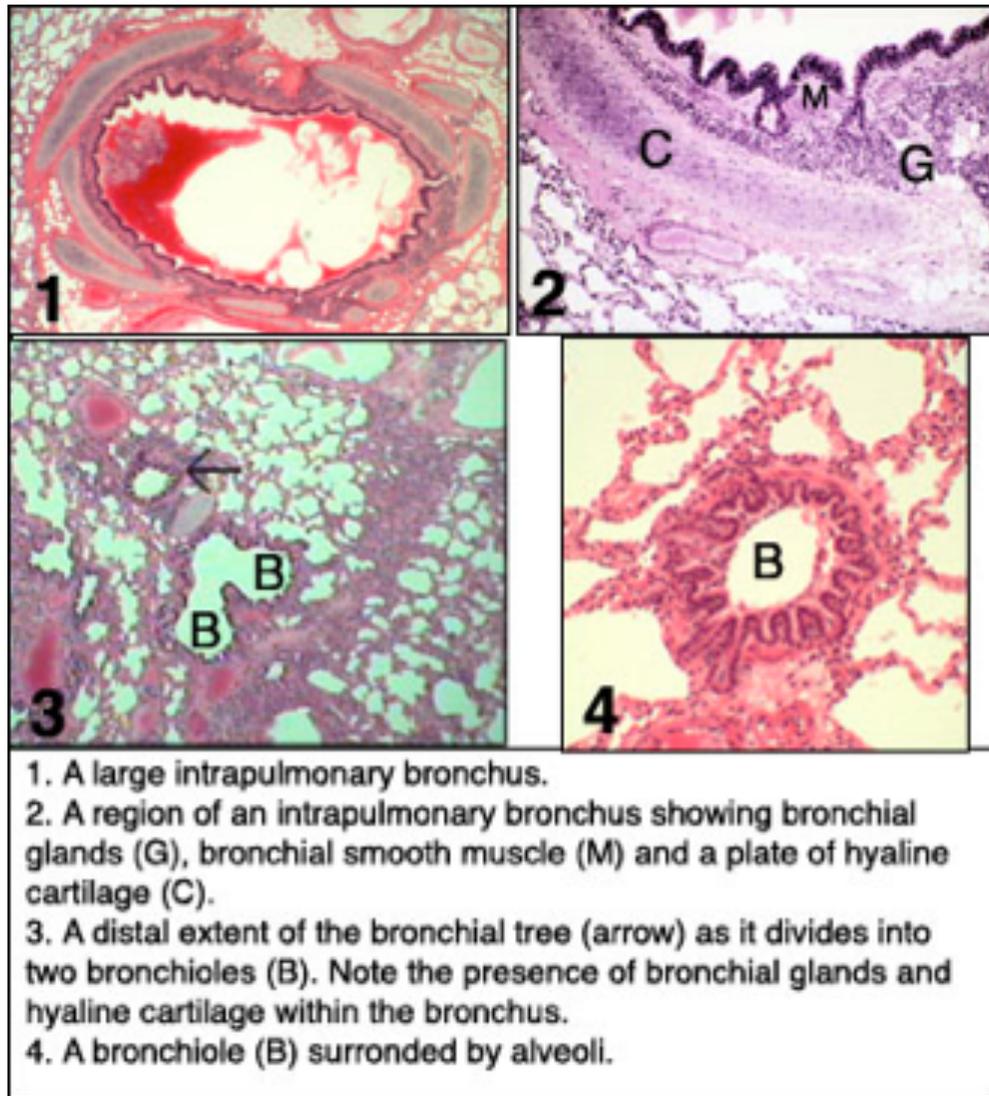


Lung/Intrapulmonary Passages



The *primary bronchi* divide to give rise to several orders of *intrapulmonary bronchi* in which the C-shaped cartilaginous rings of the primary bronchi are replaced by irregular plates of hyaline cartilage that completely surround the structure. Thus, the intrapulmonary bronchi are cylindrical and are not flattened on one side as are the main bronchi and trachea. Internally, the large intrapulmonary bronchi are lined by a mucous membrane that is continuous with and identical to that of the trachea and primary bronchi: a ciliated pseudostratified columnar epithelium with goblet cells. The lamina propria contains some diffuse lymphatic tissue and is separated from the epithelium by a prominent basal lamina. Beneath the lamina propria, a sheet of irregularly arranged smooth muscle cells runs around the bronchus in open left- or right-handed spirals. The muscle layer separates the lamina propria from the connective tissue of the submucosa, which lies immediately internal to the plates of hyaline cartilage. Mucous and mucoserous bronchial glands are present in the submucosa, their ducts penetrating the muscle layer to open onto the epithelial surface. Secretions from these glands, as well as

those throughout the respiratory tree, contain IgA, acquired from adjacent lymphoid tissue, which provides the larger respiratory passages with a degree of immunologic protection.

With successive divisions, the intrapulmonary bronchi progressively decrease in size, and although they retain the basic structure outlined above, the layers of their walls become thinner. The number of bronchial generations (branches) may be as many as 25 or as few as 10 prior to reaching the respiratory portion of the lung. The smallest of the intrapulmonary bronchi show only isolated cartilage plates and no longer are surrounded by cartilages. The epithelium is reduced to ciliated simple columnar with goblet cells. Bronchial glands are present as far down as the cartilages extend. Medium sized bronchi are the primary locations for airway resistance during breathing. This resistance can either be increased or decreased through the contraction of bronchial smooth muscle. Parasympathetic stimulation of bronchial smooth muscle constricts airway passages and increases airway resistance. Sympathetic stimulation of bronchial smooth muscle dilates airways and decreases airway resistance.

When the diameter of the tube reaches about 1 mm, cartilage disappears from the wall and the structure becomes a *bronchiole*. Glands and lymphatic tissue also disappear, but smooth muscle is fairly prominent and becomes the major supporting element. The lining epithelium varies from ciliated columnar with goblet cells in the large bronchioles to ciliated cuboidal with no goblet cells in the terminal bronchioles. Terminal bronchioles are the smallest branches of the purely conducting system. Scattered among the ciliated cells are a few non ciliated cells whose apical surfaces bulge into the lumen and bear a few microvilli. These are the Clara cells, also called bronchiolar secretory cells. They secrete protease inhibitors, oxidases, glycosaminoglycans, and proteins with immunosuppressive properties. Some of these factors (cytochrome P450) are thought to be protective against inhaled toxins and carcinogens and also may act in preventing conditions such as emphysema. The Clara cell may also play a role in surfactant elimination or production in this region.

Neuroepithelial bodies are innervated epithelial corpuscles scattered throughout the intrapulmonary airways and even may extend into alveoli. They are not present in the trachea. The corpuscles appear as ovoid or triangular bodies, 20 to 40 μm wide, set into the respiratory epithelium, where they extend from the lumen to the basement membrane. Basally, the neuroepithelial body is closely related to a capillary. The whole structure is richly innervated, and many of the nerve endings make contact with cells of the corpuscle. The neuroepithelial bodies contain 4 to 10 tall, non ciliated neuroendocrine cells with a slightly acidophilic cytoplasm that gives a positive argyrophil (silver) reaction. The oval nuclei are basally located and oriented in the long axis of the cells, which contain numerous mitochondria, moderately well-developed granular endoplasmic reticulum, small Golgi complexes, and some glycogen and multivesicular bodies. Characteristic of these cells are numerous dense-cored vesicles. The neuroepithelial bodies are believed to be chemoreceptors that react to the composition of inhaled air. When the oxygen tension of the inspired air decreases, the neuroepithelial body releases dense-cored vesicles that contain serotonin, a potent vasoconstrictor as well as additional peptides that may modulate airway tone. Thus, during local hypoxia, blood is shunted from poor to better oxygenated and ventilated areas of the lungs.

During conditions of reduced oxygen availability, three events occur to increase ventilation and to direct pulmonary blood flow to better ventilated regions of the lung. These events are (a) an increased signaling rate from glomus cells of the carotid body to respiratory centers in the brain, (b) intrinsic hypoxic vasoconstriction of pulmonary arterioles, and (c) local and central modulation by pulmonary neuroendocrine cells within the respiratory epithelium of the major airways. Each of these tissues has the ability to sense acute changes in oxygen, produce a signal and to initiate compensatory mechanisms. The heavily innervated

neuroepithelial bodies act as transducers of the hypoxia stimulus via neural input, affecting control of breathing and other pulmonary functions. As in glomus cells of the carotid body, neuroepithelial bodies release serotonin in response to hypoxia. The plasmalemma of cells forming the neuroepithelial bodies has membrane properties of excitable cells. The plasmalemma of these cells for oxygen sensing depends on interaction between the oxygen-sensing protein (NADPH oxidase) and an oxygen-sensitive potassium channel. Thus, a natural stimulus (oxygen concentration) acting on oxygen sensors in both the solitary pulmonary neuroepithelial cells and innervated clusters of pulmonary neuroepithelial cells (neuroepithelial bodies) may modulate pulmonary processes such as airway tone, pulmonary circulation, and even influences the control of breathing. There is also considerable evidence that the solitary neuroepithelial cells play a primary role in lung development based on the presence of bombesin and other peptides with growth factor-like properties expressed in human fetal lung tissue.

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