The Respiratory System

The respiratory system includes the lungs and a system of tubes that links the sites of gas exchange with the external environment. A ventilation mechanism, consisting of the thoracic cage, intercostal muscles, diaphragm, and elastic and collagen components of the lungs, is important in the movement of air through the lungs. The respiratory system is customarily divided into two principal regions: ***a conducting portion***, consisting of the nasal cavity, 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 specialized saclike structures that make up the greater part of the lungs. They are the main sites for the principal function of the lungsâ€”the exchange of O_2 and CO_2 between inspired air and blood.

The conducting portion serves two main functions: to provide a conduit through which air can travel 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 that contains a rich population of goblet cells and is known as respiratory epithelium. Typical respiratory epithelium consists of ***five cell types*** (as seen in the electron microscope). ***1- Ciliated columnar*** cells constitute the most abundant type. Each cell has about 300 cilia on its apical surface; beneath the cilia, in addition to basal bodies, are numerous small mitochondria that supply adenosine triphosphate (ATP) for ciliary beating.

The next most abundant cells in the respiratory epithelium are ***2- the mucous goblet cells***. The apical portion of these cells contains the mucous droplets composed of glycoproteins. The remaining columnar cells are known as ***3- brush cells*** because of the numerous microvilli on their apical surface. Brush cells have afferent nerve endings on their basal surfaces and are considered to be sensory receptors. ***4- Basal (short) cells*** are small rounded cells that lie on the basal lamina but do not extend to the luminal surface of the epithelium. These cells are believed to be generative stem cells that undergo mitosis and subsequently differentiate into the other cell types. The last cell type is ***5- the small granule cell***, which resembles a basal cell except that it possesses numerous granules 100 - 300 nm in diameter with dense cores. Histochemical studies reveal that these cells constitute a population of cells of the diffuse neuroendocrine system.

All cells of the ciliated pseudostratified columnar epithelium touch the basement membrane.

Nasal Cavity

The nasal cavity consists of two structures: the external vestibule and the internal nasal fossae.

Vestibule

The vestibule is the most anterior and dilated portion of the nasal cavity. The outer integument of the nose enters the nares (nostrils) and continues partway up the vestibule. Around the inner surface of the nares are numerous sebaceous and sweat glands, in addition to the thick short hairs, or vibrissae, that filter out large particles 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.

Nasal Fossae

Within the skull lie two cavernous chambers separated by the osseous nasal septum. Extending from each lateral wall are three bony shelf like projections known as conchae. Of the superior, middle, and inferior conchae, only the middle and inferior projections are covered with respiratory epithelium. The superior conchae are covered with a specialized olfactory epithelium. The narrow, ribbonlike passages created by the conchae improve the conditioning of the inspired air by increasing the surface area of respiratory epithelium and by creating 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 min, the swell bodies on one side of the nasal fossae become engorged with blood, resulting in distention 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. These periodic intervals of occlusion reduce airflow, allowing the respiratory epithelium to recover from desiccation.

In addition to swell bodies, the nasal cavity has a rich vascular system with a complex organization. Large vessels form a close-meshed latticework next to the periosteum, from which arcading branches lead toward the surface. Blood in arcading vessels flows forward from the rear region in a direction counter to the flow of inspired air. As a result, the incoming air is efficiently warmed by a countercurrent system.

Smell (Olfaction)

The olfactory chemoreceptors are located in the olfactory epithelium, a specialized area of the mucous membrane in the superior conchae, located in the roof of the nasal cavity. In humans, it is about 10 cm^2 in area. It is a pseudostratified columnar epithelium composed of three types of cells.

1-The supporting cells have 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 supporting cells contain a light yellow pigment that is responsible for the color of the olfactory mucosa.

2-The basal cells are small; they are spherical or cone shaped and form a single layer at the base of the epithelium.

Between the basal cells and the supporting cells are the olfactory cells ***3-bipolar neurons*** distinguished from the supporting cells by the position of their nuclei, which lie below the nuclei of the supporting cells. Their apexes (dendrites) possess elevated and dilated areas from which arise six to eight cilia. These cilia are very long and nonmotile, and respond to odoriferous substances by generating a receptor potential. The cilia increase the receptor surface considerably. The afferent axons of these bipolar neurons unite in small bundles directed toward the brain, where they synapse with neurons of the brain olfactory lobe.

The lamina propria of the olfactory epithelium possesses the **glands of Bowman**, which of pure serous glands and also named olfactory glands. Their secretion produces a watery fluid environment around the olfactory cilia that may clear the cilia, facilitating the access of new odoriferous substances.

Conditioning of Air

A major function of the conducting portion is to condition the inspired air. Before it enters the lungs, inspired air is cleansed, moistened, and warmed. To carry out these functions, the mucosa of the conducting portion is lined with a specialized respiratory epithelium, and there are numerous mucous and serous glands as well as a rich superficial vascular network in the lamina propria.

As the air enters the nose, large vibrissae (***specialized hairs***) remove coarse particles of dust. 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 alveolar lining from desiccation. ***A rich superficial vascular network*** also warms the incoming air.

Paranasal Sinuses

The paranasal sinuses are closed cavities in the frontal, maxillary, ethmoid, and sphenoid bones. They are lined with a thinner respiratory epithelium that contains few 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 cavity through small openings. The mucus produced in these cavities drains into the nasal passages as a result of the activity of its ciliated epithelial cells.

Nasopharynx

The nasopharynx is the first part of the pharynx, continuing caudally with the oropharynx, the oral portion of this organ. It is lined with respiratory epithelium in the portion that is in contact with the soft palate.

Larynx

The larynx is an irregular tube that connects the pharynx to the trachea. Within the lamina propria lie a number of laryngeal cartilages. ***The larger cartilages (thyroid, cricoid, and most of the arytenoids) are hyaline. The smaller cartilages (epiglottis, cuneiform, corniculate, and the tips of the arytenoids) are elastic cartilages*****.** In addition to their supporting role (maintenance of an open airway), these cartilages serve as a valve to prevent swallowed food or fluid from entering the trachea. They also participate in producing sounds for phonation.

The epiglottis, which projects from the rim of the larynx, extends into the pharynx and has both a lingual and a laryngeal surface. The entire lingual surface and the apical portion of the laryngeal surface are covered with stratified squamous epithelium. Toward the base of the epiglottis on the laryngeal surface, the epithelium undergoes a transition into ciliated pseudostratified columnar epithelium. Mixed mucous and serous glands are found beneath the epithelium.

Below the epiglottis, the mucosa forms two pairs of folds that extend into the lumen of the larynx. The upper pair constitutes the false vocal cords (vestibular folds), covered with typical respiratory epithelium beneath which lie numerous serous glands within the lamina propria. The lower pair of folds constitutes the true vocal cords. Large bundles of parallel elastic fibers that compose the vocal ligament lie within the vocal folds, which are covered with a stratified squamous epithelium. Parallel to the ligaments are bundles of skeletal muscle, the vocalis muscles, which regulate the tension of the fold and its ligaments. As air is forced between the folds, these muscles provide the means for sounds of different frequencies to be produced.

Trachea

The trachea is lined with a typical respiratory mucosa. In the lamina propria are 16 - 20 C-shaped rings of hyaline cartilage that keep the tracheal lumen open and numerous seromucous glands that produce a more fluid mucus. The open ends of these cartilage rings are located on the posterior surface of the trachea. A fibroelastic ligament and bundle of smooth muscle bind to the perichondrium and bridge the open ends of these C-shaped cartilages. The ligament prevents overdistention of the lumen, and the muscle allows regulation of the lumen (the inner space delimited by a tissue wall is the lumen of the organ).
Contraction of the muscle and the resultant narrowing of the tracheal lumen are involved in the cough reflex. The smaller bore of the trachea after contraction provides for increased velocity of expired air, which aids in clearing the air passage.

Bronchial Tree

The trachea divides into two **primary bronchi** that enter the lungs at the hilum. At each hilum, arteries enter and veins and lymphatic vessels leave. These structures are surrounded by dense connective tissue and form a unit called the pulmonary root.

After entering the lungs, the primary bronchi course downward and outward, giving rise to three bronchi in the right lung and two in the left lung, each of which supplies a pulmonary lobe. These lobar bronchi divide repeatedly, giving rise to 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.

The primary bronchi generally have the same histological appearance as the trachea. Proceeding toward the respiratory portion, the histological organization of both the epithelium and the underlying lamina propria becomes simplified. It must be stressed that this simplification is gradual; no abrupt transition can be observed between the bronchi and bronchioles. For this reason, the division of the bronchial tree into bronchi, bronchioles, etc, is to some extent artificial, although this division has both pedagogical and practical value.

Bronchi

Each primary bronchus branches dichotomously 9 - 12 times, with each branch becoming progressively smaller until it reaches a diameter of about 5 mm. *Except for* *the organization of cartilage and smooth muscle*, the mucosa of the bronchi is structurally similar to the mucosa of the trachea. The bronchial cartilages are more irregular in shape than those found in the trachea; in the larger portions of the bronchi, the cartilage rings completely encircle the lumen. As bronchial diameter decreases, the cartilage rings are replaced with isolated plates, or islands, of hyaline cartilage. Beneath the epithelium, in the bronchial lamina propria, is a smooth muscle layer consisting of crisscrossing bundles of spirally arranged smooth muscle. Bundles of smooth muscle become more prominent near the respiratory zone. Contraction of this muscle layer after death is responsible for the folded appearance of the bronchial mucosa observed in histological section. The lamina propria is rich in elastic fibers and contains an abundance of mucous and serous glands 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.

Bronchioles

Bronchioles, intralobular airways with diameters of 5 mm or less, have neither cartilage nor glands in their mucosa; there are only scattered goblet cells within the epithelium of the initial segments. In the larger bronchioles, the epithelium is ciliated pseudostratified columnar, which decreases in height and complexity to become ciliated simple columnar or cuboidal epithelium in the smaller terminal bronchioles. The epithelium of terminal bronchioles also contains **Clara cells**, which are devoid of cilia, have secretory granules in their apex, and are known to secrete proteins that protect the bronchiolar lining against oxidative pollutants and inflammation.

Bronchioles also exhibit specialized regions called neuroepithelial bodies. These are formed by groups of 80 - 100 cells that contain secretory granules and receive cholinergic nerve endings. Their function is poorly understood, but they are probably chemoreceptors that react to changes in gas composition within the airway. They also seem involved in the reparative process of airway epithelial cell renewal after injury.

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. Stimulation of the vagus nerve decreases the diameter of these structures; sympathetic stimulation produces the opposite effect.

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. The respiratory bronchiolar mucosa is structurally identical to that of the terminal bronchioles, except that their walls are interrupted by numerous 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 greatly in number, and the distance between them is markedly reduced. Between alveoli, the bronchiolar epithelium consists of ciliated cuboidal epithelium; however, the cilia may be absent in more distal portions. Smooth muscle and elastic connective tissue lie beneath the epithelium of respiratory bronchioles.

Alveolar Ducts

Proceeding distally along the respiratory bronchioles, the number of alveolar openings into the bronchiolar wall becomes ever greater until the wall consists of nothing else, and the tube is now called an alveolar duct. 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 network of smooth muscle cells. These sphincterlike smooth muscle bundles appear as knobs between adjacent alveoli. Smooth muscle disappears at the distal ends of alveolar ducts. A rich matrix of elastic and reticular fibers provides the only support of the duct and its alveoli.

Alveolar ducts open into atria that communicate with **alveolar sacs**, two or more of which arise from each atrium. Elastic and reticular fibers form a complex 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.

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. 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 the alveolar walls is specialized for enhancing diffusion between the external and internal environments. Generally, each wall lies between two neighboring alveoli and is therefore called an interalveolar septum, or wall. An interalveolar septum consists of two thin squamous epithelial layers between which lie capillaries, elastic and reticular fibers, and connective tissue matrix and cells. The capillaries and connective tissue constitute the interstitium. Within the interstitium of the interalveolar septum is found the richest capillary network in the body.

Air in the alveoli is separated from capillary blood by three components referred to collectively as the blood-air barrier: the surface lining and cytoplasm of the alveolar cells, the fused basal laminae of the closely apposed alveolar and endothelial cells, and the cytoplasm of the endothelial cells. The total thickness of these layers varies from 0.1 to 1.5 µm. Within the interalveolar septum, anastomosing pulmonary capillaries are supported by a meshwork of reticular and elastic fibers. These fibers, which are arranged to permit expansion and contraction of the interalveolar septum, are the primary means of structural support of the alveoli. The basement membrane, leukocytes, macrophages, and fibroblasts can also be found within the interstitium of the septum. The fusion of two basal laminae produced by the endothelial cells and the epithelial (alveolar) cells of the interalveolar septum forms the basement membrane.

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 considerably increase their internal exchange surface, 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. 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 is numerous pinocytotic vesicles.

alveolar epithelial cells are:

1- Type I cells, or squamous alveolar cells, are extremely attenuated cells that line the alveolar surfaces. Type I cells make up 97% of the alveolar surfaces (type II cells make up the remaining 3%). These cells are so thin (sometimes only 25 nm) that the electron microscope was needed to prove that all alveoli are covered with an epithelial lining. Organelles such as the Golgi complex, endoplasmic reticulum, and mitochondria are grouped around the nucleus, reducing the thickness of the blood-air barrier and leaving large areas of cytoplasm virtually free of organelles. The cytoplasm in the thin portion contains abundant pinocytotic vesicles, which may play a role in the turnover of surfactant (described below) and the removal of small particulate contaminants from the outer surface. In addition to desmosomes, all type I epithelial cells have occluding junctions that prevent the leakage of tissue fluid into the alveolar air space. The main role of these cells is to provide a barrier of minimal thickness that is readily permeable to gases.

2-Type II cells are interspersed among the type I alveolar cells with which they have occluding and desmosomal junctions. Type II cells are rounded cells that are usually found in groups of two or three along the alveolar surface at points at which the alveolar walls unite and form angles. These cells, which rest on the basement membrane, are part of the epithelium, with the same origin as the type I cells that line the alveolar walls. They divide by mitosis to replace their own population and also the type I population. In histological sections, they exhibit a characteristic vesicular or foamy cytoplasm. These vesicles are caused by the presence of lamellar bodies that are preserved and evident in tissue prepared for electron microscopy. Lamellar bodies, which average 1-2 μm in diameter, contain concentric or parallel lamellae limited by a unit membrane. Histochemical studies show that these bodies, which contain phospholipids, glycosaminoglycans, and proteins, are continuously synthesized and released at the apical surface of the cells. The lamellar bodies give rise to a material that spreads over the alveolar surfaces, providing an extracellular alveolar coating, pulmonary surfactant, that lowers alveolar surface tension.

The surfactant layer consists of an aqueous, proteinaceous hypophase covered with a monomolecular phospholipid film that is primarily composed of dipalmitoyl phosphatidylcholine and phosphatidylglycerol. Surfactant also contains several types of proteins. Pulmonary surfactant serves several major functions in the economy of the lung, but it primarily aids in reducing the surface tension of the alveolar cells. The reduction of surface tension means that less inspiratory force is needed to inflate the alveoli, and thus the work of breathing is reduced. In addition, without surfactant, alveoli would tend to collapse during expiration. In fetal development, surfactant appears in the last weeks of gestation and coincides with the appearance of lamellar bodies in the type II cells.

The surfactant layer is not static but is constantly being turned over. The lipoproteins are gradually removed from the surface by the pinocytotic vesicles of the squamous epithelial cells, by macrophages, and by type II alveolar cells.

Alveolar lining fluids are also removed via the conducting passages as a result of ciliary activity. As the secretions pass up through the airways, they combine with bronchial mucus, forming a bronchoalveolar fluid, which aids in the removal of particulate and noxious components from the inspired air.

Lung Macrophages

Alveolar macrophages, also called dust cells, are found in the interior of the interalveolar septum and are often seen on the surface of the alveolus. Numerous carbon- and dust-laden macrophages in the connective tissue around major blood vessels or in the pleura probably are cells that have never passed through the epithelial lining. The phagocytosed debris within these cells was most likely passed from the alveolar lumen into the interstitium by the pinocytotic activity of type I alveolar cells. The alveolar macrophages that scavenge the outer surface of the epithelium within the surfactant layer are carried to the pharynx, where they are swallowed.

Pulmonary Blood Vessels

Circulation in the lungs includes both nutrient (systemic) and functional (pulmonary) vessels. Pulmonary arteries and veins represent the functional circulation. Pulmonary arteries are thin walled as a result of the low pressures (25 mm Hg systolic, 5 mm Hg diastolic) encountered in the pulmonary circuit. Within the lung the pulmonary artery branches, accompanying the bronchial tree. Its branches are surrounded by adventitia of the bronchi and bronchioles. At the level of the alveolar duct, the branches of this artery form a capillary network in the interalveolar septum and in close contact with the alveolar epithelium. The lung has the best-developed capillary network in the body, with capillaries between all alveoli, including those in the respiratory bronchioles.

Pleura

The pleura is the serous membrane covering the lung. It consists of two layers, parietal and visceral, that are continuous in the region of the hilum. Both membranes are composed of mesothelial cells resting on a fine connective tissue layer that contains collagen and elastic fibers. The elastic fibers of the visceral pleura are continuous with those of the pulmonary parenchyma.

The parietal and visceral layers define a cavity entirely lined with squamous mesothelial cells. Under normal conditions, this pleural cavity contains only a film of liquid that acts as a lubricant, facilitating the smooth sliding of one surface over the other during respiratory movements.

In certain pathological states, the pleural cavity can become a real cavity, containing liquid or air. The walls of the pleural cavity, like all serosal cavities (peritoneal and pericardial), are quite permeable to water and other substances hence the high frequency of fluid accumulation (pleural effusion) in this cavity in pathological conditions. This fluid is derived from the blood plasma by exudation. Conversely, under certain conditions, liquids or gases in the pleural cavity can be rapidly absorbed.