Subject V INTEGUMENTS. RESPIRATORY SYSTEM

Program of lecture:

- **Skin: development, structural features, functions.**
- **Skin appendages: hairs, nails, sebaceous and sweat glands.**
- **Innervation, vascularization, age features.**
- **Respiratory system: development, structural parts, morpho-functional features. Respiratory portion of respiratory system.**
- **Air-blood barrier.**
- **Innervation, vascularization, age features.**

The integument, composed of **skin** and its appendages-the **sweat glands, sebaceous glands, hair,** and **nails-**is the largest organ of the body, constituting 16% of body weight. It invests the entire body, becoming continuous with the mucous membranes of the digestive system at the lips and the anus, the respiratory system in the nose, and the urogenital systems where they surface (Fig. 1).

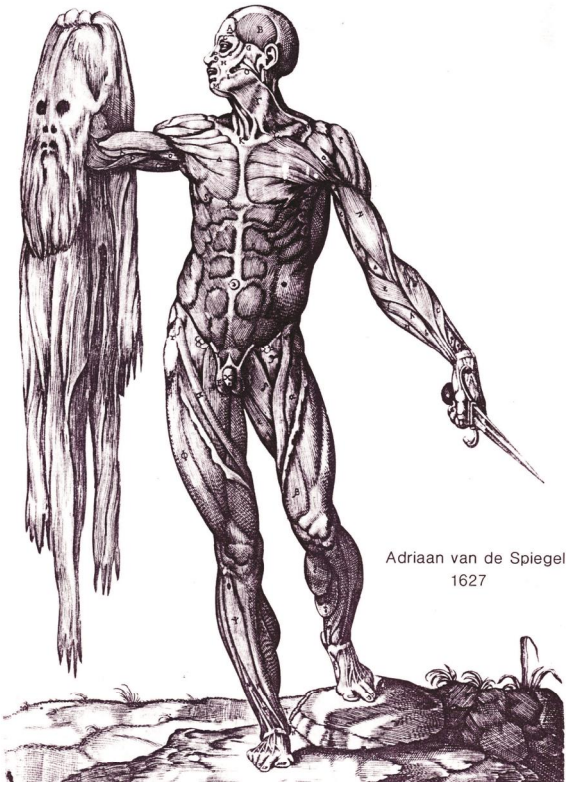

FIG. 1

Besides providing a cover for the underlying soft tissues, skin performs many additional functions, including (1) **protection** against injury, bacterial invasion, and desiccation; (2) **regulation of body temperature;** (3) **reception** of continual sensations from the environment (e.g., touch, temperature, and pain); (4) **excretion** from sweat glands; and (5) **absorption** of ultraviolet radiation from the sun for the synthesis of vitamin D.

Skin consists of two layers: an outer epidermis and a deeper connective tissue layer, the dermis (Fig. 14-1). The **epidermis** is composed of an **ectodermally** derived stratified squamous keratinized epithelium. Lying directly below and interdigitating with the epidermis is the **dermis,** derived from **mesoderm** and composed of dense, irregular collagenous connective tissue. The interface between the epidermis and dermis is formed by raised ridges of the dermis, the **dermal ridges (papillae),** which interdigitate with invaginations of the epidermis called **epidermal ridges.** Collectively, the two types of ridges are known as the **rete apparatus.** Additional downgrowths of the epidermal derivatives (i.e., hair follicles, sweat glands, and sebaceous glands) that come to lie in the dermis cause the interface to have an irregular contour (Fig. 2, 3).

The **hypodermis,** a loose connective tissue containing varying amounts of fat, underlies the skin. The hypodermis is not part of the skin but is the **superficial fascia** of gross anatomical dissection that covers the entire body, immediately deep to the skin. Individuals who are overnourished or who live in cold climates possess a large amount of fat deposited in the superficial fascia (hypodermis), named **panniculus adiposus.** (Fig. 2, 3).

EPIDERMIS

The epidermis is 0.07 to 0.12 mm in thickness over most of the body, with increased localized thickening on the palms of the hands and the soles of the feet (where it may be as much as 0.8 mm and 1.4 mm in thickness, respectively). Thicker skin on the palms and soles is evident in the fetus, but use, applied pressure, and friction result in continued increases in skin thickness in these areas over time.

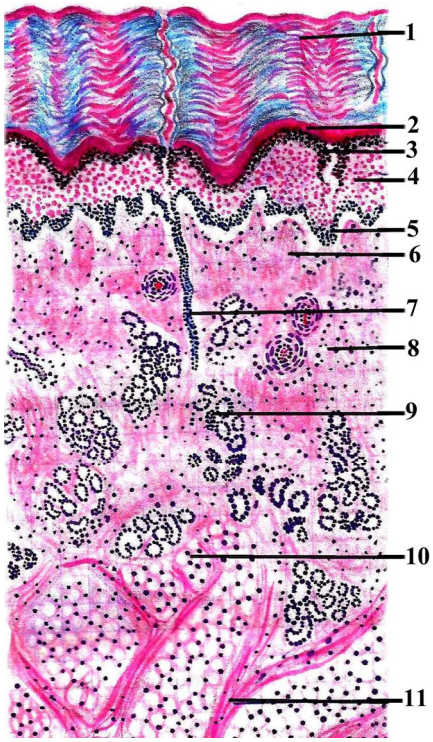

Fig. 2

The stratified squamous keratinized epithelium of skin is composed of four populations of cells.

- Keratinocytes
- Langerhans cells
- Melanocytes
- Merkel cells

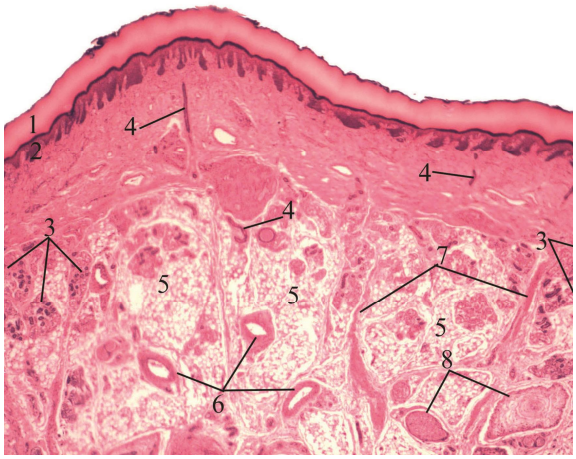

Fig. 3

Keratinocytes, which form the largest population of cells, are arranged in five recognizable layers; the remaining three cell types are interspersed among keratinocytes in specific locations (see later). Because keratinocytes are continually being sloughed from the surface of the epidermis, this cell population must be constantly renewed. Renewal is accomplished through mitotic activity of the keratinocytes in the basal layers of the epidermis. Keratinocytes undergo mitosis at night, and as the new cells are forming, the cells above continue to be pushed toward the surface. Along their way to the surface, the cells differentiate and begin to accumulate **keratin filaments** in their cytoplasm. Eventually, as they near the surface, the cells die and are sloughed off, a process that takes 20 to 30 days (Fig. 4).

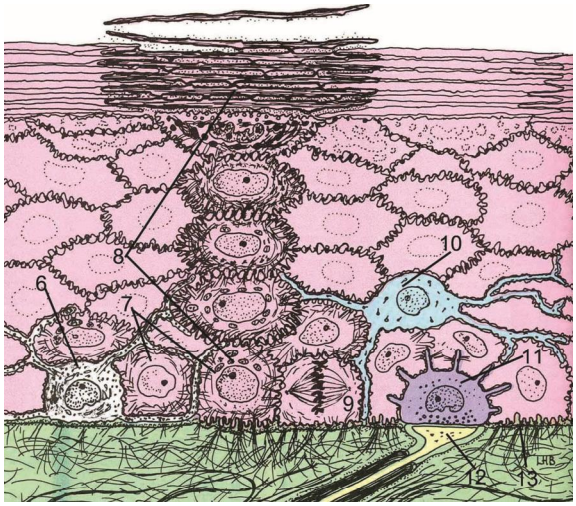

Fig. 4

Because of the **cytomorphosis** of keratinocytes during their migration from the basal layer of the epidermis to its surface, five morphologically distinct zones of the epidermis can be identified. From the inner to the outer layer, they are (1) **stratum basale (germinativum),** (2) **stratum spinosum,** (3) **stratum granulosum,** (4) **stratum lucidum,** and (5) **stratum corneum.** Skin is classified as thick or thin according to the thickness of the epidermis (see Fig. 4).

However, these two classifications are also are distinguished by the presence or absence of certain epidermal layers and the presence or absence of hair.

Thick skin covers the the palms and soles. The epidermis of thick skin, which is 400 to 600 mm thick, is characterized by the presence of all five layers. Thick skin lacks hair follicles, arrector pili muscles, and sebaceous glands but does possess sweat glands (Fig.5).

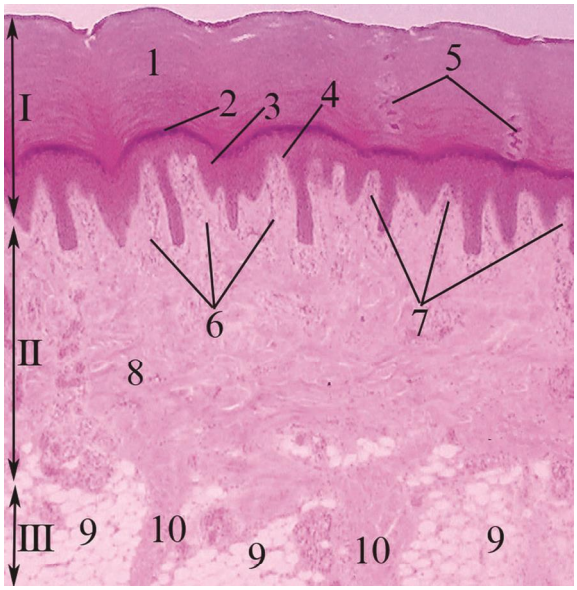

Fig. 5

Thin skin covers most of the remainder of the body. The epidermis of thin skin, which ranges from 75 to 150 mm in thickness, has a thin stratum corneum and lacks a definite stratum lucidum and stratum granulosum, although individual cells of these layers are present in their proper locations. Thin skin has **hair follicles, arrector pili muscles**, **sebaceous glands,** and **sweat glands** (Fig. 6). The deepest layer of the epidermis, the stratum basale, is supported by a **basement membrane** and sits on the dermis, forming an irregular interface. The stratum basale consists of a single layer of mitotically active, cuboidal to low columnar cells containing basophilic cytoplasm and a large nucleus. Many desmosomes are located on the lateral cell membrane attaching stratum basale cells to each other and to cells of the stratum spinosum. Basally located hemidesmosomes attach the cells to the basal lamina. Electron micrographs reveal a few mitochondria, a small Golgi complex, a few rough endoplasmic reticulum (RER) profiles, and abundant free ribosomes. Numerous bundles and single (10-nm) **intermediate filaments (tonofilaments)** course through the plaques of the laterally placed desmosomes and end in plaques of hemidesmosomes

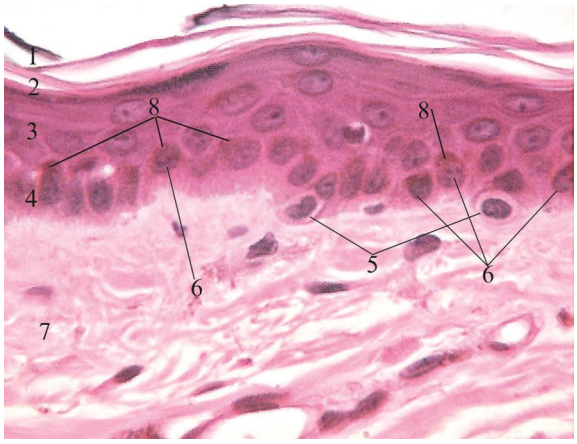

Fig. 6

Mitotic figures should be common in the stratum basale because this layer is partially responsible for cell renewal in the epithelium. However, mitosis occurs mostly during the night, and histological specimens are procured during the day; thus, mitotic figures are rarely seen in histological slides of skin. When new cells are formed via mitosis, the previous layer of cells is pushed surfaceward to join the next layer of the epidermis, the stratum spinosum.

The thickest layer of the epidermis is the stratum spinosum, composed of polyhedral to flattened cells. The basally located keratinocytes in the stratum spinosum also are mitotically active, and the two strata together, frequently referred to as the **malpighian layer,** are responsible for the turnover of epidermal keratinocytes. Keratinocytes of the stratum spinosum have the same organelle population as described for the stratum basale. However, the cells in the stratum spinosum are richer in bundles of intermediate filaments **(tonofilaments),** representing **cytokeratin,** than cells in the stratum basale. In the stratum spinosum cells, these bundles radiate outward from the perinuclear region toward highly interdigitated cellular processes, which attach adjacent cells to each other by desmosomes. These processes, called "intercellular bridges" by early histologists, give cells of the stratum spinosum a "prickle cell" appearance. As keratinocytes move toward the surface through the stratum spinosum, they continue to produce tonofilaments, which become grouped in bundles called **tonofibrils,** causing the cytoplasm to become eosinophilic. Cells of the stratum spinosum also contain cytoplasmic secretory granules (0.1 to 0.4 ε m in diameter) called **membrane-coating granules (lamellar granules).** These flattened vesicles house lipid substance arranged in a closely packed, lamellar configuration (Fig. 7).

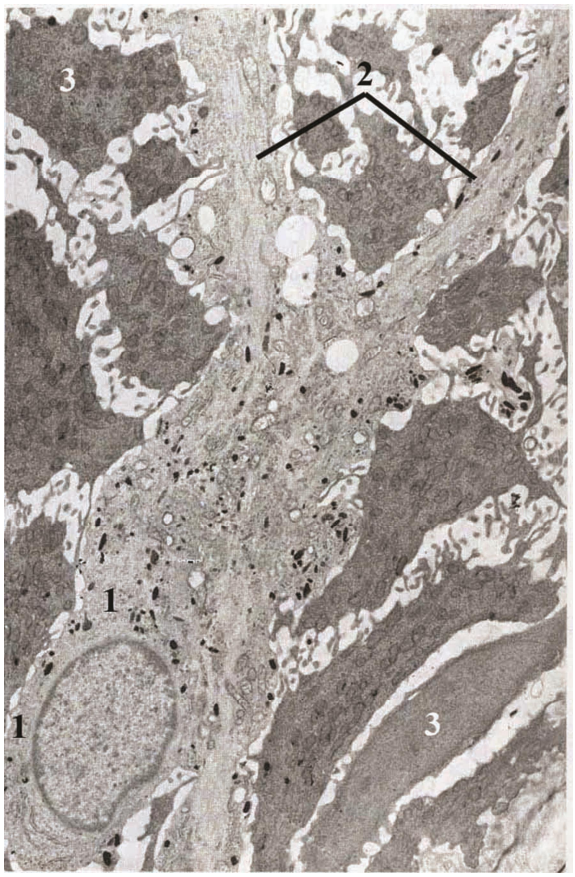

Fig. 7

The stratum granulosum, consisting of three to five layers of flattened keratinocytes, is the most superficial layer of the epidermis in which cells still possess nuclei. The cytoplasm of these keratinocytes contains large, irregularly shaped, coarse, basophilic **keratohyalin granules,** which are not membrane-bound. Bundles of keratin filaments pass through these granules (Fig. 8).

Cells of the stratum granulosum also contain membrane-coating granules. The contents of these granules are released by exocytosis into the extracellular space, forming sheets of lipid-rich substance that acts as a waterproof barrier, one of the functions of skin. This impermeable layer prevents cells lying superficial to this region from being bathed in the nutrient-filled aqueous extracellular fluid, thus hastening their death.

The clear, homogeneous, lightly staining, thin layer of cells immediately superficial to the stratum granulosum is the stratum lucidum. This layer is present only in thick skin (i.e., palms of the hands and soles of the feet). Although the flattened cells of the stratum lucidum lack organelles and nuclei, they contain densely packed keratin filaments oriented parallel to the skin surface and **eleidin,** a transformation product of keratohyalin. The cytoplasmic aspect of the plasma membrane of these cells has a thickened appearance because of the deposition of a nonkeratin protein, known as **involucrin,** whose function is not known.

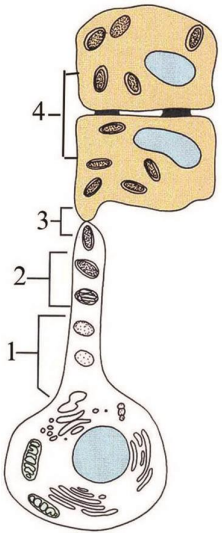

Fig. 8

The most superficial layer of skin, the stratum corneum, is composed of numerous layers of flattened, keratinized cells with a thickened plasmalemma. These cells lack nuclei and organelles but are filled with keratin filaments embedded in an amorphous matrix. Those cells farther away from the skin surface display desmosomes, whereas cells near the surface of the skin, called **squames,** or **horny cells,** lose their desmosomes and become **desquamated** (sloughed off).

Melanocytes are round to columnar cells whose long, undulating processes extend from the superficial surfaces of the cells and penetrate the intercellular spaces of the stratum spinosum (see Fig. 8). Tyrosinase produced by the RER of the melanocyte is packaged by its Golgi apparatus into oval granules known as **melanosomes** (although the melanosomes of red-haired individuals are round instead of oval). The amino acid tyrosine is preferentially transported into melanosomes, where tyrosinase converts it into **melanin** by means of a series of reactions progressing through 3,4-dihydroxyphenylalanine (dopa, methyldopa) and dopaquinone. It is interesting that the enzyme tyrosinase is activated by ultraviolet light

Melanosomes leave the cell body of the melanocytes and travel to the tips of their long processes. Once there, the tips of the melanocyte processes penetrate the cytoplasm of the

stratum spinosum cells and become pinched off via a special secretory process called **cytocrine secretion.** Each truncated melanocyte process elongates and receives more melanosomes, and the cycle is repeated. A particular melanocyte serves a number of keratinocytes with which it is associated, constituting an **epidermal melanin unit.** Within the cells of the stratum intermedium, the melanosomes are transported to the supranuclear region (that is, between the nucleus and the surfacemost region of the cell) so that the melanosomes form a protective barrier between the nucleus and the impinging ultraviolet rays from the sun. Eventually, the melanin pigment is attacked and degraded by lysosomes of the keratinocyte. This process occurs over a period of several days (Fig. 9).

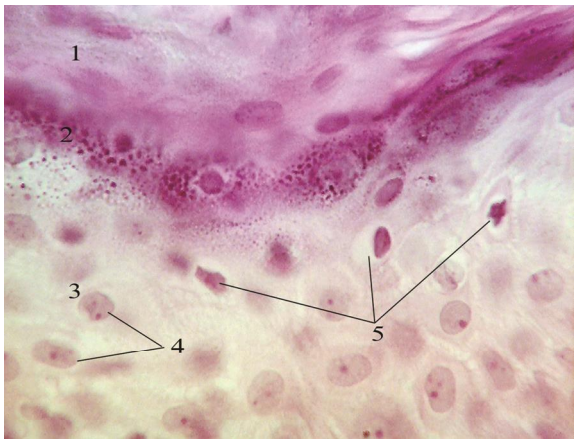

Fig. 9

The region of the skin lying directly beneath the epidermis, called the dermis, is derived from the mesoderm and is divided into two layers: the superficial, loosely woven **papillary layer** and the deeper, much denser **reticular layer.** The dermis is composed of dense, irregular collagenous connective tissue, containing mostly type I collagen fibers and networks of elastic fibers, which support the epidermis and bind the skin to the underlying **hypodermis** (superficial fascia). The dermis ranges in thickness from 0.6 mm in the eyelids to 3 mm or so on the palm of the hand and the sole of the foot. However, there is not a sharp line of demarcation at its interface with the underlying connective tissue of the superficial fascia. Normally, the dermis is thicker in men than in women and on the dorsal rather than on the ventral surfaces of the body (Fig. 10).

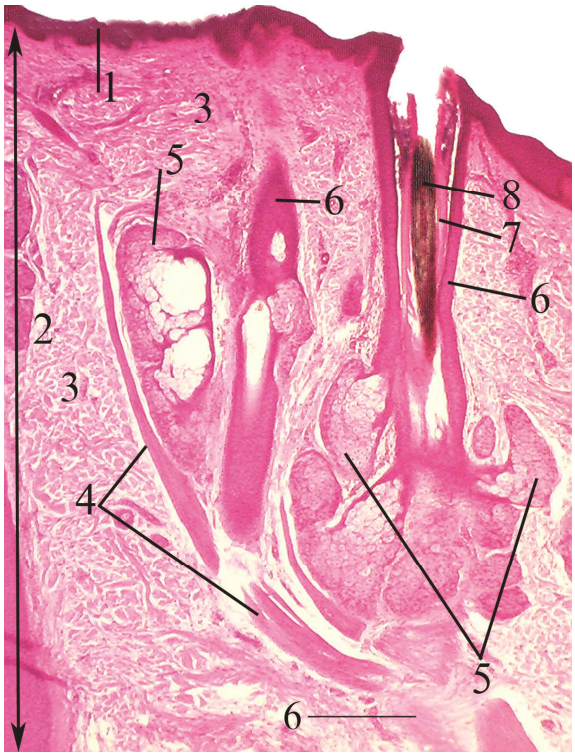

Fig. 10

Glands of the Skin

The glands of the skin include eccrine glands, apocrine sweat glands, sebaceous glands, and the mammary gland (a modified and highly specialized type of sweat gland).

Eccrine Sweat Glands

Eccrine sweat glands are about 0.4 mm in diameter and are located in the skin throughout most of the body. Numbering as many as 3 to 4 million, they are important organs of thermoregulation. Eccrine sweat glands develop as invaginations of the epithelium of the dermal ridge that grows down into the dermis, with its deep aspect becoming the glandular portion of the sweat gland. These glands, which begin to function soon after birth, excrete sweat and may secrete as much as 10 L of sweat a day under extreme conditions in highly active people engaged in vigorous exercise (Fig. 11).

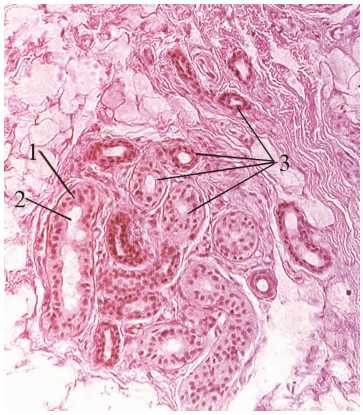

FIG. 11

Eccrine sweat glands are **simple coiled tubular glands** located deep in the dermis or in the underlying hypodermis. Passing from the secretory portion of each gland is a slender, coiled **duct** that traverses the dermis and epidermis to open on the surface of the skin at a **sweat pore.** Eccrine sweat glands are merocrine in their method of releasing their secretory product. The eccrine glands are innervated by postganglionic fibers of the sympathetic nervous system (Fig. 11).

The secretory portion of the gland is said to be a simple cuboidal to low columnar epithelium composed of dark cells and clear cells; however, some investigators consider the secretory portion to be pseudostratified (Fig. 12).

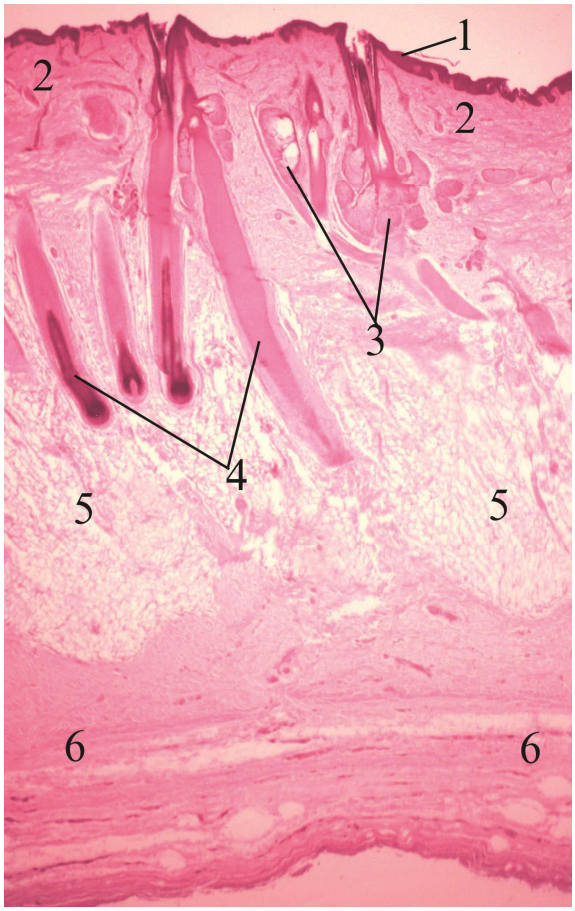

FIG. 12

Dark cells resemble an inverted cone, with the broad ends lining the lumen. The narrowed ends, which seldom reach the basal lamina, conform to fit between adjacent clear cells. Electron micrographs reveal some RER, numerous free ribosomes, elongated mitochondria, and a well-developed Golgi complex. Moderately dense glycoprotein-containing secretory granules are located in the apical cytoplasm of the dark cells, and the secretion released by these cells is **mucous** in nature.

Clear cells have a narrow apical area and a broader base that extends to the basal lamina. Unlike dark cells, clear cells do not contain secretory granules but do contain accumulations of **glycogen;** their organelles are similar to those of dark cells, except that they have little RER. The bases of the clear cells are tortuously infolded, similar to those of other cell types involved in transepithelial transport. Clear cells have limited access to the lumen of the gland because of the dark cells; therefore, their **watery secretion** enters **intercellular canaliculi** interposed between

adjacent clear cells, where it mixes with the mucous secretion of the dark cells. Myoepithelial cells surrounding the secretory portion of the eccrine sweat glands are enveloped by the basal lamina of the secretory cells. The cytoplasm of myoepithelial cells has **myosin filaments** as well as many deeply acidophil-staining **actin filaments,** which give the cell contractile capability. Contractions of the myoepithelial cells assist in expressing the fluid from the gland (Fig. 12).

The duct of an eccrine sweat gland is continuous with the secretory unit at its base but narrows as it passes through the dermis on its way to the epidermal surface. The duct is composed of a stratified cuboidal epithelium made up of two layers. The **cells of the basal layer** have a large, heterochromatic nucleus and abundant mitochondria. The **cells of the luminal layer** have an irregularly shaped nucleus, little cytoplasm, only a few organelles, and a terminal web immediately deep to the apical plasma membrane. Apocrine sweat glands are found only in certain locations: the axilla (arm pit), the areola of the nipple, and the anal region. Modified apocrine sweat glands constitute the **ceruminous (wax) glands** of the external auditory canal and the **glands of Moll** in the eyelids. Apocrine sweat glands are much larger than eccrine sweat glands, up to 3 mm in diameter. These glands are embedded in the deeper portions of the dermis and hypodermis. Unlike the ducts of eccrine sweat glands, which open onto the skin surface, the ducts of apocrine sweat glands open into canals of the hair follicles just superficial to the entry of the sebaceous gland ducts (Fig. 12). The secretory cells of apocrine glands are simple cuboidal to low columnar in profile. When the lumen of the gland is filled with secretory product, these cells may become squamous. The lumina of these glands are much larger than those of eccrine glands, and the secretory cells contain granules that are isolated from the apical membrane by a prominent terminal web. The viscous secretory product of apocrine glands is odorless upon secretion, but when metabolized by bacteria, it presents a distinctive odor. Myoepithelial cells surround the secretory portion of the apocrine sweat glands and assist in expressing the secretory product into the duct of the gland.

Hairs

Hairs are filamentous, keratinized structures that project from the epidermal surface of the skin. Hair grows over most of the body except on the vermilion zone of the lips, palms and sides of the palms, soles and sides of the feet, dorsum of the distal phalanges of the fingers and toes, glans penis, glans clitoris, labia minora, and vestibular aspect of the labia majora. Two types of hairs are present on the human body. Hairs that are soft, fine, short, and pale (e.g., those covering the eyelids) are called **vellus hairs;** those that are hard, large, coarse, long, and dark (e.g., those of the scalp and eyebrows) are called **terminal hairs.** Additionally, very fine hair called **lanugo,** is present on the fetus(Fig. 13).

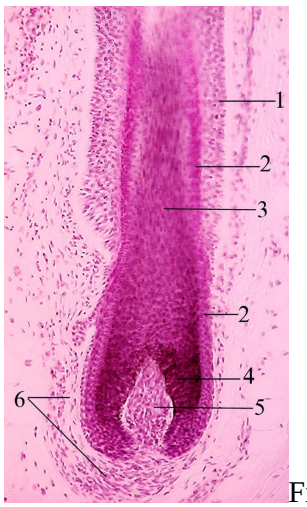

Fig. 13

The number of hairs on humans is essentially the same as on other primates, but most human hair is of the vellus type, whereas terminal hairs predominate on other primates. Human hair does not provide thermal insulation, as does the fur of animals. Instead, human hairs serve in tactile sensation, such that any stimulus that deforms a hair is translated down the shaft to sensory nerves that surround the hair follicle (Fig. 13).

Hair follicles, the organs from which hairs develop, arise from invaginations of the epidermis that invade the dermis, hypodermis, or both. Hair follicles are surrounded by dense accumulations of fibrous connective tissue belonging to the dermis. A thickened basement membrane, the **glassy membrane,** separates the dermis from the epithelium of the hair follicle (Fig. 14). The expanded terminus of the hair follicle, the **hair root,** is indented, and the concavity conforms to the shape of the **dermal papilla** occupying it. The hair root and the dermal papilla together are known as the **hair bulb.** The dermal papilla contains a rich supply of capillaries that provide nutrients and oxygen for the cells of the hair follicle. The dermal papilla also acts as an inductive force controlling the physiological activities of the hair follicle (Fig. 13).

The bulk of the cells composing the hair root is called the **matrix.** Proliferation of these matrix cells accounts for the growth of hair; thus, they are homologous to the stratum basale of the epidermis. The outer layers of follicular epithelium form the **external root sheath,** which is composed of a single layer of cells at the hair bulb and several layers of cells near the surface of the skin (Fig. 13).

The external root sheath surrounds several layers of epidermally derived cells, the **internal root sheath,** which consists of three components: (1) an outer single row of cuboidal cells, **Henle's layer,** which contacts the innermost layer of cells of the external root sheath; (2) one or two layers of flattened cells forming **Huxley's layer;** and (3) the **cuticle of the internal root sheath,** formed by overlapping scale-like cells whose free ends project toward the base of the hair follicle. The internal root sheath ends where the duct of the sebaceous gland attaches to the hair follicle.

The hair shaft is a long slender filament that extends to and through the surface of the epidermis. It consists of three regions: **medulla, cortex,** and the **cuticle of the hair.** As the cells of the matrix within the hair root proliferate and differentiate, they move toward the surface of the skin, eventually developing into the hair shaft. The cells in the center of the matrix are closest to the underlying dermal papilla and thus are most influenced by it; cells lying more and more peripheral to the matrix center are progressively less influenced by the dermal papilla (Fig. 14).

As the cells of the cortex are displaced surfaceward, they synthesize abundant **keratin filaments** and **trichohyalin granules** (resembling keratohyalin granules of the epidermis). These granules coalesce, forming an amorphous substance in which the keratin filaments are embedded. Scattered among the cells of the matrix nearest to the dermal papilla are large **melanocytes,** with long dendritic processes that transfer **melanosomes** to the cells of the cortex. The melanosomes remain in these cells, imparting to the hair a color based on the amount of melanin present. With age, the melanocytes gradually lose their ability to produce **tyrosinase,** which is essential for the production of melanin, and the hair becomes gray **(**Fig. 15, 16).

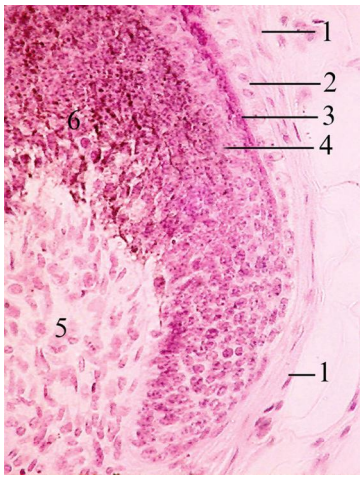

Fig. 15

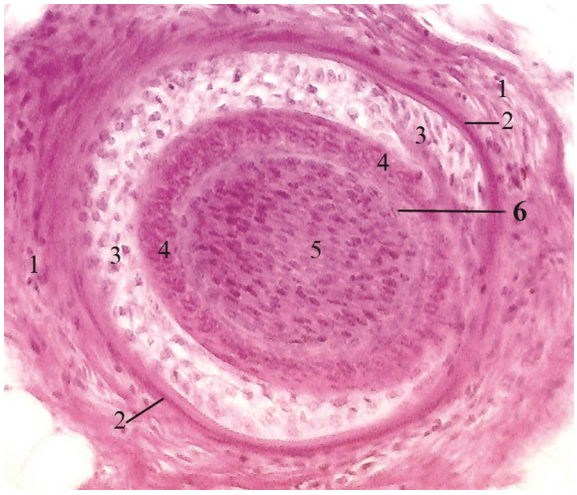

Fig. 16

Attached to the connective tissue sheath surrounding the hair follicles and to the papillary layer of the dermis are the arrector pili muscles. These smooth muscles attach to the hair follicle above its middle at an oblique angle. Contractions of these muscles depress the skin over their attachment and elevate the hair shaft and the skin around the hair shaft, forming tiny "goose bumps" on the surface of the skin. These are easily observed when a person is chilled or suddenly frightened (Fig. 16).

Nails

Nails, located on the distal phalanx of each finger and toe, are composed of plates of heavily compacted, highly keratinized epithelial cells that form the **nail plate,** lying on the epidermis, known as the **nail bed**. The nails develop from cells of the **nail matrix** that proliferate and become keratinized. The nail matrix, a region of the **nail root,** is located beneath the **proximal nail fold.** The stratum corneum of the proximal nail fold forms the **eponychium (cuticle),** which extends from the proximal end up on the nail for about 0.5 to 1 mm. Laterally, the skin turns under as **lateral nail folds,** forming the **lateral nail grooves;** the epidermis continues beneath the nail plate as the nail bed, and the nail plate occupies the position (and function) of the stratum corneum.

The white crescent observed at the proximal end of the nail is called the **lunula.** The distal end of the nail plate is not attached to the nail bed, which becomes continuous with the skin of the fingertip (or end of the toe). Near this junction is an accumulation of stratum corneum called the **hyponychium.**

Fingernails grow continuously at the rate of about 0.5 mm/week; toenails grow somewhat more slowly. The translucency of the fingernails provides a quick indication of the health of an individual; pinkness indicates a well-oxygenated blood supply.

Sebaceous glands

Except for the palms of the hands, soles of the feet, and sides of the feet inferior to the hairline, sebaceous glands are found throughout the body, embedded in the dermis and hypodermis. These glands are most abundant on the face, scalp, and the forehead. The secretory product of the sebaceous glands, **sebum,** is a wax-like, oily mixture of cholesterol, triglycerides, and secretory cellular debris. Sebum is believed to facilitate the maintenance of proper skin texture and hair flexibility (Fig. 17).

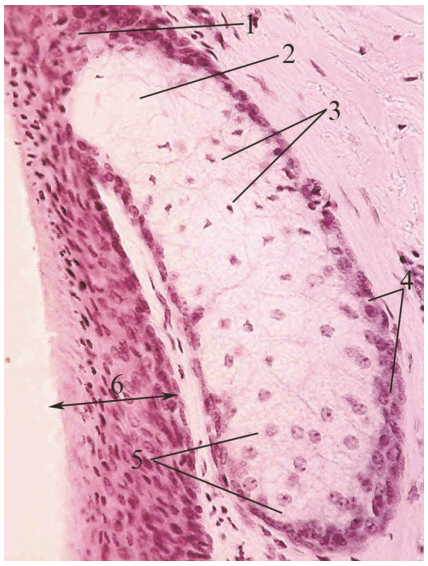

Fig. 17

Like apocrine sweat glands, sebaceous glands are appendages of hair follicles. The ducts of the sebaceous glands open into the upper third of the follicular canal, where they discharge their secretory product to coat the hair shaft and, eventually, the skin surface (see Fig. 14-8). The ducts of sebaceous glands in certain regions of the body lacking hair follicles (i.e., the lips, glans penis, areola of the nipples, labia minora, and mucous surface of the prepuce) open onto the surface of the skin to empty their secretions. Sebaceous glands are under the influence of sex hormones and increase their activity greatly after puberty.

RESPIRATORY SYSTEM

- Movement of air in and out of the lungs (**breathing** or **ventilation**)

- Exchange of O_2 in the inspired air for carbon dioxide in the blood **(external respiration)**
- Conveyance of O_2 and CO_2 to and from the cells **(transport of gases)**
- Exchange of CO_2 for O_2 in the vicinity of the cells **(internal respiration)**

The respiratory system is subdivided into two major components: the conducting portion and the respiratory portion. The **conducting portion,** situated both outside and within the lungs, conveys air from the external milieu to the lungs. The **respiratory portion,** located strictly within the lungs, functions in the actual exchange of oxygen for carbon dioxide (external respiration).

The respiratory system, comprising the lungs and a sequence of airways leading to the external environment, functions in providing oxygen (O_2) to and eliminating carbon dioxide (CO_2) from the cells of the body. The realization of this goal requires the fulfillment of the following four discrete events, collectively known as respiration:

The conducting portion of the respiratory system, listed in order from the exterior to the inside of the lung, is composed of the nasal cavity, mouth, nasopharynx, pharynx, larynx, trachea, primary bronchi, secondary bronchi (lobar bronchi), tertiary bronchi (segmental bronchi), bronchioles, and terminal bronchioles. These structures not only transport but also filter, moisten, and warm the inspired air before it reaches the respiratory portion of the lungs (Fig. 18).

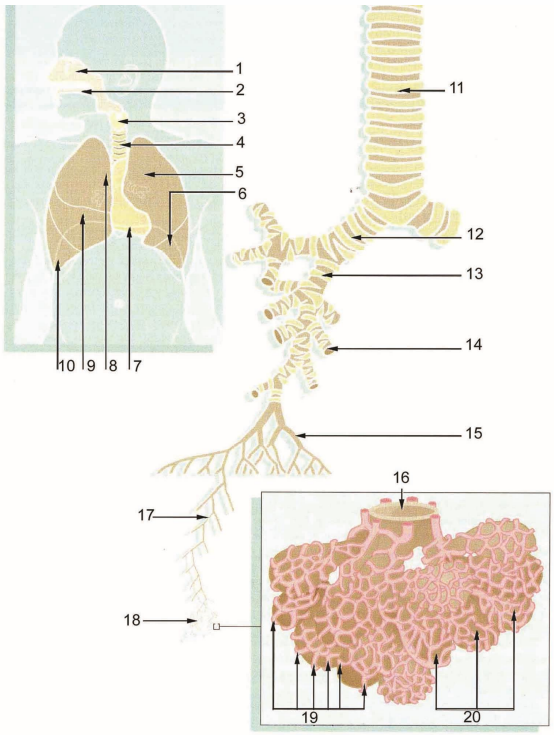

Fig. 18

The patency of the conducting airways is maintained by a combination of bone, cartilage, and fibrous elements. As the air progresses along the airway during inspiration, it encounters a branching system of tubules. Although the luminal diameter of each succeeding tubule continues to decrease, the *total* cross-sectional diameter of the various branches increases at each level of branching. As a result, the velocity of air flow for a given volume of inhaled air decreases as the air proceeds toward the respiratory portion.

The nasal cavity is divided into right and left halves by the cartilaginous and bony nasal septum. Each half of the nasal cavity is bounded laterally by a bony wall and a cartilaginous ala (wing) of the nose; it communicates with the outside, anteriorly, via the **naris** (nostril) and with the nasopharynx by way of the **choana.** Projecting from the bony lateral wall are three thin scroll-like bony shelves, situated one above the other: the superior, middle, and inferior **nasal conchae** (Fig. 19).

Except for the vestibule and the olfactory region, the nasal cavity is lined by pseudostratified ciliated columnar epithelium, frequently called the **respiratory epithelium** (see discussion of the trachea later), which is well endowed with goblet cells in the more posterior regions of the nasal cavity. The subepithelial connective tissue **(lamina propria)** is richly vascularized, especially in the region of the conchae and the anterior aspect of the nasal septum, housing large arterial plexuses and venous sinuses. The lamina propria has many seromucous glands and abundant lymphoid elements, including occasional lymphoid nodules, mast cells, and plasma cells. Antibodies produced by plasma cells (immunoglobulins IgA, IgE, and IgG) protect the nasal mucosa against inhaled antigens as well as against microbial invasion.

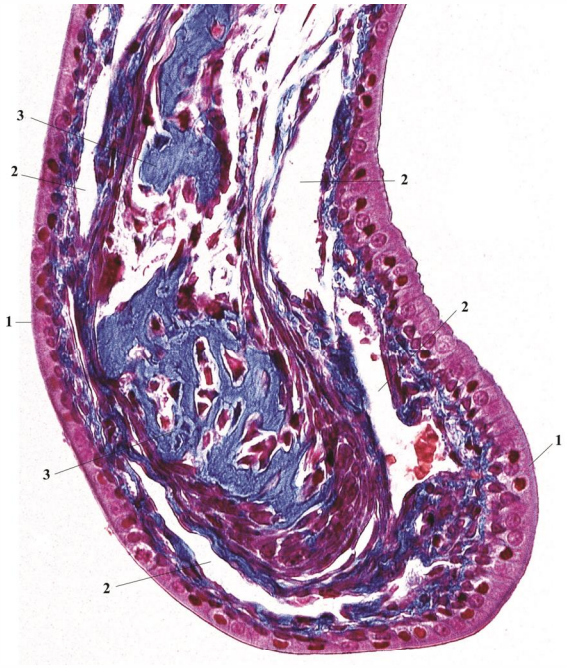

Fig. 19

Larynx

The larynx, situated between the pharynx and the trachea, is a rigid, short, cylindrical tube 4 cm in length and approximately 4 cm in diameter. It is responsible for phonation and prevents the entry of solids or liquids into the respiratory system during swallowing. The wall of the larynx is reinforced by several hyaline cartilages (the unpaired thyroid and cricoid cartilages and the inferior aspect of the paired arytenoids) and elastic cartilages (the unpaired epiglottis, the paired corniculate and cuneiform cartilages, and the superior aspect of the arytenoids). These cartilages are connected to one another by ligaments, and their movements with respect to one another are controlled by **intrinsic and extrinsic skeletal muscles (Fig. 20).**

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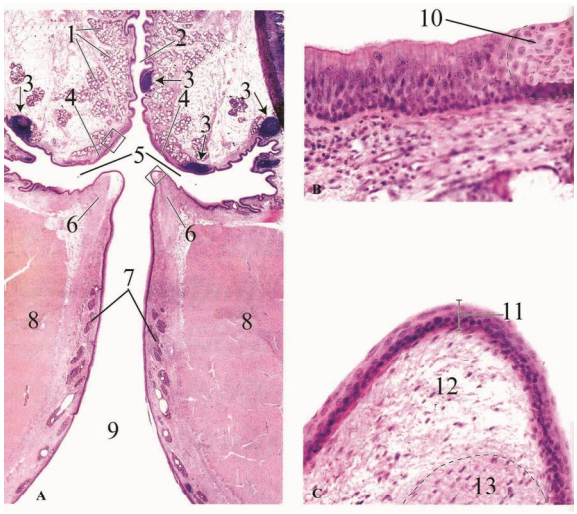

Fig. 20

The thyroid and cricoid cartilages form the cylindrical support for the larynx, whereas the epiglottis provides a cover over the laryngeal **aditus** (opening). During respiration, the epiglottis is in the vertical position, permitting the flow of air. During swallowing of food, fluids, or saliva, however, it is positioned horizontally, closing the laryngeal aditus; yet normally, even in the absence of an epiglottis, swallowed material bypasses the laryngeal opening. The arytenoid and corniculate cartilages are occasionally fused to each other, and most of the intrinsic muscles of the larynx move the two arytenoids with respect to each other and to the cricoid cartilage **(Fig. 20).**

The lumen of the larynx is characterized by two pairs of shelf-like folds, the superiorly positioned vestibular folds and the inferiorly placed vocal folds. The **vestibular folds** are immovable. Their lamina propria, composed of loose connective tissue, houses seromucous glands, adipose cells, and lymphoid elements. The free edge of each **vocal fold** is reinforced by dense, regular elastic connective tissue, the **vocal ligament.** The vocalis muscle, attached to the vocal ligament, assists the other intrinsic muscles of the larynx in altering the tension on the vocal folds. These muscles also regulate the width of the space between the vocal folds (the **rima glottidis**), thus permitting precisely regulated vibrations of their free edges by the exhaled air.

The larynx is lined by **pseudostratified ciliated columnar epithelium,** except on the superior surfaces of the epiglottis and vocal folds, which are covered by stratified squamous nonkeratinized epithelium. The cilia of the larynx beat toward the pharynx, transporting mucus and trapped particulate matter toward the mouth to be expectorated or swallowed.

Trachea

The trachea is a tube, 12 cm in length and 2 cm in diameter, that begins at the cricoid cartilage of the larynx and ends when it bifurcates to form the primary bronchi. The wall of the trachea is reinforced by 10 to 12 horseshoe-shaped hyaline cartilage rings **(C-rings).** The open ends of these rings face posteriorly and are connected to each other by smooth muscle, the trachealis muscle. Because of this arrangement of the C-rings, the trachea is rounded anteriorly but flattened posteriorly. The perichondrium of each C-ring is connected to the perichondria lying directly above and below it by fibroelastic connective tissue, which provides flexibility to the trachea and permits its elongation during inspiration. Contraction of the trachealis muscle decreases the diameter of the tracheal lumen, resulting in faster air flow, which assists in the

dislodging of foreign material (or mucus or other irritants) from the larynx by coughing (Fig. 21).

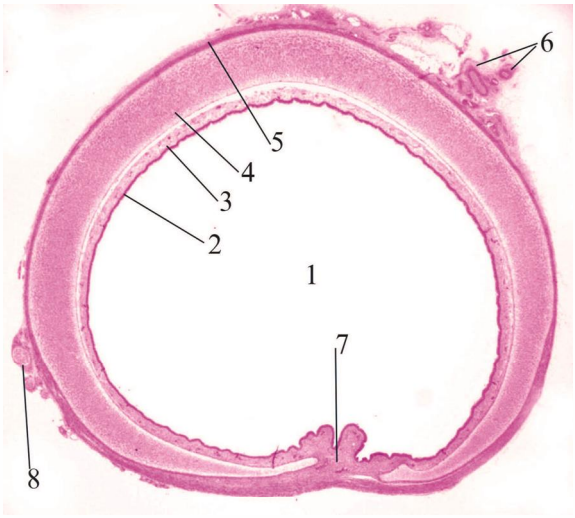

Fig. 21

The mucosal lining of the trachea is composed of pseudostratified ciliated columnar (respiratory) epithelium, the subepithelial connective tissue (lamina propria), and a relatively thick bundle of elastic fibers separating the mucosa from the submucosa (Fig. 22).

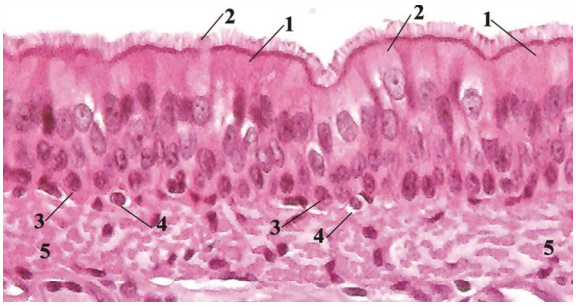

Fig. 22

The respiratory epithelium, a pseudostratified ciliated columnar epithelium, is separated from the lamina propria by a thick basement membrane. The epithelium is composed of six cell types: goblet cells, ciliated columnar cells, basal cells, brush cells, serous cells, and cells of the diffuse neuroendocrine system (DNES). All of these cells come into contact with the basement membrane, but they do not all reach the lumen.

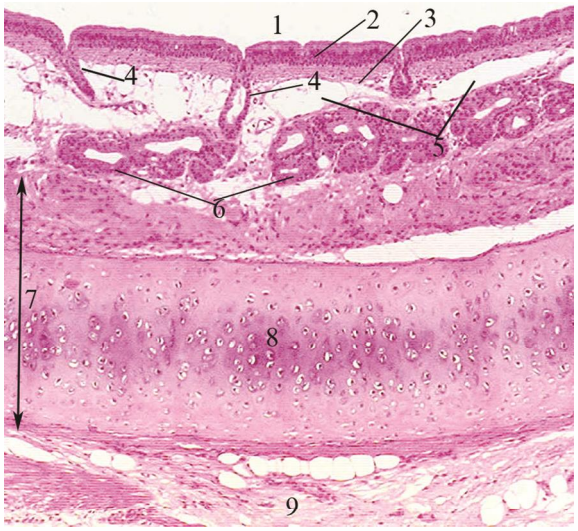

Fig. 23

Goblet cells constitute about 30% of the total cell population of the respiratory epithelium. They produce mucinogen, which becomes hydrated and is known as **mucin** when released into an aqueous environment. Like goblet cells elsewhere, goblet cells in the respiratory epithelium have a narrow, basally positioned **stem** and an expanded **theca** containing secretory granules. Electron micrography demonstrates that the nucleus and most organelles are located in the stem. This region displays a rich network of rough endoplasmic reticulum (RER), a well-developed Golgi complex, numerous mitochondria, and an abundance of ribosomes. The theca is filled with numerous mucinogen-containing secretory granules of varied diameters. The apical plasmalemma has a few short, blunt microvilli (Fig. 22, 23, 24).

Fig. 24

Ciliated columnar cells constitute approximately 30% of the total cell population. These tall, slender cells have a basally located nucleus and possess cilia and microvilli on their apical cell membrane (Fig. 24). The cytoplasm just below these structures is rich in mitochondria and has a Golgi complex. The remainder of the cytoplasm possesses some RER

and a few ribosomes. These cells move the mucus and its trapped particulate matter, via ciliary action, toward the nasopharynx for elimination.

The short **basal cells** constitute about 30% of the total cell population. They are located on the basement membrane, but their apical surfaces do not reach the lumen (see Fig. 24, 25). These relatively undifferentiated cells are considered to be stem cells that proliferate to replace defunct goblet, ciliated columnar, and brush cells.

Brush cells (small-granule mucous cells) constitute about 3% of the total cell population. They are narrow, columnar cells with tall microvilli. Their function is unknown, but they have been associated with nerve endings; thus, some investigators suggest that they may have a sensory role. Other investigators believe that brush cells are merely goblet cells that have released their mucinogen.

Serous cells, which make up about 3% of the total cell population of the respiratory epithelium, are columnar cells. They have apical microvilli and apical granules containing an electron-dense secretory product, a serous fluid of unknown composition.

DNES cells, also known as small-granule cells or Kulchitsky cells, constitute about 3% to 4% of the total cell population. Many of these cells possess long, slender processes that extend into the lumen, and it is believed that they have the ability to monitor the oxygen and carbon dioxide levels in the lumen of the airway. These cells are closely associated with naked sensory nerve endings with which they make synaptic contact, and together with these nerve fibers they are referred to as **pulmonary neuroepithelial bodies.** DNES cells contain numerous granules in their basal cytoplasm that house pharmacological agents such as amines, peptides, acetylcholine, and adenosine triphosphate. Under hypoxic conditions, these agents are released not only into the synaptic clefts but also into the connective tissue spaces of the lamina propria, where they act as paracrine hormones or may enter the vascular supply to act as hormones. Therefore, it has been suggested that these pulmonary neuroepithelial bodies can exert local effects to alleviate localized hypoxic conditions by regulating perfusion and ventilation in their vicinity or they may have generalized effects via the efferent nerve fibers that relay information about hypoxic conditions to the **respiratory regulators** located in the medulla oblongata.

The bronchial tree begins at the bifurcation of the trachea, as the right and left primary bronchi, which *arborize* (form branches that gradually decrease in size). The bronchial tree is composed of airways located outside the lungs (primary bronchi, extrapulmonary bronchi) and airways located inside the lungs: intrapulmonary bronchi (secondary and tertiary bronchi), bronchioles, terminal bronchioles, and respiratory bronchioles (Fig. 15-7). The bronchial tree divides 15 to 20 times before reaching the level of the terminal bronchioles. As the airways progressively decrease in size, several trends are observed, including a *decrease* in the amount of cartilage, the numbers of glands and goblet cells, and the height of epithelial cells and an *increase* in smooth muscle and elastic tissue (with respect to the thickness of the wall) (Fig. 25).

Each intrapulmonary bronchus is the airway to a lobe of the lung. These airways are similar to primary bronchi, with the following exceptions. The cartilage C-rings are replaced by irregular plates of hyaline cartilage that completely surround the lumina of the intrapulmonary bronchi; thus, these airways do not have a flattened region but are completely round. The smooth muscle is located at the interface of the fibroelastic lamina propria and submucosa as two distinct smooth muscle layers spiraling in opposite directions. Elastic fibers, which radiate from the adventitia, connect to elastic fibers arising from the adventitia of other parts of the bronchial tree.

As in the primary bronchi and in the trachea, seromucous glands and lymphoid elements are present in the lamina propria and the submucosa of the intrapulmonary bronchi. Ducts of these glands deliver their secretory products onto the surface of the pseudostratified, ciliated epithelial lining of the lumen. Lymphoid nodules are particularly evident where these airways branch to form increasingly smaller intrapulmonary bronchi. The smaller intrapulmonary bronchi

have thinner walls, decreasing amounts of hyaline cartilage plates, and shorter epithelium-lining cells.

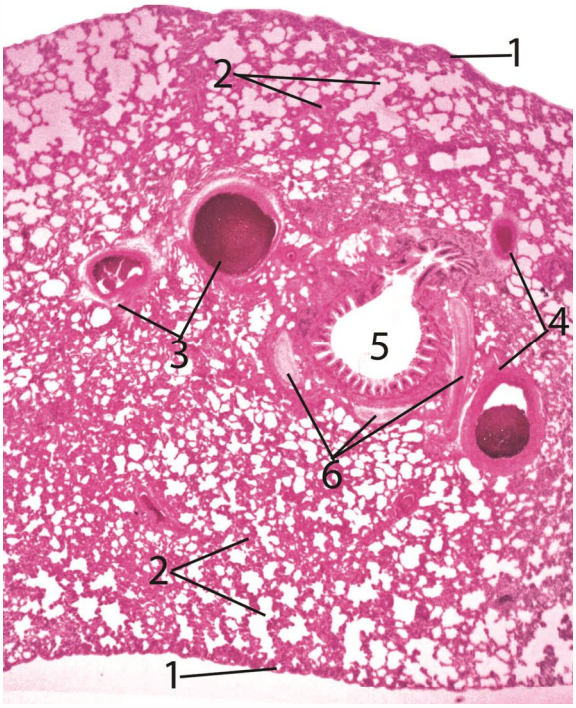

Fig. 25

Secondary bronchi, direct branches of the primary bronchi leading to the lobes of the lung, are also known as **lobar bronchi.** The left lung has two lobes and thus has two secondary bronchi; the right lung has three lobes and thus has three secondary bronchi.

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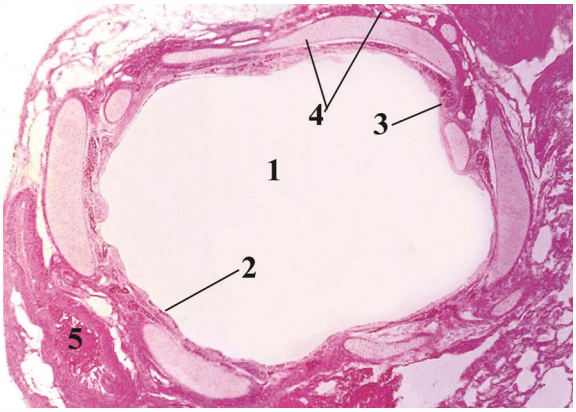

Fig. 26

As secondary bronchi enter the lobes of the lung, they subdivide into smaller branches, tertiary (segmental) bronchi. Each tertiary bronchus arborizes but leads to a discrete section of lung tissue known as a **bronchopulmonary segment.** Each lung has 10 bronchopulmonary segments that are completely separated from one another by connective tissue elements and are clinically important in surgical procedures involving the lungs (Fig. 25, 26).

Each bronchiole (or **primary bronchiole**) supplies air to a pulmonary lobule. Bronchioles are considered the 10th to 15th generation of dichotomous branching of the bronchial tree. Their diameter commonly is described as less than 1 mm, although this number varies among authors from 5 mm to 0.3 mm. This disagreement concerning the diameter of bronchioles may lead to confusion in the descriptions of their structure (but should not be regarded as a reason to complicate the life of the student). (Fig. 27, 28).

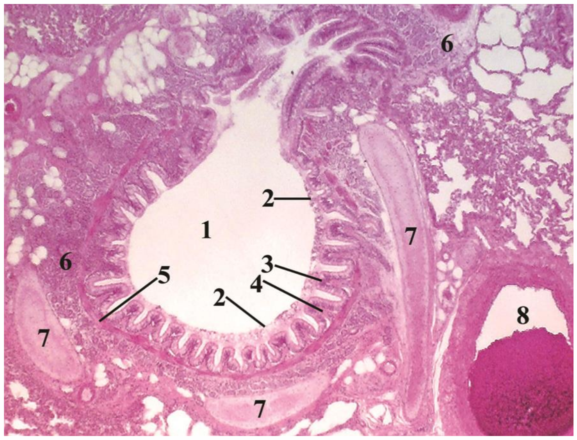

Fig. 27

The epithelial lining of bronchioles ranges from ciliated simple columnar with occasional goblet cells in larger bronchioles to simple cuboidal (many with cilia) with occasional Clara cells and no goblet cells in smaller bronchioles (Fig. 28).

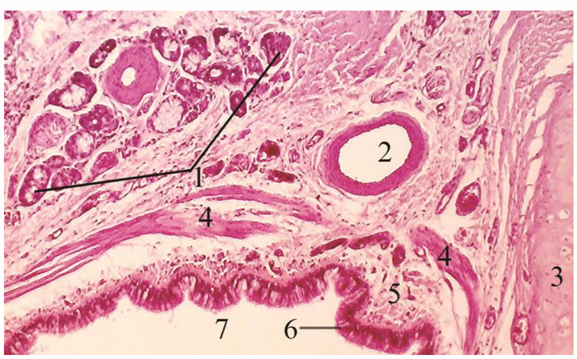

Fig. 28

Clara cells are columnar cells with dome-shaped apices that have short, blunt microvilli (Fig. 15-8). Their apical cytoplasm houses numerous secretory granules containing glycoproteins manufactured on their abundant RER. Clara cells are believed to protect the bronchiolar epithelium by lining it with their secretory product. Additionally, these cells degrade toxins in the inhaled air via cytochrome P-450 enzymes in their smooth endoplasmic reticulum. Some investigators suggest that Clara cells produce a surfactant-like material that reduces the surface tension of bronchioles and facilitates the maintenance of their patency. Moreover, Clara cells divide to regenerate the bronchiolar epithelium (Fig. 28).

The lamina propria of bronchioles has no glands; it is surrounded by a loose meshwork of helically oriented smooth muscle layers. The walls of bronchioles and their branches have no cartilage. Elastic fibers radiate from the fibroelastic connective tissue that surrounds the smooth

muscle coats of bronchioles. These elastic fibers connect to elastic fibers ramifying from other branches of the bronchial tree. During inhalation, as the lung expands in volume, the elastic fibers exert tension on the bronchiolar walls; by pulling uniformly in all directions, the elastic fibers help maintain the patency of the bronchioles.

Each bronchiole subdivides to form several smaller terminal bronchioles, which are less than 0.5 mm in diameter and constitute the terminus of the conducting portion of the respiratory system. These structures supply air to lung acini, subdivisions of the lung lobule. The epithelium of terminal bronchioles is composed of Clara cells and cuboidal cells, some with cilia. The narrow lamina propria consists of fibroelastic connective tissue and is surrounded by one or two layers of smooth muscle cells. Elastic fibers radiate from the adventitia and, as with bronchioles, bind to elastic fibers radiating from other members of the bronchial tree. Terminal bronchioles branch to give rise to respiratory bronchioles (Fig. 29, 30).

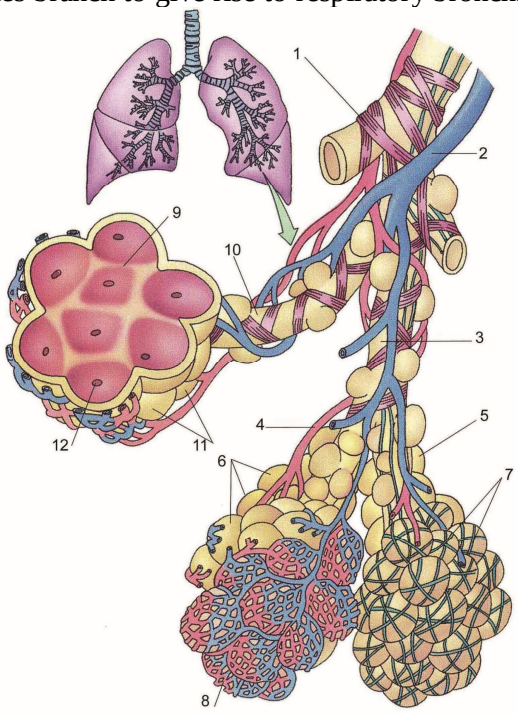

Fig. 29

The respiratory portion of the respiratory system is composed of respiratory bronchioles, alveolar ducts, alveolar sacs, and alveoli (Fig. 30, 31).

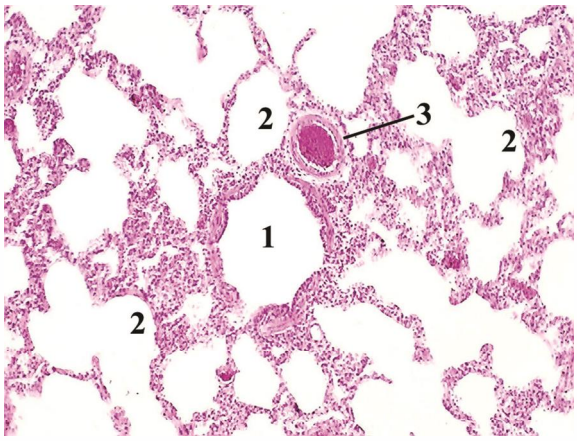

Fig. 30

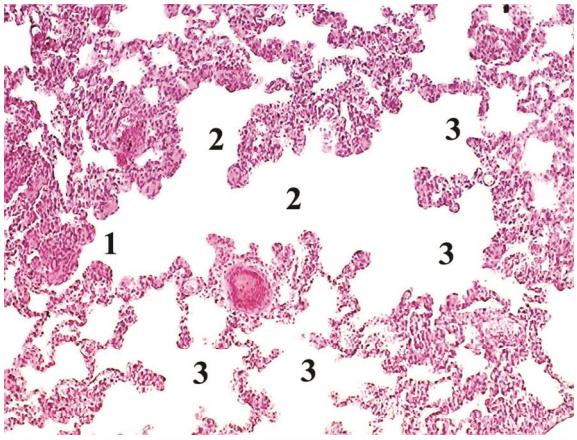

Fig. 31

Alveolar ducts do not have walls of their own; they are merely linear arrangements of alveoli. An alveolar duct that arises from a respiratory bronchiole branches, and each of the resultant alveolar ducts usually ends as a blind outpouching composed of two or more small clusters of alveoli, in which each cluster is known as an **alveolar sac.** These alveolar sacs thus open into a common space, which some investigators call the **atrium** (Fig. 31, 32).

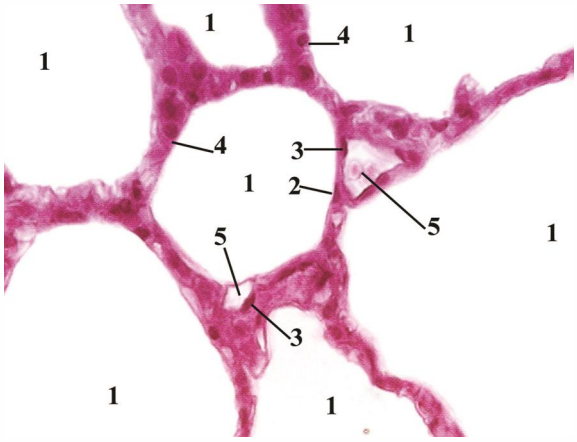

Fig. 32

Slender connective tissue elements between alveoli, the **interalveolar septa,** reinforce the alveolar duct, stabilizing it somewhat. Additionally, the opening of each alveolus to the alveolar duct is controlled by a single smooth muscle cell (smooth muscle "knob"), embedded in type III collagen, which forms a delicate sphincter regulating the diameter of the opening (Fig. 33, 34).

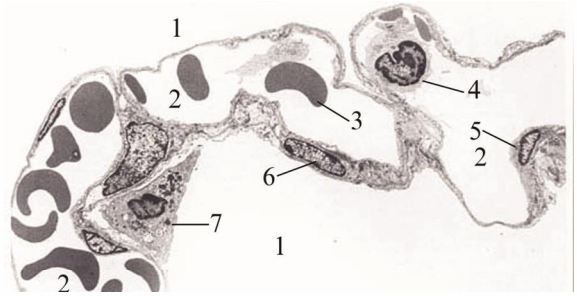

Fig. 33

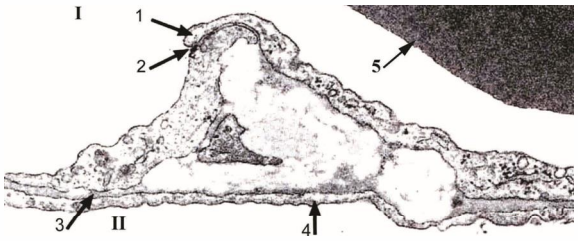

Fig. 34

Fine elastic fibers ramify from the periphery of alveolar ducts and sacs to intermingle with elastic fibers radiating from other intrapulmonary elements. This network of elastic fibers not only maintains the patency of these delicate structures during inhalation but also protects them against damage during distention and is responsible for nonforced exhalation.

Each **alveolus** is a small outpouching, about 200 εm in diameter, of respiratory bronchioles, alveolar ducts, and alveolar sacs (31, 33, 34). Alveoli form the primary structural and functional unit of the respiratory system, because their thin walls permit exchange of CO_2 for O_2 between the air in their lumina and blood in adjacent capillaries (Fig. 35). Although each alveolus is a small structure, about 0.002mm^3, their total number approximates 300 million, conferring on the lung its sponge-like consistency. It has been estimated that the total surface area of all the alveoli available for gas exchange exceeds 140 m^2.

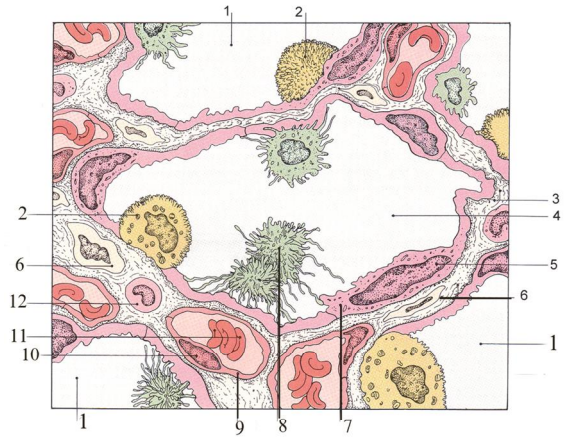

Fig. 35

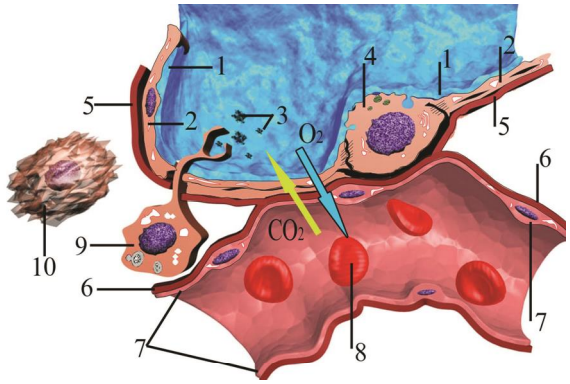

Fig. 36

Because of their large number, alveoli are frequently pressed against each other, eliminating the connective tissue interstitium between them. In such areas of contact, the air spaces of the two alveoli may communicate with each other through an **alveolar pore (pore of Kohn),** whose diameter varies from 8 to 60εm (see Fig. 36). These pores presumably function to equilibrate air pressure within pulmonary segments. The region between adjacent alveoli is known as the **interalveolar septum.** It is occupied by an extensive capillary bed composed of **continuous capillaries,** supplied by the pulmonary artery and drained by the pulmonary vein. The connective tissue of the interalveolar septum is rich in elastic fibers and type III collagen (reticular) fibers.

Approximately 95% of the alveolar surface is composed of simple squamous epithelium, whose cells are known as **type I pneumocytes** (also called **type I alveolar cells** and **squamous alveolar cells**). Because the cells of this epithelium are highly attenuated, their cytoplasm may be as thin as 80 nm in width (Fig. 34). The region of the nucleus is, as expected, wider, and it houses much of the cell's organelle population, composed of a small number of mitochondria, a few profiles of RER, and a modest Golgi apparatus.

Although **type II pneumocytes** (also known as **great alveolar cells, septal cells,** and **type II alveolar cells**) are more numerous than type I pneumocytes, they occupy only about 5% of the alveolar surface. These cuboidal cells are interspersed among, and form occluding junctions with, type I pneumocytes. Their dome-shaped apical surface juts into the lumen of the alveolus (Figs. 35, 36). Type II pneumocytes are usually located in regions where adjacent alveoli are separated from each other by a septum (hence the name septal cells), and their adluminal surface is covered by basal lamina.

Electron micrographs of type II pneumocytes display short, apical microvilli. They have a centrally placed nucleus, an abundance of RER profiles, a well-developed Golgi apparatus, and mitochondria. The most distinguishing feature of these cells is the presence of membrane-bound **lamellar bodies** that contain **pulmonary surfactant,** the secretory product of these cells.

The thinnest regions of the interalveolar septum where gases can be exchanged are called the blood-gas barriers. The narrowest blood-gas barrier, where type I pneumocytes are in intimate contact with the endothelial lining of the capillary and where the basal laminae of the two epithelia become fused, is most efficient for the exchange of O_2 (in the alveolar lumen) for CO_2 (in the blood). These regions are composed of the following structures:

- Surfactant and type I pneumocytes
- Fused basal laminae of type I pneumocytes and endothelial cells of the capillary
- Endothelial cells of the continuous capillary

The thoracic cage is separated into three regions: the left and right thoracic cavities and the centrally located mediastinum. Each thoracic cavity is lined by a serous membrane, the **pleura,** composed of simple squamous epithelium and subserous connective tissue. The pleura may be imagined as an inflated balloon; as the lung develops, it pushes against the serous membrane, as if a fist were pushing against the outer surface of a balloon. In this fashion, a portion of the pleura, the **visceral pleura,** covers and adheres to the lung, and the remainder of the pleura, the **parietal pleura,** lines and adheres to the walls of the thoracic cavity (Fig. 37).

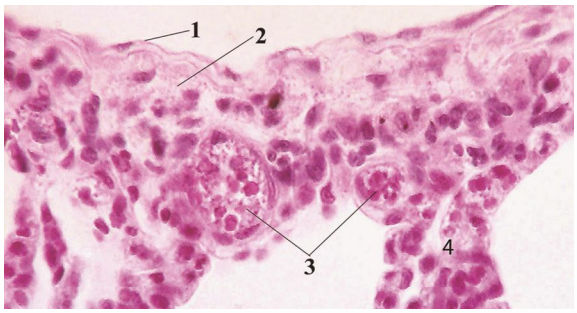

Fig. 37

The space between the visceral and parietal pleura (inside the balloon) is known as the **pleural cavity.** This space contains a slight amount of serous fluid (produced by the serous membranes) that permits a nearly frictionless movement of the lungs during **ventilation** (breathing), which involves air moving into the lungs (inhalation) and out of the lungs (exhalation).