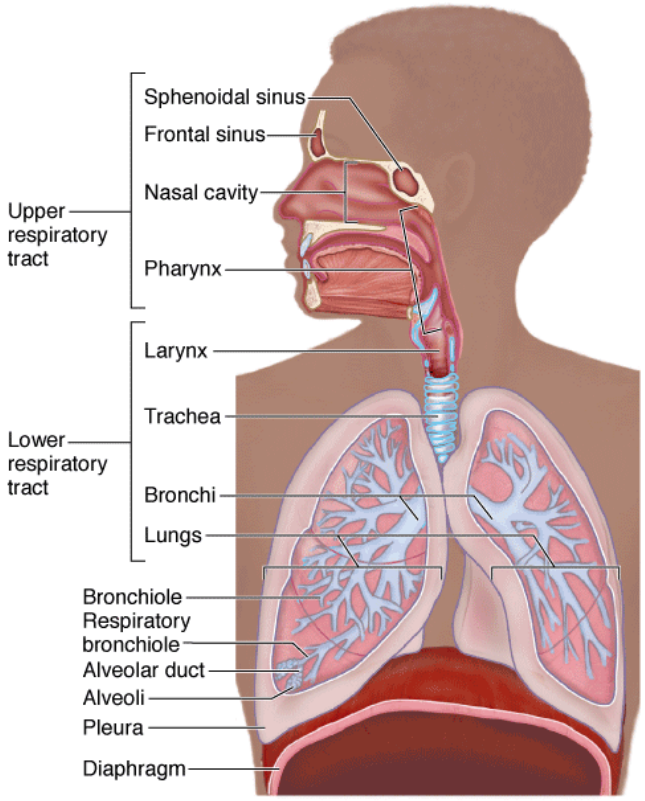
THE RESPIRATORY SYSTEM: INTRODUCTION

The respiratory system includes the **lungs** and a branching system of tubes that link the sites of gas exchange with the external environment. Air is moved through the lungs by a ventilating mechanism, consisting of the thoracic cage, intercostal muscles, diaphragm, and elastic components of the lung tissue. The respiratory system is divided anatomically into structures of the upper and lower respiratory tracts (Figure 17–1). Functionally, these structures make up the system's **conducting portion**, which consists of the nasal cavities, nasopharynx, larynx, trachea, bronchi (Gr. *bronchos,* windpipe), bronchioles, and terminal bronchioles; and a **respiratory portion** (where gas exchange takes place), consisting of respiratory bronchioles, alveolar ducts, and alveoli. **Alveoli** are saclike structures that make up the greater part of the lungs. They are the main sites for the principal function of the lungs—the exchange of O_2 and CO_2 between inspired air and blood.

Figure 17–1.



Anatomy of the respiratory system.

Anatomically, the respiratory tract has upper and lower parts. Histologically and functionally, the respiratory system has a **conducting portion**, which consists of all the components that condition air and bring it into the lungs, and a **respiratory portion**, where gas exchange actually occurs, consisting of respiratory bronchioles, alveolar ducts, and alveoli in the lungs. Portions of two sets of paranasal sinuses are shown here.

The conducting portion serves two main functions: to provide a conduit through which air moves to and from the lungs and to condition the inspired air. To ensure an uninterrupted supply of air, a combination of cartilage, elastic and collagen fibers, and smooth muscle provides the conducting portion with rigid structural support and the necessary flexibility and extensibility.

RESPIRATORY EPITHELIUM

Most of the conducting portion is lined with ciliated pseudostratified columnar epithelium known as **respiratory epithelium** (Figure 17–2). This epithelium has at least five cell types, all of which touch the thick basement membrane:

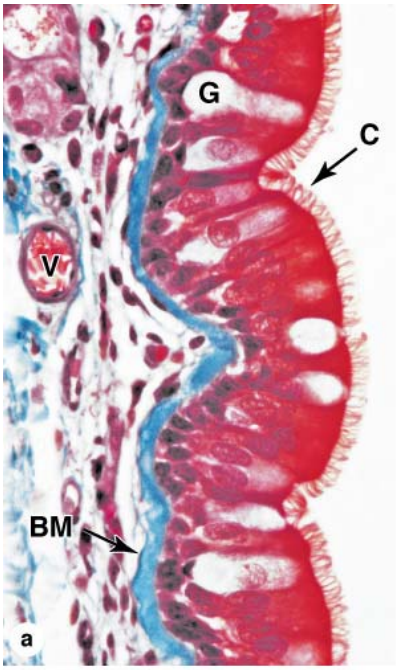
- **Ciliated columnar cells** (described in Chapter 2) are the most abundant, each with about 300 cilia on its apical surface (Figure 17–2).

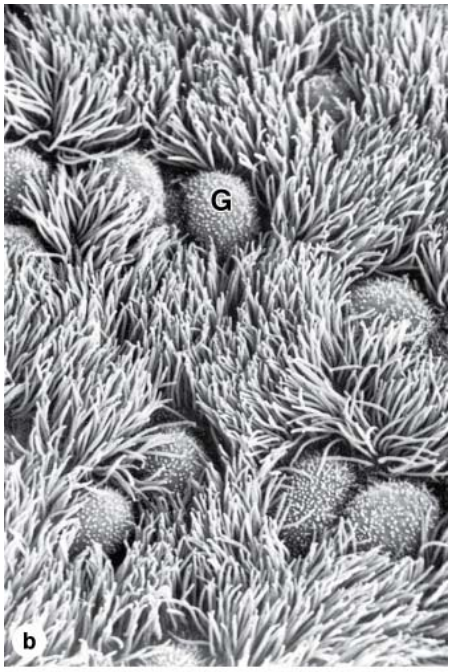
MEDICAL APPLICATION

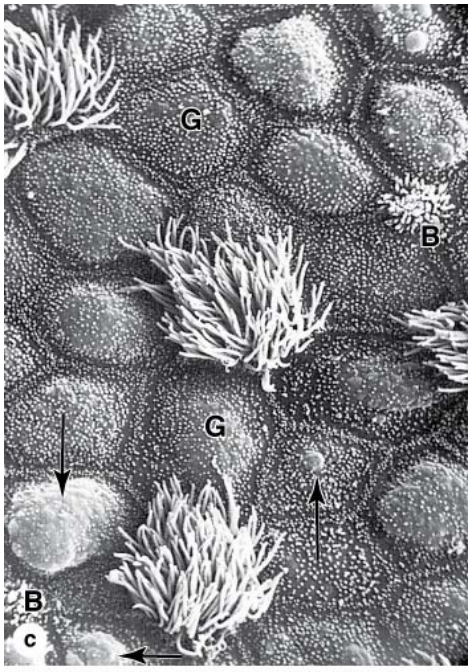
Immotile cilia syndrome, a disorder that causes infertility in men and chronic respiratory tract infections in both sexes, is caused by immobility of cilia and flagella induced, in some cases, by deficiency of **dynein,** a protein normally present in the cilia. Dynein participates in the ciliary movement (see Chapter 2).

- **Goblet cells** are also abundant in some areas of the respiratory epithelium (Figure 17–2), filled in their apical portions with granules of mucin glycoproteins.
- **Brush cells** are a much more sparsely scattered and less easily found, columnar cell type, which has a small apical surface bearing a tuft of many short, blunt microvilli (Figure 17–2c). Brush cells express some signal transduction components like those of gustatory cells and have afferent nerve endings on their basal surfaces and are considered to be chemosensory receptors.
- **Small granule cells** are also difficult to distinguish in routine preparations, but possess numerous dense core granules 100–300 nm in diameter. Like brush cells, they represent about 3% of the total cells and are part of the diffuse neuroendocrine system (Chapter 20).
- **Basal cells**, small rounded cells on the basement membrane and not extending to the luminal surface, are stem cells that give rise to the other cell types.

Figure 17–2.







Respiratory epithelium.

Respiratory epithelium is the classic example of pseudostratified ciliated columnar epithelium. **(a):** Details of its structure vary in different regions of the respiratory tract, but it usually rests on a very thick basement membrane (BM) and has several cell types, some columnar, some basal and all contacting the basement membrane. Ciliated columnar cells are the most abundant, with hundreds of long robust cilia (C) on each of their bulging apical ends which provide a lush cover of cilia on the luminal surface. Most of the small rounded cells at the basement membrane are stem cells and their differentiating progeny, which together make up about 30% of the epithelium. Intraepithelial lymphocytes and dendritic cells are also present in respiratory epithelium. Mucus-secreting goblet cells (G) are also present. The lamina propria is well-vascularized (V). X400. Mallory trichrome. **(b):** SEM shows the luminal surface of goblet cells (G) among the numerous ciliated cells. X2500. **(c):** As shown by SEM of another region, goblet cells (G) predominate in some areas, with subsurface accumulations of mucus evident in some (arrows). The film of mucus traps most airborne dust particles and microorganisms and the ciliary movements continuously propel the sheet of mucus toward the esophagus for elimination. Other columnar cells, representing only about 3% of the cells in respiratory epithelium, are brush cells (B) with small apical surfaces bearing a tuft of short, blunt microvilli. Brush cells have features of chemosensory receptors but their physiological significance is highly uncertain. X3000. (Figure 17–2b and 17–2c reprinted, with permission, from John Wiley & Sons, Inc., Am. J. Anat. 1974;139:421. Copyright © 1974.)

MEDICAL APPLICATION

From the nasal cavities through the larynx, portions of the epithelial lining are stratified squamous. This type of epithelium is evident in regions exposed to direct airflow or physical abrasion (eg, oropharynx, epiglottis, vocal folds); it provides more protection from wear and abrasion than does respiratory epithelium. In smokers the proportion of ciliated cells to goblet cells is altered to aid in clearing the increased particulate and gaseous pollutants (eg, CO, SO_2). Although the greater numbers of goblet cells in a smoker's epithelium provide for a more rapid clearance of pollutants, the reduction in ciliated cells caused by excessive intake of CO results in decreased movement of the mucus layer and frequently leads to congestion of the smaller airways.

NASAL CAVITIES

The left and right nasal cavity each has two components: the external **vestibule** and the internal **nasal cavities (or fossae).** The vestibule is the most anterior and dilated portion of each nasal cavity. Skin of the nose enters the **nares** (nostrils) partway up the vestibule and has sweat glands, sebaceous glands, and short coarse **vibrissae** (hairs) that filter out particulate material from the inspired air. Within the vestibule, the epithelium loses its keratinized nature and undergoes a transition into typical respiratory epithelium before entering the nasal fossae.

The nasal cavities lie within the skull as two cavernous chambers separated by the osseous **nasal septum.** Extending from each lateral wall are three bony shelflike projections (Figure 17–1) called **conchae**. The middle and inferior conchae are covered with respiratory epithelium; the superior conchae are covered with a specialized **olfactory epithelium.** The narrow passages between the conchae improve the conditioning of the inspired air by increasing the surface area of moist, warm respiratory epithelium and by slowing and increasing turbulence in the airflow. The result is increased contact between air streams and the mucous layer. Within the lamina propria of the conchae are large venous plexuses known as **swell bodies**. Every 20–30 minutes, the swell bodies on one side become temporarily engorged with blood, resulting in distension of the conchal mucosa and a concomitant decrease in the flow of air. During this time, most of the air is directed through the other nasal fossa, allowing the engorged respiratory mucosa to recover from dehydration.

MEDICAL APPLICATION

Allergic reactions and inflammation can cause abnormal engorgement of swell bodies in both fossae, severely restricting the air flow. The abundance of thin-walled venules in the lining of the nasal cavities and their proximity to the epithelial surface explains why nosebleeds occur so commonly.

In addition to swell bodies, the nasal cavities' mucosa has a rich vascular system with a complex organization. Large vessels form a close-meshed latticework next to the underlying periosteum, from which arcading branches lead toward the surface. Blood in these vessels flows from the rear of the cavities in a direction opposite to that of the inspired air, transferring heat to warm it quickly.

A major function of the entire conducting portion is to condition inspired air by cleaning, moistening, and warming it before it enters the lungs. In addition to the moist vibrissae, the rich vasculature in the lamina propria, and the ciliated and mucus-secreting cells of respiratory epithelium, conditioning also involves numerous mucous and serous glands in the mucosa. Once the air reaches the nasal fossae, particulate and gaseous impurities are trapped in a layer of mucus. This mucus, in conjunction with serous secretions, also serves to moisten the incoming air, protecting the delicate alveoli of the lungs from desiccation.

Smell (Olfaction)

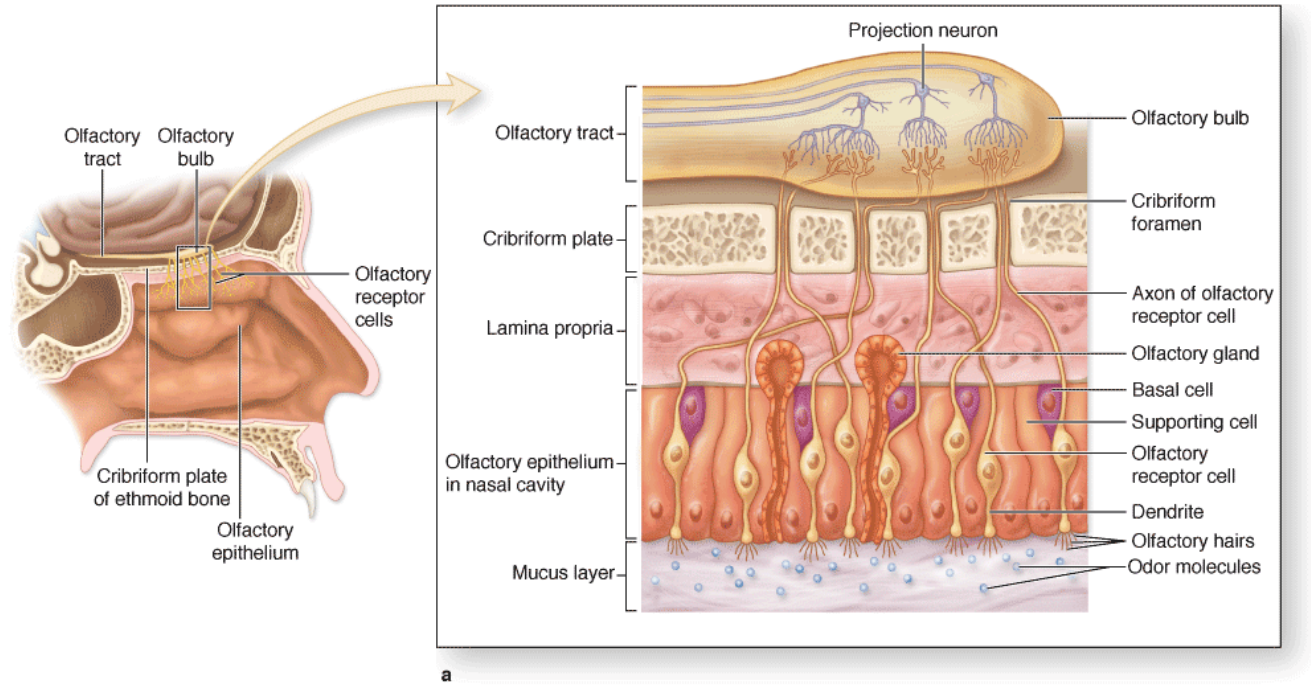
The olfactory chemoreceptors are located in the **olfactory epithelium**, a specialized region of the mucous membrane covering the superior conchae at the roof of the nasal cavity. In humans, it is about 10 cm^2 in area and up to 100 µm in thickness. It is a pseudostratified columnar epithelium composed of three types of cells (Figure 17–3):

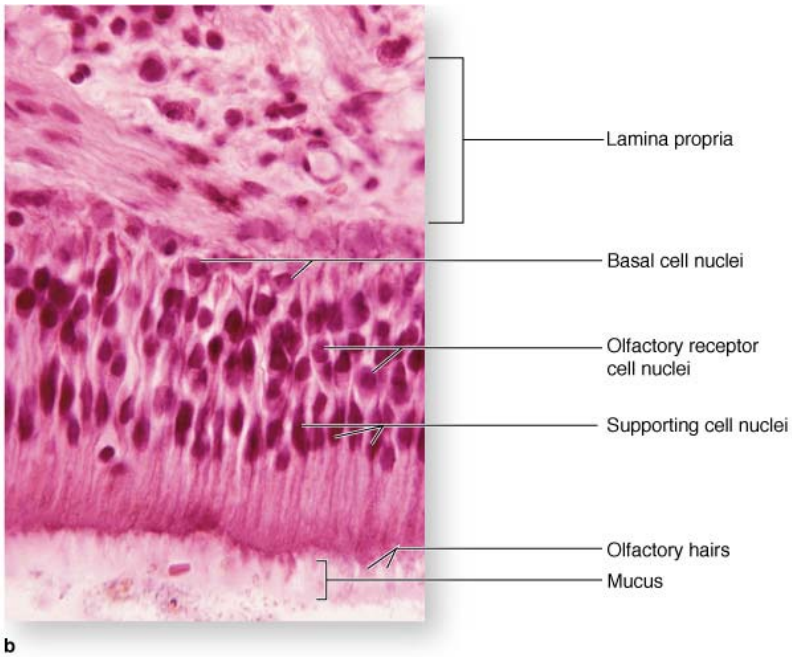
- **Basal cells** are small, spherical or cone-shaped and form a layer at the basal lamina. They are the stem cells for the other two types.
- **Supporting cells** are columnar, with broad, cylindrical apexes and narrower bases. On their free surface are microvilli submerged in a fluid layer.

Well-developed junctional complexes bind the supporting cells to the adjacent olfactory cells. The supportive role of these cells is not well-understood, but they express abundant ion channels whose function appears to be required to maintain a microenvironment conducive to olfactory function and survival.

- **Olfactory neurons** are bipolar neurons present throughout this epithelium. They are distinguished from supporting cells by the position of their nuclei, which lie between those of the supporting cells and the basal cells. The dendrite end of each olfactory neuron is the apical (luminal) pole of the cell and has a knoblike swelling with about a dozen basal bodies. From the basal bodies emerge long nonmotile cilia with defective axonemes but a considerable surface area for membrane chemoreceptors. These receptors respond to odoriferous substances by generating an action potential along the (basal) axons of these neurons, which leave the epithelium and unite in the lamina propria as very small nerves which then pass through foramina in the cribriform plate of the ethmoid bone to the brain (Figure 17–3). There they form cranial nerve I, the olfactory nerve, and eventually synapse with other neurons in the olfactory bulb.

Figure 17–3.





Olfactory epithelium.

(a, b): The olfactory epithelium covers the superior conchae bilaterally and sends axons from throughout its entire 10 cm^2 area to the brain via small openings in the cribriform plate of the ethmoid bone. It is a pseudostratified epithelium, containing basal stem cells and columnar support cells in addition to the bipolar olfactory neurons. The dendrites of these neurons are at the luminal ends and have cilia specialized with many membrane receptors for odor molecules. Binding such ligands causes depolarization which passes along basal axons to the olfactory bulb of the brain X200. H&E.

The lamina propria of the olfactory epithelium possesses large serous glands (glands of Bowman), which produce a flow of fluid surrounding the olfactory cilia and facilitating the access of new odoriferous substances.

MEDICAL APPLICATION

The olfactory neurons are some of the only neurons to be replaced regularly and constantly due to regenerative activity of the epithelial stem cells from which they arise. For this reason loss of the sense of smell due to toxic fumes or physical injury to the epithelium is usually temporary. However damage to the ethmoid bone at the base of the skull can shear the olfactory axons and lead to more permanent loss of olfaction if axonal regeneration through the cribriform plate is also blocked.

SINUSES & NASOPHARYNX

The **paranasal sinuses** are bilateral cavities in the frontal, maxillary, ethmoid, and sphenoid bones of the skull (Figure 17–1). They are lined with a thinner respiratory epithelium with fewer goblet cells. The lamina propria contains only a few small glands and is continuous with the underlying periosteum. The paranasal sinuses communicate with the nasal cavities through small openings and mucus produced in the sinuses is moved into the nasal passages by the activity of the ciliated epithelial cells.

MEDICAL APPLICATION

Sinusitis is an inflammatory process of the sinuses that may persist for long periods of time, mainly because of obstruction of drainage orifices. Chronic sinusitis and bronchitis are components of immotile cilia syndrome, which is characterized by defective ciliary action.

Posterior to the nasal cavities, the **nasopharynx** is the first part of the pharynx, continuing caudally with the oropharynx, the posterior part of the oral cavity (Figure 17–1). It is lined with respiratory epithelium and contains the medial pharyngeal tonsil and the bilateral openings of the auditory tubes to each middle ear.

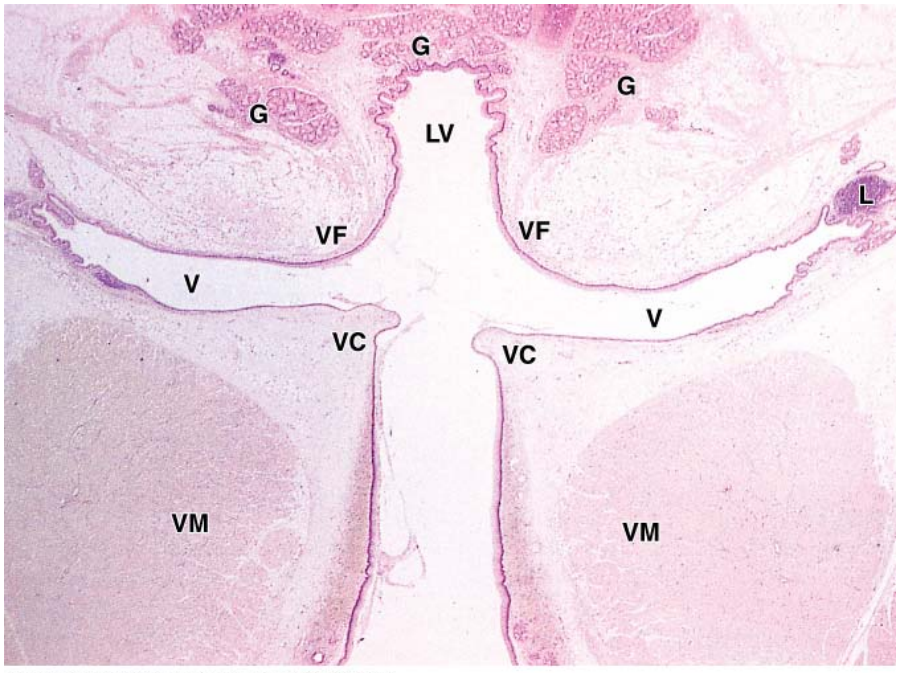
LARYNX

The **larynx** is a rigid, short (4 cm x 4 cm) passage for air between the pharynx and the trachea (Figure 7–1). Its wall is reinforced by hyaline cartilage (in the thyroid, cricoid, and the inferior arytenoid cartilages) and smaller elastic cartilages (in the epiglottis, cuneiform, corniculate, and the superior arytenoid cartilages), all connected by ligaments. In addition to maintaining an open airway, movements of these cartilages by skeletal muscles participate in sound production during phonation and the epiglottis serves as a valve to prevent swallowed food or fluid from entering the trachea.

The **epiglottis,** which projects from the upper rim of the larynx, extends into the pharynx and has lingual and laryngeal surfaces. The entire lingual surface and the apical portion of the laryngeal surface are covered with stratified squamous epithelium. At variable points on the laryngeal surface of the epiglottis the epithelium undergoes a transition to ciliated pseudostratified columnar epithelium. Mixed mucous and serous glands are found in the lamina propria beneath the epithelium.

Below the epiglottis, the mucosa of the larynx extends two pairs of folds bilaterally into the lumen (Figure 17–4). The upper pair, the **vestibular folds** or **false vocal cords**, is partly covered with typical respiratory epithelium beneath which lie numerous seromucous glands. The lower pair of folds constitutes the **vocal folds** or vocal cords. These are covered with stratified squamous epithelium and contain bundles of parallel elastic fibers (vocal ligament) and large bundles of striated **vocalis muscles**. The muscles regulate the tension of each vocal fold and its ligaments. As expelled air is forced between the folds, variable tension in these vocal cords produces different sounds. All structures and spaces in the respiratory tract above the vocal folds are involved in modifying the resonance of the sounds.

Figure 17–4.



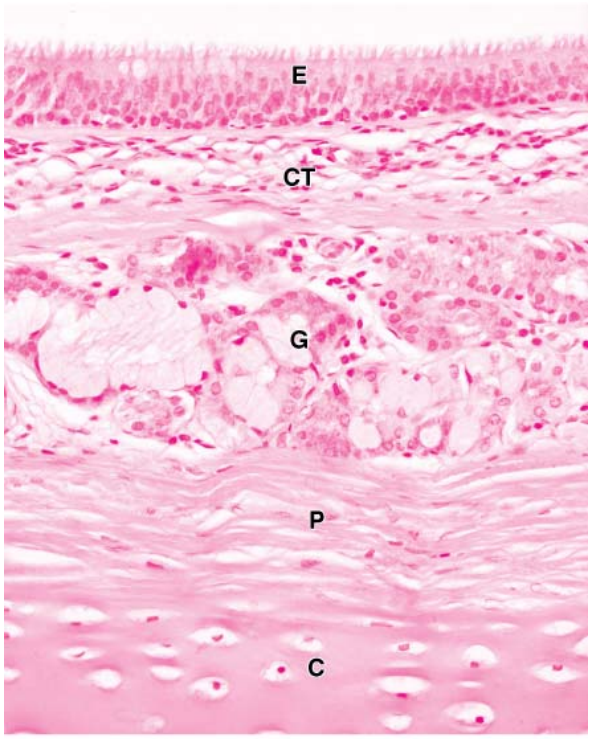
Larynx.

The larynx is a short passageway for air between the pharynx and trachea. Its wall contains skeletal muscles and pieces of cartilage, all of which make the larynx specialized for sound production. The low-power micrograph shows the upper laryngeal vestibule (LV), which is surrounded by seromucous glands (G). The lateral walls of this region bulge as a pair of broad folds, the vestibular folds (VF). These also contain seromucous glands and areolar tissue with MALT, often with lymphoid nodules (L) and are largely covered by respiratory epithelium, with regions near the epiglottis having stratified squamous epithelium. Below each large vestibular fold is a narrow space or ventricle (V), below which is another pair of lateral folds, the vocal folds or cords (VC). These are covered by stratified squamous epithelium and project more sharply into the lumen, defining the rim of the opening into the larynx itself. Each contains a large striated vocalis muscle (VM) and nearer the surface a small ligament, which is cut transversely and therefore difficult to see here. Variable tension of these ligaments caused by the muscles produces different sounds as air is expelled across the vocal cords. All the structures and spaces above these folds add resonance to the sounds and assist in phonation. X15. H&E.

TRACHEA

The **trachea** is 12-14 cm long and lined with a typical respiratory mucosa (Figure 17–5). In the lamina propria numerous seromucous glands produce watery mucus and in the submucosa 16–20 C-shaped rings of hyaline cartilage keep the tracheal lumen open (Figure 17–6). The open ends of the cartilage rings are on the posterior surface, against the esophagus, and are bridged by a bundle of smooth muscle (**trachealis muscle**) and a sheet of fibroelastic tissue attached to the perichondrium. The entire organ is surrounded by adventitia.

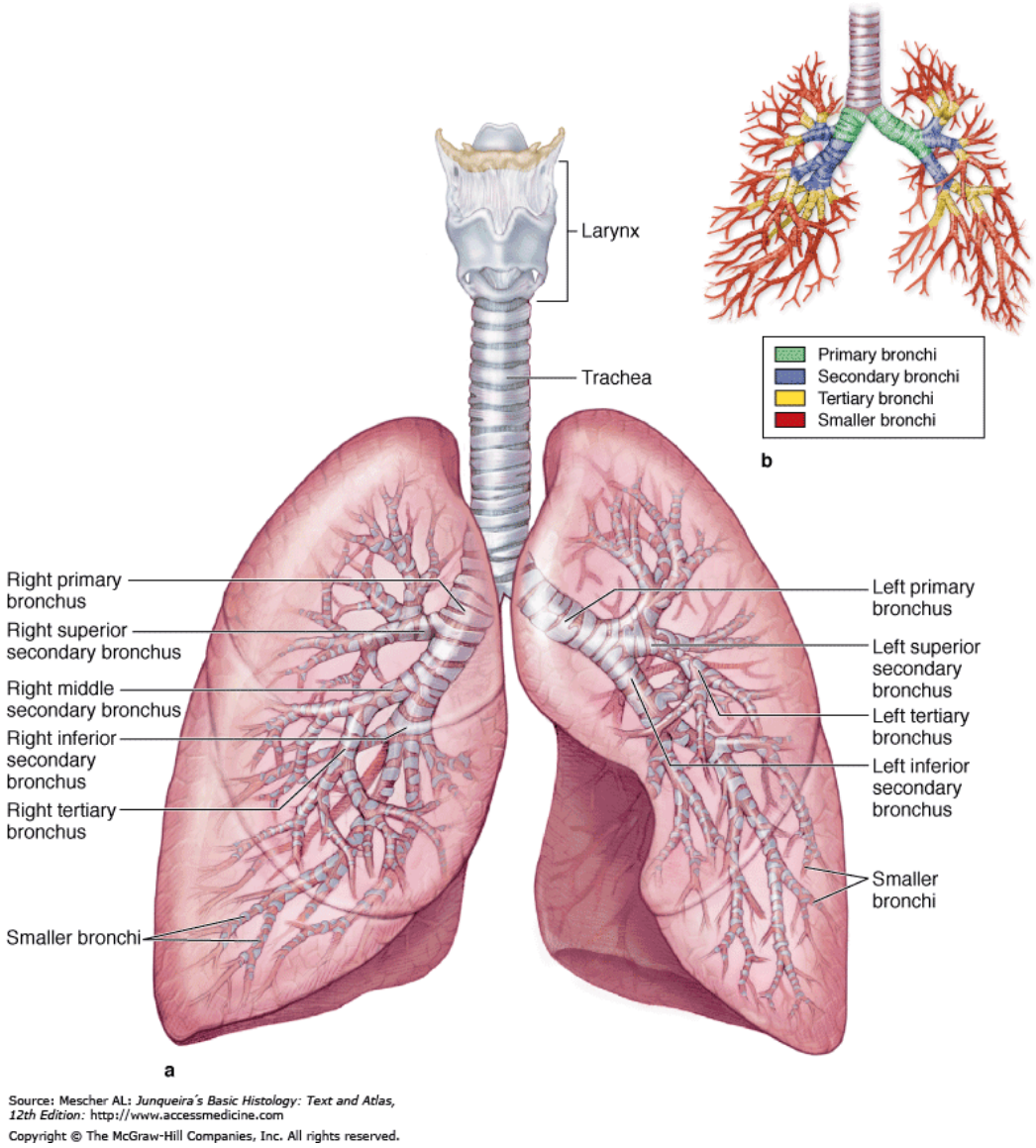
Figure 17–5.



Trachea.

The wall of the trachea is lined by typical respiratory epithelium (E) underlain by connective tissue (CT) and seromucous glands (G) in the lamina propria. The submucosa contains C-shaped rings of hyaline cartilage (C) covered by perichondrium (P). The watery mucous fluid produced by goblet cells and by the glands forms a layer that permits the ciliary movement to propel foreign particles continuously out of the respiratory system in the mucociliary escalator. The openings in the cartilage rings are on the posterior surface, against the esophagus, and contain smooth muscle and elastic tissue. These allow distention of the tracheal lumen when large pieces of food pass through the esophagus. The trachealis muscle in the opening of the C also contracts during the cough reflex to narrow the tracheal lumen and produce stronger expulsion of air and dislodged mucus in the air passages. X50. H&E.

Figure 17–6.



Bronchial tree.

The trachea bifurcates as right and left primary bronchi that enter the hilum on the posterior side of each lung along with the pulmonary vessels, lymphatics, and nerves. **(a):** Within each lung bronchi subdivide further to form the bronchial tree, the last component of the air conducting system**. (b):** Diagram shows color-coding of the major branches of the bronchial tree.

The trachealis relaxes during swallowing to facilitate the passage of food by allowing the esophagus to bulge into the lumen of the trachea, with the elastic layer preventing excessive distention of the lumen. In the cough reflex the muscle contracts to narrow the tracheal lumen and provide for increased velocity of the expelled air and better loosening of material in the air passage.

BRONCHIAL TREE & LUNG

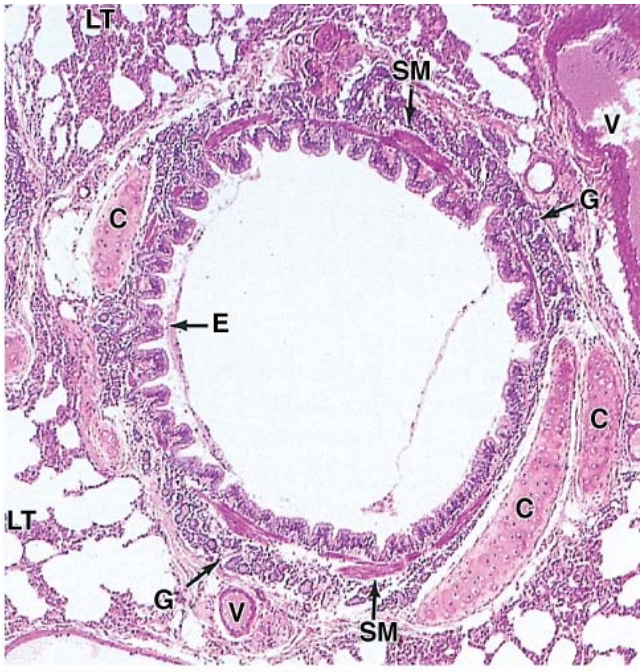
The trachea divides into two **primary bronchi** that enter the lungs at the hilum, along with arteries, veins, and lymphatic vessels. After entering the lungs, the primary bronchi course downward and outward, giving rise to three **secondary** (**lobar**) **bronchi** in the right lung and two in the left lung (Figure 17–6), each of which supplies a pulmonary lobe. These lobar bronchi again divide, forming **tertiary** (**segmental**) **bronchi**. Each of these tertiary bronchi, together with the smaller branches it supplies, constitutes a **bronchopulmonary segment**—approximately 10–12% of each lung with its own connective tissue capsule and blood supply. The existence of such lung segments facilitates the specific surgical resection of diseased lung tissue without affecting nearby healthy tissue.

The tertiary bronchi give rise to smaller and smaller bronchi, whose terminal branches are called **bronchioles**. Each bronchiole enters a pulmonary lobule, where it branches to form five to seven **terminal bronchioles.** The pulmonary lobules are pyramid-shaped, with the apex directed toward the pulmonary hilum. Each lobule is delineated by a thin connective tissue septum, best seen in the fetus. In adults these septa are frequently incomplete, resulting in a poor delineation of the lobules. Moving through the smaller bronchi and bronchioles toward the respiratory portion, the histologic organization of both the epithelium and the underlying lamina propria gradually becomes more simplified.

Bronchi

Each primary bronchus branches repeatedly, with each branch becoming progressively smaller until it reaches a diameter of about 5 mm. The mucosa of the larger bronchi is structurally similar to the tracheal mucosa except for the organization of cartilage and smooth muscle (Figure 17–7). In the primary bronchi most cartilage rings completely encircle the lumen, but as the bronchial diameter decreases, cartilage rings are gradually replaced with isolated plates of hyaline cartilage. Abundant mucous and serous glands are also present, with ducts opening into the bronchial lumen. In the bronchial lamina propria is a layer of crisscrossing bundles of spirally arranged smooth muscle (Figures 17–7 and 17–8), which become more prominent in the smaller bronchial branches. Contraction of this muscle layer is responsible for the folded appearance of the bronchial mucosa observed in histologic section.

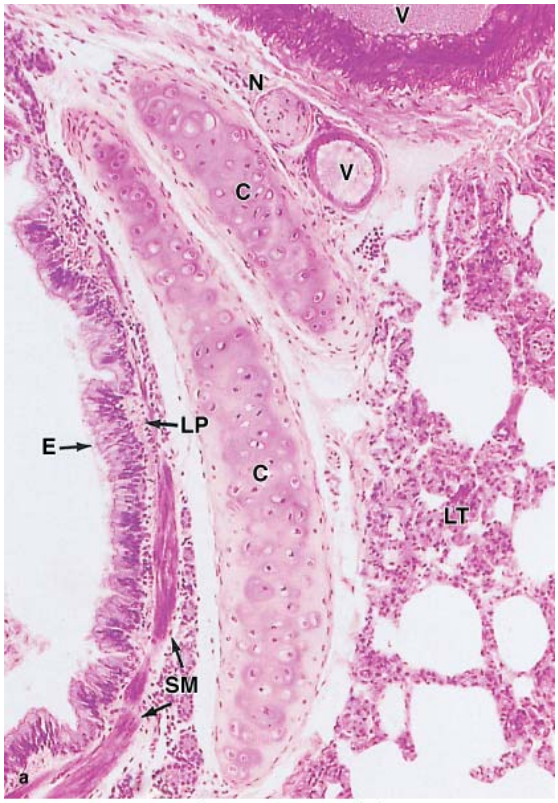
Figure 17–7.

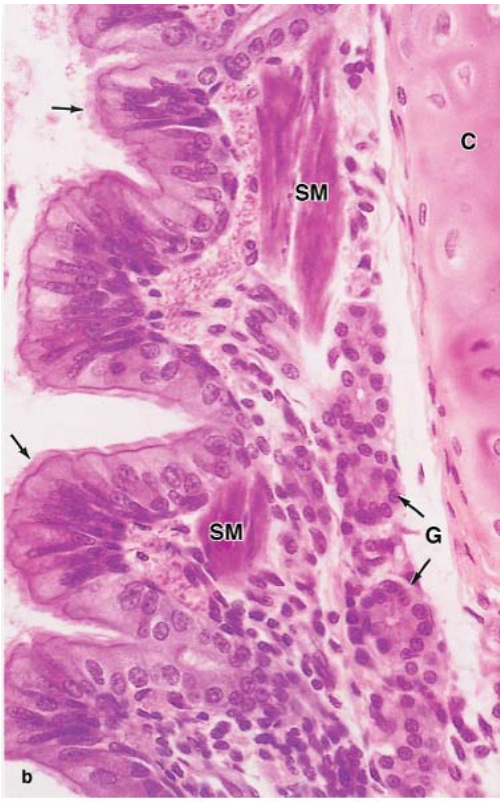


Tertiary (segmental) bronchus.

In a cross-section of a large bronchus the lining of respiratory epithelium (E) and the mucosa are folded due to contraction of its smooth muscle (SM). At this stage in the bronchial tree, the wall is also surrounded by many pieces of hyaline cartilage (C) and contains many seromucous glands (G) in the submucosa which drain into the lumen. In the connective tissue surrounding the bronchi can be seen arteries and veins (V), which are also branching as smaller and smaller vessels in the approach to the respiratory bronchioles. All bronchi are surrounded by distinctive lung tissue (LT) showing the many empty spaces of pulmonary alveoli. X56. H&E.

Figure 17–8.





Bronchial wall.

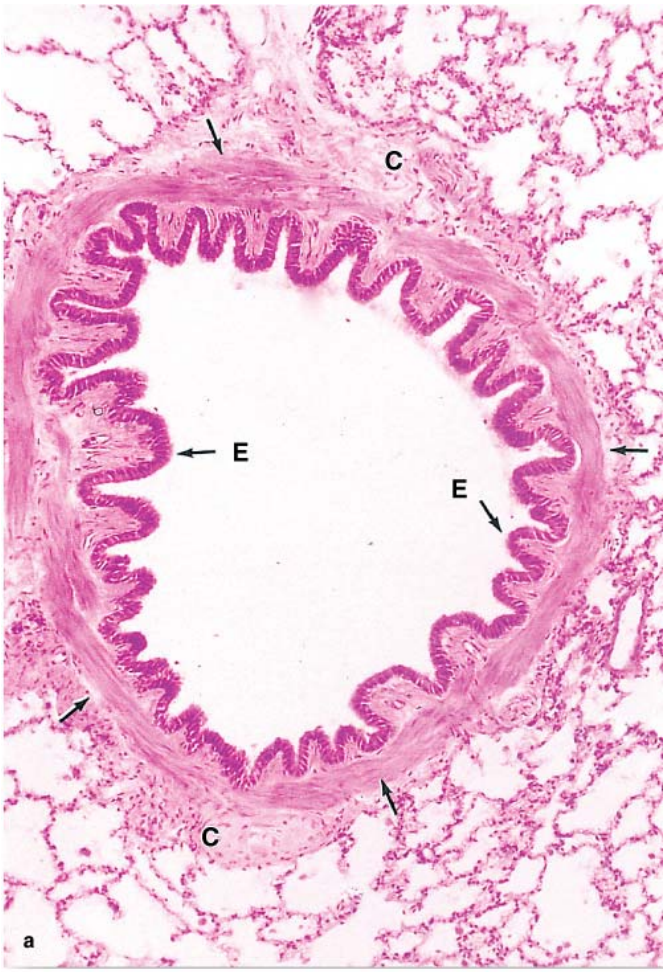
(a): A higher power view of the bronchus shows the epithelium (E) of mainly pseudostratified ciliated columnar cells with a few goblet cells. The lamina propria (LP) contains the distinct layer of smooth muscle (SM) surrounding the entire bronchus. The submucosa is the site of the supporting cartilage (C) and the adventitia includes blood vessels (V) and nerves (N). Lung tissue (LT) directly surrounds the adventitia of bronchi. X140. H&E. **(b):** This micrograph shows the epithelium of a smaller bronchus, in which the epithelium is primarily of columnar cells with cilia (arrows), with fewer goblet cells. The lamina propria has both smooth muscle (SM) and small serous glands (G) near cartilage (C). X400. H&E.

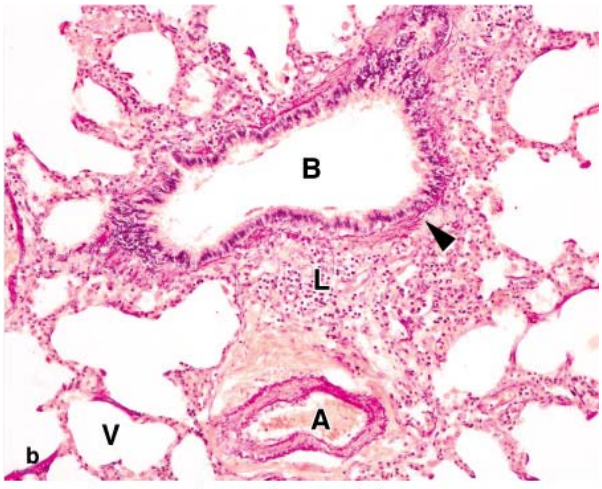
The lamina propria also contains elastic fibers and abundant mucous and serous glands (Figure 17–8) whose ducts open into the bronchial lumen. Numerous lymphocytes are found both within the lamina propria and among the epithelial cells. Lymphatic nodules are present and are particularly numerous at the branching points of the bronchial tree. Elastic fibers, smooth muscle, and MALT become relatively more abundant as bronchi become smaller and cartilage and other connective tissue are reduced.

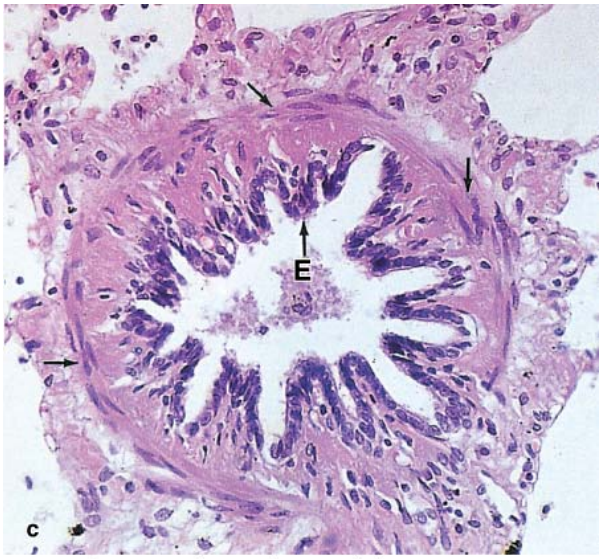
Bronchioles

Bronchioles are the intralobular airways with diameters of 5 mm or less, formed after about the tenth generation of branching, and have neither cartilage nor glands in their mucosa (Figure 17–9). In the larger bronchioles, the epithelium is still ciliated pseudostratified columnar, but this decreases in height and complexity to become ciliated simple columnar or cuboidal epithelium in the smaller terminal bronchioles. Goblet cells disappear during this transition, but the epithelium of terminal bronchioles instead contains other numerous columnar cells: the exocrine bronchiolar cells, commonly called **Clara cells** (Figure 17–10). These mitotically active cells secrete surfactant components and have various important defensive roles. Scattered neuroendocrine cells (Chapter 20) are also present, producing serotonin and other peptides that help control the tone of the local smooth muscle. Groups of similar cells, called **neuroepithelial bodies**, occur in some bronchioles and at higher levels in the bronchial tree. These are innervated by autonomic and sensory fibers and some of the cells appear to function as chemosensory receptors in monitoring air O_2 levels. Epithelial stem cells are also present in these groups of cells.

Figure 17–9.



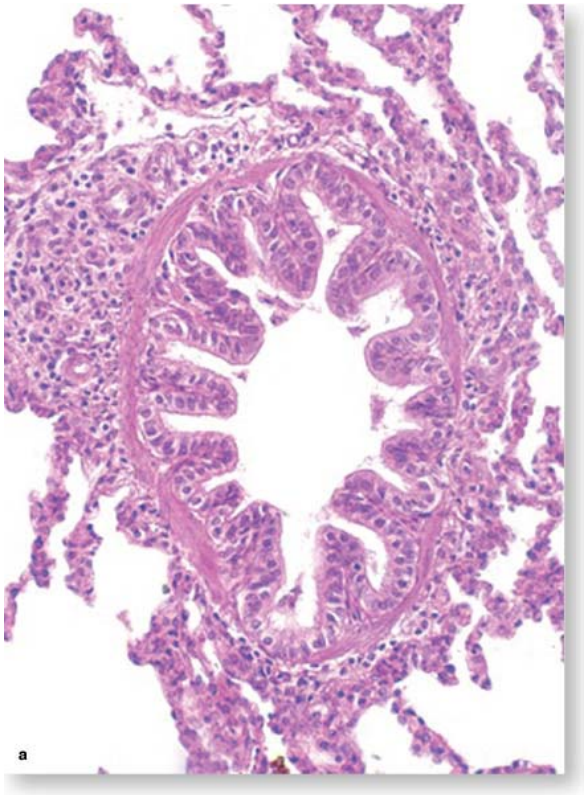


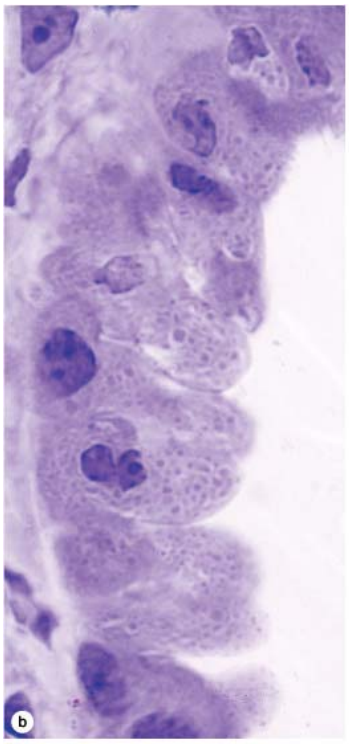


Bronchioles.

Bronchial branches less than about 5 mm in diameter lack supporting cartilage and are called bronchioles. **(a):** A large bronchiole has the characteristically folded respiratory epithelium (E) and prominent smooth muscle (arrows), but is supported only by fibrous connective tissue (C) with no glands. X140. H&E. **(b):** Staining for elastic fibers reveals the high elastic content of the smooth muscle (arrowhead) associated with the muscle of a smaller bronchiole (B) in which the epithelium is simple columnar. Darkly stained elastic fibers are also present in the tunica media of a large arteriole (A) nearby and to a lesser extent in the accompanying venule (V). The connective tissue includes many lymphocytes (L) of MALT and lymphoid nodules are also common at this level. X180. Elastic stain. **(c):** In very small bronchioles the epithelium (E) is reduced to simple low columnar and the several layers of smooth muscle cells (arrows) comprise a high proportion of the wall. X300. H&E.

Figure 17–10.





Terminal bronchiole and Clara cells.

The last parts of the air conducting system before the sites of gas exchange appear are called the terminal bronchioles, which generally have diameters of one to two mm. **(a):** Cross-section shows that a terminal bronchiole has only one or two layers of smooth muscle cells. The epithelium contains ciliated cuboidal cells and many low columnar nonciliated cells. X300. PT. **(b):** The nonciliated Clara cells with bulging domes of apical cytoplasm contain granules, as seen better in a plastic section. Named for Dr. Max Clara, the histologist who first described them in 1937, these cells have several important functions. They secrete components of surfactant which reduces surface tension and helps prevent collapse of the bronchioles. In addition, Clara cells produce enzymes that help break down mucus locally. The P450 enzyme system of their smooth ER detoxifies potentially harmful compounds in air. In other defensive functions, Clara cells also produce the secretory component for the transfer of IgA into the bronchiolar lumen; lysozyme and other enzymes active against bacteria and viruses; and several cytokines that regulate local inflammatory responses. Mitotically active cells are also present and include the stem cells for the bronchiolar epithelium. X500. PT.

The bronchiolar lamina propria is composed largely of smooth muscle and elastic fibers. The musculature of both the bronchi and the bronchioles is under the control of the vagus nerve and the sympathetic nervous system, in addition to the influence of neuroendocrine peptides. Stimulation of the vagus nerve decreases the diameter of these structures; sympathetic stimulation produces the opposite effect.

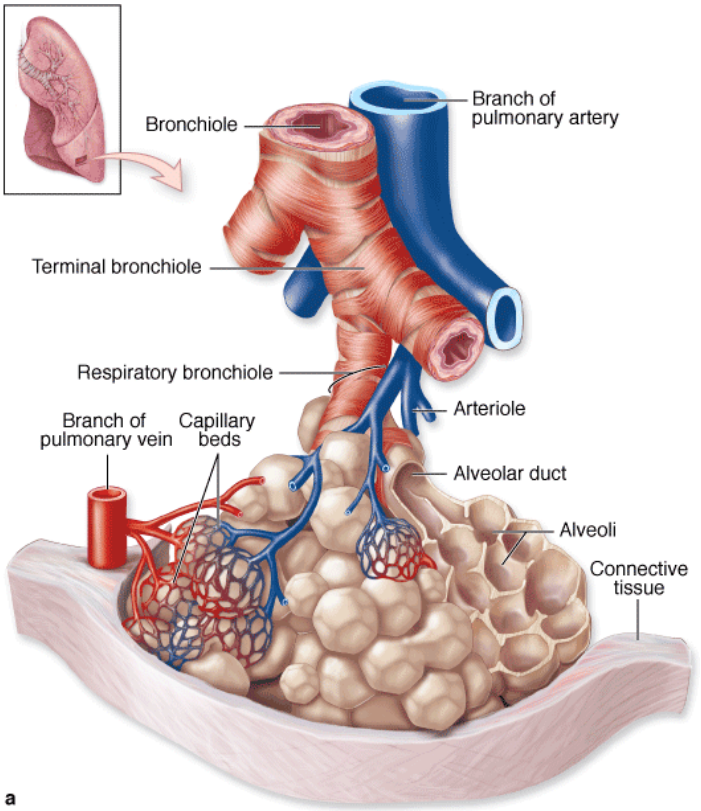
MEDICAL APPLICATION

The increase in bronchiole diameter in response to stimulation of the sympathetic nervous system explains why epinephrine and other sympathomimetic drugs are frequently used to relax smooth muscle during asthma attacks. When the thickness of the bronchial walls is compared with that of the bronchiolar walls, the bronchiolar muscle layer is seen to be proportionately greater. Increased airway resistance in asthma is believed to be due mainly to contraction of bronchiolar smooth muscle.

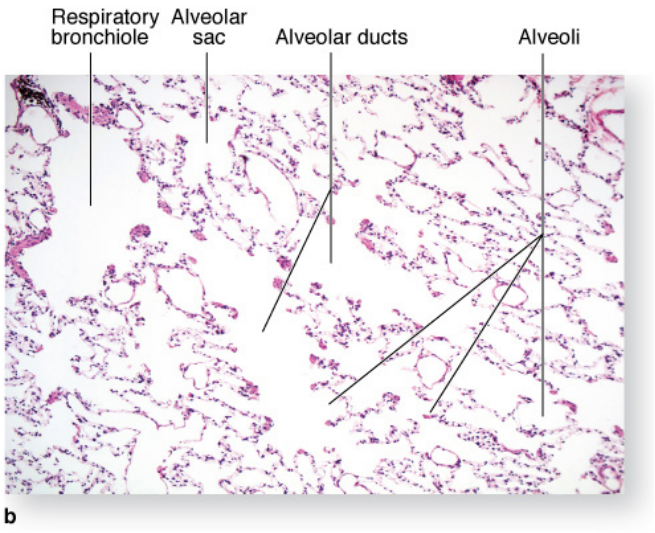
Respiratory Bronchioles

Each terminal bronchiole subdivides into two or more respiratory bronchioles that serve as regions of transition between the conducting and respiratory portions of the respiratory system (Figure 17–11). The respiratory bronchiolar mucosa is structurally identical to that of the terminal bronchioles, except that their walls are interrupted by the openings to saclike alveoli where gas exchange occurs. Portions of the respiratory bronchioles are lined with ciliated cuboidal epithelial cells and Clara cells, but at the rim of the alveolar openings the bronchiolar epithelium becomes continuous with the squamous alveolar lining cells (type I alveolar cells; see below). Proceeding distally along these bronchioles, the alveoli increase in number, and the distance between them is reduced. Between alveoli the bronchiolar epithelium consists of ciliated cuboidal epithelium, although cilia may be absent in more distal portions. Smooth muscle and elastic connective tissue lie beneath the epithelium of respiratory bronchioles.

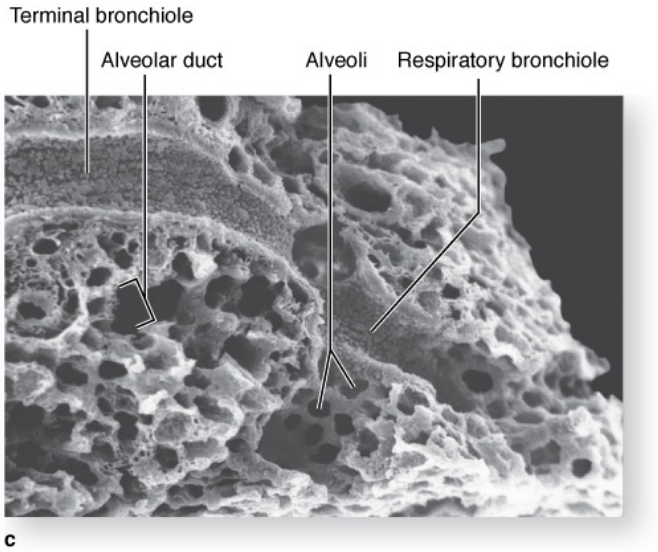
Figure 17–11.



a



b



Terminal bronchioles, respiratory bronchioles, and alveoli.

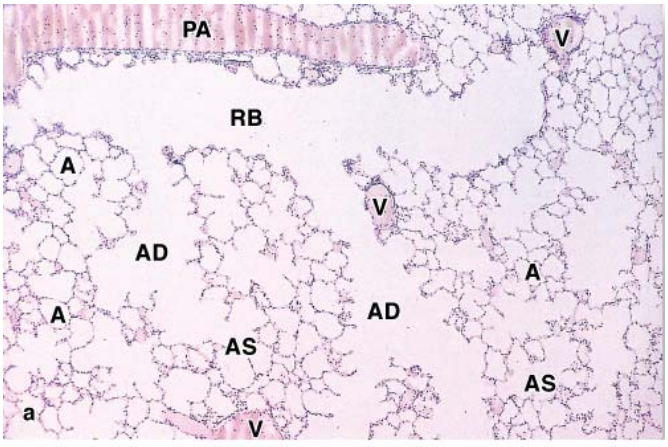
Terminal bronchioles branch into respiratory bronchioles, which then branch further into alveolar ducts and individual alveoli. Respiratory bronchioles are similar in most respects to terminal bronchioles except for the presence of scattered alveoli along their length.

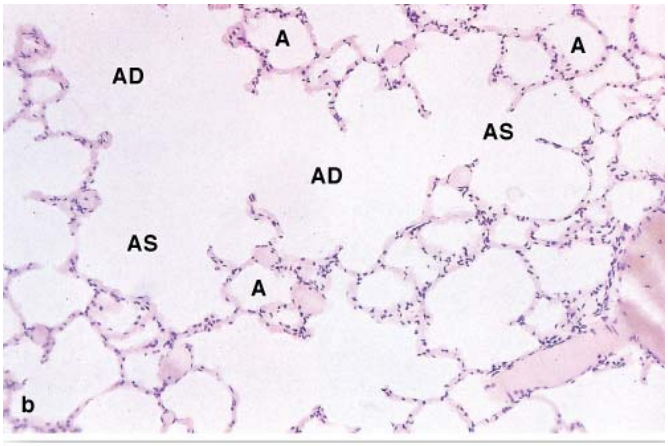
(a): Diagram shows the branching relationship, as well as the pulmonary blood vessels that travel with the bronchioles and the dense layer of branching capillaries that surrounds each alveolus for gas exchange between blood and air. **(b):** The micrograph shows the branching nature of the bronchioles in two dimensions. X60. H&E. **(c):** SEM shows in three dimensions the relationship of alveoli to terminal and respiratory bronchioles. X180.

Alveolar Ducts

Proceeding distally along the respiratory bronchioles, the number of alveolar openings in the bronchiolar wall slowly increases. Respiratory bronchioles branch into tubes called **alveolar ducts** that are completely lined by the openings of alveoli (Figure 17–12). Both the alveolar ducts and the alveoli are lined with extremely attenuated squamous alveolar cells. In the lamina propria surrounding the rim of the alveoli is a thin network of smooth muscle cells, which disappears at the distal ends of alveolar ducts. A rich matrix of elastic and collagen fibers provides the only support of the duct and its alveoli.

Figure 17–12.





Respiratory bronchioles, alveolar ducts, and alveoli.

Lung tissue has a spongy structure because of the abundant air passages and pockets called alveoli. **(a):** Typical section of lung tissue including many bronchioles, some of which are respiratory bronchioles (RB) cut lengthwise, and showing the branching continuity with alveolar ducts (AD) and sacs (AS). Respiratory bronchioles still have a layer of smooth muscle and some regions of cuboidal epithelium, but alveolar ducts have only sparse strands of smooth muscle and an epithelium consisting of only a series of neighboring alveoli. The smooth muscle fibers are sphincter-like and appear as knobs between adjacent alveoli. Individual alveoli (A) all open to the sacs or ducts. The respiratory bronchiole runs along a thin-walled branch of the pulmonary artery (PA), which has a relatively thin wall, while branches of the pulmonary vein (V) course elsewhere in the parenchyma. X14. H&E.

(b): Higher magnification shows the relationship of the many rounded, thin-walled alveoli (A) to alveolar ducts (AD). Alveolar ducts end in two or more clusters of alveoli called alveolar sacs (AS). Those alveoli shown here that do not show openings to the ducts or the sacs have their connections in adjacent planes of other sections. X140. H&E.

Alveolar ducts open into atria of two or more **alveolar sacs** (Figure 17–12). Elastic and reticular fibers form a network encircling the openings of atria, alveolar sacs, and alveoli. The elastic fibers enable the alveoli to expand with inspiration and to contract passively with expiration. The reticular fibers serve as a support that prevents overdistention and damage to the delicate capillaries and thin alveolar septa. Both fibers contribute to the connective tissue housing the network of capillaries around each alveolus.

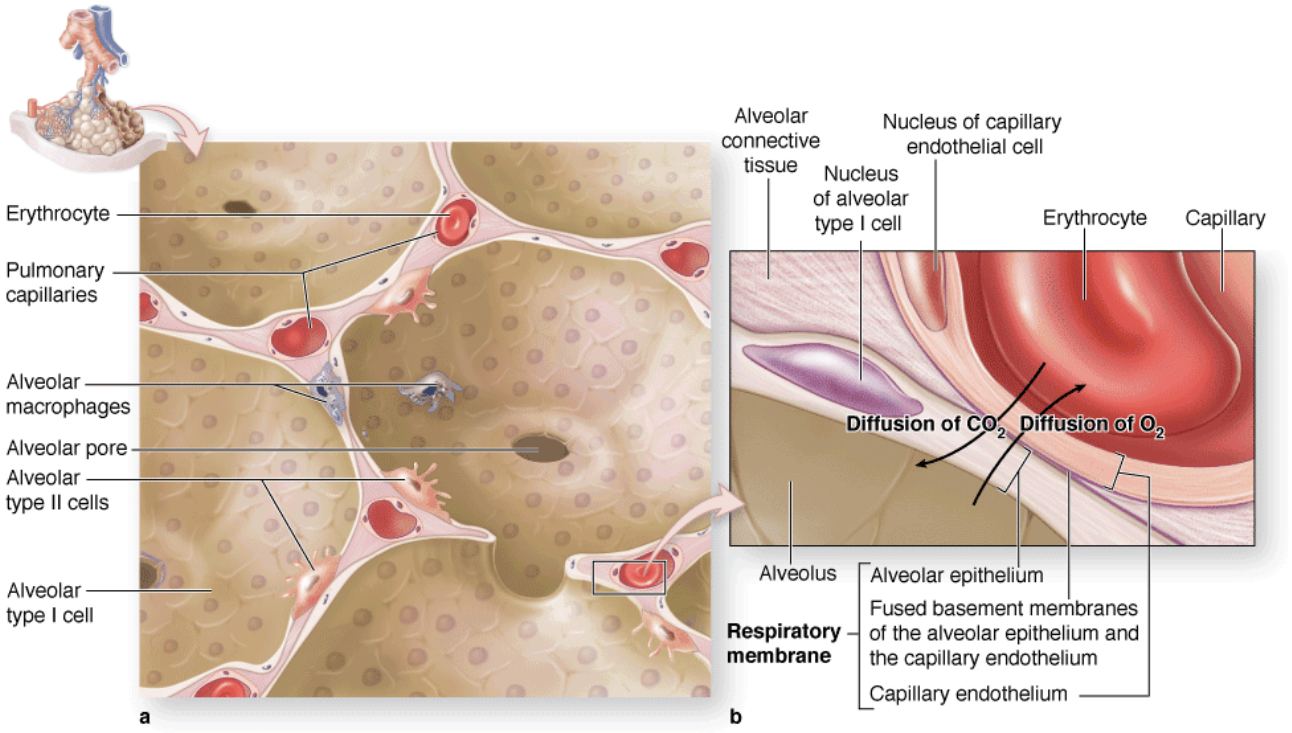
Alveoli

Alveoli are saclike evaginations (about 200 μm in diameter) of the respiratory bronchioles, alveolar ducts, and alveolar sacs. Alveoli are responsible for the spongy structure of the lungs (Figures 17–11 and 17–12). Structurally, alveoli resemble small pockets that are open on one side, similar to the honeycombs of a beehive. Within these cuplike structures, O_2 and CO_2 are exchanged between the air and the blood. The structure of alveolar walls is specialized to enhance diffusion between the external and internal environments. Generally, each wall lies between two neighboring alveoli and is therefore called an **interalveolar septum**. These septa contain the cells and ECM of connective tissue, notably the elastic and collagen fibers, which is vascularized with the richest capillary network in the body (Figure 17–11).

Air in the alveoli is separated from capillary blood by three components referred to collectively as the **respiratory membrane** or blood-air barrier:

- Surface lining and cytoplasm of the alveolar cells,
- Fused basal laminae of the closely apposed alveolar cells and capillary endothelial cells, and
- Cytoplasm of the endothelial cells (Figures 17–13, 17–14, and 17–15).

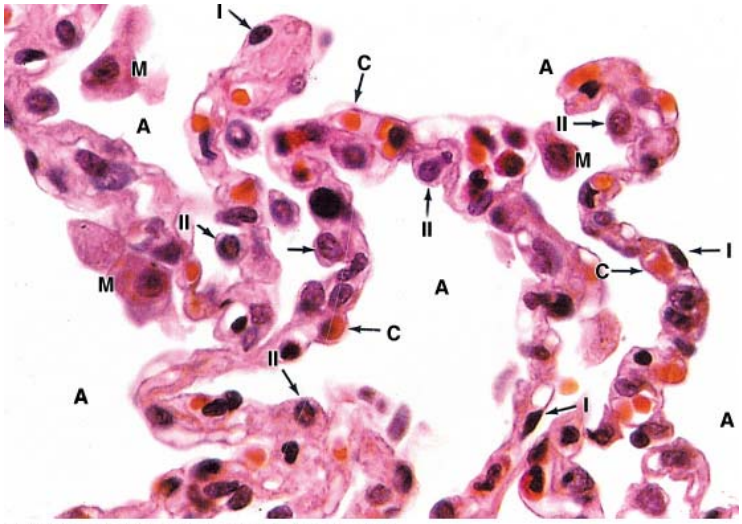
Figure 17–13.



Alveoli and the blood-air barrier.

Gas exchange between air and blood occurs at a membranous barrier between each alveolus and the capillaries surrounding it. The total area of this air-blood barrier in each lung has been calculated at approximately 70 m^2. **(a):** Diagram shows the relationship between capillaries and two or more saclike alveoli. **(b):** The air-blood barrier consists of an alveolar type I cell, a capillary endothelial cell, and their fused basement membranes. Oxygen diffuses from alveolar air into capillary blood and carbon dioxide moves in the opposite direction. The inner lining of alveoli is covered by a layer of surfactant, not depicted here, which lowers fluid surface tension and helps prevent collapse of alveoli.

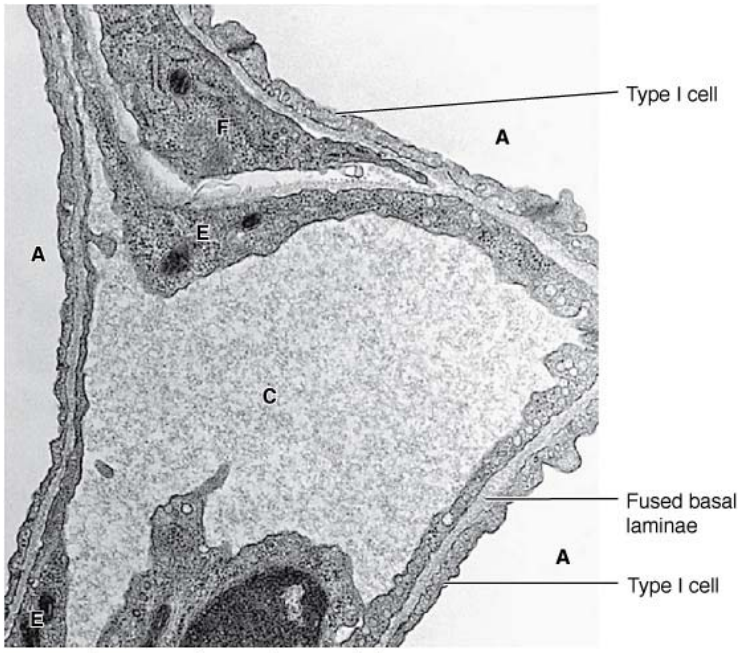
Figure 17–14.



Alveolar walls.

The wall between alveoli (A) contains several cell types. As seen here the capillaries (C) contain erythrocytes and leukocytes. The alveoli are lined mainly by squamous type I alveolar cells (I), which line almost the entire alveolus surface and across which gas exchange occurs. Type II alveolar cells line a bit of each alveolus and are large rounded cells, often bulging into the alveolus (II). These type II cells have many functions of Clara cells, including production of surfactant. Also present are alveolar macrophages (M), sometimes called dust cells, which may be in the alveoli or in the interalveolar septa.

Figure 17–15.



Ultrastructure of the blood-air barrier.

TEM of a transversely sectioned capillary (C) in an interalveolar septum shows areas for gas exchange between blood and air in three alveoli (A). The endothelium is extremely thin but not fenestrated and its basal lamina fuses with that of the alveolar cells. A fibroblast (F) can be seen in the septum and the thickened nuclear regions of two endothelial cells (E) are also included. The nucleus at the bottom belongs to an endothelial cell or a circulating leukocyte. X30,000.

The total thickness of these layers varies from 0.1 to 1.5 μm. Within the interalveolar septum, densely anastomosing pulmonary capillaries are supported by the meshwork of reticular and elastic fibers, which are the primary structural support of the alveoli. Macrophages and other leukocytes can also be found within the interstitium of the septum (Figures 17–13 and 17-14). The basal laminae of the capillary endothelial cells and the epithelial (alveolar) cells fuse as a single membranous structure (Figures 17–13 and 17–15).

Pores 10–15 μm in diameter occur in the interalveolar septum (Figure 17–13) and connect neighboring alveoli opening to different bronchioles. These pores equalize air pressure in the alveoli and promote collateral circulation of air when a bronchiole is obstructed.

O_2 from the alveolar air passes into the capillary blood through the blood-air barrier; CO_2 diffuses in the opposite direction. Liberation of CO_2 from H_2CO_3 is catalyzed by the enzyme **carbonic anhydrase** present in erythrocytes. The approximately 300 million alveoli in the lungs provide a vast internal surface for gas exchange, which has been calculated to be approximately 140 m^2.

Capillary endothelial cells are extremely thin and can be easily confused with type I alveolar epithelial cells. The endothelial lining of the capillaries is continuous and not fenestrated (Figure 17–15). Clustering of the nuclei and other organelles allows the remaining areas of the cell to become extremely thin, increasing the efficiency of gas exchange. The most prominent feature of the cytoplasm in the flattened portions of the cell are numerous pinocytotic vesicles.

Type I alveolar cells (also called type I pneumocytes or squamous alveolar cells) are extremely attenuated cells that line the alveolar surfaces. Type I cells cover 97% of the alveolar surface (type II cells covering the remainder). These cells are so thin (sometimes only 25 nm) that the electron microscope was needed to prove