

CHAPTER 1

Anatomy and Physiology of the Skin

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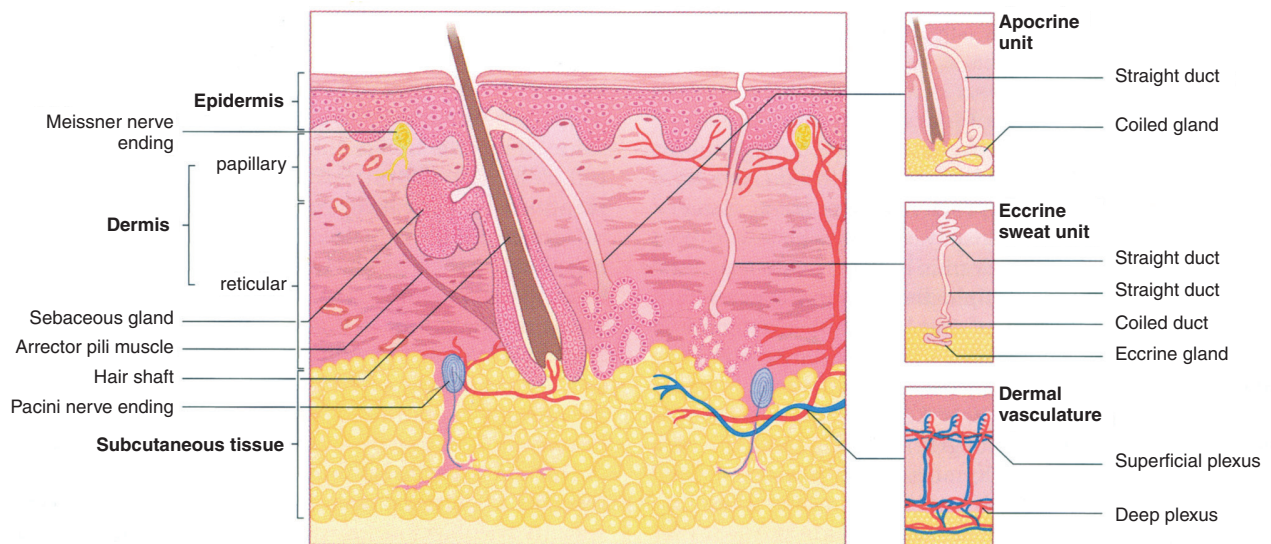
Introduction

The skin is the largest organ of the body, accounting for about 15% of the total adult body weight. It performs many vital functions, including protection against external physical, chemical, and biologic assailants, as well as prevention of excess water loss from the body and a role in thermoregulation. The skin is continuous, with the mucous membranes lining the body's surface (Kanitakis, 2002).

The integumentary system is formed by the skin and its derivative structures (see Figure 1-1). The skin is composed of three layers: the epidermis, the dermis, and subcutaneous tissue (Kanitakis, 2002). The outermost level, the *epidermis*, consists of a specific constellation of

cells known as *keratinocytes*, which function to synthesize keratin, a long, threadlike protein with a protective role. The middle layer, the *dermis*, is fundamentally made up of the fibrillar structural protein known as *collagen*. The dermis lies on the subcutaneous tissue, or *panniculus*, which contains small lobes of fat cells known as *lipocytes*. The thickness of these layers varies considerably, depending on the geographic location on the anatomy of the body. The eyelid, for example, has the thinnest layer of the epidermis, measuring less than 0.1 mm, whereas the palms and soles of the feet have the thickest epidermal layer, measuring approximately 1.5 mm. The dermis is thickest on the back, where it is 30–40 times as thick as the overlying epidermis (James, Berger, & Elston, 2006).

Figure 1-1. Cross-Section of Skin and Panniculus



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Epidermis

The epidermis is a stratified, squamous epithelium layer that is composed primarily of two types of cells: keratinocytes and dendritic cells. The keratinocytes differ from the “clear” dendritic cells by possessing intercellular bridges and ample amounts of stainable cytoplasm (Murphy, 1997). The epidermis harbors a number of other cell populations, such as melanocytes, Langerhans cells, and Merkel cells, but the keratinocyte cell type comprises the majority of the cells by far. The epidermis commonly is divided into four layers according to keratinocyte morphology and position as they differentiate into horny cells, including the basal cell layer (stratum germinativum), the squamous cell layer (stratum spinosum), the granular cell layer (stratum granulosum), and the cornified or horny cell layer (stratum corneum) (James et al., 2006; Murphy) (see Figure 1-2). The lower three layers that constitute the living, nucleated cells of the epidermis are sometimes referred to as the stratum malpighii and rete malpighii (Murphy).

The epidermis is a continually renewing layer and gives rise to derivative structures, such as pilosebaceous apparatuses, nails, and sweat glands. The basal cells of the epidermis undergo proliferation cycles that provide for the renewal of the outer epidermis. The epidermis is a dynamic tissue in which cells are constantly in unsynchronized motion, as differing

individual cell populations pass not only one another but also melanocytes and Langerhans cells as they move toward the surface of the skin (Chu, 2008).

Keratinocytes

At least 80% of cells in the epidermis are the ectodermally derived keratinocytes. The differentiation process that occurs as the cells migrate from the basal layer to the surface of the skin results in *keratinization*, a process in which the keratinocyte first passes through a synthetic and then a degradative phase (Chu, 2008). In the synthetic phase, the cell builds up a cytoplasmic supply of keratin, a fibrous intermediate filament arranged in an alpha-helical coil pattern that serves as part of the cell's cytoskeleton. Bundles of these keratin filaments converge on and terminate at the plasma membrane forming the intercellular attachment plates known as *desmosomes*. During the degradative phase of keratinization, cellular organelles are lost, the contents of the cell are consolidated into a mixture of filaments and amorphous cell envelopes, and the cell finally is known as a *horny cell* or *corneocyte*. The process of maturation resulting in cell death is known as *terminal differentiation* (James et al., 2006).

Basal Layer

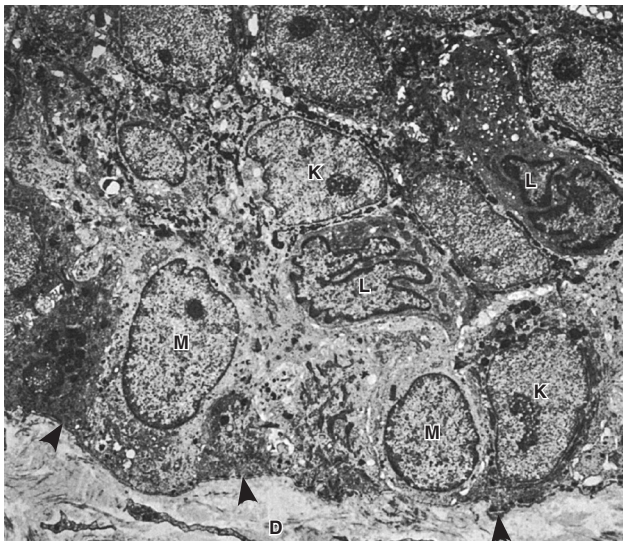
The basal layer, also known as the stratum germinativum, contains column-shaped keratinocytes that attach to the basement membrane zone with their long axis perpendicular to the dermis. These basal cells form a single layer and adhere to one another as well as to more superficial squamous cells through desmosomal junctions (Murphy, 1997). Other distinguishing features of the basal cells are their dark-staining oval or elongated nuclei and the presence of melanin pigment transferred from adjoining melanocytes (Murphy).

The basal layer is the primary location of mitotically active cells in the epidermis that give rise to cells of the outer epidermal layers. However, not all basal cells have the potential to divide (Jones, 1996; Lavker & Sun, 1982). Epidermal stem cells in the basal layer are clonogenic cells with a long lifespan that progress through the cell cycle very slowly under normal conditions. Hyperplasiogenic conditions, such as wounding, can increase the number of cycling cells in the epidermis by stimulating division of stem cells. DNA damage caused by carcinogenic agents may mutate cell proliferation machinery and can also affect the rate of cellular division. Migration of a basal cell from the basal layer to the cornified layer in humans takes at least 14 days, and the transit through the cornified layer to the outermost epidermis requires another 14 days (Chu, 2008).

Squamous Cell Layer

Overlying the basal cell layer is a layer of the epidermis that is 5–10 cells thick and known as the squamous cell layer

Figure 1-2. Three Basic Cell Types in the Epidermis



The three basic cell types in the epidermis include keratinocytes (some labeled *K*) and Langerhans cells (*L*) in the Malpighian layer and melanocytes (*M*) in the basal layer. Arrows point to the basement membrane zone, which separates the basal layer of the epidermis from the underlying dermis (*D*).

Note. From *Andrews' Diseases of the Skin: Clinical Dermatology* (10th ed., p. 4), by W.D. James, T.G. Berger, and D.M. Elston, 2006, Philadelphia: Elsevier Saunders. Copyright 2006 by Elsevier Saunders. Reprinted with permission.

or stratum spinosum (Murphy, 1997). The squamous layer is composed of a variety of cells that differ in shape, structure, and subcellular properties depending on their location. Suprabasal spinous cells, for example, are polyhedral in shape and have a rounded nucleus, whereas cells of the upper spinous layers are generally larger in size, become flatter as they are pushed toward the surface of the skin, and contain lamellar granules (Chu, 2008). Lamellar granules are membrane-bound organelles containing glycoproteins, glycolipids, phospholipids, free sterols, and a number of acid hydrolases, including lipases, proteases, acid phosphatases, and glycosidases. The abundance of hydrolytic enzymes indicates that the lamellar granules are a type of lysosome. Although the lamellar granules primarily are active in cells at the interface between the granular and cornified layers, they also function in cells of the upper spinous layer to deliver precursors of stratum corneum lipids into the intercellular space (Haake & Holbrook, 1999).

Intercellular spaces between spinous cells are bridged by abundant desmosomes that promote mechanical coupling between cells of the epidermis and provide resistance to physical stresses. Organized concentrically around the nucleus, keratin filaments in the cytoplasm are bound to desmosomal plaques at one end and remain free at the end closer to the nucleus (Murphy, 1997). The desmosomal plaques are composed of six polypeptides found on the cytoplasmic side of the cell membrane that are important in the regulation of the calcium required for desmosomal assembly and maintenance (Fairley, Scott, Jensen, Goldsmith, & Diaz, 1991; Hennings & Holbrook, 1983; Lin, Mascaró, Liu, Espana, & Diaz, 1997). The spine-like appearance of the numerous desmosomes along cell margins is where the stratum spinosum derives its name (Chu, 2008).

Gap junctions are another type of connection between epidermal cells. Essentially forming an intercellular pore, these junctions allow for physiologic communication via chemical signals that is vital in the regulation of cell metabolism, growth, and differentiation (Caputo & Peluchetti, 1977).

Granular Layer

The most superficial layer of the epidermis containing living cells, the *granular layer* or stratum granulosum, is composed of flattened cells holding abundant keratohyaline granules in their cytoplasm. These cells are responsible for further synthesis and modification of proteins involved in keratinization (Chu, 2008). The granular layer varies in thickness in proportion to that of the overlying horny cell layer. For example, under thin cornified layer areas, the granular layer may be only 1–3 cell layers in thickness, whereas under the palms of the hands and soles of the feet the granular layer may be 10 times this thickness. A very thin or absent granular layer can lead to extensive *parakeratosis* in which the nuclei of keratinocytes persist as the cells move into the stratum corneum, resulting in psoriasis (Murphy, 1997).

The *keratohyaline granules* are deeply basophilic and irregular in shape and size, and they are necessary in the formation of both the interfibrillary matrix that holds keratin filaments together and the inner lining of the horny cells. Enzymatic action of the keratohyaline granules results in the production of “soft” keratin in the epidermis by providing periodic cutting of keratin filaments. In contrast, the hair and nails do not contain keratohyaline granules, and the tonofibril filaments traversing the cell cytoplasm will harden because of the incorporation of disulfide bonds, producing “hard” keratin in those structures (Matoltsy, 1976; Schwarz, 1979).

Lysosomal enzymes present only in small amounts in the stratum basalis and stratum spinosum are found at high levels in the stratum granulosum because the granular layer is a keratogenous zone of the epidermis. Here, the dissolution of cellular organelles is prepared as the cells of the granular layer undergo the abrupt terminal differentiation process to a horny cell of the cornified layer (Chu, 2008).

Cornified Layer

Horny cells (corneocytes) of the cornified layer provide mechanical protection to the underlying epidermis and a barrier to prevent water loss and invasion by foreign substances (Jackson, Williams, Feingold, & Elias, 1993). The corneocytes, which are rich in protein and low in lipid content, are surrounded by a continuous extracellular lipid matrix (Chu, 2008). The large, flat, polyhedral-shaped horny cells have lost their nuclei during terminal differentiation and technically are considered to be dead (Chu; Murphy, 1997). The physical and biochemical properties of cells in the cornified layer vary in accordance with position in order to promote desquamation moving outward. For instance, cells in the middle have a much higher capacity for water-binding than the deeper layers because of the high concentration of free amino acids found in the cytoplasm of middle layer cells. The deep cells also are more densely compact and display a greater array of intercellular attachments than the more superficial layers. Desmosomes undergo proteolytic degradation as the cells progress outward, contributing to the shedding of corneocytes during desquamation (Haake & Hollbrook, 1999).

The Regulation of Epidermal Proliferation and Differentiation

As a perpetually regenerating tissue, the epidermis must maintain a relatively constant number of cells as well as regulate the interactions and junctions between epidermal cells. Adhesions between keratinocytes, the interactions of keratinocytes and immigrant cells, the adhesion between the basal lamina and the underlying dermis, and the process of terminal differentiation to produce corneocytes must be regulated as cells relocate during development as well as throughout life

(Haake & Hollbrook, 1999). Epidermal morphogenesis and differentiation is regulated in part by the underlying dermis, which also plays a critical role in the maintenance of postnatal structure and function. The epidermal-dermal interface is also a key site in the development of epidermal appendages.

The maintenance of a constant epidermal thickness depends also on intrinsic properties of epidermal cells, such as the ability to undergo *apoptosis*, programmed cell death. Apoptosis follows an orderly pattern of morphologic and biochemical changes resulting in cell death without injury to neighboring cells, as is often the case in necrosis. This major homeostatic mechanism is regulated by a number of cellular signaling molecules including hormones, growth factors, and cytokines. In the skin, apoptosis is important in developmental remodeling, regulation of cell numbers, and defense against mutated, virus-infected, or otherwise damaged cells. *Terminal differentiation* is a type of apoptosis evolved to convert the keratinocyte into the protective corneocyte (Haake & Hollbrook, 1999). The disruption of dynamic equilibrium maintaining constant epidermal thickness can result in conditions such as psoriasis, whereas the dysregulation of apoptosis is often seen in tumors of the skin (Kerr, Wyllie, & Currie, 1972).

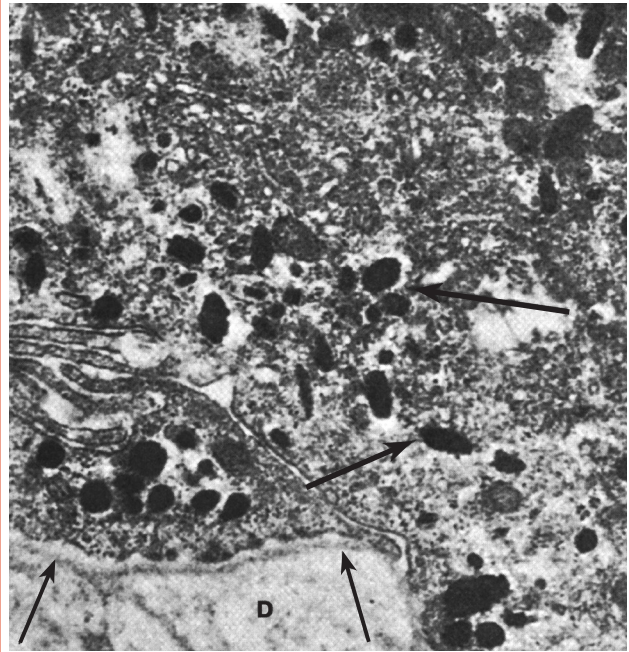
Nonkeratinocyte Cells of the Epidermis

Melanocytes

The *melanocyte* is a dendritic, pigment-synthesizing cell derived from the neural crest and confined in the skin predominantly to the basal layer (Chu, 2008). Branching into more superficial layers, extensions of the melanocyte come into contact with keratinocytes but do not form cellular junctions. Melanocytes are responsible for the production of the pigment melanin and its transfer to keratinocytes. Melanin is produced in a rounded, membrane-bound organelle known as the melanosome via a series of receptor-mediated, hormone-stimulated, enzyme-catalyzed reactions (Haake & Hollbrook, 1999).

Melanosomes are moved to the end of the melanocyte processes that lie closest to the skin surface and are transferred to keratinocytes (see Figure 1-3). In white skin, these melanosomes are aggregated into membrane-bound melanosome complexes containing two or three melanosomes, whereas melanosomes tend to be removed from these complexes more rapidly in keratinocytes of individuals with dark skin. Heavily pigmented skin can be attributed to the greater production of melanosomes in melanocytes, the higher degree of melanization in each melanosome, the larger size of melanosomes, the greater amount of dispersion of melanosomes in keratinocytes, and the slower rate of melanosome degradation in comparison to fair skin (Flaxman, Sosis, & Van Scott, 1973; Murphy, 1997; Olson, Nordquist, & Everett, 1970).

Figure 1-3. Portion of a Melanocyte From Dark Skin



Melanosomes are indicated by broad arrows. Thin arrows point to the basement membrane zone between the epidermis and the underlying dermis (D).

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Increased ultraviolet light exposure stimulates an increase in melanogenesis and a corresponding increase in melanosome transfer to keratinocytes where the melanosomes will aggregate toward the superficial side of the nucleus. This response, which results in tanning of the skin, increases the cell's ability to absorb light and thus protect genetic information in the nucleus from damaging radiation.

Merkel Cells

Merkel cells are oval-shaped, slow-adapting, type I mechanoreceptors located in sites of high tactile sensitivity that are attached to basal keratinocytes by desmosomal junctions. Merkel cells are found in the digits, lips, regions of the oral cavity, and outer root sheath of the hair follicle and are sometimes assembled into specialized structures known as tactile discs or touch domes (Moll, 1994). Relatively small deformations of adjoining keratinocytes are stimulus enough to cause Merkel cells to secrete a chemical signal that generates an action potential in the adjoining afferent neuron, which relays the signal to the brain. The high concentration of Merkel cells in certain regions such as the fingertips results in smaller and more densely

packed receptive fields and thus higher tactile resolution and sensitivity.

Langerhans Cells

Langerhans cells are involved in a variety of T-cell responses. Derived from the bone marrow, these cells migrate to a suprabasal position in the epidermis early in embryonic development and continue to circulate and repopulate the epidermis throughout life. The cells are dendritic and do not form cellular junctions with neighboring cells. Langerhans cells constitute 2%–8% of the total epidermal cell population and maintain nearly constant numbers and distributions in a particular area of the body. In the epidermis, the cells mainly are distributed among the squamous and granular layers with fewer cells in the basal layer. They are found in other squamous epithelia in addition to the epidermis, including the oral cavity, esophagus, and vagina, as well as in lymphoid organs and in the normal dermis (Chu, 2008).

Langerhans cells must recognize and process soluble antigens found in epidermal tissue. When a membrane-bound antigen is ingested via endocytosis, cell granules are formed. The contents of these granules are delivered to phagolysosomes in the cytoplasm containing hydrolytic enzymes similar to those found in macrophages. In the first stage of life, the Langerhans cells are weak stimulators of unprimed T cells but are able to ingest and process antigens. Later, once the cell has become an effective activator of naïve T cells, activation via contact with the antigen will not trigger phagocytosis but rather will stimulate cell migration (Udey, 1997).

The Dermal-Epidermal Junction

The interface between the epidermis and dermis is formed by a porous basement membrane zone that allows the exchange of cells and fluid and holds the two layers together (James et al., 2006). Basal keratinocytes are the most important components of structures of the dermal-epidermal junction; dermal fibroblasts are also involved but to a lesser extent (Gayraud, Hopfner, Jassim, Aumailley, & Bruckner-Tuderman, 1997).

The basal lamina is a layer synthesized by basal cells of the epidermis consisting mainly of type IV collagen as well as anchoring fibrils and dermal microfibrils. This includes an electron-lucent zone known as the lamina lucida as well as the lamina densa (Aumailley & Krieg, 1996; Lin et al., 1997; Masunaga et al., 1996; Wheelock & Jensen, 1992). The plasma membranes of basal cells are attached to the basal lamina by rivet-like hemidesmosomes that distribute tensile or shearing forces through the epithelium. The dermal-epidermal junction acts as support for the epidermis, establishes cell polarity and direction of growth, directs the organization of the cytoskeleton in basal cells, provides developmental signals, and functions as a semipermeable barrier between layers (Stepp, Spurr-Michaud, Tisdale, Elwell, & Gipson, 1990).

Epidermal Appendages

The skin *adnexa* are a grouping of ectodermally derived appendages, including eccrine and apocrine glands, ducts, and pilosebaceous units that originate as downgrowths from the epidermis during development. After injury, all adnexal structures are capable of reepithelialization via the migration of keratinocytes from adnexal epithelium to the surface of the epidermis. Because areas such as the face and scalp contain a large quantity of pilosebaceous units, reepithelialization occurs more rapidly after injury in these areas than in areas with fewer adnexal structures, such as the back (James et al., 2006).

Eccrine Sweat Glands

Eccrine sweat glands are involved in the regulation of heat and are most abundant on the soles of the feet and least plentiful on the back (Murphy, 1997; Sato & Dobson, 1970). The sweat glands originate as a band of epithelial cells growing downward from the epidermal ridge (Mauro & Goldsmith, 2008). This tubular, or ductal, structure is modified during development to generate the three composite parts of the eccrine sweat unit, which are the intraepidermal spiral duct, the straight dermal portion, and the coiled secretory duct (see Figure 1-1) (James et al., 2006; Mauro & Goldsmith). The spiral duct opens onto the skin surface and is composed of dermal duct cells that have migrated upward. Cells undergo cornification within the duct, and the corneocytes produced ultimately will become part of the cornified layer. The straight dermal segment connects the superficial spiral duct to the inner secretory portion of the gland.

The *secretory coil* of the eccrine unit lies deep in the dermis or within the superficial panniculus and is composed of glycogen-rich clear secretory cells, dark mucoidal cells, and myoepithelial cells specialized in contractile properties (James et al., 2006; Mauro & Goldsmith, 2008). Clear cells rest either on the basement membrane or on the myoepithelial cells and form intercellular canaliculi where two clear cells adjoin. The canaliculi open directly into the lumen of the gland (Mauro & Goldsmith). Large, glycogen-rich inner epithelial cells initiate the formation of sweat in response to a thermal stimulus. Initially an isotonic solution, the darker mucoidal cells in the secretory coil and in the dermal duct actively reabsorb sodium from sweat in the duct, thereby resulting in the extremely hypotonic solution that is emitted onto skin surface through the intraepidermal spiral duct. This response promotes cooling while conserving sodium (James et al.).

Apocrine Sweat Glands

Whereas eccrine glands are primarily involved in thermal regulation, *apocrine glands* are involved in scent release (Murphy, 1997). Apocrine sweat glands in humans are confined mainly to the regions of the axillae and perineum, and unlike eccrine and apoecrine glands, they do not open directly to

the skin surface. Instead, the intraepithelial duct opens into pilosebaceous follicles, entering in the infundibulum above the sebaceous duct. The basal secretory coil of apocrine glands, which is normally located entirely in subcutaneous fat, differs from that of eccrine glands in that it is composed exclusively of secretory cells; no ductal cells are present (Murphy).

Apocrine sweat glands develop their secretory portions and become active just before puberty, a response induced presumably by hormonal signals. The proteinaceous, viscous secretion has distinct odor and can function as a territorial marker, warning signal, and sexual attractant, but its sexual functions may now be vestigial in humans. Difficulties in acquiring pure samples of apocrine sweat have made it impossible to determine the exact chemical composition of the secretion (Mauro & Goldsmith, 2008).

Apoecrine Sweat Glands

The *apoeccrine sweat gland* (AEG) develops during puberty from eccrine-like precursors, opening directly unto the skin. Discovered during the isolation of human axillary sweat from patients with axillary *hyperhidrosis*, a condition characterized by abnormally increased rates of perspiration, the AEG is found in the adult axillae; its relative frequency varies from person to person. Like eccrine glands, the AEG opens directly to the skin surface. The AEG has a secretory rate as much as 10 times that of the eccrine gland and is therefore thought to contribute to axillary hyperhidrosis (Mauro & Goldsmith, 2008).

Hair Follicles

Hair has many valuable biologic functions including protection from the elements and distribution of sweat-gland products. In addition, it has an important psychosocial role in society. Hair follicles vary considerably in size and shape, depending on their location, but they all have the same basic structure. The number and distribution of hair follicles over the body and the future phenotype of each hair is established during fetal development; no extra follicles are added after birth (Kratochwil, Dull, Farinas, Galceran, & Grosschedl, 1996; Millar, 1997; Paus & Cotsarelis, 1999; Paus, Foitzik, Welker, Bulfone-Paus, & Eichmuller, 1997; St-Jacques et al., 1998; Zhou, Byrne, Jacobs, & Fuchs, 1995). The particular spacing and allocation of the follicles are determined by genes that are expressed very early in the morphogenesis of the follicles (Paus & Cotsarelis; St-Jacques et al.). Mesenchymal cells in the fetal dermis aggregate below the basal layer of the epidermis during embryogenesis (James et al., 2006). The basophilic cells in the basal cell layer of the epidermis overlying these mesenchymal cell sites are induced to grow at a downward angle into the dermis (Murphy, 1997). The follicle continues to develop until finally widening at the base and forming a bulb around the group of mesenchymal

cells from which the *dermal papilla* is formed (James et al.; Hashimoto, 1970a).

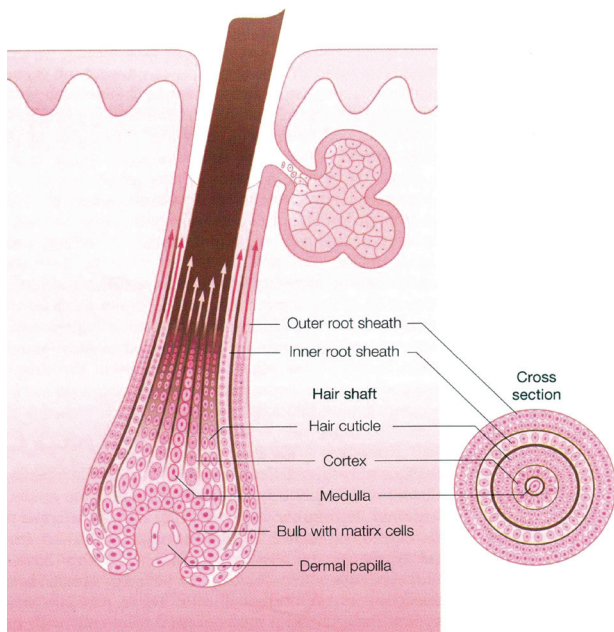
Differentiation occurs at the lower portion of the hair follicle forming the hair cone and later the hair, the cuticle, and the two inner root sheaths. Differentiation also occurs in the upper segments of the follicle producing the hair canal in the upper dermis, through the epidermis, and opening to the surface prior to the time that the growing hair cone reaches the upper follicle (Hashimoto, 1970b).

The sebaceous gland forms from a bud in the fetal hair follicle. Along the same side of the follicle but below the sebaceous gland, another bud develops into an attachment for the arrector pili muscle. The *arrector pili* (AP) are a smooth muscle bundle that attaches to the external root sheath of the follicle. The distal end of the AP muscle shows multiple branches at the level of the papillary dermis. The bulge, which is the zone of the AP muscle's follicular attachment, is thought to contain epithelial stem cells responsible for regenerating follicles, a crucial role in the hair growth cycle (Cotsarelis, Sun, & Lavker, 1990). On the opposite side of the follicle, a third bud forms above the plane of the sebaceous gland and develops into the apocrine gland. The region of the follicle above the sebaceous gland is known as the *infundibular segment*, and the region between the sebaceous duct and AP attachment is known as the *isthmus* (James et al., 2006). The region below the isthmus is known as the *inferior portion* and contains the bottom of the follicle as well as the hair bulb. The inferior segment undergoes cycles of involution and regeneration throughout life, whereas the infundibular and isthmus portions remain permanently (James et al.).

Rapidly proliferating cells in the hair bulb, called *matrix cells*, are responsible for the production of the hair shaft as well as the inner and outer root sheaths (James et al., 2006). Both the hair shaft and the inner root sheath progress upward as the hair grows until the inner sheath reaches the isthmus and sheds (James et al.). Matrix cells moving up the follicle are compressed as they enter the rigid inner root sheath (see Figure 1-4). The number of cells entering the sheath determines the size of the hair, and the dimensions and curvature of the inner root sheath determine the shape of the hair (Paus & Cotsarelis, 1999). For example, the hairs on the scalp of Caucasians are round while pubic, facial, and eyelash hairs are oval. Scalp hairs on people of African descent also are oval, causing their hair to be curly (James et al., 2006).

Hair color is determined by the distribution of melanosomes in the hair shaft. The hair bulb contains melanocytes that synthesize melanosomes and transfer them to the keratinocytes of the bulb matrix. People of African descent tend to have larger melanosomes than Caucasians, whose smaller melanosomes are amassed into membrane-bound complexes. Red hair contains spherical melanosomes. Aging causes a loss of melanocytes and a corresponding decrease in the production of melanosomes and results in graying hair (James et al., 2006).

Figure 1-4. Hair Follicle Structure



Note. From *Andrews' Diseases of the Skin: Clinical Dermatology* (10th ed., p. 8), by W.D. James, T.G. Berger, and D.M. Elston, 2006, Philadelphia: Elsevier Saunders. Copyright 2006 by Elsevier Saunders. Reprinted with permission.

Hair growth occurs in a cyclical manner, but each follicle functions as an independent unit. The hair growth cell cycle is composed of three stages: anagen, catagen, and telogen (see Figure 1-5) (Millar, 1997; Paus, 1996; St-Jacques et al., 1998). *Anagen*, the active growth stage, typically lasts approximately three to five years on the scalp, during which hairs grow at a rate of about 0.33 mm per day. The length of the anagen phase decreases with age and decreases dramatically in individuals with alopecia (James et al., 2006).

Catagen usually lasts about two weeks and is a period of involution resulting in club hair formation after many cells in the outer root sheath undergo apoptosis. The resting phase, *telogen*, lasts about three to five months on the scalp, and hairs in this stage are eventually pushed out by the growing anagen hair shaft. Other sites on the body tend to have shorter anagen and longer telogen phases, causing most body hair to be shorter and remain in place for longer periods of time (James et al., 2006).

Two secreted molecules that may have important roles in hair follicle development and cycling are the insulin-like growth factor 1 and fibroblast growth factor 7. In mice, both are produced by the dermal papilla and have receptors predominantly in overlying matrix cells (Danilenko, Ring, & Pierce, 1996). Hormonal factors controlling hair growth include estrogens, thyroid hormones, glucocorticoids, retinoids, prolactin, and growth hormone. The hormones with the most

impressive effect are the androgens: testosterone and its active metabolite, dihydrotestosterone, which act through androgen receptors in the dermal papilla. These hormones increase the size of hair follicles in androgen-dependent areas such as the beard area during adolescence. Later in life, however, they can cause miniaturization of follicles in the scalp resulting in androgen alopecia (male pattern baldness) (Kaufman, 1996; Sawaya, 1994).

Except for rare congenital hair defects caused by mutations in keratins or other structural proteins and scarring alopecias, hair loss and unwanted hair growth reflect deviations of hair follicle cycling and, therefore, are considered reversible events (Paus, 1996). The hair cycle can vary depending on a number of different physiologic factors. Pregnancy, for example, often results in a prolongation of the telogen phase and an increased number of scalp hairs in the anagen phase. When estrogen levels equilibrate after delivery, telogen hairs are lost while anagen hairs simultaneously are converted to telogen, and this great quantity of telogen hairs will be lost in three to five months. The synchronous termination of anagen or telogen is known as *telogen effluvium* and is often observed after trauma, such as childbirth, surgery, weight loss, and severe stress, and also is associated with drugs, endocrine disorders, anemia, and malnutrition (James et al., 2006). Regrowth typically follows, with the exception of any metabolic or nutritional deficiency (Headington, 1993; Paus & Cotsarelis, 1999).

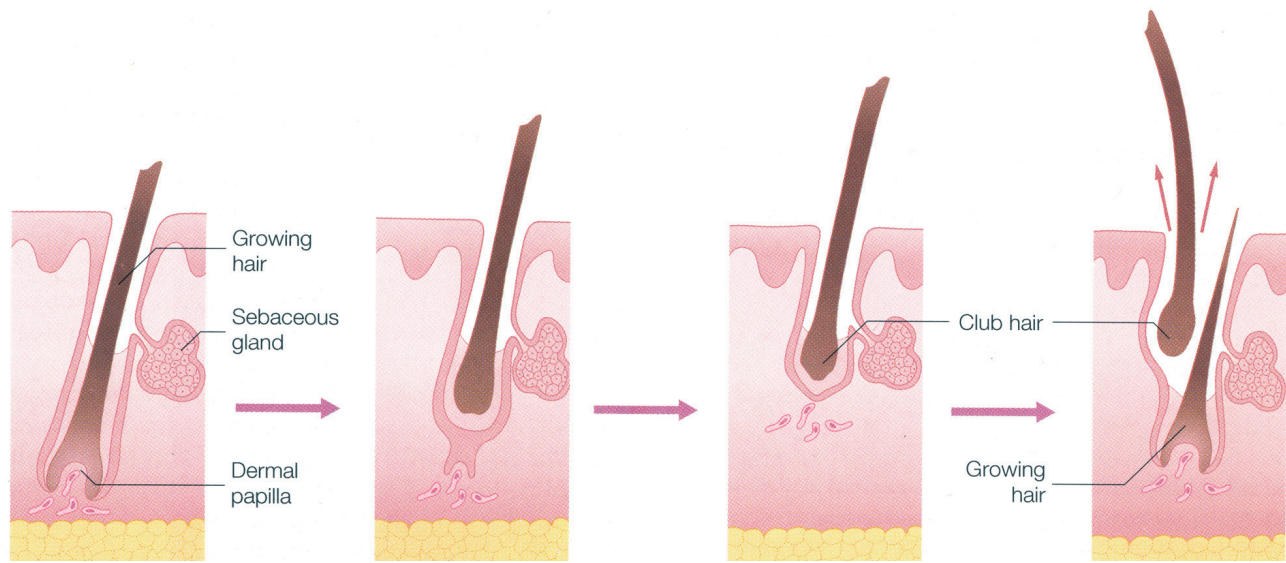
Sebaceous Glands

Sebaceous glands are found in greatest number on the face and scalp but are present on nearly all other locations of the body with the exception of the tarsal plate of the eyelids, the buccal mucosa and vermilion borders of the lip, the prepuce and mucosa lateral to the penile frenulum, the labia minora, and the female areola (James et al., 2006). Cells of the sebaceous glands contain abundant lipid droplets known as *sebum* in their cytoplasm and are arranged into lobules off the upper segment of the hair follicle. Basaloid germinative cells surrounding the lobule give rise to the lipid-filled cells, which are then expelled into the infundibular segment of the hair follicle via the sebaceous duct. The sebaceous glands are thought to be evolutionarily important in providing a secondary lubrication during the passage through the birth canal. This extra lubrication covers the surfaces that come in direct contact with the birth canal including the vertex, anterior scalp over the forehead and nose to the lower jaw line, and the shoulders, chest, and upper aspect of arms posteriorly (Danby, 2005; Thiboutot, 2004).

Nails

Fingernails provide protection to the fingertips, enhance sensation, and allow small objects to be grasped. The underlying nail bed is part of the nail matrix containing blood

Figure 1-5. Phases of Hair Growth



Note. From *Andrews' Diseases of the Skin: Clinical Dermatology* (10th ed., p. 9), by W.D. James, T.G. Berger, and D.M. Elston, 2006, Philadelphia: Elsevier Saunders. Copyright 2006 by Elsevier Saunders. Reprinted with permission.

vessels, nerves, and melanocytes and has parallel rete ridges. The nail plate is formed from matrix keratinocytes (James et al., 2006).

Fingernails grow at an average rate of 0.1 mm per day, two to three times faster than the rate of toenail growth. Because of the slow growth rate, toenails can provide information about toxic exposure or disease from many months in the past (James et al., 2006). For example, arsenic poisoning may cause a horizontal hypopigmentation across all nail plates known as Mees lines (Daniel & Scher, 1997).

The Dermis

The *dermis* is an integrated system of fibrous, filamentous, and amorphous connective tissue that accommodates stimulus-induced entry by nerve and vascular networks, epidermally derived appendages, fibroblasts, macrophages, and mast cells. Other blood-borne cells, including lymphocytes, plasma cells, and other leukocytes, enter the dermis in response to various stimuli as well. The dermis comprises the bulk of the skin and provides its pliability, elasticity, and tensile strength. It protects the body from mechanical injury, binds water, aids in thermal regulation, and includes receptors of sensory stimuli. The dermis interacts with the epidermis in maintaining the properties of both tissues. The two regions collaborate during development in the morphogenesis of the dermal-epidermal junction and epidermal appendages and interact in repairing and remodeling the skin as wounds are healed. The dermis does not undergo an obvious sequence of

differentiation that parallels epidermal differentiation, but the structure and organization of the connective tissue components are predictable in a depth-dependent manner. The matrix components, including collagen and elastic connective tissue, also vary in a depth-dependent manner and undergo turnover and remodeling in normal skin, in pathologic processes, and in response to external stimuli (Chu, 2008).

The constituents of the dermis are mesodermal in origin except for nerves, which, like melanocytes, derive from the neural crest. Until the sixth week of fetal life, the dermis is merely a pool of dendritic-shaped cells full of acid-mucopolysaccharides, which are the precursors of fibroblasts. By the 12th week, fibroblasts are actively synthesizing reticulum fibers, elastic fibers, and collagen. A vascular network develops and fat cells have appeared beneath the dermis by the 24th week. Infant dermis is composed of small collagen bundles, whereas the adult dermis contains thicker bundles of collagen. Many fibroblasts are present in the infant dermis, but few persist in adulthood (James et al., 2006).

The principal component of the dermis is *collagen*, a fibrous family of proteins with at least 15 genetically distinct types in human skin. A major structural protein for the entire body, collagen is found in tendons, ligaments, the lining of bones, and the dermis. Collagen is a major stress-resistant material of the skin. Elastic fibers, on the other hand, play a role in maintaining elasticity but do very little to resist deformation and tearing of the skin. Collagen fibers exist in a constant state of flux, being degraded by proteolytic enzymes called *matrix metalloproteinases* and replaced by new fibers. Collagen represents 70% of the skin's dry weight (James et al., 2006).

Fibroblasts integrate the procollagen molecule, a specific helical polypeptide chain. Then, the cell secretes the fibroblasts, and they assemble into collagen fibrils. The amino acids glycine, hydroxyproline, and hydroxylysine highly enrich collagen. The fibrillar collagens found in the skin comprise the major group and are the most abundant proteins in the body. The major constituent of the dermis is type I collagen. Loosely positioned collagen fibers are found in the papillary and adventitial dermis, whereas hefty collagen bundles are noted in the reticular dermis. Type IV collagen is found in the basement membrane zone, and the major structural component of anchoring fibrils is collagen type VII, which is produced primarily by keratinocytes (James et al., 2006).

The elastic fiber differs both structurally and chemically from collagen and consists of two components: protein filaments and *elastin*, an amorphous protein. The fibroblast fuses elastic fiber to the extracellular matrix of the dermis, which is composed of glycosaminoglycans. The fibers are fine in the papillary dermis and coarse in the reticular dermis. Hyaluronic acid is a minor component of the normal dermis but is the major mucopolysaccharide that accumulates in pathologic states (James et al., 2006).

Vasculature

The dermal vasculature is made up of two intercommunicating *plexuses*: the *subpapillary* or *superficial plexus* composed of postcapillary venules found at the junction of the papillary and reticular dermis and the *lower plexus* at the dermal-subcutaneous interface. The dermal papillae are supplied by capillaries, end arterioles, and venules of the superficial plexus. The deeper plexus is supplied by larger blood vessels and is more complex surrounding adnexal structures.

Blood flow in human skin fluctuates significantly in response to thermal stress because of the regulation of the preoptic-anterior hypothalamus (Boulant, 2000). Vasodilation and increased skin blood flow, along with sweating, are crucial to heat dissipation during heat exposure and exercise. During exposure to cold, vasoconstriction in the skin decreases heat loss from the body to prevent hypothermia. Altered control of skin blood flow can considerably impair the ability to maintain normal body temperature (Charkoudian, 2003). For example, impairments in cutaneous vascular control noted in patients with type II diabetes may contribute to the increased incidence of heat stroke and heat exhaustion during periods of elevated external temperatures. Similarly, menopausal hormones result in the occurrence of hot flashes (Brooks et al., 1997; Schuman, 1972; Semenza, McCullough, Flanders, McGeehin, & Lumpkin, 1999; Tankersley, Nicholas, Deaver, Mikita, & Kenney, 1992).

Muscles

Involuntary or smooth muscle of the skin occurs as AP, tunica dartos of the external genitals, and the areolas around

the nipples. The location of the nucleus in the center of the muscle cell and the absence of striation distinguishes smooth muscle from striated muscle (Murphy, 1997). The muscle fibers of the arrectores pilorum are located in the connective tissue of the upper dermis and are attached to the hair follicle below the sebaceous glands. They are situated at such an angle to the hair follicle that when contracted, the hair follicle is pulled into a vertical position, deforming the skin and causing “gooseflesh” (James et al., 2006). Different configurations make up small bundles of smooth muscle of the muscularis of veins and arteries. Glomus bodies are specialized aggregates of smooth muscle found between the arterioles and venules, which exist on the digits and lateral aspects of the palms and soles. They regulate body temperature and shunt blood (James et al.).

Striated or voluntary muscle is found in the skin of the neck as platysma and in the skin of the face as muscle of expression. The superficial muscular *aponeurotic system* is an intricate network of muscle, fascia, and aponeuroses connecting muscles with the parts that they move (James et al., 2006).

Nerves

Nerve bundles, together with arterioles and venules, are found in great quantity in neurovascular bundles of the dermis (James et al., 2006). Meissner corpuscles, found in the dermal papillae, help to mediate touch and are found predominantly on the ventral sides of the hands and feet. Meissner corpuscles occur in greater abundance on the hands, with greatest concentration in the fingertips. Vater-Pacini corpuscles are large nerve-end organs that generate a sense of pressure and are located in the deeper portion of the dermis of weight-bearing surfaces and genitalia. They also are found commonly in the nipple and anogenital region. Pain, temperature, and itch sensation are transmitted by unmyelinated nerve fibers that end around hair follicles and the papillary dermis (James et al.).

Vasoconstriction is regulated by the postganglionic adrenergic fibers of the autonomic nervous system. This system regulates the apocrine gland secretions and the contraction of AP muscles of hair follicles. Eccrine sweat secretions, on the other hand, are mediated by cholinergic fibers (James et al., 2006).

Mast Cells

Mast cells are specialized secretory cells derived from bone marrow and distributed in connective tissues throughout the body. Although present in greatest numbers in the papillary dermis, they also are present in the subcutaneous fat (Chu, 2008). In the normal dermis, mast cells appear as oval to spindle-shaped cells with a centrally located round to oval nucleus. Numerous mast cells are located around blood

vessels, especially postcapillary venules. Upon magnification, mast cells reveal numerous large and long villi at their periphery. Mast cell granules are round, oval, or angular membrane-bound structures containing histamine, heparin, serine proteinases, and certain cytokines (Murphy, 1997). The cell's surface contains hundreds of thousands of glycoprotein receptor sites for immunoglobulin E. Type I or *connective tissue mast cells* are located in the dermis and submucosa. Type II or *mucosal mast cells* are located in the respiratory tract mucosa and in the bowel (James et al., 2006).

Mast cells accumulate in the skin because of abnormal proliferation, migration, and failure of apoptosis when mastocytosis occurs. Traditionally associated with the allergic response, more recent studies suggest that these cells also may be capable of regulating inflammation, host defense, and innate immunity. Mast cells can undergo activation by antigens or allergens acting via the high-affinity receptor for immunoglobulin E, superoxides, complement proteins, neuropeptides, and lipoproteins. After activation, mast cells express histamine, leukotrienes, prostanoids, proteases, and many cytokines and chemokines. These mediators may be pivotal to the genesis of an inflammatory response. By virtue of their location and mediator expression, mast cells are thought to play an active role in many conditions such as allergy, parasitic diseases, atherosclerosis, malignancy, asthma, pulmonary fibrosis, and arthritis (Krishnaswamy, Ajitawi, & Chi, 2006).

Subcutaneous Fat

Embryologically, toward the end of the fifth month fat cells begin to develop in the subcutaneous tissue. These lobules of fat cells or lipocytes are separated by fibrous septa made up of large blood vessels and collagen. The panniculus varies in thickness depending on the skin site. Considered an endocrine organ, the subcutaneous tissue provides the body with buoyancy and functions as a storehouse of energy. Hormone conversion takes place in the panniculus, converting androstenedione into estrone by aromatase. Lipocytes produce leptin, a hormone that regulates body weight by way of the hypothalamus (James et al., 2006).

Summary

The three layers of the skin form an effective barrier to the external environment, allow the transmission of sensory information, and serve a significant role in maintaining homeostasis. The dynamic epidermis continually produces a protective outer layer of corneocytes as cells undergo the process of keratinization and terminal differentiation. Collagen and elastic filaments of the dermal layer provide the underlying tensile strength of the skin, whereas the layer of subcutaneous fat provides a store of energy for the body. The high rate of

cell proliferation in the epidermis and in epithelial tissue in general and the fact that this tissue is most frequently exposed to physical and chemical damage result in the exceedingly high rate of skin cancers found in humans as compared with other types of cancer.

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