ONE

The Normal Lung

Pathology of Pulmonary Disease, edited by Mario J. Saldana.
J. B. Lippincott Company, Philadelphia © 1994.

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The Adult Lung: Structure and Function

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Familiarity with the gross and microscopic architecture of the normal human lung is necessary for recognizing and treating pathologic manifestations in this organ. The basic facts of gross anatomy and traditional histology that pathologists should be conversant with are summarized in this chapter. The account is complemented with information from transmission electron microscopy and scanning electron microscopy studies, morphometry, immunohistochemistry, and investigations in cell biology that have significantly aided in the understanding of the association between structure and function. Because of the ultrastructural similarities among several mammalian species, this discussion of the lung relies on illustrations from both human and animal sources.

GROSS LUNG ANATOMY

Lung volume increases from about 250 mL at birth to 6000 mL in the adult, and its weight increases from 60 to approximately 800 g.[1–7] About one half of the weight is blood, and the other one half is lung tissue. The adult right lung weighs 360 to 570 g, and the left weighs 325 to 480 g. In the upright position, at total lung capacity, the average lung is 27 cm high; during normal breathing (*i.e.*, functional residual capacity), it is approximately 24 cm.

The lungs are divided into lobes by interlobar fissures. The left lung has two lobes (*i.e.*, upper and lower), and its volume is approximately 20% less than that of the right lung, which has three lobes (*i.e.*, upper, middle, and lower). The primary fissures of the right and left lungs lie in an oblique plane that runs downward and anteriorly from the posterior aspect, slightly below the apex, to the anterior part of the diaphragm. In the right lung, a second fissure runs horizontally from the anterior chest wall, at approximately the level of the fourth chondrosternal junction, to meet the main fissure, separating the lung into three lobes. The minor fissure is anatomically absent or incomplete in 25% of the population.

TRACHEA AND BRONCHI

The trachea extends from the base of the larynx to the carina. It is reinforced by a skeleton of C- or horseshoe-shaped hyaline cartilages and is approximately 22 cm long and 2 cm in diameter. The hyaline cartilage ring is surrounded by perichondrium, which blends with smooth muscle in the cartilage-free posterior zone, the membranous trachealis muscle. The primary bronchi of the right and left lungs are extrapulmonary, arising in the mediastinum from the bifurcation of the trachea at the carina. The right bronchus has a less acute angle than the left bronchus, permitting a more direct flow of air, and is shorter (*i.e.*, 1–3 cm) than the left, which is approximately 5 cm long and runs more horizontally. The hilus of each lung is the region on their mediastinal aspect, where the bronchus, the pulmonary artery, and pulmonary veins enter, carrying with them invaginations of the visceral pleura. On entering the lung, the main bronchi divide into lobar bronchi and then into segmental bronchi that supply the 20 bronchopulmonary segments of the lung (Color Fig. 1-1).

The airway branching pattern yields a total of 23 to 28 generations, depending on the counting technique used.[4–7] The larger cartilaginous bronchi comprise 9 to 12 generations, starting with the primary bronchus and terminating in bronchi with diameters of approximately 1 mm. They are followed by bronchioles, sometimes called membranous bronchioles, which are noncartilaginous airways comprising an additional 12 generations before ending as terminal bronchioles, the last purely conducting structure in the lung. Terminal bronchioles branch out in about three generations of respiratory bronchioles, followed by alveolar ducts and alveoli. The cross-sectional area is 2 to 3 cm^2 at the trachea and becomes about 700,000 cm^2 at the level of the alveolar ducts; resistance is high in the larger airways and low in small airways.

The epithelial population of cells in the lung is thought to be an expanding rather than renewing cell population. An expanding cell population is one that may proliferate, as in growth or during

repair after injury. In the trachea, the histologic compartments consist of a mucosa, submucosa, muscularis, and adventitia. Nine of the 40 cell types of the lung are found within the conducting tracheobronchial tree. The tracheal epithelium is pseudostratified columnar and contains several cell types, including ciliated columnar, goblet (*i.e.*, mucous cell), brush, and basal cells (*i.e.*, short cell). With the electron microscope, an additional neurosecretory cell (*i.e.*, Kulchitsky cell) is seen. Abundant submucosal tubuloalveolar glands, composed of ciliated and collecting duct cells, mucous cells with serous cell crescents, and myoepithelial cells, open into the lumen of the trachea at approximately 1-mm intervals.

The histology of the intrapulmonary bronchi is similar to that of the trachea except for a continuous ring of smooth muscle between the submucosa and cartilage; the cartilage rings become plates. As bronchi branch out and become smaller, the lamina propria, which contains an abundance of longitudinally oriented elastic fibers, thins out; the pseudostratified columnar epithelium becomes cuboidal; and the number of mucoserous glands wane. Although glands disappear in the more distal bronchi, mucous cells persist in the mucosa of very small bronchi and even in some membranous bronchioles.

The ciliated cell constitutes over 90% of the epithelial cell population in the conducting airways (Fig. 1-1), but the number of cilia per cell decreases from proximal to distal airways.[8–10] A central or basal nucleus, scattered fragments of rough endoplasmic reticulum (RER), free ribosomes, Golgi apparatus, and apically placed mitochondria comprise the ultrastructural features of the ciliated cell (Fig. 1-2). The apex of one ciliated cell has 200 to 300 cilia, each 6 to 7 μm long, which arise from basal bodies. Microvilli are less numerous, are about 2 to 3 μm long, and are wider than cilia.

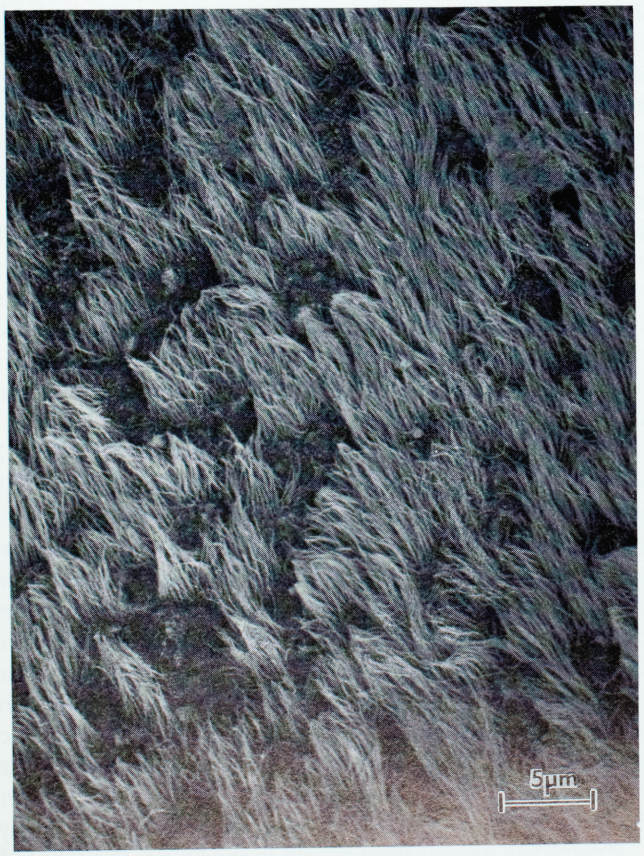

FIGURE 1-1. Scanning electron micrograph demonstrates bronchial mucosa covered with cilia and interposed mucous cells in a baboon lung.

Each cilium contains a central pair of microtubules surrounded by a ring of nine doublet microtubules (Fig. 1-3). The central tubules connect by radial spokes to the outer tubules. The outer doublet tubules have two sets of dynein arms that contain ATPase, which provides the energy for ciliary motility. The tip of the cilia has small claws to help propel mucus. Cilia beat synchronously toward the pharynx at about 1000 times per minute. The 9 + 2 microtubular structure within the cilia is altered in many diseases, including bronchiectasis (see Chap. 28). In addition to its role in the movement of mucus, the ciliated cell transports ions and water and may produce and transport glycoconjugates.

The appearance of the epithelial mucous cell (*i.e.*, nonciliated columnar or goblet cell) varies according to its secretory state.[11] When engorged with mucus, it bulges to a goblet shape and is vacuolated. The periodic acid-Schiff, Alcian blue, and mucicarmine methods stain the secretory material. Its secretory role is reflected in the ultrastructural presence of RER, Golgi apparatus, and large secretory granules (Fig. 1-4). When empty of secretory granules, the mucous cell is categorized as an intermediate (*i.e.*, indeterminate, presecretory) cell. It has been proposed that this cell is the primary progenitor cell of the tracheobronchial epithelium. This view challenges the long-held tenet that the basal cell is the stem cell for bronchial epithelium.

The basal cells of the trachea and large bronchi are small and rest on the basement membrane (see Fig. 1-2). There are no basal cells in terminal and respiratory bronchioles. They have only a few mitochondria and small Golgi apparatus but many intermediate filaments. If they do not serve as a stem cell, their function would be that of an attachment cell for the columnar cell, because the latter do not form hemidesmosomes with the basement membrane. The 60-kd and 51-kd cytokeratins, surface antigens recognized by LAM17 and LAM8, the lectin of *Griffonia simplicifolia*, and the presence of hemidesmosomes are markers for basal cells, but they are not completely specific.

Brush cells are rare but can be found from the trachea to the alveolus.[5,6,9] They cannot be identified definitively in light microscopic sections. Ultrastructurally, their surface is covered by 200-nm-wide microvilli with central fibrils. Coated and uncoated vesicles are below the microvilli, and the cytoplasm contains Golgi apparatus, lysosomes, tonofilaments, and a basal nucleus. Brush cells may be involved in liquid absorption, perhaps act as a chemoreceptor, or be involved in detoxification.

The Kulchitsky cell is part of the amine precursor uptake and decarboxylation or paraneuron series of cells that secrete polypeptides and contain biogenic amines.[12] It has clear cytoplasm and contains small cytoplasmic granules that measure 60 to 200 nm in diameter (Fig. 1-5). They can occur singly or in clusters known as neuroepithelial bodies at the level of bronchioles. The isolated neuroendocrine cells appear to be innervated by cholinergic, adrenergic, and purinergic neural profiles. The neuroepithelial bodies that are covered by Clara cells tend to occur just beyond airway bifurcations and appear to regulate airway or pulmonary blood vessel diameter. Their capillaries have a fenestrated epithelium. They stain with chromogranin and neuron-specific enolase. The cells yield a yellow fluorescence after formaldehyde vapor treatment because of the biogenic amines in their granules, and they can be stained by argentaffin and argyrophilic silver techniques.

The bronchial glands contain mucous and serous epithelial

FIGURE 1-2. Ciliated cells are elongated and have centrally placed nuclei. Several mucus cells are intermingled among the ciliated cells. Beneath these cells are the basal cells (B), which abut the basement membrane in this baboon lung. (Uranyl acetate–lead citrate stain.)

cells, myoepithelial cells, ciliated and collecting duct cells, and some Kulchitsky cells. The mucous and serous cell populations have well-developed endoplasmic reticulum and Golgi apparatus. The secretory granule in the mucous cell shows finely granular material, but the serous cell shows electron-dense granules. The bronchial glands are under neural control and produce more than 90% of the mucus needed for mucociliary function. The secretory component of IgA is synthesized on the basolateral surfaces of bronchial gland cells, where IgA dimers synthesized by plasma cells bind. The complex is endocytosed by the glandular cell and secreted from its luminal surface.

Among the defense mechanisms in the lung, including airway reflexes, cough, bronchoconstriction, secretions (*e.g.*, secretory IgA, lysozyme, lactoferrin) and cellular immune responses, the mucociliary apparatus is perhaps the most important. The ciliated

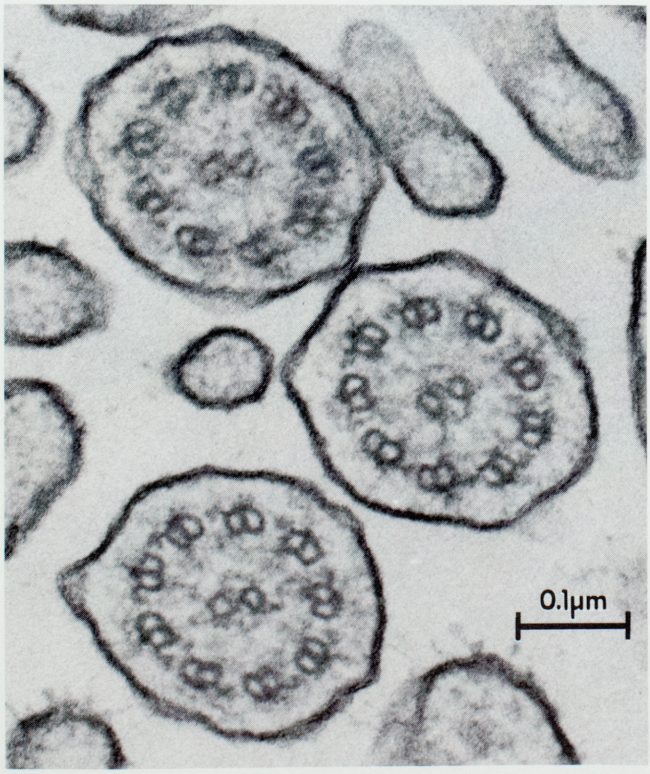

FIGURE 1-3. A cross section of cilia in a human lung shows the central pair and nine peripheral doublets of microtubules. Dynein arms joining the doublets are seen occasionally. (Uranyl acetate–lead citrate stain.)

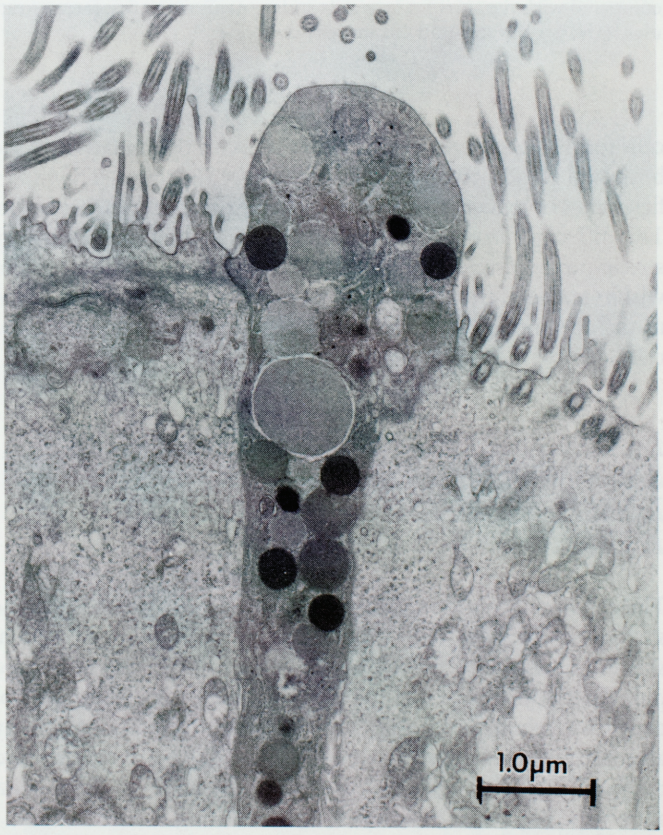

FIGURE 1-4. The cytoplasm of the mucus cell is crowded with secretory granules of various staining intensities. The granules fuse to the apical cell membrane and are secreted into the lumen (*i.e.*, merocrine secretion). (Uranyl acetate–lead citrate stain.)

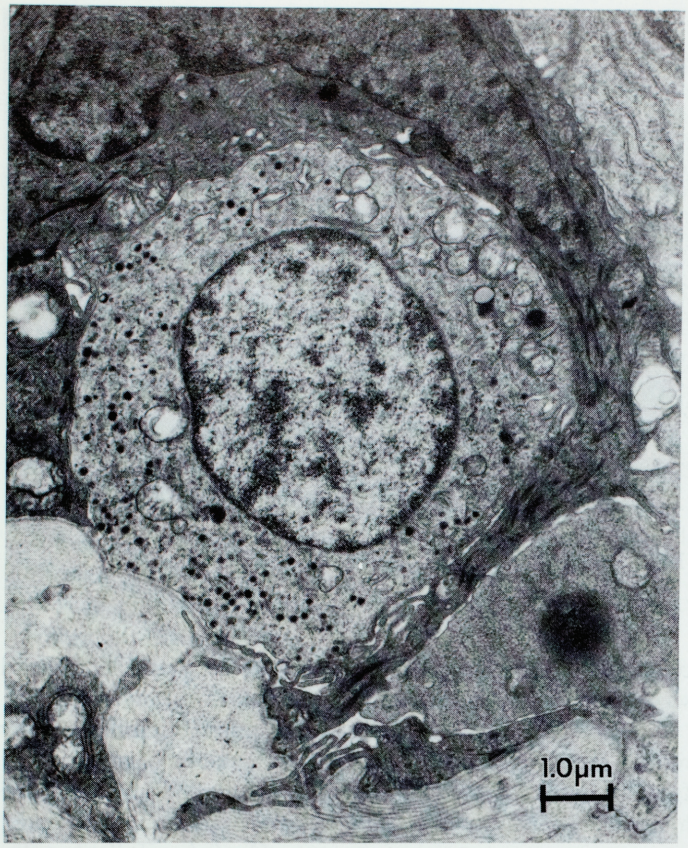

FIGURE 1-5. The Kulchitsky cell in a human lung has clear cytoplasm compared with the surrounding cells and contains many dense core granules. (Uranyl acetate–lead citrate stain.)

cells form a nearly continuous layer and, with the mucus from the bronchial glands, comprise the mucociliary apparatus. The superficial layer of mucus is more viscous than that of the deeper layers. This difference in consistency allows the cilia's power and recovery stroke mechanism to function optimally. There is a lining film within terminal bronchioles whose exact composition is thought to include surfactant and another secretory product from Clara cells.

BRONCHOPULMONARY SEGMENTS, SECONDARY LOBULES, PRIMARY LOBULES, ACINI, AND TERMINAL RESPIRATORY UNITS

The 20 bronchopulmonary segments can be demarcated over the surface of the lung (see Color Fig. 1-1).[1,5,6,13] An adventitial sheath of connective tissue surrounds the bronchi and associated pulmonary and bronchial vessels. The pulmonary veins do not course with the airways; they travel in between regions supplied by adjacent bronchi, and their adventitial sheaths continue outward to blend with the surrounding visceral pleura. This disposition allows the segmental removal of diseased lung.

Secondary lobules are discrete units of respiratory tissue enclosed to a variable degree within connective tissue septa. As shown by Reid and Simon, there is considerable variation in septation, and only in a few areas did they divide the lung into well-defined compartments (Color Fig. 1-2).[13] In their classic study of bronchograms of the distal pathways, they described a coarser pattern of branching, occurring at 0.5- to 1.0-cm intervals, merging into a finer pattern at 0.2- to 0.3-cm intervals (*i.e.*, the centimeter and millimeter pattern). They suggested that the transition from a centimeter to a millimeter pattern of branching demarcates a secondary lobule, such as a membranous bronchiole from which terminal bronchioles arise, constituting a unit of about 1 to 2 cm in diameter. The secondary lobule is defined as a cluster of three to five terminal bronchioles and their associated respiratory tissue (Fig. 1-6). The acinus is a single terminal bronchiole and its divisions (*i.e.*, respiratory bronchioles, alveolar ducts, and alveoli). This unit corresponds to Reid and Simon's millimeter unit (see Chap. 28).

Several other terms are used less frequently and are not consistently defined. Structures distal to one terminal bronchiole have been referred to as acini, primary lobules, or terminal respiratory units (TRU). A primary lobule has also been defined as a respiratory bronchiole and its subsidiary divisions. A TRU is composed of several alveolar ducts with their accompanying alveoli; an acinus contains 10 to 12 TRUs. At functional residual capacity, a TRU measures 3.5 mm in diameter and has a volume of 0.02 mL. There are 150,000 such units in the normal adult lung. It is thought that sequential ventilation occurs at the level of the TRU. Air remains in the alveolar duct while exchange by diffusion takes place in adjacent alveoli. During the next breath, the inspired fresh air fills the alveolar ducts while the alveoli fill with the end-expiratory alveolar duct gas from the prior breath.[14]

The gas exchange units do not contribute to anatomic dead space. The summed volume of the bronchi below the trachea

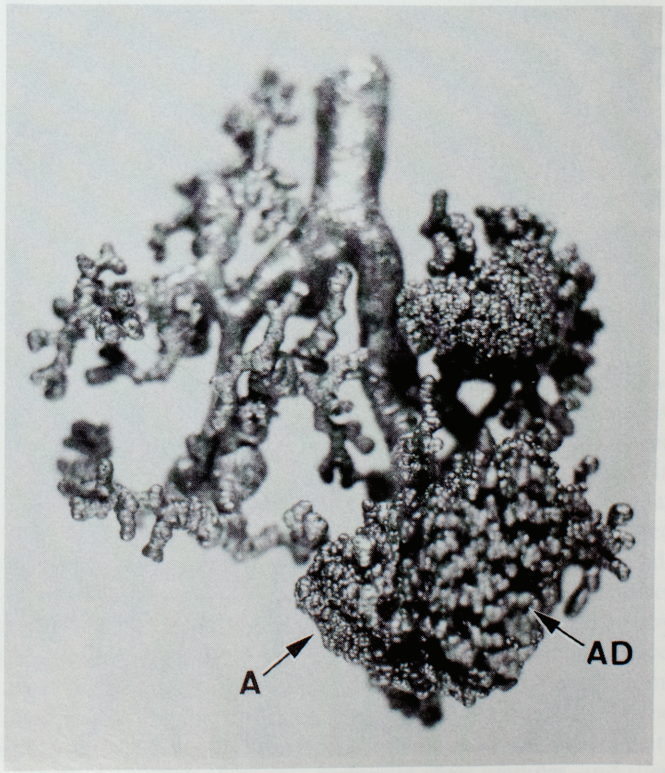

FIGURE 1-6. In this Wood metal cast of a secondary lobule in a human lung, portions of the lobule have been removed to show the branches. Alveolar ducts (AD) and alveoli (A) are indicated.

accounts for almost one half of the anatomic dead space, and the other one half lies above the carina. In that portion distal to the carina, more than 90% is localized within the large bronchi. Bronchioles passively dilate and contract with increases and decreases in lung volume because they are directly attached to the connective tissue framework of the lung. Constriction of the airways increases their resistance to airflow in proportion to the fourth power of the radius. Because the alveolar duct rings contain smooth muscle, they also have the potential to regulate volume and distensibility of the alveoli.

BRONCHIOLES

A bronchiole (*i.e.*, small airway) is characterized by columnar epithelium, in which the mucous cell is replaced by the secretory Clara cell; by an increased muscular layer; and by a lack of submucous glands and cartilage (Fig. 1-7).[5,6,15] Occasionally referred to as membranous bronchioles, they are about 1 mm in diameter and become terminal bronchioles at about 0.5 mm in diameter. There are 30,000 to 85,000 terminal bronchioles in the normal lung. The terminal bronchiole branches into three orders of respiratory bronchioles with increasing numbers of alveoli in their walls (Fig. 1-8). Respiratory bronchioles are about 0.15 to 0.2 mm in diameter and give rise to alveolar ducts (Fig. 1-9).

The alveolar duct is the conduit from which a series of alveoli open. It is histologically characterized by small clublike ends that contain muscle sphincters and elastic fibers (Fig. 1-10). The alveolar ducts open into round spaces or atria representing the center of alveolar sacs to which several cup-shaped alveoli abut (Fig. 1-11). Normal adults have 225×10^6 to 600×10^6 alveoli. Because of larger lung volumes, the total number of alveoli is larger in men. An individual alveolus measures about 200 nm in diameter and about 15,000 alveoli connect to a single terminal bronchiole.

In the bronchiolar epithelium there is a ratio of about three ciliated to two nonciliated cells. The nonciliated Clara cell is a dome or tongue-shaped cell that usually protrudes into the bronchiolar lumen above the shorter ciliated cells.[15,16] It possesses an abundance of RER, mitochondria, and prominent secretory granules (Fig. 1-12). The Clara cell has a secretory function, but three

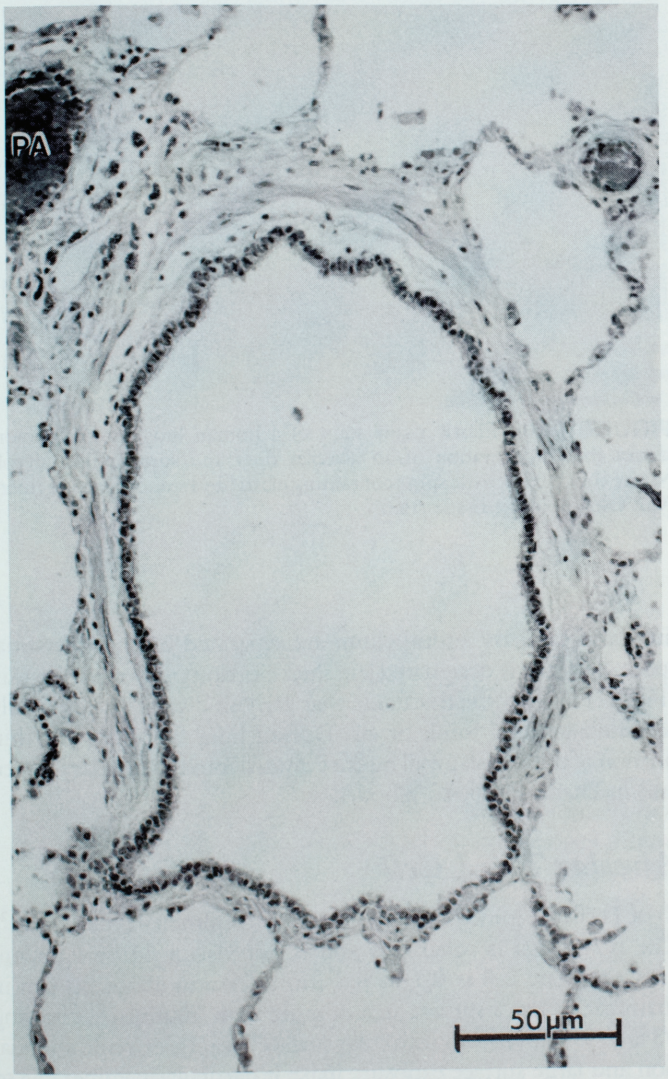

FIGURE 1-7. A microscopic view of a human lung shows a bronchiole, which is lined with columnar epithelium and has an investment of smooth muscle in its wall. Notice its accompanying pulmonary artery (PA). Had this bronchiole connected with a respiratory bronchiole, it could be called a terminal bronchiole; otherwise, it is designated a bronchiole. (H & E stain.)

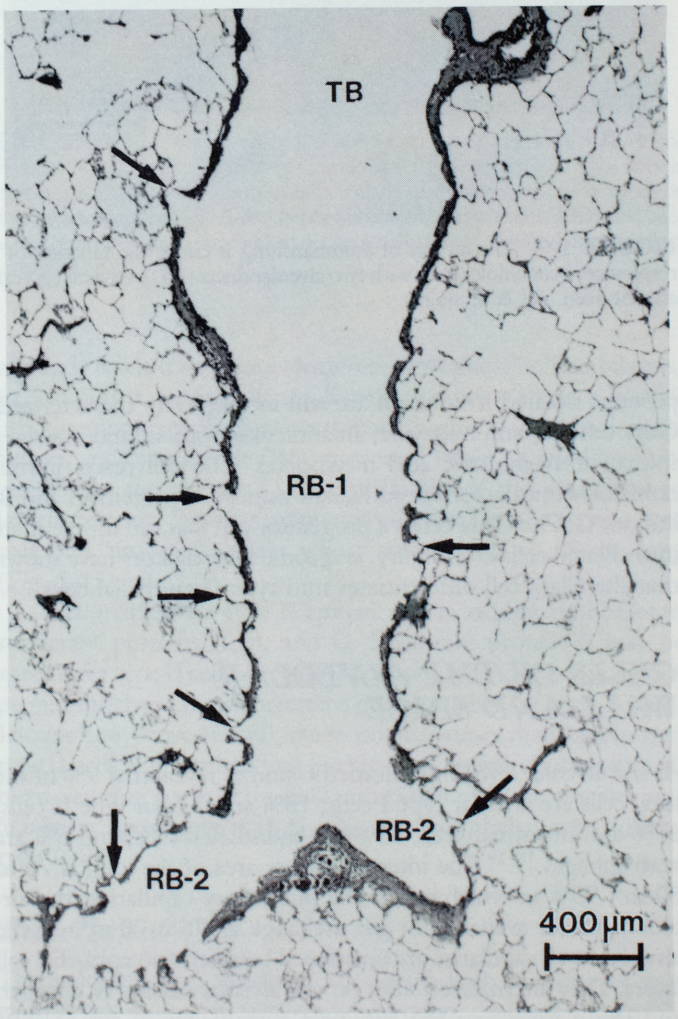

FIGURE 1-8. This micrograph of a human lung depicts a cut through a terminal bronchiole (TB) that opens into a respiratory bronchiole (RB-1) and its branches (RB-2). Notice how the spans of bronchiolar epithelium decrease in length as the number of alveoli (*arrows*) increase. (H & E stain.)

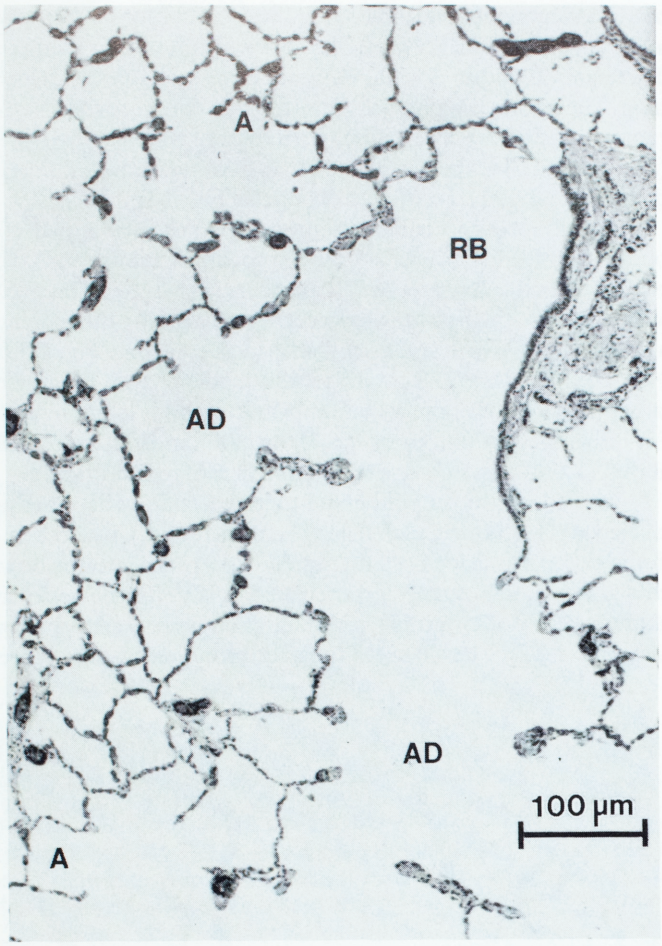

FIGURE 1-9. The airway of a human lung is cut at the junction of a respiratory bronchiole (RB) with two alveolar ducts (AD). Alveoli (A) can also be seen. (H & E stain.)

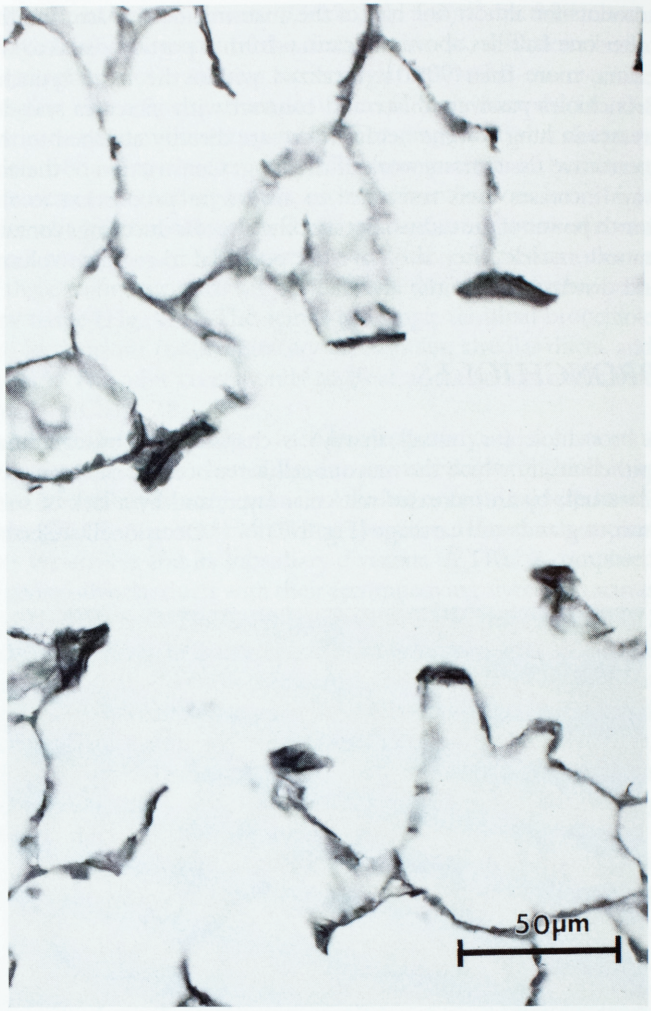

FIGURE 1-10. Elastic tissue stain of a human lung sample demonstrates the configuration of an alveolar duct and surrounding alveoli. Notice the characteristic spurs containing elastic and smooth muscle fibers. (van Gieson elastic tissue stain.)

proteins isolated from them are still incompletely characterized. Clara cells contain lysozyme, an antileukoprotease, and may be a source of arachidonic acid metabolites. The cell reacts immunohistochemically for the surfactant-associated proteins A and B, but not C. The Clara cell is a progenitor cell that can differentiate into ciliated cells after injury, and some investigators have shown that the Clara cell differentiates into type II epithelial cells.

CELLS OF THE ALVEOLAR WALL AND SPACE

At the alveolar level, morphometric studies reveal that 9% of the total cells are alveolar type I cells, 15% are alveolar type II cells, 37% are interstitial cells, 33% are endothelial cells, and 6% are macrophages.[17–19] The internal surface area of the lung is 70 to 80 m^2, 90% of which covers the pulmonary capillaries; the air-blood surface available for gas exchange is 60 to 70 m^2. At the alveolar level, capillaries are positioned between two epithelial cell layers. They alternatively abut on one alveolar surface or another, and the place where the basement membranes of the alveolar epithelium and capillary endothelium are fused is designated the thin portion of the alveolar capillary wall. It is this site where gas exchange takes place. On the opposite side, the capillary epithelium and capillary endothelium are separated by the interstitial space, and this is designated the thick portion of the alveolar wall (Fig. 1-13). It is the thick side that early in disease preferentially accumulates cells, fluid, or air. During lung deflation, the thin portion of the alveolar wall buckles inward into the capillary lumen and mechanically slows blood flow.

Alveolar Type I Cell

Type I cells are joined by tight junctions to epithelial type II cells.[20] The type I cell is squamous and is not visualized by light microscopy. The cell is 0.1 to 0.3 μm thick and about 50 μm in diameter. It has a surface area of more than 5000 μm^2, covering 93% to 97% of the total alveolar surface area. Its extreme attenuation and large surface exposure make it particularly vulnerable to injury. Few organelles can be seen at the ultrastructural level; among these are pinocytotic vesicles, a small Golgi apparatus, a few RER cisternae, and mitochondria. Its primary function is the diffusion of gases between alveolar air and capillary blood, but its pinocytotic system may transport albumin and immunoglobulin

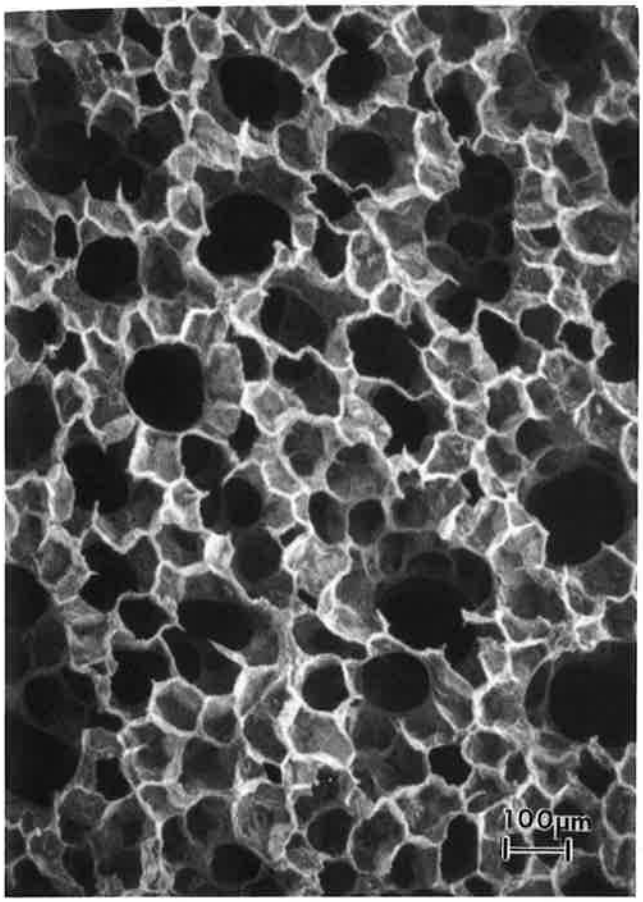

FIGURE 1-11. A scanning electron micrograph of a well-inflated baboon lung shows the relation among alveoli (*small spaces*), atria (*round spaces where several alveoli abut*), and alveolar ducts (*larger irregular spaces*).

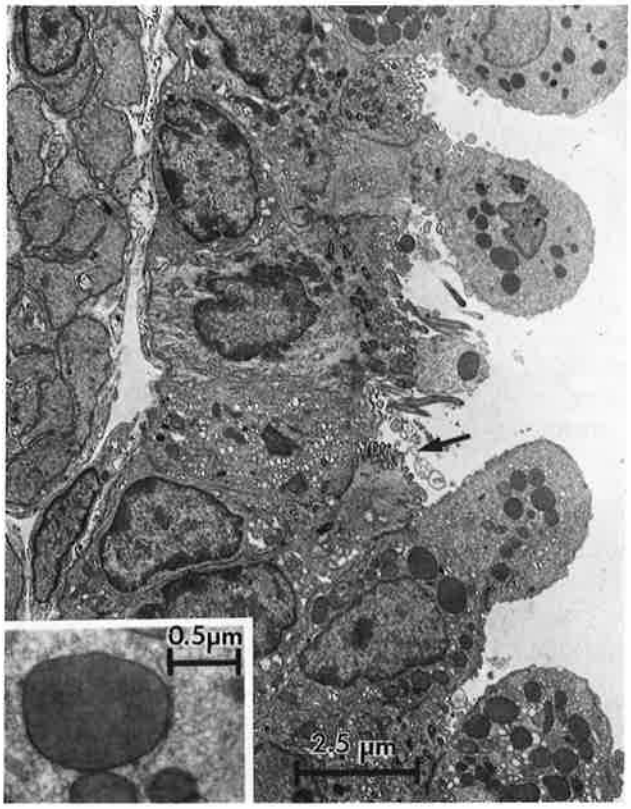

FIGURE 1-12. The bronchiolar epithelium in a pig lung shows numerous Clara cells containing characteristic secretory granules. Their apices protrude into the lumen, which gives them their domed or tonguelike appearance. A brush cell (*arrow*) is also present. Characteristic apical granules are contained in a Clara cell (*inset*). (Uranyl acetate–lead citrate stain.)

in small quantities. It cannot divide and must be replenished by the stem cell, the alveolar type II cell.

Alveolar Type II Cell and the Production of Surfactant

The type II cell is cuboidal and about 9 μm in diameter. There is approximately one per alveolus.[21] It can be seen by light microscopy and was called a corner cell, niche cell, or septal cell by early histologists. Its volume is about 900 μm^3, and that of the type I cell is 1800 μm^3. Type II cells, like type I cells, occasionally face two separate alveolar surfaces, filling potential pores of Kohn.

The alveolar type II cell is a source of surfactant, which is the substance needed to reduce surface tension at the alveolar level. It also synthesizes and secretes connective tissue components of the basement membrane, including fibronectin; synthesizes and secretes components of the complement system; and expresses class II proteins of the major histocompatibility complex. Each type II cell has characteristic 0.1-μm-wide surface microvilli and about 150 cytoplasmic lamellar inclusions, which are the intracellular cytoplasmic storage form of surfactant (Fig. 1-14). The inclusions are thought to evolve from multivesicular bodies or lysosomal granules, which progressively acquire the characteristic lamellae. Studied with the freeze-fracture technique, they are composed of regularly stacked lamellae, which represent phospholipid bilayers. In addition to surfactant, the lamellar bodies contain a host of other components, such as phosphatase, esterase, catalase, transferases, and cytochrome P450 isozymes. When secreted by exocytosis into the alveolus, a reorganization of the phospholipid lamellae occurs, forming tubular myelin that in cross section consists of a lattice of squares whose sides are 45 to 55 nm long (Fig. 1-15).

Cell markers for type II epithelial cells include antibodies to surfactant proteins A, B, and C. Surfactant protein C may be specific for type II cells, because it does not stain Clara cells. cRNA probes for the various surfactant proteins label the type II cells. Lectins have proved useful; the lectin of *Maclura pomifera* binds to type II cells in preembedding ferritin-based methods. Postembedment staining with lectin-gold complexes of *Helix pomatia* and *Sambucus nigra* stain type II cells and endothelial cells but not type I cells.

Endothelial Cell

The endothelial cell is difficult to identify with certainty by light microscopy unless it surrounds an open capillary lumen.[5,6,9] Ultrastructurally, the pulmonary endothelium is usually a little thicker than the type I epithelium and contains a few profiles of RER, few mitochondria, and many caveolae, the walls of which

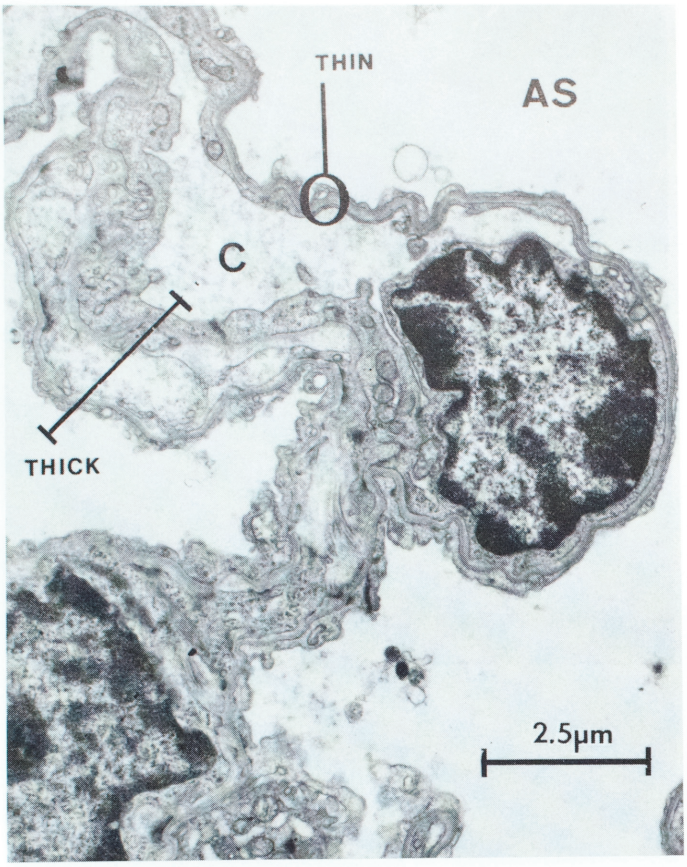

FIGURE 1-13. The thin, air-exchange side of the alveolar wall in a monkey lung can be compared with the thick portion, in which the basement membranes are separated by the interstitium and its contents. (AS, alveolar space; C, capillary lumen; uranyl acetate–lead citrate stain.)

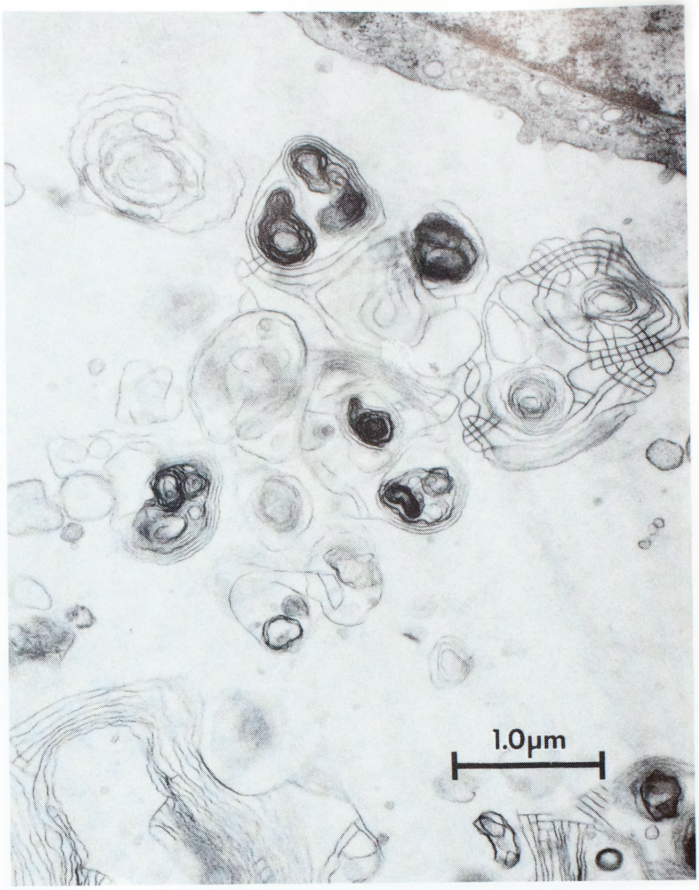

FIGURE 1-15. Tissue culture of type II pneumocytes from a rat. Lamellar bodies released from the cells form the characteristic lattice of tubular myelin. (Uranyl acetate–lead citrate stain; courtesy of Richard King, Ph.D., San Antonio, TX.)

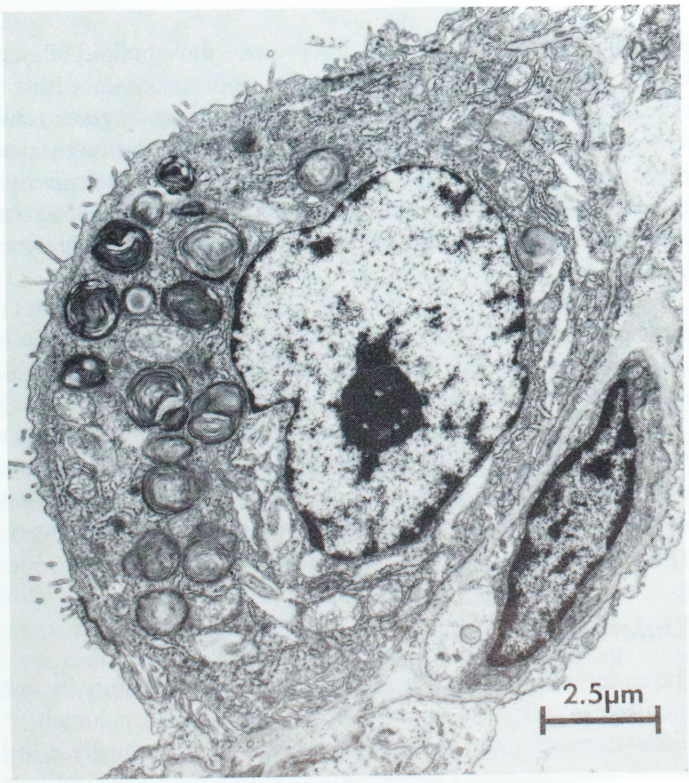

FIGURE 1-14. The cytoplasm of a type II cell in a monkey lung contains many mitochondria and osmiophilic lamellar bodies. Microvilli extend over the surface of the cell. (Uranyl acetate–lead citrate stain.)

are sites of enzyme activity. It is continuous; tight junctions join endothelial cells. Adenine nucleotides, various peptides, prostaglandins, and biogenic amines can be metabolized and taken up within the extensive capillary bed. The endothelium plays an important role in the diffusion of gas exchange and it is a major site of liquid and solid exchange. The widely used cell marker for endothelial cells is factor VIII antibody, but endothelial cells can also be stained with antibodies against ABO blood groups. The antibody to *Ulex europaeus* also binds to endothelial cells in paraffin-embedded sections.

Interstitial Cells

The interstitium of the alveolar wall is not well delineated at the light microscopic level.[5,6,9] The interstitial cell population includes resident and migratory cell populations. Pleuripotential cells, fibroblasts, smooth muscle cells, rare inflammatory cells such as lymphocytes and monocytes, pericytes, and cells with features of myofibroblasts are present. The myofibroblast represents a mixed-cell population with different contractile protein patterns. These cells react to hypoxia and are thought to decrease alveolar size and assist in the autoregulation of ventilation-perfusion ratios.

Alveolar Macrophages

At the alveolar level, the alveolar macrophage is responsible for phagocytosis of inhaled particles smaller than 5 μm that are not captured by the mucociliary blanket.[22,23] Although seen free floating in alveolar spaces by light microscopy, the alveolar macrophage

crawls along the alveolar surface epithelium, adhering with its filopodia (Fig. 1-16). The cell's lysosomal populations vary, and the amount of Golgi complex and ribosomes depends on its functional state. Alveolar macrophages are thought to derive from blood monocytes. Some directly enter the alveolus; others sojourn in the interstitium for an unknown period. It appears that the turnover time of resident macrophages is about 25 days. Injury can increase replication up to 45-fold. Several subpopulations of macrophages have been identified: intraalveolar, septal (*i.e.*, interstitial), intravascular, and airway. The cells play a role in surfactant removal or catabolism; surfactant material can be found often within the cytoplasm of macrophages (see Fig. 1-16).

FIBROUS SKELETON OF THE LUNG

The lung has three functional components of connective tissue: the axial connective tissue of bronchi, bronchioles, and pulmonary vessels; the parenchymatous connective tissue within the alveolar septa; and the peripheral connective tissue of the pleura, interlobar, and interlobular septa.[7] It extends from the visceral pleura to the hilum and is thereby connected with the mediastinum.

The connective tissue matrix of the lung contains proteoglycans, glycoproteins, collagens, and elastins. The fibers are composed of collagen types I, II, and III, microfibrils, and elastic fibers. Basement membranes are constituted of type IV collagen, proteoglycans, and glycoproteins. The elastic fiber network extends in and around the muscularis and the cartilage plates. Reticulin fibers follow approximately the same distribution as the elastic fibers. The elastic and collagen fibers are arranged in spirals that invest the walls of airways. Within bronchioles, elastic fibers become more circular and then continue to branch out and envelop alveolar ducts and alveoli.

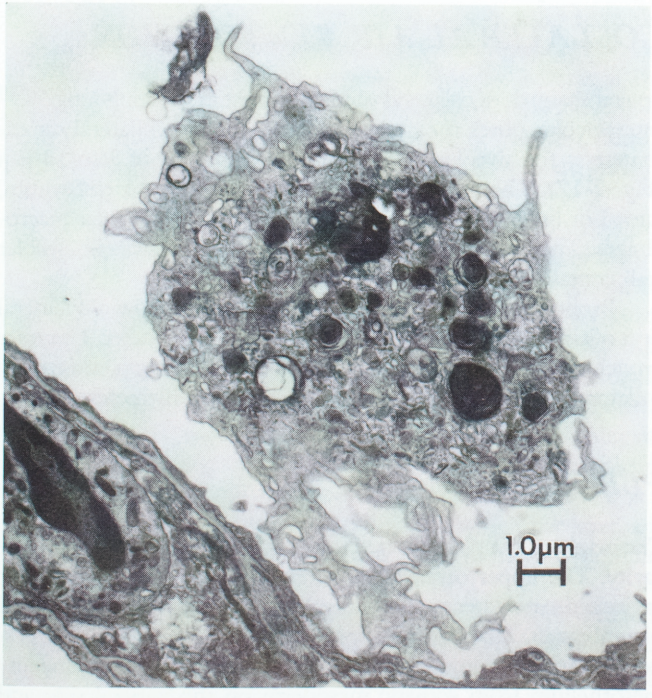

FIGURE 1-16. In this human lung sample, an alveolar macrophage is attached to the underlying alveolar wall by characteristic filopodia. There is variation in the cytoplasmic contents, including the presence of surfactant remnants. (Uranyl acetate–lead citrate stain.)

Smooth muscle bundles extend from the major bronchi to respiratory bronchioles. Transverse bundles of muscle connect the ends of the cartilage in the trachea and main bronchi, but they become a complete ring in more distal bronchi. At the bronchiolar level, the muscle runs in an oblique fashion that allows narrowing and shortening of the airway during contraction.

LUNG VASCULATURE

The lung is richly endowed with a double vascular supply from pulmonary and bronchial arterial sources.[4–6] The supplies have been designated "public" and "private." The former serves the body as a whole, and the latter sustains the pulmonary parenchyma, particularly the bronchi.

Pulmonary Circulation

At birth, the pulmonary artery and aorta are comparable in medial thickness, elastic configuration, and diameter. By 1 to 2 years of age, elastic tissue has decreased in the pulmonary artery, and its thickness is about 60% that of the aorta. Instead of condensed elastic laminae as seen in the aorta, the pulmonary artery has elastic fiber disruption and an increase of collagen fibers with age.

On entering the lung, the pulmonary arteries retain the same elastic fiber configuration until they are about 1 mm in diameter. They merge into muscular pulmonary arteries that range in external diameter between 100 and 1000 μm. Elastic fibers form the internal and external elastic lamina that separate a thin medial muscular layer. The medial thickness is 3% to 8% (mean, 5%) of the external diameter. The muscular pulmonary arteries provide the tone needed to regulate the low-pressure, low-resistance pulmonary circuit. At an external diameter of about 90 to 100 μm, the muscular pulmonary artery loses its muscular coat, and the external elastic lamina (*i.e.*, endothelial cell) rests on the remaining internal elastic lamina. Pericytes can be identified in these nonmuscular arteries or arterioles.

On the venous side, postcapillary venules are structurally identical to precapillary arterioles and can only be separated by serial section techniques. Pulmonary veins are located in the fibrous septa at the periphery of the lung lobules and have diameters greater than 100 μm. Their walls contain collagen, elastic fibers, and some smooth muscle with no clear demarcation between media and adventitia, unlike the larger veins that possess an internal elastic lamina. The extrapulmonary veins have irregular bundles of smooth muscle admixed with elastic and collagen fibers. There are no valves in pulmonary veins. The pulmonary arteries and veins have a dichotomous branching pattern, but numerous supernumerary branches arise perpendicularly or obliquely.

Stretching between arterioles and venules, there is a rich capillary network supported by the walls of alveoli. The gas exchange takes place here, particularly at the thin portion of the alveolar-capillary membrane (see Fig. 1-13). Of about 200 mL of capillary bed volume, only one third is used at rest for gas exchange.

Bronchial Circulation

Although two major bronchial arteries for each lung is considered a common pattern, it occurs in less than 40% of the population. There are usually two bronchial arteries in the left lung and one in

the right. The left bronchial arteries usually arise from the upper portion of the descending aorta. The right bronchial artery can arise from the descending aorta, a right intercostal branch, subclavian artery, or internal thoracic artery. The bronchial arteries enter the wall of the lower trachea, ramify with the bronchi (usually on the posterior aspect), and nourish the bronchial tree down to the level of the respiratory bronchioles; at this level, they give off capillaries that communicate with pulmonary capillaries. The diameter of the bronchial artery is much smaller than that of the accompanying pulmonary artery, and it has an internal elastic lamina and media but no external elastic lamina. It has a thicker media in relation to its wall size than the pulmonary artery. Bronchial arteries also supply the visceral pleura. They proliferate in certain lung diseases, liver disease, and congenital heart disease.

Bronchial-to-pulmonary arterial anastomoses can occur (see Chap. 2). There are fewer between bronchial arteries and none connecting pulmonary arteries. Bronchopulmonary shunts become more prominent in disease. In bronchiectasis, tuberculosis, and congenital heart disease, large anastomoses develop between the bronchial and pulmonary artery circuits. Bronchial arteries also supply primary bronchogenic carcinomas (see Chap. 25).

LYMPHATICS

The lung has abundant lymphatic vessels within its interstitium (*i.e.*, deep or parenchymal plexus) and pleura (*i.e.*, pleural or superficial plexus).[1–6] The superficial lymphatic vessels in the pleura form a pattern of irregular polyhedra that demarcate the secondary lobules. The two plexuses anastomose at the hilum. The walls of lymphatics are not easily identified in normal lungs. They are thin and found in the connective sheaths in and around arteries, veins, and airways and within the interlobular septa. They become obvious when filled with tumor cells in carcinomatosis of the lung. Larger lymphatics may contain a few muscle fibers similar to pulmonary veins. Their prominence in respiratory distress syndrome in infants and conditions of congestion and edema in adults makes them readily identifiable. There are no lymphatics within the alveolar walls, but the interstitium is in continuity with lymphatic vessels.

BRONCHUS-ASSOCIATED LYMPHOID TISSUE

Immunocompetent cells in the lung can be found in bronchoalveolar air spaces, the submucosa of the tracheobronchial tree, tracheobronchial lymphatics, and lymph nodes.[5,6] In bronchoalveolar lavage fluid, 90% of the cells are alveolar macrophages and 1% to 5% are lymphocytes; of the latter, 60% to 70% are T cells and 5% to 10% are B cells.[18,19] Bronchus-associated lymphoid tissue (BALT) appears as isolated nodules in the connective tissue of the lamina propria of the bronchial tree and produces primarily IgG and secretory IgA. The collections of BALT cells tend to occur at airway bifurcations and are covered by a special epithelium that can pinocytose and transport solutes and particulate antigens. BALT is sparse at birth, but it starts accumulating thereafter; although most of the cells are B lymphocytes, T cells are also found.

NEURAL SUPPLY

There is a common embryologic origin of the nerves and smooth muscle of the gastrointestinal tract and the lungs.[2,4–6] After forming the pericardial and extrapulmonary plexuses, migrating neuroblasts in the region of vagal, lower cervical, and upper thoracic ganglia establish in the walls of the future trachea and lung buds. After the separation of the trachea and foregut is accomplished, the neuroblasts form the ganglia of the airways. Blood is supplied to these ganglia from bronchial arteries.

The basic pattern of innervation in the lung is a parasympathetic supply from the vagus nerve and a sympathetic supply from the sympathetic trunk. Functions of the two autonomic systems are fairly well defined. The smooth muscle of airways, blood vessels, epithelium of bronchial glands, and goblet cells are innervated by postganglionic fibers from the vagus, providing stimulation for contraction of smooth muscle, secretion of glands, and vasodilation. The sympathetic system through α-adrenergic stimulation induces bronchial and vascular smooth muscle cell constriction, and β-adrenergic stimulation induces decreased secretion of bronchial glands and bronchodilatation.

In addition to the cholinergic (*i.e.*, parasympathetic) and sympathetic (*i.e.*, adrenergic) nerve fibers, a nonadrenergic-noncholinergic or purinergic (*i.e.*, peptidergic) system appears to be involved in bronchial smooth muscle relaxation. Two peptides, vasoactive intestinal peptide and substance P, may be mediators in this system. There exist vagal sensory receptors that control some functions of breathing, cough, smooth muscle tone of airways, changes in heart rate, and quantity and composition of secreted mucus. In the lung, nerve fiber bundles traverse with the major bronchi and blood vessels to the level of the respiratory bronchiole and alveolar wall. Intraepithelial nerves have been seen in most epithelial cell types, particularly in basal cells.

COLLATERAL AIR VENTILATION

Several channels of collateral ventilation exist in the adult lung.[4–6,14] Interalveolar pores (*i.e.*, pores of Kohn) allow collateral air exchange at the alveolar level; they have diameters of 3 to 13 μm (Fig. 1-17). These can be open, covered by type I epithelium, joined or lined by a type II cell, or traversed by alveolar macrophages. They are rare in the newborn lung. The average alveolar wall contains one to six pores.

Bronchiole-to-bronchiole communications allow a collateral drift of air, and they are about 80 to 150 μm in diameter. There are bronchiole-to-alveoli openings (*i.e.*, canals of Lambert) that allow collateral flow of air and are about 30 μm in diameter.

PLEURA

The origin of the pleura is tied to the partitioning of the coelomic cavity. The upper cephalad portion of the embryonic coelomic cavity ultimately becomes a central pericardium and two bilateral pleural canals. Through partitioning by the diaphragm, pleuroperitoneal canals become separated, and the pleural cavity is lined by mesothelium from somatic mesoderm on the parietal side and splanchnic mesoderm on the visceral side. When the lung branches, the central mass of mesenchyme that resides between the

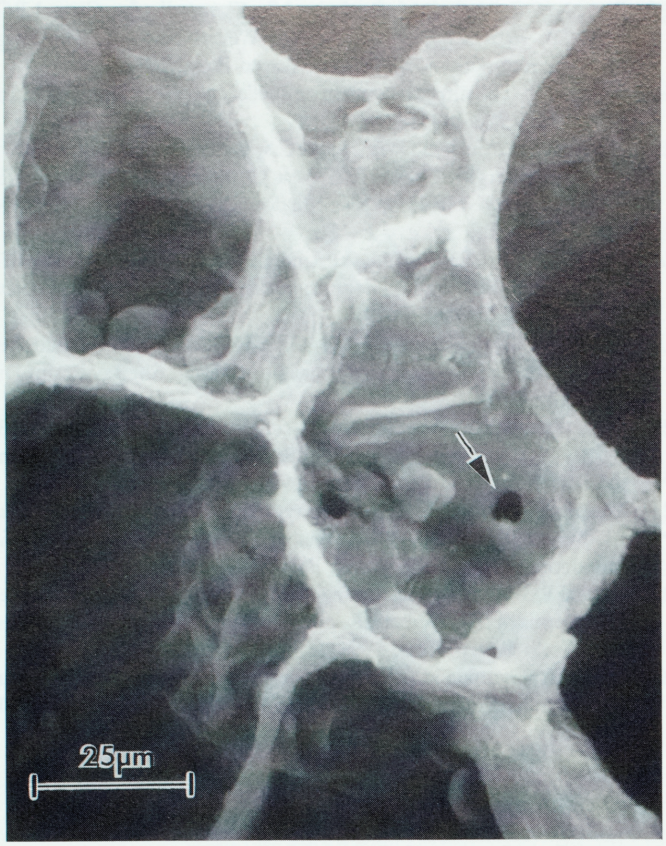

FIGURE 1-17. In this scanning electron micrograph of a baboon lung, a pore of Kohn (*arrow*) is present in one alveolar wall. Several macrophages are noted on the alveolar surface.

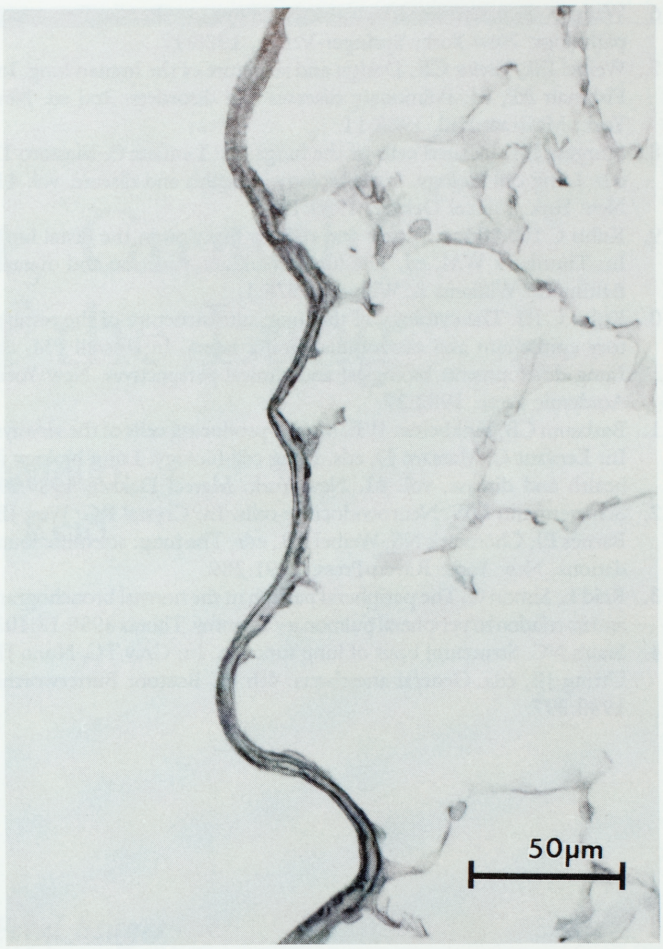

FIGURE 1-18. Elastic tissue stain of the human pleura demonstrates its bilayer composition. (van Gieson elastic tissue stain.)

two pleural cavities becomes the mediastinum. As lungs grow into the pleural cavities, they carry the lining mesothelium from the splanchnic mesoderm that becomes the visceral pleura. The visceral pleura extends into the interlobar fissures, reflects at the hilum, and becomes continuous with the parietal pleura that lines the mediastinum, thoracic wall, and diaphragm. The thin, double fold of pleura that extends from below the hilum to the diaphragm becomes the pulmonary ligament.

The mesothelial cells are distensible. They are 15 to 30 μm wide and 1 to 4 μm thick. Seen by light microscopy, they form a flat cuboidal or columnar lining epithelium. They are joined by tight and gap junctions and a few desmosomes.[5,6] There is considerable variation in the density of microvilli on mesothelial cells from cell to cell and region to region. In addition to the microvilli, the cells are characterized ultrastructurally by many mitochondria, prekeratin fibrils, and pinocytotic vesicles. The parietal pleura sits on a base of collagen, fat, and elastic fibers, but the visceral pleura has several layers. From the mesothelial cell inward, there is a sparse connective tissue layer, a prominent elastic fiber layer, another loose connective tissue layer, and a second elastic layer intermixed with some collagen fibers (Fig. 1-18).

The blood supplies for the two pleura are from different systemic sources. The visceral pleura is supplied by the bronchial artery, and the parietal pleura is supplied by intercostal arteries (*i.e.*, costal portion) and the pericardiophrenic branch of the internal mammary artery (*i.e.*, mediastinal and diaphragmatic portions). The visceral pleura is supplied by autonomic nerves, and the parietal is supplied by sensory branches of the spinal, intercostal, and phrenic nerves.

Stomata are found in the infracostal and mediastinal regions of the parietal pleura in the lower thorax. These stomata allow entry of larger particles and removal of lymph from the pleural cavity. The pleural cavity is a virtual space that separates the visceral and parietal pleura; it is lined by a layer of pleural fluid rich in hyaluronic acid. It is estimated that 50% of the available fluid is intermeshed within the long, bushy microvilli of the mesothelial cells.

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