EMBRYOLOGY

The stages of lung development (1–9) are summarized in Table 1-1 and figure 1-1. In the embryo, the developing lower respiratory tract is first seen as a groove in the floor of the primitive pharynx, caudal to the pharyngeal pouches. The groove evaginates into a distinct laryngotraheal diverticulum, which elongates caudally into the primitive mesenchyme as the primordial lung bud. Bronchial buds arise by progressive dichotomous division, and the segmental, subsegmental, and more distal airways are formed. Orderly branching is influenced by the surrounding mesodermal component and its extracellular matrix in which soluble growth factors activate proliferation genes at the points of branching (2). Bronchial cartilage, muscle, and connective tissue are derived from the mesenchyme surrounding the bronchial buds. The development of the major airways, termed the embryonic phase, occurs between 3 and 6 weeks’ gestation.

From the 6th to 16th week of gestation, the small airways, up to the terminal bronchioles, are formed; 16 weeks after conception, the formation of the conducting airways is complete. This is termed the pseudoglandular phase (fig. 1-2).

The next stage of development, the canalicular phase, occurs between 16 and 28 weeks. The acinus and its accompanying vascular supply develop and terminal bronchioles give rise to respiratory bronchioles, with terminal sacs representing primitive alveoli (fig. 1-3). Some respiratory function may be possible toward the end of this phase because of the presence of vascularized terminal sacs.

The saccular phase is identifiable by the 28th week and extends to the 36th week of gestation. Saccules form and are lined by flattened type 1 alveolar lining cells. The alveolar capillary network develops in the surrounding mesenchyme, and lymphatics are formed.

The alveolus is distinguished by the following features: it arises from an alveolar duct, it is lined almost exclusively by alveolar lining cells, and the capillaries in the alveolar wall are exposed to at least two contiguous alveoli (1). The alveolar phase begins at approximately 36 weeks’ gestation and extends to as late as 8 years of age. Vascularized alveoli become fully formed and are lined by attenuated type 1 alveolar lining cells (fig. 1-4). Although the alveolar stage begins at about 36 weeks of gestation, mature

<table>
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<tr>
<th>Phase</th>
<th>Gestation</th>
<th>Major Events</th>
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<td>Embryonic</td>
<td>26 days to 6 weeks</td>
<td>Development of major airways</td>
</tr>
<tr>
<td>Pseudoglandular</td>
<td>6 to 16 weeks</td>
<td>Development of airways to terminal bronchioles</td>
</tr>
<tr>
<td>Canalicular</td>
<td>16 to 28 weeks</td>
<td>Development of the acinus and its vascularization</td>
</tr>
<tr>
<td>Saccular</td>
<td>28 to 36 weeks</td>
<td>Subdivision of saccules by secondary crests</td>
</tr>
<tr>
<td>Alveolar</td>
<td>36 weeks to term (and up to 4 years of age)</td>
<td>Acquisition of alveoli</td>
</tr>
</tbody>
</table>

*Modified from reference 5.
Non-Neoplastic Disorders of the Lower Respiratory Tract

Figure 1-1
EARLY EMBRYOLOGIC DEVELOPMENT OF THE LUNG

The embryonic lungs first arise as the laryngotracheal diverticulum in the primitive gut. This elongates and forms bronchial buds which progressively divide dichotomously within the splanchnic mesenchyme. (Figures 10-1 and 10-4 from Moore KL, Herbst M, Thompson M. Essentials of human embryology. St. Louis: Mosby Yearbook; 1988.)
Figure 1-2

PSEUDOGLANDULAR PHASE OF LUNG DEVELOPMENT

The primitive right lung is seen in the chest cavity of this 7-week-old fetus (left). Three lobes covered by mesothelium are apparent. Simple tubular structures divide within a primitive mesenchymal matrix (right). The epithelium is reminiscent of endometrial epithelium.

Figure 1-3

CANALICULAR PHASE OF LUNG DEVELOPMENT (26-WEEK FETUS)

Early vascularized air sacs are lined by cuboidal epithelium. There is marked interstitial thickening. Note the relatively small pulmonary artery compared to the bronchiole.
alveoli are not found until approximately 5 weeks after birth.

The pulmonary artery is formed from the 6th branchial arch which first appears at approximately 32 days of gestation. Branches arise from this arch and extend into the mesenchyme along the lung buds. Thereafter, the pulmonary arterial system forms in tandem with the branching bronchial buds. Arteries that follow the airways are termed conventional pulmonary arteries. Supernumerary arteries are also recognized; they come off at right angles to supply airspaces adjacent to bronchovascular bundles. Muscularization of the arteries does not keep up with the pace of appearance of new bronchioles. Muscularization of pulmonary arteries beyond the level of the terminal bronchiole begins only in the first year of life and progresses to early adulthood, when it is seen all the way to the alveolar wall. In the fetus and neonate, the walls of pulmonary arteries appear thick in histologic sections, since until birth the pulmonary circulation is a high pressure system similar to the systemic circulation. After birth, there is progressive decrease in the proportion of the arterial media as the pulmonary system becomes a low pressure system (fig. 1-4).

The pulmonary venous system develops from an evagination in the wall of the atrium in the sino-atrial region. The primitive pulmonary vein grows toward the lung buds, and ultimately, following fusions and further divisions, four major pulmonary veins are formed which enter the left atrium. Branches of the veins grow into the mesenchyme around the lung buds and into interlobular septa.

The visceral and parietal pleurae arise within the primordial mesenchyme surrounding the developing lung (fig. 1-2).

The development of the lung can be divided into lung growth, corresponding to cell multiplication, and lung maturation, referring to attainment of normal distensibility and compliance (1). Lung growth can be assessed by: lung weight and/or volume and its ratio to total fetal weight/volume; DNA amount or concentration in the lung; total alveolar surface area; and total alveolar number. Lung growth is affected by the available intrathoracic space and by the volume of liquid in the fetal lung (3). Disruption of lung liquid dynamics is associated with abnormalities in lung growth: oligohydramnios (decreased lung liquid) leads to lung hypoplasia, whereas experimental tracheal ligation (which increases lung liquid) is associated with increased lung growth (hyperplasia).

Normal lung maturation leads to a stable, distensible and compliant lung, and is affected by many physical and hormonal factors (1). Lung maturation requires normal synthesis, storage, and secretion of surfactant, and this can be affected by hormones (including steroid hormones, insulin, and epinephrine), growth factors, and many other agents (8). At birth, the lung is a liquid-filled organ that must quickly adapt to being an air-filled organ, probably by decreased secretion and increased reabsorption of lung liquid.
ANATOMY AND HISTOLOGY

The anatomy and histology of the lung are well described (10–36). The average weight of both lungs for men is approximately 850 g and for women, 750 g. The lungs are divided into five lobes: the right upper, right middle, and right lower lobes and the left upper and left lower lobes. The proximal bronchial branches define 10 bronchopulmonary segments within these lobes (fig. 1-5). A lobule is the smallest anatomic compartment of the lung that is grossly apparent. Lobules are 1 to 2 cm in diameter, polygonal, and bound by complete or incomplete connective tissue interlobular septa. Lobules and their demarcating septa are best appreciated grossly in the periphery of the lung, particularly in cigarette smokers, where the septa are highlighted by accumulations of anthracotic pigment in the septal lymphatics (fig. 1-6). Lobules have centrally located bronchovascular bundles. Identification of lobules has become important for correlating radiologic studies of the lung, particularly high-resolution computed tomography (HRCT), with the gross and histologic findings.

The functional unit of the lung is the pulmonary acinus, where gas transfer takes place. A lobule may contain from 3 to 30 acini. An acinus is defined as “the complex of all airways that are distal to terminal bronchioles and thus are served by a first order respiratory bronchiolus,” which is termed a “transitional bronchiole” (17). Acini include multiple respiratory bronchioles and their supplied alveolar ducts.
and alveoli. Acinar volume averages 187 mm³ (17), and acini may be up to 9 mm in greatest dimension (average, 7.5 mm) (17, 29). Assuming an average diameter of 7.5 mm, there are approximately 25,000 acini in normal adult male lungs, with a volume of 5.25 L (29).

The airways undergo up to about 23 generations of dichotomous branching beyond the carina, 20 proximal to the level of the respiratory bronchioles. The trachea and bronchi have cartilage in their walls. Tracheal cartilage is U-shaped, with a posterior band of smooth muscle. The bronchi have circumferential cartilaginous rings. The bronchi and the bronchioles are the conducting airways of the lung. The smallest bronchi (cartilaginous airways) are approximately 1 mm in diameter; airways smaller than 1 mm are bronchioles (membranous airways). Bronchioles lack cartilaginous rings and have a smooth muscle investment in their walls. Respiratory bronchioles have functional alveoli in their walls and are part of the pulmonary acinus. The term “small airways” has been used for airways 2 mm in diameter and smaller, and refers to both small bronchi as well as bronchioles.

Within the acinus (respiratory bronchioles, alveolar ducts, alveoli) (fig. 1-7), gas transfer takes place across a very thin membrane between the air-blood interface. This membrane is comprised of cytoplasm of a type 1 alveolar lining cell, fused basement membranes of the type 1 alveolar lining cell and the adjacent endothelial cell, and the attenuated endothelial cell cytoplasm of the alveolar capillary. Adjacent alveoli communicate by the pores of Kohn. These develop after birth. They average 13 to 21 per alveolus and are thought to be involved in collateral ventilation (18).

Lambert’s canals communicate directly between airways and adjacent alveoli. These are rarely observed morphologically, but their functional effects in collateral ventilation are apparent to physiologists. Healing inflammatory changes in the bronchioles may be associated with peribronchiolar metaplasia, with growth of bronchiolar epithelium through Lambert’s canals (fig. 1-8).

The lung has a dual vascular supply. The pulmonary arteries accompany airways into the lung periphery where they progressively divide into a ramifying capillary network in the alveolar wall. The rich alveolar capillary network is interanastomosing and wraps around the axis of the alveolar wall to provide a maximum surface area for blood-gas exchange (fig. 1-9). Bronchial arteries are systemic, arising from the aorta or intercostal arteries; they form a plexus in the bronchial wall which extends peripherally as far as the respiratory bronchioles. Proximally, bronchial arteries anastomose with those that supply the trachea, which derive from branches
A membranous bronchiole connects with a respiratory bronchiole (left), which is continuous with alveolar ducts and alveoli adjacent to the septum and pleura. The alveolar walls are delicate and thin (right), and allow maximum surface area for gas exchange.

This histologic section of a normal bronchiole shows a direct communication between the bronchiolar lumen and an adjacent alveolus.
of the inferior thyroid artery. Branches of the bronchial arteries also supply the visceral pleura and some of the interstitial connective tissue.

The pulmonary venous system arises from the efferent blood flow through the alveolar capillary network of the periphery of the lobules, where small veins can be seen entering pulmonary septa. Bronchopulmonary segments are often drained by more than one pulmonary vein.

In histologic sections, pulmonary arteries have an internal and external elastic membrane, whereas veins have a single external elastica (fig. 1-10). In pathologic states, especially those with fibrosis or pulmonary hypertension, distinction between arteries and veins may be difficult, even with elastic tissue stains. This is because veins may be “arterialized,” and their elastica may be reduplicated. In such instances, anatomic location is extremely important, since arteries accompany airways and veins can be identified within interlobular septa. In histologic sections of adult lungs, the pulmonary artery and its accompanying bronchiole should be about the same size; in pathologic conditions a discrepancy can be seen in the size of either of these structures (36).

The lymphatic drainage of the lung is quite complex (fig. 1-11). In general, the lymphatics follow the bronchovascular structures and are found in the pleura and septa. They can be identified along pulmonary arteries, airways to the level of respiratory bronchioles, venules in the periphery of lobules, and veins in the septa. A rich lymphatic network is also found in the visceral pleura. Lymphatics are generally inapparent in histologic sections but become more obvious in pathologic states such as pulmonary edema and lymphangitic carcinoma. Pulmonary lymphatics contain valves (in contrast to pulmonary veins).

Lymphoid tissue, including clusters of histiocytes, can be found along lymphatic vessels, particularly at sites of branching of larger airways where inhaled particulate antigens are likely to settle and where there is respiratory epithelium specialized for absorption. This lymphoid tissue is termed bronchus-associated lymphoid tissue (BALT) and is generally not apparent histologically in the absence of antigenic stimulation (30). It is organized into discrete lymph nodes around the larger bronchi (intrapulmonary peribronchial lymph nodes) and in the hilum. Lymph nodes are occasionally found in the periphery of the lung, usually in the pleura or in the septa (19). Lymphatic drainage from the pulmonary lymphatics is primarily cephalad to lymph node groups in the chest, but also to lymph nodes in the abdomen (fig. 1-12).

BALT is part of the generalized mucosa-associated lymphoid tissue (MALT) found in a number of organs in the body, most notably the gastrointestinal tract (10,11,16,30). Technically,
the term BALT is used for lymphoid tissue along the airways, but hyperplasia of this tissue is commonly accompanied by hyperplastic lymphoid tissue along all of the lymphatic routes in the lung, including the septa and pleura. Lymphoid hyperplasia along airways shows a close apposition of lymphoid follicles to the overlying airway epithelium, which may be somewhat flattened and infiltrated by lymphocytes.

The major cell types found in the lower respiratory tract are summarized in Tables 1-2 and 1-3. The cells lining the airways and alveoli are endodermally derived and have a number of specialized modifications. The respiratory tract is organized to produce and to propel mucus proximally, and to facilitate gas transfer distally (figs. 1-13, 1-14). In the large airways, the goblet cells (and the submucosal glands [see below]) produce mucus, which forms a coat lining the airways. This mucus coat is propelled proximally by the ciliated cells of the airways. It is composed of glycoprotein (which includes mucins), lipids, proteoglycans, immunoglobulins (secretory IgA), lysozyme, lactoferrin, peroxidase, actin, DNA, and other substances which together form a potent defense mechanism (33). The mucus also traps particulate debris. Normal function of the mucociliary escalator depends on normal maintenance of the airway epithelium. Inflammatory and irritative states may change the cellular composition of the mucosa of the airways (for example, increased goblet cells and increased mucus production, squamous metaplasia with loss of ciliated cells), and alter normal function and produce or contribute to pathologic states. Basal cells in the airway epithelium are precursors to goblet and ciliated cells. Scattered neuroendocrine cells, some of which have dendritic processes, are present in the basal layer of the airway epithelium but not the alveoli. They represent 0.17 percent of all airway epithelial cells (12). Small clusters of neuroendocrine cells
(neuroepithelial bodies) can be identified at airway branch points. The ultrastructural features of the ciliated cells are well described (20,21), and in syndromes associated with abnormal ciliary function, ultrastructural abnormalities may be identified (see chapter 9).

In small airways, there is a progressive decrease in number of goblet cells and ciliated cells and a concomitant increase in Clara cells. The mucosa assumes a cuboidal appearance in contrast to the pseudostratified columnar pattern seen in large airways (fig. 1-13).

The major cells found in the alveoli include type 1 (squamous) alveolar lining cells, which cover over 90 percent of the alveolar surface area; type 2 alveolar lining cells (granular pneumocytes); and alveolar macrophages. Ultrastructurally, type 2 alveolar lining cells contain lamellar inclusions which represent precursors of surfactant. Type 2 alveolar lining cells represent precursor cells to type 1 cells and proliferate following injury and during chronic inflammatory states. Scavenger alveolar macrophages are present within the alveoli (and increase in chronic inflammatory and irritative states); they are involved in phagocytosis of foreign material and are a major component of the inflammatory and immune response. Type 1 alveolar lining cells have thin, very attenuated cytoplasm, inapparent in routine hematoxylin and eosin-stained sections but easily appreciated with immunohistochemical stains for
LYMPHATIC DRAINAGE OF THE LUNG

The drainage is primarily cephalad along the right paratracheal route (A), right brachiocephalic route (B), left paratracheal route (C), and para-aortic route (D). Some deep drainage into the abdomen (E) takes place from the inferior thoracic cavity. (Figure 4 from Okaha Y. Lymphatic system of the human lung. Kyoto, Japan: Kinpodo Publishing; 1989.)

epithelia (such as cytokeratin or epithelial membrane antigen), whereas type 2 alveolar lining cells are easily appreciated in routine sections.

Glands of minor salivary type are found in the submucosa of the trachea and bronchi (but not the bronchioles). Anatomically, three regions are recognized in these glands: the ciliated duct, the connecting duct, and the secretory tubules lined by serous and mucous cells. These seromucous glands are invested by a myoepithelial cell layer which probably functions in secretion. Particularly in older individuals, oncocyes (oncocytic metaplasia) may be found in the connecting duct, or replacing serous or mucous cells in the secretory tubules.

The lung contains an interstitial compartment which provides its connective tissue framework. The interstitium is generally inconspicuous but can be recognized along bronchovascular bundles, around veins, and where it forms interlobular septa. Within the interstitium, there are collagen fibers, elastic fibers, mesenchymal cells, and a few inflammatory cells. In the pediatric lung, the interstitial space is more apparent, usually manifesting as a thickening of the alveolar walls; this pattern is present up to about 4 years of age.
### Table 1-2

**MAJOR CELLS OF THE LOWER RESPIRATORY TRACT**

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Main Features</th>
<th>Functions</th>
<th>Location</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciliated</td>
<td>Columnar, cuboidal, ciliated bronchial lining cells; each cell has approximately 250 cilia at the apical surface and each cilium is approximately 6 µm long</td>
<td>Proximal transport of mucus stream (mucociliary escalator)</td>
<td>Bronchi and bronchioles</td>
<td>Increased number and morphologic abnormalities seen with chronic irritation</td>
</tr>
<tr>
<td>Goblet</td>
<td>Columnar mucus-secreting cells; contain mucus or glycoprotein which discharges apically</td>
<td>Contribute to airway mucus</td>
<td>Bronchi, more numerous proximally; small numbers in bronchioles</td>
<td>Increased number in chronic airway irritation</td>
</tr>
<tr>
<td>Basal</td>
<td>Short cells with relatively little cytoplasm oriented along the membrane; do not reach the luminal surface of the epithelium</td>
<td>Precursor cell of ciliated and goblet cells</td>
<td>Bronchi; rare in bronchioles</td>
<td>---</td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>Basal-oriented cells with numerous dense-core (neurosecretory) granules single or in groups (neuroepithelial bodies); the latter near the airway bifurcation system</td>
<td>Specific functions not known in detail; considered part of the diffuse neuroendocrine system</td>
<td>Bronchi and bronchioles</td>
<td>---</td>
</tr>
<tr>
<td>Oncocytic</td>
<td>Eosinophilic mitochondrial-rich cells in submucosal gland ducts</td>
<td>Ion secretory functions</td>
<td>Submucosal glands</td>
<td>Increasing number with aging</td>
</tr>
<tr>
<td>Squamous (metaplasia)</td>
<td>Stratified squamous epithelium is an abnormal reaction, replacing normal pseudostratified respiratory epithelium</td>
<td>Protective, reparative</td>
<td>Bronchi and bronchioles; scarred alveoli</td>
<td>Metaplastic response to irritation or repair</td>
</tr>
<tr>
<td>Clara</td>
<td>Columnar nonciliated bronchiolar cells; protuberant apical cytoplasm with large ovoid electron-dense granules; comprise the majority of nonciliated bronchial cells</td>
<td>Secretory functions contributing to the mucus pool and maintaining extracellular lining fluid; progenitor of other bronchiolar cells; role in surfactant and protease inhibitor production</td>
<td>Predominantly in bronchioles</td>
<td>---</td>
</tr>
<tr>
<td>Type 1 alveolar pneumocyte</td>
<td>Large, flat, squamous alveolar lining cells; cover approximately 93% of alveolar surface area; incapable of division</td>
<td>Provide a thin air-blood interface for gas transfer</td>
<td>Alveoli</td>
<td>---</td>
</tr>
<tr>
<td>Type 2 alveolar pneumocyte</td>
<td>Columnar alveolar lining cells comprising 16% of the lung parenchyma; microvillous surface; synthesize and secrete surfactant (lamellar ultrastructural inclusions); capable of division</td>
<td>Maintain alveolar stability and produce surfactant; stem cell alveoli acting as progenitor type 1 pneumocytes</td>
<td>Alveoli</td>
<td>Increased in reparative states and as a response to chronic injury</td>
</tr>
<tr>
<td>Alveolar macrophages</td>
<td>Marrow-derived phagocytic cells</td>
<td>Involved in alveolar defense, cytokine production, and inflammatory and immune processes</td>
<td>Alveoli, airway, submucosa, lymphatic, and lymphoid tissue</td>
<td>---</td>
</tr>
</tbody>
</table>
Columnar ciliated cells are most prominent in the bronchus, whereas cuboidal-shaped cells and Clara cells with apical protrusions containing granules are more prominent in the bronchiole. The alveolus contains primarily type 1 (membranous) alveolar lining cells to facilitate gas transfer, interspersed with type 2 cells that protrude into the alveolar lumen. (Figure 2-6 from Weibel ER, Taylor CR. Design and structure of the human lung. In: Fishman AP, ed. Pulmonary diseases and disorders, vol. 1, 2nd ed. New York: McGraw-Hill; 1988.)

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<td>OTHER CELLS OF THE LOWER RESPIRATORY TRACT</td>
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<td>Endothelial cells and pericytes</td>
</tr>
<tr>
<td>Interstitial fibrocytes, fibroblasts, and myofibroblasts</td>
</tr>
<tr>
<td>Lymphocytes (intravascular and interstitial)</td>
</tr>
<tr>
<td>Langerhans type histiocytes (in airway mucosa)</td>
</tr>
<tr>
<td>Intravascular megakaryocytes</td>
</tr>
<tr>
<td>Mast cells</td>
</tr>
</tbody>
</table>

*Figure 1-13*

SCHEMATIC REPRESENTATION OF THE SURFACE EPITHELIUM OF THE RESPIRATORY TRACT
Non-Neoplastic Disorders of the Lower Respiratory Tract

Figure 1-14
ULTRASTRUCTURAL SCHEMATIC REPRESENTATION OF RESPIRATORY TRACT EPITHELIUM IN A BRONCHUS

The various cell types comprising this epithelium are illustrated along with their ultrastructural features. Brush cells had been primarily recognized in animals. (Figure 25-11 from Sorokin SP. The respiratory system. In: Weiss L, ed. Cell and tissue biology: a textbook of histology. Baltimore: Urban & Schwarzenberg; 1988).

Embryology

Anatomy and Histology