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Chapter 1

The normal lung: histology, embryology, development, aging and function

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Introduction

Knowledge of normal lung anatomy and function is important for the interpretation of lung biopsies and resections. An understanding of different cell structures and functions allows for a greater appreciation of disease states. In addition basic pulmonary embryology explains congenital pulmonary defects. At the other extreme of life, knowledge of how the lung ages is important, not only for consideration of other diseases, such as hiatus hernias with co-existent aspiration, but also because of the world's increasing elderly population.

Development

The key events of pulmonary embryogenesis and postnatal development are discussed in this chapter. For a more detailed account, the reader is referred to two monographs[1,2] and several review articles.[3–7]

The events of human lung growth are divided into five continuous stages, based on anatomic and histological characteristics.[8] These are the embryonic, pseudoglandular, canalicular, saccular and alveolar stages (Table 1) (Figures 1 and 2). Airway and vascular development are closely related. The conducting airways are formed in the embryonic and pseudoglandular stages, while gas exchange units characterized by vascularization and reduction of mesenchyme are formed in the canalicular, saccular and alveolar stages.[6]

Table 1 Stages of lung growth

Stage	Time	Main events
Embryonic	0–7 weeks	Formation of trachea, right and left main bronchi, segmental bronchi, and vasculogenesis around airway buds
Pseudoglandular	7–17 weeks	Differentiation of epithelial cells, formation of conduction airways and terminal bronchioles, formation of pulmonary arteries and veins
Canalicular	17–27 weeks	Formation of respiratory bronchioles, alveolar ducts and primitive alveoli, differentiation of type I and type II pneumocytes and formation of alveolar capillary barrier
Saccular	27–36 weeks	Increment in gas exchange areas, further differentiation of type I and type II cells
Alveolar	36 weeks – 2 years Up to 18–22 years	Septation and multiplication of alveoli Enlargement of terminal bronchioles and alveoli

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Airway and airspace development

The lung first appears as a diverticulum or bud from the ventral wall of the foregut 22 to 26 days after fertilization. This bud grows caudally, with the epithelial cells from the foregut endoderm invading the surrounding mesenchyme to form the trachea (Figure 3). During the fourth week of gestation, the caudal end of the trachea divides into two bronchial buds, each proceeding to form the right and left main bronchi. By 32 to 35 days, the lobar bronchial buds form and up to 10 days later, the segmental and subsegmental bronchial buds develop.[1] Further dichotomous branching continues and by 14 weeks 70% of the total airway is formed.[9] At the end of the pseudoglandular stage (17 weeks), the development of conducting airways up to the terminal bronchioles is complete.[10]

Human lung contains undifferentiated lung stem cells, nested in niches in the distal airways. These cells are self-renewing, clonogenic, and multipotent in vitro. After injection into damaged mouse lung in vivo, human lung stem cells form human bronchioles, alveoli and pulmonary vessels integrated

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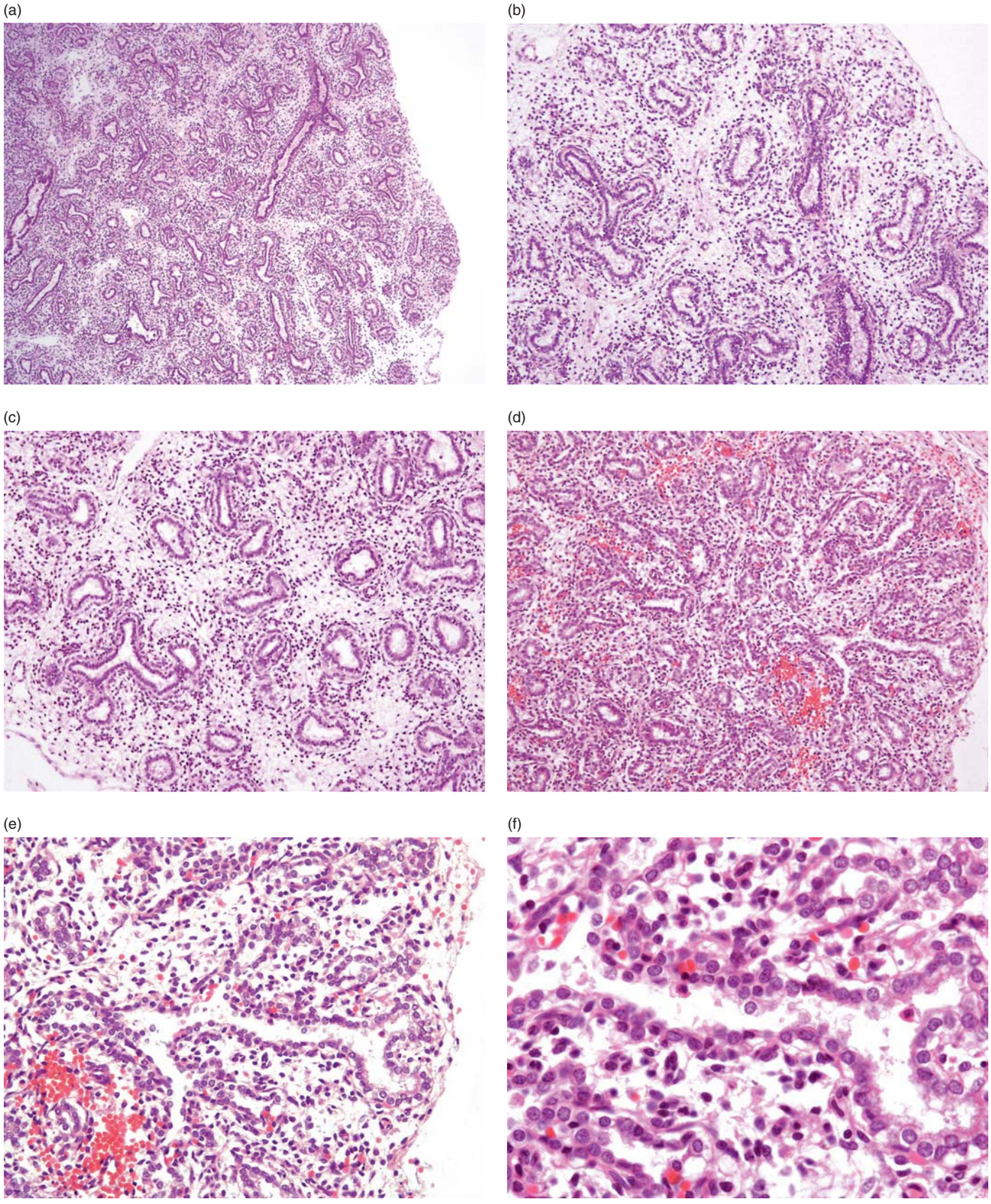

Figure 1. (a–c) Developing lung at 14 weeks. Very immature lung at the late pseudoglandular stage. Developing airways are lined by cuboidal undifferentiated cells containing glycogen. Interstitium is wide and relatively poorly vascularized but new vessels are rapidly formed by vasculogenesis within the mesenchyme. (d–f) Fetal lung at 20 weeks. Canalicular stage lung with more elongated developing airways. Interstitium is reduced; vascularization is increased and some capillaries are starting to push into the cuboidal epithelium visible mainly at the airway branch points. (Images provided by Dr Stephen Gould, Oxford, UK.)

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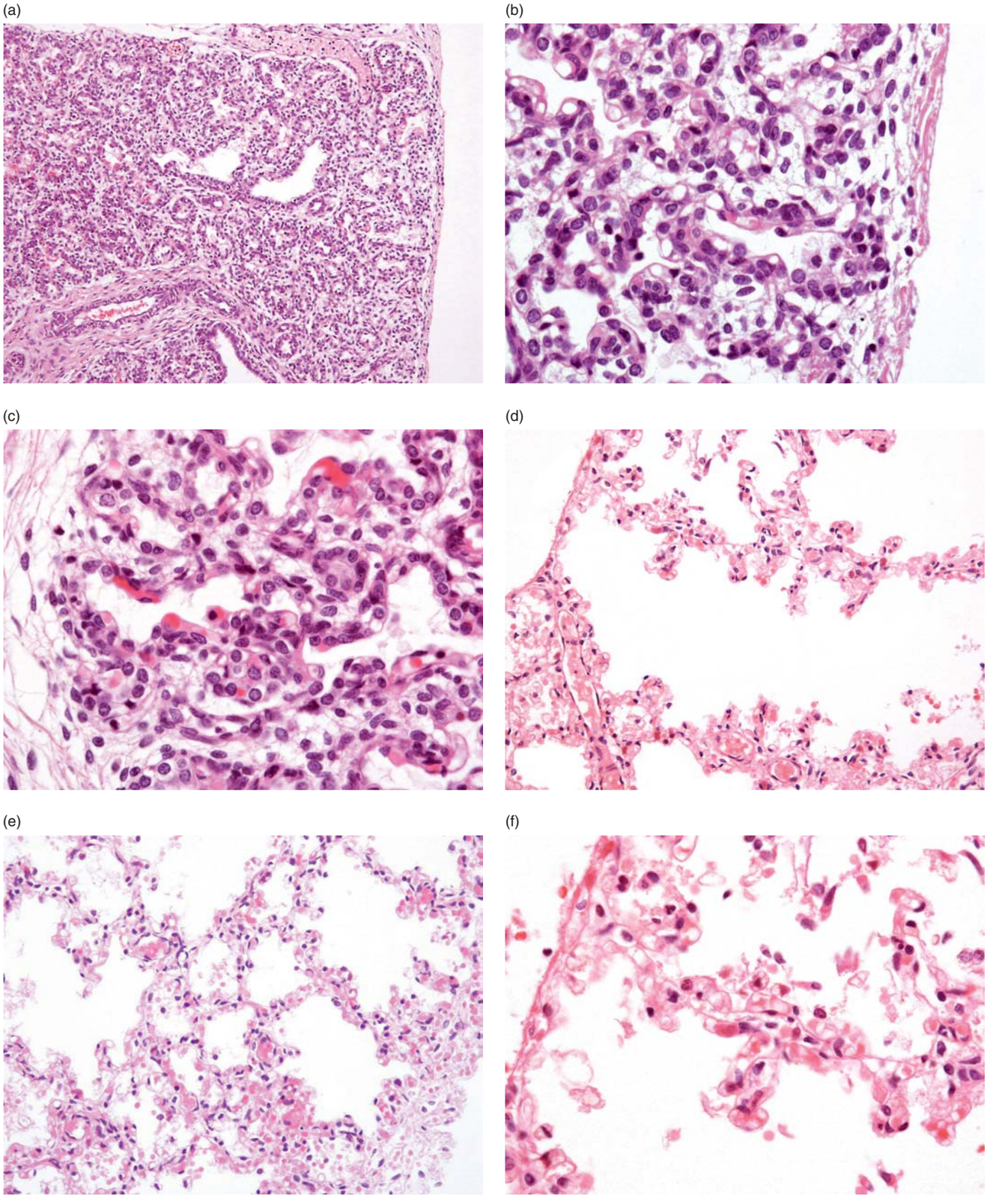

Figure 2. Stages in lung development. (a–c) Lung at 26 weeks. Late canalicular/early saccular stage, with increasingly close contact between the capillaries and the airway lumen. The blood-gas barriers are approaching the thinness found in the adult. Hence it is around this stage that premature infant survival may be possible. Cuboidal type II pneumocytes which, at least ultrastructurally, are producing surfactant are still very visible but type I pneumocytes are also differentiating over the capillaries. (d–f) The lung at 38 weeks. The lung is relatively mature and alveolarization is progressing quickly. By this stage, some 30–50% of the alveoli present in the adult have been formed. (Images provided by Dr Stephen Gould, Oxford, UK.)

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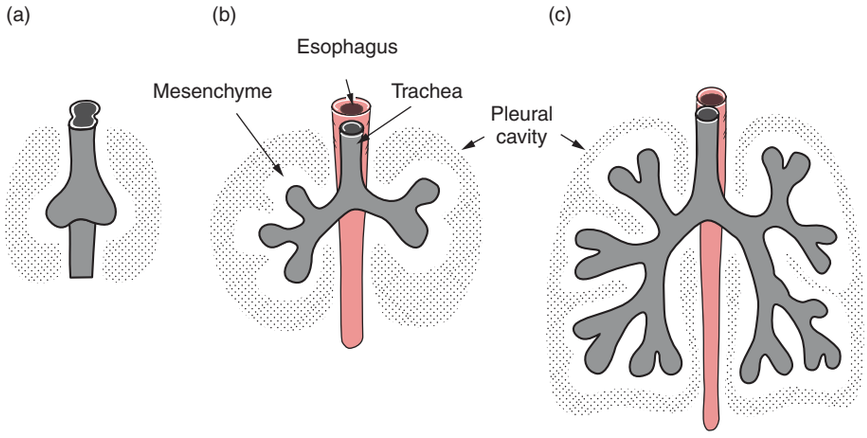

Figure 3. Diagram showing (a) the growth of the trachea and esophagus from primitive buds, (b) into the main bronchi surrounded by mesenchyme and (c) further differentiation of bronchi. Adapted from Sadler TW. *Langman's Medical Embryology*, 6th ed. Williams and Wilkins, Baltimore, 1990.

structurally and functionally with the damaged organ. The formation of a chimeric lung was confirmed by detection of human transcripts for epithelial and vascular genes. In addition, the self-renewal and long-term proliferation of human lung stem cells was shown in serial-transplantation assays.[11]

A population of endogenous or lung-resident (LR) mesenchymal stromal cells (MSCs) in human adult lungs has been identified in transplanted allograft bronchoalveolar lavage (BAL).[12] Lung-resident mesenchymal stromal cells (LR-MSCs) were characterized as fibroblast-like clonal cells that differentiated into adipocytes, chondrocytes and osteocytes in vitro. They expressed mesenchymal markers, vimentin and prolyl-4-hydroxylase, and stem cell markers CD73, CD90, and CD105. Hematopoietic markers, CD14, CD34, and CD45, were not detected. More than 95% of the lungs' MSCs were donor-derived. Using sex-mismatched lung transplant donor-recipient pairs, the data suggested a population of self-renewing LR-MSCs.

The same authors[13] demonstrated that lavage LR-MSCs were increased within 3 months, as well as more than 2 years after lung transplantation. Greater numbers of LR-MSCs were found in association with a recent diagnosis of BOS (bronchiolitis obliterans syndrome), a histological diagnosis of bronchiolitis obliterans (BO), or histopathological organizing pneumonia (OP).

During this pseudoglandular stage, the epithelial and mesenchymal cells differentiate to form cartilage, submucosal glands, bronchial smooth muscle and the different epithelial cells. At this time, the airways are lined by tall columnar cells proximally and cuboidal cells distally. Ciliated, non-ciliated, basal, and goblet cells are also present.

The respiratory bronchioles, alveolar ducts, and primitive alveoli form during the canalicular stage. Two important events occur in this stage, namely differentiation of pulmonary epithelium into type I and type II pneumocytes and formation of the alveolar capillary barrier with a marked increase in the vasculogenesis of the primitive interstitium. Surfactant protein is detectable by 24 weeks of intrauterine life.[4]

During the saccular stage, further enlargement and dilatation of the primitive alveoli into saccules occurs, with thinning of the airway walls due to reduction in the mesenchyme. This process continues into the alveolar stage, with development of true alveoli by formation of interalveolar walls (called secondary septa). This leads to an extensive increase in surface area. Alveolar multiplication then continues for at least 2 years, into postnatal life.[14]

Radial count estimation correlates better with total gestational age, crown-rump length, body weight, and fixed lung volume than any other morphometric parameter assessed. The radial count method provides a reliable index of lung growth in intrauterine and early postnatal development. The radial count method of Emery and Mithal was applied to the lungs of 37 infants of gestational age 19–42 weeks.[15] There was a progressive increase in complexity of the terminal lung units throughout gestation. In intrauterine and early post-natal groups radial counts correlated very closely with the total gestational age (gestational age plus survival time after birth) of the child.

Vascular development

The airways and vessels develop simultaneously, with the airways acting as a template for the development of pulmonary blood vessels. The pulmonary vasculature develops via two separate processes, angiogenesis and vasculogenesis. Angiogenesis is the sprouting of new vessels from existing ones and vasculogenesis is the *de novo* formation of vessels from the mesenchymal endothelial precursor cells.[3] The proximal pulmonary arteries are thought to grow by the process of angiogenesis, originating from the sixth aortic arch, while peripheral blood vessels develop from vasculogenesis.[5,16]

The initial development sequence begins by formation of the heart at the end of the third week. The heart expels blood into the paired cranial ventral aortae, which are connected to the dorsal aortae by six aortic arches. The main pulmonary artery and the left and right main pulmonary arteries arise from the sixth aortic arch (Figure 4). The pulmonary arteries then continue to grow by angiogenesis around the airway buds from 4 to 16 weeks. The pre-acinar pulmonary veins also develop during this period.

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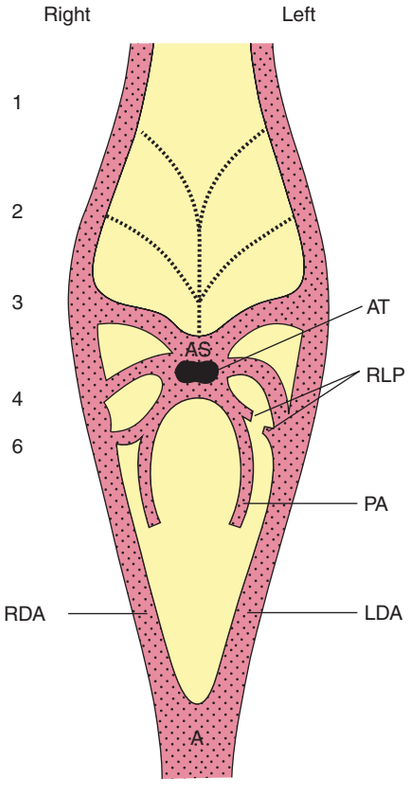

Figure 4. Brachial arch arteries connecting the ventral aortic sac (AS) with the right and left dorsal aortae (LDA and RDA) in a 5 mm embryo. On the left, the dorsal and ventral sprouts of the sixth (pulmonary) arch have nearly met (RLP). On the right side, the arch is complete. From the ventral sprouts, plexiform vessels (PA) pass to the lung bud. Adapted from Congdon ED. Transformation of the aortic arch system during the development of the human embryo. *Contribution to Embryology* (Carnegie Institute) Washington 1922; 14:47.

The capillaries form by vasculogenesis. The process begins with the formation of spaces in the primitive mesenchyme, which harbor groups of progenitor endothelial cells called angioblasts. These cells differentiate and form endothelial cells. The endothelial cells fuse to form capillary channels and tubes. The newly formed tubes then connect to the existing vessels.[5,17]

During the alveolar stage of lung development, the secondary septa in the alveoli contain a double capillary network, with intervening supportive central connective tissue. During the postnatal period, the double capillary network gradually merges as a single capillary layer, termed microvascular maturation.[18]

Factors regulating lung development

The development and growth of the lung is influenced by many factors including fetal lung fluid secretion and fetal breathing movements, environmental factors, such as tobacco smoke and pollutants including ozone and particulate matters, and various growth and transcriptional factors including hormones (Table 2).[4]

The major factor responsible for the pulmonary vascular development is vascular endothelial growth factor (VEGF). Vascular endothelial growth factor is a pluripotent growth and permeability factor; many different lung cells produce VEGF and also respond to it. Besides its critical role in fetal lung development, it also serves as a maintenance factor during adult life. In addition to the physiological functions of this protein, there is increasing evidence VEGF also plays a role in several acute and chronic lung diseases, such as acute lung injury, severe pulmonary hypertension, and emphysema (see Chapters 9, 17, and 18).[19]

Several genes play a role in the very early development of the trachea and primary lung buds. One of the most important is fibroblast growth factor (FGF). A full account of the growth factor signaling is given in an excellent chapter, which forms the basis of this section.[20] FGF 1, 2, 9, 10, and 18 play overlapping but distinct roles in the developing lung.

Table 2 Possible role of some growth and transcriptional factors in lung growth

Transcriptional and growth factors	Possible role in lung growth and development
FOXA1, FOXA2, GATA4 and *GATA6*	Formation and maintenance of foregut
Tbx4	Localization of bud site
Fibroblast growth factors (FGFs)	Localization of organs derived from foregut Induction of budding and branching (FGF10) Alveolization Type II cell differentiation and induction of Surfactant protein C (FGF 2, FGF 7)
Sonic hedgehog	Suppresses FGF 10 expression and prevents branching events at sites where branching is stereotypically determined not to take place
Bone morphogenic protein 4	Formation and control of dorsal and ventral branches
HOX genes	Defines overall three-dimensional orientation
Epidermal growth factor	Airway proliferation, differentiation and branching
Platelet-derived growth factor	Alveolization
Retinoic acid	Induction of FGF 10 and endodermal differentiation
Transforming growth factor	Lung repair after pulmonary insult and matrix production Inhibits cell proliferation
Insulin-like growth factor	Airway proliferation
Vascular endothelial growth factor	Vasculogenesis, angiogenesis and lymphangiogenesis
Granulocyte-macrophage colony-stimulating factor	Macrophage differentiation

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FGF 10 has been linked with mesenchymal-epithelial interaction, especially during branching. It is expressed focally in the distal mesenchyme, adjacent to stereotypically determined branching sites. It is hypothesized that FGF 10 governs the directional outgrowth of lung buds during branching by triggering chemotaxis and proliferation of the adjacent epithelium. This causes unidirectional growth of the primary lung buds. The chemotactic response of the lung endoderm involves the coordinated movement of the entire epithelial tip, with all its cells, towards an FGF 10 source.

An equally important factor in determining the specificity of the FGF signaling response may be the presence or absence of key downstream intermediate genes. One such example is tyrosine protein phosphatase Shp2, present in embryonic lung branch tips. This gene is essential for FGF transduction.

In addition FGF 10 controls the differentiation of epithelium by inducing surfactant protein C (SP-C) expression and upregulating expression of bone morphogenetic protein 4 (BMP4), a regulator of lung epithelial differentiation.

Transforming growth factor-p signaling, mediated by transforming growth factor-p type II receptor, plays distinct roles in developing mouse lung epithelium. The integrated functions of this receptor are very important in embryonic lung branching morphogenesis and development of alveoli in the post-natal lung. The developmental immaturity of lung structure and function, resulting from loss-of-function mutations in transforming growth factor-β signaling pathway components, may contribute to early post-natal respiratory problems, such as bronchopulmonary dysplasia (see Chapter 3). It may also increase the susceptibility to respiratory diseases later in life, including emphysema.[21] Overexpression of TGFβ1 in the developing fetal monkey lung causes severe progressive pulmonary and pleural fibrosis, as well as pulmonary hypoplasia.[22] TGFβ1 overexpression triggered mesenchymal cell proliferation that appeared to continue after the overexpression of exogenous TGFβ1 was discontinued.

Recessive mutations in latent transforming growth factor-b binding protein 4 (LTBP4) gene leading to disrupted pulmonary, gastrointestinal, urinary, musculoskeletal, craniofacial, and dermal development have been described.[23] Patients have severe respiratory distress, with cystic and atelectatic changes in the lungs, complicated by tracheomalacia and diaphragmatic hernia. Respiratory failure is the usual cause of death. Impaired synthesis and deficient deposition of LTBP4 into the extracellular matrix appears responsible for defective elastic fiber assembly in all tissues affected by the disease.

Abrogation of TGF-p type II receptor (TpRII) in mouse lung epithelium causes retardation of post-natal lung alveolarization, with markedly decreased numbers of type I alveolar epithelial cells. No abnormalities in prenatal lung development are observed. In contrast, blockade of TpRII in mesoderm-derived tissues, including lung mesenchyme, results in mildly abnormal lung branching and reduced cell proliferation after mid-gestation. This is accompanied by multiple defects in other organs, including diaphragmatic hernia.

Effect of sex on lung growth

Transcriptomic analyses by Kho *et al.* provide interesting findings regarding lung development.[24] They showed a major influence of surfactant-associated genes, even in the early phase of lung development. At the canalicular and saccular periods, more mature lung development has been described in the female fetus than in the male.[25] The synthesis of surfactant in the fetal lung is sexually dimorphic.[26] Female neonates are more responsive to hormonal accelerators of surfactant production. The influence of sex on the expression profiles has been studied in mice but only in a narrow gestational age range.[27] Such studies may help in the understanding of why the male lung is disadvantaged at birth.

Post-natal lung development

The early years of life are extremely important in lung development. This is the time when many chronic respiratory diseases appear to have their origins. For example, bronchial asthma arises from interactions between genetic predisposition and infection, while allergy-induced airway inflammation leads to airway remodeling as early as the first 3 years of life.[28] In cystic fibrosis lung disease appears to start soon after birth with pulmonary inflammation leading to functional change within the first few months of life[29] and structural damage.[30]

Extremely low gestational age newborns are at increased risk of chronic lung disease (bronchopulmonary dysplasia) and developmental delay (see Chapter 3).[31] In addition, low birth weight and lower weight gain in early childhood are associated with modest reductions in adult lung function across a broad range of measures including lung volumes and diffusing capacity. These findings are independent of a number of potential confounding factors, including low socioeconomic status and maternal smoking.[32] Weight gain between birth and the age of 3 years is also associated with higher values for static lung volumes in the fully adjusted analyses, which is consistent with this being the main stage of alveolar development. These findings partially correlate with the morphological results that all the alveoli are present by the age of 2 years but further lung growth continues to the age of 8.[32]

Tracheal growth

Wailoo and Emery studied 452 children with apparently normal tracheas ranging from 28 weeks' gestation to 14 years.[33] In the neonatal period the trachea is funnel-shaped with the upper end wider than the lower. It becomes cylindrical with increasing age. The ratio of cartilage to muscle remains constant throughout childhood. The trachea appears to grow at a greater rate in relation to crown-rump length from 1 month to 4 years of age than in utero or around puberty.

Lung

At birth a complete set of airways are present but the most peripheral are relatively short. The formation of alveoli starts in late uterine life but most of these air sacs (more than 85%)

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are formed after birth.[34] The alveoli are formed from tissue ridges on the existing primary septa. This produces a large number of small buds along the primary septa. Myofibroblasts, elastic fibers and collagen fibrils are the probable driving forces for septation. Inside the pre-existing septa platelet-derived growth factor (PDGF) receptor-positive smooth muscle precursors proliferate and move to locations where the new septa are to be formed. Alveolarization does not occur in PDGF-A-deficient mice.[6]

Alveolarization of the acinus primarily occurs between birth and 2 years; significant but slower growth is seen up to 8 years.

The ratio of pulmonary diffusion to alveolar volume remains constant in the first 2 years of life. This is consistent with lung growth in this age group occurring because of an increase in the number of alveoli rather than an expansion of the same number of alveoli.[35] These findings are in keeping with morphometric data on number of alveoli per unit volume and mean linear intercept in the post-natal period.[36] After this time, values plateau, suggesting alveolarization is complete. Radial counts correlate well with the chronological age of the child.[37]

Pulmonary diffusing capacity and alveolar volume, measured by DL_{CO} and alveolar volume, increase with age and somatic size among infants and toddlers. Sex differences are primarily related to somatic size. There are no sex differences when pulmonary diffusing capacity is related to alveolar volume. However, in a morphometric study, individual lung units, alveolar dimensions, and number of alveoli per unit area and volume did not differ between boys and girls, but boys had bigger lungs than girls for the same stature. This resulted in a larger total number of alveoli and a larger alveolar surface area in boys than in girls for a given age and stature. Boys may have more respiratory units than girls.[36]

Stem/progenitor cells in the lung

This is a "hot" area for research, as stem cells offer new tools for the investigation of pathogenetic and developmental pathways. It is likely that many stem cell populations exist in the lung with distinct lineage potential. The ability to purify and functionally assay these populations requires consistent use of well-defined protocols for isolation, culturing, and functional assays.[38] This area is still in its infancy and, while continuously "offering" new possible treatments, has yet to provide a proven therapeutic return.

An unanswered question is whether adult lung epithelial stem cells are a distinct population or whether some multipotential embryonic progenitors persist into adult life. Evidence suggests that in liver and pancreas, the embryonic cells that build tissue are different from those that repair and maintain it.[39] In the lung evidence suggests lung embryonic progenitors and adult stem cells are separate, although lineage-linked, populations.[40]

The pools of epithelial stem/progenitor cells are widely distributed over the alveolar surface.[41] They are located in the basal layer of the upper airways, within or near neuroendocrine cell rests, at the bronchoalveolar junctions, as well as within the alveolar epithelial surface.[42] The most important of these are the alveolar epithelial cells, which have a large surface area. Either alveolar epithelial cells contain a subpopulation of progenitor cells or most alveolar epithelial cells can reactivate into a progenitor-like state in response to injury.

Another subset of Club (Clara) cells has been identified, based on their location at the bronchiolar-alveolar junction. They co-express secretoglobin 1a1 (Scgb1a1, also known as CC10 or CCSP), and an alveolar type II cell marker surfactant protein C (SftpC or SpC). These cells proliferate following lung injury. Based on their in vitro differentiation potential, it has been proposed that they are bronchioalveolar stem cells (BASCs) that give rise to both bronchiolar and alveolar cells in vivo.[43]

Normal organization

Airways

For convenience of anatomical description, the airways are divided into the upper and lower respiratory systems. The upper respiratory system comprises the nasal cavity, paranasal sinuses, and pharynx, while the larynx, trachea, bronchi, and bronchioles are the lower respiratory tract. The nose and paranasal sinuses act as a first line of defense against bacteria and inhaled particles, through the filtering function of the nasal hairs, as well as the irregular structure of the nasal bones and mucosa. In addition these structures warm and humidify the inspired air. Thus in a patient with a tracheostomy, this first line of defense is bypassed. The mechanics of the upper airways, important in obstructive and sleep apnea, Cheyne-Stokes respiration, and the obesity hypoventilation syndrome, are often neglected by the histopathologist. An excellent review article is available.[44]

The trachea divides into the right and left primary extrapulmonary or mainstem bronchi. Each of these then gives rise to secondary (lobar) bronchi, which supply the lung lobes. These further ramify into tertiary (segmental) bronchi, which supply the segments of each lobe. The bronchi branch progressively into bronchioles. The smallest are terminal bronchioles that constitute the most distal component of the conducting part of the airways. The terminal bronchioles give rise to the acinus, which is the part of the respiratory system involved in gas exchange and comprises respiratory bronchioles, alveolar ducts, alveolar sacs, and the alveoli.

The trachea

The trachea begins anterior to the sixth cervical vertebral body, where it is attached to the inferior portion of the cricoid cartilage of the larynx. It ends in the mediastinum at the level of the fifth thoracic vertebral body, where it branches to form the right and left primary bronchi. The total length and diameter are approximately 11 cm and 2.5 cm, respectively. The trachea is formed of 15–20 C-shaped cartilage rings, the

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open sides facing posteriorly, where the trachealis muscle completes the circumference. These rings protect the trachea from frontal injury and also prevent collapse during the negative intrathoracic pressure associated with respiration.

The primary bronchi

The trachea branches into the right and left primary bronchi, which are separated by an internal ridge called the carina. The structure of these primary bronchi is similar to that of the trachea, being formed of C-shaped cartilage rings. The right primary bronchus is larger in diameter than the left. It closely follows the general direction of the trachea, whereas the left diverges at a greater angle, especially in females. For years it was thought that such anatomy resulted in greater right lung aspiration but recent studies call this into question.[45]

Each primary bronchus enters the corresponding lung at the pulmonary hilum or root, a groove along the medial surface of each lung, which also provides entry to pulmonary arteries and veins, nerves and lymphatics. All these structures at the root of the lung are surrounded by connective tissue. The relationship of the pulmonary artery, mainstem bronchus, and pulmonary veins is well defined and constant.[46]

The lungs

Each lung lies in its corresponding pleural cavity. The apex of each lung extends above the first rib, while the concave base rests on the superior surface of the diaphragm. In general, the right lung is wider than the left, due to the projection of the heart towards the left side. Conversely, the left lung is longer than the right as the dome of the diaphragm is higher on the right side, because of the underlying liver.[47]

The right lung is heavier than the left, weighing approximately 700 g in adult men and 500 g in adult women as compared to 600 g for the left lung in men and 450 g in women.[47] There is a wide variation in autopsy weights, in part due to differences in the degree of terminal pulmonary edema and congestion from one individual to another. In a study of the organ weights in 684 adult Caucasian forensic autopsies,[48] the mean lung weight ± standard deviation was 663 ± 239 g for the right lung in males, 583 ± 216 g for the left lung in males, 546 ± 207 g for the right lung in females and 467 ± 174 g for the left lung in females. Such organ weight tables need regular updating, as the normal values of organ weight change with time, secondary to genetic and environmental factors.[48] Lung weight tends to diminish slightly in the elderly, probably due to alveolar enlargement (see Chapter 17).

The lungs are normally divided into lobes that are separated by fissures. Interlobar fissures are deep depressions that extend from the outer lung surface towards the center. The visceral pleura also dips into the fissure, making the lung surfaces lying within the fissures smooth and thus allowing free movement of individual lobes.[47]

The right lung is divided into upper, middle and lower lobes, with the horizontal/minor fissure separating the upper and middle lobes. The oblique fissure separates the upper and middle lobes from the lower lobe. The horizontal fissure is usually less well developed than the oblique. The left lung is divided into upper and lower lobes, separated by the oblique fissure. A rudimentary structure, the lingula, is present on the left and is considered the equivalent of the middle lobe. It is, however, part of the left upper lobe, rather than a separate lobe, and appears antero-inferiorly as a small tongue-like projection.

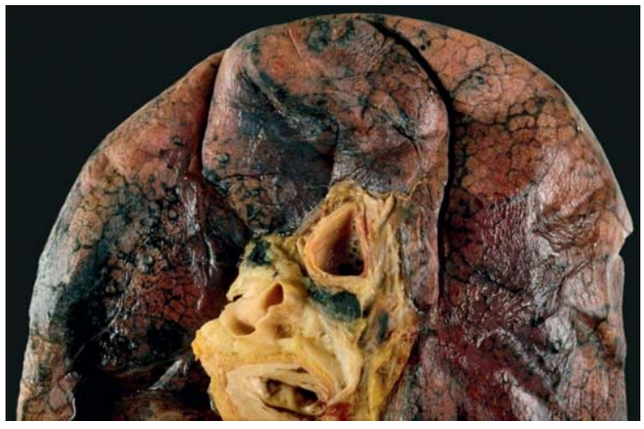

Figure 5. Macroscopic image of the azygous lobe.

Variations in the anatomy of fissures are common and include accessory fissures, fissures in abnormal locations and incomplete or absent lobar fissures. Such structural anomalies have no functional significance but may cause radiological confusion. The prevalence of these abnormalities varies between studies.[49–52] A well-known anomaly is the azygous lobe, present in 1% of normal individuals. This is caused by extrinsic compression of the lung by an aberrant azygous vein in the right upper thorax, resulting in a depression (fissure) from the top to the bottom of the right upper lobe (Figure 5). It does not reflect any underlying segmental division of the bronchi.

Within the lung, the primary bronchi divide to form secondary (lobar) bronchi. One secondary bronchus goes to each lobe, so the right lung has three secondary bronchi and the left lung has two secondary bronchi. The right primary bronchus gives rise to the right upper lobe bronchus and continues as the bronchus intermedius. It then divides into the right middle lobe bronchus and right lower lobe bronchus. The left primary (main) bronchus is longer than the right and divides into the left upper lobe bronchus and left lower lobe bronchus. The secondary bronchi branch to form tertiary (segmental) bronchi (Figure 6). Each tertiary bronchus supplies air to a single bronchopulmonary segment.

Bronchopulmonary segments are considered the anatomic units of the lung, each possessing its own bronchus, and pulmonary arterial, venous and lymphatic systems. They are constant in their topographic anatomy (Figures 7, 8 and 9).[47] Each segment is surrounded by connective tissue septa, which are continuous with the pleural surface. The segmental bronchus traverses down the center of the segment, accompanied

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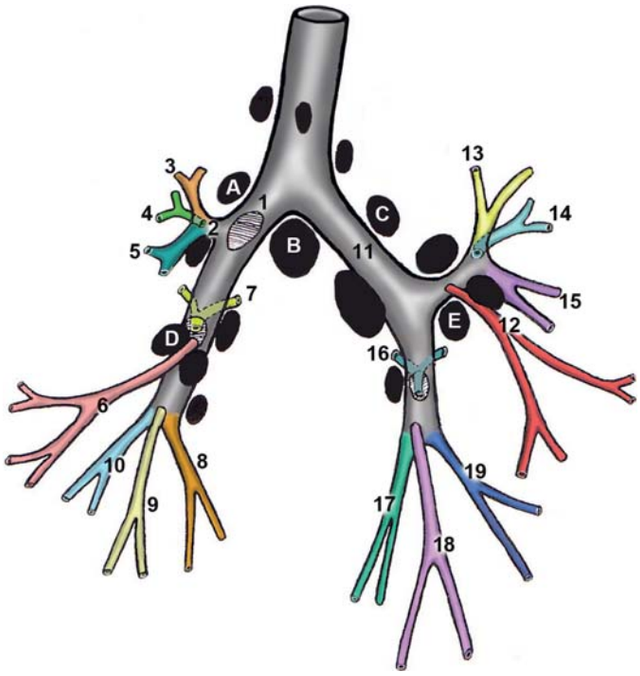

Figure 6. The segmental bronchi and the principal groups of lymph nodes related to the hilar region of the bronchi. 1. Right main bronchus. 2. Right epiarterial bronchus. 3. Right upper apical segmental bronchus. 4. Right upper posterior segmental bronchus. 5. Right upper anterior segmental bronchus. 6. Right middle lobar bronchus dividing into lateral and medial divisions. 7. Right lower superior (apical) segmental bronchus. 8. Right lower lobe anterior basal segmental bronchus. 9. Right lower lobe lateral basal segmental bronchus. 10. Right lower lobe posterior basal segmental bronchus. 11. Left main bronchus. 12. Lingular bronchus dividing into superior and inferior lingular segmental branches. 13. Left upper lobe apical segmental bronchus. 14. Left upper lobe posterior segmental bronchus (usually 13 and 14 arise by a common bronchus from the left upper lobe bronchus). 15. Left upper lobe anterior segmental bronchus. 16. Left lower lobe superior (apical) segmental bronchus. 17. Left lower lobe anterio-medial basal segmental bronchus. 18. Left lower lobe lateral basal segmental bronchus. 19. Left lower lobe posterior-basal segmental bronchus. A. Right superior bronchial nodes. B. Inferior tracheobronchial nodes. C. Left superior bronchial nodes. D. Nodes around the root of the middle lobe bronchus. E. Lingular nodes.

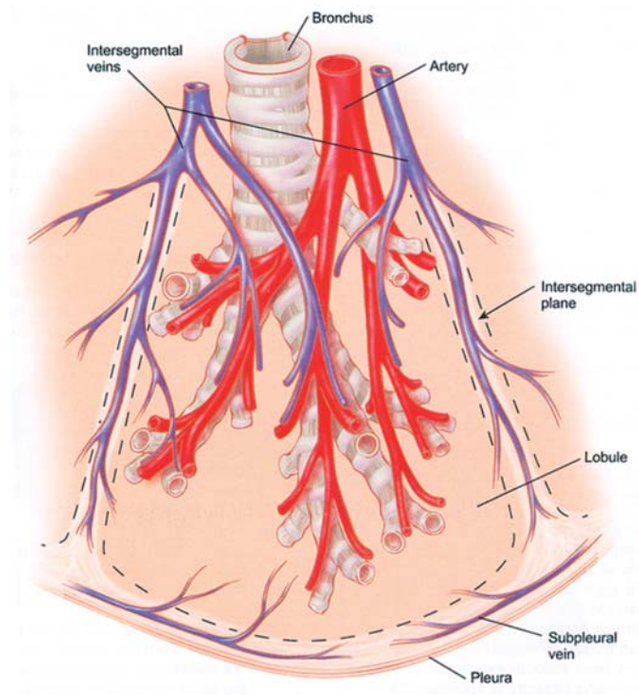

Figure 7. Anatomy of the bronchopulmonary segment. The draining pulmonary vein circulates in the intersegmental plane, marking the boundaries of the segment. (Reprinted from Ugalde P, Camargo J, Deslauriers J. Lobes, fissures and bronchopulmonary segments. *Thorac Surg Clin* 2007;17:587–99, with permission from Elsevier.)

by a corresponding branch of the pulmonary artery. The draining veins, on the other hand, run in the intersegmental planes. The right lung has ten bronchopulmonary segments, while the left has eight.

From the trachea to the terminal bronchioles, the airways have a purely conducting function. Each tertiary bronchus branches several times and ultimately forms the non-respiratory or membranous bronchioles, which differ from bronchi by the absence of cartilage and seromucinous glands in their walls. Terminal bronchioles form the most distal branches of the non-respiratory bronchioles. The terminal bronchioles are 0.7–1 mm in diameter tubes and correspond on average to the 16th dichotomous division of the airway tree.[53] Terminal bronchioles are the smallest airways completely lined by bronchial epithelial cells and the last of the alveoli-free conducting airways.

Bronchoscopy is a widely performed procedure for assessment of the airways with many indications. Some of these require knowledge of airway dimensions to optimize the interventions or assess disease progression. Bronchoscopists may rely on pre-procedure imaging, usually with computed tomography (CT), or on derivation of quantitative information directly from bronchoscopic images. Recently, anatomical optical coherence tomography has been described as an emerging technique for measuring airway dimensions during bronchoscopy.[54]

The acinus is distal to the terminal bronchiole and its components have an increasing number of alveoli in their walls, where most of the gas exchange occurs. An acinus is usually defined as the lung tissue supplied by a single terminal bronchiole and is composed of respiratory bronchioles, alveolar ducts, and alveolar sacs with their alveoli.[55,56] Each terminal bronchiole divides into two to five respiratory bronchioles, which progressively have more alveoli in their walls.[57] A respiratory bronchiole in turn divides into two or three alveolar ducts. Each alveolar duct usually ends in four alveolar sacs, which are common chambers connected to multiple individual alveoli.

In a stereological analysis of six adult human lungs, the mean number of alveoli was 480 million (range 274–790 million) and was closely related to the total lung volume.[58]

The alveolar surface area in adults is approximately 70–80 m^2.[56] Stereology is the technique of quantitative characterization of irregular 3D objects based on measurements

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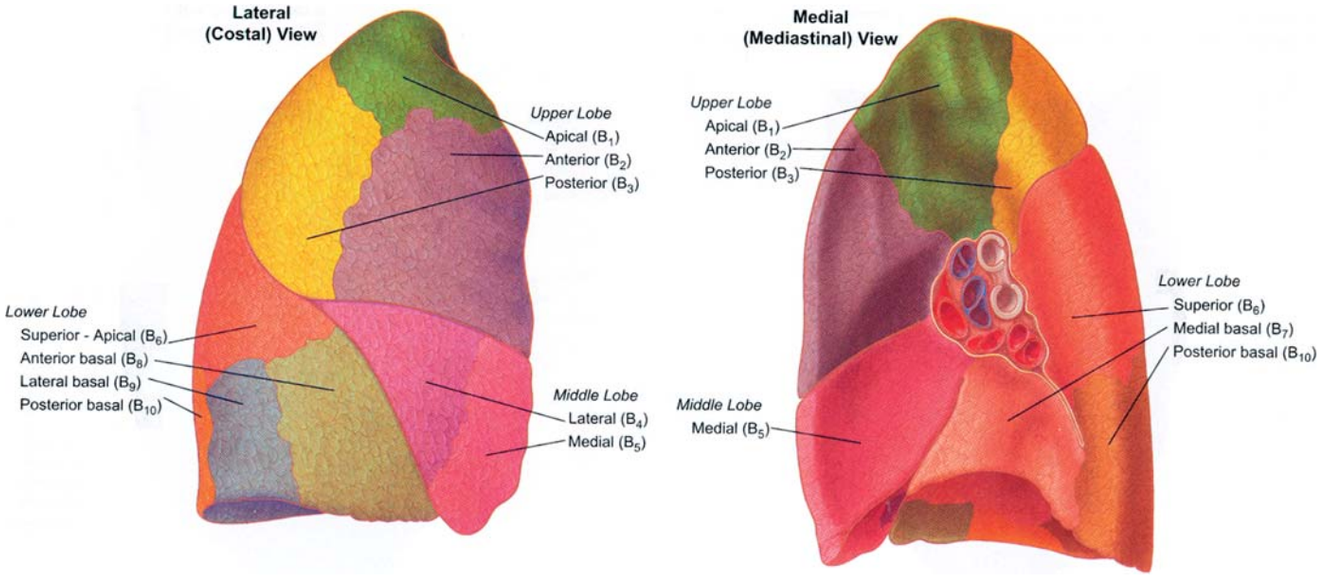

Figure 8. Topographic anatomy and numerical designation of the ten right bronchopulmonary segments. (Reprinted from Ugalde P, Camargo J, Deslauriers J. Lobes, fissures and bronchopulmonary segments. *Thorac Surg Clin* 2007;17:587–99, with permission from Elsevier.)

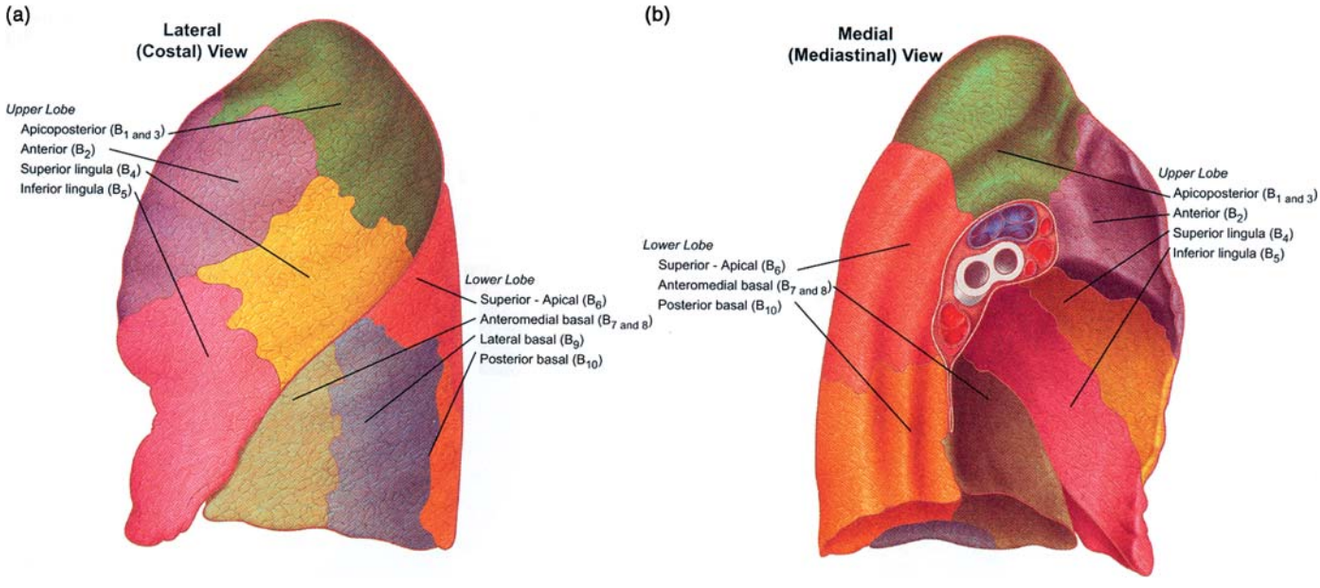

Figure 9. Topographic anatomy and numerical designation of the eight left bronchopulmonary segments. (Reprinted from Ugalde P, Camargo J, Deslauriers J. Lobes, fissures and bronchopulmonary segments. *Thorac Surg Clin* 2007;17:587–99, with permission from Elsevier.)

made on 2D sections. This technique acts as a bridge between the understanding of lung structure and function in various studies on the lung.[59,60]

The connective tissues from the lung hila extend progressively into the lung parenchyma in the form of fibrous partitions or trabeculae. The smallest unit separated by the trabeculae is called the pulmonary lobule or the secondary lobule of Miller (Figure 10).[61] Each pulmonary lobule consists of three to five acini.[62] The trabeculae of the subpleural lobules (at the periphery of the lung) are continuous with the connective tissue of the visceral pleura.

Blood supply

The lungs have a dual circulation. The low-pressure, high-volume pulmonary system carries deoxygenated blood from the right side of the heart to the lungs for gas exchange with the inspired air in the alveolar spaces. The high-pressure,

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