Skin

The skin is the heaviest single organ of the body, accounting for about 16% of total body weight and, in adults, presenting 1.2-2.3 m^2 of surface to the external environment. It is composed of the **epidermis,** an epithelial layer of ectodermal origin, and the **dermis,** a layer of connective tissue of mesodermal origin. Based on the comparative thickness of the epidermis, **thick** and **thin** skin can be distinguished. 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.** In three dimensions, these interdigitations may be of the peg-and-socket variety (thin skin) or formed of ridges and grooves (thick skin). Epidermal derivatives include hairs, nails, and sebaceous and sweat glands. Beneath the dermis lies the **hypodermis** (Gr. *hypo,* under, + *derma,* skin), or **subcutaneous tissue,** a loose connective tissue that may contain a pad of adipose cells, the **panniculus adiposus.** The hypodermis, which is not considered part of the skin, binds skin loosely to the subjacent tissues and corresponds to the superficial fascia of gross anatomy.

The external layer of the skin is relatively impermeable to water; this prevents water loss by evaporation and allows for terrestrial life. The skin functions as a receptor organ in continuous communication with the environment and protects the organism from impact and friction injuries. **Melanin,** a pigment produced and stored in the cells of the epidermis, provides further protective action against the sun's ultraviolet (UV) rays. Glands of the skin, blood vessels, and adipose tissue participate in thermoregulation, body metabolism, and the excretion of various substances. Under the action of solar radiation received by skin, active vitamin D$_3$ is formed from precursors synthesized by the organism through the modification of molecules introduced with foodstuff. Because skin is elastic, it can expand to cover large areas in conditions associated with swelling, such as edema and pregnancy.

Upon close observation, certain portions of human skin show ridges and grooves arranged in distinctive patterns. These ridges first appear during intrauterine life: at 13 weeks in the tips of the fingers and later in the volar surfaces of the hands and feet (palm and sole). The patterns assumed by ridges and intervening sulci are known as **dermatoglyphics.** They are unique for each individual, appearing as loops, arches, whorls, or combinations of these forms. These configurations, which are used for personal identification (fingerprints), are probably determined by multiple genes; the field of dermatoglyphics has come to be of considerable medical and anthropological as well as legal interest.

Epidermis

The epidermis consists mainly of a stratified squamous keratinized epithelium, but it also contains three less abundant cell types: **melanocytes, Langerhans cells,** and **Merkel's cells.** The keratinizing epidermal cells are called keratinocytes. It is customary to

distinguish between the **thick skin** (**glabrous,** or smooth and nonhairy) found on the palms and soles and the **thin skin** (hairy) found elsewhere on the body. The designations "thick" and "thin" refer to the thickness of the epidermal layer, which varies between 75 and 150 m for thin skin and 400 and 600 m 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.

From the dermis outward, the epidermis consists of five layers of keratin-producing cells (keratinocytes).

1- *Stratum Basale (Stratum Germinativum)*

The stratum basale consists of a single layer of basophilic columnar or cuboidal cells resting on the basement membrane at the dermal–epidermal junction (Figure 18–1). Desmosomes bind the cells of this layer together in their lateral and upper surfaces. Hemidesmosomes, found in the basal plasmalemma, help bind these cells to the basal lamina. The stratum basale, containing stem cells, is characterized by intense mitotic activity and is responsible, in conjunction with the initial portion of the next layer, for constant renewal of epidermal cells. The human epidermis is renewed about every 15-30 days, depending on age, the region of the body, and other factors. All cells in the stratum basale contain intermediate keratin filaments about 10 nm in diameter. As the cells progress upward, the number of filaments increases until they represent half the total protein in the stratum corneum.

2- *Stratum Spinosum*

The stratum spinosum consists of cuboidal, or slightly flattened, cells with a central nucleus and a cytoplasm whose processes are filled with bundles of keratin filaments. These bundles converge into many small cellular extensions, terminating with desmosomes located at the tips of these spiny projections . The cells of this layer are firmly bound together by the filament-filled cytoplasmic spines and desmosomes that punctuate the cell surface, providing a spine-studded appearance. These keratin bundles, visible under the light microscope, are called **tonofilaments;** they end at and insert into the cytoplasmic densities of the desmosomes. The filaments play an important role in maintaining cohesion among cells and resisting the effects of abrasion. 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 tonofilaments and desmosomes. All mitoses are confined to what is termed the **malpighian layer,** which consists of both the stratum basale and the stratum spinosum. Only the malpighian layer contains epidermal stem cells.

3- Stratum Granulosum

The stratum granulosum consists of three to five layers of flattened polygonal cells whose cytoplasm is filled with coarse basophilic granules called **keratohyalin granules.** The proteins of these granules contain a phosphorylated histidine-rich protein as well as proteins containing cystine. The numerous phosphate groups account for the intense basophilia of keratohyalin granules, which are not surrounded by a membrane.

Another characteristic structure in the cells of the granular layer of epidermis that can be seen with the electron microscope is the membrane-coated **lamellar granule,** a small (0.1- 0.3 µm) ovoid or rodlike structure containing lamellar disks that are formed by lipid bilayers. These granules fuse with the cell membrane and discharge their contents into the intercellular spaces of the stratum granulosum, where they are deposited in the form of sheets containing lipid. The function of this extruded material is similar to that of intercellular cement in that it acts as a barrier to penetration by foreign materials and provides a very important sealing effect in the skin. Formation of this barrier, which appeared first in reptiles, was one of the important evolutionary events that permitted development of terrestrial life.

4- Stratum Lucidum

More apparent in thick skin, the stratum lucidum is a translucent, thin layer of extremely flattened eosinophilic epidermal cells. The organelles and nuclei are no longer evident, and the cytoplasm consists primarily of densely packed keratin filaments embedded in an electron-dense matrix. Desmosomes are still evident between adjacent cells.

5- Stratum Corneum

The stratum corneum consists of 15-20 layers of flattened nonnucleated keratinized cells whose cytoplasm is filled with a birefringent filamentous scleroprotein, **keratin.** The composition of tonofilaments changes as epidermal cells differentiate. Basal cells contain polypeptides of lower molecular weight, whereas more differentiated cells synthesize higher-molecular-weight polypeptides. Tonofilaments are packed together in a matrix contributed by the keratohyalin granules.

After keratinization, the cells consist of only fibrillar and amorphous proteins and thickened plasma membranes; they are called **horny cells.** During keratinization, lysosomal hydrolytic enzymes play a role in the disappearance of the cytoplasmic organelles. These cells are continuously shed at the surface of the stratum corneum.

This description of the epidermis corresponds to its most complex structure in areas where it is very thick, as on the soles of the feet.

In thin skin, the stratum granulosum and the stratum lucidum are often less well developed, and the stratum corneum may be quite thin .

Nonkeratogenic cells of the epidermis

1- Melanocytes

The color of the skin is the result of several factors, the most important of which are its content of **melanin** and **carotene,** the number of blood vessels in the dermis, and the color of the blood flowing in them. **Eumelanin** is a dark brown pigment produced by the **melanocyte**, a specialized cell of the epidermis found beneath or between the cells of the stratum basale and in the hair follicles. The pigment found in red hair is called **pheomelanin** (Gr. *phaios,* dusky, + *melas,* black) and contains **cysteine** as part of its structure. Melanocytes are derived from neural crest cells. They have rounded cell bodies from which long irregular extensions branch into the epidermis, running between the cells of the strata basale and spinosum. Tips of these extensions terminate in invaginations of the cells present in the two layers. The electron microscope reveals a pale-staining cell containing numerous small mitochondria, a well-developed Golgi complex, and short cisternae of rough endoplasmic reticulum. Although melanocytes are not attached to the adjacent keratinocytes by desmosomes, they are bound to the basal lamina by hemidesmosomes.

Melanin is synthesized in the melanocyte, with tyrosinase playing an important role in the process.

2- Langerhans Cells

Langerhans cells, star-shaped cells found mainly in the stratum spinosum of the epidermis, represent 2-8% of the epidermal cells. They are bone marrow derived, carried to the skin by the blood, and capable of binding, processing, and presenting antigens to T lymphocytes, thus participating in the stimulation of these cells. Consequently, they have a significant role in immunological skin reactions. Langerhans cells are **antigen-presenting** cells.

3- Merkel's Cells

Merkel's cells, generally present in the thick skin of palms and soles, somewhat resemble the epidermal epithelial cells but have small dense granules in their cytoplasm. The composition of these granules is not known. Free nerve endings that form an expanded terminal disk are present at the base of Merkel's cells. These cells may serve as sensory mechanoreceptors, although other evidence suggests that they have functions related to the diffuse neuroendocrine system.

Immunological Activity in the Skin

Because of its large size, the skin has an impressive number of lymphocytes and antigen-presenting cells (Langerhans cells), and because of its location it is in close contact with many antigenic molecules. For these reasons, the epidermis has an important role in some types of immune responses. Most lymphocytes found in the skin are "homed" in the epidermis.

Dermis

The dermis is the connective tissue 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. Dermal papillae are more numerous in skin that is subjected to frequent pressure; they increase and reinforce the dermal–epidermal junction. During embryonic development, the dermis determines the developmental pattern of the overlying epidermis. Dermis obtained from the sole always induces the formation of a heavily keratinized epidermis irrespective of the site of origin of the epithelial cells. A **basal lamina** is always found between the stratum germinativum and the papillary layer of the dermis and follows the contour of the interdigitations between these layers. Underlying the basal lamina is a delicate net of reticular fibers, the **lamina reticularis.** This composite structure is called the **basement membrane** and can be seen with the light microscope The dermis contains two layers with rather indistinct boundaries the outermost papillary layer and the deeper reticular layer. The thin **papillary layer** is composed of loose connective tissue; fibroblasts and other connective tissue cells, such as mast cells and macrophages, are present. Extravasated leukocytes are also seen. The papillary layer is so called because it constitutes the major part of the dermal papillae. From this layer, special collagen fibrils insert into the basal lamina and extend into the dermis. They bind the dermis to the epidermis and are called **anchoring fibrils.** The **reticular layer** is thicker, composed of irregular dense connective tissue (mainly type I collagen), and therefore has more fibers and fewer cells than does the papillary layer. The principal glycosaminoglycan is dermatan sulfate. The dermis contains a network of fibers of the elastic system, with the thicker fibers characteristically found in the reticular layer. From this region emerge fibers that become gradually thinner and end by inserting into the basal lamina. As these fibers progress toward the basal lamina, they gradually lose their amorphous elastin component , and only the microfibrillar component inserts into the basal lamina. This elastic network is responsible for the elasticity of the skin. The dermis also contains epidermal derivatives such as the hair follicles and sweat and sebaceous glands. There is a rich supply of nerves in the dermis, and the effector nerves to the skin are postganglionic fibers of sympathetic ganglia of the paravertebral chain. No parasympathetic innervation is present. The afferent nerve endings form a superficial

dermal network with free nerve endings, a hair follicle network, and the innervation of encapsulated sensory organs.

Subcutaneous Tissue

The subcutaneous tissue layer consists of loose connective tissue that binds the skin loosely to the subjacent organs, making it possible for the skin to slide over them. The hypodermis often contains fat cells that vary in number according to the area of the body and vary in size according to nutritional state. This layer is also referred to as the superficial fascia and, where thick enough, the panniculus adiposus.

Vessels & Skin Sensorial Receptors

The connective tissue of the skin contains a rich network of blood and lymphatic vessels. The arterial vessels that nourish the skin form two plexuses. One is located between the papillary and reticular layers; the other is located between the dermis and the subcutaneous tissue. Thin branches leave these plexuses and vascularize the dermal papillae. Each papilla has only one arterial ascending branch and one venous descending branch. Veins are disposed in three plexuses, two in the position described for arterial vessels and the third in the middle of the dermis. Arteriovenous anastomoses with glomera are frequent in the skin, participating in the regulation of body temperature. Lymphatic vessels begin as closed sacs in the papillae of the dermis and converge to form two plexuses, as described for the arterial vessels. One of the most important functions of the skin, with its great extension and abundant sensory innervation, is to receive stimuli from the environment. The skin is the most extensive sensory receptor. In addition to numerous free nerve endings in the epidermis, hair follicles, and cutaneous glands, encapsulated and expanded receptors are present in the dermis and subcutaneous tissue; they are more frequently found in the dermal papillae. Free nerve endings are sensitive to touch-pressure (pressure is sustained touch), tactile reception, high and low temperatures, pain, itching, and other sensations. The expanded ending includes the **Ruffini endings,** and the encapsulated ending includes the **Vater-Pacini, Meissner,** and **Krause** corpuscles. There is evidence that the expanded and encapsulated corpuscles are not necessary for cutaneous sensation. Their distribution is irregular, with many areas of skin containing only free nerve endings. However, when present, the expanded and encapsulated receptors respond to tactile stimuli, functioning as mechanoreceptors. Vater Pacini corpuscles and Ruffini endings are also found in the connective tissue of organs located deep in the body, where they probably are sensitive to movements of internal organs and to pressure of one organ over another.

Hairs

Hairs are elongated keratinized structures derived from invaginations of epidermal epithelium. Their color, size, and disposition vary according to race, age, sex, and region of

the body. Hairs are found everywhere on the body except on 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 and have periods of growth followed by periods of rest. This growth does not occur synchronously in all regions of the body or even in the same area; rather, it tends to occur in patches. The duration of the growth and rest periods also varies according to the region of the body. Thus, in the scalp, the growth periods (anagen) may last for several years, whereas the rest periods (catagen and telogen) average 3 months. Hair growth in such regions of the body as the scalp, face, and pubis is strongly influenced not only by sex hormones especially androgens but also by adrenal and thyroid hormones.

Each hair arises from an epidermal invagination, the **hair follicle**, that during its growth period has a terminal dilatation called a **hair bulb.** At the base of the hair bulb, a **dermal papilla** can be observed. The dermal papilla contains a capillary network that is vital in sustaining the hair follicle. Loss of blood flow or loss of the vitality of the dermal papilla will result 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, which protrudes beyond the skin.

During periods of growth, the epithelial cells that make up the hair bulb are equivalent to those in the stratum germinativum of the skin. They divide constantly and differentiate 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. Root cells multiply and differentiate into heavily keratinized, compactly grouped fusiform cells that form the **hair cortex.** Farther toward the periphery are the cells that produce the **hair cuticle,** a layer of cells that is cuboidal midway up the bulb, then becomes tall and columnar. Higher up, these cells change from horizontal to vertical, at which point they form a layer of flattened, heavily keratinized, shinglelike cells covering the cortex. These cuticle cells are the last cell type in the hair follicle to differentiate.

The outermost cells give rise to the **internal root sheath,** which completely surrounds the initial part of the hair shaft. The internal sheath is a transient structure whose cells degenerate and disappear above the level of the sebaceous glands. The **external root sheath** is continuous with epidermal cells and, near the surface, shows all the layers of epidermis. Near the dermal papilla, the external root sheath is thinner and is composed of cells corresponding to the stratum germinativum of the epidermis.

Separating the hair follicle from the dermis is a noncellular hyaline layer, the **glassy membrane**, which results from a thickening of the basal lamina. The dermis that surrounds the follicle is denser, forming a sheath of connective tissue. Bound to this sheath and connecting it to the papillary layer of the dermis are bundles of smooth muscle cells, the **arrector pili** muscles. They are disposed in an oblique direction, and their contraction

results in the erection of the hair shaft to a more upright position. Contraction of arrector pili muscles also causes a depression in the skin where the muscles attach to the dermis. This contraction produces the "gooseflesh" of common parlance.

Hair color is created by the activity of melanocytes located between the papilla and the epithelial cells of the hair root. The epithelial cells produce the pigment found in the medullary and cortical cells of the hair shaft. The melanocytes produce and transfer melanin to the epithelial cells by a mechanism similar to that described for the epidermis.

Although the keratinization processes in the epidermis and hair appear to be similar, they differ in several ways:

1. The epidermis produces relatively *soft* keratinized outer layers of dead cells that adhere slightly to the skin and desquamate continuously. The opposite occurs in the hair, which has a *hard* and compact keratinized structure.

2. 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*. The connective tissue of the hair papilla has an inductive action on the covering epithelial cells, promoting their proliferation and differentiation. Injuries to the dermal papillae thus result in the loss of hair.

3. Contrary to what happens in the epidermis, where the differentiation of all cells *in the same direction* gives rise to the final keratinized layer, cells in the hair root differentiate into *various cell types* that differ in ultrastructure, histochemical characteristics, and function.

Mitotic activity in hair follicles is influenced by androgens.

Nails

Nails are plates of keratinized epithelial cells on the dorsal surface of each distal phalanx. The proximal part of the nail, hidden in the nail groove, is the **nail root.** The epithelium of the fold of skin covering the nail root consists of the usual layers of cells. The stratum corneum of this epithelium forms the **eponychium,** or **cuticle.** The **nail plate,** which corresponds to the stratum corneum of the skin, rests on a bed of epidermis called the **nail bed.** Only the stratum basale and the stratum spinosum are present in the nail bed. Nail plate epithelium arises from the **nail matrix.** The proximal end of the matrix extends deep to the nail root. Cells of the matrix divide, move distally, and eventually cornify, forming the proximal part of the nail plate. The nail plate then slides forward over the nail bed (which makes no contribution to the formation of the plate). The distal end of the plate becomes free of the nail bed 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.

Glands of the Skin

Sebaceous Glands

Sebaceous glands are embedded in the dermis over most of the body surface. There are about 100 of these glands per square centimeter over most of the body, but the frequency increases to 400 - 900/cm^2 in the face, forehead, and scalp. Sebaceous glands, which are not found in the glabrous skin of the palms and soles, are acinar glands that usually have several acini opening into a short duct. This duct usually ends in the upper portion of a hair follicle; *in certain regions, such as the glans penis, glans clitoridis, and lips, it opens directly onto the epidermal surface.* The acini consist of a basal layer of undifferentiated flattened epithelial cells that rests on the basal lamina. These cells proliferate and differentiate, filling the acini with rounded cells containing increasing amounts of fat droplets in their cytoplasm. Their nuclei gradually shrink, and the cells simultaneously become filled with fat droplets and burst. The product of this process is **sebum,** the secretion of the sebaceous gland, which is gradually moved to the surface of the skin.

The sebaceous gland is an example of a **holocrine** gland, because its product of secretion is released with remnants of dead cells. This product comprises a complex mixture of lipids that includes triglycerides, waxes, squalene, and cholesterol and its esters. Sebaceous glands begin to function at puberty. The primary controlling factor of sebaceous gland secretion in men is testosterone; in women it is a combination of ovarian and adrenal androgens.

The functions of sebum in humans are largely unknown. It may have weak antibacterial and antifungal properties. Sebum does not have any importance in preventing water loss.

Sweat Glands

Sweat glands are widely distributed in the skin *except for certain regions, such as the glans penis.*

The **merocrine** sweat glands are simple, coiled tubular glands whose ducts open at the skin surface . Their ducts do not divide, and their diameter is thinner than that of the secretory portion. The secretory part of the gland is embedded in the dermis; it measures approximately 0.4 mm in diameter and is surrounded by myoepithelial cells. Contraction of these cells helps to discharge the secretion. Two types of cells have been described in the secretory portion of sweat glands. **Dark cells** are pyramidal cells that line most of the luminal surface of this portion of the gland. Their basal surface does not touch the basal lamina. Secretory granules containing glycoproteins are abundant in their apical cytoplasm. **Clear cells** are devoid of secretory granules. Their basal plasmalemma has the numerous

invaginations characteristic of cells involved in transepithelial salt and fluid transport. The ducts of these glands are lined with stratified cuboidal epithelium.

The fluid secreted by sweat glands is not viscous and contains little protein. Its main components are water, sodium chloride, urea, ammonia, and uric acid. Its sodium content of 85 mEq/L is distinctly below that of blood (144 mEq/L), and the cells present in the sweat ducts are responsible for sodium absorption, to prevent excessive loss of this ion. The fluid in the lumen of the secretory portion of the gland is an ultrafiltrate of the blood plasma. This ultrafiltrate is derived from a network of capillaries that intimately envelops the secretory region of each gland. After its release on the surface of the skin, sweat evaporates, cooling the surface. In addition to its important cooling role, sweat glands also function as an auxiliary excretory organ, eliminating several substances not necessary for the organism.

In addition to the merocrine sweat glands just described, another type of sweat gland the **apocrine** gland is present in the axillary, areolar, and anal regions. Apocrine glands are much larger (3-5 mm in diameter) than merocrine sweat glands. They are embedded in the dermis and hypodermis, and their ducts open into hair follicles. These glands produce a viscous secretion that is initially odorless but may acquire a distinctive odor as a result of bacterial decomposition.

Apocrine glands are innervated by adrenergic nerve endings, whereas merocrine glands receive cholinergic fibers.

The glands of Moll in the margins of the eyelids and the ceruminous glands of the ear are modified sweat glands.