Histology of the Skin

The Skin (Integument)

OBJECTIVES

At the end of the lectures one should able to do the following:

1. *Recognize five epidermal layers in a section of thick skin and explain their functional significance*
2. *Summarize the essential differences between thick skin and thin skin*
3. *Outline the cellular basis of skin pigmentation*
4. *Summarize the structure of the hair follicle with its associated skin components*
5. *Recognize two different types of glands in a section of thin skin*

The skin is the largest organ of the body, typically accounting for 15–20% of body weight and, in adults, presenting 1.2–2.3 (**1.73**) m^2 of body surface area.
The skin composed of the:
Epidermis (E), an epithelial layer of *ectodermal* origin, and the
Dermis (D), a layer of *mesodermal* connective tissue.
The junction of D & E is irregular, and projections of the dermis called **papillae** interdigitate with evaginations of the epidermis known as **epidermal ridges**.

* The functions of the skin:

1. ***Protection*** of body from invasion of pathogens; prevention of tissue damage by toxic chemicals and ultraviolet light
2. ***Prevention*** of dehydration and loss of body fluids (impermeable to water)
3. ***Regulation*** of body temperature (production and excretion of sweat, vascular shunts)
4. ***Sensation*** of touch, pain, temperature, pressure, and vibration; important for communication, dexterity, and injury prevention
5. ***Immunological function*** of Langerhans cells (antigen-presenting cells) present antigens to lymphocytes in the immune responses
6. ***Production*** of vitamin D from precursors under the effects of steroids and sunlight

* Types:

1. ***Thick skin (glabrous, or smooth and non hairy)*** found on the palms and soles
2. ***Thin skin (hairy)*** found elsewhere on the body.

The designations "thick" and "thin" refer to the thickness of the epidermal layer.
Total skin thickness (D+E) 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.

* *Hypodermis (Subcutaneous Tissue)*

A loose connective tissue lies beneath the dermis that may contain a pad of adipose cells (*Panniculus adiposus*), Binds skin loosely to subjacent tissues, it corresponds to the superficial fascia and not considered part of the skin.

* *Dermatoglyphics*:

Upon close observation, certain portions of human skin show ridges and grooves arranged in distinctive patterns. These ridges 1st appear during intrauterine life (13 weeks) in the tips of the fingers and later in the palm and sole. Are probably determined by multiple genes and they are unique for each individual, appearing as ***loops, arches, whorls,*** or combinations of these forms. Used for personal identification (fingerprints).

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EPIDERMIS

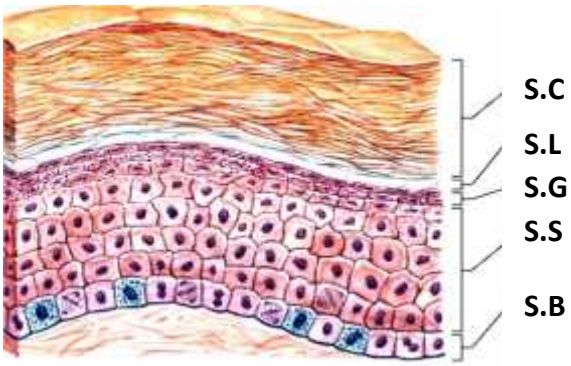
- ***Stratified Squamous Keratinized Epithelium***
- **Cells:**

1. keratin-producing cells (keratinocytes)
2. Three less abundant cell types: Melanocytes, Langerhans, Merkel's Cells

- **Layers:** *From in to out epidermis consists of 5 layers of keratinocytes*

- Stratum **B**asale
- Stratum **S**pinosum
- Stratum **G**ranulosum
- Stratum **L**ucidum
- Stratum **C**orneum

Be Smiley to Gain Love & Confidence



Stratum **B**asale ("base layer"):

One layer of basophilic columnar or cuboidal cells resting on the basement membrane at the D.E.J., Contain intermediate keratin filaments
Desmosomes bind the cells in their lateral and upper surfaces. Hemidesmosomes help bind these cells to the basal lamina.

The S.B, containing stem cells, is responsible (with S.S) for constant renewal of epidermal cells. The human epidermis is renewed about every 15-30 days**.**

Stratum **S**pinosum ("spiny layer")

Normally the thickest epidermal layer, consists of polyhedral or slightly flattened cells having central nuclei with nucleoli and cytoplasm actively synthesizing keratin filaments.
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, leading to the appearance of many short spines or prickles at the cell surfaces (so they are sometimes referred to as prickle cells)
The epidermis of areas subjected to continuous friction and pressure has a thicker stratum spinosum with more abundant tonofibrils and desmosomes.

- All mitoses are confined to what is termed the **Malpighian layer (stratum germinativum),** which consists of both S.B & S.S, Only the malpighian layer contains epidermal stem cells.

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Stratum Granulosum ("grainy layer")

3-5 layers of flattened polygonal cells whose cytoplasm is filled with coarse basophilic granules (**keratohyalin granules**)
lamellar granule: seen on EM, a membrane-coated**,** small ovoid or rod like 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 S.S., The layer of lipid envelopes is a major component of the epidermal barrier against the loss of water from skin.
Together, keratinization and production of the lipid-rich layer also have a crucial *sealing effect, forming the barrier to penetration by foreign materials*.

Stratum Lucidum ("light" or "clear layer")

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

Stratum Corneum ("horny layer")

The S.C consists of 15-20 layers of flattened nonnucleated keratinized cells whose cytoplasm is filled with a filamentous scleroprotein, **keratin.**
The composition of tonofilaments changes as epidermal cells differentiate and 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.**
These cells are continuously shed at the surface of the S.C.

Psoriasis: *Common skin disease, characterized by:*

- *Increase in the number of proliferating cells in the malpighian layer.*
- *Decrease in the cycle time of these cells.*

This results in greater epidermal thickness and more rapid renewal of epidermis.

Skin Pigmentation

The color of the skin is the result of several factors:

1. The content of **melanin** and **carotene.**
2. The number of blood vessels in the dermis.
3. The color of the blood flowing in the vessels

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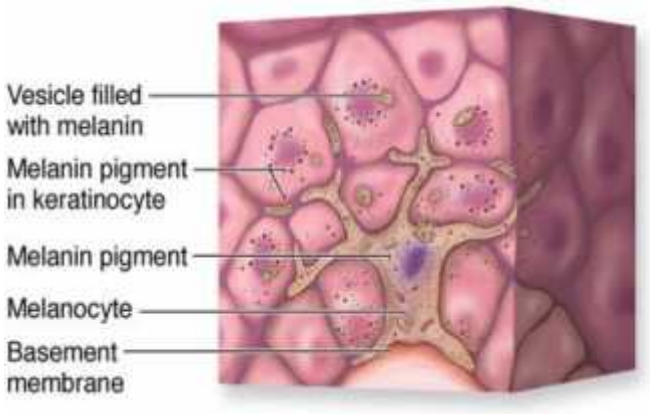
MELANOCYTES

A specialized cell of the epidermis found beneath or between the cells of the S.B and in the hair follicles. 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 S.B & S.S. Tips of these extensions terminate in invaginations of the cells present in the two layers.

- **Eumelanin** is a dark brown pigment produced by the melanocyte
- **Pheomelanin** pigment found in red hair and contains **cysteine** as part of its structure.

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. Melanin accumulates in these vesicles until they form mature granules called **melanosomes**, which are elliptical structures about 1micro m in length.
Melanin granules are essentially injected into keratinocytes (S.B & S.S). They accumulate in the supranuclear region of the cytoplasm. Thus protecting the nuclei from the deleterious effects of solar UV radiation. *This explains why people with light skin have a higher incidence of skin cancer than people with dark skin.*

Epidermal-Melanin Unit



Melanocytes can be easily seen by incubating fragments of epidermis in dopa. This compound is converted to dark brown deposits of melanin in melanocytes, a reaction catalyzed by the enzyme tyrosinase.
This method makes it possible to count the number of melanocytes per unit area of the epidermis. Such studies show that these cells are not distributed at random among keratinocytes; rather, there is a pattern in their distribution, called the ***epidermal-melanin unit***.
Sex or race does not influence the number of melanocytes per unit area; *differences in skin color are due mainly to differences in the number of melanin granules in the keratinocytes.*
Darkening of the skin (tanning) after exposure to solar radiation 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.

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- 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**.
- **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.

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.

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.

MERKEL CELLS

Epithelial tactile cells (**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 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. Tactile cells have functions related to the diffuse neuroendocrine system in addition to their contributions as mechanoreceptors in the sense of touch.

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DERMIS

The dermis is the C.T that supports the epidermis and binds it to the hypodermis. 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 DEJ.
A **basal lamina** is always found between the S.B and the papillary layer of the dermis. 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 LM.

- **Papillary layer**: This thin layer is composed of loose CT; fibroblasts, mast cells and macrophages. 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.**
- **Reticular layer**: This is thicker, composed of irregular dense C.T ,and therefore has more fibers and fewer cells than does the papillary layer

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.

SENSORY RECEPTORS

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.
The ***unencapsulated*** **receptors** include the following:

1. **Tactile discs** associated with the epidermal tactile cells which function as receptors for light touch.
2. **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.
3. **Root hair plexuses**, a web of sensory fibers surrounding the bases of hair follicles in the reticular dermis that detects movements of the hairs.

The following ***encapsulated*** **receptors** are tactile mechanoreceptors:

1. **Tactile corpuscles** (**Meissner corpuscles**) are elliptical structures, perpendicular to the epidermis in the dermal papillae and papillary layer of the fingertips, palms and soles. They detect light touch.
2. **Lamellated (Pacinian) corpuscles** are large oval structures, 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. 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.
3. **Krause corpuscles and Ruffini corpuscles** are other encapsulated, pressure-sensing mechanoreceptors in dermis, but are more poorly characterized structurally.

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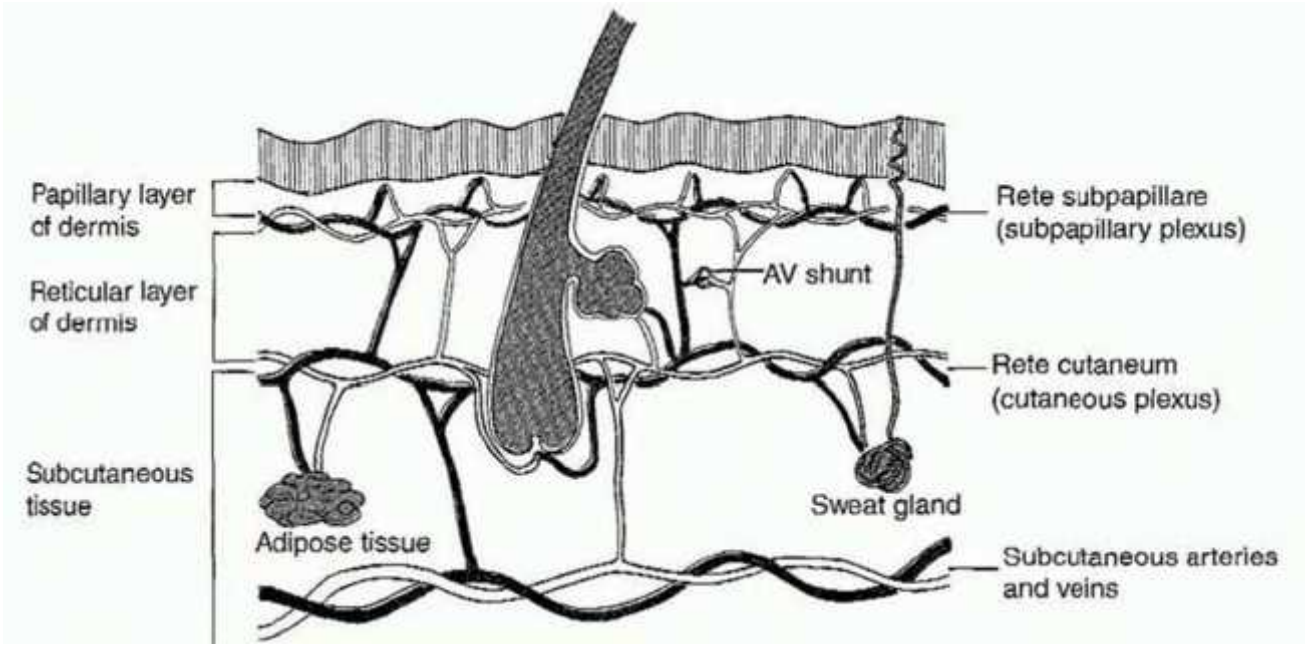
VESSELS

Arterial branches from the underlying subcutaneous arteries extend up to the border between dermis and subcutaneous tissue, where they constitute a deep plexus of anastomosing arteries called the rete *cutaneum or cutaneous plexus* Smaller arterial branches extend downward from the cutaneous plexus into the subcutaneous tissue and supply secretory portions of sweat glands, lower regions of hair follicles, and subcutaneous adipose tissue.
Other small arterial branches extend upward from the cutaneous plexus into the dermis. These branches supply the *rete subpapillare or subpapillary plexus*, situated along the border between papillary and reticular layers of dermis. The pink color of skin is due primarily to the blood seen in venules of this plexus. Capillaries that extend up from the subpapillary plexus supply dermal papillae and nourish the overlying epidermis through diffusion. Other capillaries that arise from this plexus supply the more superficial portions of sweat glands and hair follicles, together with the majority of sebaceous glands.
Blood leaves the skin by way of small veins that accompany subcutanwus arteries.



Epidermal derivatives

Include Hairs, Nails, and Sebaceous and Sweat glands

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HAIR

Are elongated keratinized structures derived from invaginations of epidermal epithelium. Found everywhere except on the **palms, soles, lips, glans penis, clitoris, and labia minora.** The face has about **600** hairs/cm^2 , Remainder of the body has **60**/cm^2.

- **Hair Growth**
  1. **Anagen is the growing phase.**
  2. **Catagen is the resting phase**
  3. **Telogen is the shedding phase**

Hair growth on the face and pubis is strongly influenced by sex hormones, especially androgens.

During anagen the hair follicle has a terminal dilatation called a **hair bulb.**

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.

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. Other cells differentiate into heavily keratinized, compactly grouped fusiform cells that form the hair **cortex**.

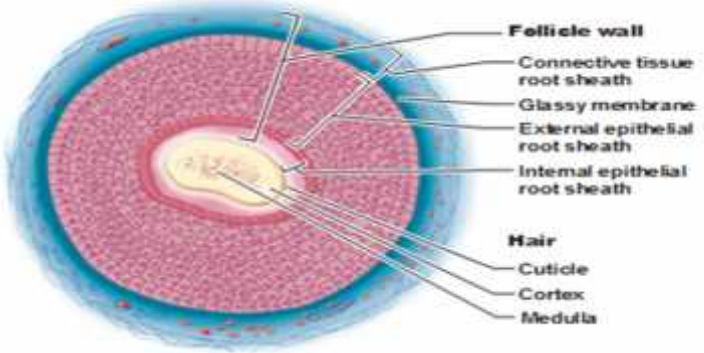
The most peripheral cells produce the hair **cuticle,** a thin layer of heavily keratinized, shingle-like cells covering the cortex.

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.**

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 pili muscle.** 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.



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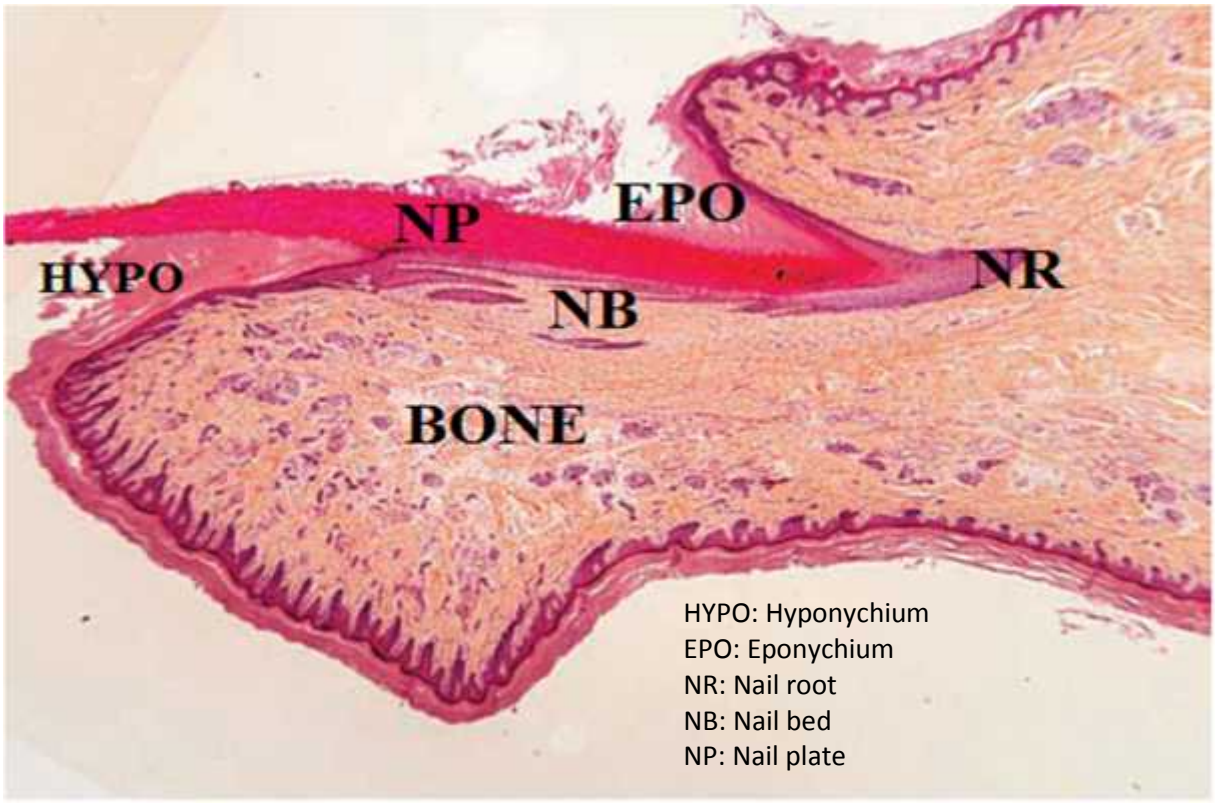
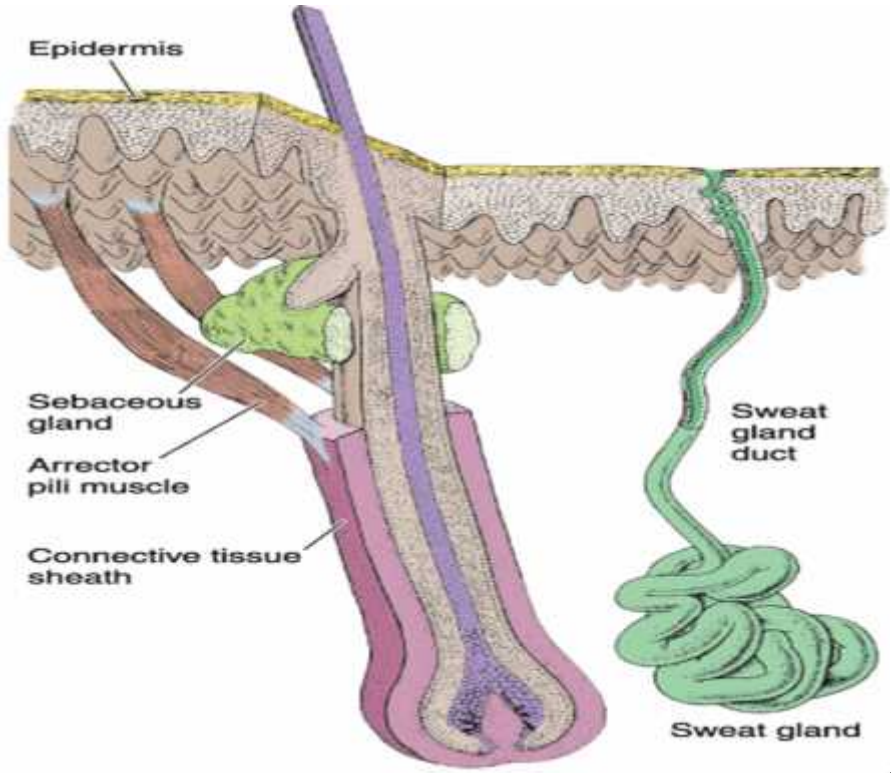
NAILS

Are hard, flexible plates of keratin on the dorsal surface of each distal phalanx.
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.
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.



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.
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.
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.
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.
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.
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.



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Sweat Glands

Sweat glands are epithelial derivatives embedded in the dermis which open to the skin surface or into hair follicles.

Types: Eccrine and apocrine sweat glands have different distributions, functions, and structural details.

Eccrine sweat glands

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, exceeding that of other exocrine glands.

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. 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. 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 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 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.

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Comparison of Thick and Thin Skin

Type of Skin	Epidermis	Hair/Hair Follicles	Glands	Sensory Receptors	Location/ Distribution	Special Features
Thick skin	Five layers; thick stratum corneum; thick stratum granulosum	No	Lack of sebaceous glands; more eccrine sweat glands	More receptors	Palms of the hand and soles of the feet	*Thick epidermis:* thick stratum corneum; stratum lucidum present; several cell layers of stratum granulosum
Thin skin	Four layers; no stratum lucidum; single layer of or no stratum granulosum	Present in most areas (except a few places, such as lips, labia minora, and glans penis)	Many sebaceous glands; fewer eccrine sweat glands	Fewer receptors	Entire body except thick skin areas	*Thin epidermis:* thin stratum corneum; stratum lucidum absent; one layer or no stratum granulosum