thickened basement membrane called the **glassy membrane** (Figure 18–13). The surrounding dermis forms a connective tissue sheath. Running from a midpoint on this sheath and to the dermal papillary layer is a small bundle of smooth muscle cells, the **arrector pilimuscle** (Figures 18–1 and 18–12). Contraction of these muscles pulls the hair shafts to a more erect position, usually when it is cold in an effort to trap a layer of warm air near the skin. In regions where hair is fine, contraction of arrector pili muscles is seen to produce tiny bumps on the skin surface ("goose bumps") where each contracting muscle distorts the attached dermis.

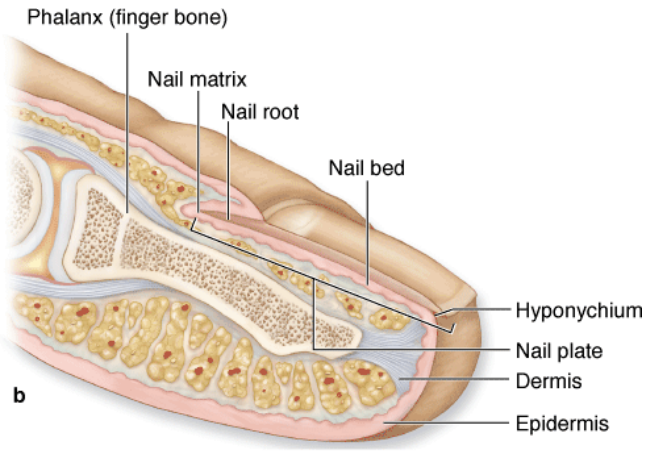
Hair color is produced by the activity of melanocytes located between the papilla and the epithelial cells of the hair root. The melanocytes produce and transfer melanin granules to these keratinocytes by a mechanism that is generally similar to that described for the epidermis. However, keratinization to produce hair does differ in some respects. Unlike epidermal keratinization where terminal differentiation of all cells gives rise to the stratum corneum, cells in the hair root differentiate into the cell types of the hair medulla, cortex, and cuticle which differ somewhat in ultrastructure, histochemical characteristics, and function. Keratin of hair has a harder and more compact nature that that of stratum corneum, maintaining its structure much longer. Finally, although keratinization in the epidermis occurs continuously and over the entire surface, it is intermittent in the hair and occurs only in the hair root.

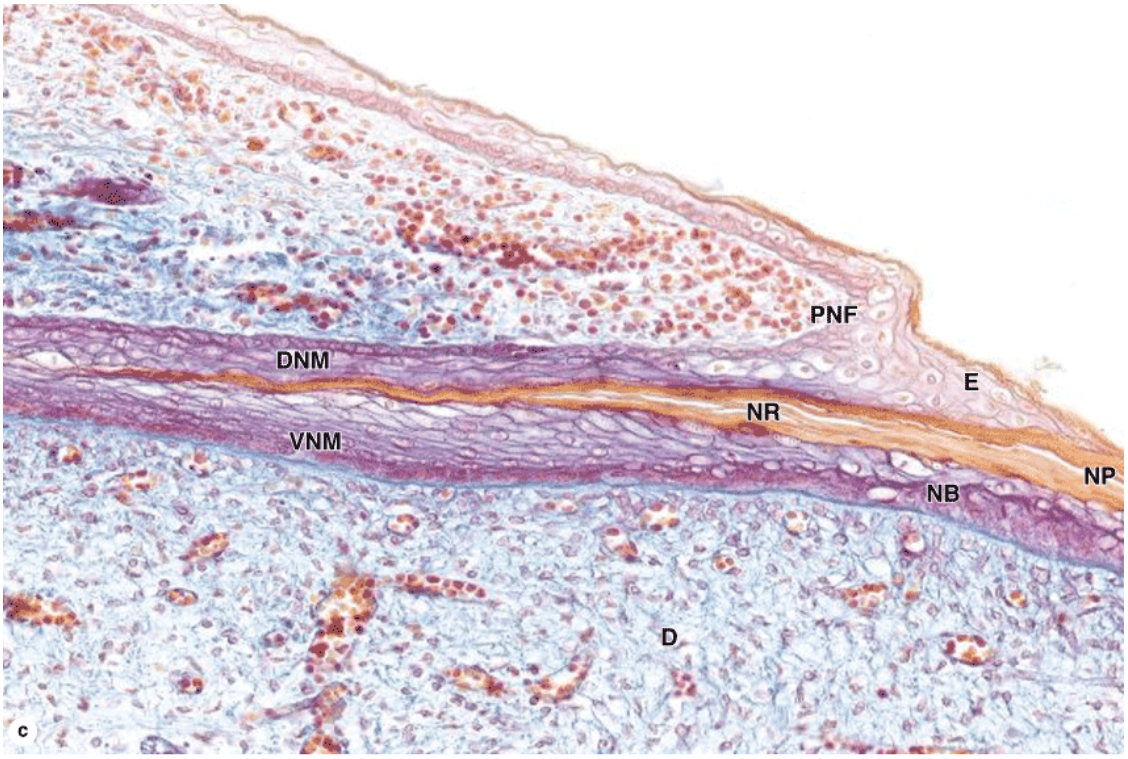
NAILS

A similar process of keratinization produces the **nails**, which are hard, flexible plates of keratin on the dorsal surface of each distal phalanx (Figure 18–14). The proximal part of the nail is the **nail root** and is covered by the proximal skin fold which is thin and lacks both hair and glands. The epidermal stratum corneum extending from the proximal nail fold forms the **cuticle**, or **eponychium**. The keratinized **nail plate** is bound to a bed of epidermis called the **nail bed**, which contains only the basal and spinous layers (Figure 18–14). The nail plate arises from the **nail matrix,** which extends from the nail root. Cells of the matrix divide, move distally, and become keratinized, forming the nail root. This matures as the nail plate, which continuous growth in the matrix pushes forward over the nail bed (which makes no contribution to the plate) at about 3 mm/month for fingernails and 1 mm/month for toenails. The distal end of the plate becomes free of the nail bed at the epidermal fold called the **hyponychium** and is worn away or cut off. The nearly transparent nail plate and the thin epithelium of the nail bed provide a useful window on the amount of oxygen in the blood by showing the color of blood in the dermal vessels.

Figure 18–14.







Nails.

Nails are hard, keratinized derivatives formed in a process similar to that of the stratum corneum and hair. **(a):** Surface view of a finger shows the nail's major parts, including the crescent-shaped white area called the lunula, which derives its color from the opaque nail matrix and immature nail plate below it. **(b):** Diagram of a sagittal section includes major internal details and shows the hyponychium at which the free end of the nail plate is bound to epidermis.

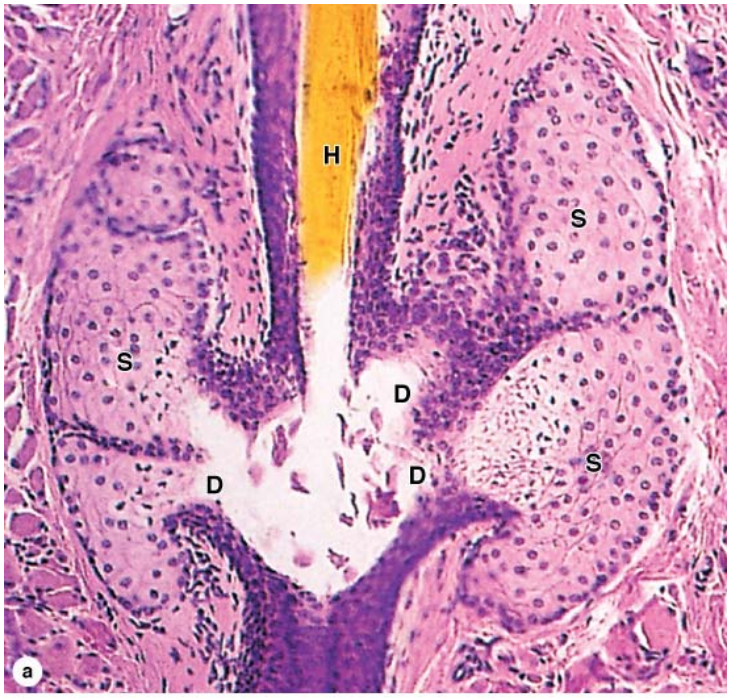
(c): A micrograph of a sagittal section from a fetal finger shows of the proximal nail fold (PNF) and its epidermal extension, the eponychium (E) or cuticle. The nail root (NR), the most proximal region of the nail plate (NP), is formed like the hair root by a matrix of proliferating, differentiating keratinocytes. These cells make up the dorsal nail matrix (DNM) and ventral nail matrix (VNM), which contribute keratinized cells to the nail root. The mature nail plate remains attached to the nail bed (NB), which consists of basal and spinous epidermal layers over dermis (D), but is pushed forward on this bed by continuous growth in the nail matrix. X100. Mallory trichrome.

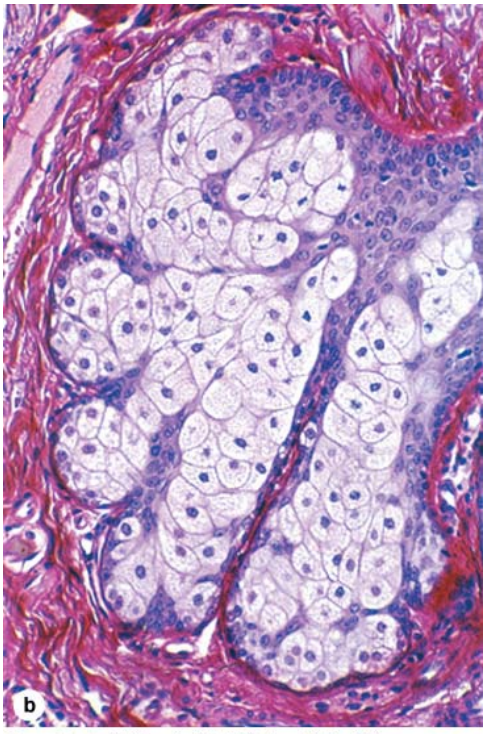
GLANDS OF THE SKIN

Sebaceous Glands

Sebaceous glands are embedded in the dermis over most of the body surface, except the thick, hairless (glabrous) skin of the palms and soles. There is an average of about 100 such glands per square centimeter of skin, but the frequency increases to 400–900/cm^2 in the face and scalp. Sebaceous glands are branched acinar glands with several acini converging at a short duct which usually empties into the upper portion of a hair follicle (Figure 18–12). The bulge region of the follicle is a stem cell niche generating cells of the hair follicle and matrix, the neighboring epidermis, and associated sebaceous glands. In certain hairless regions, such as the genital glands, eyelids, and nipples, sebaceous ducts open directly onto the epidermal surface. The acini consist of a basal layer of undifferentiated flattened epithelial cells on the basal lamina. These cells proliferate and are displaced toward the middle of the acinus, undergoing terminal differentiation as distinctly large, lipid-producing **sebocytes** which have their cytoplasm filled with small fat droplets (Figure 18–15). Their nuclei shrink and undergo autophagy along with other organelles and near the duct the cells disintegrate and release the lipids via holocrine secretion. The product of this process is **sebum,** which is gradually moved to the surface of the skin along the hair follicle or duct.

Figure 18–15.





Sebaceous glands.

Sebaceous glands secrete a complex mixture of lipids called sebum into short ducts which generally open into hair follicles **(a):** Micrograph shows small cells near the connective tissue capsule which proliferate and give rise to an acinus composed of large sebocytes (S), which undergo terminal differentiation by filling with small lipid droplets and then disintegrating at the ducts (D) near the hair (H) shaft, with the loss of nuclei and other organelles. X122. H&E. (b): Micrograph showing the gland's capsule and differentiating sebocytes at higher magnification X400. H&E. Sebum production is the classic example of holocrine secretion, in which the entire cell dies and contributes to the secretory product. Steady proliferation of the peripheral cells inside the capsule pushes sebum slowly and continuously into the ducts. Myoepithelial cells are not present.

Sebum is a complex mixture of lipids that includes wax esters, squalene, cholesterol and triglycerides which are hydrolyzed by bacterial enzymes after secretion. Secretion from sebaceous glands greatly increases at puberty, stimulated primarily by testosterone in men and by ovarian and adrenal androgens in women. Specific functions of sebum appear to include helping maintain the stratum corneum and hair, as well as exerting weak antibacterial and antifungal properties on the skin surface.

MEDICAL APPLICATION

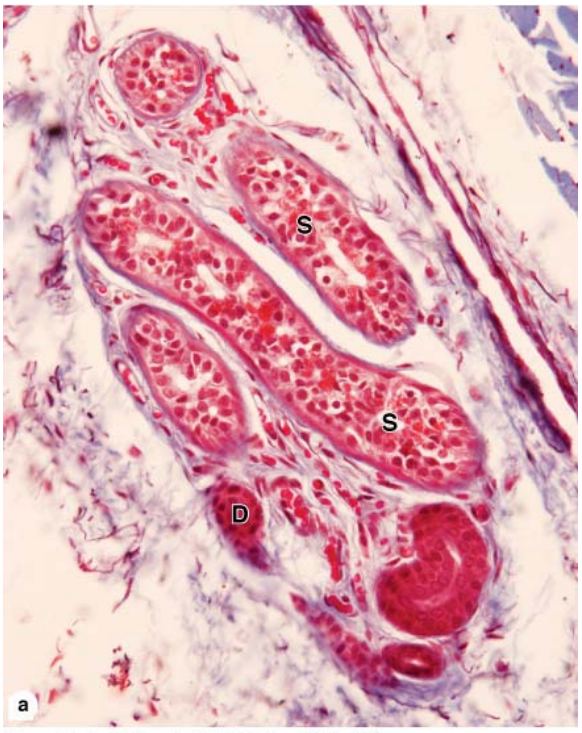
The flow of sebum is continuous, and a disturbance in the normal secretion and flow of sebum is one of the reasons for the development of **acne**, a chronic inflammation of obstructed sebaceous glands common during and after puberty.

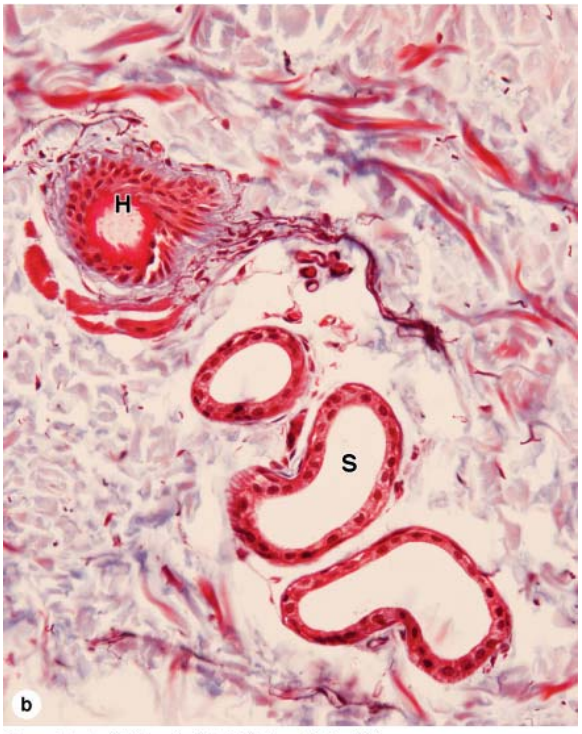
Sweat Glands

Sweat glands are epithelial derivatives embedded in the dermis which open to the skin surface (Figure 18–1) or into hair follicles. Eccrine sweat glands and apocrine sweat glands have different distributions, functions, and structural details.

Eccrine sweat glands (Figures 18–16 and 18–17) are widely distributed in the skin and are most numerous on the soles of the feet (620/cm^2). Collectively the 3 million eccrine sweat glands of the average person roughly equal the mass of a kidney and can produce as much as 10 L/day, a secretory rate far exceeding that of other exocrine glands. Sweating is the physiological response to increased body temperature during physical exercise or thermal stress and in humans the most effective means of temperature regulation.

Figure 18–16.

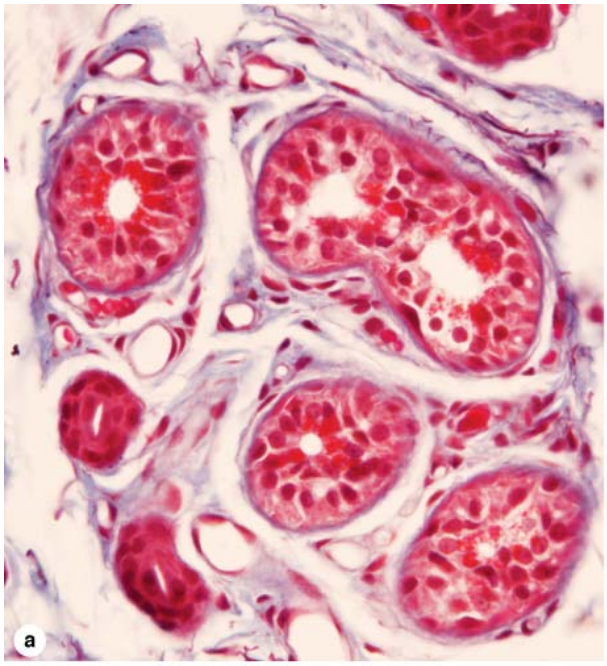


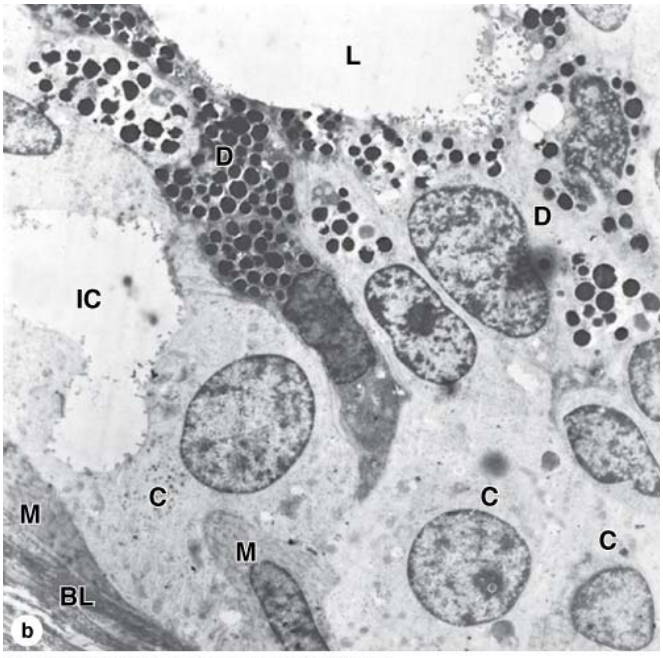


Eccrine and apocrine sweat glands.

(a): Micrograph of an eccrine sweat gland which plays an important thermoregulatory function in production of fluid which evaporates on the body surface, thereby cooling that surface. Histologically eccrine glands have small lumens in the secretory portions (S) and the ducts (D), both of which have an irregular stratified cuboidal appearance. **(b):** Apocrine sweat glands are restricted mainly to the axillae and perineum and produce a more protein-rich secretion with pheromonal properties. The lumens of apocrine gland secretory portion (S) are much larger than those of eccrine glands and their ducts open into hair follicles (H) rather than to the epidermal surface. Both X200. Mallory trichrome.

Figure 18–17.





Eccrine sweat gland secretory cells.

(a): The secretory portions of eccrine sweat glands have a stratified cuboidal epithelium, containing cell types with different staining properties. Cells closest to the lumen contain eosinophilic granules. X400. Mallory trichrome.

(b): TEM reveals three cell types. Myoepithelial cells (M) are thin cells present at the basal lamina (BL). Irregular pyramidal cells called dark cells (D) border the lumen (L) and are filled with the eosinophilic secretory granules which are electron-dense. Among the products released from these granules are bactericidal peptides and other components of innate immunity. Clear cells (C) are columnar and have their basal ends on the basal lamina and function in the rapid transport of water from interstitial fluid in the capillary-rich dermis directly into the lumen or into intercellular canaliculi (IC) which are continuous with the lumen. Na^+ ions are recovered from this fluid through the action of cells in the ducts, which are seen in the lower left corner of (a). X6500.

Both the secretory portions and ducts of eccrine sweat glands are coiled and have small lumens. The secretory part is generally more pale-staining than the ducts and has stratified cuboidal epithelium consisting of three cell types (Figure 18–17). Pale pyramidal or columnar **clear cells** produce the sweat, having abundant mitochondria and microvilli to provide large surface areas. Interstitial fluid from the capillary-rich dermis around the gland is transported through the clear cells, either directly into the lumen or into intercellular canaliculi that open to the lumen. As numerous as the clear cells are pyramidal **dark cells** which line most of the luminal surface and do not touch the basal lamina (Figure 18–17). Dark cells are mucoid and filled with glycoprotein-containing granules whose functions are not well-understood but include components of innate immunity with bactericidal activity. **Myoepithelial cells** on the basal lamina (Figure 4–27) produce contractions that help discharge secretion into the duct.

The ducts of eccrine sweat glands consist of two layers of more acidophilic epithelial cells filled with mitochondria and having membranes rich in Na^+, K^+-ATPase. These duct cells absorb Na^+ ions to prevent excessive loss of this electrolyte. After its release on the surface of the skin sweat evaporates, cooling the skin. Besides its important cooling role, sweat glands also function as an auxiliary excretory organ, eliminating small amounts of nitrogenous waste and excess salts.

Apocrine sweat glands are largely confined to skin of the axillary and perineal regions. Their development (but not functional activity) depends on sex hormones and is not complete until puberty. The most obvious histological difference between the two kinds of sweat glands is the much larger lumen of apocrine glands (Figure 18–16). The secretory portions of apocrine sweat glands consist of simple cuboidal, eosinophilic cells with numerous apical secretory granules that undergo exocytosis. Thus the

glands are misnamed: their cells show merocrine, not apocrine, secretion. Lumens of apocrine glands often show stored, protein-rich product, which myoepithelial cells help move into ducts opening into hair follicles. The wall of the ducts is similar to that of the eccrine glands. The slightly viscous secretion is initially odorless but may acquire a distinctive odor as a result of bacterial activity. The production of pheromones by apocrine glands is well-established in many mammals and likely in humans, although in a reduced or vestigial capacity. Apocrine sweat glands are innervated by adrenergic nerve endings, whereas eccrine sweat glands receive cholinergic fibers.