SECTION **A**

ANATOMY AND DEVELOPMENT OF THE RESPIRATORY TRACT

1 *ANATOMY*

KURT H. ALBERTINE, PHD, FAAAS, FAAA • MARIA I. RAMIREZ, PHD • RORY E. MORTY, PHD

INTRODUCTION

The lung has two essential, interdependent functions. One essential function is ventilation-perfusion matching to deliver *oxygen* (O_2) to the body and to remove the *carbon dioxide* (CO_2) produced by the body (Fig. 1.1). The second essential function is host defense against the onslaught of airborne pathogens, chemicals, and particulates. These essential functions are emphasized through the gross, subgross, histologic, cellular, and molecular determinants of the respiratory gas-exchange process in the normal human lung.[1] Other secondary functions of the lung, which support the essential functions, are important, such as cellular functions of surfactant synthesis, secretion and recycling, mucociliary clearance, neuroendocrine signaling, and synthesis and secretion of myriad molecules by the epithelial and endothelial cells of the lung. The diversity of secondary functions emphasizes the importance of the lung in homeostasis. Finally, the widespread use of murine models in lung research as surrogates for the human lung highlights the need to understand the similarities and differences of the lung between these species. The anatomic features that support the essential and secondary functions and comparative anatomy topics are the focus of this chapter. In addition, online supplemental digital videos linked to this chapter provide views of lung movements related to changes in tidal volume, airway pressures, and respiratory rate. (Videos 1.1 to 1.5).

GROSS AND SUBGROSS ORGANIZATION

The position of the lungs in the chest and in relationship to the heart is shown in Fig. 1.2. Fig. 1.2A shows a midfrontal section through the thorax of a frozen human cadaver. Fig. 1.2B shows a posterior-anterior chest radiograph of a normal human at *functional residual capacity* (FRC). The two illustrations represent the extremes of the approaches to study lung anatomy. On one hand, the cadaver lung (see Fig. 1.2A) shows the gross anatomic arrangements and relationships. The main distortion is that the lungs are at low volume. The height of the lungs is only about 18 cm, which is well below FRC height (see Fig. 1.2A). The diaphragm is markedly elevated in Fig. 1.2A, probably about 5 cm relative to its end-expiratory position in life. Another distortion is the abnormally wide pleural space. However, that fixation shrinkage artifact serves as a useful reminder that the lung is not normally attached to the chest wall. In life, the separation between the parietal and visceral pleurae is only several micrometers.[2,3] On the other hand, the chest radiograph (see Fig. 1.2B) shows that the height of

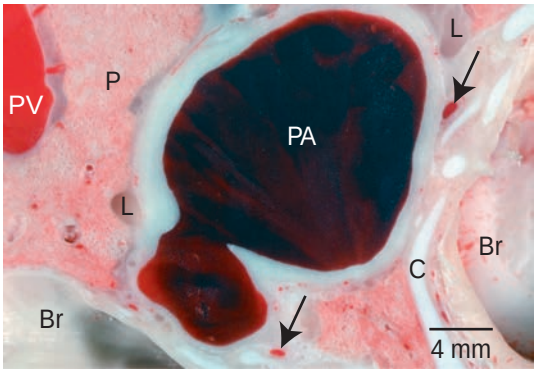

Figure 1.1 Levels of oxygenation of blood in a frozen block of lung tissue. Air is brought into the lung via the bronchus (Br). Pulmonary arterial (PA) blood is dark purple because it is poorly oxygenated. Gas exchange across the lung's parenchyma (P) results in oxygenated pulmonary venous (PV) blood, which is crimson. Also present in the peribronchovascular connective tissue are bronchial arteries *(arrows),* cartilage (C), and lymphatics (L). (Frozen sheep lung, unstained.)

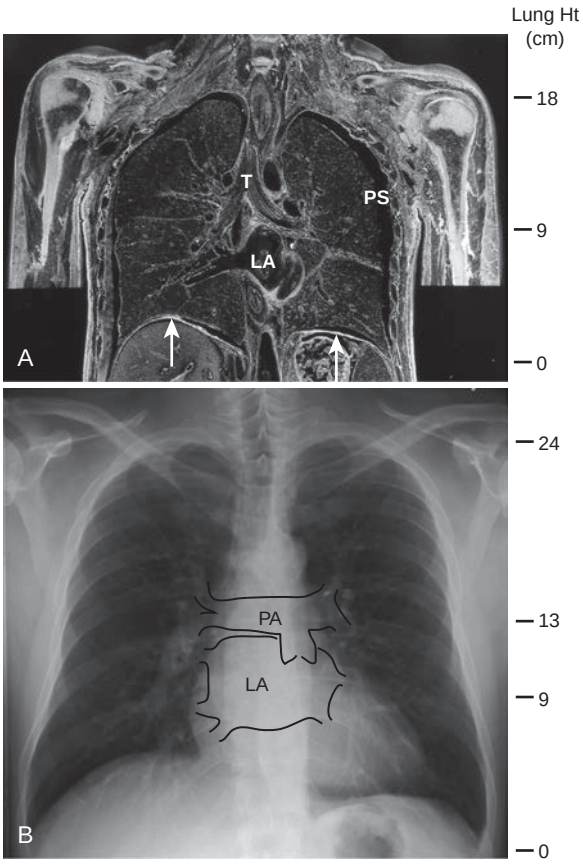

Figure 1.2 Comparison views of the position of the lungs in the chest and their relationship to the heart. (A) Midfrontal section through the thorax of a frozen cadaver of a 35-year-old human. The cadaver was prepared by routine embalming procedures, stored horizontally for 3 months in 30% alcohol, and frozen in the horizontal position for 1 week at −20°C. Frontal sections were cut with a band saw. Because the cadaver was preserved in the horizontal position, the weight of the abdominal organs compressed the contents of the thoracic cavity. The domes of the diaphragm *(arrows)* are elevated about 5 cm relative to their end-expiratory position in life. Pleural space (PS) width is artifactually enlarged; normally, in life it is several micrometers in width. The trachea (T) is flanked on its left by the aortic arch and on its right by the azygos vein. The left pulmonary artery lies on the superior aspect of the left mainstem bronchus. Pulmonary veins from the right lung enter the left atrium (LA), which is located about 7 cm above the lung's base. These structures at the root of the lungs caused the esophagus to be cut twice as it follows a curved path behind them to reach the stomach. (B) Chest radiograph of a normal human adult taken in the upright position at functional residual capacity. The lung height (cm) was measured from the costodiaphragmatic angle to the tubercle of the first rib. The main pulmonary artery (PA) and LA are outlined. The vascular structures, especially the pulmonary veins, are more easily seen near the base of the lung. This is partly because vascular distending pressures are greater near the bottom. The density of the lung is also graded, being higher at the bottom than the top and higher near the hilum than peripherally. (From Koritké JG, Sick H. *Atlas of Sectional Human Anatomy.* vol. 1: *Head, Neck, Thorax.* Baltimore: Urban and Schwarzenberg; 1983:83.)

the lung at FRC is approximately 24 cm, with the level of the bifurcation of the pulmonary artery about halfway up the lungs. The diaphragm is lower and flatter than in the cadaver. However, the radiographic image is only a shadow of dense structures.

In life, the human lungs weigh 900 to 1000 g, of which nearly 40–50% is blood.[4,5] At end-expiration, the gas volume is about 2.5 L, whereas, at maximal inspiration, the gas volume may be 6 L. Thus, overall lung density varies from 0.30 g/mL at FRC to 0.14 g/mL at *total lung capacity* (TLC). However, the density of the lung is not distributed uniformly, being about 1 g/mL near the hilum and 0.1 g/mL peripherally. If one likens each lung to a half cylinder, more than 50% of all the lung's alveoli are located in the outer 30% of the lung radius (hilum to chest wall). This is why the peripheral portion of the lung appears relatively empty in the chest radiograph (see Fig. 1.2). Variability in density also exists from top to bottom. In Fig. 1.2, the blood vessels are more distended in the lower lung fields. The increasing distention of vessels from apex to base also illustrates the increase in vascular distending pressures at the rate of 1 cm H_2O/cm height down the lung.

The composition of the various tissues that comprise the lung is summarized in Table 1.1. An amazing point is how little tissue is involved in the architecture of the alveolar walls.[6,7] However, this is as it should be because the major physical obstacle to gas exchange is the slowness of O_2 diffusion through water.[8,9] Thus, the alveolar walls must be extremely thin. In fact, the thickness of the *red blood cell* (RBC) forms a substantial portion of the air-blood diffusion pathway. Advantage was taken of this fact to separate the carbon monoxide diffusing capacity measurement into two components: the capillary blood volume and the membrane diffusing capacity.[10] (For a discussion of diffusing capacity, see Chapter 31.)

The lung has two well-defined interstitial connective tissue compartments arranged in series, as described by Hayek[11] (Fig. 1.3). These are the parenchymal (alveolar wall) interstitium and the loose binding (extra-alveolar) connective tissue (peribronchovascular sheaths, interlobular septa, and visceral pleura). The connective tissue fibrils (collagen, elastin, and reticulin) form a three-dimensional basket-like structure around the alveoli and airways (Fig. 1.4).[12] This basket-like arrangement allows the lung to expand in all directions without developing excessive tissue recoil. Because the connective tissue fibrils in the parenchymal interstitium are extensions of the coarser fibers in the loose-binding connective tissue, stresses imposed at the alveolar wall level during lung

Table 1.1 Components of Normal Human Lung

Component	Volume or Mass (mL)	Thickness (μm)	Reference
Gas	2400		9
Tissue	900		4, 5
Blood	400		5
Lung	500		9
Support structures	225		6
Alveolar walls	275		6, 7
Epithelium	60	0.18	6, 7
Endothelium	50	0.10	6, 7
Interstitium	110	0.22	6, 7
Alveolar macrophages	55		7

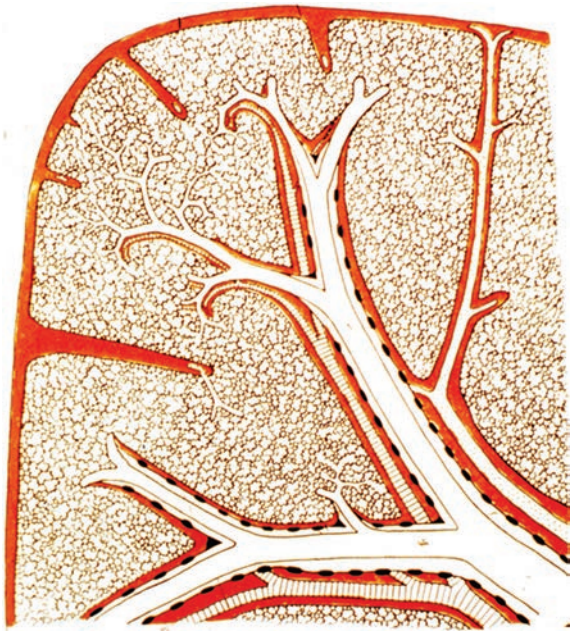

Figure 1.3 General plan depicting the interstitial connective tissue compartments of the lung. All of the extra-alveolar support structures (airways, blood vessels, interlobular septa, visceral pleura) are subsumed under the term, loose-binding connective tissue. The alveolar walls' interstitium comprises the parenchymal interstitium. This organizational plan of the lung follows the general organization of all organs. (From Hayek H. *The Human Lung.* New York: Hafner; 1960:298–314.)

inflation are transmitted not only to adjacent alveoli, which abut each other, but also to surrounding alveolar ducts and bronchioles, and then to the loose-binding connective tissue supporting the whole lobule, and ultimately to the visceral pleural surface (see Fig. 1.3). These relations become more apparent in certain pathologic conditions. For example, in interstitial emphysema,[13] air enters the loose-binding connective tissue and dissects along the peribronchovascular sheaths to the hilum and along the lobular septa to the visceral pleura. Interstitial pulmonary edema fluid enters and moves along the same interstitial pathways (Fig. 1.5).[14]

The bulk of the interstitium is occupied by a matrix of proteoglycans (Fig. 1.6).[15,16] Proteoglycans constitute a complex group of gigantic polysaccharide molecules (≈30

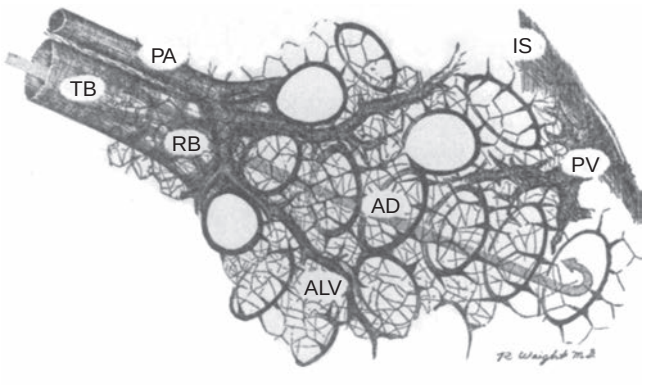

Figure 1.4 Illustration of the connective tissue support of the normal human adult lung lobule. The weave of fibers composing the "elastic continuum" is demonstrated. AD, alveolar duct; ALV, alveolus; IS, interstitial space; PA, pulmonary artery; PV, pulmonary vein; RB, respiratory bronchiole; TB, terminal bronchiole. (From Wright RR. Elastic tissue of normal and emphysematous lungs. *Am J Pathol.* 1961;39:355–363.)

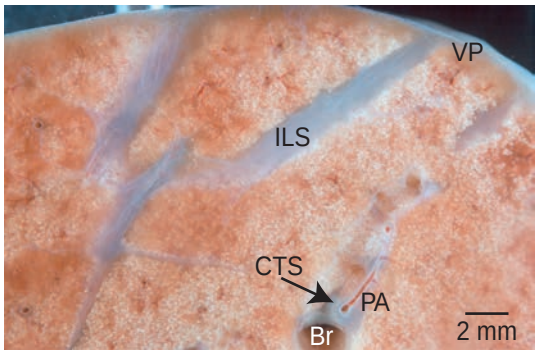

Figure 1.5 Accumulation of interstitial pulmonary edema in the loose-binding interstitial spaces. The edema fluid accentuates the loose-binding (peribronchovascular) connective tissue spaces (CTS) that surround the bronchi (Br) and pulmonary arteries (PA). Interstitial edema also expanded the interlobular septa (ILS) that are contiguous with the connective tissue of the visceral pleura (VP). (Frozen sheep lung, unstained.)

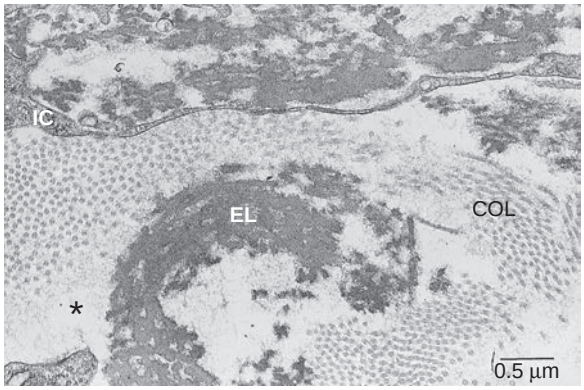

Figure 1.6 Structure of the interstitial compartment. The connective tissue compartment of the lung contains interstitial cells (IC; fibroblasts), fibrils of collagen (COL), and bundles of elastin (EL). The bulk of the interstitium, however, is occupied by matrix constituents (asterisk), such as glycosaminoglycans. (Human lung surgical specimen, transmission electron microscopy.)

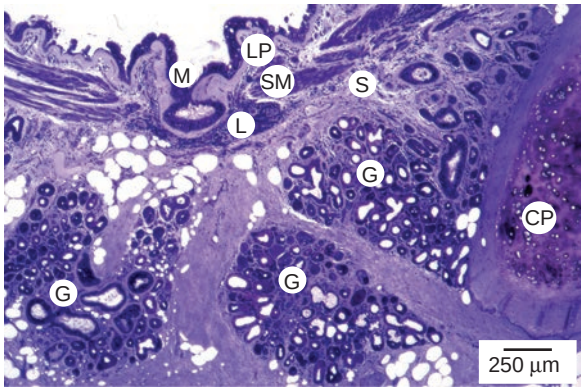

Figure 1.7 Wall structure of a bronchus. The bronchial wall is composed of mucosa (M), lamina propria (LP), smooth muscle (SM), and submucosa (S). Seromucous glands (G) are located between the spiral bands of SM and cartilaginous plates (CP). Diffuse lymphoid tissue (L) has infiltrated the lamina propria and submucosa. (Human lung surgical specimen, right middle lobar bronchus, 2-µm–thick glycol methacrylate section, light microscopy.)

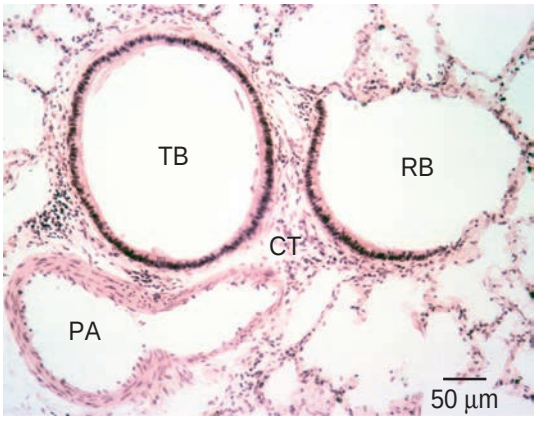

Figure 1.8 Differences in wall structure of terminal bronchioles and respiratory bronchioles. The wall of the terminal bronchiole (TB) is constructed of a single layer of ciliated, cuboidal epithelium that rests over thin, discontinuous bands of smooth muscle and loose areolar connective tissue (CT). In contrast, the wall of the respiratory bronchiole (RB) is only partially lined by ciliated cuboidal epithelium *(lower left)*. The remainder of its wall is lined by squamous epithelium *(upper right)*. The connective tissue also surrounds the adjacent pulmonary arteriole (PA). (Human lung surgical specimen, 10-µm–thick paraffin section, light microscopy.)

different core proteins, with great diversity of glycosaminoglycan side chains) whose entanglements impart a gel-like structure to the interstitium. That structural role, although essential, is not the sole role of these important molecules. A growing view is emerging of the lung's extracellular matrix components as regulators of lung physiology, such as determining epithelial cell phenotype; binding of and subsequent signaling by cytokines; chemokines and growth factors; and cell proliferation, migration, differentiation, and apoptosis.[17–24] In disease states, degradation products of extracellular matrix components may activate the Toll-like receptor pathways (see discussion later), thus the degradation products may serve as endogenous sentinels of tissue damage and initiators of innate immune responses.[19,23–25] Within this gel-like interstitium reside several varieties of interstitial cells (contractile and noncontractile interstitial cells,[26,27] mast cells, plasma cells, and occasional leukocytes). The remainder of the interstitium is composed of laminin, collagens, elastin and reticulin fibrils, fibronectin, and tenascin (see Fig. 1.6). (For more details on the lung mesenchyme see Chapter 5.)

AIRWAYS

The airways, forming the connection between the outside world and the *terminal respiratory units* (TRUs), are of central importance to lung function in health and disease.[28,29] Intrapulmonary airways are divided into three major groups: bronchi (conducting airways with cartilage) (Fig. 1.7), membranous bronchioles (distal conducting airways without cartilage) (Fig. 1.8), and respiratory bronchioles (distal airways participating to some extent in gas exchange) (Fig. 1.9; Table 1.2). Bronchi, by definition, have cartilage in their wall. The trachea, bronchi, and membranous bronchioles peripherally to and including terminal bronchioles (together the *conducting airways*) do not participate in respiratory gas exchange. Respiratory bronchioles serve a dual function as airways and as part of the alveolar volume that participates in respiratory gas exchange.[29]

The anatomic dead space, as measured by the single-breath nitrogen dilution technique, is approximately 30% of each tidal volume. Anatomically, this dead space

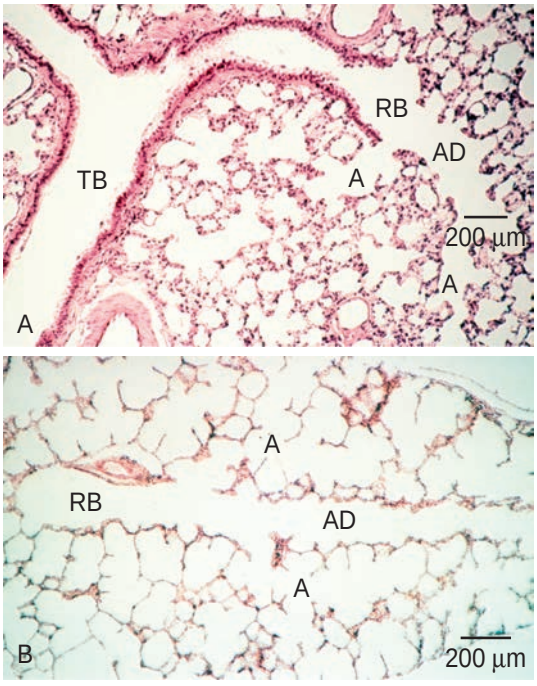

Figure 1.9 Longitudinal sections along membranous bronchioles. (A) Diameter remains relatively constant along the terminal bronchiole (TB), respiratory bronchiole (RB), and alveolar duct (AD). Alveoli (A) communicate with the gas-exchange duct. (B) This longitudinal section along an RB and AD shows that their diameter is relatively constant and that both gas-exchange ducts communicate with clusters of alveoli (A). (Human lung surgical specimen, 10-µm–thick paraffin section, light microscopy.)

is accounted for principally by the volume of the extrapulmonary (upper) airways, including the nasopharynx, trachea, and the intrapulmonary bronchi.[30] The trachea and bronchi are cartilaginous and do not change shape substantially with ventilation. The membranous bronchioles (noncartilaginous airways of ≈1-mm diameter or less), although exceedingly numerous, are short. They

Table 1.2 Characteristics of Airway Generations in Humans

Airway Generation	Generations	Characteristic	Role	TRU	Reference
Trachea	0	Cartilaginous	Conducting		28, 29
Bronchi	1–3	Cartilaginous	Conducting		28, 29
Bronchioles	4–13	Membranous	Conducting		28, 29
Terminal bronchioles	14	Membranous	Conducting		96
Respiratory bronchioles	16–18	Partially membranous	Partially conducting and gas exchange	Yes	96
Alveolar ducts	19–22		Gas exchange	Yes	96
Alveoli	23		Gas exchange	Yes	96

TRU, terminal respiratory unit.

consist of about five branching generations and end at the terminal bronchioles. In contrast to the bronchi, the membranous bronchioles are tightly embedded in the connective tissue framework of the lung and therefore enlarge passively as lung volume increases.[31] Histologically, the bronchioles down to and including the terminal bronchioles ought to contribute about 25% to the anatomic dead space. In life, however, they contribute little because of gas-phase diffusion and mechanical mixing along the distal airways, resulting from the cardiac impulse (refer to the supplemental videos on lung movements). By definition, the respiratory bronchioles and alveolar ducts participate in gas exchange and thus do not contribute to the anatomic dead space. The volume of the respiratory bronchiole-alveolar duct system is approximately one-third of the total alveolar volume, and it is into this space that the fresh-air ventilation enters during inspiration.

Most airway resistance arises from the upper airways and bronchi. Normally, the large airways are partially constricted. The minimum airway diameter in the human lung, about 0.5 mm, is reached at the level of the terminal bronchioles; succeeding generations of exchange ducts (respiratory bronchioles and alveolar ducts) are of constant diameter (see Fig. 1.9).[29,32] The functional significance of centralized resistance is that the TRUs are regionally ventilated chiefly in proportion to their individual distensibilities (compliances) because most of their airway resistance is common. This is demonstrated normally by the finding that regional lung ventilation is dependent primarily upon the initial volumes of the alveoli. TRUs toward the top of the lung, which are more expanded at FRC, do not receive as great a share of the inspiratory volume as do the TRUs near the bottom of the lung.

Airway diameter represents a balance between anatomic dead space volume and airflow resistance. Airway diameter ought to be as small as possible to minimize anatomic dead space and maximize efficient alveolar ventilation by reducing the dead space–to–tidal volume ratio, whereas airway diameter ought to be as large as possible to minimize airway resistance and the work of breathing. In disease, airways are often narrowed (Fig. 1.10), which increases resistance and the work of breathing.

The presence of apical junctional complexes between airway epithelial cells (Fig. 1.11) has important functional implications for metabolically regulated secretion into and absorption of electrolytes and water from the lining liquid.

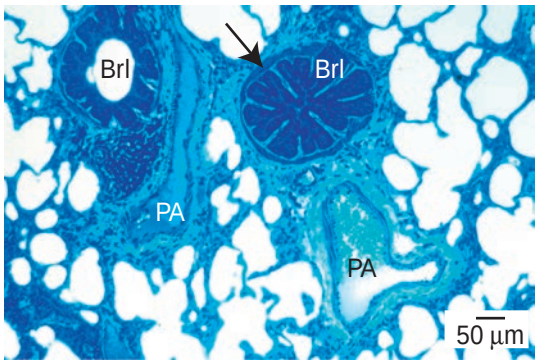

Figure 1.10 Cross-sections of two bronchioles that would contribute to increased airway resistance. On the left is a bronchiole (Brl) that is partially narrowed, evident by the folded and thick epithelium. The bronchiole to the right is completely narrowed. Its lumen is obliterated by the infolded epithelium. This bronchiole's smooth muscle is thick *(arrow)*, suggesting that the narrowing is related to constriction of the smooth muscle. Each bronchiole is flanked by a pulmonary arteriole (PA). (Sheep lung, 5-µm–thick paraffin section, light microscopy.)

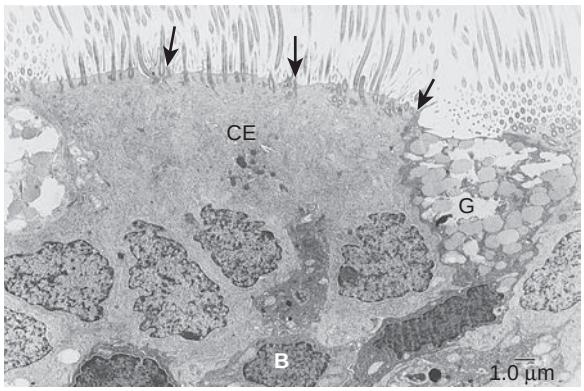

Figure 1.11 Cells constituting the bronchial epithelium. The *arrows* at the apical surface of the airway cells indicate the location of junctional complexes between contiguous epithelial cells. The bronchial epithelium has ciliated epithelial cells (CE), goblet cells (G), and basal cells (B). Goblet cells have abundant mucous granules in the cytoplasm, and their apical surface is devoid of cilia. Basal cells, as their name indicates, are located along the abluminal portion of the lining epithelium, adjacent to the basal lamina. (Human lung surgical specimen, transmission electron microscopy.)

Apical junctional complexes consist of three elements: *zonula occludens* (tight junction), *zonula adherens*, and *macula adherens* (desmosome).[33] Tight junctions serve two important functions: (1) restriction of passive diffusion by

blocking the lateral intercellular space and (2) polarization of cellular functions (ion and water transport) between the apical and basolateral membranes.[34] Polarization of chloride and sodium transport allows the airway epithelium either to secrete or absorb ions, with associated passive water movement (see Chapter 3).

Trapping of foreign material, such as particulates or bacteria, is accomplished by mucins. Mucins are complex glycoproteins that form gels. MUC5AC and MUC5B are the main gel-forming mucins in human airways.[35,36] MUC5AC is produced by surface epithelia in proximal cartilaginous airways.[37] Normally, MUC5B is produced by airway glandular cells[37,38] but, in a variety of pulmonary diseases, its cell source is expanded. Other mucins (e.g., MUC5B, MUC7)[38,39] become expressed by airway epithelial cells in diseases, such as cystic fibrosis. In that disease, MUC5B is produced by airway epithelial cells.[40]

Glands are limited to the submucosa of the bronchi. Airway glands secrete water, electrolytes, and mucins into the lumen. Studies of regulation of secretion in vivo and by explant culture systems in vitro show that secretion can be modulated by neurotransmitters, including cholinergic, adrenergic, and peptidergic transmitters,[41,42] and by inflammatory mediators, such as histamine,[43] platelet-activating factor,[44] and eicosanoids.[45] The absence of airway glands and goblet cells distal to ciliated epithelial cells makes teleologic sense because that arrangement should minimize the flow of mucus backward into alveolar ducts and alveoli.

Although most foreign material and immunologic stimuli are carried up the airways by mucociliary action, some are cleared by the lymphatics. In addition, lymphoid tissue is found within the lungs and referred to as *inducible bronchus-associated lymphoid tissue* (iBALT).[46] These lymphoid aggregates are distributed along the tracheobronchial tree (see Fig. 1.7) and, to a lesser extent, along the blood vessels.[46–48] BALT in the human lung is called inducible because it is not present at birth in humans or in germ-free animals but develops after antigenic stimulation.[47,48] Lymphocytes in these structures are principally B cells, which often form follicles.[49] The presence of lymphocytes along the airways provides a reminder that the respiratory system is constantly challenged by airborne immunologic stimuli. The tracheobronchial lymphoid tissue appears to provide an important locus for both antibody-mediated and cell-mediated immune responses.[50] Another important locus of immune response is provided by the epithelial cells that line the airways and comprise the airway glands. The importance of epithelial cells arises from their expression of *Toll-like receptors* (TLRs), whose role is identification of pathogen-associated molecular patterns.[51] Activation of TLRs leads to downstream signaling cascades involved in mucin production, leukocyte recruitment, antimicrobial peptide production, and wound repair[52–57] (see also Chapter 15).

BRONCHIAL CIRCULATION

The trachea (and esophagus), mainstem bronchi, and pulmonary vessels entering the lung (see Fig. 1.1), as well as the visceral pleura in humans (see "Pleural Space and Pleural Membranes" toward the end of this chapter), are supplied by the bronchial (systemic) blood circulation.[58–60] Measurements of bronchial circulation, by microsphere studies in animals, indicate that flow is 0.5–1.5% of cardiac output and is predominantly to the large airways.[58,59,61–64] The bronchial arteries arborize into bronchial capillaries that form a network in the lamina propria (the underlying connective tissue), in the submucosa, and in the region external to the cartilage of bronchi, as well as in the lamina propria of neighboring pulmonary arteries.[65] Venous blood from the trachea and large airways enters bronchial venules, which converge to form bronchial veins that drain into the azygos or hemiazygos veins. Thus, most bronchial blood flow returns to the right side of the heart. Deeper in the lung, however, bronchial blood passes via short anastomotic vessels into the pulmonary venules, thus reaching the left side of the heart to contribute to the venous admixture. The relationships among the bronchial, pulmonary, and systemic arterial and venous circulations are diagrammed in eFig. 1.1.

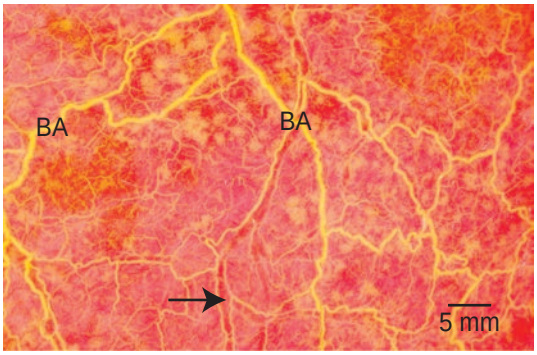

Figure 1.12 Surface view of the visceral pleura. Yellow latex polymer fills the rich network of the bronchial arteries (BA) and subsequent microvascular network. Some bronchial arterioles flank lymphatics *(arrow)* that comprise the superficial lymphatic plexus of the lung. (Sheep lung visceral pleural surface.)

The bronchial circulation has enormous growth potential in contrast to the pulmonary circulation, which, after childhood, is unresponsive to growth signals. As a result, the bronchial circulation is the primary source of new vessels for repair of tissue after lung injury. In long-standing inflammatory and proliferative diseases, such as bronchiectasis or carcinoma, bronchial blood flow may be greatly increased.[59,66] Scar tissue and tumors greater than 1 mm in diameter receive their blood supply via the bronchial circulation.[67,68] As will be discussed near the end of this chapter, the bronchial circulation also supplies the visceral pleura of species that have thick visceral pleura (Fig. 1.12), which includes humans.

PULMONARY CIRCULATION

In humans, the pulmonary artery enters each lung at the hilum in a loose connective tissue sheath adjacent to the main bronchus (see Fig. 1.1). The pulmonary artery travels adjacent to and branches with each airway generation (Fig. 1.13) down to the level of the respiratory bronchiole (see Fig. 1.8). The anatomic arrangements of the pulmonary arteries and the airways are a continual reminder of the relationship between perfusion and ventilation

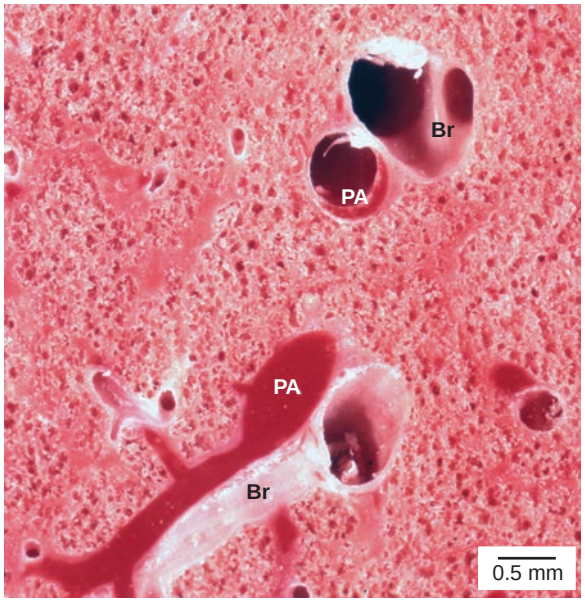

Figure 1.13 Divisions of the pulmonary artery (PA) within the lung. The PA divides and travels beside the bronchi and bronchioles (Br) out to the respiratory bronchioles. Thus, at all airway generations, an intimate relationship exists with pulmonary arterial generations. Note that the loose-binding (peribronchovascular) connective tissue sheaths are not distended, compared to the interstitial edema cuffs in Fig. 1.5. (Frozen normal sheep lung, unstained.)

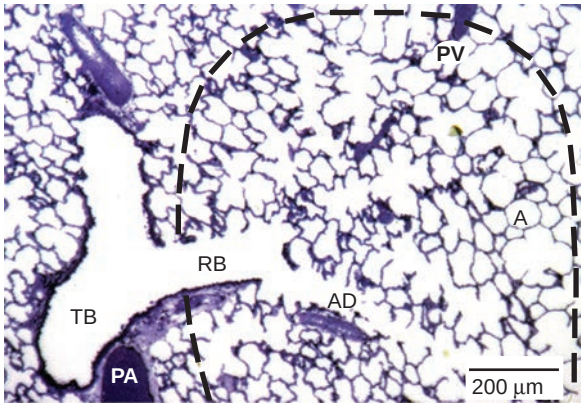

Figure 1.14 Anatomy of terminal respiratory units. Terminal respiratory units (the physiologist's alveolus) consist of the alveoli (A) and alveolar ducts (AD) arising from a respiratory bronchiole (RB). Each unit is roughly spherical, as suggested by the *dashed outline*. Pulmonary venous vessels (PV) are peripherally located. PA, pulmonary artery; TB, terminal bronchiole. (Normal sheep lung, somewhat underinflated, 2-µm–thick glycol methacrylate section, light microscopy.)

that determines the efficiency of normal lung function. Although the pulmonary veins also lie in loose connective tissue sheaths adjacent to the main-stem bronchus and pulmonary artery at the hilum, once inside the lung they follow Miller's dictum that the veins will generally be found as far away from the airways as possible.[58] Peripherally, the pulmonary arteries branch out into the TRU, whereas the veins occupy the surrounding connective tissue envelope (Fig. 1.14). Each small muscular pulmonary artery supplies a specific volume of respiratory tissue, whereas each vein drains portions of several such zones.

Table 1.3 Quantitative Data on Intrapulmonary Blood Vessels in Humans

Vessel Class (With Diameter)	Volume (mL)	Surface Area (m^2)	Reference
Arteries (>500 µm)	68	0.4	69
Arterioles (13–500 µm)	18	1.0	69
Capillaries (10 µm)	60–200	50–70	70
Venules (13–500 µm)	13	1.2	71
Veins (>500 µm)	58	0.1	71

Considerable quantitative data about the pulmonary circulation are available for the human lung (Table 1.3).[69–71] Although most of the intrapulmonary blood volume is in the larger vessels down to approximately 500 µm diameter, nearly all of the surface area is in the smaller vessels. For example, the surface area of arterioles 20 to 500 µm in diameter exceeds that of the larger vessels by a factor of two, and the maximal capillary surface area is 20 times that of all other vessels. Such impressive expansion of surface area maximizes the area for respiratory gas exchange.

Because the vertical height of the lung at FRC is about 24 cm (see Fig. 1.2), the pressure within the pulmonary blood vessels varies by approximately 24 cm H_2O over the full height of the lung. Thus, if pulmonary arterial pressure is taken as 20 cm H_2O (15 mm Hg, 1.9 kPA)* at the level of the main pulmonary artery, which is about halfway up the height of the lung, pressure in the pulmonary arteries near the top of the lung will be about 12 cm H_2O, whereas pressure in pulmonary arteries near the bottom will be about 36 cm H_2O. Pulmonary venous pressure, which is about 8 cm H_2O at the level of the pulmonary artery in midchest (left atrial pressure), would be −4 cm H_2O near the top of the lung and +20 cm H_2O at the bottom. In the normal lung, the blood volume is greater at the bottom because of increased luminal pressure, which expands those vessels and increases their volume. This effect of distention also decreases the contribution of the blood vessels at the bottom of the lung to total pulmonary vascular resistance.

From birth through adulthood, the normal pulmonary circulation is a low-resistance circuit. The resistance is distributed somewhat differently than in the systemic circulation, where the major drop in resistance is across the arterioles. In the pulmonary circulation, although the pressure drop along the pulmonary capillaries is only a few centimeters of water (similar to the pressure drop in systemic capillaries), the pulmonary arterial and venous resistances are low, so a relatively larger fraction of the total pulmonary vascular resistance (35–45%) resides in the alveolar capillaries at FRC.[72,73] (For further information about pulmonary circulation in health and disease see Chapters 6 and 83.)

Vasoactivity plays an important part in the local regulation of blood flow in relation to ventilation.[74,75] Because smooth muscle surrounds the pulmonary vessels on both

*To convert from kPA to cm H_2O, multiply by 10.3; to mm Hg, multiply by 7.5.

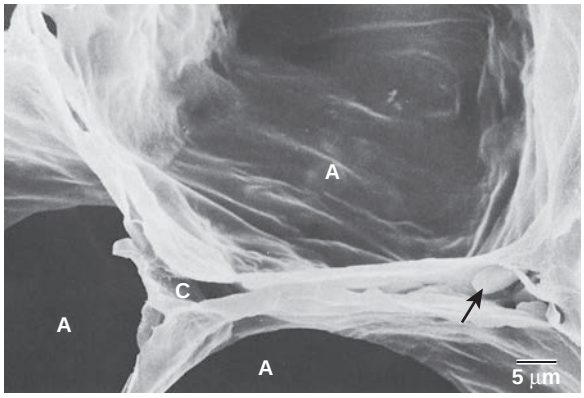

Figure 1.15 Alveolar capillaries are long. An alveolar capillary (C) is shared longitudinally along its path across three alveoli (A). The alveolar walls are flattened, and the wall junctions are sharply curved because the lung is fixed in zone 1 conditions. Some red blood cells remain in the capillary at an alveolar corner *(arrow)*. (Perfusion-fixed normal rat lung; airway pressure = 30 cm H_2O, pulmonary artery pressure = 25 cm H_2O, left atrial pressure = 6 cm H_2O, scanning electron microscopy.)

the arterial and the venous side down to precapillary and postcapillary vessels,[76,77] any segment can contribute to active vasomotion.[78] In pathologic conditions, vascular smooth muscle may extend down to the capillary level.[79,80]

Theoretically, gas exchange may take place through the thin wall of almost any pulmonary vessel. At normal alveolar O_2 tensions, however, little O_2 and CO_2 is exchanged before the blood reaches the true capillaries.[81] In the pulmonary arterioles, because of their small volume (see Table 1.3), blood flow is rapid. As blood enters the vast alveolar wall capillary network, its velocity slows, averaging about 1000 μm/s (or 1 mm/s). Flow in the microcirculation is pulsatile because of the low arterial resistance.[82] Pulsations reach the microvascular bed from both the arterial and the venous sides. In fact, one sign of severe pulmonary hypertension is the disappearance of capillary pulsations.[83]

The capillary network is long and crosses several alveoli (Fig. 1.15) before coalescing into venules. The vast extent of the capillary bed together with the length of the individual paths allows a transit time for RBCs sufficient for gas exchange to take place. The estimate based on anatomy of approximately 0.5- to 1-second average transit time is essentially the same as that found using the carbon monoxide diffusing capacity method, in which one divides capillary blood volume by cardiac output to obtain mean capillary transit time.[84] In the normal lung, there is sufficient time for equilibrium between the O_2 and CO_2 tensions in the alveoli and the erythrocytes in the pulmonary capillaries. Only under extreme stress (heavy exercise at low inspired O_2 tensions) or in severe restrictive lung disease are the RBCs predicted to pass through the microcirculation without enough time to reach diffusion equilibrium.[85]

Normally, capillary blood volume is equal to or greater than stroke volume. Under normal resting conditions, the volume of blood in the pulmonary capillaries is well below its maximal capacity, however. Recruitment can increase this volume by a factor of about three. Thus, the normal capillary blood volume of 60 to 75 mL is one-third of the capacity (200 mL) measured by quantitative histology.[6] This reserve capacity of the capillaries allows them to accommodate rapid increases in cardiac output during times of high demand.

Anatomically, the pulmonary blood vessels can be divided into two groups: extra-alveolar and alveolar. *Extra-alveolar vessels* lie in the loose-binding connective tissue (peribronchovascular sheaths, interlobular septa). Extra-alveolar vessels extend into the TRUs. *Alveolar vessels* lie within the alveolar walls and are embedded in the parenchymal connective tissue. They are subject to whatever forces operate at the alveolar level. They are referred to as alveolar vessels in the sense that the effective hydrostatic pressure external to them is alveolar pressure. Not all of the alveolar vessels are capillaries, however. Small arterioles and venules, which bulge into the air spaces, may also be affected by changes in alveolar pressure. Likewise, not all of the capillary bed is subjected to alveolar pressure under all conditions.[86] The corner capillaries in the alveolar wall junctions are protected from the full effects of alveolar pressure by the curvature and alveolar air-liquid surface tension.[87] This may account for the fact that, even under conditions in which alveolar pressure exceeds both arterial and venous pressure ("zone 1"),[88] some blood continues to flow through the lung.[89] One has to go several centimeters up into zone 1 before blood flow stops completely. (For a discussion of distribution of pulmonary blood flow and lung zones, see Chapter 10.)

An important question is whether the normal human lung contains connections between the pulmonary arteries and veins that permit some portion of pulmonary blood flow to bypass the capillary network. Whereas such vessels may develop congenitally or pathologically,[90] functioning short circuits probably do not exist in the normal lung. (Pathologic arteriovenous communications are discussed in Chapter 88.)

In addition to its function in gas exchange, the pulmonary circulation is involved in a number of other functions important to homeostasis. The pulmonary vascular bed serves as a capacitance reservoir between the right and left sides of the heart. Consequently, the reservoir of blood in the pulmonary circulation is sufficient to buffer changes in right ventricular output for two to three heartbeats. The pulmonary vascular bed also serves as a filter, trapping embolic material and preventing it from reaching systemic vascular beds. For example, during intravascular coagulation or in processes involving platelet or neutrophil aggregation, the predominant site of sequestration is the lung. The main anatomic reason for this is that 75% of the total circulating blood volume is in the venous circuit, and the lung's microvascular bed is the first set of small vessels through which the blood flows. Moderate numbers of microemboli generally produce no detectable dysfunction in the lung because of the huge array of parallel pathways in the pulmonary microcirculation. At most, microemboli temporarily block flow to a portion of or to an entire TRU. The fate of such emboli is not clear. Some are phagocytosed and removed into the lung tissue.[91] Some emboli can be degraded to a small size, pass through into the systemic circulation, and be removed by the reticuloendothelial system. The filtering function of the lung enables such clinical studies as the perfusion scan, in which macroaggregated albumin is trapped by the lung vessels as a measure of perfusion. (Further information about the pathophysiology of thromboembolic disorders is presented in Chapter 81.)

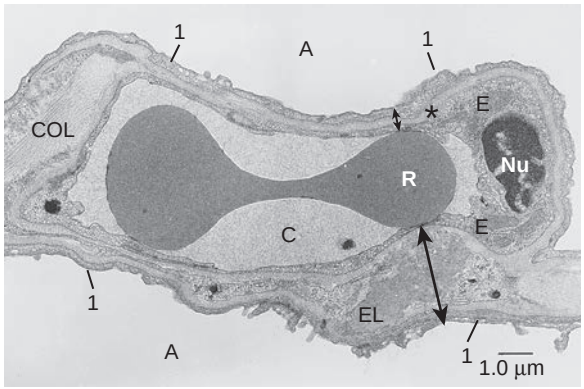

Figure 1.16 Cross-section of an alveolar wall showing the path for oxygen and carbon dioxide diffusion. The thin side of the alveolar wall barrier *(short double-headed arrow)* consists of type 1 epithelium (1), interstitium (asterisk) formed by the fused basal laminae of the epithelial and endothelial cells, capillary endothelium (E), plasma in the alveolar capillary (C), and finally the cytoplasm of the red blood cell (R). The thick side of the gas-exchange barrier *(long double-headed arrow)* has an accumulation of elastin (EL), collagen (COL), and matrix that jointly separate the alveolar epithelium from the alveolar capillary endothelium. As long as the red blood cells are flowing, oxygen and carbon dioxide probably diffuse across both sides of the air-blood barrier. (See also Video 3.1 for a three-dimensional ultrastructural view of alveolar walls.) A, alveolus; Nu, nucleus of the capillary endothelial cell. (Human lung surgical specimen, transmission electron microscopy.)

TERMINAL RESPIRATORY UNITS

The TRU consists of a respiratory bronchiole and all the alveolar ducts together with their accompanying alveolar ducts and alveoli (see Fig. 1.14; see Table 1.2). The TRU has both a structural and a functional existence and was first described in the human lung by Hayek.[11] In the human lung, this unit contains approximately 100 alveolar ducts and 2000 alveoli. At FRC, the unit is approximately 5 mm in diameter, with a volume of 0.02 mL. There are about 150,000 such units in the lungs of normal adult humans.[6]

The functional definition of the TRU is physiologic; namely, gas-phase diffusion is so rapid along patent airways that the partial pressures of O_2 and CO_2 are uniform throughout the unit.[28] Therefore, physiologically, O_2 in the gas phase anywhere along the TRU will diffuse along its concentration gradient across the extremely thin walls into RBCs flowing in the capillaries (Fig. 1.16), where O_2 combines with hemoglobin. CO_2 diffuses in the opposite direction along its concentration gradient. A key point about diffusion is that the process is much faster in the gas phase than in the liquid phase. Thus, the TRU size is defined in part by the fact that gas molecules can diffuse and equilibrate anywhere within the unit more rapidly than they can diffuse across the air-blood barrier into the blood. Of note, the solubility of O_2 in water is low relative to its concentration in gas. CO_2 is much more soluble in water (20 times the solubility of O_2 in water), and therefore CO_2 diffuses rapidly into the gas phase, even though the driving pressure for CO_2 diffusion is only one-tenth that for O_2 entering the blood.

A source of confusion is the term *acinus* in the context of the lung. Historically, the term acinus has been defined differently by different fields. In pathology, the acinus is bigger than a TRU. The pathologists' *acinus* consists of a terminal bronchiole and all of the subsequent respiratory bronchioles together with their accompanying alveolar ducts and alveoli.[92–95] Alas, the term *acinus* also has been used to describe the TRU unit.[96] This chapter uses the physiologists' *alveolus:* the TRU. The physiologists' *alveolus* is the TRU because the unit's definition is functional.

In general, O_2 diffusion is not limiting in the normal lung, except during heavy exercise while breathing gas containing very low O_2 concentrations (e.g., at high altitudes).[85] Even at that, it is not so much diffusion that is limiting, but the fact that the transit time of the RBCs is reduced due to increased cardiac output. However, most disorders of oxygenation are due to ventilation-perfusion inequalities[97] (see also Chapter 44).

All portions of the TRU participate in volume changes with breathing.[98,99] When a unit increases its volume from FRC, the alveolar gas that had been in the alveolar duct system enters the expanding alveoli, together with a small portion of the fresh air. Most of the fresh air remains in the alveolar duct system. This does not lead to any significant gradient of alveolar O_2 and CO_2 partial pressures because diffusion in the gas phase is so rapid that there is equilibrium within a few milliseconds. However, nondiffusible (suspended or particulate) matter remains away from the alveolar walls and is expelled in the subsequent expiration.[100] This explains why it is difficult to deposit aerosols on the alveolar walls and why large inspired volumes and breath-holding are needed for efficient alveolar deposition.

The anatomic alveolus is not spherical (Fig. 1.17, see Fig. 1.15). It is a complex geometric structure with flat walls and sharp curvature at the junctions between adjacent walls. The most stable configuration is for three alveolar walls to join together, as in foams.[6] The resting volume of an alveolus is at 10–14% of TLC. When alveoli go below their resting volume, they must fold up because their walls have a finite mass (see Fig. 1.17). Most of the work required to inflate the normal lung is expended across the air-liquid interface to overcome surface tension; the importance of the air-liquid interface is demonstrated by the low pressure required to "inflate" a liquid-filled lung with more liquid[101] (see Fig. 3.5 and Chapter 3).

The phenomenon of TRU, or alveolar, stability is complex because not only is air-liquid interfacial tension involved but each flat alveolar wall is part of two alveoli, and both must participate in any volume change. Therefore atelectasis does not usually involve individual alveoli but rather relatively large units (Fig. 1.18).[102]

The alveolar walls are composed predominantly of pulmonary capillaries. In the congested alveolar wall the blood volume may be greater than 75% of the total wall volume. Alveoli near the top of the lung show less filling of the capillaries than those at the bottom.[103,104] This affects regional diffusing capacity, which is dependent on the volume of RBCs in the capillaries.

The transition from a cuboidal epithelium of the respiratory bronchiole to the squamous epithelium of the alveolus is abrupt (Fig. 1.19). Little is known about the function, if any, of this transitional junction. Although Macklin[105] speculated that the permeability of the bronchiole-alveolar epithelial junctions might be unique, no definitive difference has been demonstrated.[106] The controversy continues as to whether this region shows unique permeability features that might participate in clearance of particles or leakage of edema.[107–109]

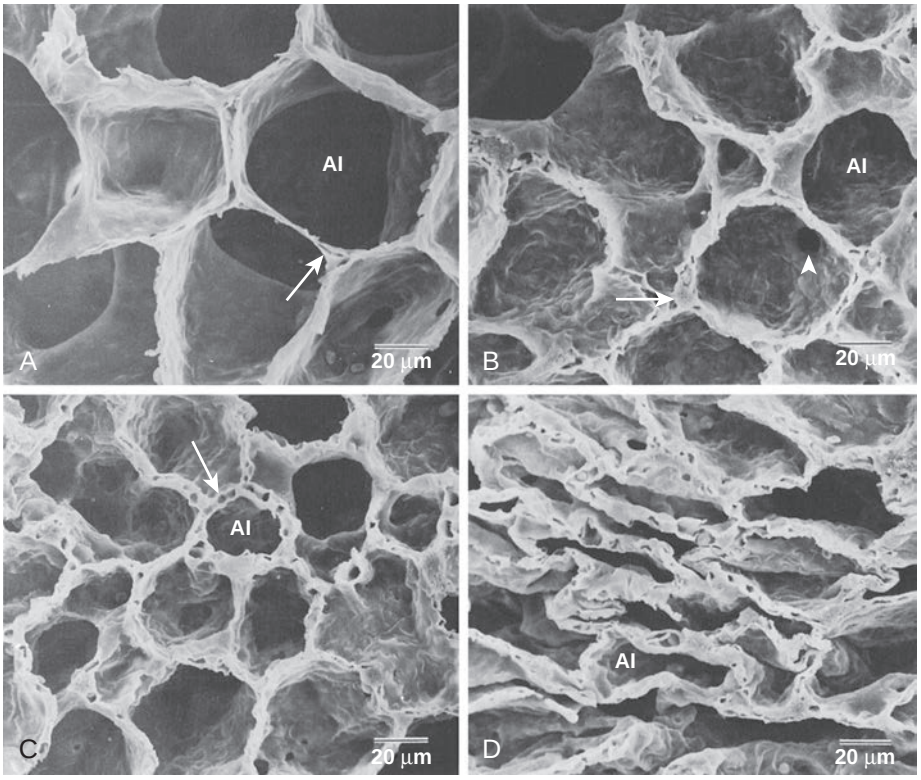

Figure 1.17 Alveolar shape changes at representative points along the air deflation pressure-volume curve of the lung. The four micrographs are at the same magnification. The air deflation pressure points are as follows: (A) airway pressure = 30 cm H_2O (total lung capacity [TLC]); (B) 8 cm H_2O (≈50% TLC); (C) 4 cm H_2O (near functional residual capacity [FRC]); and (D) 0 cm H_2O (minimal volume). Vascular pressures are constant (pulmonary artery presssure = 25 cm H_2O and left atrial pressure = 6 cm H_2O). Intrinsic alveolar shape (AI) is maintained from TLC to FRC (A–C). The alveolar walls are flat, and there is sharp curvature at the junctions between adjacent walls. Note the flat shape of the alveolar capillaries *(arrow)* at TLC ([A] lung zone 1 conditions) compared to their round shape *(arrow)* at FRC ([C] lung zone 3 conditions). The alveolar walls are folded and alveolar shape is distorted at minimal lung volume (D). The *arrow* in (B) identifies an alveolar type 2 cell at an alveolar corner. The *arrowhead* in (B) identifies a pore of Kohn. (Perfusion-fixed normal rat lungs, scanning electron microscopy.)

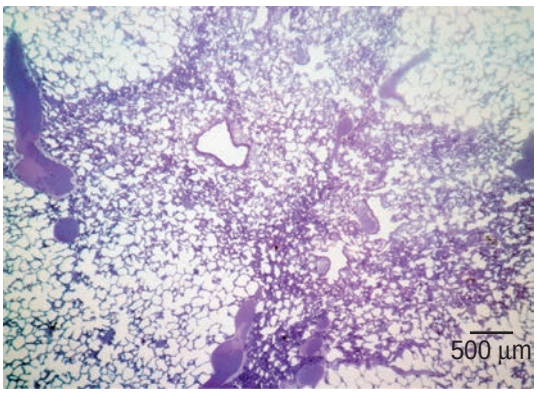

Figure 1.18 Histologic appearance of atelectasis. Atelectasis usually involves relatively large units of lung parenchyma, rather than individual alveoli. Alveolar walls in the atelectatic units are folded, distorting alveolar air space and capillary shape, as shown in Fig. 1.17D. (Sheep lung injured by air emboli, 2 μm–thick glycol methacrylate section, light microscopy.)

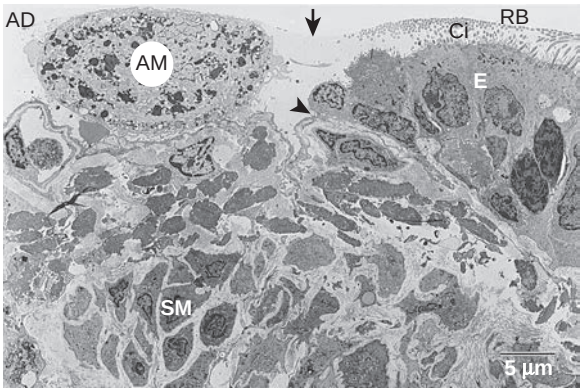

Figure 1.19 The respiratory bronchiole (RB)–alveolar duct (AD) junction is abrupt. The junction is demarcated by an abrupt transition *(arrowhead)* from low cuboidal epithelial cells (E) with cilia to squamous epithelial cells. Submerged in the lining liquid *(arrow)* are an alveolar macrophage (AM) and cilia (Ci). Airway smooth muscle cells (SM) extend to this level of the airway tree. (Human lung surgical specimen, transmission electron microscopy.)

Trapping and clearance of particulate matter impinging on the alveolar surfaces is vital and takes place in the alveolar surface liquid. Within this liquid are suspended alveolar macrophages (see Fig. 1.19).[110] The majority of alveolar macrophages that reach the terminal airways via the slow, upward flow of alveolar lining liquid are expelled with the surface film as it is pulled up onto the mucociliary escalator.[111,112]

LYMPHATICS

Another route for clearance of particulate matter and fluid from the lung is the pulmonary lymphatic system (see Chapter 7). Lymphatics of the lung are subdivided into two principal groups based on their location: a deep plexus and a superficial plexus.[11,58,113,114] Both plexuses are made up of initial and collecting lymphatics, with communications between the two.[11,58,108,113] The *deep plexus* is situated in the peribronchovascular connective tissue sheaths of the lung (see Fig. 1.1).[11,58,108,113] Lymphatics in the deep plexus are distributed around the airways, extending peripherally to the respiratory bronchioles and next to branches of the pulmonary arteries and veins.[11,58,108,113] Lymphatics are not found in the alveolar walls. The *superficial plexus* is located in the connective tissue of the visceral pleura. This plexus is

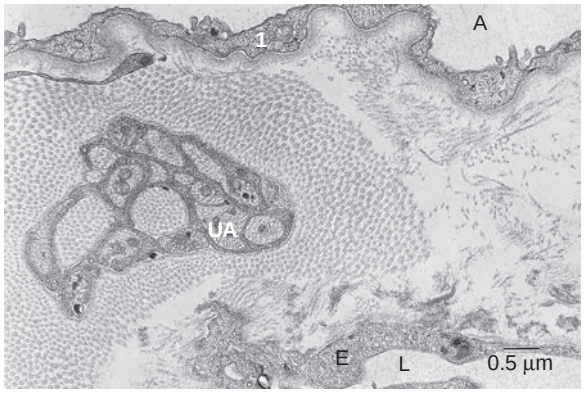

Figure 1.20 Ultrastructure of unmyelinated axons in the lung parenchyma. Unmyelinated axons (UA), known as C fibers, are shown situated in the interstitium of a respiratory bronchiole, between an alveolar type 1 cell (*white 1*) lining an alveolus (A) and an initial lymphatic (L). Although the presence of small clear vesicles is suggestive of cholinergic (autonomic) axons, unequivocal identification as either motor or sensory fibers is not possible in random thin sections. E, lymphatic endothelial cell. (Human lung surgical specimen, transmission electron microscopy.)

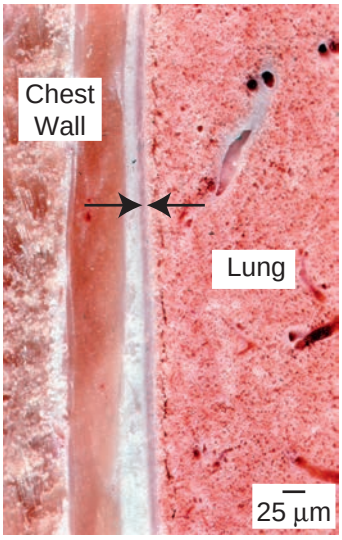

Figure 1.21 The pleural space is a real space. The dark band delimited by the *opposed arrows* is the pleural space, which is located between the chest wall and lung. (Frozen sheep chest wall and lung, unstained.)

prominent in the lung of species with thick visceral pleura, including human lung (see the section "Pleural Space and Pleural Membranes").[11,58,113] Collecting lymphatics have one-way valves and in large species, such as humans and sheep, a discontinuous, thin layer of smooth muscle. Of note, the visceral pleural lymphatics do not open into the pleural space and do not participate in pleural liquid clearance.

Lymph is propelled centripetally toward the lung's hilum or pulmonary ligament by movements of the lungs through the respiratory cycle and by heart pulsations, to reach regional lymph nodes. In the human, pulmonary lymph flows to extrapulmonary lymph nodes located around the primary bronchi and trachea.[11,58,113]

INNERVATION

Innervation of the human lung consists of sensory (afferent) and motor (efferent) pathways.[92,113,115,116] Fibers of the sensory pathway include myelinated, slowly adapting stretch receptors (Hering-Breuer reflex) and irritant receptors, but most sensory fibers are unmyelinated, slow-conducting C fibers located in the TRUs, either along the bronchioles or within the alveolar walls (Fig. 1.20). Investigators have speculated about the function of C fibers since Paintal first suggested that they played a role in sensing parenchymal connective tissue distortion, as during pulmonary vascular congestion and interstitial edema.[117–120] The speculation has neither been proven nor disproven.

The motor pathways reach the lung through the sympathetic and parasympathetic nervous systems. Preganglionic contributions to the sympathetic nerves arise from the upper four or five thoracic paravertebral ganglia, whereas the preganglionic parasympathetic nerves originate in the brainstem motor nuclei associated with the vagus nerves. Postganglionic sympathetic nerve fibers terminate near airways, vascular smooth muscle cells, or submucosal glands. Postganglionic parasympathetic fibers extend from ganglia mainly located external to the smooth muscle and cartilage. Some submucosal ganglia exist, but they are generally smaller and have fewer neurons.

PLEURAL SPACE AND PLEURAL MEMBRANES

As stated earlier, the primary function of the lung is ensuring efficient gas exchange between alveolar air and alveolar capillary blood. This vital function is met, in part, by extensive and rapid movement of the lung within the pleural space and its pleural liquid.[121,122] Online supplemental digital videos linked to this chapter provide a glimpse of the view that surgeons have during dissection through the intercostal muscles: The lungs glide along the deep surface of the translucent endothoracic fascia and parietal pleura (see Videos 1.1 to 1.5). The pleural space also serves as an outlet into which pulmonary edema liquid can escape.[123,124] The pleural liquid also serves to couple the lung to the chest wall.[125] What are the anatomic features of the pleural space and pleurae that contribute to these functions?

An important anatomic fact is that the pleural space is a real space (Fig. 1.21); it is not a potential space.[3,125] The pleural space surrounds the lung, except at its hilum, where the parietal pleura and visceral pleura join.[11,91] Separations are present between the parietal and visceral pleurae along the interlobar fissures and costodiaphragmatic recesses. The normal volume of pleural liquid is 0.1 to 0.2 mL/kg body weight in most mammals.[125,126] This volume is distributed across a pleural surface area of approximately 1000 cm^2/lung and pleural space width of 10 to 20 µm (see Fig. 1.21).[3,125] Normally, there is little or no contact across the pleural space because the microvilli that extend from the parietal and visceral mesothelial cells are only 3 to 5 µm long.[2,3,127,128]

The unique anatomic features of the parietal pleura are the lymphatic stomata.[128–133] The lymphatic stomata are openings (≈1–12 µm in diameter) between parietal and mesothelial cells (Fig. 1.22), which are continuous with

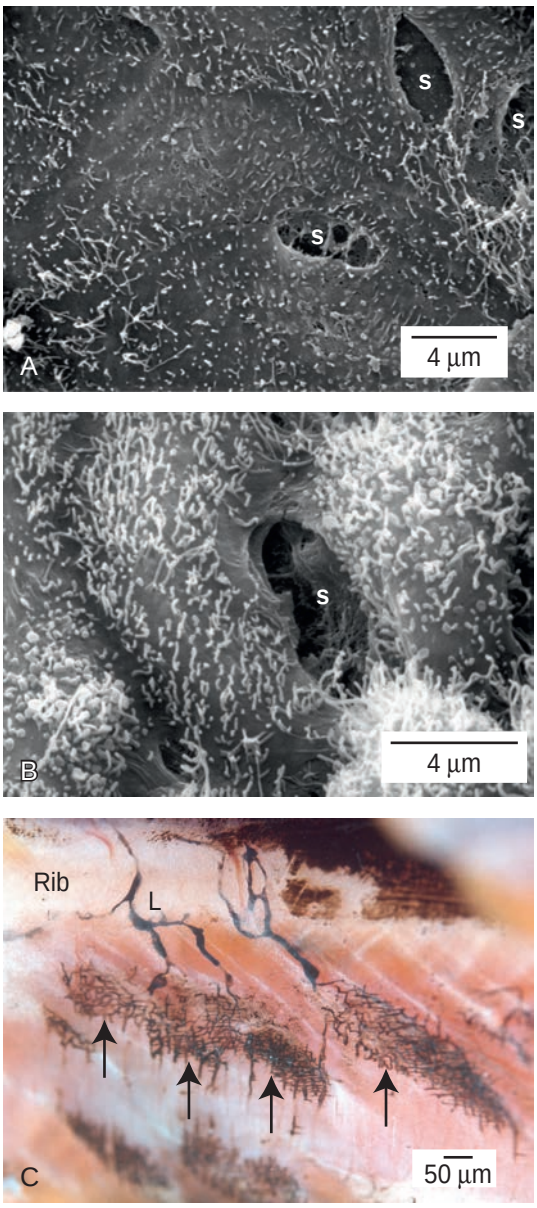

Figure 1.22 Surface view of lymphatics stomata, initial lymphatics, and collecting lymphatics of the parietal pleura. (A–B) Scanning electron micrographs that show the unique structure of lymphatic stomata (S). Stomata are apertures between the pleural space and the initial lymphatics in the parietal pleura. Three stomata are visible in a low-magnification field of view in (A). Stomata are located over intercostal muscles. (B) shows a different stoma at a higher magnification. Microvilli are not present at the aperture of the stomata, which are lined by mesothelial cells. (Sheep parietal pleura, scanning electron microscopy.) (C) shows a portion of the parietal pleura, where colloidal carbon is seen in four beds of initial lymphatics *(arrows)* located over an intercostal space. Colloidal carbon is also in collecting lymphatics (L) that cross a rib, where the collecting lymphatics drain into lymphatic vessels that accompany the intercostal vessels. (Rabbit, macroscopic view of the parietal pleural after colloidal carbon was placed in the pleural space in situ.)

the lumen of lymphatic capillaries. The size likely varies as the chest moves with ventilation. Tracer studies reveal that India ink and chicken RBCs (which are nucleated and therefore easily identifiable) are cleared almost exclusively from the pleural space by the stomata, which are located over the intercostal spaces in the distal half of the thorax, and along the sternum and pericardium of experimental animals that have been studied.[128,134] Physiologic studies showed that protein and particulate matter in the pleural space are cleared almost entirely by the parietal pleural system of stomata and lymphatics.[129,135] The lymphatics transport the cleared pleural liquid (lymph) to regional lymph nodes along the sternum and vertebral column and then, to the thoracic duct and right lymphatic duct. In these regards, normal pleural liquid is cleared by mechanisms consistent with normal interstitial liquid turnover in the peritoneum.

CELLULAR ANATOMY OF THE LUNG

AIRWAY LINING CELLS

The airway epithelium of the human proximal conducting airways contains different types of epithelial cells with specific functions. These cells include basal cells, ciliated cells, and goblet cells, as well as some club cells and a small number of brush cells, single neuroendocrine cells,[136–139] and ionocytes.[140,141] Submucosal gland epithelium, contiguous to the airway surface epithelium, contains serous and goblet secretory cells.[142] The proportion of the different epithelial cell types that form the healthy adult human airways varies along the proximal-to-distal axis, with a decreasing number of submucosal glands and an increasing number of club secretory cells.[137,143]

Basal cells function as progenitor cells within the airway epithelium because these cells are able to self-renew or differentiate into secretory, goblet, and ciliated cells in homeostasis and during injury repair[144,145] (see Chapter 8). In humans, basal cells cover most of the airway basement membrane[146]; however, they do not reach the airway lumen and thereby contribute to the pseudostratified appearance of the airway epithelium. These cells interact with columnar epithelium, basement membrane, and underlying mesenchymal cells, inflammatory cells, lymphocytes, and dendritic cells.[147,148]

Ciliated cells protect the TRUs by filtering the inhaled air for solid particles and removing them by mucociliary clearance. Nearly half of the epithelial cells in the normal human airway are ciliated at all airway generations (Fig. 1.23), down to bronchioles (see Fig. 1.19).[149] Each ciliated cell has multiple cilia (≈200 cilia) that have a specialized capping clawlike structure called a ciliary crown, to make the distal portion stiff to propel the liquid lining layer along the airways and to promote debris clearance from the airways. The cilia have structural and motor proteins that produce coordinated and directional beating at 8 to 15 Hz, which is critical for mucociliary clearance.[136–138,150] As the airway superficial lining liquid moves centripetally, it encounters larger and fewer airways, which have a smaller *total* perimeter. For example, the total perimeter of approximately 150,000 terminal bronchioles is much greater than the total perimeter of the five lobar bronchi.[6] If the lining liquid volume remained constant, the liquid layer ought to grow in thickness, but this does not happen, suggesting that much of the liquid is reabsorbed during its ascent along the airways.

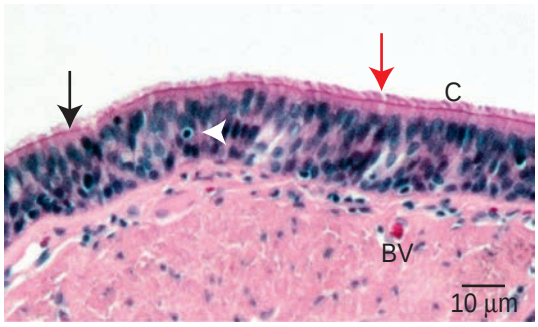

Figure 1.23 Structure of bronchial mucosa. The bronchial mucosa consists of pseudostratified, columnar epithelium with cilia (C) and goblet cells *(red arrow)*. The cilia, which form a thick carpet, move rhythmically and thereby propel liquid, mucus, cells, and debris centrally toward the pharynx. The dark band immediately beneath the cilia *(black arrow)* is produced by the basal bodies. By transmission electron microscopy, basal bodies are recognized as modified centrioles. A lymphocyte *(white arrowhead)* is intercalated among the epithelial cells. A bronchial blood vessel (BV) is located beneath the mucosal layer. (Human lung surgical specimen, 10 µm–thick paraffin section, light microscopy.)

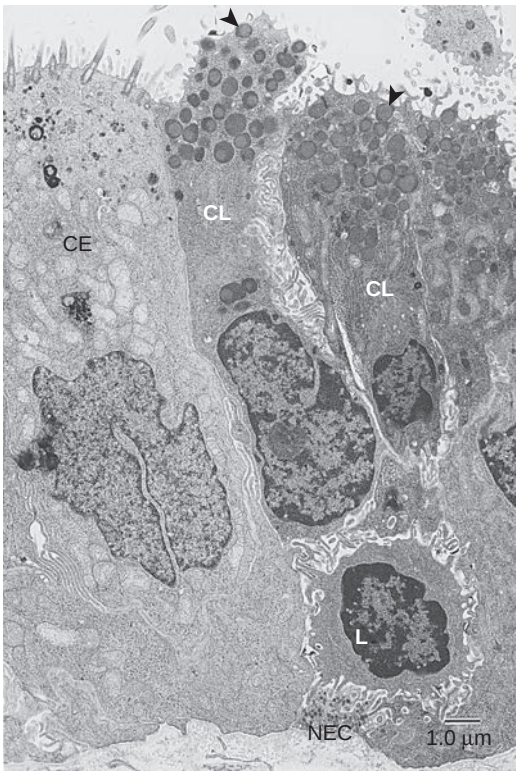

Figure 1.24 Cellular structure of terminal airway epithelium. The epithelium consists mainly of ciliated epithelium (CE) and nonciliated club cells (CL). Club cells have the ultrastructural features of secretory cells; namely, they possess basally located rough endoplasmic reticulum, perinuclear Golgi apparatus, apically located smooth endoplasmic reticulum, and prominent membrane-bound granules *(arrowheads)*. A lymphocyte (L) is intercalated among the epithelial cells. A small portion of a neuroendocrine cell (NEC) containing characteristic dense-cored vesicles is also visible at the base of the epithelial cells. (Human lung surgical specimen, transmission electron microscopy.)

Goblet cells are secretory cells that produce and store mucus in granules of about 800 nm diameter. Secretion of the correct amount of mucus with an optimum viscoelastic profile is essential for maintenance of normal mucociliary clearance.[137,151] Goblet cells also secrete inflammatory mediators that participate in the recruitment and activation of immune cells. Goblet cells are found on the airway surface and in the submucosal glands.[11,58] Furthermore, goblet cells are capable of division and may show stem cell multipotency.[152]

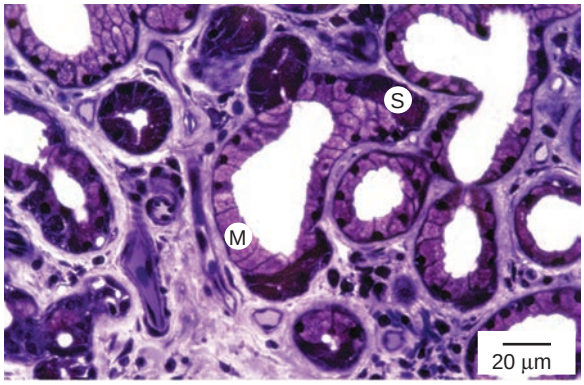

Figure 1.25 Structure of submucosal glands. This figure provides a higher magnification view of a region shown in Fig. 1.7. The mixed, compound tubuloacinar glands contain mucus-secreting cells (M) and serous-secreting cells (S). The latter type form crescentic caps, or demilunes, over the ends of the acini, the rounded secretory units of the gland. Mucous cells are the predominant glandular cell type. (Human lung surgical specimen, right middle lobar bronchus, 2 µm–thick glycol methacrylate section, light microscopy.)

Club cells[153] are dome-shaped cells with dense cytoplasmic granules and microvilli that, in humans, are restricted to terminal and respiratory bronchioles,[154,155] where club cells serve as facultative progenitors for themselves and for ciliated epithelial cells, and they maintain the normal epithelium of the distal conducting airways (see Fig. 1.24).[154,156] Single-cell transcriptome analyses have suggested novel roles for club cells in host defense, antiprotease activity, and physical barrier function.[157] Club cells also secrete secretoglobin 1A1; surfactant proteins A, B, and D; and lipids.[156,158,159]

Submucosal gland epithelial cells line the submucosal glands (Fig. 1.25), which are continuous with the airway epithelium and are located below the airway luminal surface of all of the cartilaginous proximal airways. Submucosal gland epithelial cells secrete mucins, water and electrolytes, and other substances that help protect the lungs from particles and infectious agents. Studies of the regulation of secretion in vivo and in vitro show that secretion is modulated by neurotransmitters, including cholinergic, adrenergic, and peptidergic transmitters,[42] and by inflammatory mediators, such as histamine,[43] platelet-activating factor,[44] and eicosanoids.[45] Submucosal glands are connected to the airway surface by a duct lined by epithelial cells identified as ductal cells.[160] The submucosal gland epithelium contains goblet cells (described earlier) and serous cells. *Serous cells* are the defensive cells of the mucosa because they secrete innate immunity proteins, such as lysozyme, SPLUNC1, β-defensins,[161] mucins, and electrolytes, including chloride and bicarbonate, to control the fluidity of the mucus. These cells, in contrast to goblet cells, have discrete electron-dense granules of about 600 nm diameter. A few serous cells are also present in the surface epithelium of the human bronchioles.[162]

Rare lung epithelial cell types include pulmonary neuroendocrine cells, ionocytes, and brush (tuft) cells. These cell

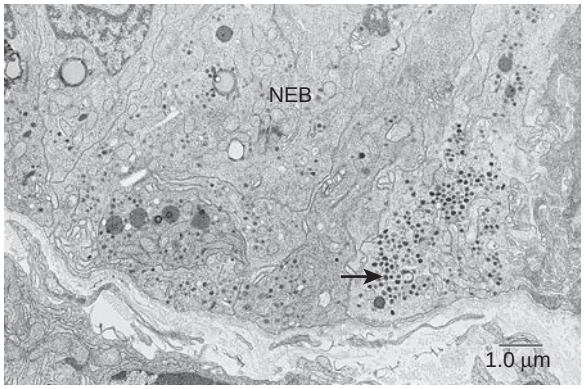

Figure 1.26 Neuroepithelial body (NEB) located in a peripheral airway. Neuroepithelial bodies contain aggregates of neuroendocrine cells. A characteristic ultrastructural feature of neuroendocrine cells is the presence of small (0.1–0.3 µm in diameter) dense-cored vesicles in their cytoplasm *(arrow)*. Each dense-cored vesicle is bounded by a unit membrane. (Human lung surgical specimen, transmission electron microscopy.)

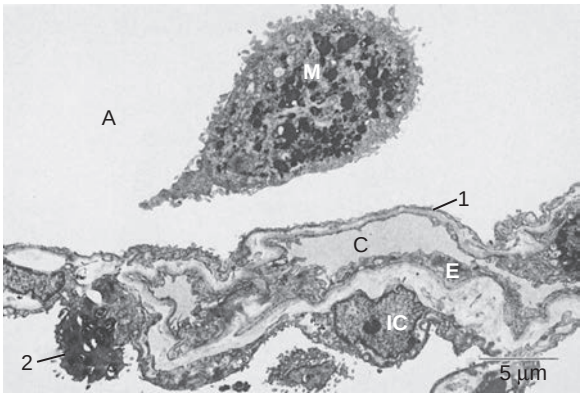

Figure 1.27 Cells of the terminal respiratory unit. An alveolar macrophage (M) is located in an alveolus (A). Alveolar macrophages are the air space scavengers that are cleared either up the mucociliary escalator or into the interstitium. These cells can be activated to express and secrete cytokines, which may interact with other cells. Cells of the alveolar wall are the lining alveolar type 1 and 2 cells (1 and 2, respectively) and the enclosed capillary (C), endothelial cells (E), and interstitial cells (IC; fibroblasts). (Human lung surgical specimen, transmission electron microscopy.)

types are continually and directly replenished by basal progenitor cells.

Pulmonary neuroendocrine cells serve as O_2 sensors[163,164] and release hormones that affect smooth muscle (e.g., vasoactive intestinal peptide[165,166] and substance P).[167–170] Pulmonary neuroendocrine cells represent less than 1% of airway epithelial cells and are a component of the diffuse neuroendocrine system called the amine uptake and decarboxylation system.[171,172] This system is composed of single neuroendocrine cells and clusters of such cells, known as neuroepithelial bodies,[173] distributed along the airway epithelium down to the region of alveolar ducts.[174–177] The neuroepithelial bodies are preferentially located at airway bifurcations. Pulmonary neuroendocrine cells are ultrastructurally characterized by dense-cored vesicles in their cytoplasm (Fig. 1.26). The dense-cored vesicles are the storage sites of amine hormones (serotonin, dopamine, norepinephrine) and peptide hormones (bombesin, calcitonin, leu-enkephalin).[166] Neurons are also associated with neuroendocrine cells.

Ionocytes are a recently identified and rare cell population that serves as the primary source of cystic fibrosis transmembrane conductance regulator activity in the conducting airway epithelium in mice and humans.[140,141] The cystic fibrosis transmembrane conductance regulator is a membrane protein that conducts chloride ions and water across epithelial cell membranes. Mutations in this gene cause cystic fibrosis (see Chapters 67 and 68).

Brush (tuft) cells are pear-shaped cells, with a narrow apex from which extend a tuft of blunt, squat microvilli that stretch their filaments into the underlying cytoplasm. Brush cells also contain numerous intracytoplasmic membrane-bound inclusions and seem to have a chemosensory role, although their function has not been clearly defined.[178]

The complex and diverse cellular composition of the airway epithelium in mammalian organisms has evolved to support the main functions of the airways, namely to connect the outside world to the TRUs, to maintain a balanced secretion and absorption of electrolytes and water from the lining liquid, and to facilitate mucociliary clearance.

ALVEOLAR LINING CELLS

The alveolar epithelial cells that line the anatomic alveoli include *alveolar type 1* (AT1) and *alveolar type 2* (AT2) cells and a minor subpopulation of *alveolar epithelial progenitors* (AEPs), all supported by a shared basal membrane and the subjacent capillaries and fibroblasts.[179,180] AT2 cells outnumber AT1 cells (≈15% vs. 8–10% of total peripheral lung cells, respectively). However, AT1 cells account for approximately 90–95% of the alveolar surface area of the peripheral lung.[181] (See also Video 3.1 for a three-dimensional ultrastructural view of AT1 cells.)

AT1 cells have extensive, attenuated cytoplasmic processes that form a large, thin surface area for gas exchange (Figs. 1.27 and 1.28). AT1 cells express water channels[182] and also epithelial sodium channels and membrane sodium-potassium–adenosine triphosphatase,[183,184] which play a role in pulmonary water flux.[185] Adult rodent and human AT1 cells have a limited proliferative capacity and are sensitive to injury. Under normal conditions, AT1 cells attach via tight junctions to neighboring AT2 cells to form a relatively impermeable seal between alveolar air and alveolar wall interstitial spaces. AT1 cells contain many small, non–clathrin-coated vesicles, or caveolae, that are open either to the alveolar lumen or interstitium or are detached from the surface as free vesicles in the cytoplasm.[186] The vesicles contain caveolin-1 protein, a scaffolding protein that organizes specialized membrane phospholipids and proteins into vesicles. Caveolin-1 can bind free cholesterol and modulate the efflux of cholesterol from the cell when intracellular concentrations rise.[187,188] Caveolae appear to sequester various proteins into the vesicles, such proteins that include growth factor receptors, signaling molecules such as G proteins, calcium ion receptors, and pumps.

AT2 cells are small (≈300 μm^3) cuboidal cells with short stubby apical microvilli (see Figs. 1.27 and 1.29). AT2 cells are specialized in the production and recycling of proteins and phospholipids that form surfactant. Surfactant is stored in cytoplasmic lamellar bodies, which are membrane-bound inclusions (diameter from <0.1–2.5 µm) that are stacked layers of cell membrane-like material (Fig. 1.29) composed

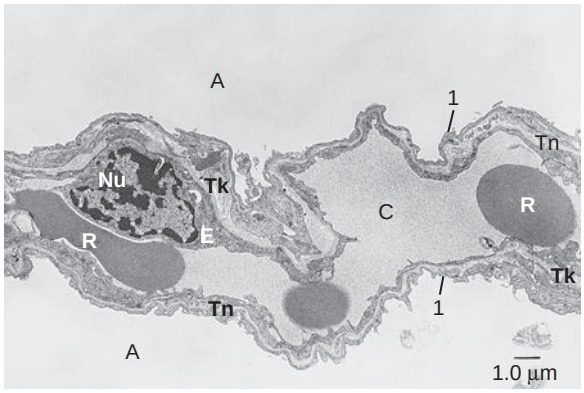

Figure 1.28 Ultrastructure of alveolar walls. The thick (Tk) and thin (Tn) sides of an alveolar capillary (C) change as the capillary crosses between alveoli (A). The basal laminae of the capillary endothelium and alveolar epithelium fuse in the thin regions. The nucleus (Nu) of an endothelial cell (E) is visible above a red blood cell (R). (See also Video 3.1 for a three-dimensional ultrastructural view of alveolar walls.) 1, alveolar type 1 cell. (Human lung surgical specimen, transmission electron microscopy.)

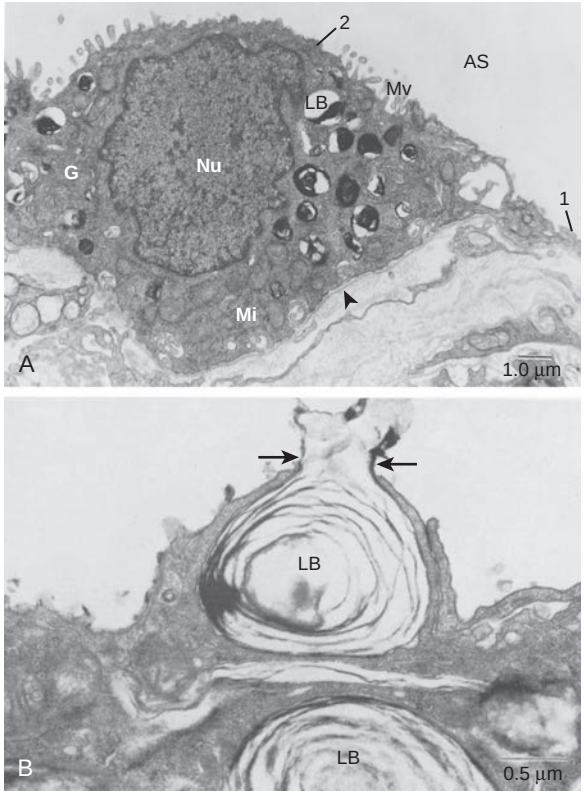

Figure 1.29 Cellular structure of alveolar type 2 cells. (A) Alveolar type 2 (or granular) cells (2) are cuboidal epithelial cells that contain characteristic lamellar bodies (LB) in their cytoplasm and have stubby microvilli (Mv) that extend from the apical surface into the alveolar air space (AS). Other prominent cytoplasmic organelles in alveolar type 2 cells are mitochondria (Mi) and Golgi apparatus (G). Adjacent to the alveolar type 2 cell is a process of an alveolar type 1 cell (1). The abluminal surface of the epithelial cells rests on a continuous basal lamina *(arrowhead)*. Nu, nucleus of an alveolar type 2 cell. (B) The apical region of an alveolar type 2 cell contains two LB, one of which has been fixed in the process of secretion by exocytosis *(arrows)*. The lamellar osmiophilic bodies are the source of surface-active material (surfactant). Alveolar type 2 cells are usually located in the alveolar corners (see Fig. 1.17B). (Human lung surgical specimen, transmission electron microscopy.)

of phospholipids[189] and various proteins, including surfactant proteins A, B, C, and D; lysosomal enzymes; and other molecules.[190,191] Surfactant is secreted to the alveolar space where it decreases the alveolar surface tension.[181] AT2 cells also have immunomodulatory functions. The presence of various ion channels and transporters supports earlier evidence that AT2 cells are actively involved in liquid resorption and transepithelial water fluxes.[192] Studies in mice support a role for AT2 cells as the facultative stem cells of the alveolar epithelium because AT2 cells can both self-renew and differentiate into AT1 cells.[193–195]AEP cells are a subpopulation of AT2 cells that can serve as alveolar epithelial progenitors. AEPs have been identified in adult mouse and human alveoli.[194,195] Human AEPs can be directly isolated by virtue of their expression of the conserved cell surface marker TM4SF1.[194] AEPs are a stable lineage during steady-state turnover in homeostasis but rapidly expand to regenerate the alveolar epithelium after acute lung injury.

The above epithelial cells that line the alveoli are critical for the ultimate function of the lung, which is the gas-exchange process. These cells are shaped and arranged in a way that allows the formation of very thin alveolar septa, where the epithelial cells are in close contact with the capillaries to support the diffusion of gases between air and blood. AT2 cuboidal epithelial cells maintain the integrity of the respiratory units and produce surfactant to control the surface tension of the alveoli.

MESENCHYMAL CELLS

Vascular endothelial cells of both pulmonary and bronchial vessels are continuous (nonfenestrated) endothelial cells (see Fig. 1.16). These flattened cells have an individual area of 1000 to 3000 μm^2 and an average volume of 600 μm^3.[196] The pulmonary capillary bed covers a total surface area of approximately 130 m^2, or the equivalent of one side of a doubles tennis court (260 m^2). Other structural features of capillary endothelial cells are the large number of plasmalemmal vesicles and small number of organelles. Despite having relatively few organelles, capillary endothelial cells have organelles involved in protein synthesis, such as endoplasmic reticulum, ribosomes, and Golgi apparatus, and vesicles, such as caveolae, multivesicular bodies, and lysosomes.[197] The endocytic apparatus participates in receptor-mediated uptake and transport (transcytosis) of albumin, low-density lipoproteins, and thyroxine.[198–202] Vascular endothelial cell functions include O_2 and nutrient transport, control of blood coagulation, interaction with inflammatory cells, and maintenance of epithelial homeostasis.[203] Although all vascular endothelial cells share core properties, there are differences among the endothelial cells in large blood vessels versus capillaries.[204] The large artery endothelium, for example, has a lower barrier strength and angiogenic potential than the capillary endothelium.

Lymphatic endothelial cells share many of the structural and functional characteristics of vascular endothelial cells. The ultrastructural distinction of initial lymphatics (lymphatic capillaries) is that their basement membrane is discontinuous, whereas that of pulmonary and bronchial capillaries is continuous.[205,206]

Fibroblasts are located subjacent to epithelial cell layers of airways or in the interstitium, between the epithelial

and endothelial layers of alveolar walls.[207,208] Fibroblasts produce extracellular matrix components and direct cell growth and differentiation of neighboring cells by cell-cell and cell-matrix interactions. Lung fibroblast populations are highly heterogeneous.[209] For instance, human lung fibroblasts derived from the airway or alveolar regions differ in their gene expression patterns and their phenotype. *Airway fibroblasts* are morphologically and functionally distinct from alveolar fibroblasts, with differences in contractile forces and in gene expression.[210,211] Genes highly expressed in airway fibroblasts are involved in extracellular matrix deposition and organization, whereas genes highly expressed in alveolar fibroblasts participate in actin binding and cytoskeletal organization. Airway fibroblasts synthesize more collagen and eotaxin-1 than alveolar fibroblasts. Also, airway fibroblasts proliferate faster and are more myofibroblast-like, expressing higher levels of α-smooth muscle actin than alveolar fibroblasts. *Alveolar fibroblasts* play an important role during alveologenesis. During lung alveologenesis, two distinct subpopulations of fibroblasts are located in the growing secondary septa: alveolar myofibroblasts and lipofibroblasts.[212] *Myofibroblasts* are considered to be the cell type responsible for secondary septa formation. These cells are located at the tip of growing secondary septa, where they deposit elastin in the apical tip. Myofibroblasts express α-smooth muscle actin and high levels of platelet-derived growth factor receptor-β and contain myofibrils oriented parallel to the alveolar walls. Myofibroblasts differentiate from different precursor cells in disease, being the principal cell in the fibrotic foci.[213,214] *Lipofibroblasts* are characterized by the presence of lipid droplets and specific molecular markers and are located close to AT2 epithelial cells, which is consistent with lipofibroblast support of growth and differentiation of AT2 cells by providing the lipids for surfactant production. Lipofibroblasts are abundant in the late stages of lung development and postnatally. The expression of lipofibroblast marker genes, such as adipose differentiation-related protein, is reduced in the lungs of individuals with interstitial pulmonary fibrosis.[213,215] However, the existence of lipofibroblasts in human lung is still controversial because some electron microscopy studies have not detected lipofibroblasts in developing human lung.[216,217]

Smooth muscle cells in the lung are of two major subtypes[218,219] that differ in their origin and function. *Airway smooth muscle* cells form circular bands around the airway epithelium (see Figs. 1.7 and 1.10) and extend from the trachea throughout the bronchial tree to the terminal bronchioles. Airway smooth muscle cells derive from undifferentiated mesenchymal cells in closest proximity to prodifferentiation signals released from the lung epithelial layer. Newly differentiated airway smooth muscle cells in the embryonic lung are proliferative, but their proliferative capacity decreases with maturation in the fetal and postnatal stages of lung development. The spontaneous phasic contraction of fetal airway smooth muscle cells is important for normal lung development by regulating intraluminal fluid movement. In the adult lung, this phasic contraction is absent and regulation of tonic contraction and airflow is under neuronal and humoral control. Airway smooth muscle responsiveness contributes to the pathophysiology of lung diseases such as asthma.[220] Airway smooth muscle expresses heavy chain α-smooth muscle actin arranged in contractile filaments, along with other contractile proteins.[221,222] *Vascular smooth muscle cells* play an essential physiologic role in regulation of blood flow through the pulmonary and bronchial vasculature. Smooth muscle forming around these vessels derives partly through proliferation/migration of the neighboring airway smooth muscle cell population and de novo differentiation of mesenchymal cells. Airway and vascular smooth muscle cells have differences in phenotype and gene expression that support their distinct structure and function within the lung.[222]

Pericytes are another mesenchymal cell type located along capillary basement membranes in close contact with the endothelial cells.[208,223,224] Pericytes are contractile, sharing characteristics of vascular smooth muscle cells and myofibroblasts. Lung pericytes might serve as myofibroblast progenitors and amplify inflammatory responses by expressing cytokines and adhesion molecules.[225,226]

Chondrocytes are embedded in a collagenous extracellular matrix rich in proteoglycan and elastin fibers that form the C-shaped cartilaginous rings around bronchi.[227,228]

Mesenchymal cells as a group provide the lungs with the structural support, elasticity, and blood supply necessary for sustaining respiratory movements, oxygenation of the lung tissue, and gas exchange at the capillary level in the alveoli.

NEURAL CELLS

Innervation of the lung is mediated by intrinsic neurons, whose cell bodies reside within the lung, and extrinsic neurons, whose cell bodies are located elsewhere. Intrinsic neurons originate in the neural crest and are located asymmetrically around the trachea and primary bronchi.[229] These intrinsic neurons are located close to innervated tissues, including smooth muscle cells in the trachea, airways, and neuroendocrine cells, and their numbers decrease along the proximal-distal axis of the lung.[229]

Extrinsic neuron axons, when found, resemble known sensory endings in other organs (<1 μm in diameter, electron-lucent, and containing microtubules and smooth endoplasmic reticulum).[230] The terminal processes of sympathetic efferent fibers and parasympathetic efferent fibers pierce the epithelial basement membrane, where they initiate airway reflexes, such as bronchoconstriction and cough.[231,232]

HEMATOPOIETIC AND LYMPHOID CELLS

Resident immune cells, including peribronchial and perivascular interstitial macrophages and alveolar macrophages (see Figs. 1.19 and 1.27), control the immune response during homeostasis and disease. Interstitial macrophages and alveolar macrophages, however, have different functional properties. *Interstitial macrophages* are involved in homeostasis and protection against continuous pathogen exposure from the environment. Interstitial macrophages have a high turnover rate and a short life span in the steady state. Interstitial macrophages have been proved to derive from blood monocytes and serve as intermediates for differentiation into alveolar macrophages in primates and in mice.[233]

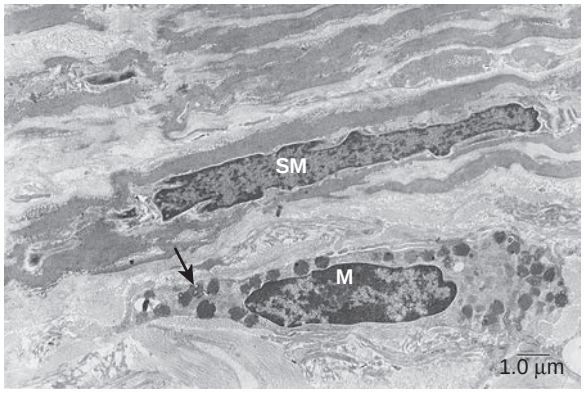

Figure 1.30 Mast cell (M) located adjacent to an airway. The mast cell flanks airway smooth muscle cells (SM). Granules in mast cells demonstrate heterogeneous morphology, including whorled and scrolled contents *(arrow)*. (Human lung surgical specimen, transmission electron microscopy.)

Alveolar macrophages, by comparison, are relatively static under normal conditions, but undergo apoptosis and replacement by interstitial macrophages after exposure to bacterial endotoxin or *Streptococcus* pneumonia.[234,235] Alveolar macrophages actively express and secrete cytokines, such as tumor necrosis factor-α and transforming growth factor-α, and function in surfactant homeostasis and innate immunity.[236] Alveolar macrophages are weak antigen-presenting cells but are active in phagocytosis and production of host defense molecules, such as nitric oxide and cytokines.[237]

Immune response cells, including monocyte-derived macrophages, recruited to the lung during inflammation or infections, migrate through the epithelial basement membrane and pass through to the luminal surface, where some remain intercalated within the surface epithelium. Other immune cells that can be found in the lung, particularly in disease, are mast cells, lymphocytes, eosinophils, neutrophils, basophils, and megakaryocytes.[238] Mast cells in the human lung contain membrane-bound secretory granules (Fig. 1.30) that contain a host of inflammatory mediators, including histamine, proteoglycans, lysosomal enzymes, and metabolites of arachidonic acid.[239] Not only can these mediators induce bronchoconstriction, they can also stimulate mucus production and induce mucosal edema by increasing permeability of bronchial vessels. Lymphocytes are frequently seen intercalated between airway epithelial cells (see Figs. 1.23 and 1.24). These cytotoxic T lymphocytes undergo immunoglobulin A–class antibody responses.[240] T and B lymphocytes also accumulate in the lamina propria beneath the airway epithelium.[240]

The lung is one of the organs in the body in direct contact with the environment. The presence or recruitment of immune cells to the lung is of high importance as a first-line protective mechanism to fight infections, control inflammatory responses, and provide innate immunity.

PLEURAL CELLS

Two types of pleurae exist in the chest: the visceral pleura, which covers the lungs and other chest structures, and the parietal pleura, which is attached to the chest wall.[241] Both visceral and parietal pleurae have a superficial layer of

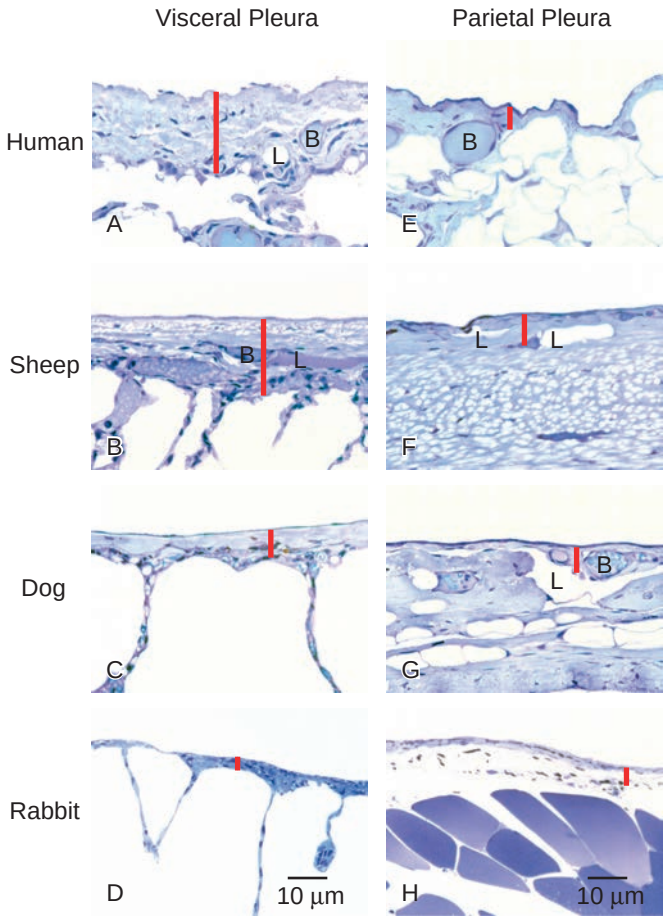

Figure 1.31 Comparative histologic features of the visceral and parietal pleurae among humans, sheep, dogs, and rabbits. The eight panels are shown at the same magnifications. (A–D) Visceral pleura. (E–H) Parietal pleura. The most obvious feature of the visceral pleura is its greater thickness *(longer red vertical bars)* among humans and sheep compared to thinner visceral pleura of dogs and rabbits *(shorter red vertical bars)*. The parietal pleura is thinner and consistently so among species. Both the visceral and parietal pleurae are lined by a single layer of mesothelial cells that have microvilli extending from their surface into the pleural space. Subjacent to the mesothelial cell lining layer is loose areolar connective tissue. Among species with "thick" visceral pleura, the loose areolar connective tissue is traversed by bronchial microvessels (B), lymphatics (L), and nerves. By comparison, among species with "thin" visceral pleura, the loose areolar connective tissue is devoid of microvessels, other than the subjacent pulmonary microvessels at the perimeter of the most superficial alveoli. Lymphatics and nerves are infrequent. In the parietal pleura's loose areolar connective tissue are systemic blood microvessels (B), lymphatics (L), and nerves. This histologic organization is consistent among species. (Human, sheep, dog, and rabbit lung, 2 µm–thick glycol methacrylate sections, light microscopy.)

simple, cuboidal or flattened, mesothelial cells, with various amounts of microvilli on the luminal surface[128,131,132,134] (Fig. 1.31). This mesothelial cell layer is supported by a thin submesothelial connective tissue layer, which includes a basal lamina. Subjacent to this layer is a thin superficial elastic layer, a loose connective tissue layer containing vessels and lymphatics, and a deep fibroelastic layer. Among these layers, thickness of the loose connective tissue layer of the visceral pleura is different across species. For species with thick visceral pleura (human, sheep; see Fig. 1.31), the loose connective tissue layer is much thicker compared to species with thin visceral pleura (dog, rabbit; see Fig. 1.31; rat and mouse; Albertine, unpublished results).

Table 1.4 Comparative Anatomy of Human and Mouse Lungs

Anatomic Feature of the Lung	Human	Mouse
Visceral pleura thickness	25–100 μm	5–20 μm
Visceral pleura arterial supply	Systemic (bronchial)	Pulmonary
Lobes	3 right; 2 left	4 right; 1 left
Airway generations	17–21	13–17
Airway branching pattern	Dichotomous	Monopodial
Main bronchus diameter	≈10–15 mm	≈1 mm
Intrapulmonary airway cartilage	Yes	No
Tracheal epithelium thickness	50–100 μm	11–14 μm
Tracheal club cells	None	≈50%
Tracheal goblet cells	Present	Absent
Tracheal cartilaginous rings	15–20	15–18
Tracheal submucosal glands	Present	Absent
Proximal intrapulmonary airway thickness	40–50 μm	8–17 μm
Proximal intrapulmonary airway club cells	None	≈60%
Proximal intrapulmonary airway goblet cells	Present	Absent
Proximal intrapulmonary airway submucosal glands	Present	Absent
Terminal bronchiole diameter	≈600 μm	≈10 μm
Terminal bronchiole thickness	Not determined	≈8 μm
Terminal bronchiole club cells	≈11%	≈70%
Respiratory bronchioles	Present (≈150,000)	Absent (or 1)
Respiratory bronchiole club cells	≈20%	Absent
Lung parenchyma/total lung volume ratio	≈12%	≈18%
Alveolar diameter	100–200 μm	30–80 μm
Number of alveoli	≈500 million	≈15 million
Alveolar lipofibroblasts	Absent	Present
Blood-air barrier thickness	≈0.68 μm	≈0.32 μm
Pulmonary venule location	Along interlobular septa	Next to bronchioles
Developmental stage at full term	Alveolar	Saccular

Modified from references 154, 155, and 247–249.

The pleural cells provide a smooth tissue surface on the lung and the chest wall. The normal amount of fluid in the pleural cavity facilitates the movement of the lung during breathing.

MOLECULAR ANATOMY OF THE LUNG

Advances in cell isolation and molecular methodologies during the past 3 decades are allowing identification of genes uniquely expressed in the different cell types that form the lung, thus serving as markers to recognize the distinct populations and study their function in health and disease (eTable 1.1). Most markers were first identified in rodents because these models allow genetic manipulation to perform cell lineage tracing to establish lineage and location, as well as cell-specific mutations to study cell-specific function. However, although many markers are common among rodents and humans (see eTable 1.1, uppercase genes), others have been identified only in rodents (see eTable 1.1, lowercase genes) or only in humans (see eTable 1.1, asterisk).

Remarkable technologic advances in the last few years in high-throughput methods for single-cell genomic and transcriptomic analyses and in bioinformatics methodologies have revolutionized the field of lung cell biology. These methods allow studying individual cells within a tissue to classify their cell types, identify new cell types, and characterize variations in their molecular profiles in health and disease.[242] The Human Lung Atlas project[243] is working toward mapping the different structures of the human lung and identifying their cellular and molecular composition. Initial studies show high diversity within each cell population of the lung and emphasize that our knowledge about the number and type of cells that form the human lung in health and disease is incomplete. These single-cell approaches will soon provide a comprehensive cellular composition of the healthy lung[244] and allow dissecting the alterations in cell composition and function associated with the initiation, progression, and resolution of human lung diseases.[245,246]

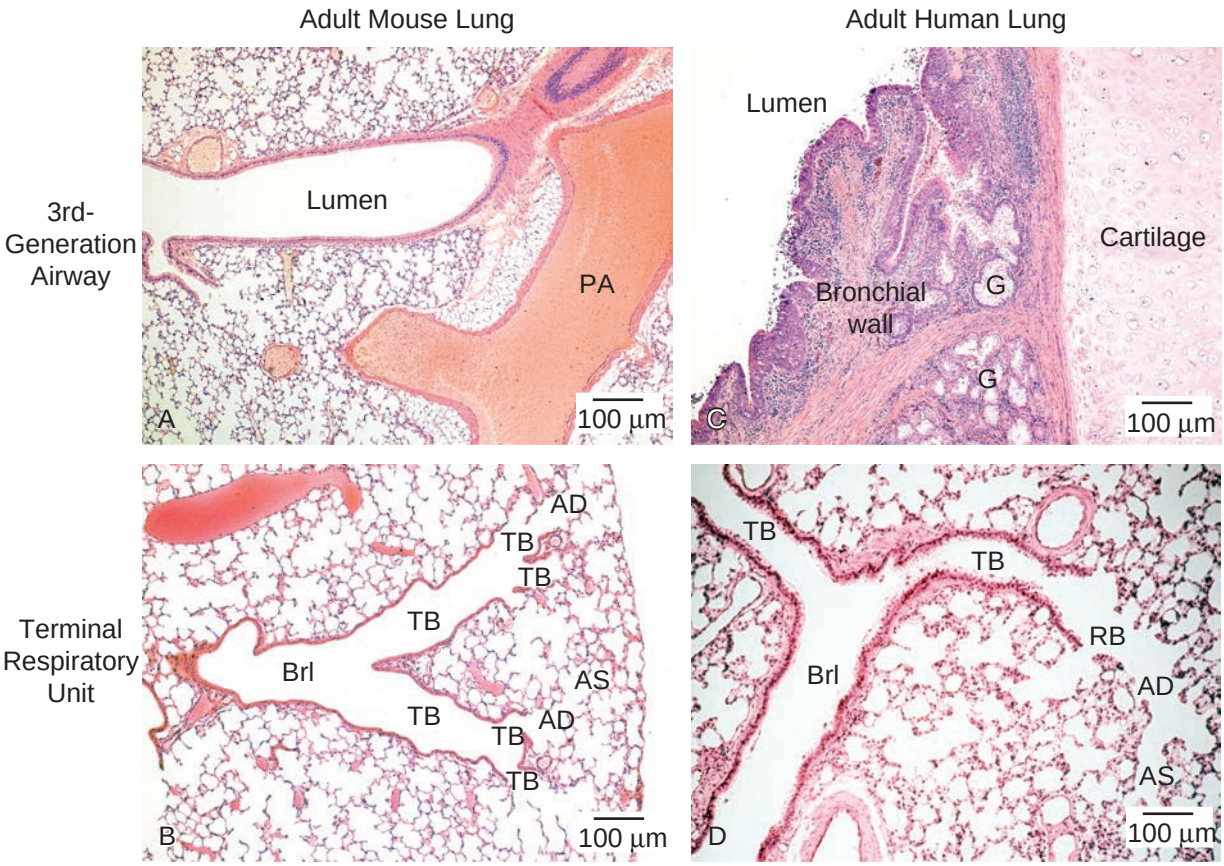

Figure 1.32 Comparison of lung morphology between adult mice *(left column)* and humans *(right column).* The four panels are the same magnification, as shown by the scale bar in each panel. The upper row compares third-generation, intrapulmonary airways between mouse (A) and human (C). The mouse's airway lumen is narrower than the same generation airway (bronchus) in the human. Absent from the wall of the mouse's airway wall are cartilage and submucosal glands (G), both of which are obvious in the wall of the bronchus of the human airway. The lower row compares terminal respiratory units between mouse (B) and human (D). The mouse's terminal respiratory units do not have respiratory bronchioles; therefore terminal bronchioles (TB) open directly into alveolar ducts (AD). By comparison, the human's terminal respiratory units have respiratory bronchioles, which open into ADs. AS, air space; Brl, bronchiole; PA, pulmonary artery. (Mouse and human lung tissue, 5 µm–thick paraffin-embedded sections, light microscopy.)

COMPARISON OF THE LUNG OF HUMANS AND MICE

A point made in the previous section is that species variations are significant in the visceral pleural structure (see Fig. 1.31) and the blood supply to the lung. This point raises the question of what other species variations are found in the lung. For the purpose of this chapter, comparison is made between human and mouse, owing to the fantastic discoveries about genetic and molecular regulation of lung biology by making mouse constructs to identify normal lung structure and function, as well as to study the impact of disease on lung structure and function. For this discussion, the lung will be divided into the conducting airways (bronchi through terminal bronchioles), which do not participate in respiratory gas exchange, and the lung parenchyma (respiratory bronchioles, alveolar ducts, and alveoli), which do participate in respiratory gas exchange.

Key structural features of human and mouse pulmonary morphology are summarized in Table 1.4.[247–249] This table reveals that many anatomic and developmental differences are present in both the conducting airways and lung parenchyma of the human and mouse lower respiratory systems. Although the general anatomic organization of the human and mouse lower respiratory system is largely similar, important differences also exist, at both the gross anatomy level and in the cellular composition of the lower respiratory system.

Human and mouse lungs have different lobe structures. The human lung has five lobes, with the right lung divided into three lobes by the oblique and horizontal interlobar fissures, whereas the left lung is divided into two lobes by the oblique fissure. The lobe structure of the mouse lung is markedly different, with the right lung divided into four lobes and the left lung consisting of a single lobe. The upper airways in the human lung include the trachea and bronchi, whereas the upper airway in the mouse lung is the trachea alone.[250] In the human lung, airway branching is dichotomous, where the parent airway divides at an approximately 45-degree angle into two daughter segments, generating 17 to 21 generations of branches between the trachea and the lung parenchyma, at which point terminal bronchioles transition into up to three generations of respiratory bronchioles, which are part of the lung parenchyma in humans. In contrast, branching in the mouse lung is monopodial (asynchronous), yielding 13 to 17 generations of airways, with a single axial airway (the central bronchiole) running the entire length of its associated lobe, with lateral branches

forming irregularly along the length of the central bronchiole. The lateral branches (lateral bronchioles) bifurcate repeatedly before terminating into short terminal bronchioles that abruptly give rise to alveolar ducts at the bronchoalveolar duct junctions, which are part of the lung parenchyma in mice. Furthermore, in contrast to the human lung, the walls of intrapulmonary conducting airways in mice do not have cartilage, which may impact the distribution of airway resistance compared to the human lung (Fig. 1.32). A potential impact of the fewer airway generations, as well as narrower conducting airways, in the mouse lung is that the deposition of inhaled particulates may have a different distribution in the lungs of mice compared to those of humans. Also, because the mouse lung has fewer airway generations, the parenchyma makes up a larger proportion of total lung volume (≈18%) compared to humans (≈12%). Furthermore, the different lobar structure of the mouse lung has implications for studies on compensatory lung regrowth after unilateral pneumonectomy. For example, left pneumonectomy in mice allows prominent expansion of the right lung, predominantly of the cardiac (often called the accessory) lobe. Thus, the lobar structure of the mouse lungs facilitates studies on lung regeneration, which may be more difficult in lungs from species with a different lobar structure.

The lung parenchyma of human and mouse lungs also has important differences. In the human lung, the terminal bronchioles transition into respiratory bronchioles, of which the human lung has about 150,000 (see Fig. 1.32). These respiratory bronchioles transition into as many as 11 alveolar ducts, which then subsequently transition into up to six alveolar sacs, which are lined by, in total, approximately 500 million alveoli in the adult human lung.[251] In contrast, in the mouse lung, respiratory bronchioles are essentially absent, and the lung parenchyma encompasses exclusively alveolar ducts and alveoli, with the approximately 15 million alveoli in the adult mouse lung constituting the terminus of the lung parenchyma.[252] Thus, the mouse lung has fewer airway generations than the human lung. In both human and mouse lungs, adjacent alveoli are physically connected through pores of Kohn, which facilitate the maintenance of similar pressures across the alveoli by allowing collateral ventilation. Although these pores are similar in human and mouse lungs, the number of pores increase with age in human lungs, whereas in the mouse the number of pores does not change with age.[253,254]

The cellular structure of human and mouse lungs also has marked contrasts. In the conducting airways, the inner surface of both the human and the mouse trachea is lined by a pseudostratified columnar epithelial layer. In humans, the bulk of the cells lining the trachea are ciliated cells, including columnar, basal, and goblet cells; whereas the mouse trachea is lined largely with nonciliated cells. Indeed, in the upper airways of the human lung, the principal secretory cells are goblet cells (see Fig. 1.32), whereas, in the upper airways of the mouse lung, the principal secretory epithelial cells are club cells. Club cells in the human lung are found in the terminal airways. In addition, in the upper airways of the human lung, additional secretory cells are mucous and serous epithelial cells in submucosal glands, which extend along the trachea and bronchi, whereas in the mouse lung, submucosal glands are limited to the proximal aspect of the trachea. Thus, different cell types contribute to airway secretions, and hence airway defense in the two species. Likewise, the distribution of BALT is different between the two species. In the human lung, BALT is located along bronchi. In the mouse lung, BALT is limited to bronchioles.[255]

Differences in the cellular composition of human *versus* mouse lungs have also been noted in the lung parenchyma, taking the example of the lipofibroblast, a lipid-laden fibroblast subset that has been credited with a key role in lung development and repair. To date, lipofibroblasts remain elusive in human lungs. Lipofibroblasts are present in abundance in mouse lungs.[217] The cellular composition of the conducting vessels of the pulmonary circulation in human *versus* mouse lungs also exhibits differences, notably, cardiomyocytes. In humans, cardiomyocytes are not typically detected in intrapulmonary veins in healthy individuals.[256] Cardiomyocytes are present as part of the pulmonary vein structure in mice, extending along the pulmonary vein beyond the hilum, and surrounding individual intrapulmonary veins, even those of small (<100 μm) diameter. Their presence may lead to misidentification of intrapulmonary veins in mice as intrapulmonary arteries, if the cardiomyocyte layer, which may be substantial, is mistaken for vascular smooth muscle. These differences in cellular composition present some challenges for the extrapolation of experimental studies in mice to human pulmonary physiology. For example, the critical role ascribed to lipofibroblasts during distal lung development cannot be generalized to all mammalian lung development if lipofibroblasts are not present in human lungs.

The lung's developmental stage at full term is different between humans and mice. In humans, lung development at full term is at the beginning of the alveolar stage. In mice, lung development at full term is the saccular stage. This timing difference is helpful to keep in mind when developmental comparisons are made and is particularly relevant to studies addressing lung maturation in preterm-born infants; preterm infants born between the 27th and 36th week of gestational age and mouse pups are both delivered in the saccular stage of lung development. Despite being born at a comparatively earlier stage in terms of lung development, term-born mouse pups in the saccular stage of lung development are fully competent for gas exchange, whereas preterm-born infants in the same stage of lung development may require respiratory and supplemental O_2 support due to a limited capacity for gas exchange. This phenomenon highlights important developmental differences between humans and mice during late lung maturation.[257]

Differences in the structure and cellular composition of lungs are not only evident between species but also between strains of the same species. For example, the apparent size of the alveolar unit in the C3H/He mouse strains is appreciably larger than in four other mouse strains—C57BL/6, BALB/c, FVB/N, and DBA/2—by visual inspection of lung sections, a phenomenon confirmed by the determination of the mean linear intercept,

a very rough surrogate for the distance between adjacent alveolar walls.[258,259] This is important in experimental studies that assess the impact of an intervention (such as genetic interference) on alveolar development or alveolar structure, because mice on a complete or partial C3H/He strain background will have intrinsic differences in the dimensions of their alveoli compared with other mouse strains.

Key Points

- The primary function of the lung is gas exchange, achieved by ventilation-perfusion matching between alveolar air and alveolar capillary blood.
- The anatomic arrangements of the pulmonary arteries beside the airways are a reminder that the relationship between perfusion and ventilation determines the efficiency of normal lung function.
- The major obstacle for gas exchange is the slow rate of oxygen diffusion through water. Thus, the alveolar walls must be extremely thin. Because of that thinness, the thickness of the red blood cell forms a substantial portion of the air-blood diffusion pathway.
- The airways form the connection between the outside world and the terminal respiratory units.
- Smooth muscle cells form circular bands around the airway epithelium as far peripherally as the respiratory bronchioles. Tone in the smooth muscle is altered by the autonomic nervous system and by mediators released from mast cells, inflammatory cells, and neuroendocrine cells.
- Normally, capillary blood volume is equal to or greater than stroke volume and, under normal resting conditions, the volume of blood in the pulmonary capillaries is well below its maximal capacity. Recruitment can increase capillary blood volume threefold.
- The alveolar type 2 cell is the major synthesizing and secreting factory of the alveolar epithelium and implements epithelial repair via its ability to proliferate.
- The terminal respiratory unit consists of all the alveolar ducts together with their accompanying alveoli that stem from the most proximal (first) respiratory bronchiole, and contains approximately 100 alveolar ducts and 2000 alveoli. The functional definition of the terminal respiratory unit is that, because gas phase diffusion is so rapid, the partial pressures of oxygen and carbon dioxide are uniform throughout the unit.
- Genes uniquely expressed in the different cell types that form the lung are serving as markers to recognize the distinct populations and study their function in health and disease.
- Although mouse and human lung share many common characteristics, there are a number of differences in structure, cell composition, and development that need to be considered when using mouse models to study human lung function and structure.

Key Readings

Bienenstock J. The lung as an immunologic organ. *Annu Rev Med*. 1984;35:49–62.

Clements JA. Surface phenomena in relation to pulmonary function. *Physiologist*. 1962;5:11–28.

Coleridge JC, Coleridge HM. Afferent vagal C fibre innervation of the lungs and airways and its functional significance. *Rev Physiol Biochem Pharmacol*. 1984;99:1–110.

Comroe Jr JH. *Physiology of Respiration*. 2nd ed. Chicago: Yearbook; 1974.

Cutz E. Neuroendocrine cells of the lung. an overview of morphologic characteristics and development. *Exp Lung Res*. 1982;3:185–208.

Dawson CA. Role of pulmonary vasomotion in physiology of the lung. *Physiol Rev*. 1984;64:544–616.

Forster RE. Exchange of gases between alveolar air and pulmonary capillary blood: pulmonary diffusing capacity. *Physiol Rev*. 1957;37:391–452.

Fung YC. Stress, deformation, and atelectasis of the lung. *Circ Res*. 1975;37:481–496.

Horsfield K, Cumming G. Morphology of the bronchial tree in man. *J Appl Physiol*. 1968;24:373–383.

Johnson MD, Widdicombe JH, Allen L, Barbry P, Dobbs LG. Alveolar epithelial type I cells contain transport proteins and transport sodium, supporting an active role for type I cells in regulation of lung liquid homeostasis. *Proc Natl Acad Sci USA*. 2002;99(4):1966–1971.

Lai-Fook SJ. Pleural mechanics and fluid exchange. *Physiol Rev*. 2004;84:358–410.

Mason RJ, Dobbs LG, Greenleaf RD, Williams MC. Alveolar type II cells. *Fed Proc*. 1977;36:2697–2702.

Murray JF. *The Normal Lung: The Basis for Diagnosis and Treatment of Pulmonary Disease*. Philadelphia: Saunders; 1986.

Plasschaert LW, Zilionis R, Choo-Wing R, et al. A single-cell atlas of the airway epithelium reveals the CFTR-rich pulmonary ionocyte. *Nature*. 2018;560(7718):377–381.

Schiller HB, Montoro DT, Simon LM, et al. The human lung cell atlas: a high-resolution reference map of the human lung in health and disease. *Am J Respir Cell Mol Biol*. 2019;61(1):31–41.

Staub NC, Albertine KH. Biology of lung lymphatics. In: Johnston M, ed. *Experimental Biology of the Lymphatic Circulation*. Amsterdam: Elsevier Science; 1985:305–325.

Staub NC. Pulmonary edema. *Physiol Rev*. 1974;54:678–811.

Weibel ER. It takes more than cells to make a good lung. *Am J Respir Crit Care Med*. 2013;187:342–346.

Complete reference list available at ExpertConsult.com.