# DEPARTMENT OF HISTOLOGY-EMBRYOLOGY

## HISTOLOGY II LECTURE

# INTEGUMENTARY SYSTEM AND SENSE ORGANS

# INTEGUMENTARY SYSTEM

- SKIN
- SKIN'S APPENDAGEAL STRUCTURES

# SKIN

- The skin is the largest single organ of the body, typically accounting for 15%-20% of total body weight. Also known as the **integument** (L. *integumentum*, covering) or **cutaneous layer**, the skin is composed of the **epidermis**, an epithelial layer of ectodermal origin, and the **dermis**, a layer of mesodermal connective tissue.
- At the irregular junction between the dermis and epidermis, projections called **dermal papillae** interdigitate with invaginating **epidermal ridges** to strengthen adhesion of the two layers. Epidermal derivatives include hairs, nails, and sebaceous, sweat, and mammary glands.
- Beneath the dermis lies the **subcutaneous tissue** or **hypodermis** (Gr. *hypo*, under + *derma*, skin), a loose connective tissue layer usually containing pads of adipocytes. The subcutaneous tissue binds the skin loosely to the underlying tissues and corresponds to the superficial fascia of gross anatomy.

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

**Protective:** It provides a physical barrier against thermal and mechanical insults such as friction and against most potential pathogens and other material. Microorganisms that do penetrate skin alert resident lymphocytes and antigen-presenting cells (APCs) in skin and an immune response is mounted. The dark pigment melanin in the epidermis protects cell nuclei from ultraviolet (UV) radiation. Skin is also a permeability barrier against excessive loss or uptake of water, which has allowed for terrestrial life. Skin's selective permeability allows some lipophilic drugs such as certain steroid hormones and medications to be administered via skin patches.

**Sensory:** Many types of sensory receptors allow skin to constantly monitor the environment, and various skin mechanoreceptors help regulate the body's interactions with physical objects.

- **Thermoregulatory:** A constant body temperature is normally easily maintained thanks to the skin's insulating components (e.g., the fatty layer and hair on the head) and its mechanisms for accelerating heat loss (sweat production and a dense superficial microvasculature).
- **Metabolic:** Cells of skin synthesize vitamin D3, needed in calcium metabolism and proper bone formation, through the local action of UV light on the vitamin's precursor. Excess electrolytes can be removed in sweat, and the subcutaneous layer stores a significant amount of energy in the form of fat.
- **Sexual signaling:** Many features of skin, such as pigmentation and hair, are visual indicators of health involved in attraction between the sexes in all vertebrate species, including humans. The effects of sex pheromones produced by the apocrine sweat glands and other skin glands are also important for this attraction.

# SKIN HISTOLOGY

There are three main layers to the skin:

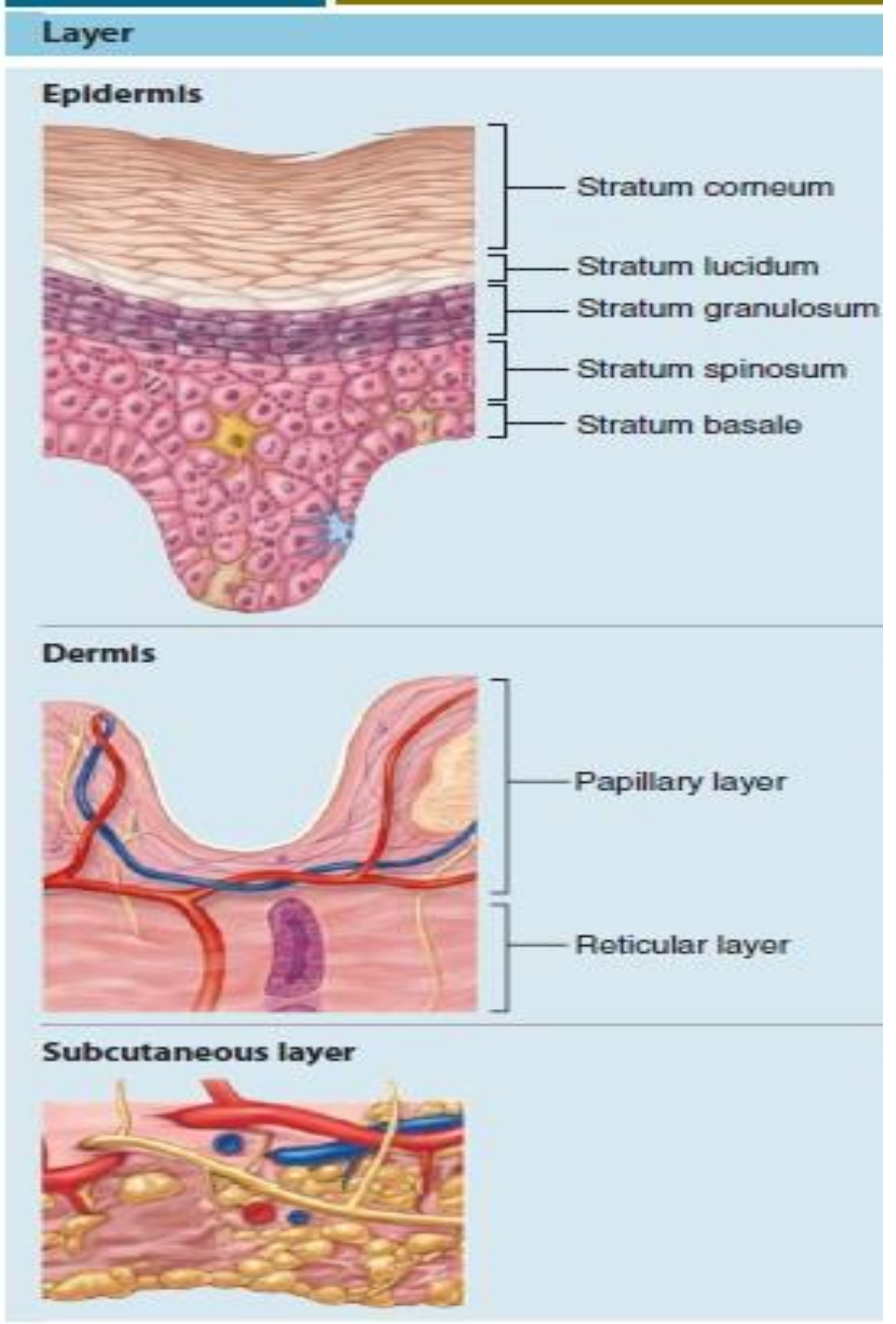
- ❖ **Epidermis,**
- ❖ **Dermis,**
- ❖ **Hypodermis**

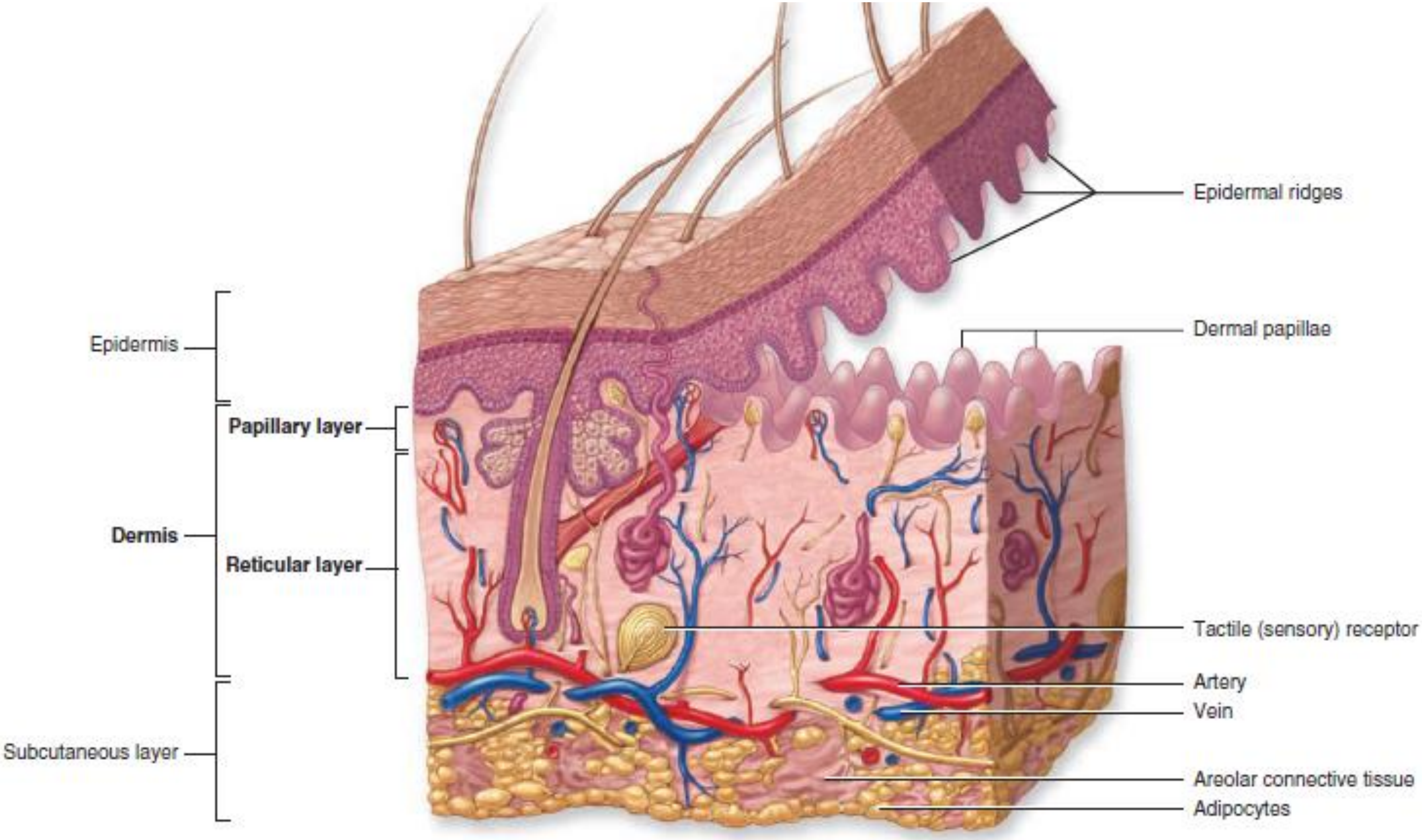
Within the epidermis, the principal skin cell is the keratinocyte. Other cells found in the epidermis include melanocytes, Merkel cells, and Langerhans cells.

The main cell type found within the dermis is the fibroblast. Fibroblasts make collagen, which forms the mechanical support for the skin. The dermis is a region of high vascularity.

The subcutaneous fat tissue is found directly beneath the dermis and is composed primarily of adipocytes. This tissue's main functions are storage of energy, insulation, and cushioning. The adipocytes are closely packed in a connective tissue septum with associated blood vessels and nerve endings.

Cross-section of the skin, showing its constituent elements: - the three layers of the epidermis with a close-up of the keratocytes, a melanocyte (blue), and the stratum germiativum (pink); - the dermis, including the hair follicle (brown) and its sebaceous gland, sweat glands (purple), sensory receptors (green) and blood vessels (red and blue); - the hypodermis (yellow).





Epidermal ridges
Dermal papillae
Epidermis
Papillary layer
Dermis
Reticular layer
Tactile (sensory) receptor
Artery
Vein
Subcutaneous layer
Areolar connective tissue
Adipocytes

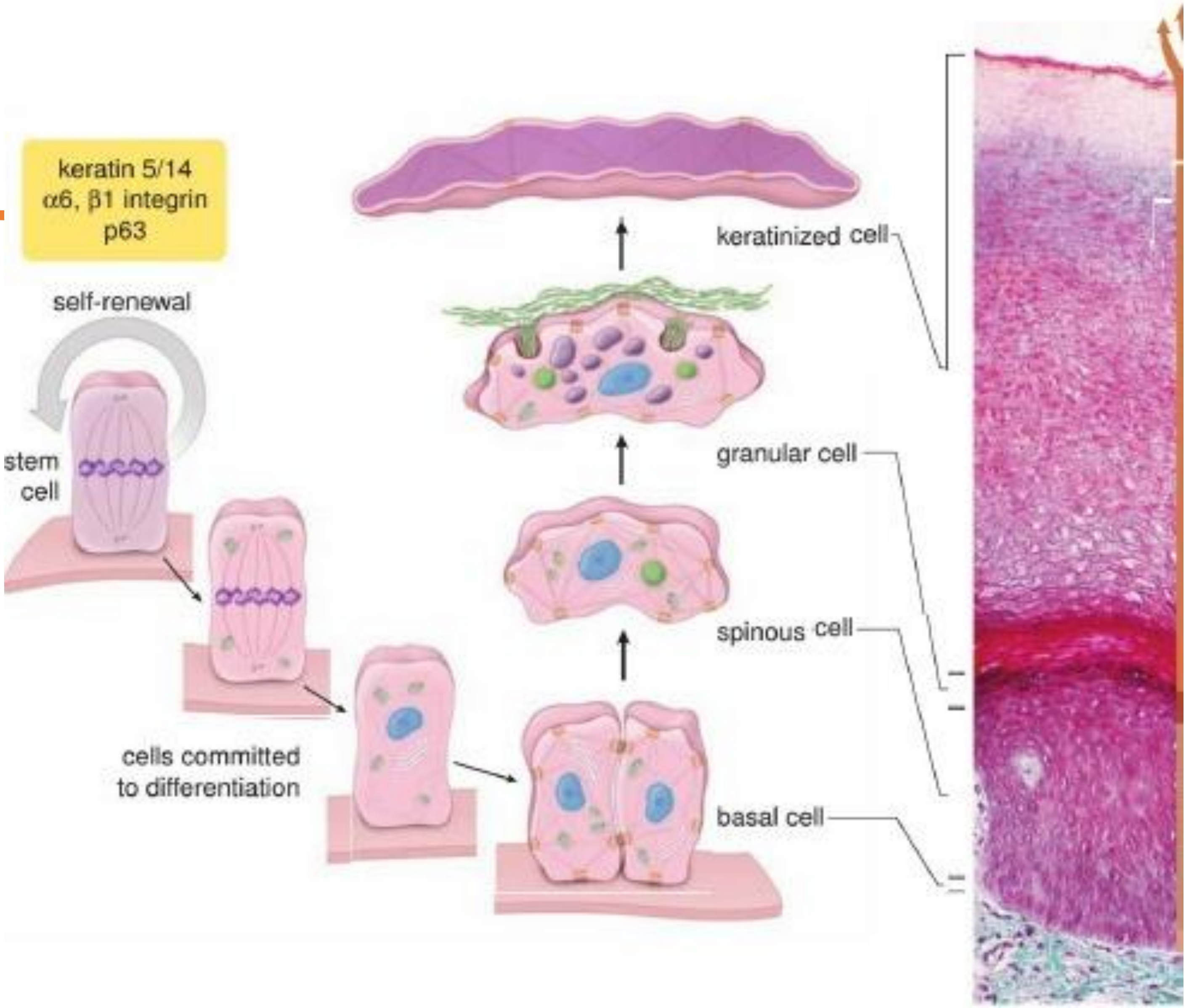
# EPIDERMIS

The epidermis can be subdivided into five components:

- **Stratum basale,**
- **Stratum spinosum,**
- **Stratum granulosum,**
- **Stratum lucidum,**
- **Stratum corneum**

Each layer of the epidermis has important anatomical and physiological functions.

- **The stratum basale** is the deepest layer. The stratum basale contains the proliferating **keratinocytes**, which are constantly undergoing replication to replace the overlying epidermis. It takes approximately 28 days for a basal keratinocyte to progress to the outermost layer of the stratum corneum. **Melanocytes** and **Merkel cells** can also be found within the stratum basale. Melanocytes are pigment-forming cells; they transfer their pigment to neighboring keratinocytes. Merkel cells are modified nerve endings and have been found to be important as mechanoreceptors.



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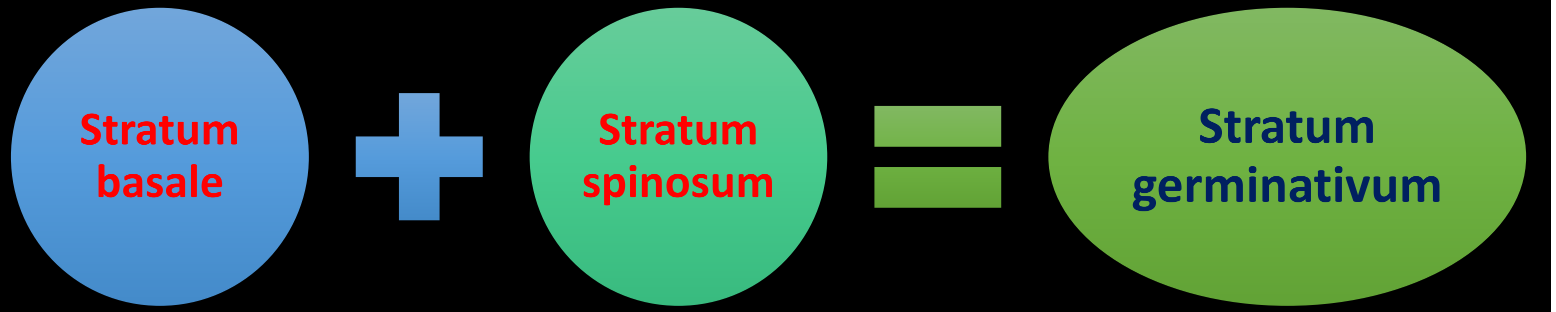
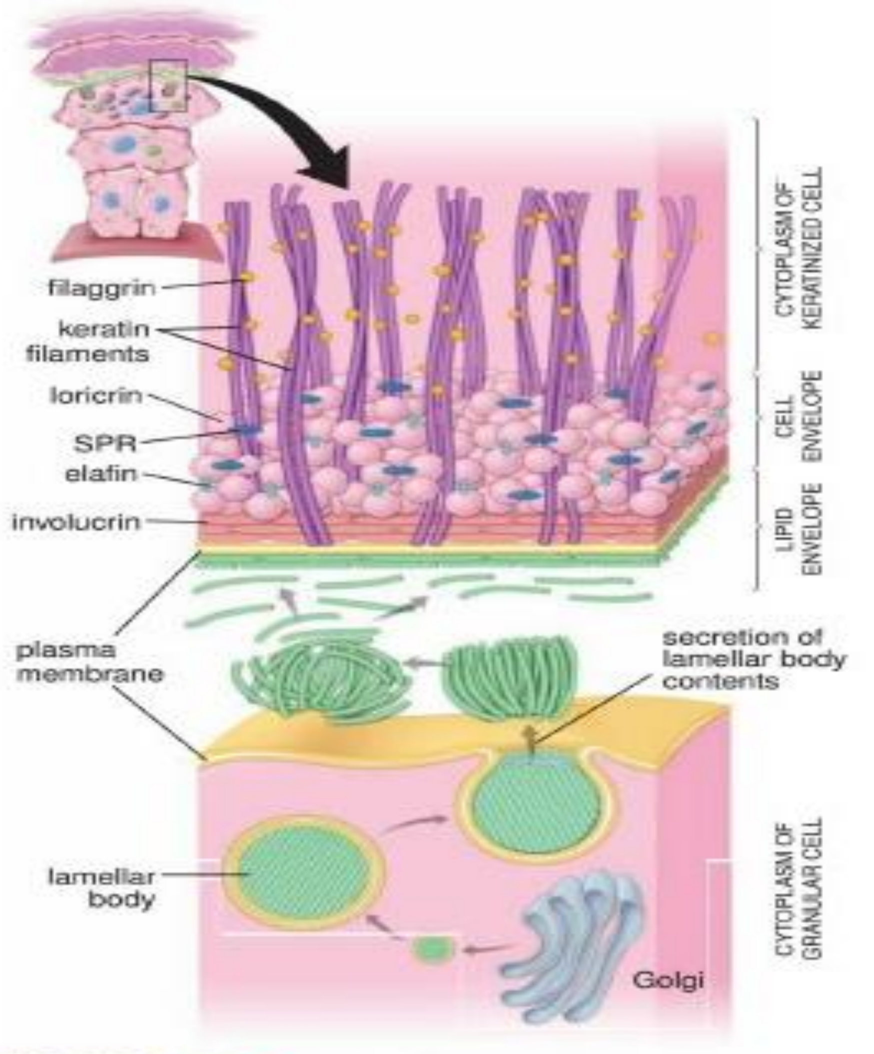
- The **spinous layer (stratum spinosum)** is normally the thickest layer and consists of generally polyhedral cells having central nuclei with nucleoli and cytoplasm actively synthesizing keratins. Just above the basal layer, some cells may still divide and this combined zone is sometimes called the **stratum germinativum**.

- The keratin filaments assemble here into microscopically visible bundles called **tonofibrils**, which converge and terminate at the numerous desmosomes holding the cell layers together. The cells extend slightly around the tonofibrils on both sides of each desmosome (and the extensions elongate if the cells shrink slightly during histologic processing), leading to the appearance of many short "spines" or prickles at the cell surfaces. The epidermis of thick skin subject to continuous friction and pressure (such as the foot soles) has a thicker stratum spinosum with more abundant tonofibrils and desmosomes.



- The **granular layer (stratum granulosum)** consists of three to five layers of flattened cells, now undergoing the terminal differentiation process of **keratinization**. Their cytoplasm is filled with intensely basophilic masses called **keratohyaline granules**. These are dense, non-membrane-bound masses of **filaggrin** and other proteins associated with the keratins of tonofibrils, linking them further into large cytoplasmic structures.

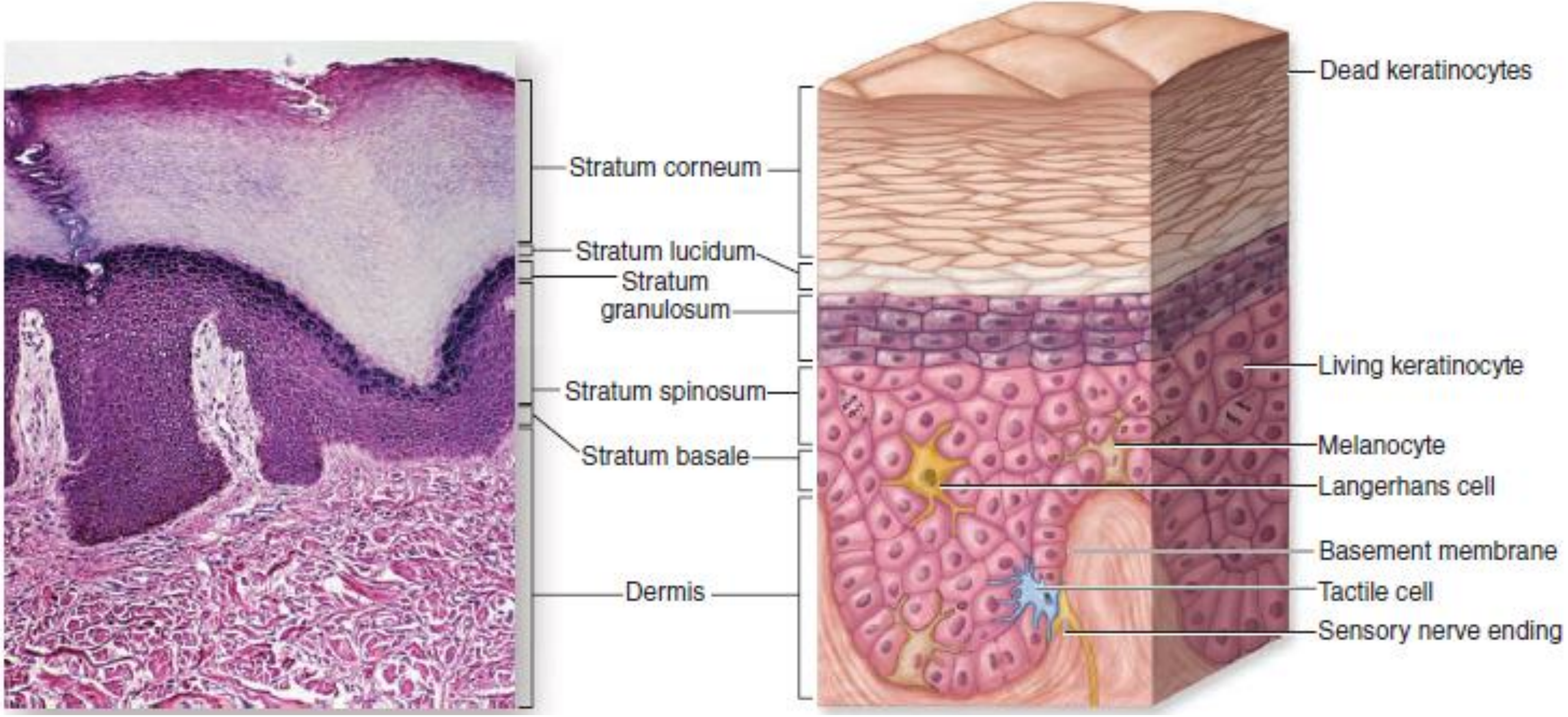
- Characteristic features in cells of the granular layer also include Golgi-derived **lamellar granules**, small ovoid (100 × 300 nm) structures with many lamellae containing various lipids and glycolipids. Among the last activities of the keratinocytes, the lamellar granules undergo exocytosis, producing a lipid-rich, impermeable layer around the cells. This material forms a major part of the skin's barrier against water loss. Formation of this barrier, which appeared first in ancestral reptiles, was a key evolutionary process that permitted animals to develop on land. Together, keratinization and production of the lipid-rich layer also have a crucial sealing effect in skin, forming the barrier to penetration by most foreign materials.




**Schematic diagram of the epidermal water barrier.** The heterogeneous mixture of glycosphingolipids, phospholipids, and ceramides makes up the lamellae of the lamellar bodies. The lamellar bodies, produced within the Golgi apparatus, are secreted by exocytosis into the intercellular spaces between the stratum granulosum and stratum corneum, where they form the lipid envelope. The lamellar arrangement of lipid molecules is depicted in the intercellular space just below the thickened plasma membrane and forms the cell envelope of the keratinized keratinocyte. The innermost part of the cell envelope consists primarily of loricrin molecules (*pink spheres*) that are cross-linked by small proline-rich (SPR) proteins and elafin. The layer adjacent to the cytoplasmic surface of the plasma membrane consists of the two tightly packed proteins involucrin and cystatin α. Keratin filaments (tonofilaments) bound by filaggrin are anchored into the cell envelope.

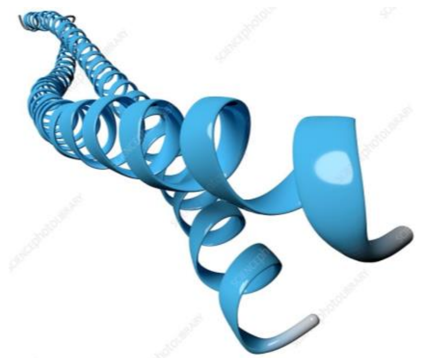
- The **stratum lucidum**, found only in thick skin, consists of a thin, translucent layer of flattened eosinophilic keratinocytes held together by desmosomes. Nuclei and organelles have been lost, and the cytoplasm consists almost exclusively of packed keratin filaments embedded in an electron-dense matrix.

- The **stratum corneum** consists of 15-20 layers of squamous, keratinized cells filled with birefringent filamentous keratins. Keratin filaments contain at least six different polypeptides with molecular masses ranging from 40 to 70 kDa, synthesized during cell differentiation in the immature layers. As they form, keratin tonofibrils become heavily massed with filaggrin and other proteins in keratohyaline granules. By the end of keratinization, the cells contain only amorphous, fibrillar proteins with plasma membranes surrounded by the lipid-rich layer. These fully keratinized or cornified cells called **squames** are continuously shed at the epidermal surface as the desmosomes and lipid-rich cell envelopes break down.

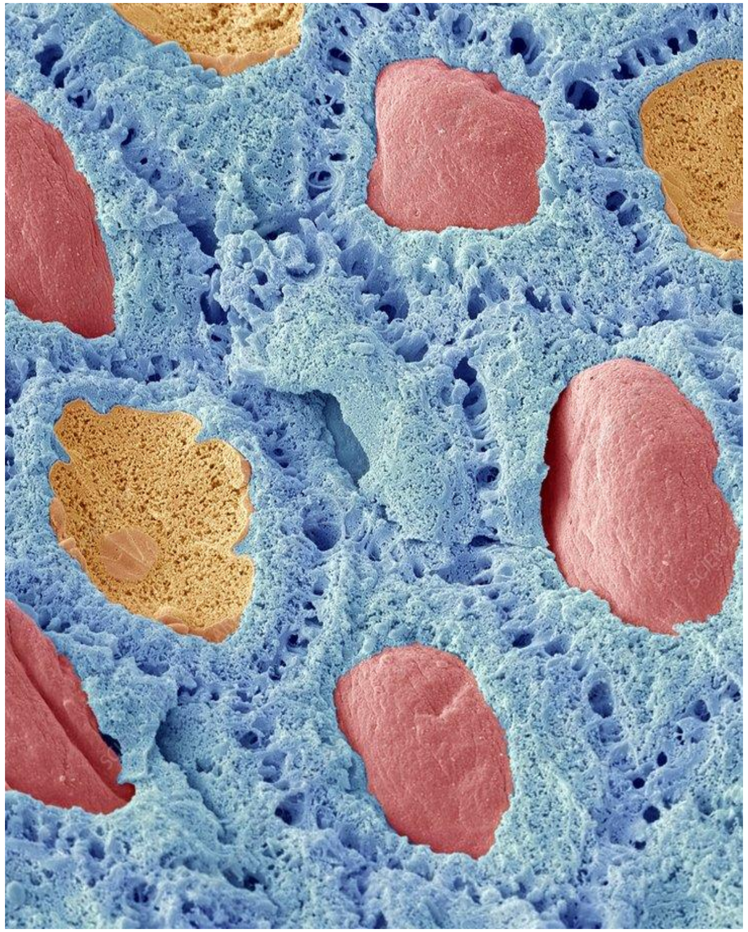


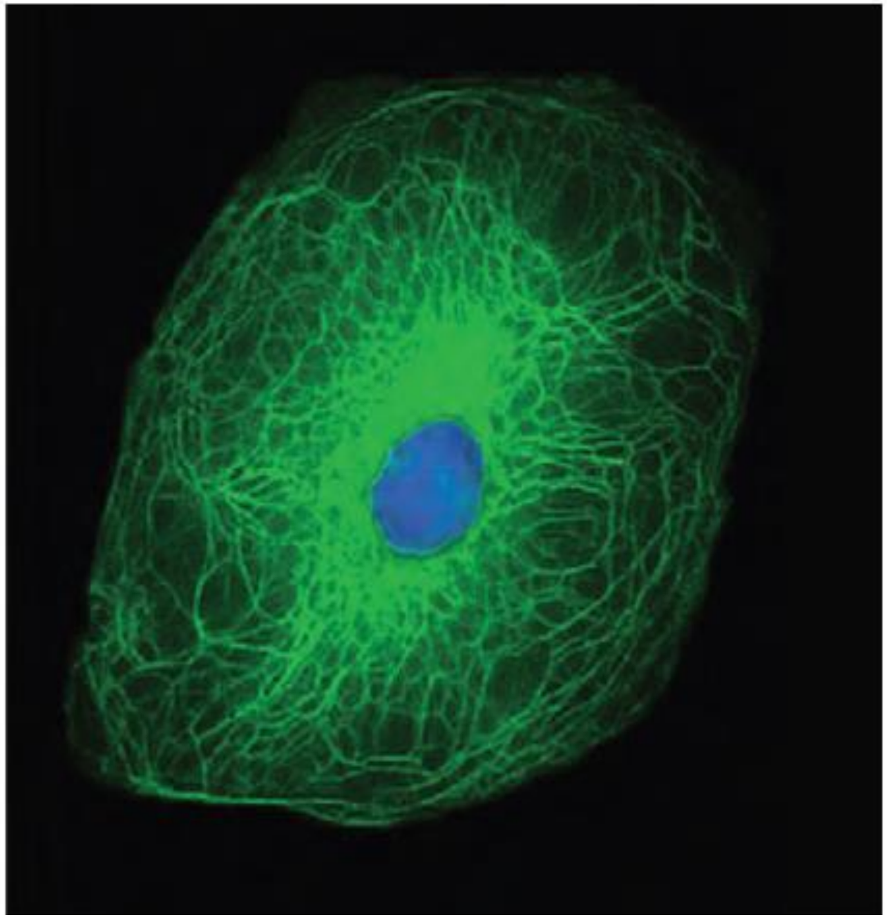
Stratum corneum
Stratum lucidum
Stratum granulosum
Stratum spinosum
Stratum basale
Dermis
Dead keratinocytes
Living keratinocyte
Melanocyte
Langerhans cell
Basement membrane
Tactile cell
Sensory nerve ending

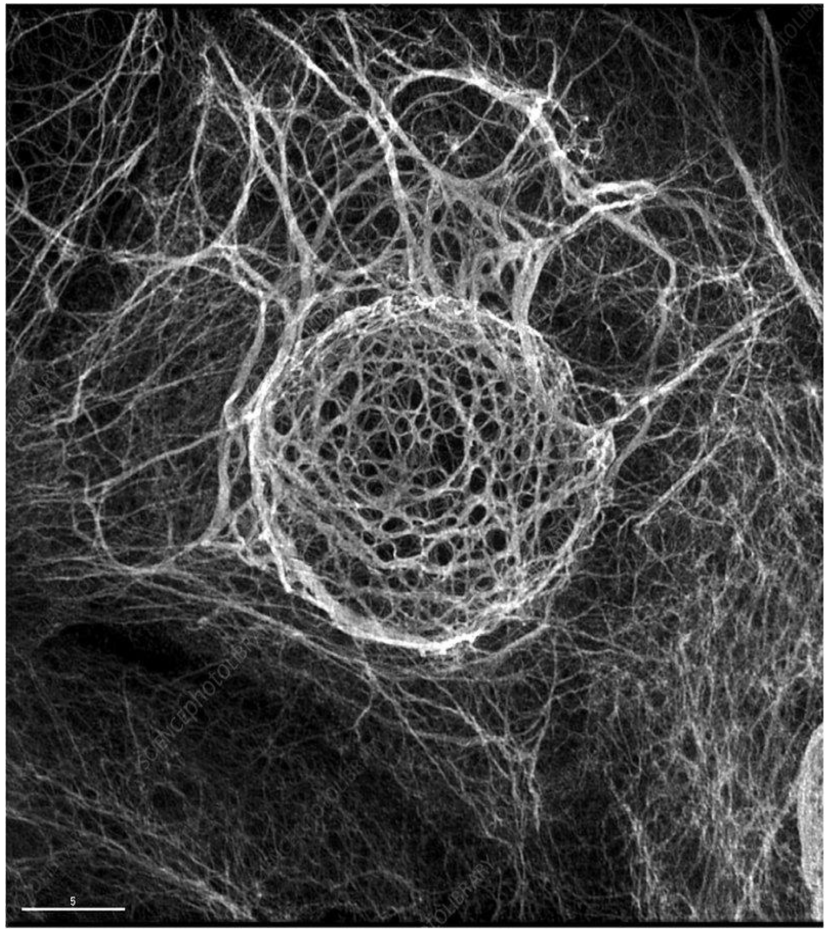
# KERATIONOCYTES



- An important feature of all keratinocytes is the cytoskeletal **keratins**, intermediate filaments about 10 nm in diameter. During differentiation, the cells move upward and the amount and types of keratin filaments increase until they represent half the total protein in the superficial keratinocytes.







# KERATINIZATION

Keratinization, also known as cornification, is unique to the epithelium of the skin. Keratinization of the skin is of paramount importance. The process of keratinization begins in the basal layer of the epidermis and continues upward until full keratinization has occurred in the stratum corneum. The function and purpose of keratinization is to form the stratum corneum.

The stratum corneum is a highly organized layer that is relatively strong and resistant to physical and chemical insults. This layer is critically important in keeping out microorganisms; it is the first line of defense against ultraviolet radiation; and it contains many enzymes that can degrade and detoxify external chemicals. The stratum corneum is also a semipermeable structure that selectively allows different hydrophilic and lipophilic agents passage. However, the most obvious and most studied aspect of the stratum corneum is its ability to protect against excessive water and electrolyte loss.

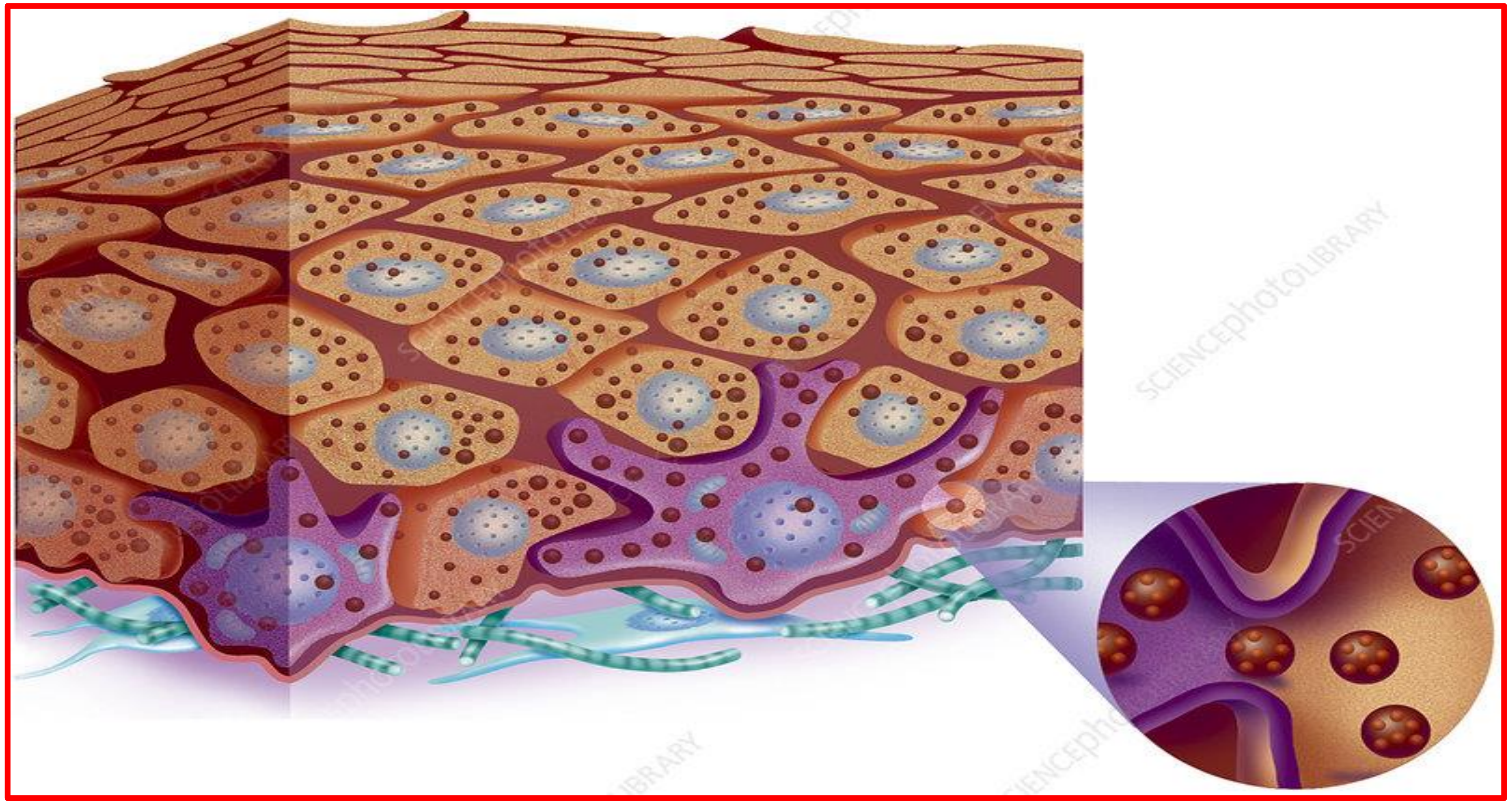
It acts as a barrier to keep chemicals out, but more importantly,it keeps water and electrolytes inside the body. Transepidermal water loss (TEWL) increases as the stratum corneum is damaged or disrupted. The main lipids responsible for protection against water loss are the ceramides and the sphingolipids. These molecules are capable of binding many water molecules.

# KERATINIZATION

- The cells continue to move toward the surface of the skin and begin to lose their nucleus and cellular organelles. The loss of these organelles is mediated by the activation of certain proteases that can quickly degrade protein, DNA, RNA, and the nuclear membrane. Once the cells reach the outer layers of the stratum corneum, they begin to be shed.
- On average, a keratinocyte spends 2 weeks in the stratum corneum before being shed from the skin surface in a process called desquamation.

# MELANOCYTES

- The color of the skin is the result of several factors, the most important of which are the keratinocytes' content of **melanin** and **carotene** and the number of blood vessels in the dermis.
- **Eumelanins** are brown or black pigments produced by the **melanocyte,** a specialized cell of the epidermis found among the cells of the basal layer and in hair follicles. The similar pigment found in red hair is called **pheomelanin** (Gr. *phaios*, dusky + *melas*, black).
- Melanocytes have pale-staining, rounded cell bodies attached by hemidesmosomes to the basal lamina, but lacking attachments to the neighboring keratinocytes. Several long irregular cytoplasmic extensions from each melanocyte cell body penetrate the epidermis, running between the cells of the basal and spinous layers and terminating in invaginations of 5-10 keratinocytes. Ultrastructurally a melanocyte has numerous small mitochondria, short cisternae of RER, and a well-developed Golgi apparatus.
- The first step in melanin synthesis is catalyzed by **tyrosinase**, a transmembrane enzyme in Golgi-derived vesicles. Tyrosinase activity converts tyrosine into **3,4-dihydroxyphenylalanine (DOPA)**, which is then further transformed and polymerized into the different forms of melanin. Melanin pigment is linked to a matrix of structural proteins and accumulates in the vesicles until they form mature elliptical granules about 1-µm long called **melanosomes.**



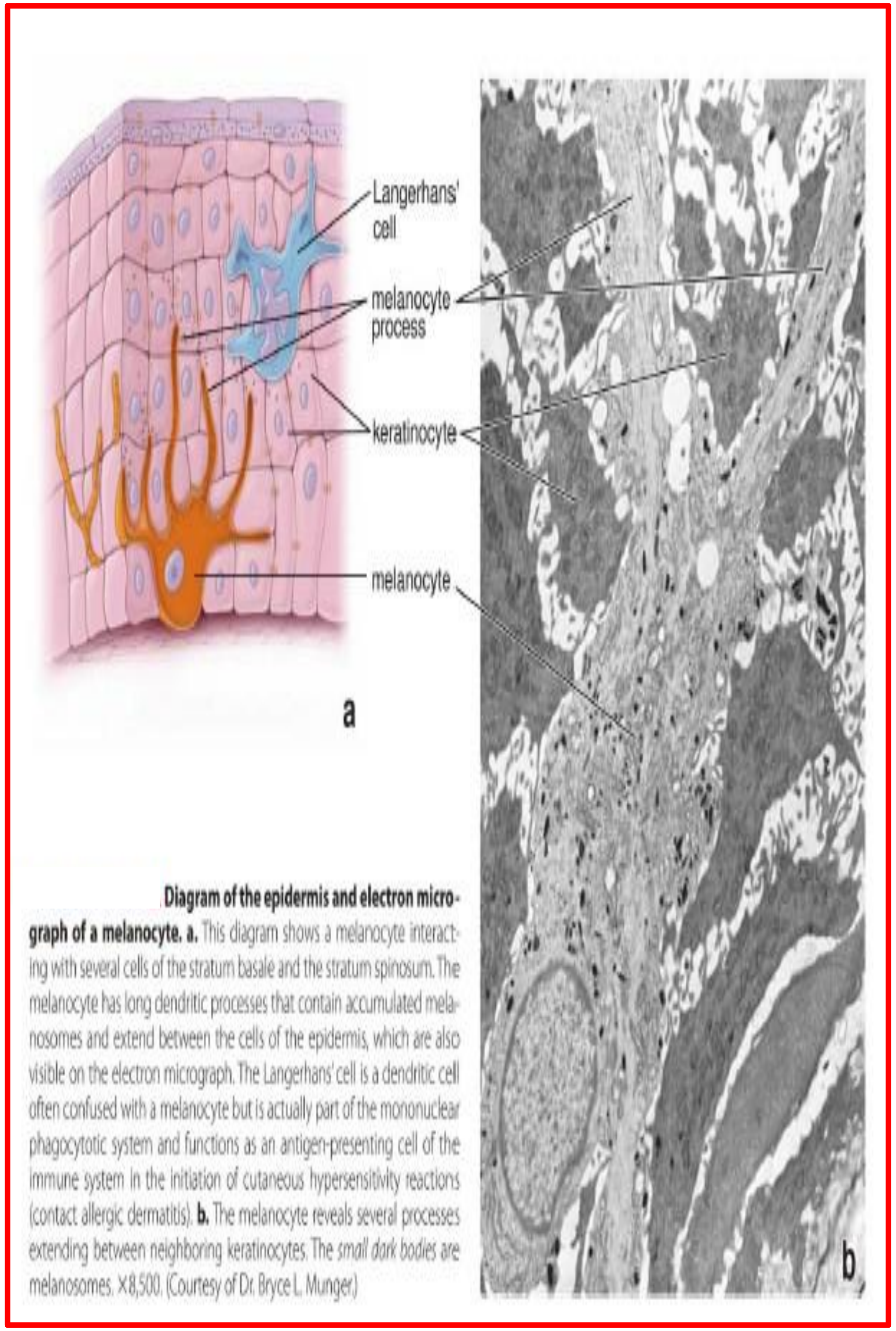
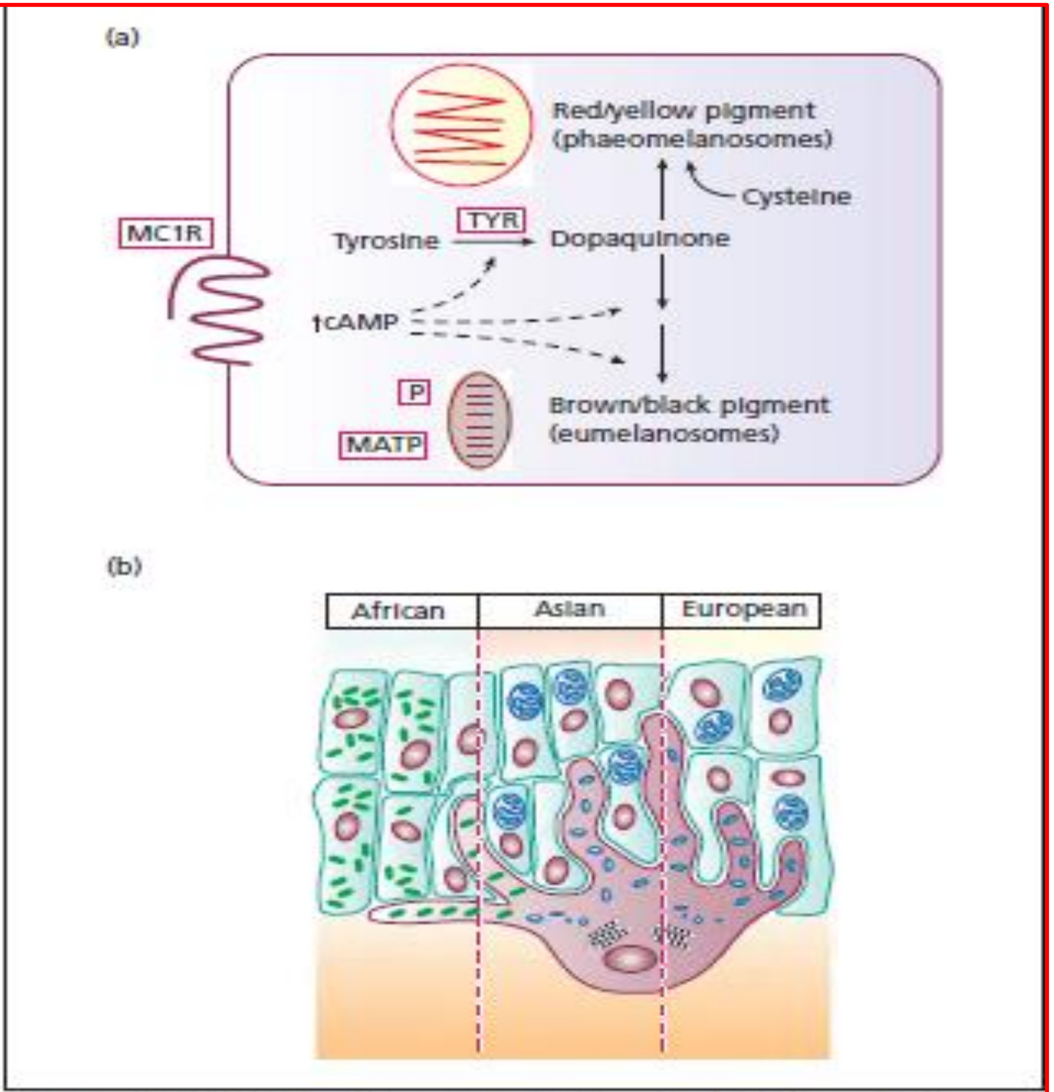
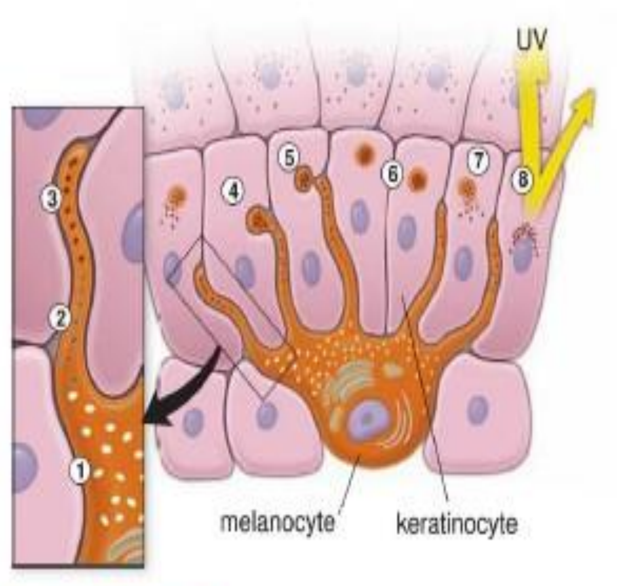



**Diagram of the epidermis and electron micrograph of a melanocyte. a.** This diagram shows a melanocyte interacting with several cells of the stratum basale and the stratum spinosum. The melanocyte has long dendritic processes that contain accumulated melanosomes and extend between the cells of the epidermis, which are also visible on the electron micrograph. The Langerhans' cell is a dendritic cell often confused with a melanocyte but is actually part of the mononuclear phagocytotic system and functions as an antigen-presenting cell of the immune system in the initiation of cutaneous hypersensitivity reactions (contact allergic dermatitis). **b.** The melanocyte reveals several processes extending between neighboring keratinocytes. The *small dark bodies* are melanosomes. ×8,500. (Courtesy of Dr. Bryce L. Munger.)

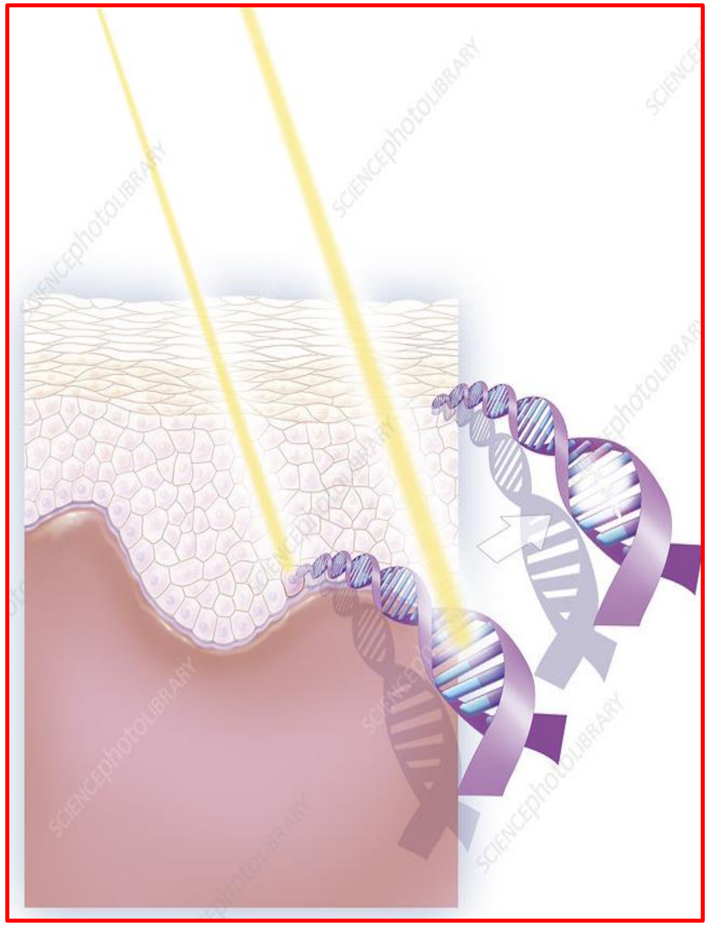
- Melanosomes are then transported via kinesin to the tips of the cytoplasmic extensions. The neighboring keratinocytes phagocytose the tips of these dendrites, take in the melanosomes, and transport them by dynein toward their nuclei. The melanosomes accumulate within keratinocytes as a supranuclear cap that prior to keratinization absorbs and scatters sunlight, protecting DNA of the living cells from the ionizing, mutagenic effects of UV radiation.
- Although melanocytes produce melanosomes, the keratinocytes are the melanin depot and contain more of this pigment than the cells that make it. One melanocyte plus the keratinocytes into which it transfers melanosomes make up an **epidermal-melanin unit**.

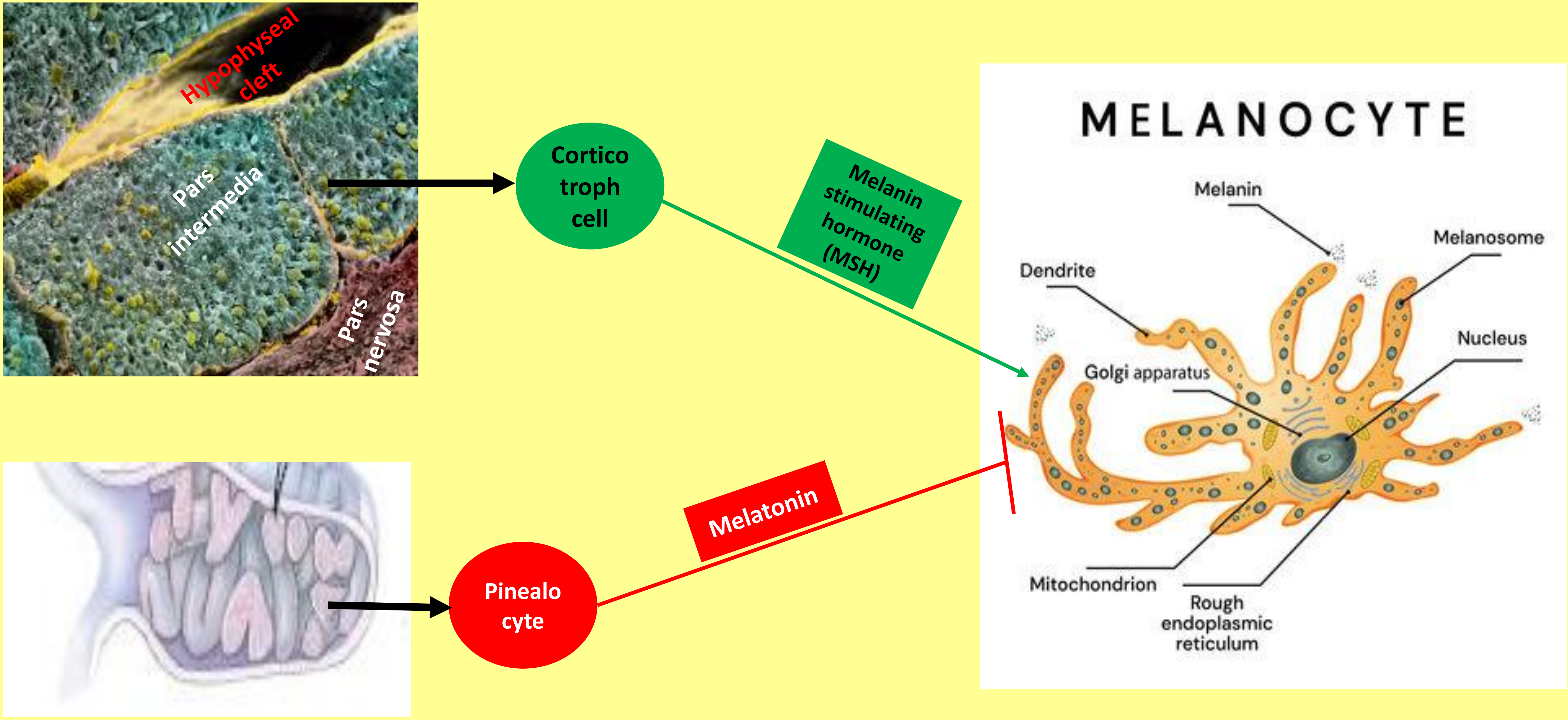



(a) Activation of the melanocortin 1 receptor (MC1R) promotes the synthesis of eumelanin at the expense of phaeomelanin. Oxidation of tyrosine by tyrosinase (TYR), however, is required for synthesis of both pigment types. Melanosomal membrane components, including the membrane-associated transport protein (MATP) and the pink-eyed dilution protein (P), play a role in determining the amount of pigment synthesis within melanosomes. (b) In African, Asian and European skin there is a gradient of melanosome size and number; in addition, melanosomes in African skin are more widely dispersed.



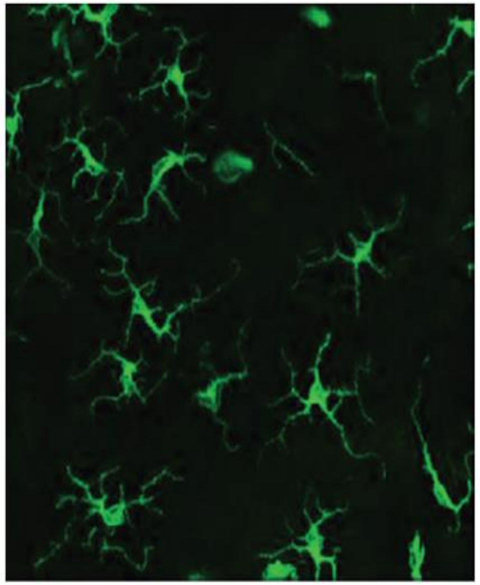

**Formation of melanin and mechanism of pigment donation.** Melanocytes produce lysosome-related membrane-bound structures that originate from the Golgi apparatus as premelanosomes **(1)** that are involved in melanin synthesis. Melanin is produced from tyrosine by a series of enzymatic reactions and its accumulation is visible in the early melanosomes **(2)**. As maturation progresses, melanosomes travel toward the ends of the melanocyte processes. Mature melanosomes **(3)** have a high concentration of melanin and accumulate at the ends of melanocyte processes that invaginate into the keratinocyte's cell membrane **(4)**. Keratinocytes phagocytose the tips of the melanocyte processes containing the melanosomes **(5)**. In the process described as pigment donation, melanin is transferred to neighboring keratinocytes in vesicles containing melanosomes with a small amount of melanocyte cytoplasm **(6)**. Once inside the keratinocytes, melanosomes are released into the cytoplasm **(7)**. Melanosomes are distributed within the keratinocytes with more pronounced accumulation in areas over the nuclei, creating "dark umbrellas" **(8)** that protect the nuclear DNA from the sun's harmful ultraviolet radiation.

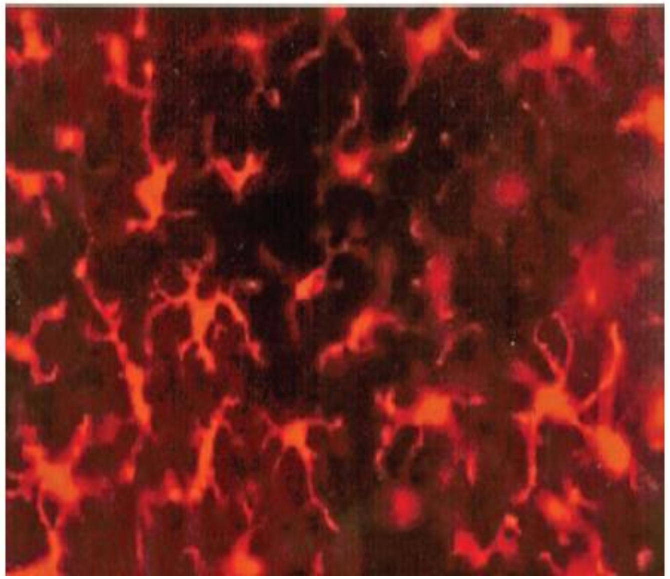





**This diagram represents the regulation of melanin pigment synthesized in melanocytes. Pinealocytes, the main cell type in the pineal gland, secrete the hormone melanin derived from dopamine and inhibit the production of melanin in melanocytes. However, corticotrope cells in the pars intermedia secrete MSH, which increases the melanin content of melanocytes. In other words, corticotropic cells act against pinealocytes.**

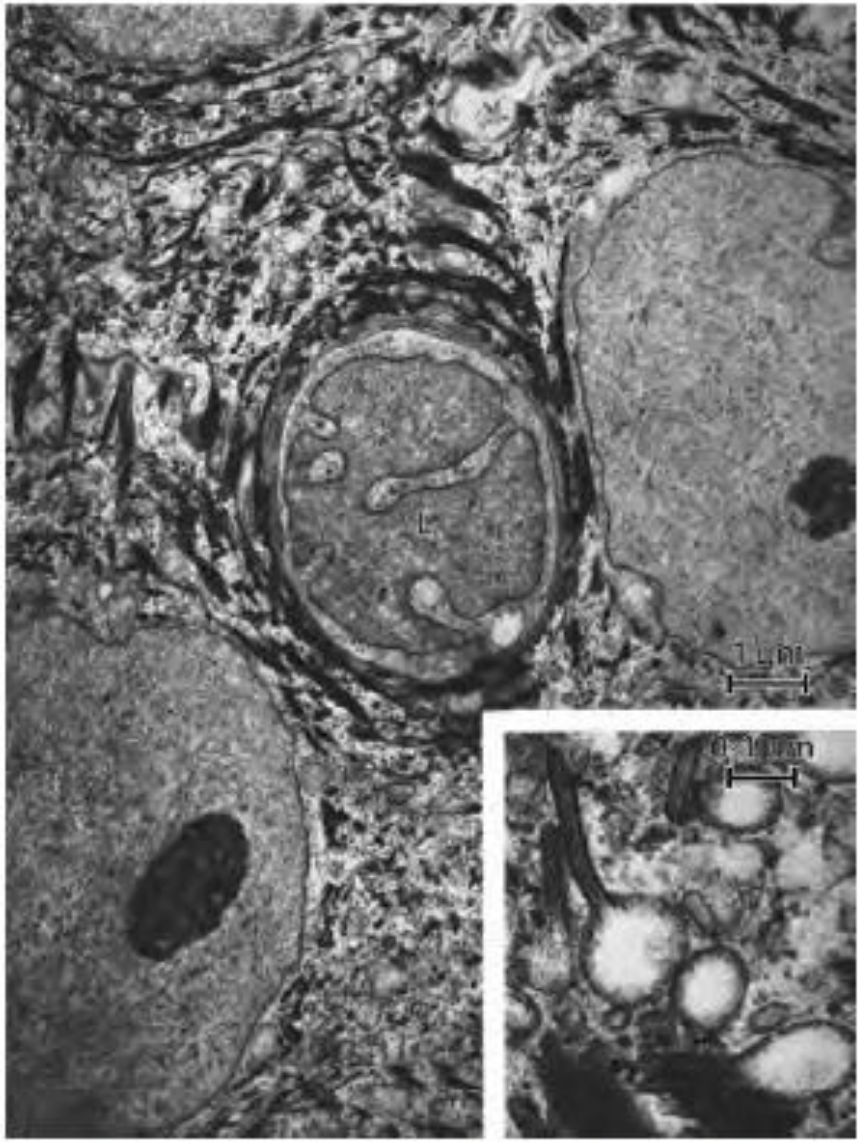
# LANGERHANS CELLS



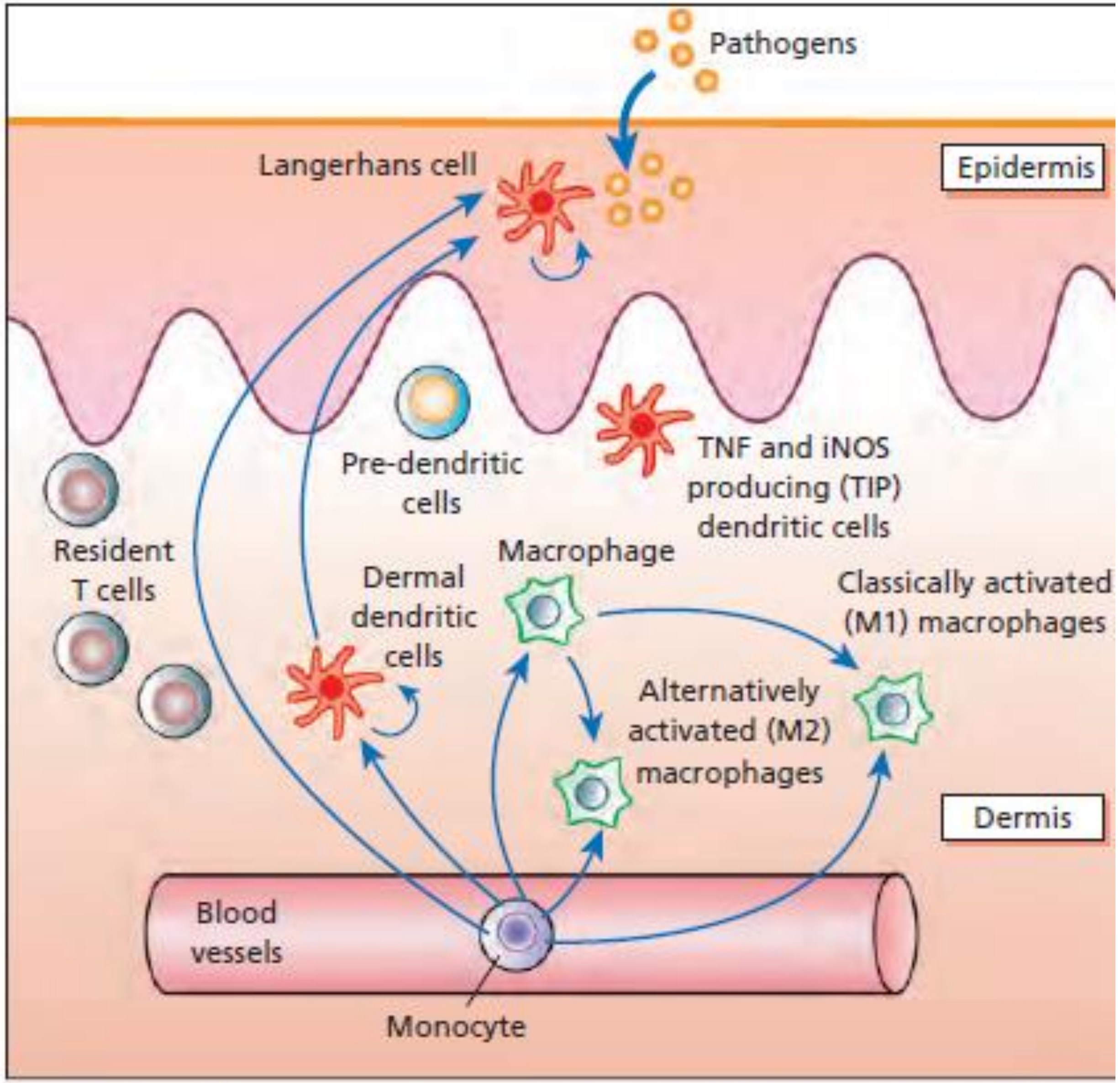


- Antigen-presenting cells called **Langerhans cells**, derived from monocytes, represent 2%-8% of the cells in epidermis and are usually most clearly seen in the spinous layer. Cytoplasmic processes extend from these dendritic cells between keratinocytes of all the layers, forming a fairly dense network in the epidermis. Langerhans cells bind, process, and present antigens to T lymphocytes in the same manner as immune dendritic cells in other organs. Microorganisms cannot penetrate the epidermis without alerting these dendritic cells and triggering an immune response. Langerhans cells, along with more scattered epidermal lymphocytes and other APCs in the dermis, comprise a major component of the skin's adaptive immunity.

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




Langerhans cell (L) with its characteristically indented nucleus, situated between keratinocytes. The inset shows Langerhans cell granules with racquet-shaped profiles. (Courtesy of Professor A. S. Breathnach.)

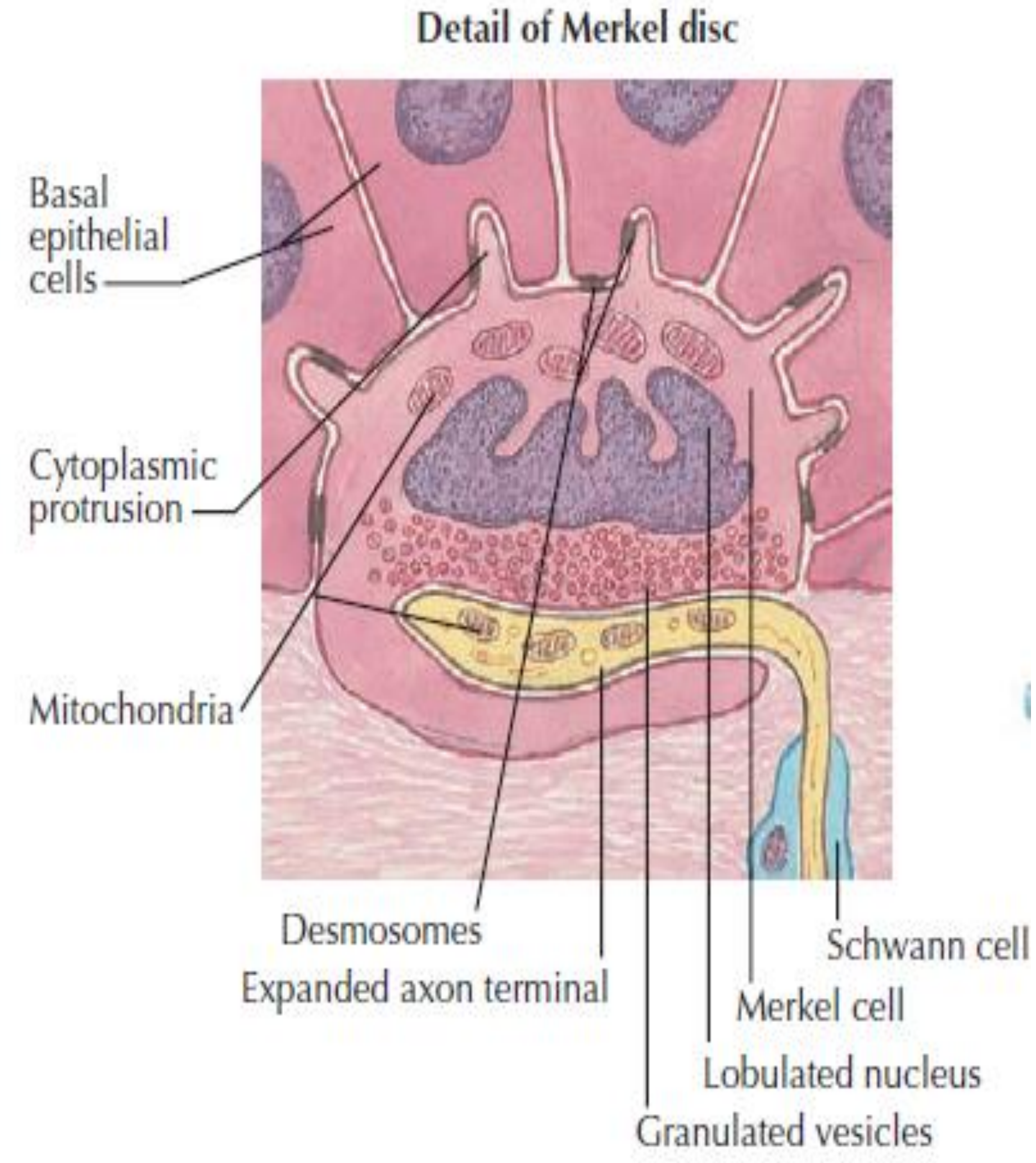


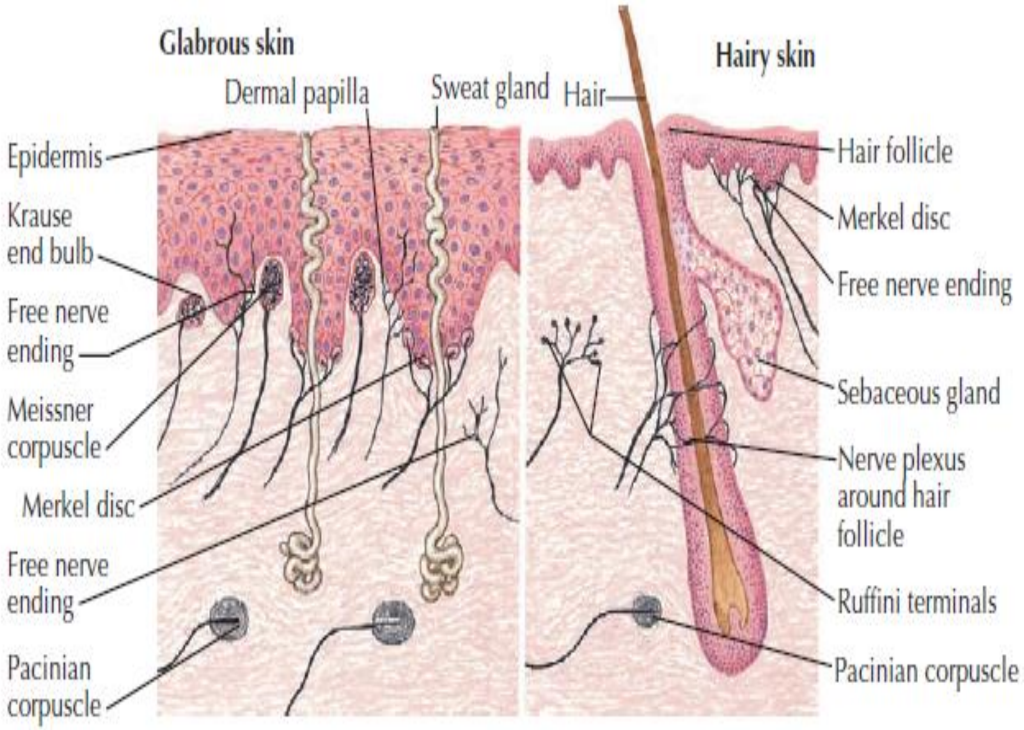

Immune surveillance in normal skin is carried out by an array of skin-based dendritic cells, macrophages and resident T cells. iNOS, inducible nitric oxide synthase; TNF, tumour necrosis factor.

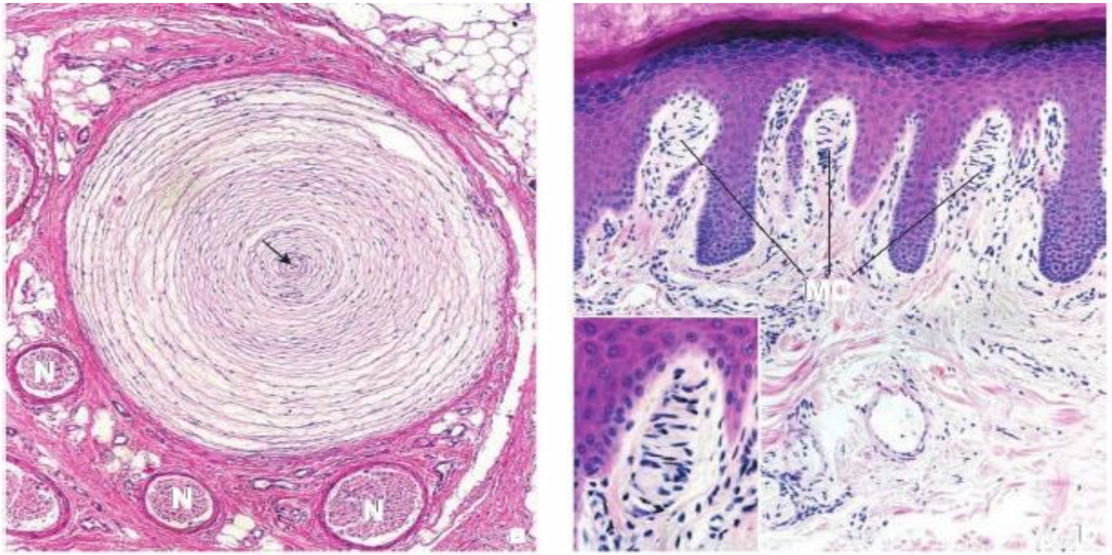
# MERKEL CELLS

- **Merkel cells**, or **epithelial tactile cells**, are low-threshold mechanoreceptors essential for sensing gentle touch. They are abundant in highly sensitive skin like that of fingertips and at the bases of some hair follicles. Joined by desmosomes to keratinocytes of the basal epidermal layer, present in both thick and thin skin Merkel cells resemble the surrounding keratinocytes, with which they share a stem cell origin, but contain few, if any, melanosomes.

- Instead, they are characterized by small, Golgi-derived dense-core granules concentrated in areas near the basolateral surface where the cells have synaptic contacts with the expanded terminal discs of unmyelinated afferent fibers penetrating the basal lamina. Light touch to the skin initiates release of neurotransmitters and sensation from that location.






**Pacinian and Meissner's corpuscles in H&E preparations. a.** In this photomicrograph, the concentric cellular lamellae of the Pacinian corpuscle are visible because of flat, fibroblast-like supportive cells. Although not evident within the tissue section, these cells are continuous with the endoneurium of the nerve fiber. The spaces between lamellae contain mostly fluid. The neural portion of the Pacinian corpuscle travels longitudinally through the center of the structure (*arrow*). Several nerves (*N*) are present adjacent to the corpuscle. ×85. **b.** Three Meissner's corpuscles (*MC*) are shown residing within the dermal papillae. Note the direct proximity of the corpuscle to the undersurface of the epidermis. ×150. **Inset.** A higher magnification of a Meissner's corpuscle. The nerve fiber terminates at the superficial pole of the corpuscle. Note that supporting cells are oriented approximately at right angles to the long axis of the corpuscle. ×320.

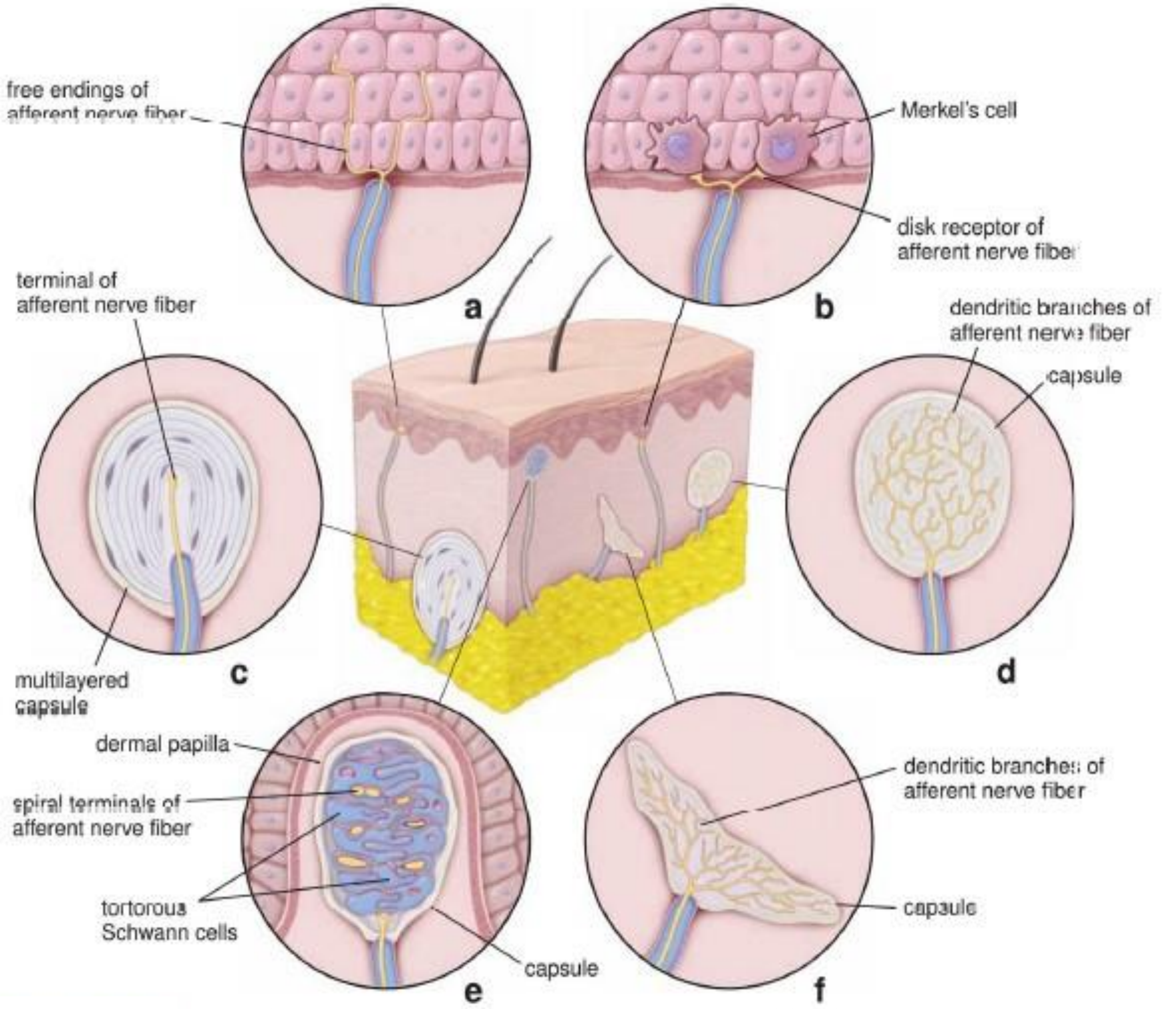



**Diagram of the sensory receptors in skin. a.** Epidermal free endings. **b.** Merkel's corpuscles containing Merkel's cells and disc receptors of afferent myelinated nerve fiber. **c.** Pacinian corpuscle located in the deep layer of deep dermis and hypodermis. **d.** Krause's end bulb serves as cold receptor. **e.** Meissner's corpuscle in dermal papilla. **f.** Ruffini's corpuscle in deep layers of the dermis. Note that sensory nerve fibers in receptors **c-f** are encapsulated.

# SUMMARY

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<tr><th>Layer</th><th>Specific Layer</th><th>Description</th></tr>
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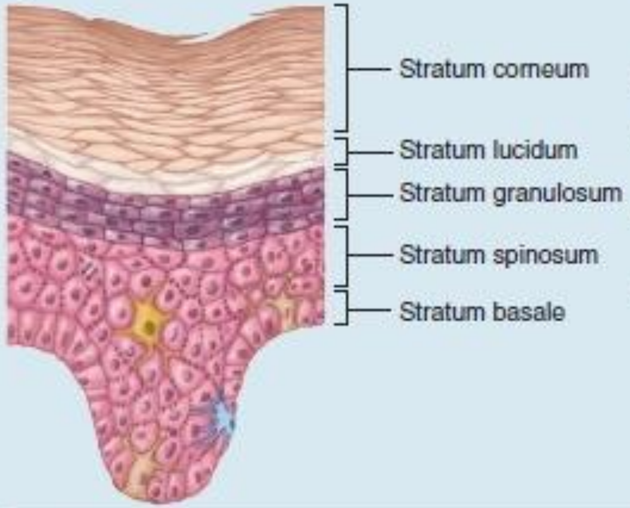
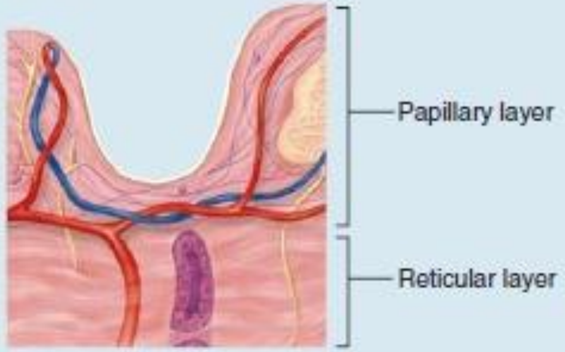
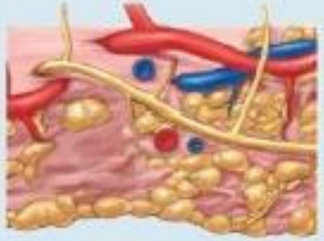


</td><td>Stratum corneum</td><td>Most superficial layer; 20-30 layers of dead, flattened, anucleate, keratin-filled keratinocytes; protects against friction and water loss</td></tr>
<tr><td>Stratum lucidum</td><td>2-3 layers of anucleate, dead cells; seen only in thick skin</td></tr>
<tr><td>Stratum granulosum</td><td>3-5 layers of keratinocytes with distinct kerato-hyaline granules</td></tr>
<tr><td>Stratum spinosum</td><td>Several layers of keratinocytes all joined by desmosomes; Langerhans cells present</td></tr>
<tr><td>Stratum basale</td><td>Deepest, single layer of cuboidal to low columnar cells in contact with basement membrane; mitosis occurs here; melanocytes and Merkel cells also</td></tr>
<tr><td rowspan="2">Dermis



</td><td>Papillary layer</td><td>More superficial layer of dermis; composed of areolar connective tissue; forms dermal papillae; contains subpapillary vascular plexus</td></tr>
<tr><td>Reticular layer</td><td>Deeper layer of dermis; dense irregular connective tissue surrounding hair follicles, sebaceous glands and sweat glands, nerves, and deep plexus of blood vessels extending into subcutaneous layer</td></tr>
<tr><td>Subcutaneous layer


</td><td>No specific layers</td><td>Not considered part of the integument; deep to dermis; composed of areolar and adipose connective tissue</td></tr>
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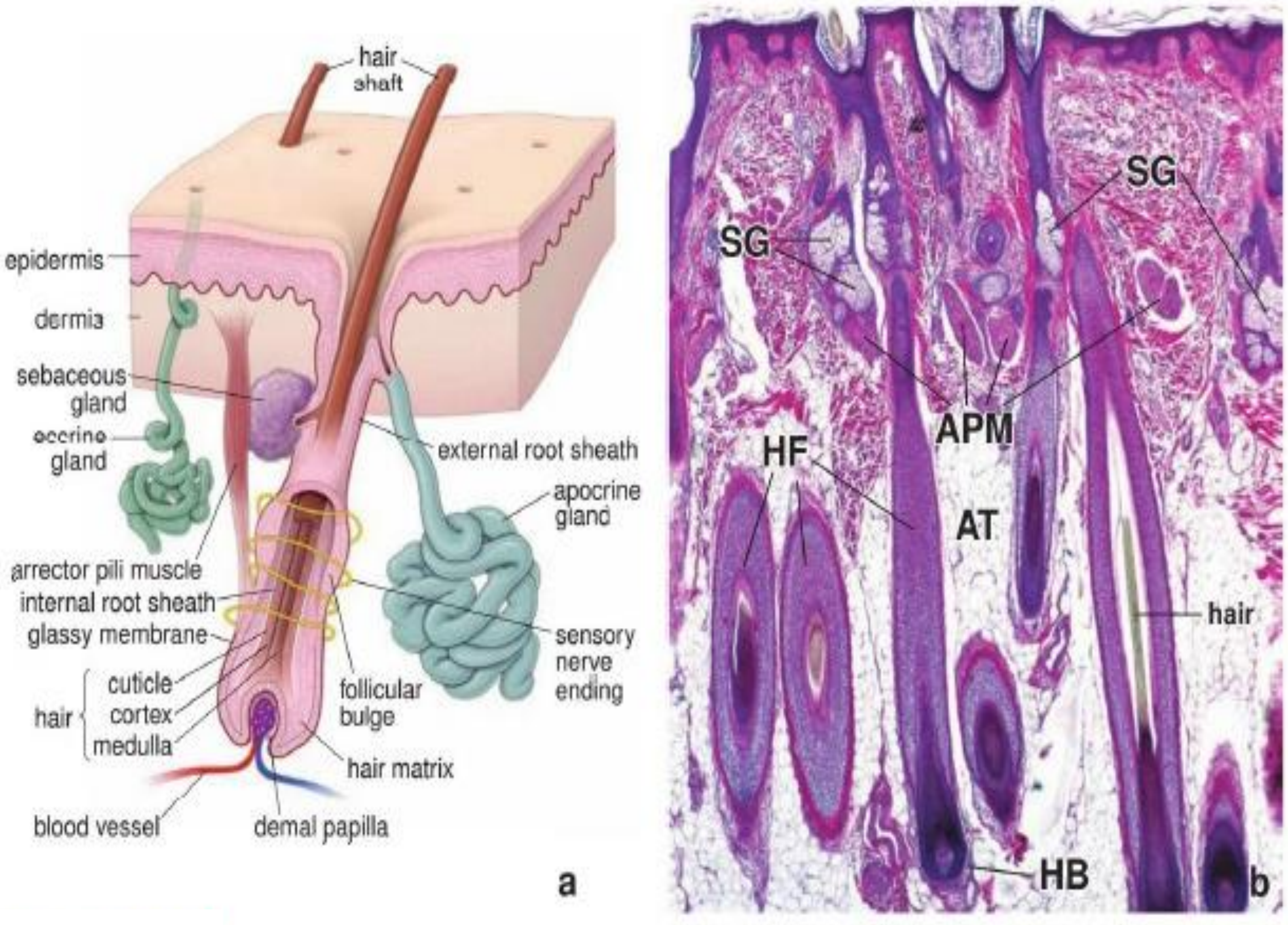
# APPENDAGEAL STRUCTURES

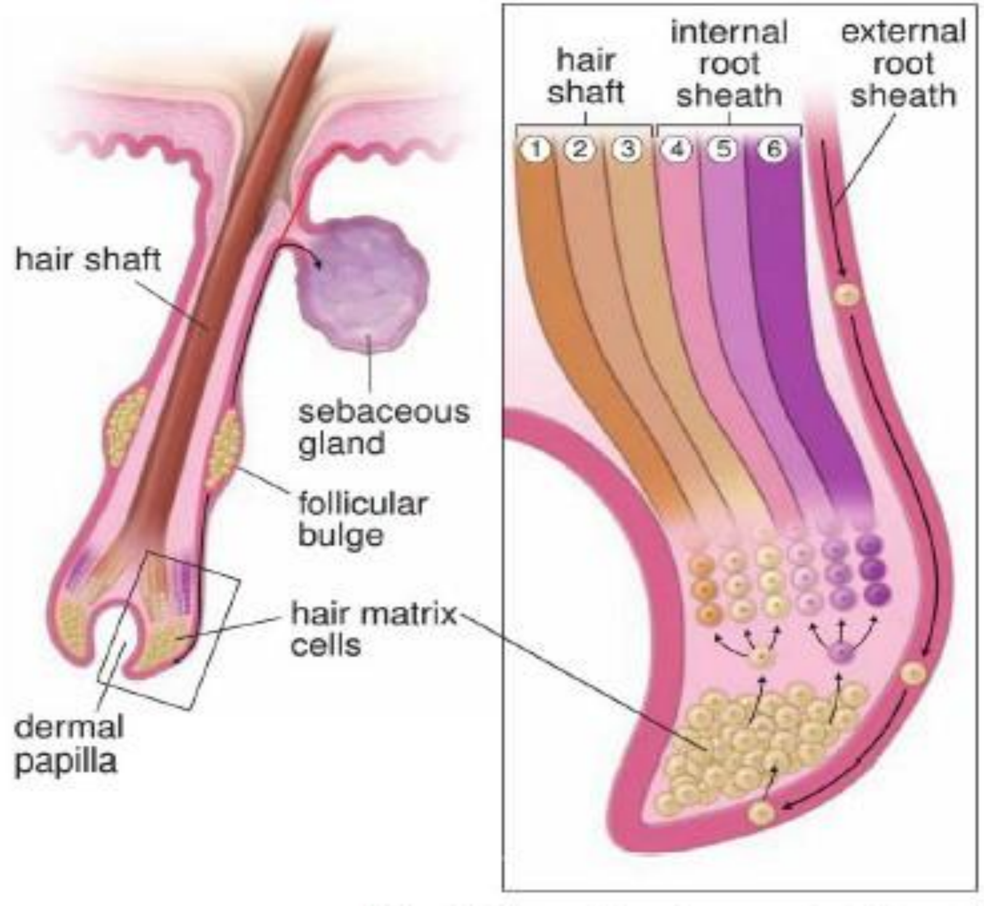
- HAIR FOLLICLES
- VARIOUS GLANDS (SEBACEOUS GLAND, ECCRINE GLAND, APOCRINE GLAND, AND MAMMARY GLAND)

# HAIR

- **Hairs** are elongated keratinized structures that form within epidermal invaginations, the **hair follicles**. The color, size, shape, and texture of hairs vary according to age, genetic background, and region of the body. Hairs grow discontinuously, with periods of growth followed by periods of rest, and this growth does not occur synchronously in all regions of the body or even in the same area.
-
- The growing hair follicle has a terminal dilation 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. Keratinocytes continuous with those of the basal epidermis cover the dermal papilla. These cells form the matrix of the elongating **hair root**; the part of a hair extending beyond the skin surface is the **hair shaft**.




**Hair follicle and other skin appendages. a.** Diagram showing a hair follicle. Note the cell layers that form the hair shaft and the surrounding external and internal root sheaths. The sebaceous gland consists of the secretory portion and a short duct that empties into the infundibulum, the upper part of the hair follicle. The arrector pili muscle accompanies the sebaceous gland; contraction of this smooth muscle assists in gland secretion and discharges the sebum into the infundibulum of the hair follicle. Projection of the external root sheath near insertion of the arrector pili muscle forms the follicular bulge that contains epidermal stem cells. Nerve endings (*yellow*) surround the follicular bulge with nearby insertion of arrector pili muscle. The apocrine sweat gland also empties into the infundibulum. Note that eccrine sweat glands are independent structures and are not associated directly with the hair follicle. **b.** Photomicrograph of H&E–stained section of thin skin from human scalp. The growing end of a hair follicle consists of an expanded hair bulb (*HB*) of epithelial cells that is invaginated by a connective tissue dermal papilla. Hair matrix that fills the bulb consists of cells that differentiate into the hair shaft and the internal root sheath of the hair follicle (*HF*). Note that several oblique and longitudinal sections of the hair follicles are embedded in the adipose tissue (*AT*) of the hypodermis. Some of them reveal a section of the hair. Sebaceous glands (*SG*) are visible in conjunction with the infundibulum of the hair follicle. ×60. APM, arrector pili muscle.




**Hair follicle and pathways of epidermal stem cell migration.** This diagram shows the location and migration pathways of epidermal stem cells that reside in the follicular bulge. Under normal conditions, epidermal stem cells migrate upward to the sebaceous gland and downward to reach the hair matrix in the bulb of the follicle (*black arrows*). Hair matrix is formed by differentiating cells that migrate along the external root sheath from the follicular bulge. As the differentiation progresses, cells leave the matrix; they form cell layers that differentiate into the hair shaft containing **(1)** medulla, **(2)** hair cortex, and **(3)** hair cuticle, and the internal root sheath containing **(4)** internal root sheath cuticle, **(5)** Huxley's layer, and **(6)** Henle's layer. During injury of the epidermis, the epidermal stem cells migrate from the follicular bulge toward the skin surface (*red arrow*) and participate in the initial resurfacing of damaged epidermis.

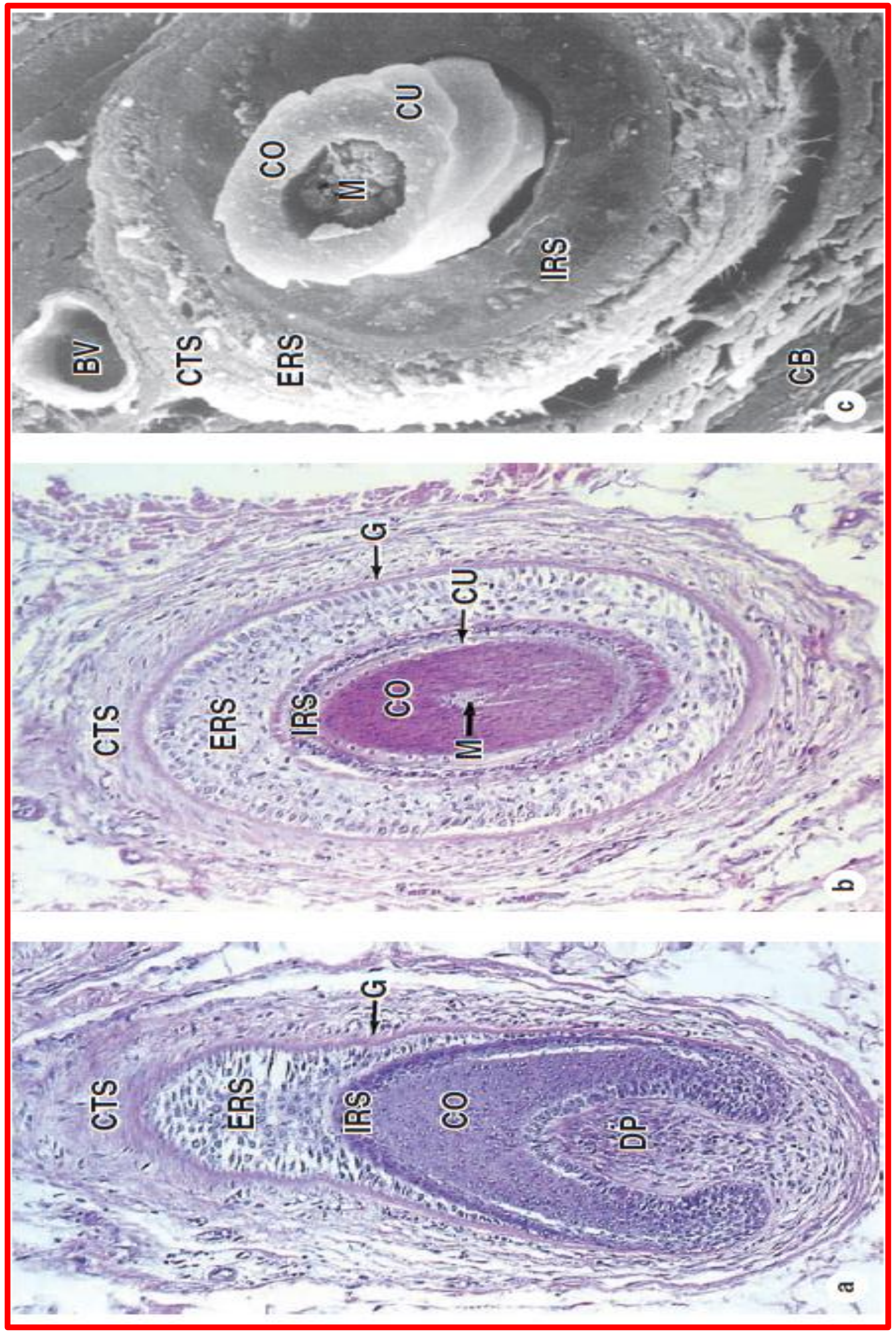
- The keratinocytes of the hair bulb are generally similar to those in the basal and spinous layers of epidermis. They divide rapidly in a matrix region immediately around the dermal papilla and then undergo keratinization, melanin accumulation, and terminal differentiation. Melanocytes in the hair bulb matrix transfer melanosomes into the epithelial cells that will later differentiate to form the hair.

- Unlike the epidermis in which all keratinocytes give rise to the stratum corneum, cells in the hair root matrix differentiate with variable amounts and types of keratin. The keratin of hair is harder and more compact than that of the stratum corneum, maintaining its structure as the hair shaft much longer.

- In most thick hairs large, vacuolated, and moderately keratinized cells form the central medulla of the hair root. Heavily keratinized, densely packed cells make up the cortex around the medulla. The most peripheral cells of the hair root comprise the cuticle, a thin layer of heavily keratinized, squamous 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 root 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.

- The arrector pili muscle, a small bundle of smooth muscle cells, extends from the midpoint of the fibrous sheath to the dermal papillary layer. 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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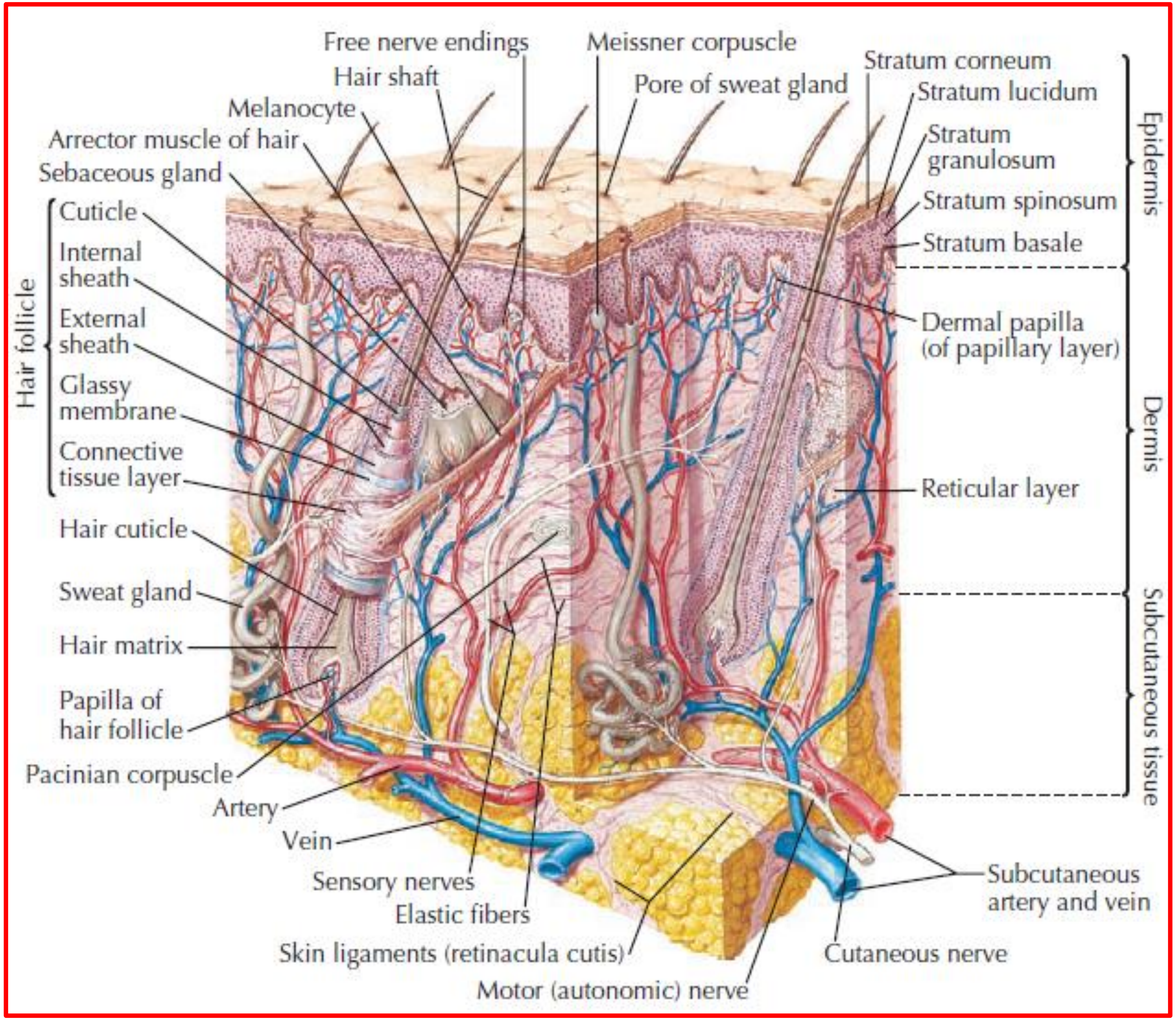
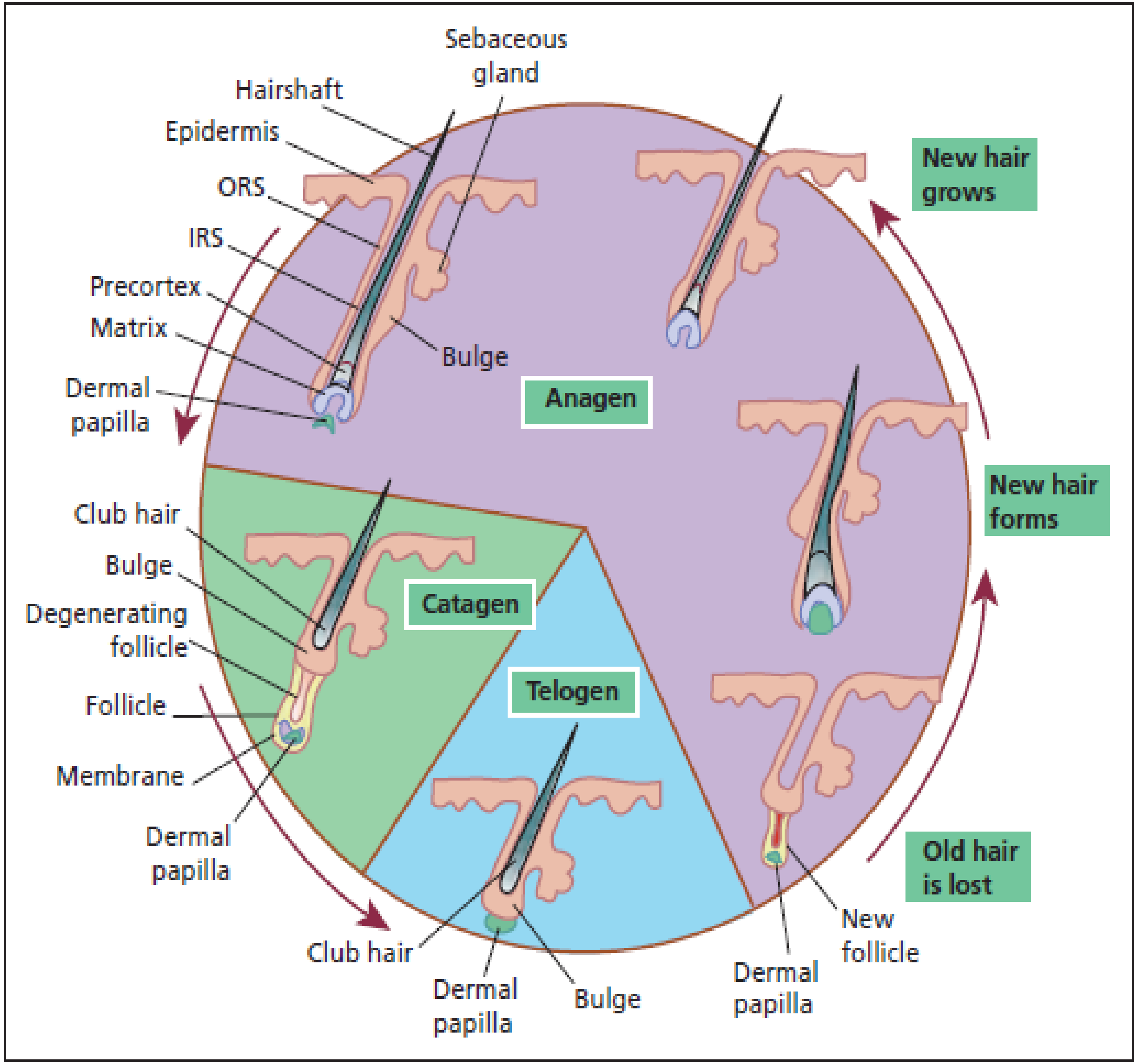

Free nerve endings
Meissner corpuscle
Hair shaft
Pore of sweat gland
Stratum corneum
Stratum lucidum
Melanocyte
Arrector muscle of hair
Sebaceous gland
Stratum granulosum
Stratum spinosum
Stratum basale
Epidermis
Hair follicle
Cuticle
Internal sheath
External sheath
Glassy membrane
Connective tissue layer
Dermal papilla (of papillary layer)
Dermis
Reticular layer
Hair cuticle
Sweat gland
Hair matrix
Papilla of hair follicle
Subcutaneous tissue
Pacinian corpuscle
Artery
Vein
Sensory nerves
Elastic fibers
Skin ligaments (retinacula cutis)
Motor (autonomic) nerve
Cutaneous nerve
Subcutaneous artery and vein

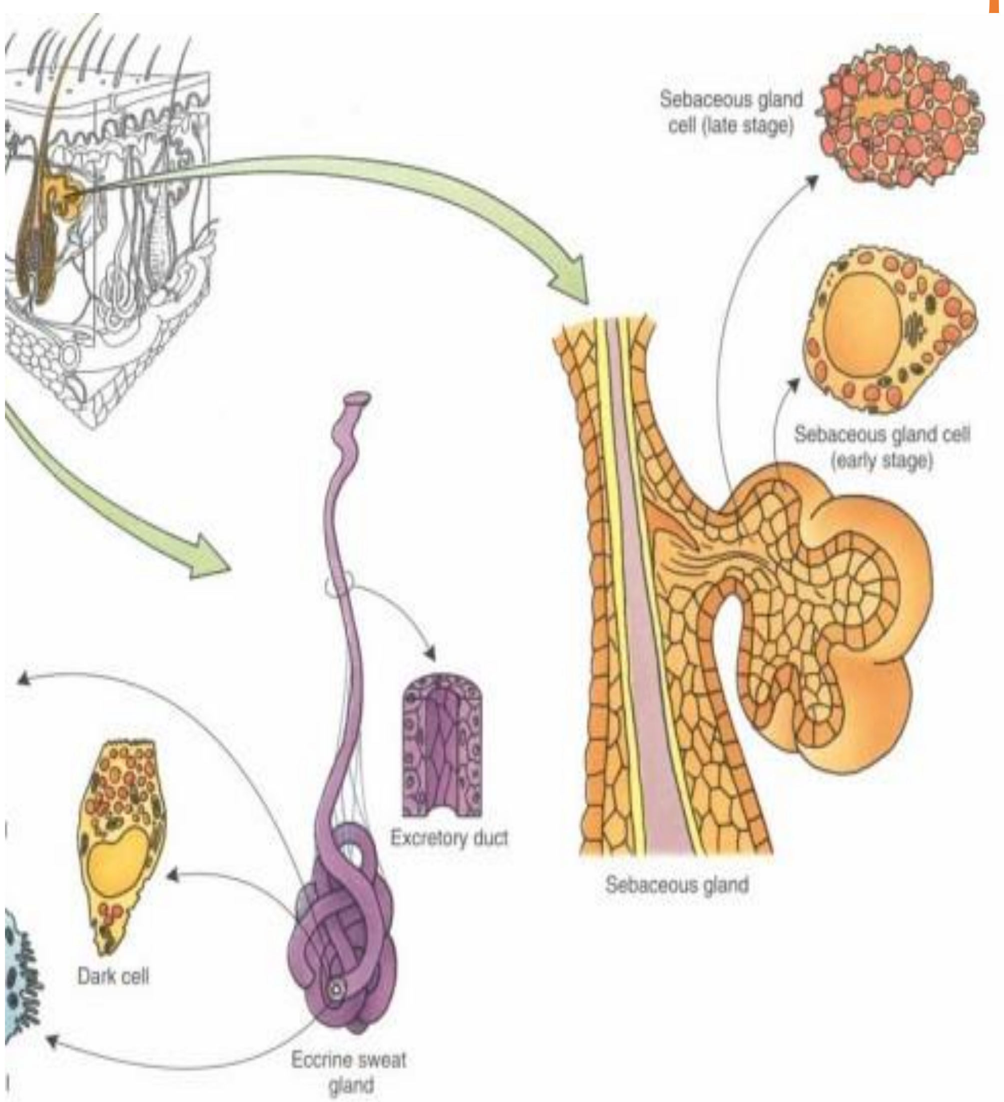



As mentioned earlier hairs grow asynchronously, cyclically, and at different rates in different regions of the body. The hair growth cycle has three major phases:

- A generally long period of mitotic activity and growth **(anagen).**
- A brief period of arrested growth and regression of the hair bulb **(catagen).**
- A final long period of inactivity **(telogen)** during which the hair may be shed.

There are three components to the hair cycle: anagen (where new hair forms and grows), followed by catagen (regressing phase) and telogen (resting phase), and then loss of old hair. The hair cycle is associated with discrete changes in hair follicle anatomy, both in the shape of the follicle and in the subjacent dermal papilla. IRS, inner root sheath; ORS, outer root sheath.

# SKIN GLANDS




## Sebaceous Glands

- Sebaceous glands are embedded in the dermis over most of the body, except in the thick, glabrous skin of the palms and soles. Sebaceous glands are branched acinar glands with several acini converging at a short duct that usually empties into the upper portion of a hair follicle. A hair follicle and its associated sebaceous glands make up a **pilosebaceous unit**. In certain hairless regions, such as the penis, clitoris, eyelids, and nipples, sebaceous ducts open directly onto the epidermal surface.

- The acini of sebaceous glands are the classic example of holocrine secretion. They have a basal layer of flattened epithelial cells on the basal lamina, which proliferate and are displaced centrally, undergoing terminal differentiation as large, lipid-producing **sebocytes** filled with small fat droplets. Their nuclei shrink and undergo autophagy along with other organelles, and near the duct the cells disintegrate, releasing the lipids as the main secretory product. This product, called **sebum**, gradually covers the surfaces of both the epidermis and hair shafts.

# SWEAT GLANDS

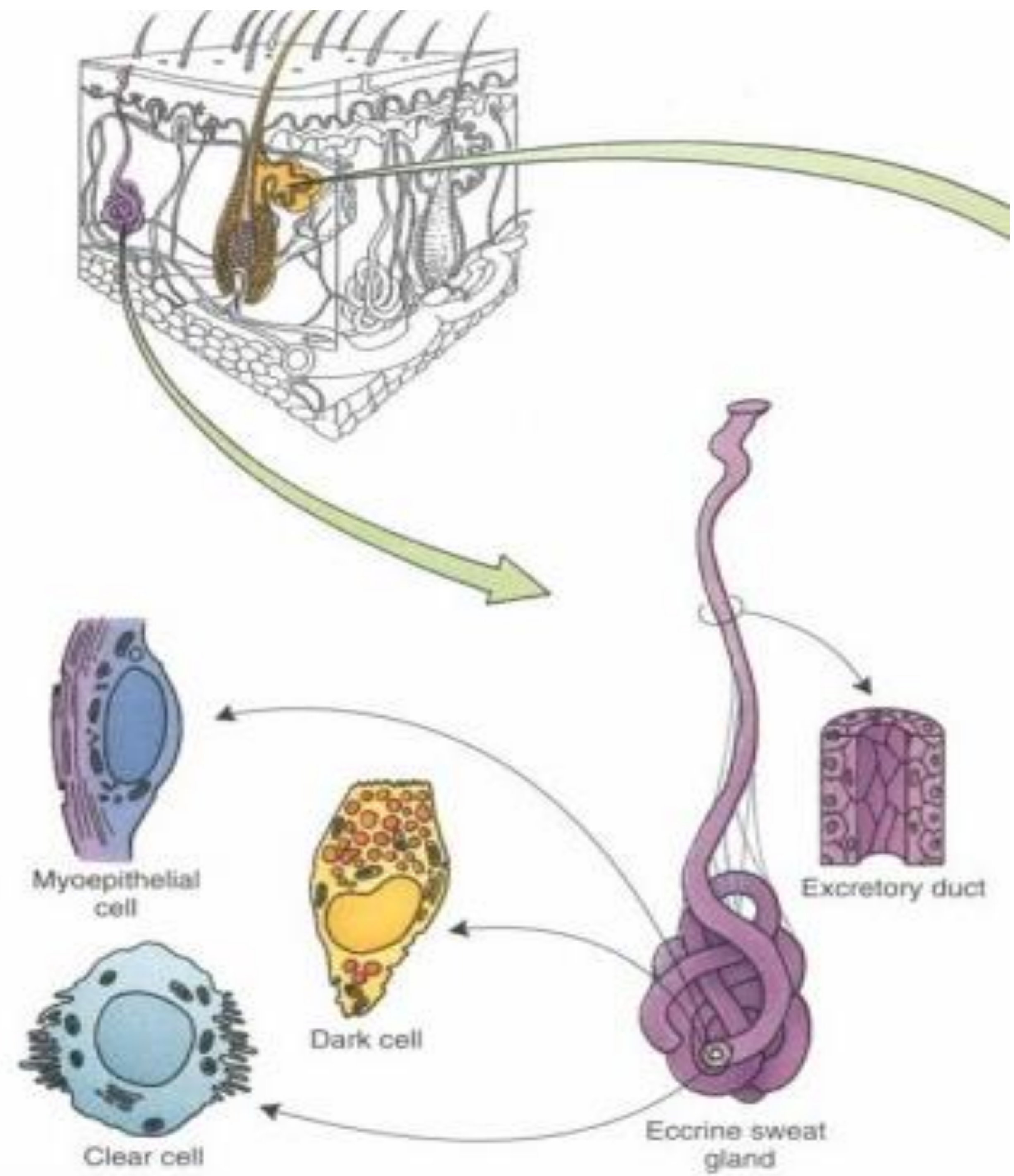
Sweat glands develop as long epidermal invaginations embedded in the dermis. There are two types of sweat glands, eccrine and apocrine, with distinct functions, distributions, and structural details.

- **Eccrine sweat glands** are widely distributed in the skin. Sweating is a physiologic response to increased body temperature during physical exercise or thermal stress and is the most effective means of temperature regulation of mammalian species.
- Both the secretory components and ducts of eccrine sweat glands are coiled and have small lumens. The **secretory part** is generally more pale-staining than the ducts and consists of an unusual stratified cuboidal epithelium with three cell types:

a. Pale-staining **clear cells** located on the basal lamina 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 gland's lumen or into intercellular canaliculi that open to the lumen.

**b.** **Dark cells** filled with strongly eosinophilic granules line most of the lumen and do not contact the basal lamina. The granules undergo merocrine secretion to release a poorly understood mixture of glycoproteins with bactericidal activity.

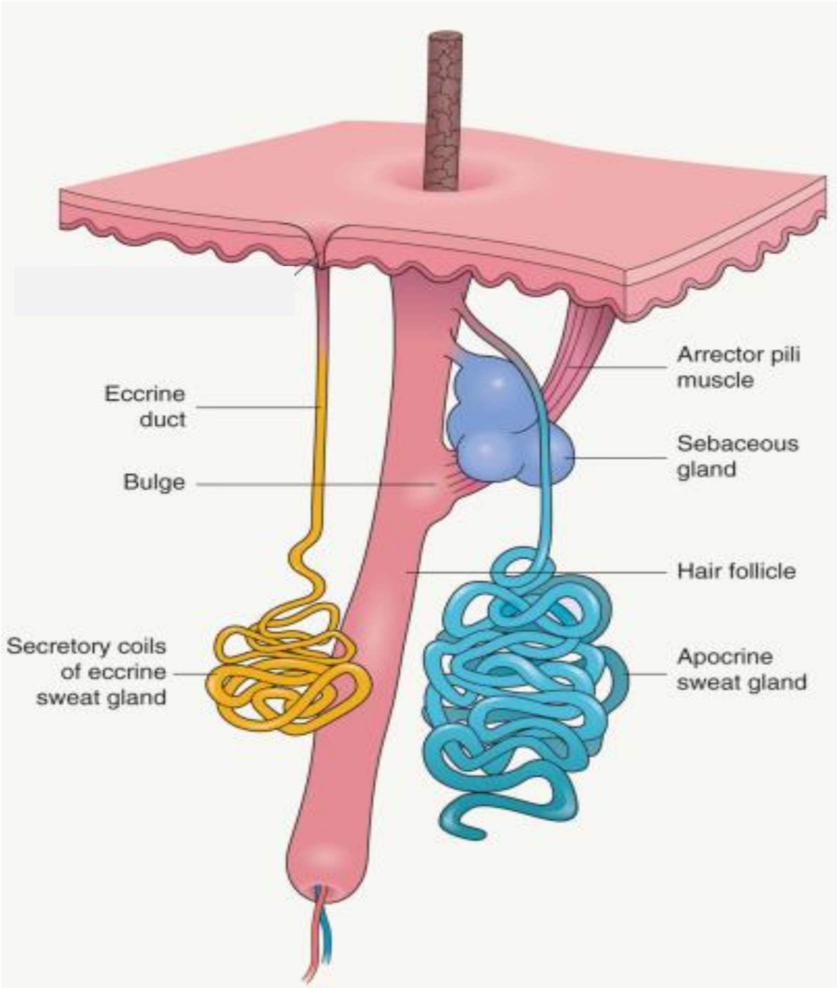
**c.** **Myoepithelial cells** on the basal lamina contract to move the watery secretion into the duct.




Sweat pore. Coloured scanning electron micrograph (SEM) of a sweat gland pore (purple) opening onto the surface of human skin. This pore brings sweat from a sweat gland to the skin surface. The sweat evaporates, removing heat and playing a vital role in cooling the body and preventing it from overheating. Skin cells can be seen flaking off the skin around the pore opening. Sweat pores vary in shape and size over the body.

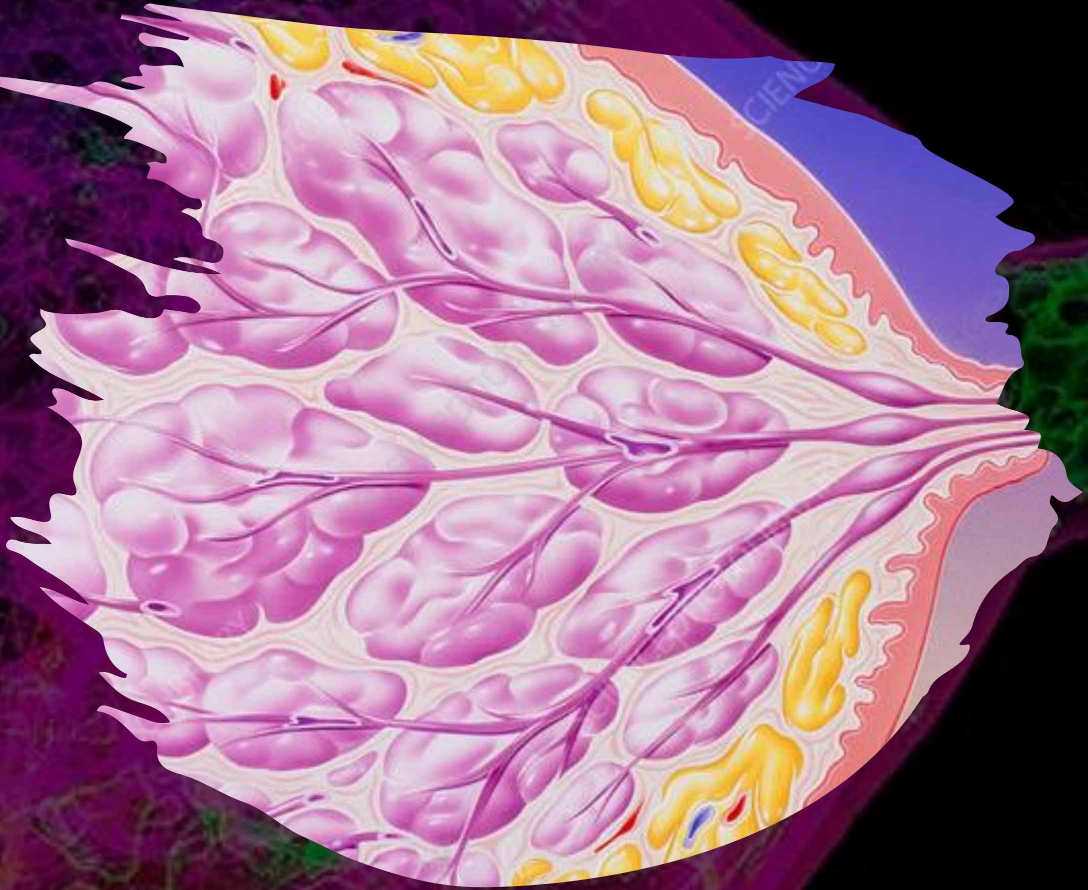
- **Apocrine sweat glands** are largely confined to skin of the axillary and perineal regions. Their development depends on sex hormones and is not complete and functional until after puberty. The secretory components of apocrine glands have much larger lumens than those of the eccrine glands and consist of simple cuboidal, eosinophilic cells with numerous secretory granules that also undergo exocytosis. Thus, the glands are misnamed: their cells show merocrine, not apocrine, secretion.

- The ducts of apocrine glands are similar to those of the eccrine glands, but they usually open into hair follicles at the epidermis and may contain the protein-rich product. 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 is 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.



# MAMMARY GLANDS

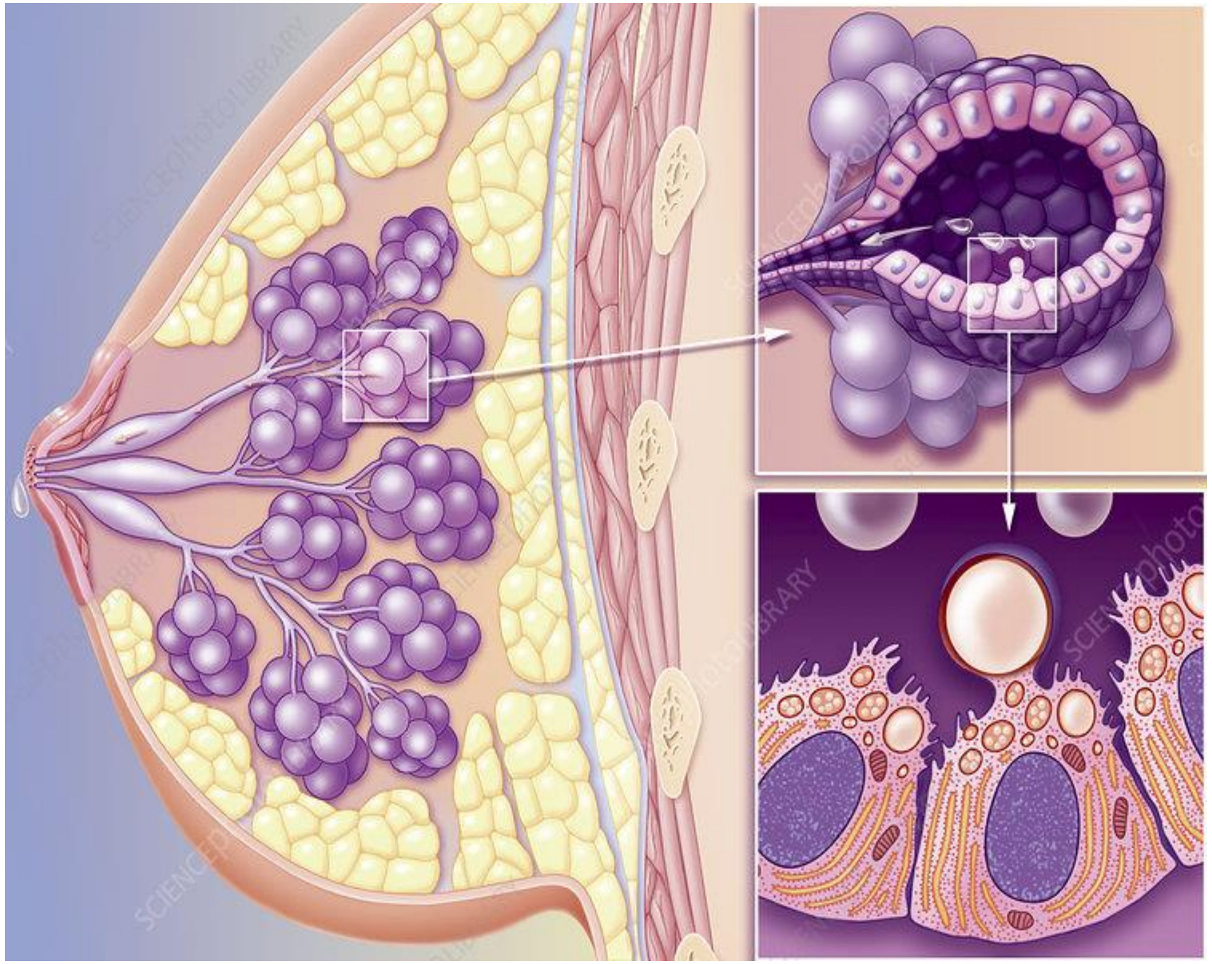
- The **mammary glands** of the breasts develop embryologically as invaginations of surface ectoderm along two ventral lines, the milk lines, from the axillae to the groin. Each mammary gland consists of the **lobes** of the compound tubuloalveolar type whose function is to secrete nutritive milk for newborns. Each lobe, separated from the others by dense connective tissue with much adipose tissue, is a separate gland with its own excretory **lactiferous duct**. These ducts emerge independently in the **nipple (teat)**.
- Each mammary gland lobe consists of many **lobules**, sometimes called **terminal duct lobular units (TDLU)**. Each lobule has several small, branching ducts, but the attached secretory units are small and rudimentary. Lactiferous sinuses are lined with stratified cuboidal epithelium, and the lining of the lactiferous ducts and terminal ducts is simple cuboidal epithelium with many myoepithelial cells. Sparse fibers of smooth muscle also encircle the larger ducts. The duct system is embedded in loose, vascular connective tissue, and a denser, less cellular connective tissue separates the lobes.

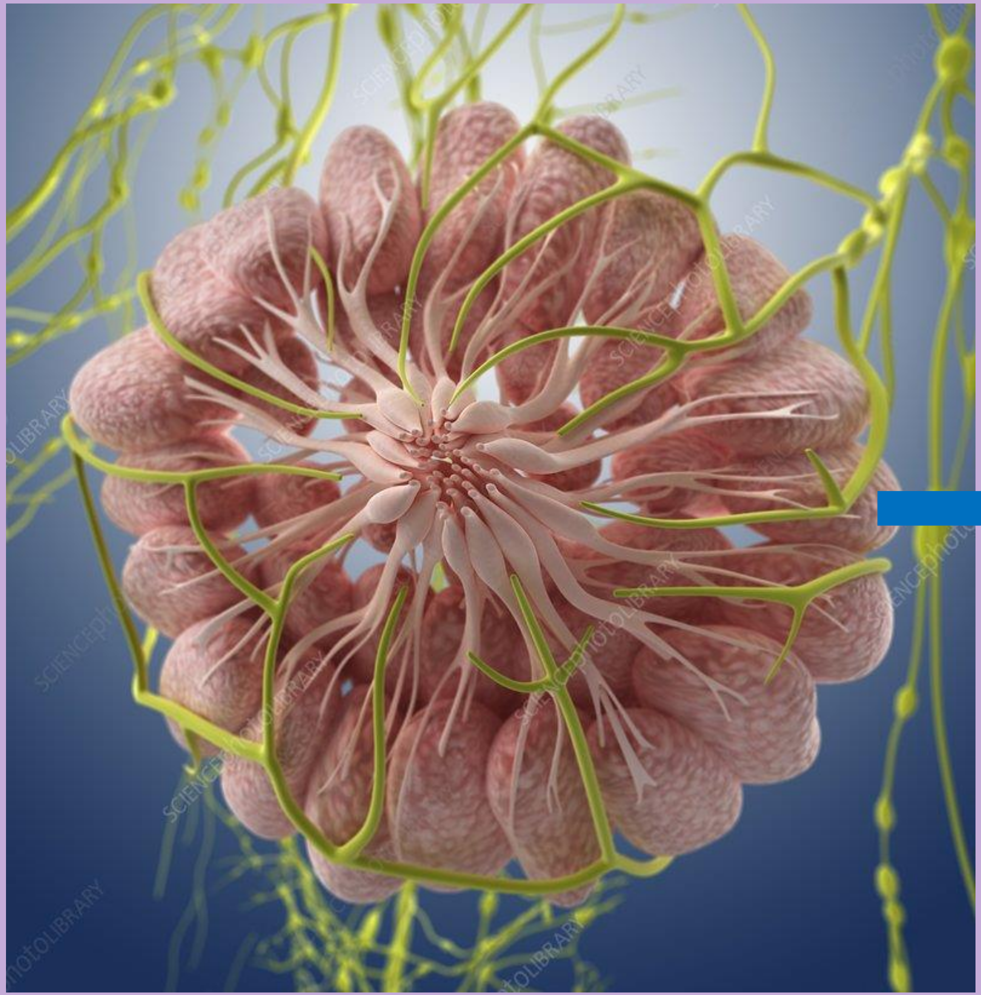


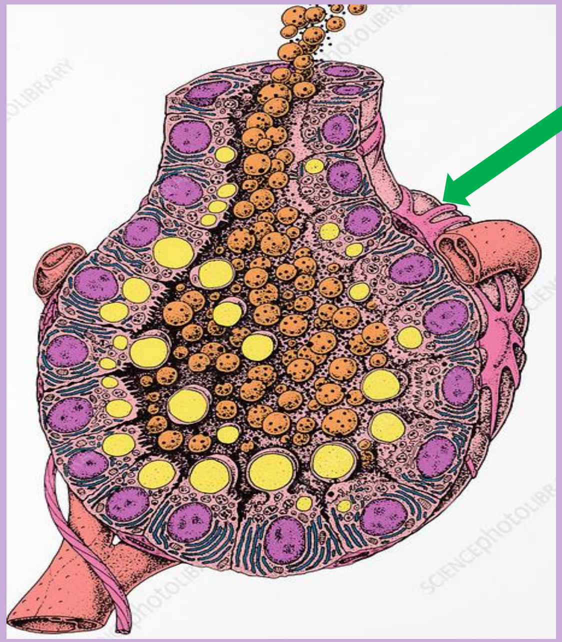
# ALVEOLI

- Secretory alveoli of the mammary gland are spherical to ovoid in shape with a large lumen. Continuous milk production enlarges the lumen, and adjacent alveoli may fuse partially. Shortly after milking, as the alveolus begins a new secretory cycle, the lumen is partially collapsed and irregular in outline.

- The epithelium of the alveoli varies markedly in height during various stages of secretory activity. During active secretion, the basal portion of the columnar epithelial cells contains a well developed rough endoplasmic reticulum. The spherical nuclei are located near the center of the cell. Lipid droplets, in close association with mitochondria, and vesicles, filled with micelles of milk protein, occur throughout the cell apex. As the secretory cycle continues, the lipid droplets move toward the cell surface that protrudes into the alveolar lumen. Myoepithelial cells, surrounding the alveolar epithelial cells, contract in response to oxytocin released from the neurohypophysis.

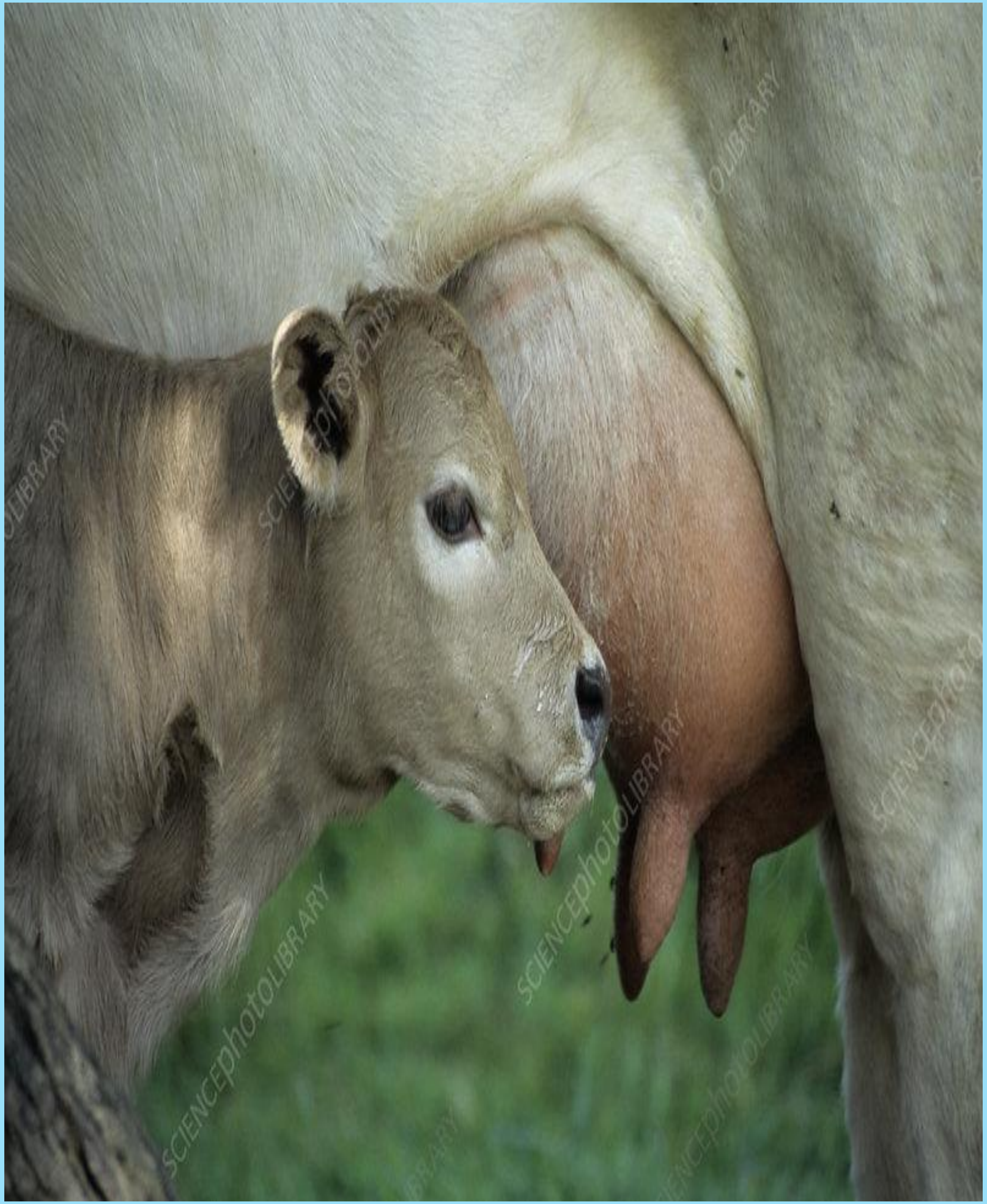






# DUCTS

- The duct system begins with an **intralobular duct**, which drains into an **interlobular duct.** The interlobular duct, in turn, drains into a **lactiferous duct,** which is the primary excretory duct for a lobe.
  - The intralobular duct epithelium is simple cuboidal. Spindle-shaped myoepithelial cells may be associated with these ducts.
  - Interlobular ducts are lined proximally by a simple cuboidal epithelium and, more distally, by two layers of cuboidal cells. Longitudinal smooth muscle fibers become associated with these ducts as they merge with other interlobular ducts to form the large lactiferous ducts.
  - The two-layered cuboidal epithelium continues in these larger ducts, and smooth muscle becomes more prominent. Sacculations result from variations in the diameter of the lumen. The constrictions between these sacculations may have an annular fold containing smooth muscle. Several lactiferous ducts empty into a **lactiferous sinus** (gland sinus) at the base of the teat.



# SENSE ORGANS

# EYES

- **Eyes** are highly developed photosensitive organs for analyzing the form, intensity, and color of light reflected from objects and providing the sense of sight. Protected within the orbits of the skull which also contain adipose cushions, each eyeball consists externally of a tough, fibrous globe, which maintains an eye's overall shape. Internally the eye contains transparent tissues that refract light to focus the image, a layer of photosensitive cells, and a system of neurons that collect, process, and transmit visual information to the brain.

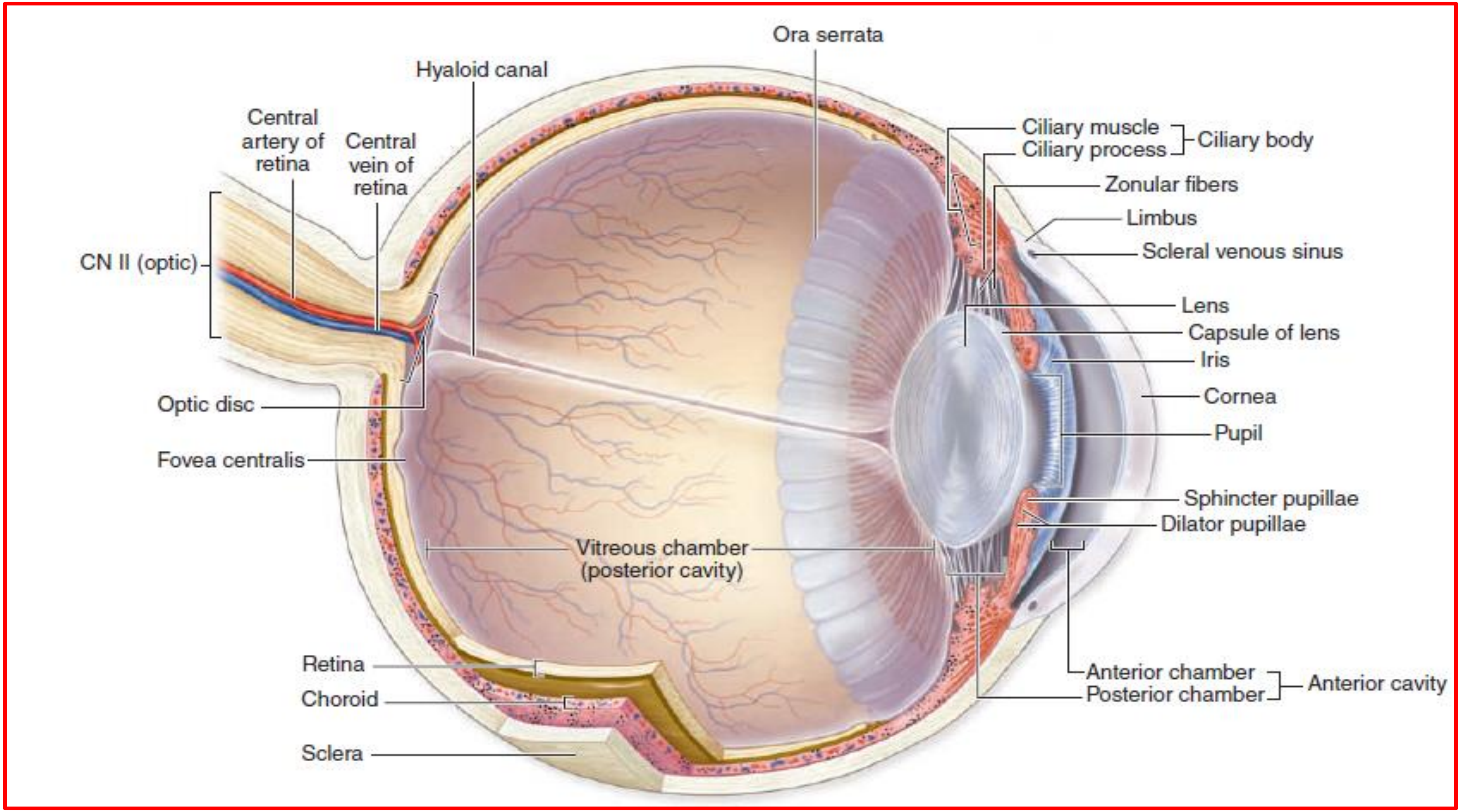
- Each eye is composed of three concentric tunics or layers:

✓ A tough external **fibrous layer** consisting of the **sclera** and the transparent **cornea**;

✓ A middle **vascular layer** consisting of the **choroid**, **ciliary body**, and **iris**; and

✓ An inner sensory layer, the **retina**, which communicates with the cerebrum through the posterior **optic nerve**

- Not part of these layers, the **lens** is a perfectly transparent biconvex structure held in place by a circular system of **zonular fibers** that attach it to the **ciliary body** and by close apposition to the posterior vitreous body. Partly covering the anterior surface of the lens is an opaque pigmented extension of the middle layer called the **iris**, which surrounds a central opening, the **pupil**.
- Located in the anterior portion of the eye, the iris and lens are bathed in clear **aqueous humor** filling both the **anterior chamber** between the cornea and iris and the **posterior chamber** between the iris and lens. Aqueous humor flows through the pupil that connects these two chambers.
- The posterior **vitreous chamber**, surrounded by the retina, lies behind the lens and its zonular fibers and contains a large gelatinous mass of transparent connective tissue called the **vitreous body**.


Ora serrata
Hyaloid canal
Central artery of retina
Central vein of retina
CN II (optic)
Ciliary muscle
Ciliary process
Ciliary body
Zonular fibers
Limbus
Scleral venous sinus
Lens
Capsule of lens
Iris
Cornea
Pupil
Optic disc
Fovea centralis
Sphincter pupillae
Dilator pupillae
Vitreous chamber (posterior cavity)
Retina
Choroid
Sclera
Anterior chamber
Posterior chamber
Anterior cavity

# 1. FIBROUS LAYER

- This layer includes two major regions, the posterior **sclera** and the anterior **cornea**, joined at the **limbus.**

## SCLERA

- The fibrous, external layer of the eyeball protects the more delicate internal structures and provides sites for muscle insertion. The white posterior five-sixths of this layer is the **sclera**, which encloses a portion of the eyeball. The sclera consists mainly of dense connective tissue, with flat bundles of type I collagen parallel to the organ surface but intersecting in various directions; microvasculature is present near the outer surface.
- Tendons of the **extraocular muscles** which move the eyes insert into the anterior region of the sclera. Where it surrounds the choroid, the sclera includes an inner **suprachoroid lamina**, with less collagen, more fibroblasts, elastic fibers, and melanocytes.

# CORNEA

- In contrast to the sclera, the anterior one-sixth of the eye—the **cornea**—is transparent and completely avascular. A section of the cornea shows five distinct layers:

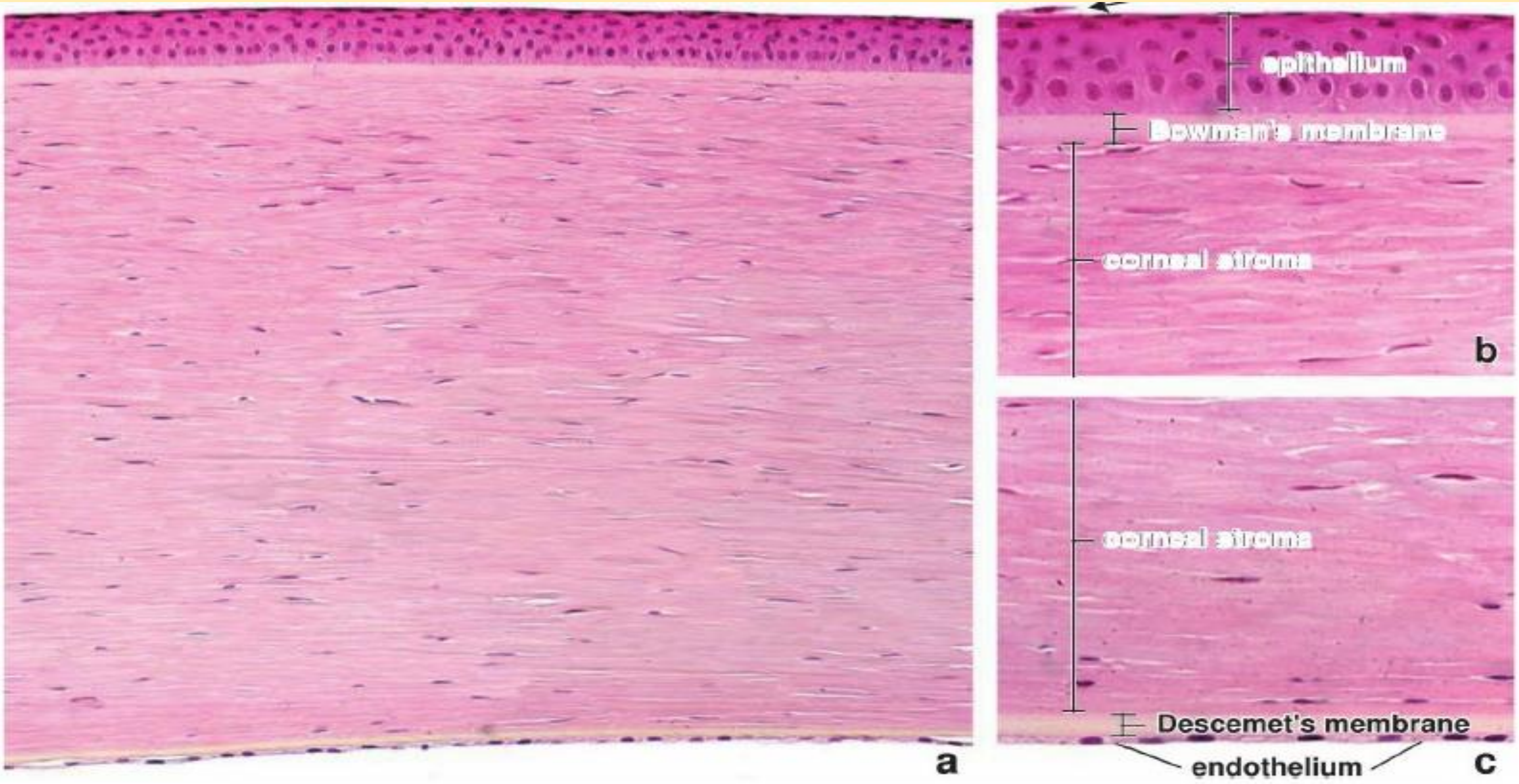
➢ An external **corneal epithelium**, which is a stratified squamous epithelium;

➢ An **anterior limiting membrane (Bowman membrane)**, which is the basement membrane beneath the corneal epithelium;

➢ The thick **stroma**;

➢ A **posterior limiting membrane (Descemet's membrane)**, which is the basement membrane of the endothelium; and

➢ An inner simple squamous **endothelium**.




**Photomicrograph of the cornea. a.** This photomicrograph of a section through the full thickness of the cornea shows the corneal stroma and the two corneal surfaces covered by different types of epithelia. The corneal stroma does not contain blood or lymphatic vessels. ×140. **b.** A higher magnification of the anterior surface of the cornea showing the corneal stroma covered by a stratified squamous (corneal) epithelium. The basal cells that rest on Bowman's membrane, which is a homogeneous condensed layer of corneal stroma, are low columnar in contrast to the squamous surface cells. Note that one of the surface cells is in the process of desquamation (*arrow*). ×280. **c.** A higher magnification photomicrograph of the posterior surface of the cornea covered by a thin layer of simple squamous epithelium (corneal endothelium). These cells are in direct contact with the aqueous humor of the anterior chamber of the eye. Note the very thick Descemet's membrane (basal lamina) of the corneal endothelial cells. ×280.

# CORNEA

- The corneal epithelium is nonkeratinized, five or six cell layers thick, and comprises about 10% of the corneal thickness. The basal cells have a high proliferative capacity important for renewal and repair of the corneal surface and emerge from stem cells in the **corneoscleral limbus** encircling the cornea. The flattened surface cells have microvilli protruding into a protective tear film of lipid, glycoprotein, and water. As another protective adaptation, the corneal epithelium also has one of the richest sensory nerve supplies of any tissue.

- The basement membrane of this epithelium, often called **Bowman membrane**, is very thick and contributes to the stability and strength of the cornea, helping to protect against infection of the underlying stroma.

- The **stroma**, or substantia propria, makes up 90% of the cornea's thickness and consists of approximately 60 layers of parallel collagen bundles aligned at approximately right angles to each other and extending almost the full diameter of the cornea. The uniform orthogonal array of collagen fibrils contributes to the transparency of this avascular tissue. Between the collagen lamellae are cytoplasmic extensions of flattened fibroblast-like cells called **keratocytes**. The ground substance around these cells contains proteoglycans such as lumican, with keratan sulfate and chondroitin sulfate, which help maintain the precise organization and spacing of the collagen fibrils.

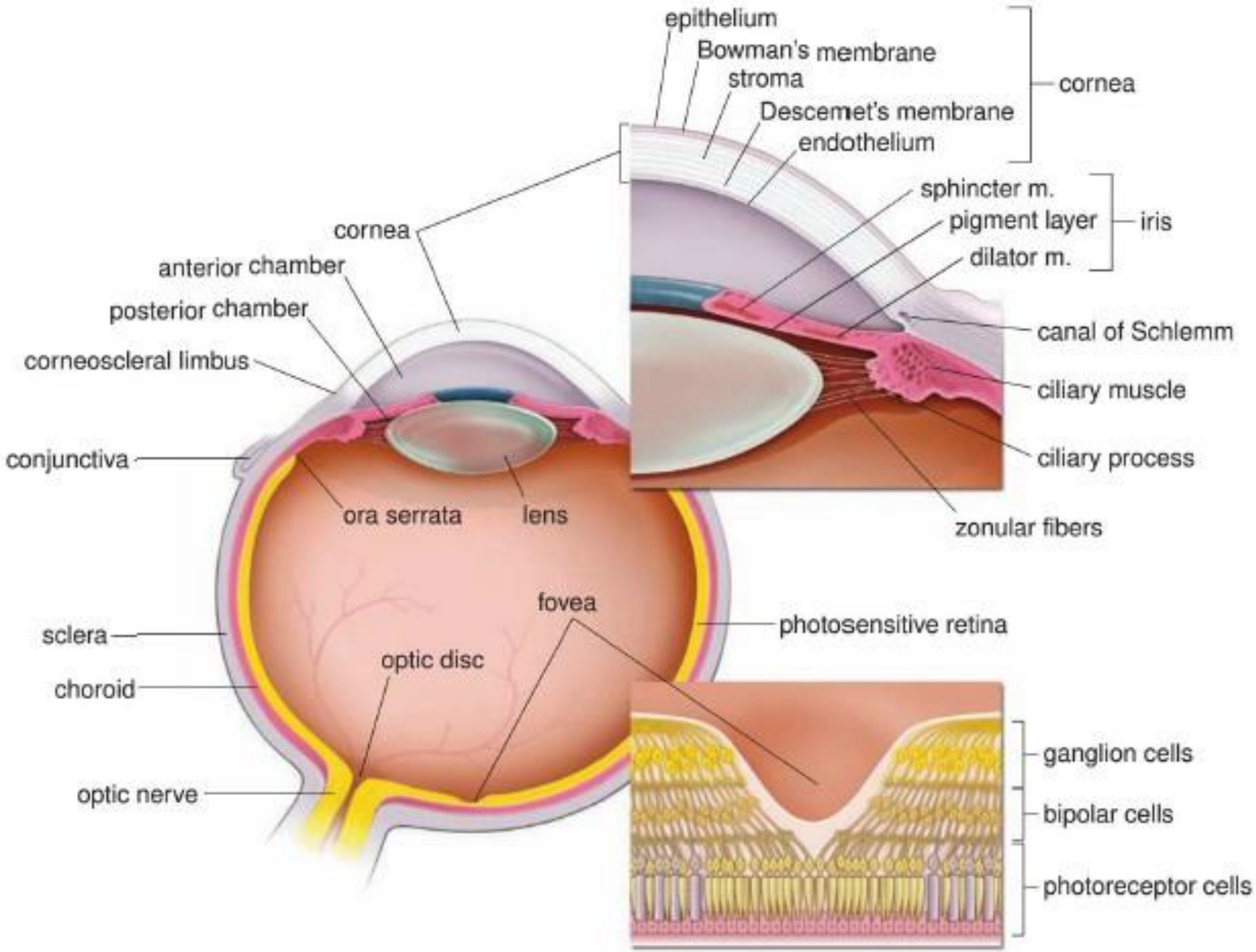
- The posterior surface of the stroma is bounded by another thick basement membrane, called **Descemet's membrane**, which supports the **internal simple squamous corneal endothelium**.

- This endothelium maintains Descemet's membrane and includes the most metabolically active cells of the cornea. $Na^+/K^+$ ATPase pumps in the basolateral membranes of these cells are largely responsible for regulating the proper hydration state of the corneal stroma to provide maximal transparency and optimal light refraction.

# LIMBUS

- Encircling the cornea is the **limbus**, a transitional area where the transparent cornea merges with the opaque sclera. Here Bowman's membrane ends and the surface epithelium becomes more stratified as the **conjunctiva** that covers the anterior part of the sclera (and lines the eyelids). As mentioned previously, epithelial stem cells located at the limbus surface give rise to rapidly dividing progenitor cells, which then move centripetally into the corneal epithelium. The stroma becomes vascular and less well-organized at the limbus, as the collagen bundles merge with those of the sclera.

- Also at the limbus Descemet's membrane and its simple endothelium are replaced with a system of irregular endothelium-lined channels called the **trabecular meshwork**. These penetrate the stroma at the corneoscleral junction and allow slow, continuous drainage of aqueous humor from the anterior chamber. This fluid moves from these channels into the adjacent larger space of the **scleral venous sinus**, or **canal of Schlemm**, which encircles the eye. From this sinus aqueous humor drains into small blood vessels (veins) of the sclera.


epithelium
Bowman's membrane
stroma
Descemet's membrane
endothelium
cornea
sphincter m.
pigment layer
dilator m.
iris
canal of Schlemm
ciliary muscle
ciliary process
zonular fibers
cornea
anterior chamber
posterior chamber
corneoscleral limbus
conjunctiva
ora serrata
lens
fovea
photosensitive retina
sclera
optic disc
choroid
optic nerve
ganglion cells
bipolar cells
photoreceptor cells

# VASCULAR LAYER

The eye's more vascular middle layer, known as the **uvea**, consists of three parts, from posterior to anterior:

**Choroid,**

**Ciliary body,**

**Iris**

# CHOROID

Located in the posterior two-thirds of the eye, the **choroid** consists of loose, well-vascularized connective tissue and contains numerous melanocytes. These form a characteristic black layer in the choroid and prevent light from entering the eye except through the pupil. Two layers make up the choroid:

a) The inner **choroidocapillary lamina** has a rich microvasculature important for nutrition of the outer retinal layers.

**b)** **Bruch membrane**, a thin extracellular sheet, is composed of collagen and elastic fibers surrounding the adjacent microvasculature and basal lamina of the retina's pigmented layer.

# CILIARY BODY

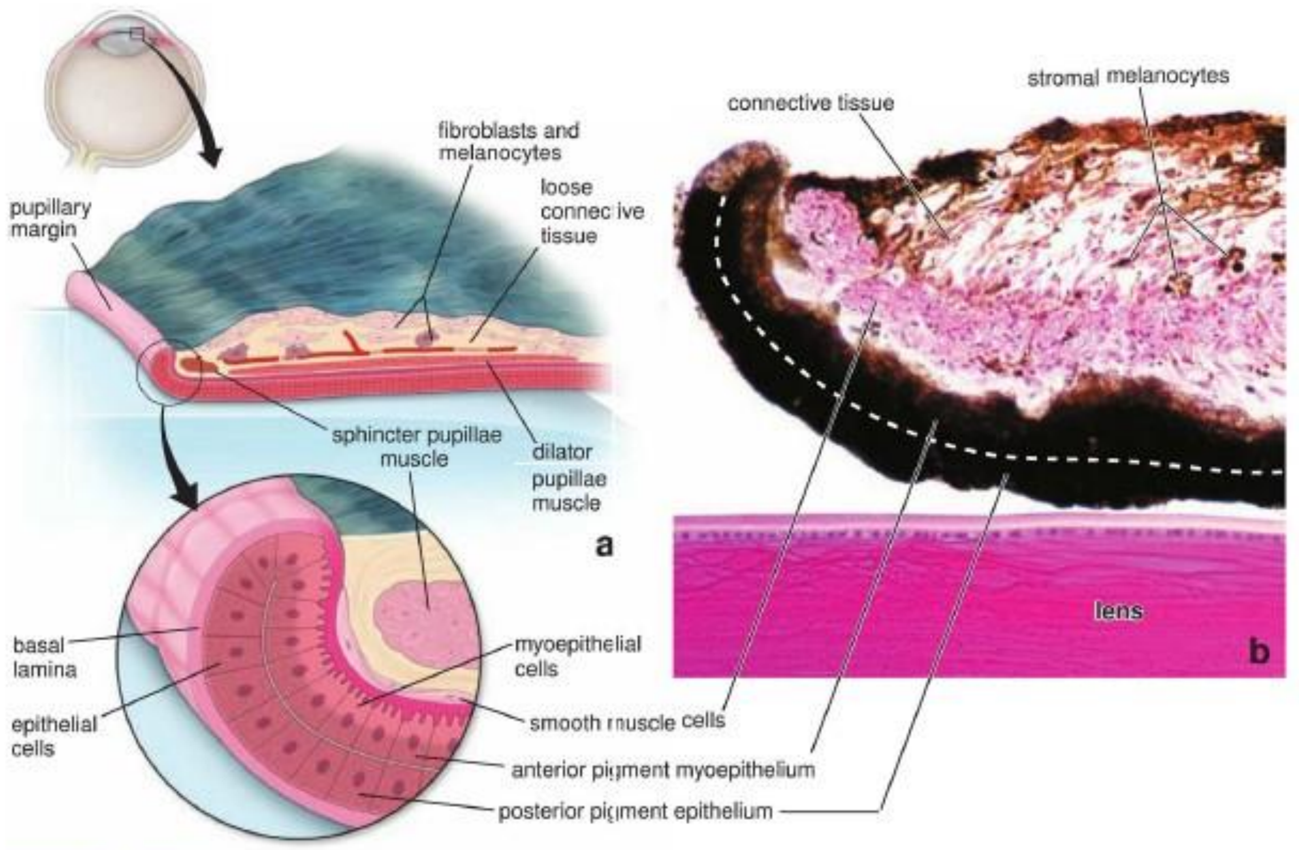
The **ciliary body**, the anterior expansion of the uvea that encircles the lens, lies posterior to the limbus. Like the choroid, most of the ciliary body rests on the sclera. Important structures associated with the ciliary body include the following:

- **Ciliary muscle** makes up most of the ciliary body's stroma and consists of three groups of smooth muscle fibers. Contraction of these muscles affects the shape of the lens and is important in visual accommodation.
- **Ciliary processes** are a radially arranged series of ridges extending from the inner highly vascular region of the ciliary body. These provide a large surface area covered by a double layer of low columnar epithelial cells, the ciliary epithelium. The epithelial cells directly covering the stroma contain much melanin and correspond to the anterior projection of the pigmented retina epithelium. The surface layer of cells lacks melanin and is contiguous with the sensory layer of the retina.
- Cells of this dual epithelium have extensive basolateral folds with $Na^+/K^+$-ATPase activity and are specialized for secretion of **aqueous humor**. Fluid from the stromal microvasculature moves across this epithelium as aqueous humor, with an inorganic ion composition similar to that of plasma but almost no protein. aqueous humor is secreted by ciliary processes into the posterior chamber, flows through the pupil into the anterior chamber, and drains at the angle formed by the cornea and the iris into the channels of the trabecular meshwork and the scleral venous sinus, from which it enters venules of the sclera.
- The **ciliary zonule** is a system of many radially oriented fibers composed largely of fibrillin-1 and -2 produced by the nonpigmented epithelial cells on the ciliary processes. The fibers extend from grooves between the ciliary processes and attach to the surface of the lens, holding that structure in place.

# IRIS

- The **iris** is the most anterior extension of the middle uveal layer which covers part of the lens, leaving a round central **pupil**. The anterior surface of the iris, exposed to aqueous humor in the anterior chamber, consists of a dense layer of fibroblasts and melanocytes with interdigitating processes and is unusual for its lack of an epithelial covering. Deeper in the iris, the stroma consists of loose connective tissue with melanocytes and sparse microvasculature.

- The posterior surface of the iris has a two-layered epithelium continuous with that covering the ciliary processes, but very heavily filled with melanin. The highly pigmented posterior epithelium of the iris blocks all light from entering the eye except that passing through the pupil. **Myoepithelial cells** form a partially pigmented epithelial layer and extend contractile processes radially as the very thin **dilator pupillae muscle**. Smooth muscle fibers form a circular bundle near the pupil as the **sphincter pupillae muscle**. The dilator and sphincter muscles of the iris have sympathetic and parasympathetic innervation, respectively, for enlarging and constricting the pupil.



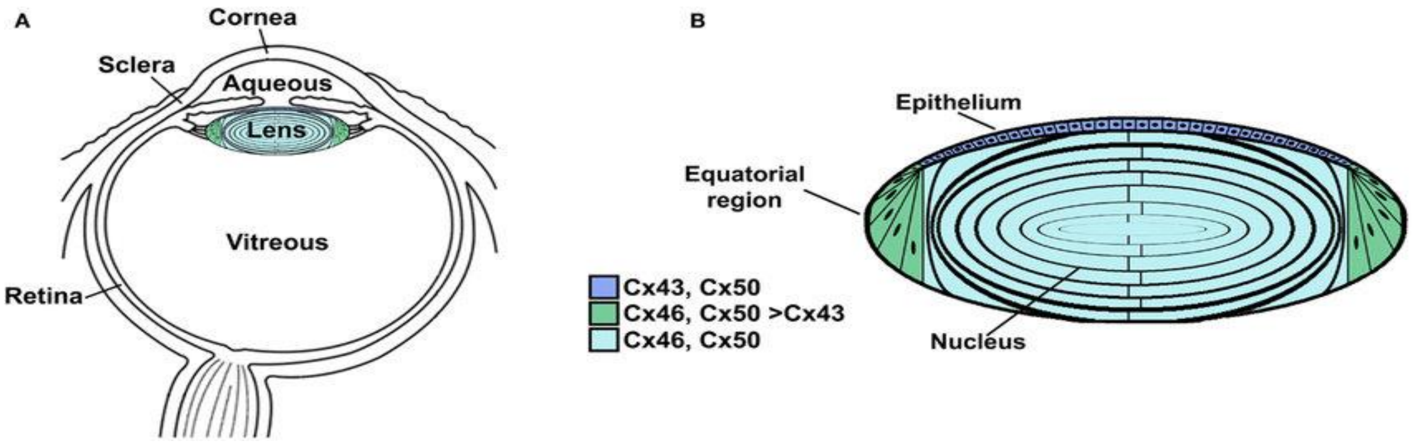

**Structure of the iris. a.** This schematic diagram shows the layers of the iris. Note that the pigmented epithelial cells are reflected as occurs at the pupillary margin of the iris. The two layers of pigmented epithelial cells are in contact with the dilator pupillae muscle. The incomplete layer of fibroblasts and stromal melanocytes is indicated on the anterior surface of the iris. **b.** Photomicrograph of the iris showing the histologic features of this structure. The lens, which lies posterior to the iris, is included for orientation. The iris is composed of a connective tissue stroma covered on its posterior surface by the posterior pigment epithelium. The basal lamina (not visible) faces the posterior chamber of the eye. Because of intense pigmentation, the histologic features of these cells are not discernible. Just anterior to these cells is the anterior pigment myoepithelium layer (the *dashed line* separates the two layers). Note that the posterior portion of the myoepithelial cells contains melanin, whereas the anterior portion contains contractile elements forming the dilator pupillae muscle of the iris. The sphincter pupillae muscle is evident in the stroma. The color of the iris depends on the number of stromal melanocytes scattered throughout the connective tissue stroma. At the *bottom*, note the presence of the lens. ×570.

# LENS

The **lens** is a transparent biconvex structure suspended immediately behind the iris, which focuses light on the retina. The lens is a unique avascular tissue and is highly elastic, a property that normally decreases with age. The lens has three principal components:

A thick (10-20 µm), homogeneous **lens capsule** composed of proteoglycans and type IV collagen surrounds the lens and provides the place of attachment for the fibers of the ciliary zonule. This layer originates as the basement membrane of the embryonic lens vesicle.

A subcapsular **lens epithelium** consists of a single layer of cuboidal cells present only on the anterior surface of the lens. The epithelial cells attach basally to the surrounding lens capsule and their apical surfaces bind to the internal lens fibers.



- **Lens fibers** are highly elongated, terminally differentiated cells that appear as thin, flattened structures. Developing from cells in the lens epithelium, lens fibers typically become 7-10 mm long, with cross-section dimensions of only 2 by 8 μm. The cytoplasm becomes filled with a group of proteins called **crystallins**, and the organelles and nuclei undergo autophagy. Lens fibers are packed tightly together and form a perfectly transparent tissue highly specialized for light refraction.

- The lens is held in place by fibers of the **ciliary zonule**, which extend from the lens capsule to the ciliary body. Together with the ciliary muscles, this structure allows the process of visual **accommodation**, which permits focusing on near and far objects by changing the curvature of the lens. When the eye is at rest or gazing at distant objects, ciliary muscles relax and the resulting shape of the ciliary body puts tension on the zonule fibers, which pulls the lens into a flatter shape. To focus on a close object the ciliary muscles contract, causing forward displacement of the ciliary body, which relieves some of the tension on the zonule and allows the lens to return to a more rounded shape and keep the object in focus.

# Vitreous Body

- The **vitreous body** occupies the large vitreous chamber behind the lens. It consists of transparent, gel-like connective tissue that is 99% water (vitreous humor), with collagen fibrils and hyaluronate, contained within an external lamina called the vitreous membrane.

- The only cells in the vitreous body are a small mesenchymal population near the membrane called **hyalocytes**, which synthesize the hyaluronate and collagen, and a few macrophages.

# Retina

- The **retina**, the innermost tunic of the eye, develops with two fundamental sublayers from the inner and outer layers of embryonic optic cup:

- The outer **pigmented layer** is a simple cuboidal epithelium attached to Bruch's membrane and the choroidocapillary lamina of the choroid. This heavily pigmented layer forms the other part of the dual epithelium covering the ciliary body and posterior iris.

- The inner retinal region, the **neural layer**, is thick and stratified with various neurons and photoreceptors. Although its neural structure and visual function extend anterior only as far as the **ora serrata**, this layer continues as part of the dual cuboidal epithelium that covers the surface of the ciliary body and posterior iris.

# Retina Pigmented Epithelium

- The pigmented epithelial layer consists of cuboidal or low columnar cells with basal nuclei and surrounds the neural layer of the retina. The cells have well-developed junctional complexes, gap junctions, and numerous invaginations of the basal membranes associated with mitochondria. The apical ends of the cells extend processes and sheath-like projections surrounding the tips of the photoreceptors. Melanin granules are numerous in these extensions and in the apical cytoplasm. This cellular region also contains numerous phagocytic vacuoles and secondary lysosomes, peroxisomes, and abundant smooth ER (SER) specialized for **retinal** (vitamin A) isomerization. The diverse functions of the retinal pigmented epithelium include the following:
- The pigmented layer **absorbs scattered light** that passes through the neural layer, supplementing the choroid in this regard.
- With many tight junctions, cells of the pigmented epithelium form an important part of the protective **blood-retina barrier** isolating retina photoreceptors from the highly vascular choroid and regulating **ion transport** between these compartments.
- The cells play key roles in the visual cycle of **retinal regeneration**, having enzyme systems that isomerize all-*trans*-retinal released from photoreceptors and produce 11-*cis*-retinal that is then transferred back to the photoreceptors.
- **Phagocytosis** of shed components from the adjacent photoreceptors and degradation of this material occurs in these epithelial cells.
- Cells of pigmented epithelium **remove free radicals** by various protective antioxidant activities and **support the neural retina** by secretion of ATP, various polypeptide growth factors, and immunomodulatory factors.

# Neural Retina

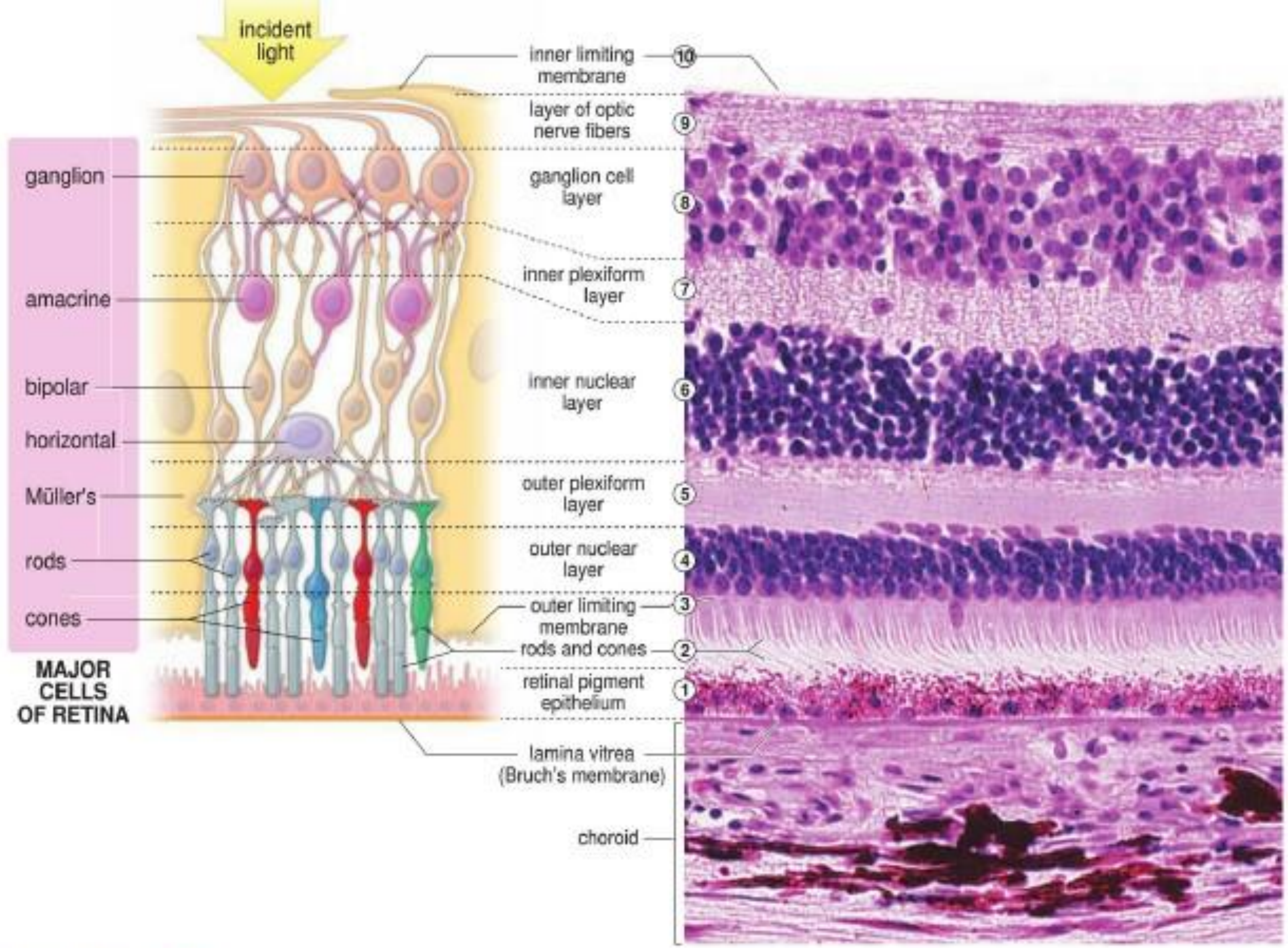
- True to its embryonic origin, the neural retina functions as an outpost of the CNS with glia and several interconnected neuronal subtypes in well-organized strata. Nine distinct layers comprise the neural retina, described here with their functional significance.

**Three major layers contain the nuclei of the interconnected neurons:**

a) Near the pigmented epithelium, the **outer nuclear layer (ONL)** contains cell bodies of photoreceptors (the rod and cone cells). These cells, like the pigmented epithelial cells, receive O2 and nutrients by diffusion from the choroidocapillary lamina of the choroid.

b) The **inner nuclear layer (INL)** contains the nuclei of various neurons, notably the bipolar cells, amacrine cells, and horizontal cells, all of which make specific connections with other neurons and integrate signals from rods and cones over a wide area of the retina.

c) Near the vitreous, the **ganglionic layer (GL)** has neurons (ganglion cells) with much longer axons. These axons make up the **nerve fiber layer (NFL)** and converge to form the **optic nerve**, which leaves the eye and passes to the brain. The GL is thickest near the central, macular region of the retina, but it thins peripherally to only one layer of cells.




**Schematic drawing and photomicrograph of the layers of the retina.** On the basis of histologic features that are evident in the photomicrograph *on right*, the retina can be divided into ten layers. The layers correspond to the diagram *on left*, which shows the distribution of major cells of the retina. Note that light enters the retina and passes through its inner layers before reaching the photoreceptors of the rods and cones that are closely associated with retinal pigment epithelium. Also, the interrelationship between the bipolar neurons and ganglion cells that carry electrical impulses from the retina to the brain is clearly visible. The Bruch's membrane (lamina vitrea) separates the inner layer of the vascular coat (choroid) from the retinal pigment epithelium. ×440.

- Between the three layers with cell nuclei are two fibrous or “plexiform” regions containing only axons and dendrites connected by synapses:

- The **outer plexiform layer (OPL)** includes axons of the photoreceptors and dendrites of association neurons in the INL.

- The **inner plexiform layer (IPL)** consists of axons and dendrites connecting neurons of the INL with the ganglion cells.

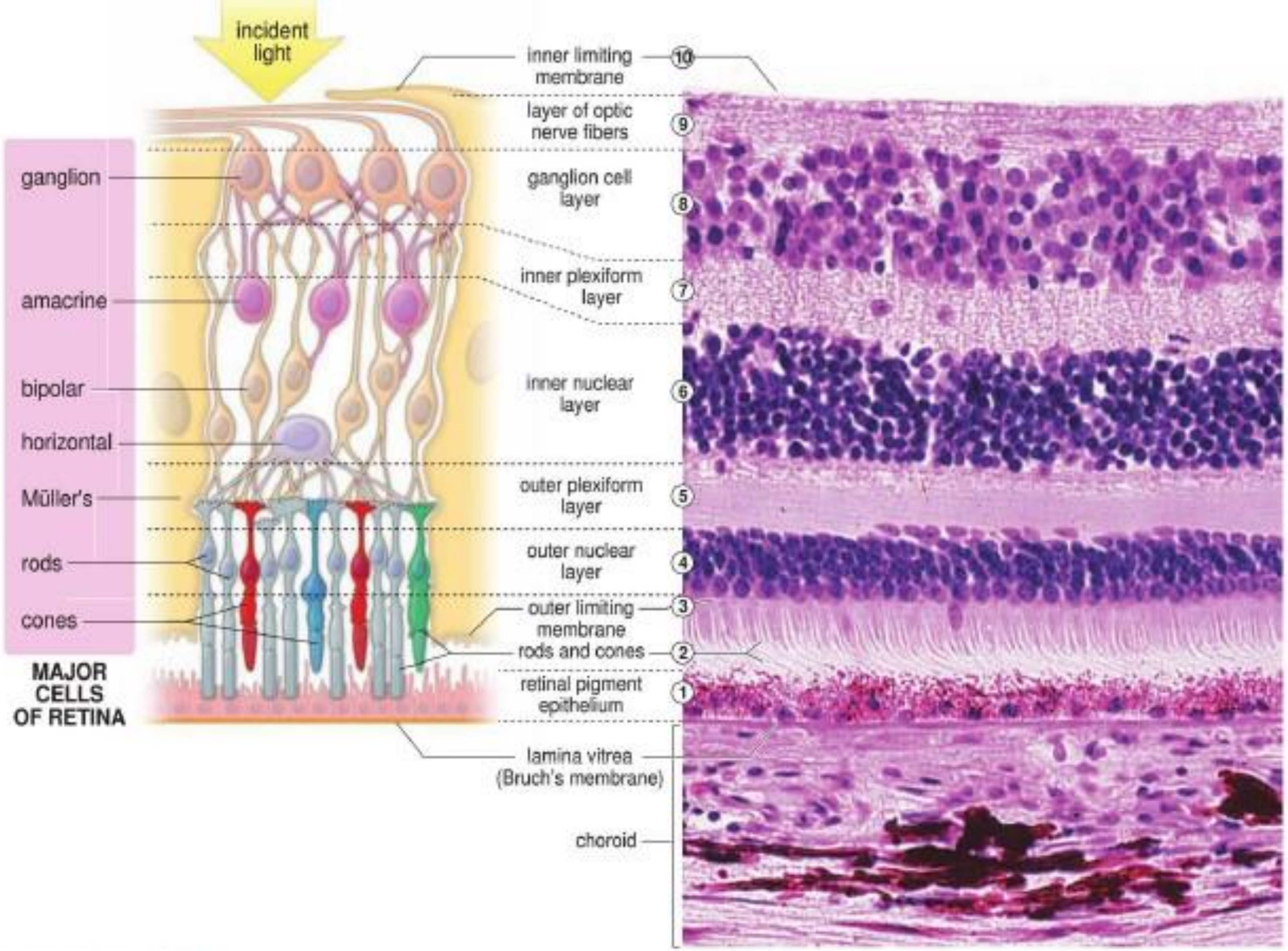
- The rod and cone cells, named for the shape of their outer segments, are polarized neurons with their photosensitive portions aligned in the retina's **rod and cone layer (RCL)** and their axons in the OPL. All neurons of the retina are supported metabolically by elongated, regularly arranged glial cells called **Müller cells**.

- Müller cells extend processes that span the entire thickness of the neural retina. From these major Müller cell processes smaller lateral extensions ramify in each layer and ensheath virtually all the neuronal processes, cell bodies, and blood vessels. Müller cells are critical for retinal function, providing neurotrophic substances, removing waste products, regulating ion and water homeostasis, regulating blood flow, and maintaining a blood-inner retina barrier.

- Müller cells also organize two boundaries that appear as very thin retinal “layers”:

- The **outer limiting layer (OLL)** is a poorly stained but well-defined series of adherent junctions (zonula adherentes) between the photoreceptors and Müller cells.

- The **inner limiting membrane (ILM)** consists of terminal expansions of Müller cell processes, which cover the collagenous membrane of the vitreous body and form this inner surface of the retina. All these layers of the retina can be seen by routine light microscopy. It is important to note that light must pass through all the layers of the neural retina before reaching the layer of rods and cones. Branches of the central retinal artery and vein run mainly within the nerve fiber and GLs, surrounded by peri-vascular feet of Müller cells and astrocytes which are located there. In some retina regions capillaries extend as deeply as the INL. A few scattered microglial cells occur throughout the neural retina.

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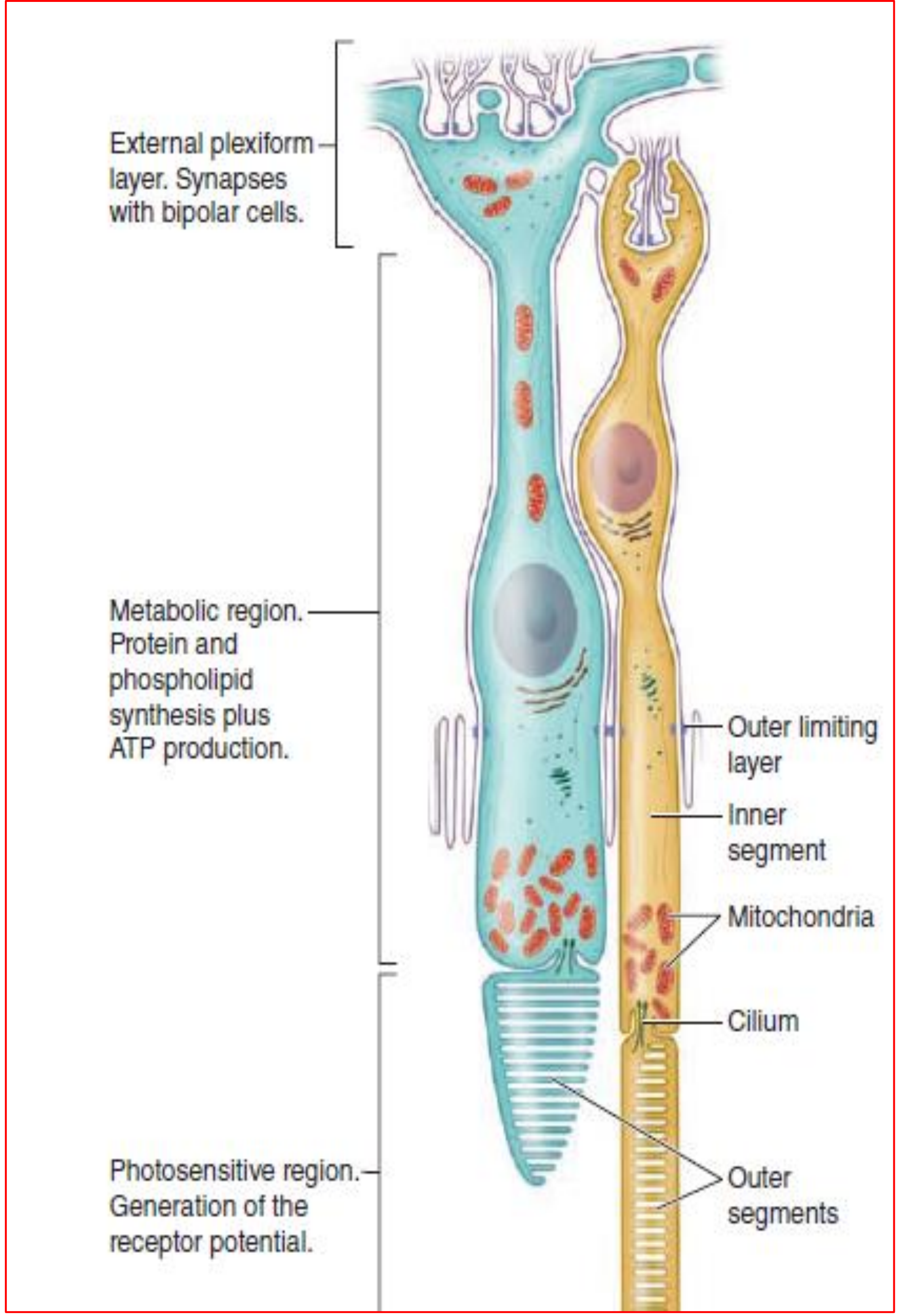
## Cone Cells:

- Less numerous and less light-sensitive than rods, the 4.6 million **cone cells** in the typical human retina produce color vision in adequately bright light. There are **three morphologically similar classes** of cones, each containing one type of the visual pigment **iodopsin** (or photopsins).
- Each of the three iodopsins has maximal sensitivity to light of a different wavelength, in the red, blue, or green regions of the visible spectrum, respectively. By mixing neural input produced by these visual pigments, cones produce a color image.
- Like rods, cone cell are elongated, with outer and inner segments, a modified cilium connecting stalk, and an accumulation of mitochondria and polyribosomes.




## Rod Cells:

- The retina contains on average 92 million **rod cells**. They are extremely sensitive to light, responding to a single photon, and allow some vision even with light low levels, such as at dusk or nighttime. Rod cells are thin, elongated cells (50 µm × 3 µm), composed of two functionally distinct segments.
- The **outer segment** is a modified primary cilium, photosensitive, and shaped like a short rod; the inner segment contains glycogen, mitochondria, and polyribosomes for the cell's biosynthetic activity.

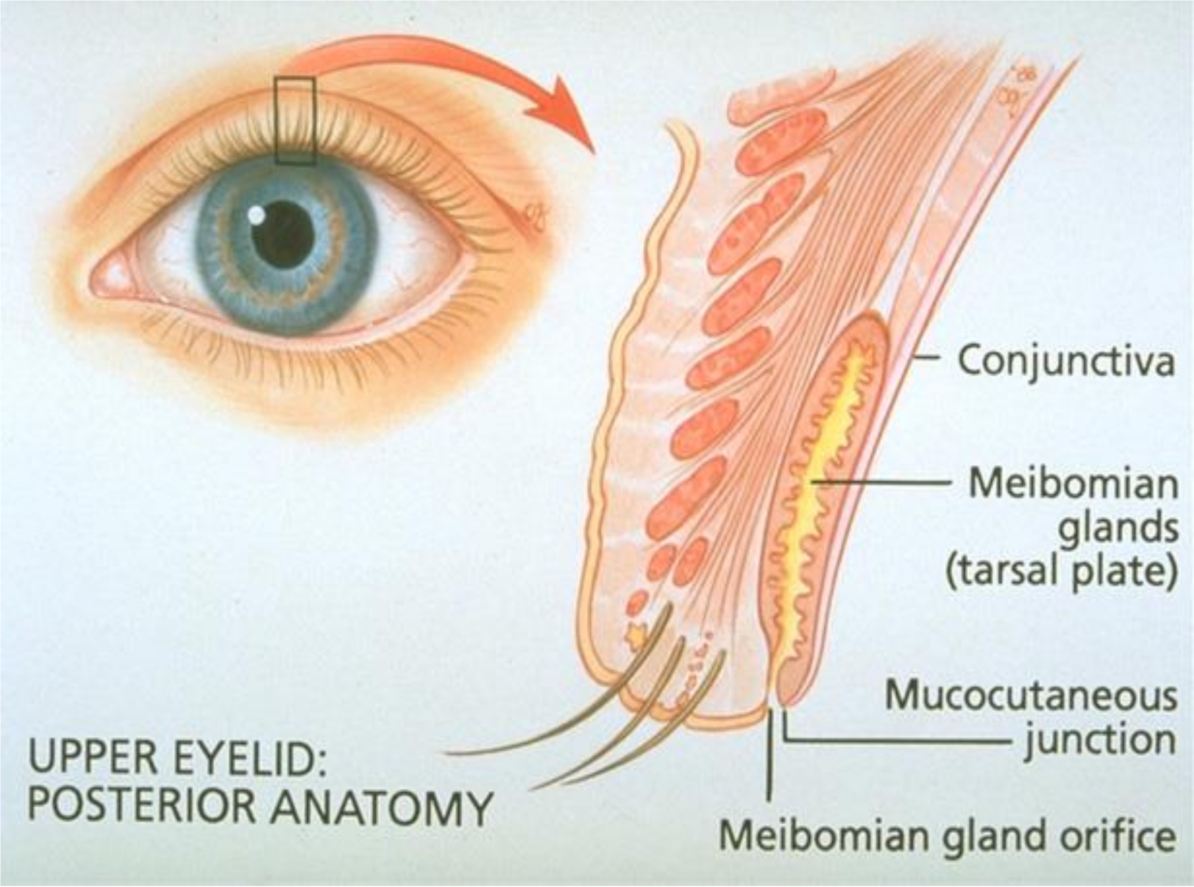
# Accessory Structures of the Eye

## 1. Conjunctiva

The **conjunctiva** is a thin, transparent mucosa that covers the exposed, anterior portion of the sclera and continues as the lining on the inner surface of the eyelids. It consists of a stratified columnar epithelium, with numerous small goblet cells, supported by a thin lamina propria of loose vascular connective tissue. Mucous secretions from conjunctiva cells are added to the tear film that coats this epithelium and the cornea.

# 2. Eyelids

- **Eyelids** are pliable, protective structures consisting of skin, muscle, and conjunctiva. The skin is loose and elastic, lacks fat, and has only very small hair follicles and fine hair, except at the distal edge, where large follicles with eyelashes are present. Associated with the follicles of eyelashes are sebaceous glands and modified apocrine sweat glands.
- Beneath the skin are striated fascicles of the orbicularis oculi and levator palpebrae muscles, which fold the eyelids. Adjacent to the conjunctiva is a dense fibroelastic plate called the **tarsus** supporting the other tissues. The tarsus surrounds a series of 20-25 large sebaceous glands, each with many acini secreting into a long central duct that opens among the eyelashes. Oils in the sebum produced by these **tarsal glands**, also called **Meibomian glands**, form a surface layer on the tear film, reducing its rate of evaporation, and help lubricate the ocular surface.



# 3. Lacrimal Glands

- The **lacrimal glands** produce fluid continuously for the tear film that moistens and lubricates the cornea and conjunctiva and supplies O2 to the corneal epithelial cells. Tear fluid also contains various metabolites, electrolytes, and proteins of innate immunity such as lysozyme. The main lacrimal glands are located in the upper temporal portion of the orbit and have several lobes, which drain through individual excretory ducts into the superior fornix, the conjunctiva-lined recess between the eyelids and the eye.
- The lacrimal glands have acini composed of large serous cells filled with lightly stained secretory granules and surrounded by well-developed myoepithelial cells and a sparse, vascular stroma.
- Tear film moves across the ocular surface and collects in other parts of the bilateral **lacrimal apparatus**: flowing through two small round openings (0.5 mm in diameter) to canaliculi at the medial margins of the upper and lower eyelids, then passing into the lacrimal sac, and finally draining into the nasal cavity via the nasolacrimal duct. The canaliculi are lined by stratified squamous epithelium, but the more distal sac and duct are lined by pseudostratified ciliated epithelium like that of the nasal cavity.

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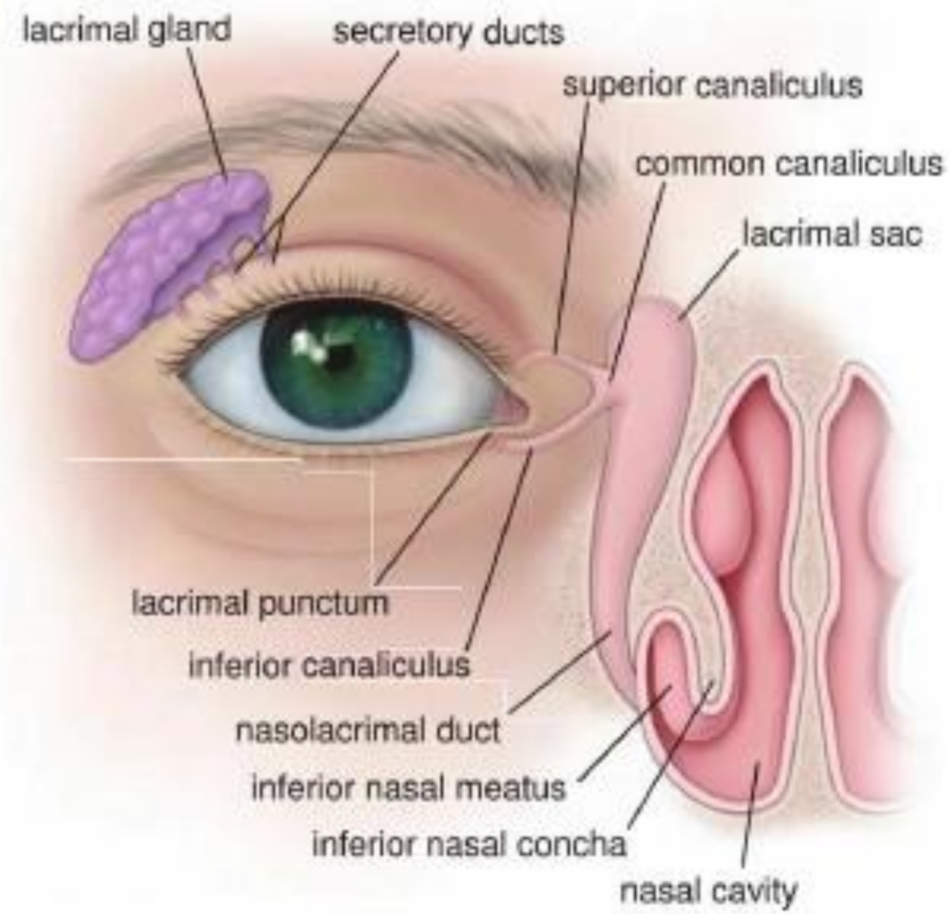
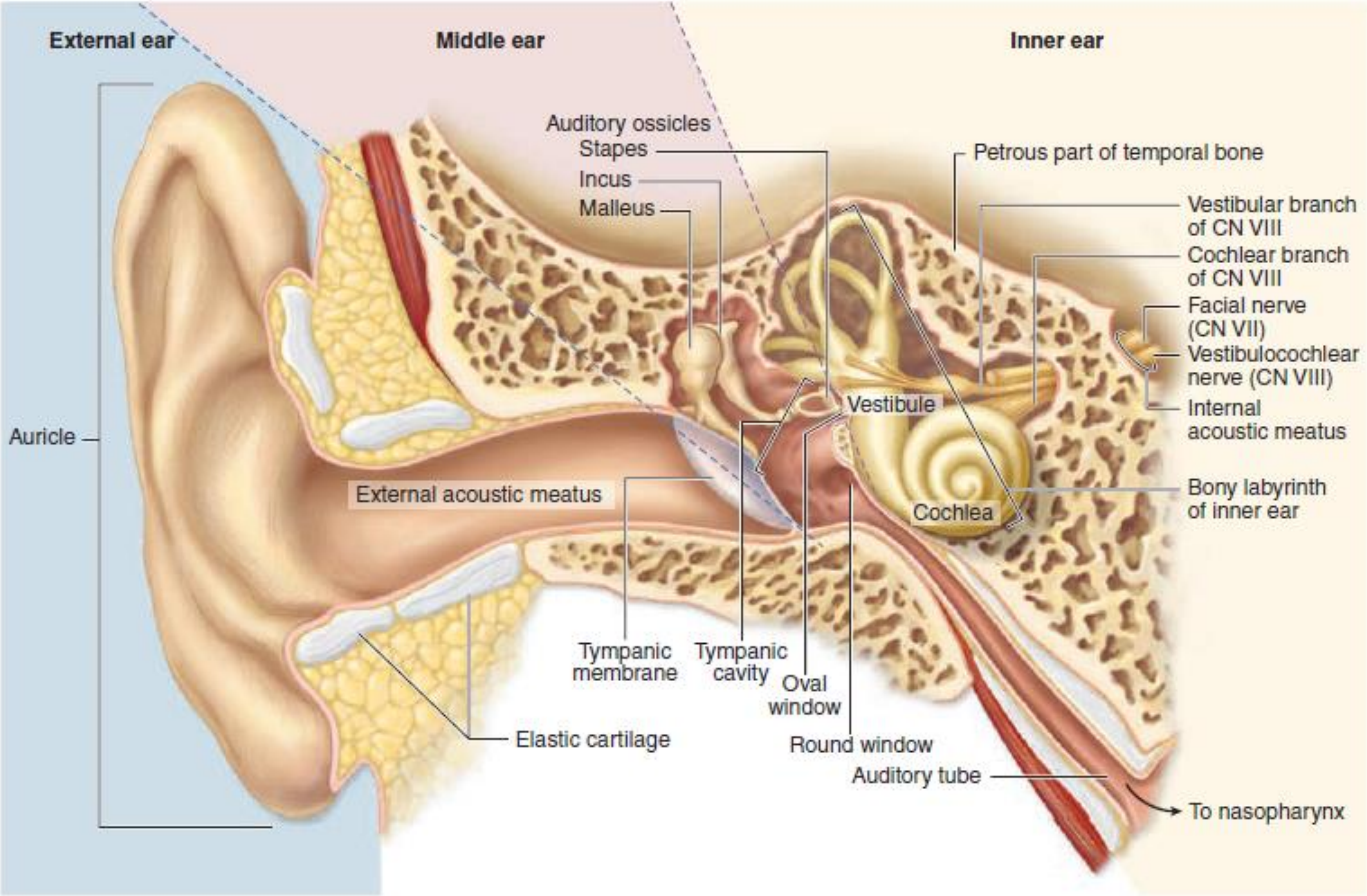



**Schematic diagram of the eye and lacrimal apparatus.** This drawing shows the location of the lacrimal gland and components of the lacrimal apparatus, which drains the lacrimal fluid into the nasal cavity.

# EARS

Tissues of the ear mediate the senses of equilibrium and hearing. Each ear consists of three major parts:

- The **external ear**, which receives sound waves
- The **middle ear**, in which sound waves are transmitted from air to fluids of the internal ear via a set of small bones
- The **internal ear**, in which these fluid movements are transduced to nerve impulses passing via the acoustic nerve to the CNS. In addition to the auditory organ, or cochlea, the internal ear also contains the vestibular organ that allows the body to maintain equilibrium.


External ear
Middle ear
Inner ear
Auditory ossicles
Stapes
Incus
Malleus
Petrous part of temporal bone
Vestibular branch of CN VIII
Cochlear branch of CN VIII
Facial nerve (CN VII)
Vestibulocochlear nerve (CN VIII)
Internal acoustic meatus
Vestibule
Auricle
External acoustic meatus
Bony labyrinth of inner ear
Cochlea
Tympanic membrane
Tympanic cavity
Oval window
Round window
Elastic cartilage
Auditory tube
To nasopharynx

# EXTERNAL EAR

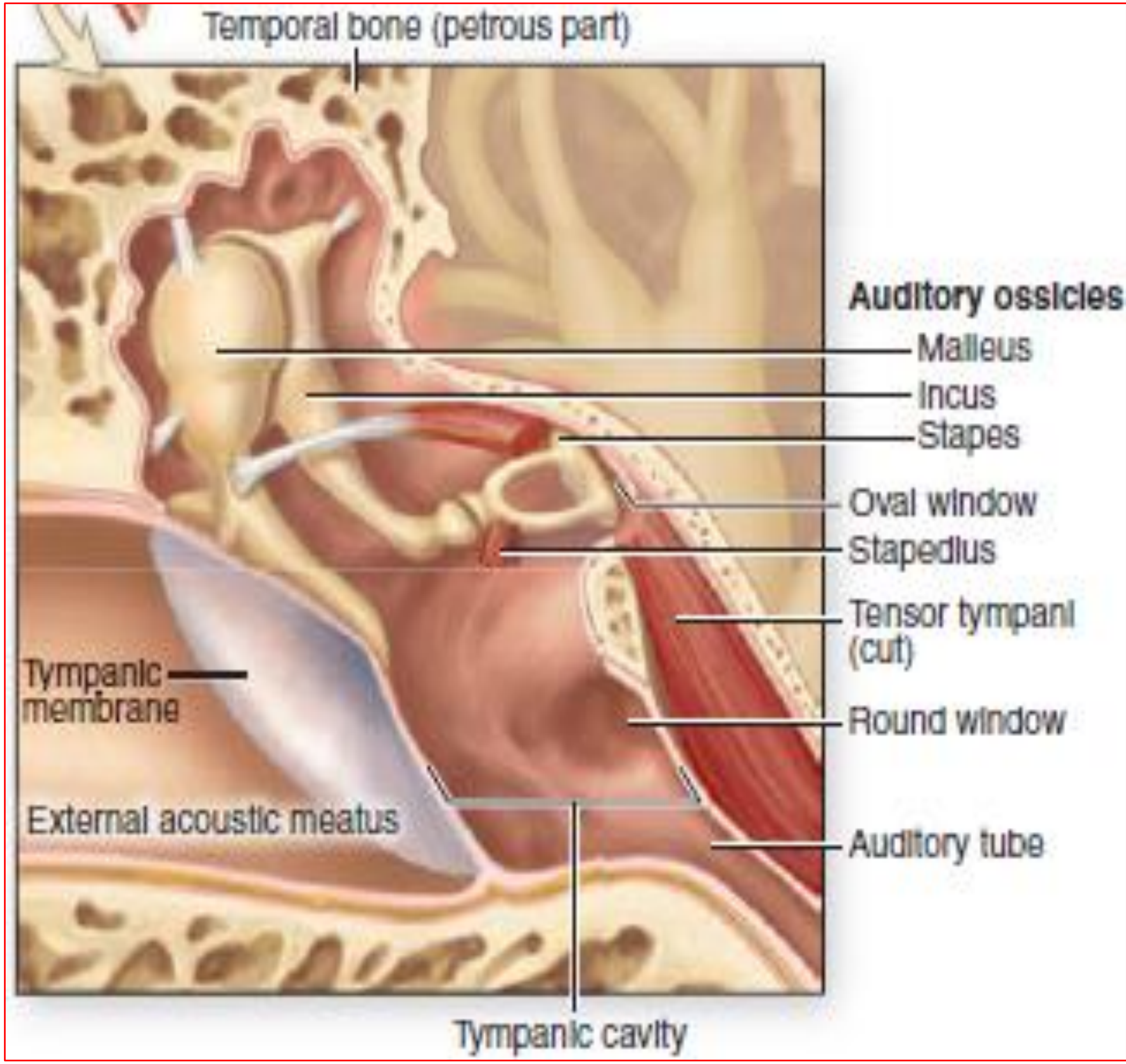
- The **auricle**, or **pinna** (L. *pinna*, wing) is an irregular, funnel-shaped plate of elastic cartilage, covered by tightly adherent skin, which directs sound waves into the ear.
- Sound waves enter the **external acoustic meatus** (L. passage), a canal lined with stratified squamous epithelium that extends from the auricle to the middle ear. Near its opening hair follicles, sebaceous glands, and modified apocrine sweat glands called **ceruminous glands** are found in the submucosa. **Cerumen**, the waxy material formed from secretions of the sebaceous and ceruminous glands, contains various proteins, saturated fatty acids, and sloughed keratinocytes and has protective, antimicrobial properties. The wall of the external acoustic meatus is supported by elastic cartilage in its outer third, while the temporal bone encloses the inner part.
- Across the deep end of the external acoustic meatus lies a thin, somewhat transparent sheet called the **tympanic membrane** or **eardrum**. This membrane consists of fibroelastic connective tissue covered externally with epidermis and internally by the simple cuboidal epithelium of the mucosa lining the middle ear cavity. Sound waves cause vibrations of the tympanic membrane, which transmit energy to the middle ear

# MIDDLE EAR

- The **middle ear** contains the air-filled **tympanic cavity**, an irregular space lying within the temporal bone between the tympanic membrane and the bony surface of the internal ear. Anteriorly, this cavity communicates with the pharynx via the **auditory tube** (also called the **eustachian** or **pharyngotympanic tube**) and posteriorly with the smaller, air-filled mastoid cavities of the temporal bone.
- The simple cuboidal epithelium lining the cavity rests on a thin lamina propria continuous with periosteum. Entering the auditory tube, this simple epithelium is gradually replaced by the ciliated pseudostratified columnar epithelium that lines the tube. Below the temporal bone this tube is usually collapsed; swallowing opens it briefly, which serves to balance the air pressure in the middle ear with atmospheric pressure.
- In the medial bony wall of the middle ear are two small, membrane-covered regions devoid of bone: the **oval** and **round windows** with the internal ear behind them.

- The tympanic membrane is connected to the oval window by a series of three small bones, the **auditory ossicles**, which transmit the mechanical vibrations of the tympanic membrane to the internal ear. The three ossicles are named for their shapes the **malleus**, **incus**, and **stapes**, from the Latin words for “hammer,” “anvil,” and “stirrup,” respectively.

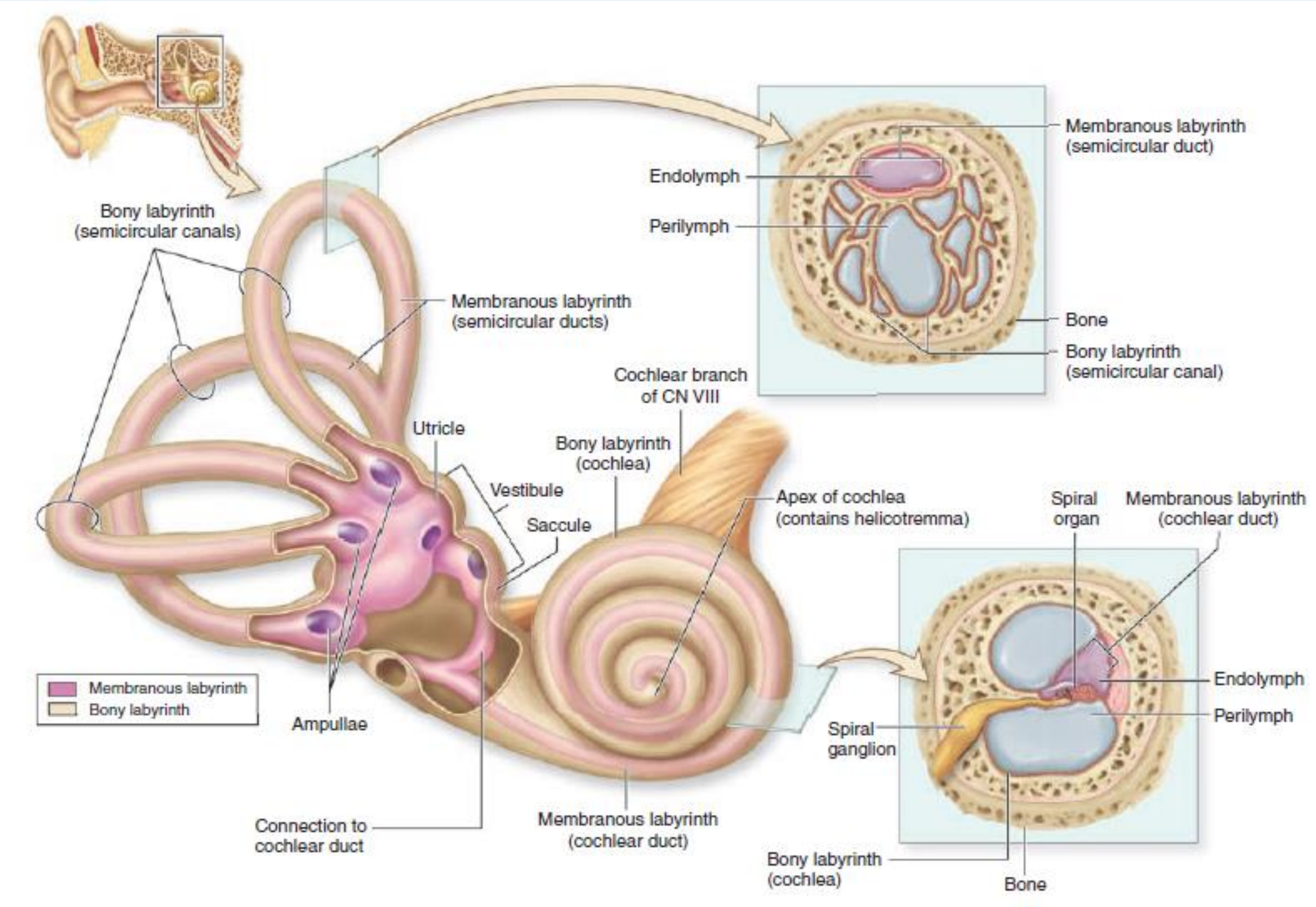
- The malleus is attached to the tympanic membrane and the stapes to the membrane across the oval window. The ossicles articulate at synovial joints, which along with periosteum are completely covered with simple squamous epithelium. Two small skeletal muscles, the tensor tympani and stapedius, insert into the malleus and stapes, respectively, restricting ossicle movements and protecting the oval window and inner ear from potential damage caused by extremely loud sound.



# INTERNAL EAR

- The **internal ear** is located completely within the temporal bone, where an intricate set of interconnected spaces, the **bony labyrinth**, houses the smaller **membranous labyrinth**, a set of continuous fluid-filled, epithelium-lined tubes and chambers.
- Two connected sacs called the **utricle** and the **saccule**,
- Three **semicircular ducts** continuous with the utricle, and
- The **cochlear duct**, which provides for hearing and is continuous with the saccule.

- Mediating the functions of the inner ear, each of these structures contains in its epithelial lining large areas with columnar mechanoreceptor cells, called **hair cells**, in specialized sensory regions:
- Two **maculae** of the utricle and saccule,
- Three **cristae ampullares** in the enlarged ampullary regions of each semicircular duct, and
- The long **spiral organ of Corti** in the cochlear duct.


Bony labyrinth
(semicircular canals)
Membranous labyrinth
(semicircular ducts)
Membranous labyrinth
(semicircular duct)
Endolymph
Perilymph
Bone
Bony labyrinth
(semicircular canal)
Cochlear branch
of CN VIII
Utricle
Bony labyrinth
(cochlea)
Vestibule
Saccule
Apex of cochlea
(contains helicotremma)
Spiral
organ
Membranous labyrinth
(cochlear duct)
Endolymph
Perilymph
Spiral
ganglion
Membranous labyrinth
Bony labyrinth
Ampullae
Connection to
cochlear duct
Membranous labyrinth
(cochlear duct)
Bony labyrinth
(cochlea)
Bone

The entire membranous labyrinth is within the bony labyrinth, which includes the following regions:

- An irregular central cavity, the **vestibule** (L. *vestibulum*, area for entering) houses the saccule and the utricle.
- Behind this, three osseous **semicircular canals** enclose the semicircular ducts.
- On the other side of the vestibule, the **cochlea** (L. snail, screw) contains the cochlear duct. The cochlea makes 2¾ turns around a bony core called the **modiolus** (L. hub of wheel). The modiolus contains blood vessels and surrounds the cell bodies and processes of the acoustic branch of the eighth cranial nerve in the large **spiral** or **cochlear ganglion**.

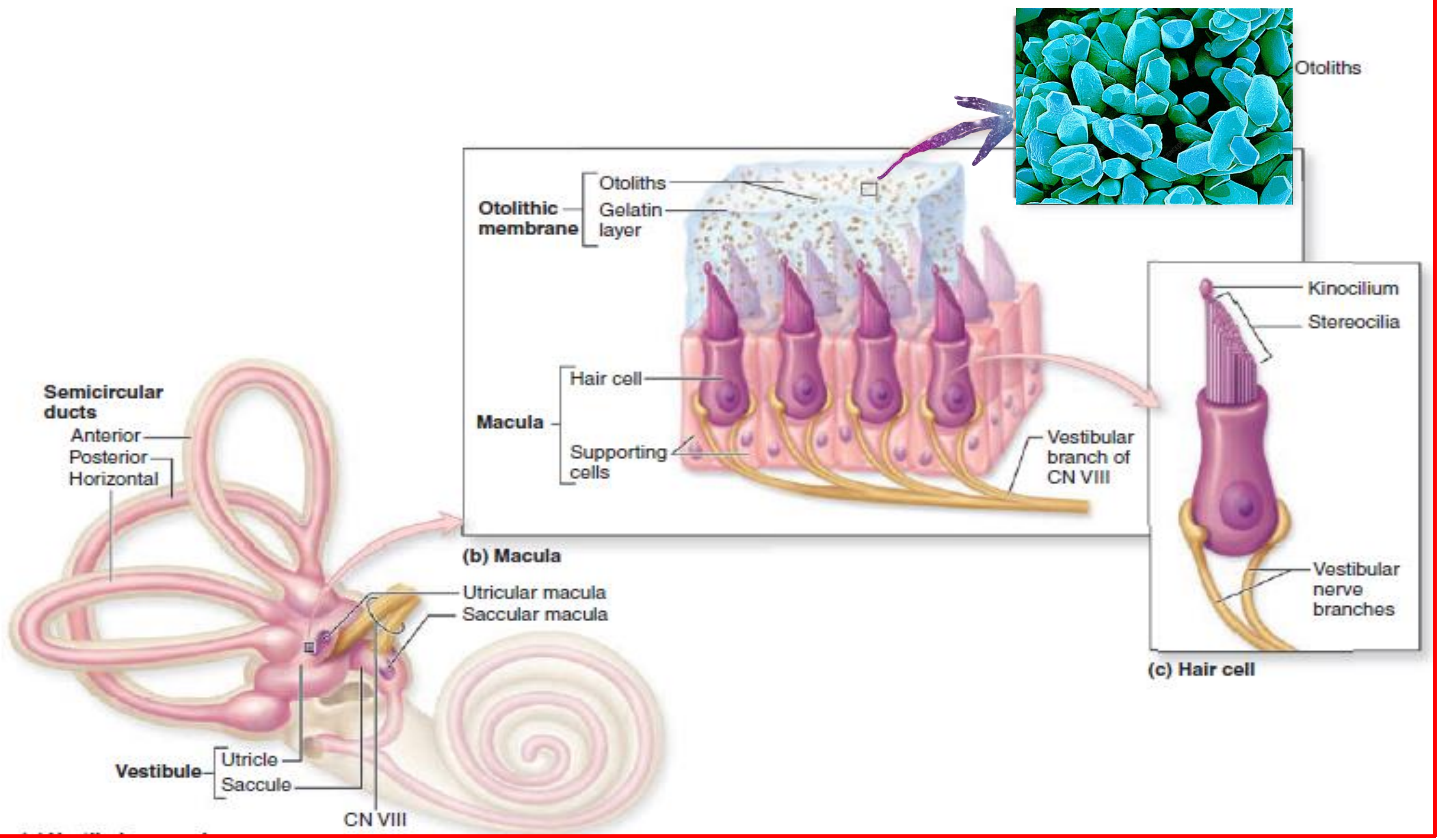
- The bony and membranous labyrinths contain two different fluids. The separation and ionic differences between these fluids are important for inner ear function.
- **Perilymph** fills all regions of the bony labyrinth and has an ionic composition similar to that of cerebrospinal fluid and the extracellular fluid of other tissues, but it contains little protein. Perilymph emerges from the microvasculature of the periosteum and drains via a perilymphatic duct into the adjoining subarachnoid space. Perilymph suspends and supports the closed membranous labyrinth, protecting it from the hard wall of the bony labyrinth.
- **Endolymph** fills the membranous labyrinth and is characterized by a high-K+ (150 mM) and low-Na+ (16 mM) content, similar to that of intracellular fluid. Endolymph is produced in a specialized area in the wall of the cochlear duct (described below) and drains via a small endolymphatic duct into venous sinuses of the dura mater.

# UTRICLE AND SACCULE

- The interconnected, membranous **utricle** and the **saccule** are composed of a very thin connective tissue sheath lined with simple squamous epithelium and are bound to the periosteum of the bony labyrinth by strands of connective tissue containing microvasculature.
- The maculae in the walls of the utricle and saccule are small areas of columnar neuroepithelial cells innervated by branches of the vestibular nerve. The macula of the saccule lies in a plane perpendicular to that of the utricle, but both are similar histologically.
- Each consists of a thickening of the wall containing several thousand columnar hair cells, each with surrounding supporting cells and synaptic connections to nerve endings.

- Hair cells act as mechanoelectrical transducers, converting mechanical energy into the electrical energy of nerve action potentials. Each has an apical hair bundle consisting of one rigid cilium, the **kinocilium**, up to 40-μm long, and a bundle of 30-50 rigid, unbranched **stereocilia**. The base of each stereocilium is tapered and connected to an actin-rich region of apical cytoplasm, the cuticular plate, which returns these rigid projecting structures to a normal upright position after bending.

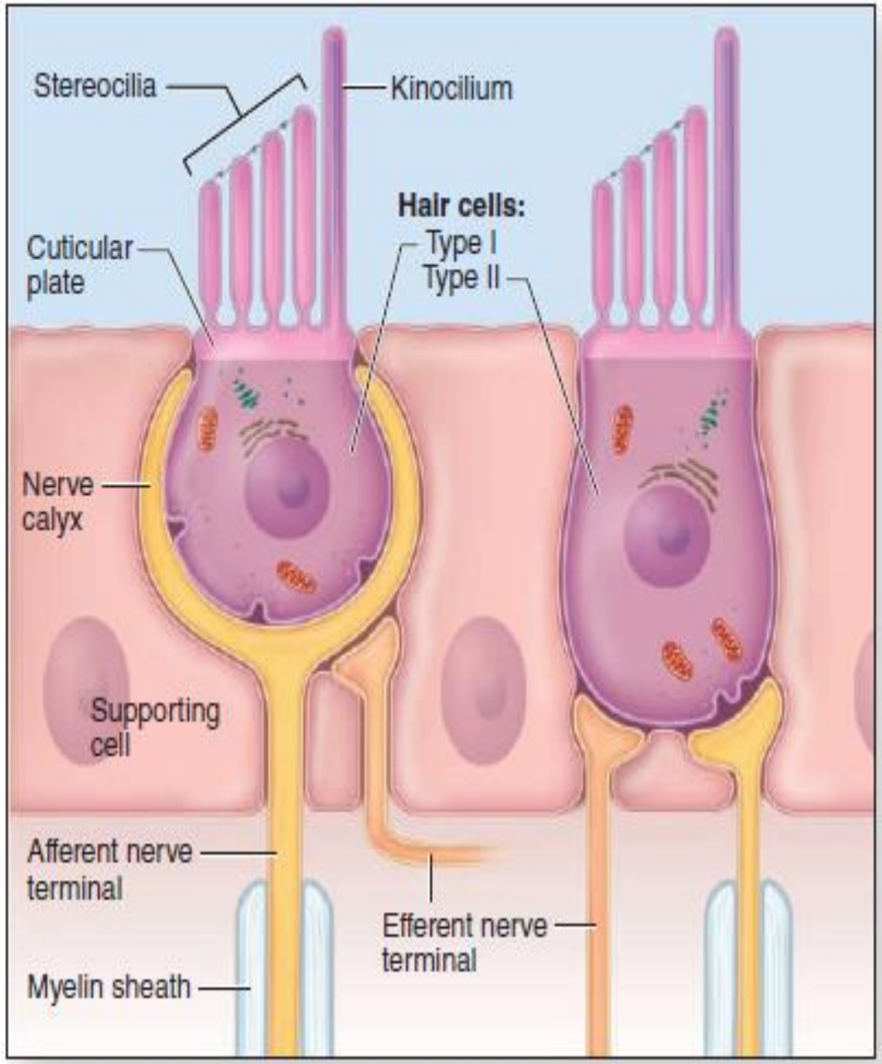
- They are arranged in rows of decreasing length, with the longest adjacent to the kinocilium. The tips of the stereocilia and kinocilium are embedded in a thick, gelatinous layer of proteoglycans called the **otolithic membrane**. The outer region of this layer contains barrel-shaped crystals of CaCO3 and protein called **otoliths** (or otoconia) typically 5-10 μm in diameter


Otoliths
Otolithic membrane
Otoliths
Gelatin layer
Macula
Hair cell
Supporting cells
Vestibular branch of CN VIII
Kinocilium
Stereocilia
Vestibular nerve branches
(b) Macula
(c) Hair cell
Semicircular ducts
Anterior
Posterior
Horizontal
Utricular macula
Saccular macula
Vestibule
Utricle
Saccule
CN VIII

All hair cells have basal synapses with afferent (to the brain) nerve endings but are of two types:

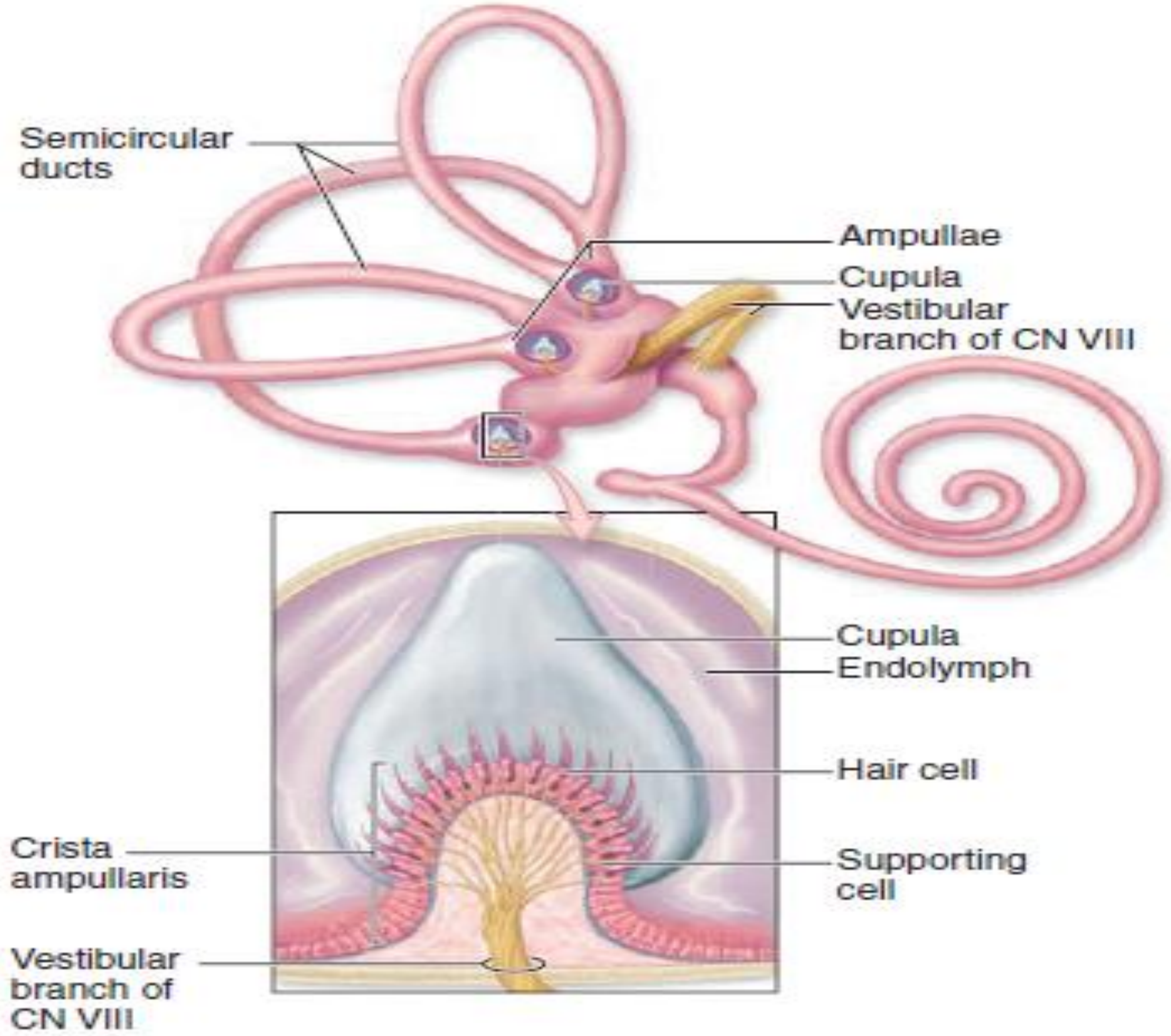
- Type I hair cells have rounded basal ends completely surrounded by an afferent terminal calyx (L, cup).

- The more numerous type II hair cells are cylindrical, with bouton endings from afferent nerves.



# SEMICIRCULAR DUCTS

- The three **semicircular ducts** extend from and return to the wall of the utricle. They lie in three different spatial planes, at approximately right angles to one another.
- Each semicircular duct has one enlarged ampulla end containing hair cells and supporting cells on a crest of the wall called the **crista ampullaris**. Each crista ampullaris is perpendicular to the long axis of the duct. Cristae are histologically similar to maculae, but the proteoglycan layer called the **cupola** attached to the hair cells apically lacks otoliths and is thicker. The cupula extends completely across the ampulla, contacting the opposite nonsensory wall.
- The hair cells of the cristae ampullares act as mechanoelectrical transducers like those of the maculae in the utricle and saccule, signaling afferent axons by pulsed transmitter release determined by depolarization and hyperpolarization states. Here the mechanoreceptors detect **rotational movements** of the head as they are deflected by endolymph movement in the semicircular ducts. The cells are oriented with opposite polarity on each side of the side, so that turning the head causes hair cell depolarization on one side and hyperpolarization on the other. Neurons of the **vestibular nuclei** in the CNS receive input from the sets of semicircular ducts on each side simultaneously and interpret head rotation on the basis of the relative transmitter discharge rates of the two sides.



Semicircular ducts
Ampullae
Cupula
Vestibular branch of CN VIII
Cupula
Endolymph
Hair cell
Crista ampullaris
Supporting cell
Vestibular branch of CN VIII

# COCHLEAR DUCT

- The **cochlear duct**, a part of the membranous labyrinth shaped as a spiral tube, contains the hair cells and other structures that allow auditory function. Held in place within the bony cochlea, this duct is one of three parallel compartments, or scalae (L., ramps or ladders) which coil 2¾ turns within the cochlea:
- The cochlear duct itself forms the middle compartment, or **scala media**, filled with endolymph. It is continuous with the saccule and ends at the apex of the cochlea.
- The larger **scala vestibuli** contains perilymph and is separated from the scala media by the very thin **vestibular membrane (Reissner membrane)** lined on each side by simple squamous epithelium. Extensive tight junctions between cells of this membrane block ion diffusion between perilymph and endolymph.
- The **scala tympani** also contains perilymph and is separated from the scala media by the fibroelastic **basilar membrane**.

- The scalae tympani and vestibuli communicate with each other at the apex of the cochlea via a small opening called the **helicotrema**. Thus these two spaces with perilymph are actually one long tube; the scala vestibuli begins near the vestibular oval window and the scala tympani ends at the round window.

- The **stria vascularis**, located in the lateral wall of the cochlear duct (scala media), produces the endolymph with high levels of K+ that fills the entire membranous labyrinth. Stratified epithelial cells of the stria vascularis extend cytoplasmic processes and folds around the capillaries of an unusual intraepithelial plexus. K+ released from the capillaries is transported across tightly joined cells at the strial surface into the endolymph, which bathes the stereocilia of hair cells and produces conditions optimal for these cells' depolarization.

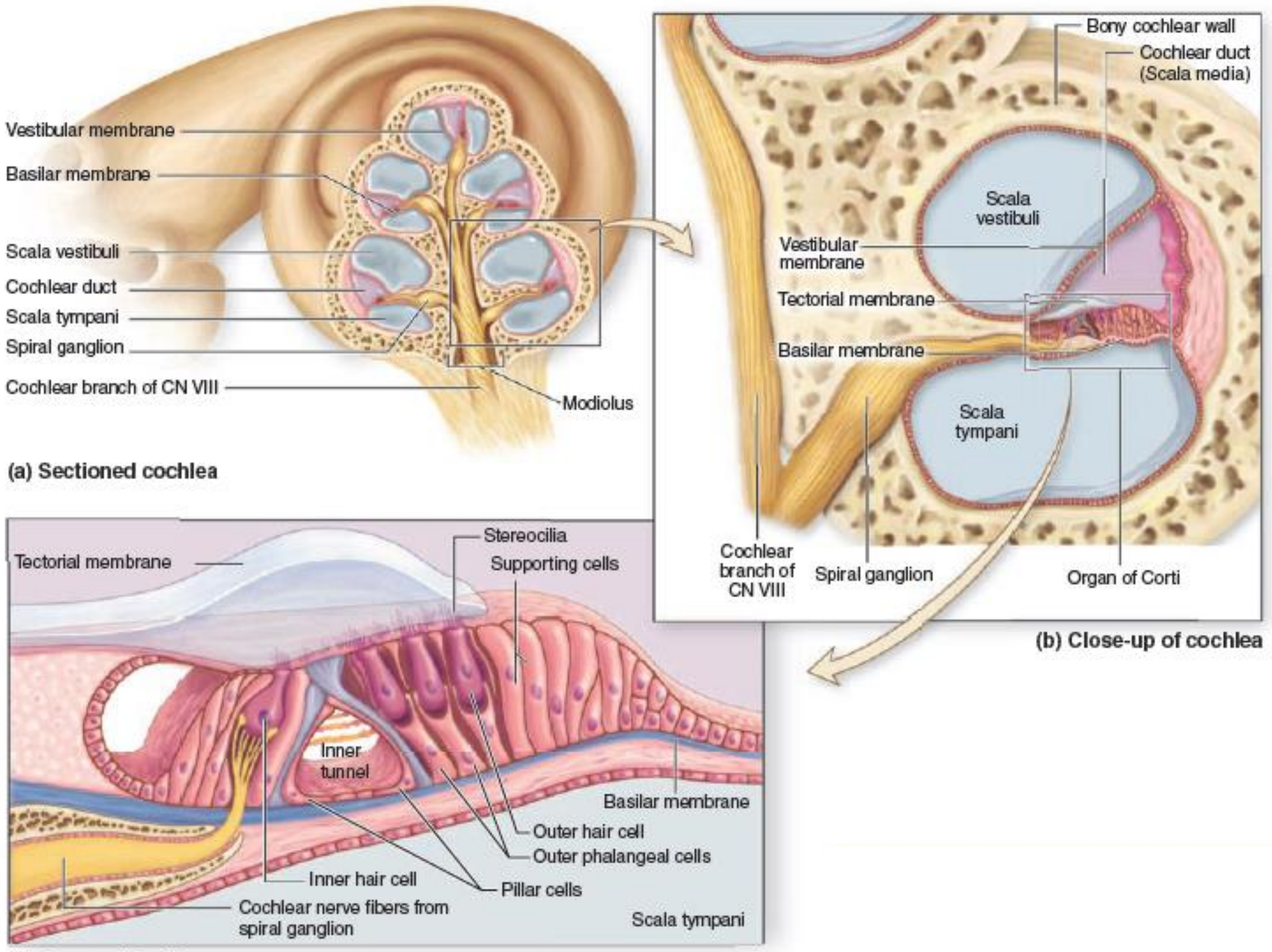
- The **organ of Corti**, or **spiral organ**, where sound vibrations of different frequencies are detected, consists of hair cells and other epithelial structures supported by the basilar membrane. Here the sensory hair cells have precisely arranged V-shaped bundles of rigid stereocilia

- Both outer and inner hair cells have synaptic connections with afferent and efferent nerve endings, with the inner row of cells more heavily innervated. The cell bodies of the afferent bipolar neurons constitute the **spiral ganglion** located in the bony core of the modiolus.
- Two major types of columnar supporting cells are attached to the basilar membrane in the organ of Corti:

❑ Inner and outer **phalangeal cells** extend apical processes, which intimately surround and support the basolateral parts of both inner and outer hair cells and the synaptic nerve endings. The apical ends of phalangeal cells are joined to those of the hair cells by tight zonulae occludens, forming an apical plate across the spiral organ through which the stereocilia bundles project into endolymph.

❑ **Pillar cells** are stiffened by heavy bundles of keratin and outline a triangular space, the inner tunnel, between the outer and inner complexes of hair cells and phalangeal cells. The stiff inner tunnel also plays a role in sound transmission.

- On the outer hair cells the tips of the tallest stereocilia are embedded in the gel-like **tectorial membrane**, an acellular layer extending over the organ of Corti from the connective tissue around the modiolus. The tectorial membrane consists of fine bundles of collagen (types II, V, IX, and XI) associated with proteoglycans and forms during the embryonic period from secretions of cells lining this region.




(a) Sectioned cochlea

(b) Close-up of cochlea

(c) Organ of Corti

THANK YOU FOR YOUR ATTENTION