2 Lung

Portia A. Kreiger

The process of fetal development is continuous; however, the developing lung can be subdivided into five morphologic stages (embryonic, pseudoglandular, canalicular, saccular, and alveolar). Based on various authors' observations, differing transition times from one stage to another have been proposed. This is thought to be due, at least in part, to the fact that lung development is not completely synchronous. Specifically, lung development is more rapid in cranial regions than caudal areas [1]. The five developmental stages can be identified by histology and each stage of lung development is marked by a major developmental milestone (*see* Fig. 2-1) [1–3].

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Five Stages of Lung Formation		
Developmental stage	**Age range**	**Developmental milestone**
Embryonic	3–4 wk to 6–8 wk gestational age	Proximal airways
Pseudoglandular	6–8 wk to 16 wk gestational age	Distal (pre-acinar) airways
Canalicular	16 wk to 26–28 wk gestational age	Acinus* and primitive capillary network
Saccular	26–28 wk to 32–36 wk gestational age	Maturing alveolar–capillary interface
Alveolar	32–36 wk to 2–4 y postnatal age	Increasing acquisition of alveoli

*Acinus encompasses the respiratory bronchioles, alveolar ducts, and terminal sacs.

Figure 2-1. Five stages of lung formation. The general time ranges and developmental milestones for the five stages of lung formation are shown here. The embryology and histology of the lung are discussed with reference to these five morphologic stages.

Embryology

The lung arises at approximately 3 to 4 weeks gestation from the foregut endoderm as a ventral diverticulum, which is destined to ultimately become the larynx and trachea proximally and the bronchi and lung parenchyma distally. This ventral foregut diverticulum develops within a mass of mesenchyme and forms the primary lung bud by 4 2/7 weeks postfertilization age (PFA) [4–6]. The primary lung bud bifurcates laterally to form right and left primary bronchial buds at about 4 4/7 weeks PFA and subsequently begins to branch asymmetrically, forming lobar buds (three right and two left) at 5 1/7 weeks PFA, segmental buds at 5 6/7 weeks PFA, and subsegmental buds at 6 2/7 weeks PFA [1,4,5]. These sequential endodermal buds carry with them coats of mesenchyme. Within this mesenchyme, islands of precartilage appear within proximal branches concurrent with segmental buds and will ultimately form the cartilage plates of bronchi [4,5]. In addition, this mesenchyme will ultimately form the muscular and connective tissue components of the airways and the interstitial connective tissue of the alveolar parenchyma [6]. The vascular network of the lung also arises from this mesenchyme [7]. These events correspond to the embryonic stage of lung development [1,4,6].

During the pseudoglandular stage of lung development, subsegmental buds branch rapidly and dichotomously to form sequential generations of airways [1,4,6]. By 16 weeks gestation, all pre-acinar airways (*ie*, airways to the level of the terminal bronchioles) have formed [4,6]. This process is accomplished largely through complex epithelial–mesenchymal interactions. Also, the epithelial lining of these endodermal buds is beginning to be organized in a proximal to distal pattern. The more proximal branches will form the airways and the more distal branches will form the alveolar parenchyma [4]. Within the accompanying mesenchyme, generations of vessels develop alongside sequential generations of branching airways. This process of vasculogenesis forms the accompanying arteries and veins to the level of the terminal bronchiole and is complete by the end of the pseudoglandular stage [4,7]. The subsequent venous network develops synchronously but independently from the arterial and airway network [4,7]. Lymphatics arise initially within the hilar regions at approximately 8 weeks gestation and develop within the lung by about 10 weeks gestation [1].

During the ensuing canalicular stage of lung development, lung growth increases substantially. The development of the acinus, *ie*, respiratory bronchioles, alveolar ducts, and early airspaces (terminal sacs), occurs during this time. However, the expansion of the mesenchymal capillary network is also greatest at this time. As this capillary network expands, the mesenchymal bed in which these capillaries grow begins to thin. By the end of the canalicular stage, the formation of primitive capillary–airspace interfaces has begun [1,6].

During the saccular stage of lung development, increasingly complex airspace development occurs. The more primitive airspaces of the canalicular period are subdivided by the ingrowth of ridges of mesenchymal tissue containing capillaries, known as "secondary crests." Vasculogenesis continues to increase and mature, and mesenchyme continues to thin. With these events, concomitant progressive differentiation of airspace lining epithelium results in a maturing surface required for postnatal blood–gas exchange [1,6].

The final, alveolar stage of lung development is characterized by the formation of increasing numbers of mature alveoli with well-formed alveolar–capillary interfaces [1,7]. The lung at birth contains a reported 24 million alveoli. However, alveologenesis continues postnatally. The majority of alveoli are thought to be formed by 2 years of age and by adulthood the lung contains between 300–600 million alveoli [1,3,6,7].

Histology

General Overview of Postnatal Pulmonary Histology

The fully formed, mature lung consists of three lobes on the right and two lobes on the left. Each lobe is invested by a thin layer of visceral pleura composed of a monolayer of mesothelium and subjacent fibroconnective tissue containing small blood vessels and lymphatics (*see* Fig. 2-2). Each lung is supplied by a primary bronchus and each lobe is supplied by a secondary bronchus. The pulmonary lobes are further subdivided into bronchopulmonary segments, each associated with a tertiary bronchus (*see* Figs. 2-3 and 2-4). Each segment is further subdivided into pulmonary lobules, each of which is supplied by a terminal bronchiole. Each bronchiole is accompanied by an arteriole. Together these two structures form a bronchovascular bundle (*see* Fig. 2-5), which is invested in fibroconnective tissue that also contains lymphatics and nerves. Beyond the terminal bronchiole is the pulmonary acinus. The acinus encompasses a respiratory bronchiole and all its branches, including alveolar ducts and terminal alveoli (*see* Figs. 2-6 and 2-7). The perimeter of each lobule is demarcated by interlobular septa (*see* Figs. 2-8 and 2-9), which consists of bands of fibroconnective tissue containing veins or venules and lymphatics [6].

Bronchi are supported by cartilage plates (*see* Figs. 2-10 and 2-11), which are larger proximally and become progressively smaller proceeding distally; bronchi are also associated with seromucinous glands. In contrast, bronchioles (*see* Fig. 2-12) contain neither a cartilage support structure nor associated seromucinous glands. However, both bronchi and bronchioles are supported by smooth muscle and connective tissue. The epithelial lining of bronchi is pseudostratified ciliated respiratory in type. Bronchioles show similar ciliated respiratory-type epithelium, but this epithelium is simple rather than pseudostratified [6]. The respiratory epithelium of airways incorporates occasional goblet cells, which are more prevalent proximally than distally, and Clara cells, which are present primarily within distal bronchioles. Neuroendocrine cells are also present, though normally inconspicuous, along both airways and airspaces. Infolding of airway-lining epithelium is seen within larger bronchi and bronchioles, and is likely related to the contraction of airway smooth muscle [2,6]. Aggregates of lymphoid tissue, known as bronchus-associated lymphoid tissue (BALT), may be seen postnatally along the airways of normal infants and children (*see* Fig. 2-13) [6]. BALT may be first recognized in utero at approximately 16 weeks gestation; however, it is typically sparse in fetal life but may become prominent in cases of in utero infection [8,9].

Alveoli are lined predominantly by simple flattened epithelium, known as type I pneumocytes (*see* Figs. 2-14 and 2-15). Type I pneumocytes provide a thin air–blood interface with the abundant capillary network of the intervening alveolar septa. Alveoli also contain interspersed type II pneumocytes, which are more cuboidal in shape. Type II pneumocytes produce surfactants and represent the progenitors of type I pneumocytes [1,6].

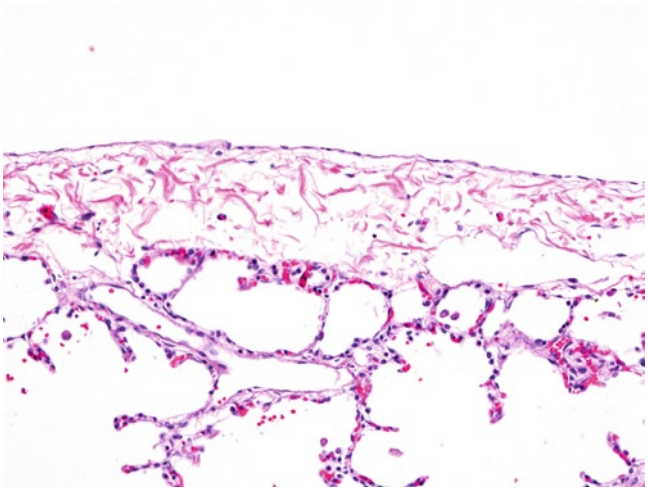

Figure 2-2. Normal 5-month postnatal lung I. The visceral pleural surface of the lung consists of a simple layer of mesothelium and subjacent loose fibroconnective tissue, which contains occasional small blood vessels and lymphatics. (Hematoxylin and eosin [H&E], 20×.)

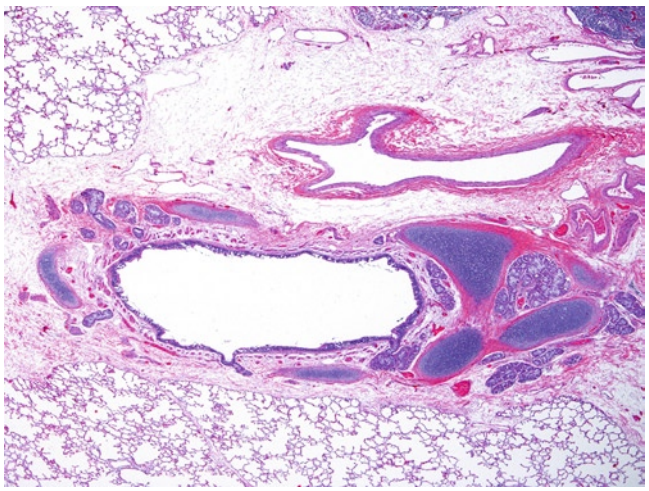

Figure 2-3. Normal 5-month postnatal lung II. This tertiary bronchus is surrounded by fibroconnective tissue, which contains cartilage plates, seromucinous glands, and smooth muscle. (H&E, 2×.)

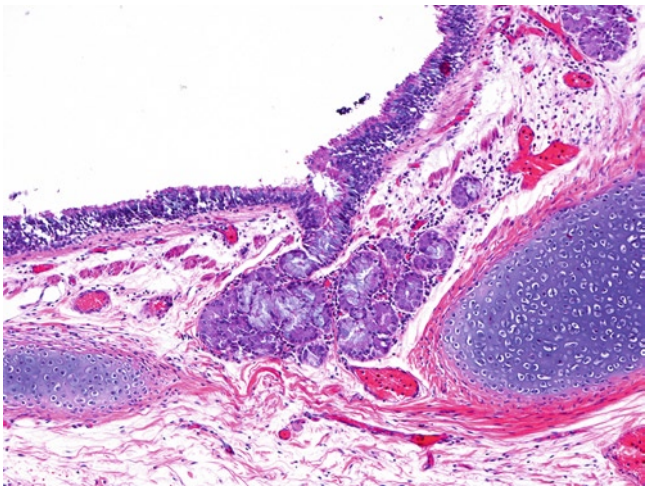

Figure 2-4. Normal 5-month postnatal lung III. Seromucinous glands connect to the respiratory mucosal surface in this high-power image of a tertiary bronchus; smooth muscle and cartilage are also seen. (H&E, 10×.)

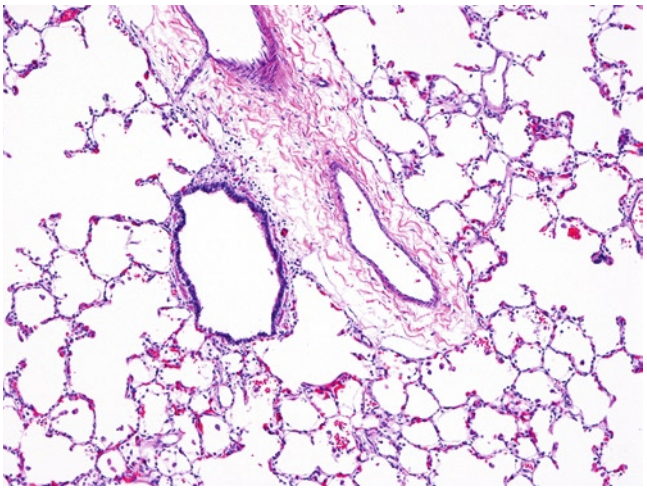

Figure 2-5. Normal 5-month postnatal lung IV. This bronchovascular bundle contains both a terminal bronchiole and accompanying arteriole. These structures are invested in a fibroconnective tissue sheath that also contains lymphatics but not venules. (H&E, 10×.)

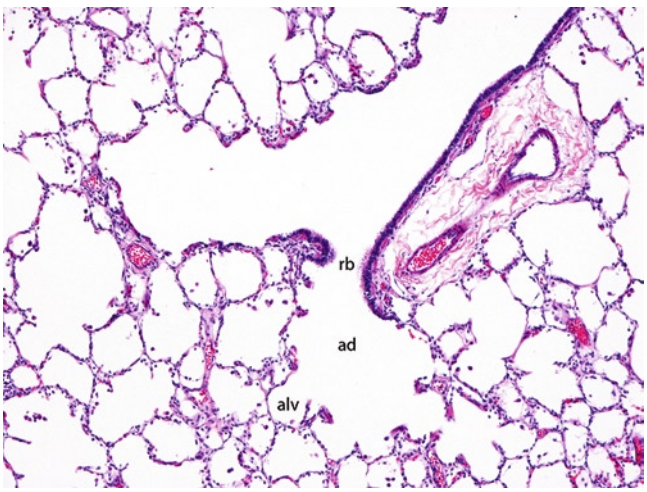

Figure 2-6. Normal 5-month postnatal lung V. A pulmonary acinus consists of a respiratory bronchiole (rb) with associated alveolar ducts (ad) and alveoli (alv). (H&E, 10×.)

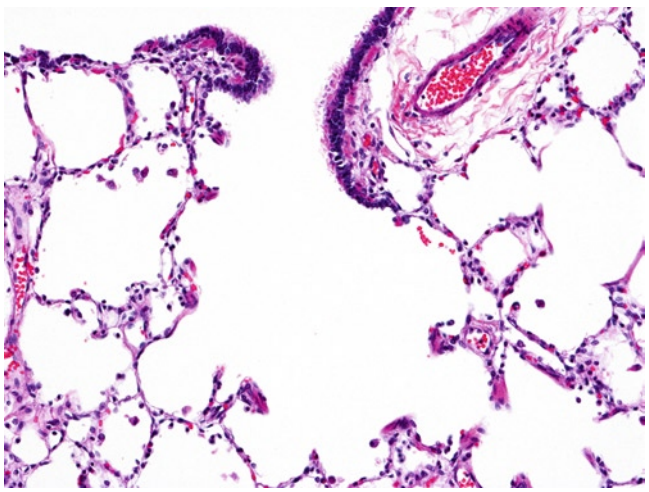

Figure 2-7. Normal 5-month postnatal lung VI. At high power, the transition from ciliated columnar bronchiolar epithelium to flattened alveolar epithelium can be seen in this pulmonary acinus. (H&E, 20×.)

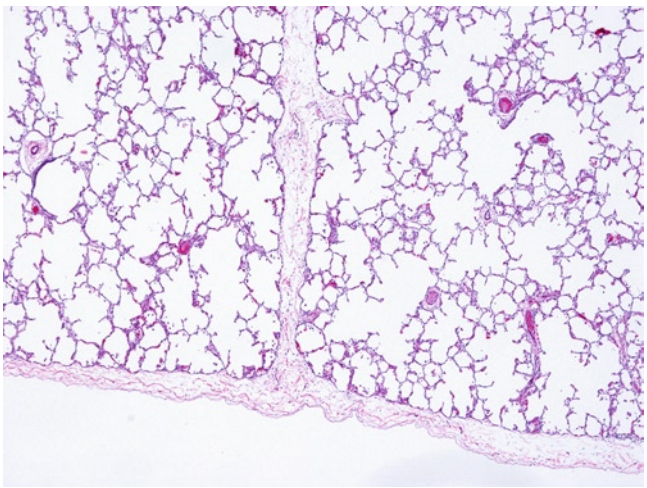

Figure 2-8. Normal 5-month postnatal lung VII. Interlobular septa demarcate pulmonary lobules and consist of bands of connective tissue, which intersect peripherally with the visceral pleura. (H&E, 4×.)

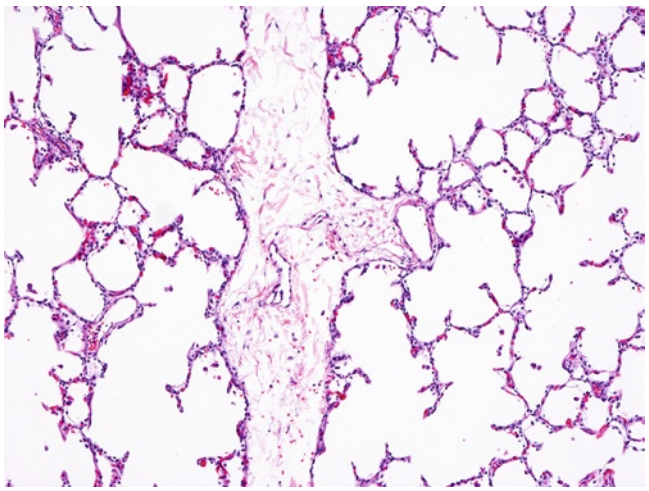

Figure 2-9. Normal 5-month postnatal lung VIII. Interlobular septa may contain occasional venous or lymphatic channels. (H&E, 10×.)

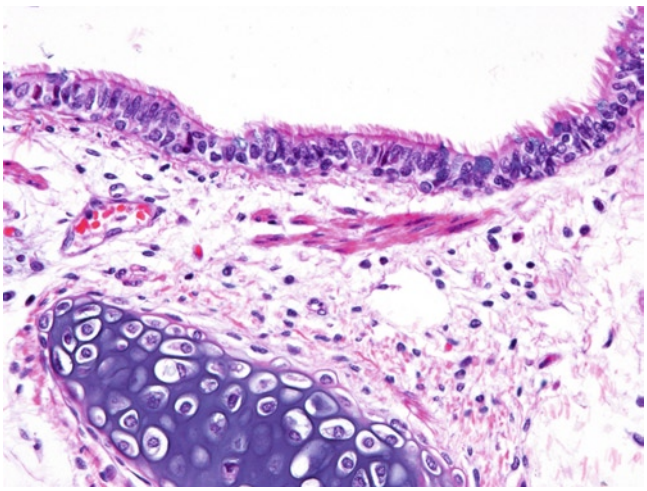

Figure 2-10. Normal 5-month postnatal lung IX. Bronchi are respiratory mucosal-lined and contain subepithelial connective tissue incorporating cartilage and smooth muscle, which is more abundant proximally than distally. (H&E, 20×.)

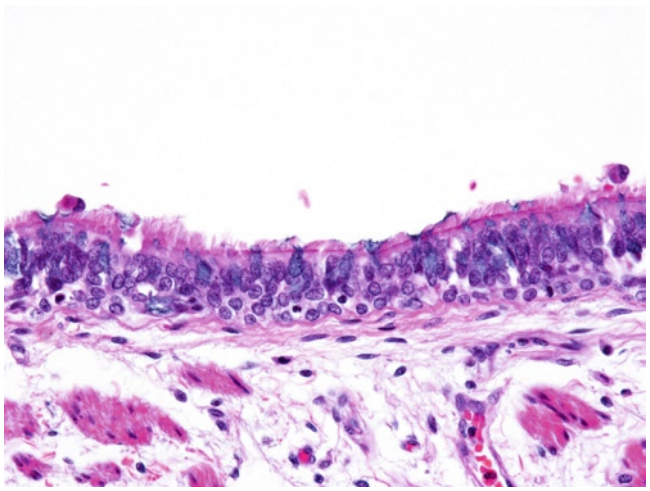

Figure 2-11. Normal 5-month postnatal lung X. Bronchial mucosa consists of pseudostratified ciliated columnar epithelium. (H&E, 40×.)

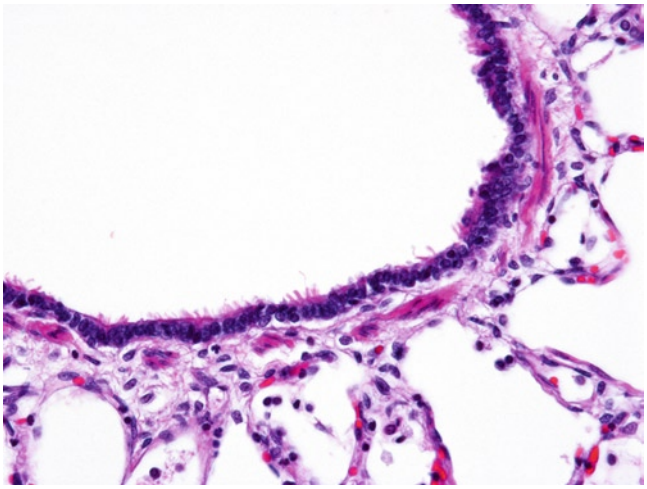

Figure 2-12. Normal 5-month postnatal lung XI. Bronchioles are lined by mostly simple ciliated columnar epithelium. No cartilage is present. (H&E, 40×.)

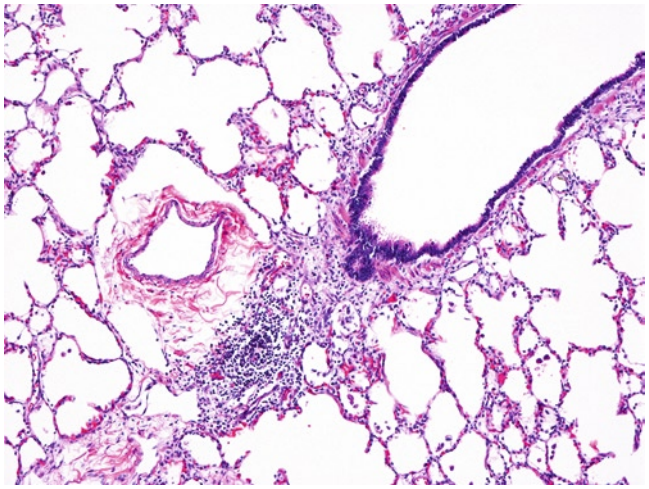

Figure 2-13. Normal 5-month postnatal lung XII. Bronchus-associated lymphoid tissue may be seen as small aggregates of lymphocytes along the airways in the normal postnatal lung, but is not typically prominent in the normal fetal lung. (H&E, 10×.)

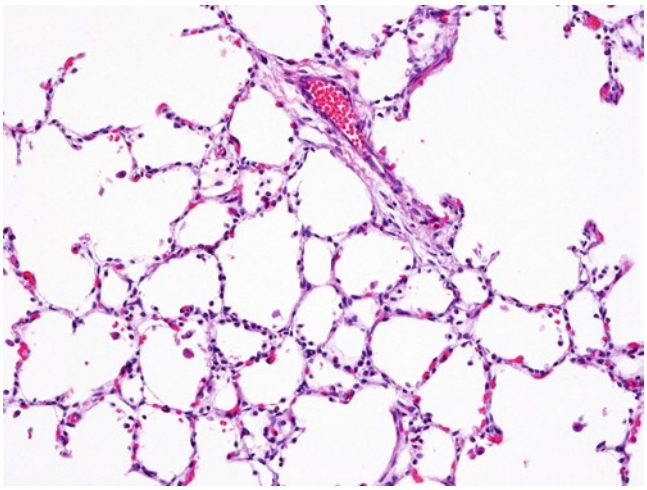

Figure 2-14. Normal 5-month postnatal lung XIII. Mature alveoli consist of polyhedral airspaces separated from one another by thin alveolar septa, which contain an abundant capillary network and occasional small thin-walled intra-acinar arterioles. (H&E, 20×.)

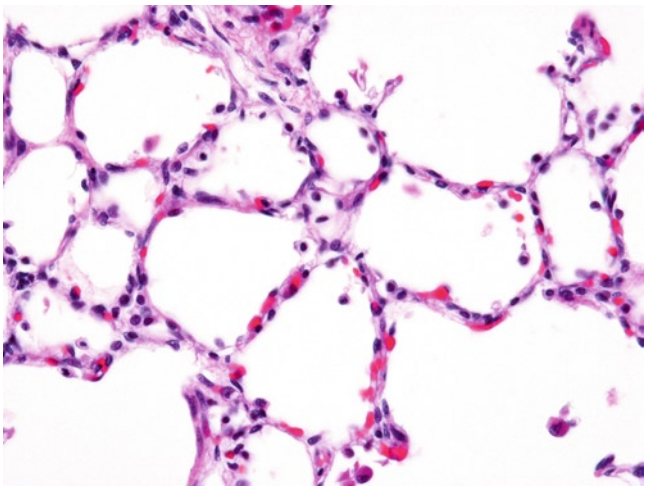

Figure 2-15. Normal 5-month postnatal lung XIV. Alveoli are lined by predominantly flattened type I pneumocytes. (H&E, 40×.)

Fetal Pulmonary Developmental Stages

Embryonic stage

During the earliest stage of lung development, the embryonic stage, the lung consists of rather primitive bronchial buds. These bronchial buds consist of small simple tubules, which are lined by a thick layer of endodermally derived epithelium and are situated within a bed of abundant loose mesenchyme (see Figs. 2-16–2-18) [1].

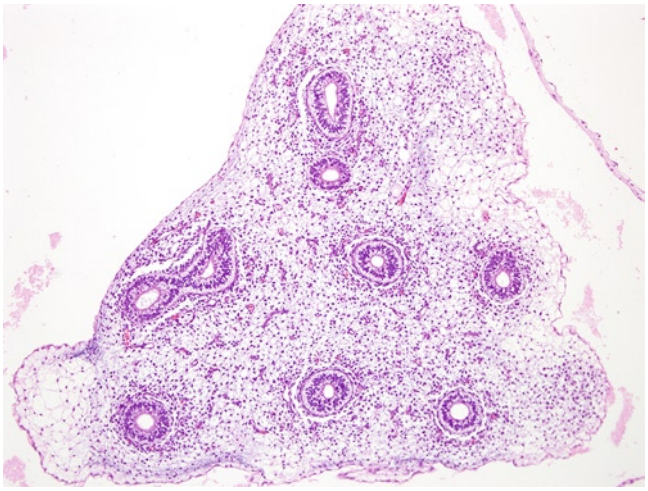

Figure 2-16. Embryonic stage I: normal lung at 7 weeks gestation. The embryonic stage of lung development is characterized by small primitive tubules set amidst an abundant loose mesenchymal stroma. (H&E, 10×.)

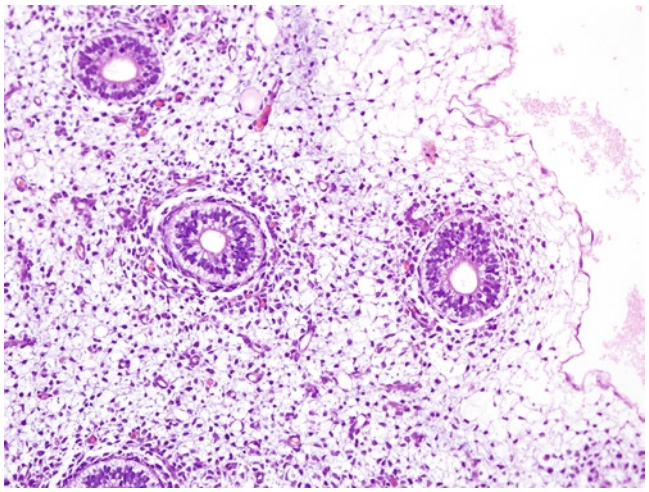

Figure 2-17. Embryonic stage II: normal lung at 7 weeks gestation. Mesenchyme shows some condensation around endodermal tubules. (H&E, 20×.)

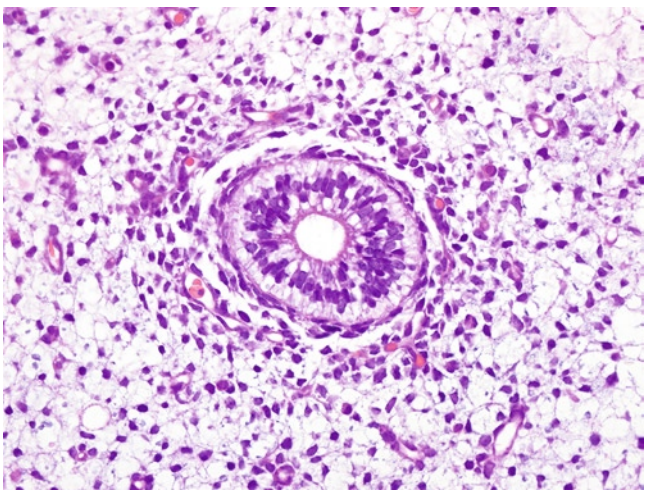

Figure 2-18. Embryonic stage III: normal lung at 7 weeks gestation. Tubules are lined by thick pseudostratified endodermal epithelium. (H&E, 40×.)

Pseudoglandular stage

During the pseudoglandular stage, progressive branching of bronchial buds gives rise to increasing generations of airways. Early in the pseudoglandular stage (*see* Figs. 2-19–2-21), these airways remain small simple tubules lined by pseudostratified endoderm. However, with progressive branching, by approximately 13 weeks gestation these airways enlarge and the endodermal lining thins. The more proximal airways become lined by ciliated respiratory epithelium with interspersed goblet cells. The more distal airways become lined by simple columnar epithelium. This epithelium is notable for prominent subnuclear vacuolization, conferring a "pseudoglandular" appearance to these simple tubules (*see* Figs. 2-22–2-24). Similar to the embryonic period, these tubules are set amidst a relatively abundant loose interstitial mesenchyme, which appears somewhat condensed around bronchial buds [6,10]. Cartilage formation around proximal airways and smooth muscle around airways and major vessels is also first appreciable during this stage [1].

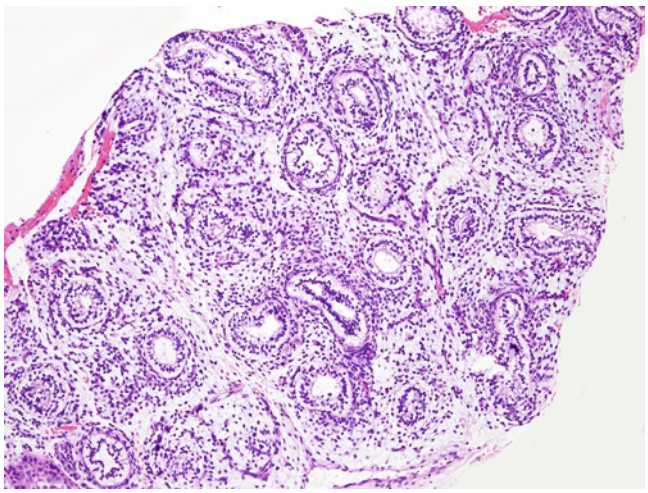

Figure 2-19. Early pseudoglandular stage I: lung at 10 to 11 weeks gestation. Early in the pseudoglandular stage, the lung consists of simple tubules, which are increased in number compared with the embryonic stage. (H&E, 10×.)

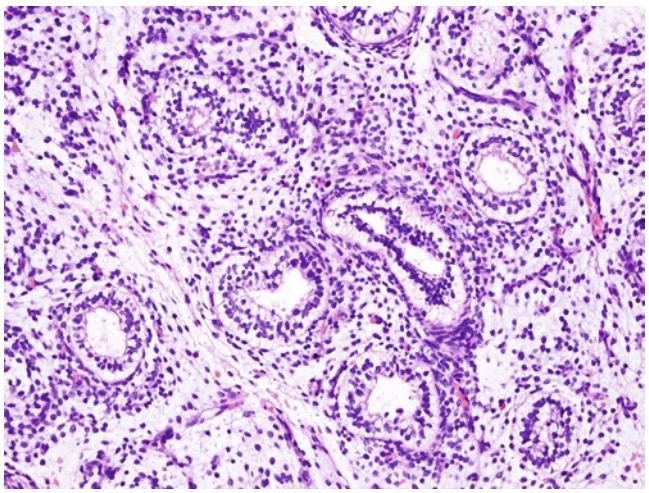

Figure 2-20. Early pseudoglandular stage II: lung at 10 to 11 weeks gestation. These tubules remain situated amidst a relatively abundant loose mesenchymal stroma, similar to the embryonic stage. (H&E, 20×.)

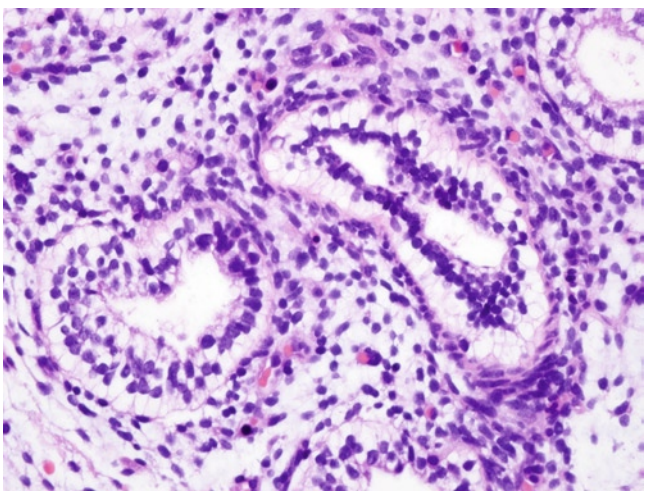

Figure 2-21. Early pseudoglandular stage III: lung at 10 to 11 weeks gestation. Tubules are lined by pseudostratified to simple columnar endodermal epithelium. (H&E, 40×.)

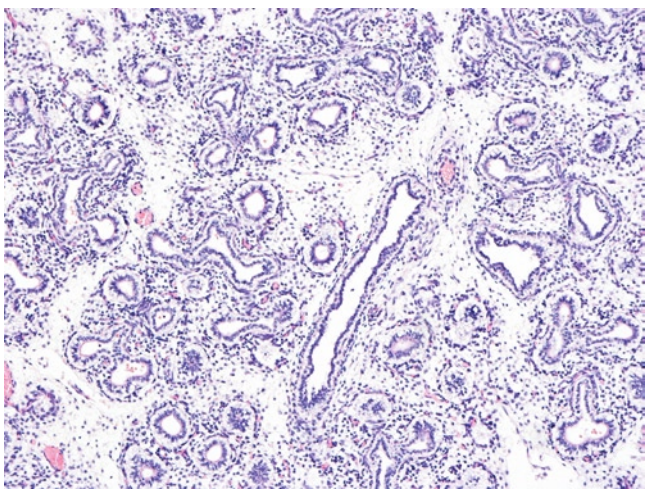

Figure 2-22. Late pseudoglandular stage IV: lung at 15 weeks gestation. Late in the pseudoglandular stage, the lung remains composed of simple tubules amidst a loose mesenchymal stroma. (H&E, 10×.)

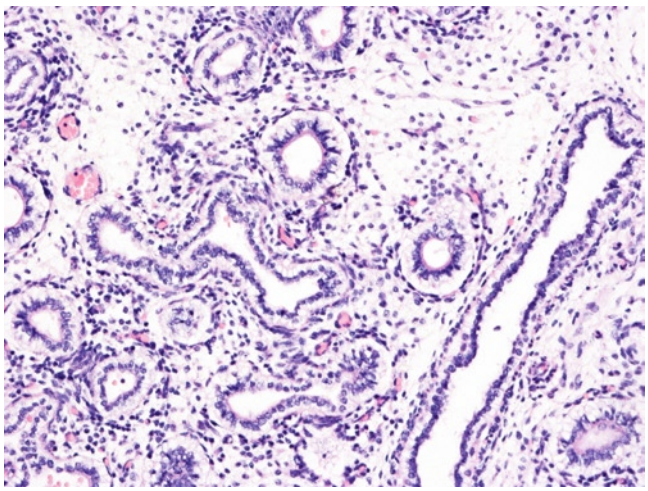

Figure 2-23. Late pseudoglandular stage V: lung at 15 weeks gestation. Tubules are lined by simple columnar epithelium. (H&E, 20×.)

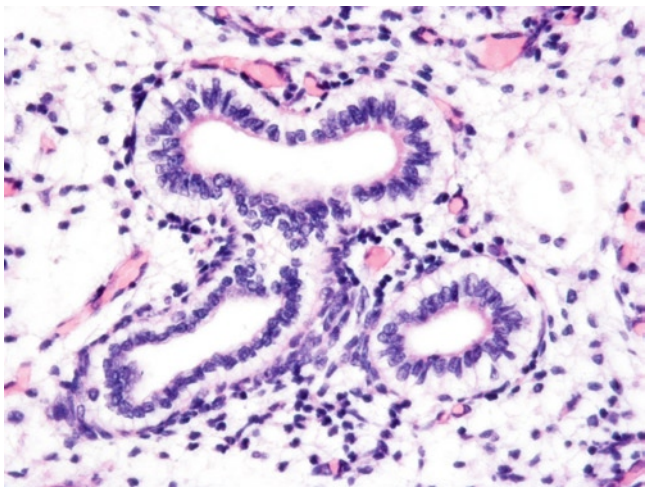

Figure 2-24. Late pseudoglandular stage VI: lung at 15 weeks gestation. Epithelium is notable for prominent subnuclear vacuoles. (H&E, 40×.)

Canalicular stage

The canalicular stage is marked by the initiation of airspace development and the beginnings of capillarization of these primitive airspaces. The onset of the canalicular stage is first recognizable as capillaries becoming apposed to and even extended between airspace epithelial cells, whereby the airspaces are "canalized." Early in the canalicular stage (see Figs. 2-25–2-27), simple tubules transition from being lined by columnar vacuolated epithelium to cuboidal nonvacuolated epithelium. A rather abundant mesenchyme remains. However, as the canalicular stage proceeds (see Fig. 2-28–2-30), there is increasing enlargement and complexity to these simple tubular structures. The outlines of these early airspaces change from tubular to rather wavy or undulating. The lining epithelium becomes progressively simple cuboidal in type and as early as 20 to 22 weeks gestation a subset of epithelium may even become flattened. This epithelial transition represents the initiation of mature pneumocyte differentiation. Ultimately, type II pneumocytes will remain cuboidal and type I pneumocytes will be flattened. In addition, the amount of interstitial mesenchyme begins to decrease. The beginning of pneumocyte differentiation in combination with the canalization and decreasing interstitial mesenchyme of this stage results in a primitive air–capillary membrane, also as early as 20 to 22 weeks gestation. Airways show condensation of surrounding elastic tissue, and by the end of this stage the most distal airways show differentiation of lining epithelium to form ciliated respiratory epithelium and Clara cells [1,6,10].

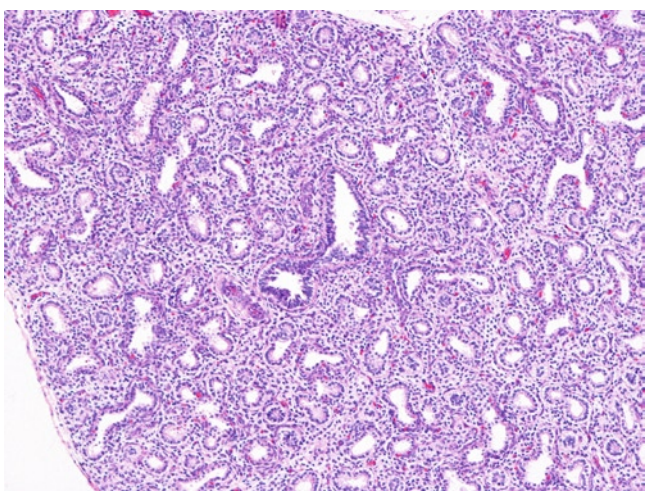

Figure 2-25. Early canalicular stage I: lung at 18 weeks gestation. Early in the canalicular stage, the lung is characterized by increasingly branched tubules. (H&E, 10×.)

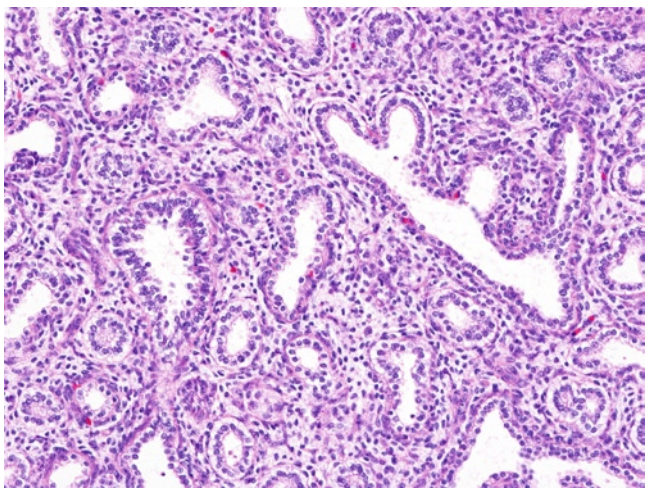

Figure 2-26. Early canalicular stage II: lung at 18 weeks gestation. Tubules are increasingly branched, but abundant mesenchyme remains. (H&E, 20×.)

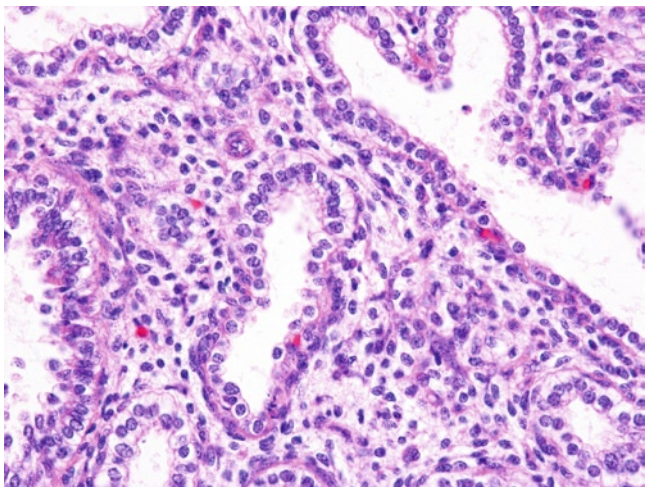

Figure 2-27. Early canalicular stage III: lung at 18 weeks gestation. The lining epithelium is transitioning from columnar and vacuolated to cuboidal and nonvacuolated. Capillaries are just beginning to protrude between these epithelial cells. (H&E, 40×.)

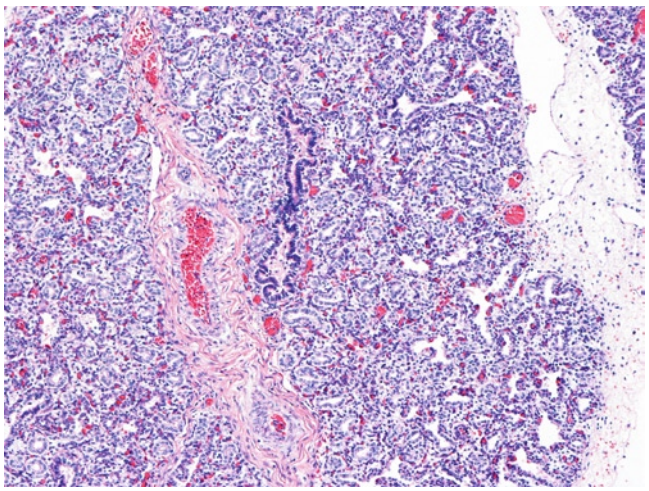

Figure 2-28. Late canalicular stage I: lung at 23 weeks gestation. Late in the canalicular stage the lung is characterized by more complex airspaces. The amount of interstitial mesenchyme is beginning to decrease compared with earlier gestations. Distal airways are readily recognizable among airspaces. (H&E, 10×.)

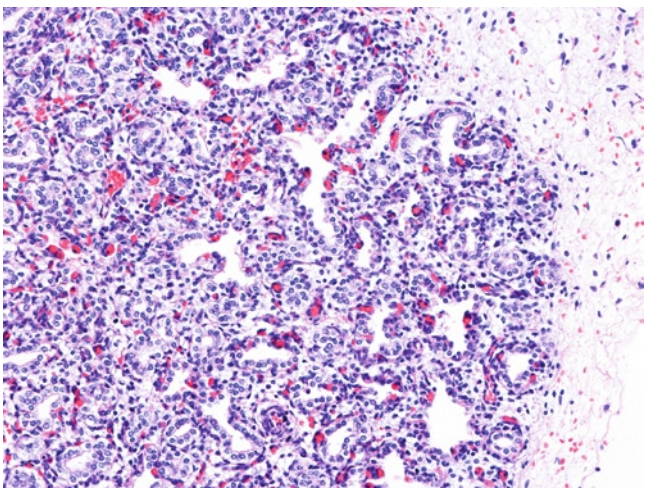

Figure 2-29. Late canalicular stage II: lung at 23 weeks gestation. Airspaces show slightly undulating outlines. (H&E, 20×.)

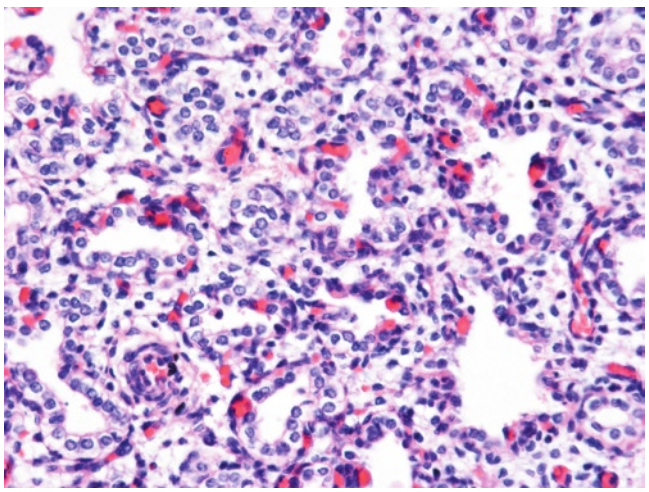

Figure 2-30. Late canalicular stage III: lung at 23 weeks gestation. A primitive capillary network is beginning to emerge. Airspaces are lined by predominantly cuboidal to, in areas, flattened nonvacuolated epithelium. Many capillaries are apposed to and protrude between airspace epithelial cells. (H&E, 40×.)

Saccular stage

The saccular stage is heralded by the formation of *secondary crests*. These ridges of epithelial-surfaced mesenchyme contain a double-layered capillary network and protrude into airspaces, subdividing them into increasingly more complex structures known as *saccules*. With the ingrowth of secondary crests and expansion of the capillary network, the saccules become vascularized initially with two layers of capillaries (*see* Figs. 2-31–2-33). The saccular stage is also marked by progressive thinning of the interstitial mesenchyme and an increasing framework of elastic tissue around not only airways but also between airspaces. By the latter saccular stage (*see* Figs. 2-34–2-36), the double-layered capillary network begins to coapt into a single capillary layer. The formation of a single-layered capillary network in concert with the differentiation of airspace epithelium to flattened pneumocytes provides for the maturing capillary–airspace interface necessary for eventual postnatal respiration [1,6,10].

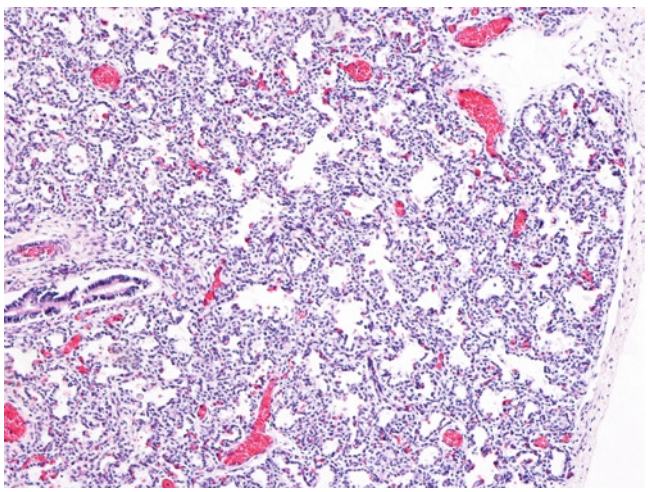

Figure 2-31. Early saccular stage I: lung at 28 weeks gestation. The early saccular stage is characterized by more complex airspaces with decreasing amounts of interstitial mesenchyme and an expanding capillary network. (H&E, 10×.)

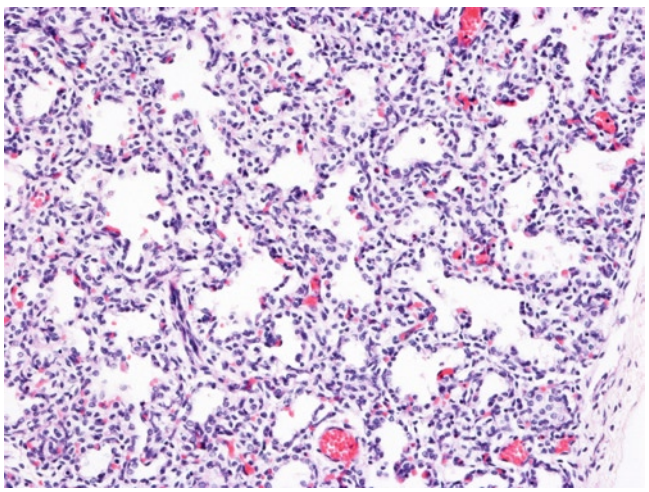

Figure 2-32. Early saccular stage II: lung at 28 weeks gestation. Airspaces show a wavy outline and an expanding capillary network. (H&E, 20×.)

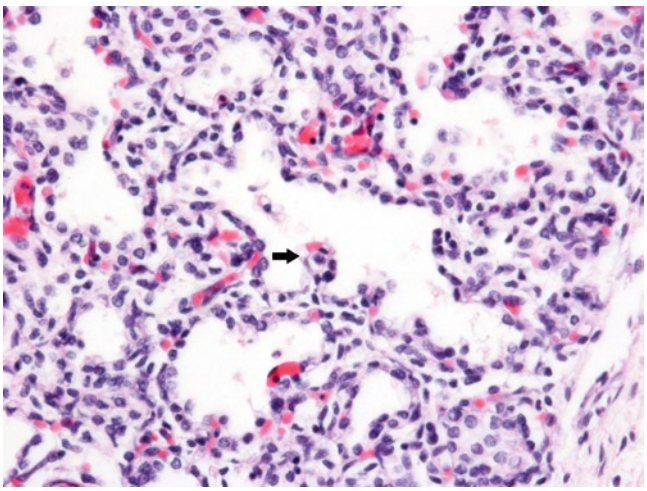

Figure 2-33. Early saccular stage III: lung at 28 weeks gestation. Airspaces are now becoming subdivided by "secondary crests" (*arrow*), to form "saccules." These saccules are increasingly lined by flattened epithelium. Secondary crests initially form a double capillary network within the interstitium. (H&E, 40×.)

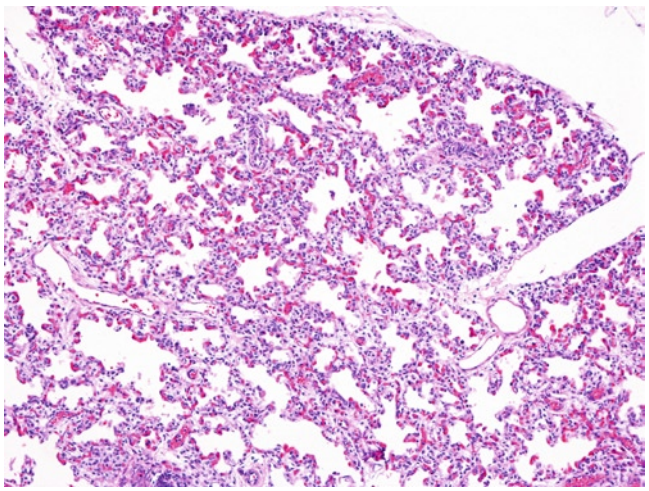

Figure 2-34. Late saccular stage I: lung at 31 2/7 weeks gestation. The late saccular stage is characterized by increasing numbers of saccules. (H&E, 10×.)

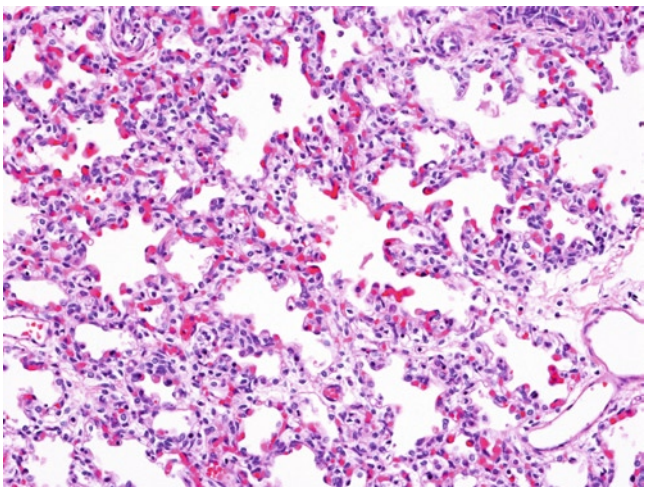

Figure 2-35. Late saccular stage II: lung at 31 2/7 weeks gestation. The interstitial capillary network is expanding and is also transitioning from a double-layered network to a single layer of capillaries. (H&E, 20×.)

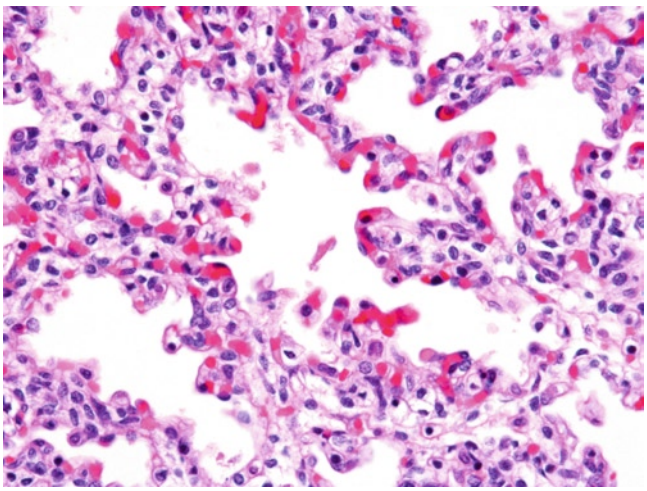

Figure 2-36. Late saccular stage III: lung at 31 2/7 weeks gestation. Saccules are lined by flattened epithelium with an increasingly thin interstitium. (H&E, 40×.)

Alveolar stage

During the alveolar stage, the amount of interstitial mesenchyme decreases substantially to form thin interalveolar septa. Alveoli now show their mature back-to-back configuration and are lined by flattened mature epithelium. Alveoli attain a more polyhedral configuration compared with the rounded sacs of the saccular stage, a process thought to be related to increasing elastin deposition within the interstitium of the lung (see Figs. 2-37–2-39). Capillaries appear as thin single layers within alveolar septa and directly coapt with airspace-lining epithelium [1,6,7]. By the completion of the alveolar stage of lung development, the lung has attained its full complement of structures, including lymphatics, vasculature, airways, and airspaces, and a fully mature alveolar–capillary surface for postnatal respiration has been achieved [1].

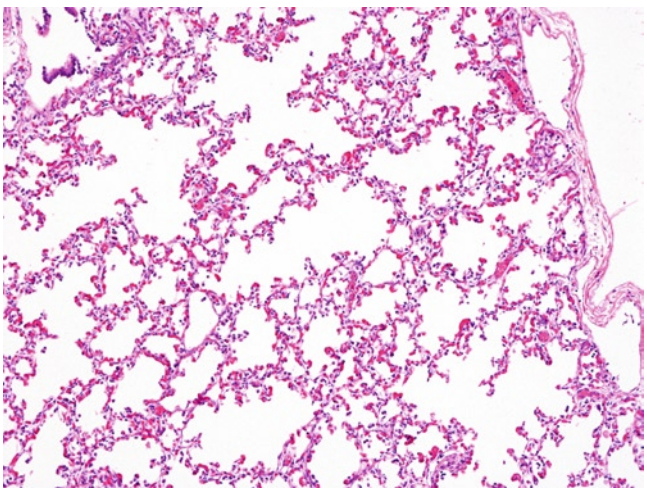

Figure 2-37. Alveolar stage I: lung at 36 3/7 weeks gestation. The beginnings of the alveolar stage are characterized by the attainment of thin interalveolar septa separating now back-to-back alveoli. (H&E, 4×.)

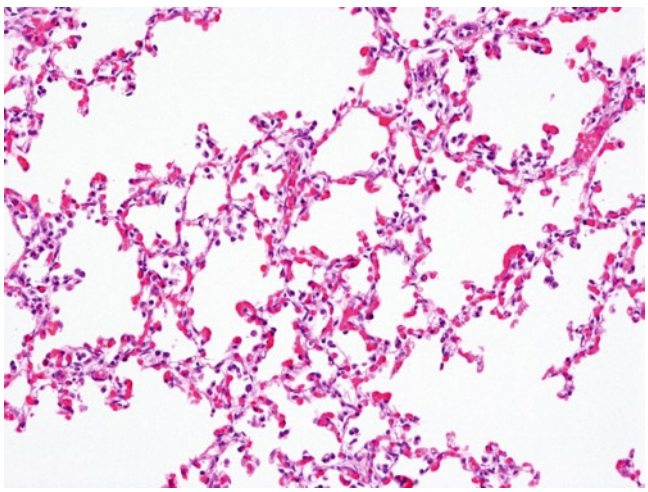

Figure 2-38. Alveolar stage II: lung at 36 3/7 weeks gestation. Alveolar septa contain an abundant single-layered interalveolar capillary network. (H&E, 10×.)

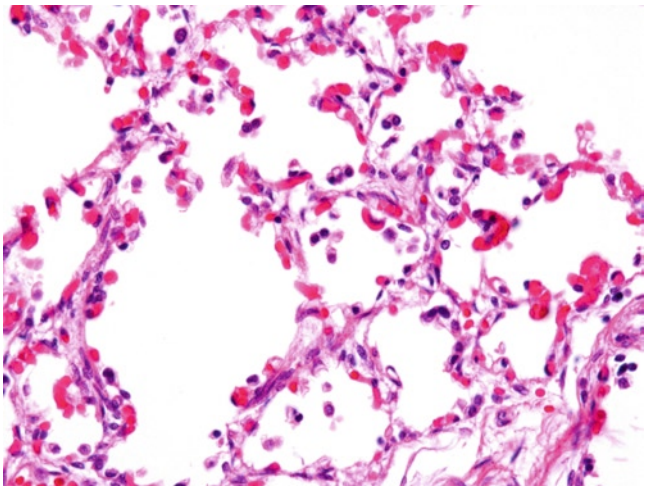

Figure 2-39. Alveolar stage III: lung at 36 3/7 weeks gestation. Alveoli are lined by flattened epithelium and the abundant capillaries bulge into the alveoli. (H&E, 40×.)

Special Considerations

Intra-acinar Pulmonary Arterioles

The alveolated lung parenchyma contains the most distal arterioles, which supply the alveolar capillary network. These intra-acinar precapillary arterioles are located within the interalveolar septa beyond the level of the bronchovascular bundle. These intra-acinar arterioles in the fetus and newborn normally are thin-walled and nonmuscularized (*see* Figs. 2-40 and 2-41). However, in pathologic states either in utero or postnatally, these arterioles may appear thick-walled from muscularization. Smooth muscle does, however, normally extend to within these intra-acinar arterioles beginning at approximately 6 months postnatal age [1,4,6].

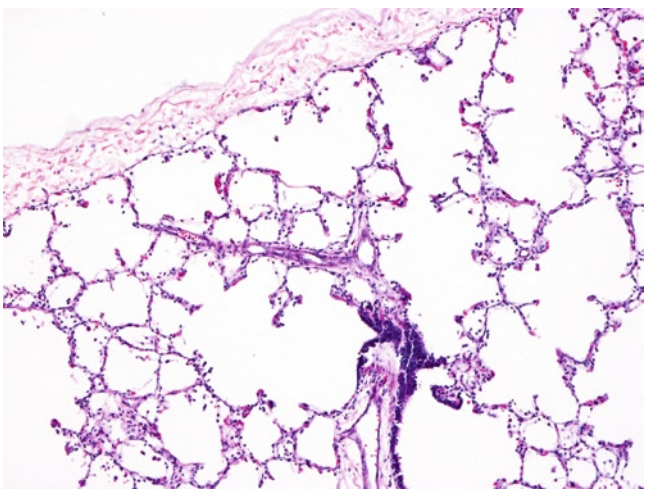

Figure 2-40. Intra-acinar arterioles I: normal 5-month postnatal lung. Normal intra-acinar arterioles are present within the alveolar parenchyma beyond the level of the bronchovascular bundle. (H&E, 10×.)

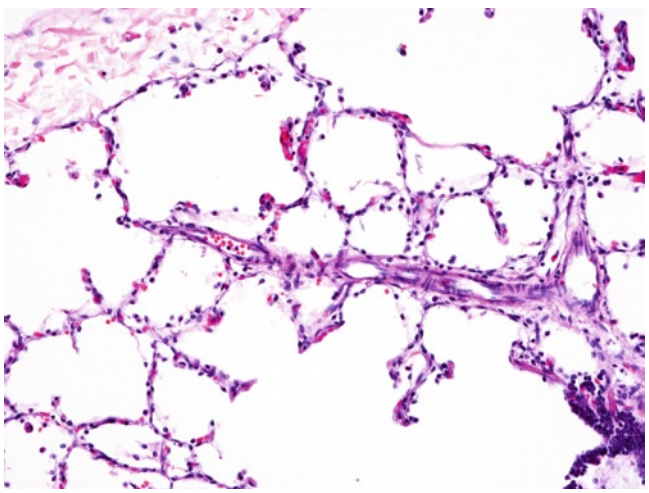

Figure 2-41. Intra-acinar arterioles II: normal 5-month postnatal lung. Intra-acinar arterioles normally appear to be progressively thin-walled as they extend through the parenchyma toward the pleural surface. (H&E, 20×.)

Intrapulmonary Karyorrhectic Cells

The normal fetal lung, particularly in the midtrimester, may contain prominent karyorrhectic material. This material may be the result of apoptosis, which is likely integral to the normal development of the lung [11,12]. Karyorrhectic material within fetal airways and airspaces may mimic neutrophils, an important distinction (see Fig. 2-42).

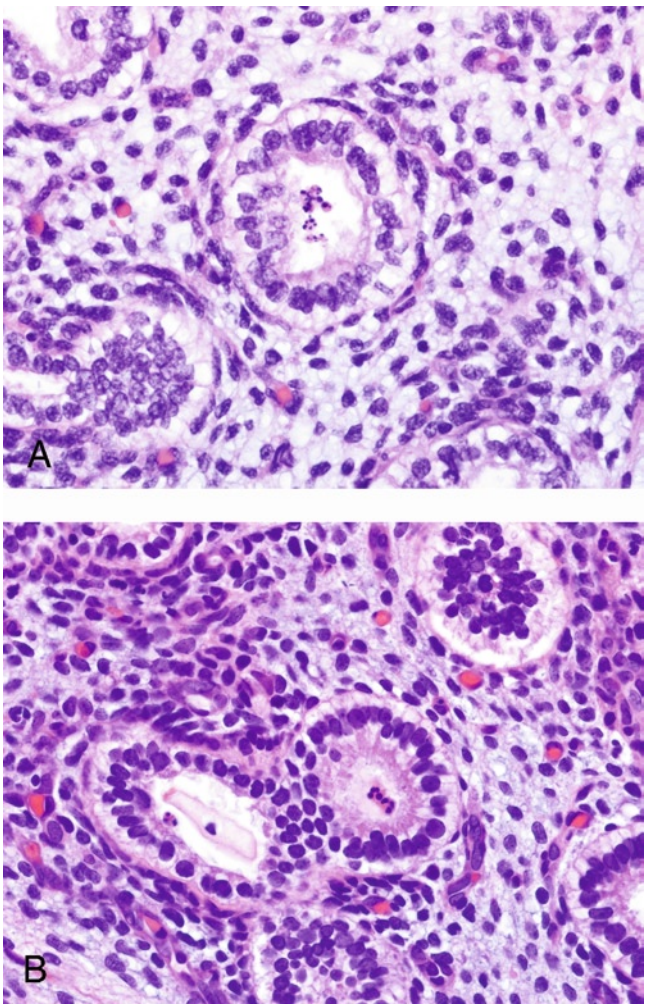

Figure 2-42. Karyorrhectic material: lung at 16 weeks (**A**) and 14 weeks (**B**) gestation. Karyorrhectic material (**A**) is present within the lung of a midtrimester fetus. This material should not be mistaken for neutrophils, which have better defined nuclear lobes as seen in **B**, an in utero infection. (H&E, 60×.)

Intrapulmonary Squamous Cells

A few scattered squamous cells within the fetal airways and airspaces of later gestations are a normal finding. These squamous cells enter the lung via fetal inspiration of amniotic fluid. However, large numbers of squamous cells in the fetal lung are considered to be pathologic and a sign of fetal hypoxia (see Fig. 2-43) [6].

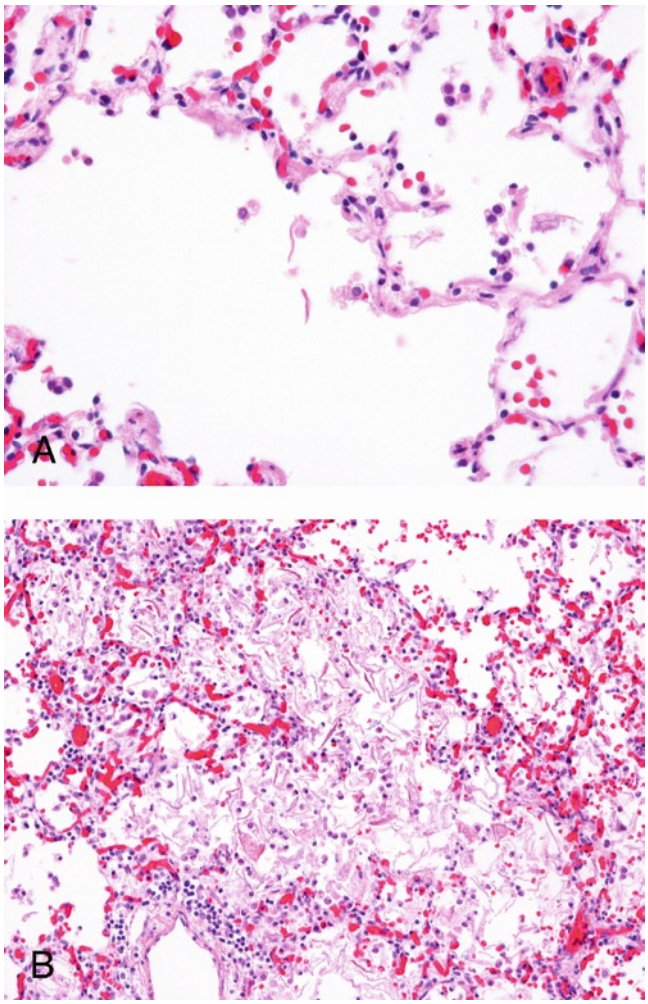

Figure 2-43. Squamous cells. Lung at 41 weeks gestation is shown. Occasional squamous cells are present within this late gestation lung (**A**); this is generally considered to be within normal limits. However, large numbers of squames, as seen in this late gestation lung (**B**), are considered to be pathologic. (H&E, **A**, 40× and **B**, 20×.)

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