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Development, Growth, and Aging of the Lung

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At various stages of development, the lung changes in size and in its architectural blueprint. The newborn lung is not the adult lung in miniature, nor is the premature or the just viable lung a miniature of the normal newborn. Development includes growth in size and maturation or differentiation in function.

Growth includes times of major change in the pattern or blueprint to which the growing lung conforms. The airways, alveoli, and arteries have their own rates of growth and development. It is not always necessary for a given phase to be completed before development shifts its focus. To establish that development has been normal, structural maturation must be assessed by the number of the various units. A quantitative analysis of the lung, even using relatively simple techniques, adds significant information. The practical assessment of the gross specimen and microscopic slides by the pathologist is an important part of understanding development.

Understanding lung growth is of interest in itself and has practical application in the diagnosis of disease. It is intellectually gratifying to be able to correlate normal or morbid structural findings with the radiograph, lung function tests, and symptoms.

ORGANOGENESIS

Development of the human embryonic lung begins in week 4 of intrauterine life, when a diverticulum arises from the ventral surface of the foregut.[1] This diverticulum is lined by epithelium and invested with mesenchyme. From the beginning, epithelial and mesenchymal interaction is essential for the organization, proliferation, migration, and differentiation of future airways, air spaces, and vascular channels.

Fetal Stages

From the appearance of fetal lung in microscopic section, three stages of intrauterine lung development are identifiable: the pseudoglandular stage, the canalicular stage, and the terminal sac or alveolar period (Fig. 2-1).

As illustrated in Figure 2-2, during the pseudoglandular stage (*i.e.*, 5–16 weeks of gestation), branching of the future airways is completed. During the canalicular stage (*i.e.*, 16–24 weeks of gestation), the distal air spaces differentiate to form the respiratory surface or future alveoli. During the terminal sac or alveolar period (*i.e.*, week 24 of gestation–term), alveolar spaces multiply. Capillaries migrate toward the alveolar luminal surface, and the blood-gas barrier forms by fusion of the capillary and epithelial basement membranes. Within the epithelial lining, the type I and II pneumocytes appear and differentiate biochemically.

Aberrant epithelial and mesenchymal interaction early in fetal life causes developmental anomalies such as tracheal or bronchial cyst, intralobar or extralobar sequestration, agenesis of lung, dysplasia, cystic-adenomatoid malformation, and polyalveolar lobe (Fig. 2-3). For details on these pathologic conditions, see Chapters 6 through 10.

Lung Development

The template for normal lung growth is different at various ages; sometimes increased activity results in an increase in number of units, and sometimes the emphasis is on remodeling of units.[1] Development of the airways, alveoli, and vessels occurs at different times and at different rates, normally with an overall coordination of steps and timing. In disease, the degree of dissociation between

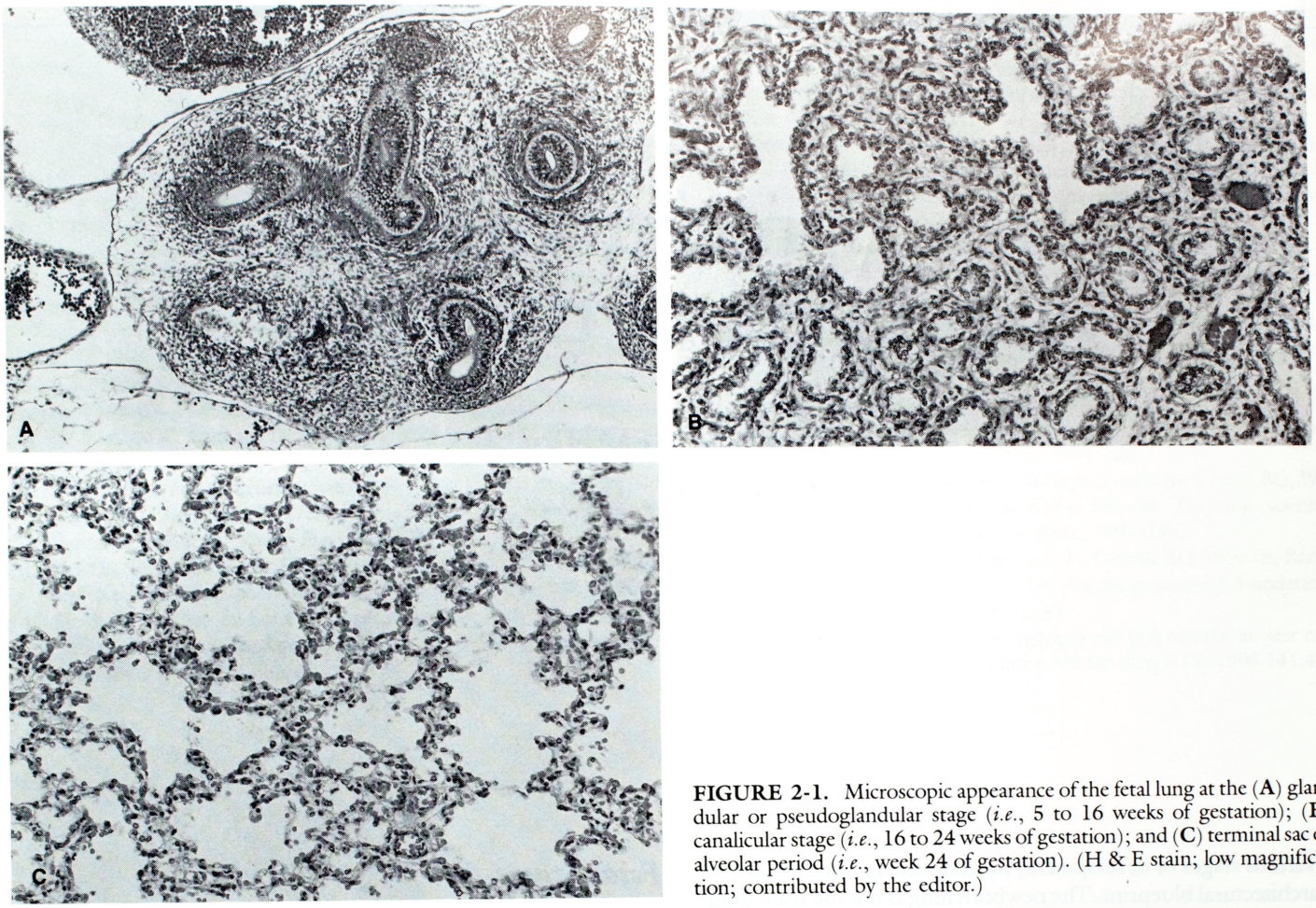

FIGURE 2-1. Microscopic appearance of the fetal lung at the (**A**) glandular or pseudoglandular stage (*i.e.*, 5 to 16 weeks of gestation); (**B**) canalicular stage (*i.e.*, 16 to 24 weeks of gestation); and (**C**) terminal sac or alveolar period (*i.e.*, week 24 of gestation). (H & E stain; low magnification; contributed by the editor.)

them often becomes apparent. Development of the three main structural components of lung occurs in three stages. The airways develop *in utero*, and alveolar development is largely a postnatal event; the precursor saccules are formed near the end of gestation.

AIRWAY DEVELOPMENT

By week 16 of intrauterine life, the conducting airways (*i.e.*, bronchi and bronchioli) are formed; during the pseudoglandular stage, all adult airways develop by branching of the ventral foregut diverticulum.[2] By week 5 of intrauterine life, the lobar and segmental bronchi are forming, and cartilage plates and mucosal glands appear in the trachea and intrapulmonary airways (see Fig. 2-2). Acinar development occurs next during the canalicular phase of lung growth.[3] An acinus is a functional unit of lung analogous to a nephron in the kidney or to a hepatic lobule. It is the portion of the lung that is subtended by the terminal bronchiolus and includes the respiratory bronchioli, alveolar ducts, and alveolar sacs.

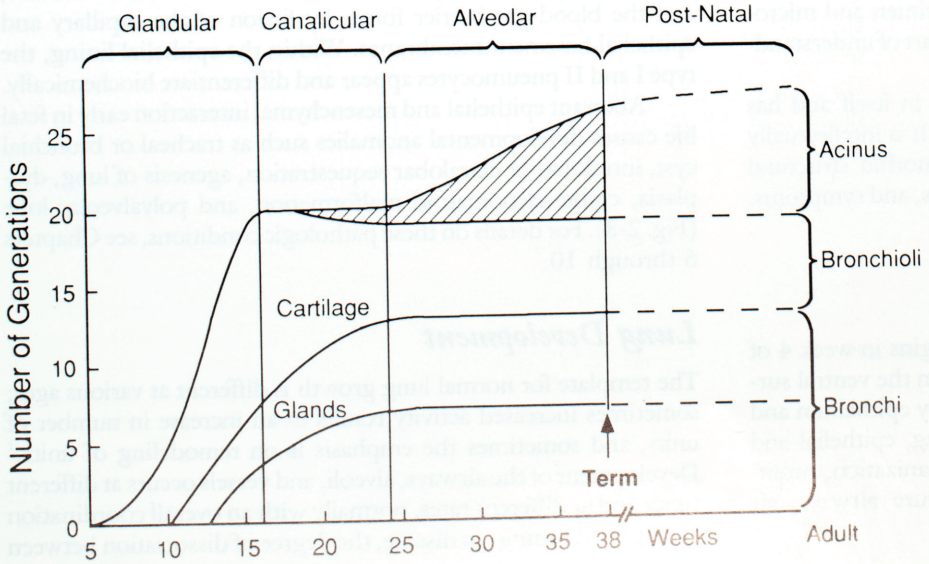

FIGURE 2-2. The lobar bronchi appear at about week 5 of gestation, and the bronchial tree beyond develops between weeks 6 and 16 of intrauterine life. Cartilage and gland development lag behind the airway. (From Bucher UG, Reid L. Development of the intrasegmental bronchial tree: the pattern of branching and development of cartilage at various stages of intrauterine life. Thorax 1961;16:207.)

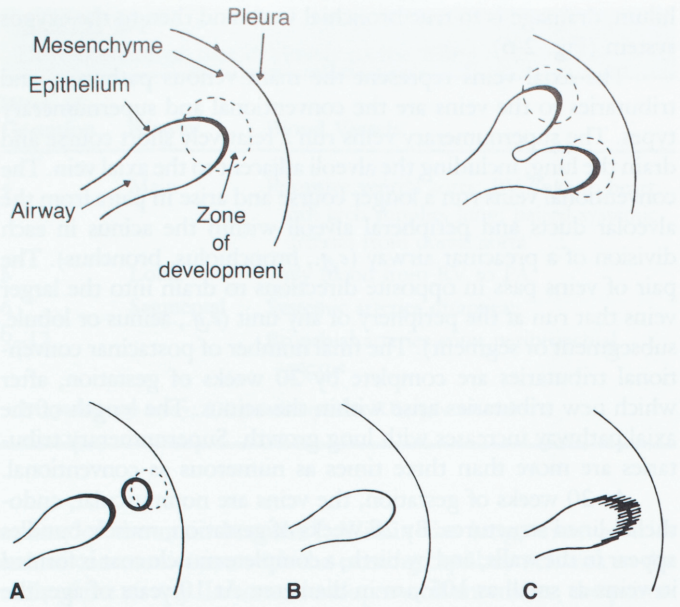

FIGURE 2-3. A ventral diverticulum arises from the embryonic foregut and branches dichotomously within a coat of mesenchyme to form the future airways. Epithelial-mesenchymal interaction at the zone of development is essential to normal airway branching and lung differentiation. Abnormalities occur as (**A**) an extra focus represented by tracheal or bronchial cyst, (**B**) absence of budding by aplasia, or (**C**) abnormal organization by dysplasia. (From deMello DE, Davies P, Reid LM. Lung growth and development In: Simmons D, ed. Current pulmonology. Chicago: Year Book, 1989:159.

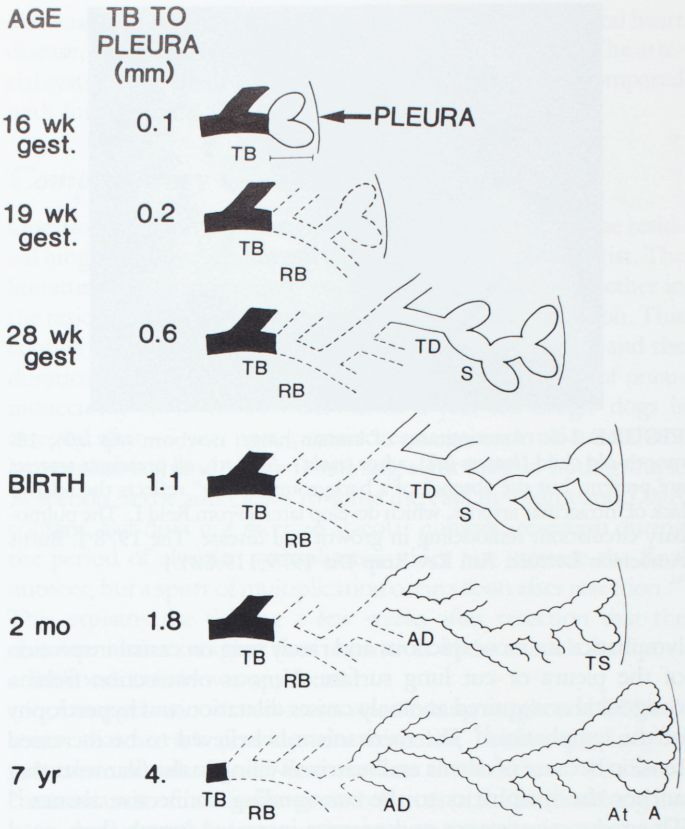

FIGURE 2-4. Growth of the acinus in the fetus and child. (A, alveolus; AD, alveolar duct; At, atrium; RB, respiratory bronchiolus; S, saccule; TB, terminal bronchiolus; TD, terminal duct; TS, terminal sac; from Hislop A, Reid L. Growth and development of the respiratory system—anatomical development. In: Davis JA, Dobbing J, eds. Scientific foundations of pediatrics. London: William Heinemann, 1974:214.)

ALVEOLAR DEVELOPMENT

At birth, there are about 20 million primitive saccules.[4] As alveoli multiply after birth, the adult complement of about 300 million alveoli is achieved by about 8 years of age.[5] Multiplication is most rapid during the first 4 years of life. In these early years, as the thorax increases in size, alveolar density assessed as alveolar number per unit volume does not change significantly. During late childhood, the thoracic wall growth is relatively faster, and alveolar multiplication lags so that alveolar size increases and alveolar density decreases.

A convenient way to assess alveolar multiplication on standard microscopic sections is the radial alveolar count described by Emery and Mithal.[6] A count is made of the alveolar spaces transected by an imaginary radian drawn perpendicular to the edge of the acinus, as defined by a vein, connective tissue septum, or pleura, from the lumen of the respiratory bronchiolus. The change in alveolar number from birth through 6 years of age is depicted in Figure 2-4.

VASCULAR GROWTH

Vascular growth parallels the pattern of development of preacinar airways and alveoli.[7] The preacinar branches of the pulmonary artery, those that accompany bronchi or bronchioli, develop at the same time as the airways they accompany. Intraacinar arteries develop as the alveoli grow.[8,9]

The pulmonary artery gives off two types of branches.[10] The conventional artery that accompanies an airway branches as the airway branches and ultimately supplies the alveolar capillary bed beyond each terminal bronchiolus. The supernumerary arteries arise along the length of the pulmonary artery and run a short course to supply the alveoli adjacent to the pulmonary artery. Some conventional arteries are right angled, and some are acute angled; supernumeraries usually arise at right angles from the parent vessel. The supernumeraries represent a collateral pathway to the periphery of an acinus, which becomes important in certain pathologic conditions for providing a collateral blood supply to tissues beyond a block.

A change in arterial growth in terms of density of intraacinar arteries is evident in Figure 2-5, which depicts arteriograms of the human lung at three ages. In the newborn, all the preacinar arteries are present. Because the intraacinar arterial density is poor, the background haze that is produced by the filling of intraacinar arteries is absent. At 18 months of age and in the adult, this background haze is evident.

Lymphatics

The lung has two sets of lymphatics, one superficial and one deep, and both drain to the hilum.[11,12] The superficial lymphatics form a rich plexus within the pleura, and the deep ones pass in the connective tissue sheaths of the bronchoarterial bundles and of the veins; alveoli are devoid of lymphatics. All lymphatics draw to the hilar lymph nodes. On the left, lymphatics then drain into the thoracic duct, and on the right, they drain into the right lymphatic duct. The left lower lobe lymph often passes through infrahilar nodes and lymphatics to the right hilum. In health, the lungs'

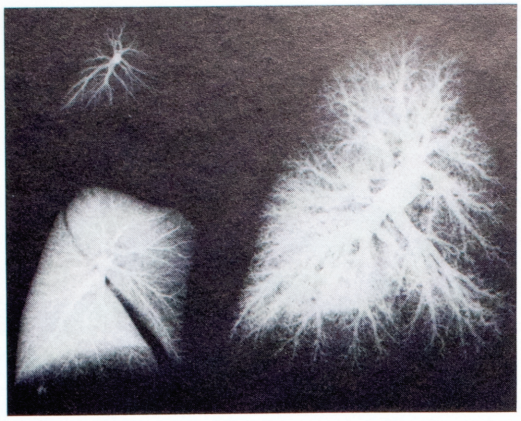

FIGURE 2-5. Arteriograms of human lungs: newborn (*top left*), 18-month-old child (*bottom left*), adult (*right*). At birth, all preacinar arteries are present, but the absence of a background "haze" reflects the relative lack of intraacinar arteries, which develop later. (From Reid L. The pulmonary circulation: remodeling in growth and disease. The 1978 J. Burns Amberson Lecture. Am Rev Resp Dis 1979;119:531.)

lymphatics are inconspicuous and rarely seen on casual inspection of the pleura or cut lung surface. Venous obstruction from a congenital or acquired anomaly causes dilatation and hypertrophy of the lymphatics.[13] The mechanism is believed to be increased tension because of edema and matrix swelling in the filaments that anchor the lymphatics to the surrounding connective tissues.[14] This reduces resistance and permits increased lymph flow.

Veins

The preacinar pulmonary veins occur at the periphery of the acinus within a connective tissue sheath.[10] Along their course from the acinus to the hilum, the veins receive tributaries and increase progressively in size. All intrapulmonary structures, airways, and alveoli drain to the pulmonary veins; from a small region at the hilum, drainage is to true bronchial veins and then to the azygos system (Fig. 2-6).

The axial veins represent the main venous pathways, and tributaries to the veins are the conventional and supernumerary types. The supernumerary veins run a relatively short course and drain the lung, including the alveoli adjacent to the axial vein. The conventional veins run a longer course and arise in pairs from the alveolar ducts and peripheral alveoli within the acinus in each division of a preacinar airway (*e.g.*, bronchiolus, bronchus). The pair of veins pass in opposite directions to drain into the larger veins that run at the periphery of any unit (*e.g.*, acinus or lobule, subsegment or segment). The final number of postacinar conventional tributaries are complete by 20 weeks of gestation, after which new tributaries arise within the acinus. The length of the axial pathway increases with lung growth. Supernumerary tributaries are more than three times as numerous as conventional.

At 20 weeks of gestation, the veins are nonmuscular, endothelial-lined structures. By 28 weeks of gestation, muscle bundles appear in the walls, and by birth, a complete muscle coat is formed in veins as small as 105 μm in diameter. At 10 years of age, the smallest muscular vein is 70 μm in diameter.

Although development of the postacinar drainage pattern is complete by the middle of gestation, development of intraacinar vessels continues during childhood. There are more supernumerary veins than arteries so that there are more vessels that leave the capillary bed than enter it. These are present at birth when clearance of lung liquid occurs.[15]

Bronchial Circulation

Nutrition for the developing lung is provided by the bronchial arteries, which at 4 weeks of embryonic life arise from the dorsal aorta close to the celiac axis when this axis is in the neck (Table 2-1). These primitive bronchial arteries disappear at about week 6 of gestation; the definitive bronchial arteries arise from the aorta at about 12 weeks of life and pass into the lung along the dorsal

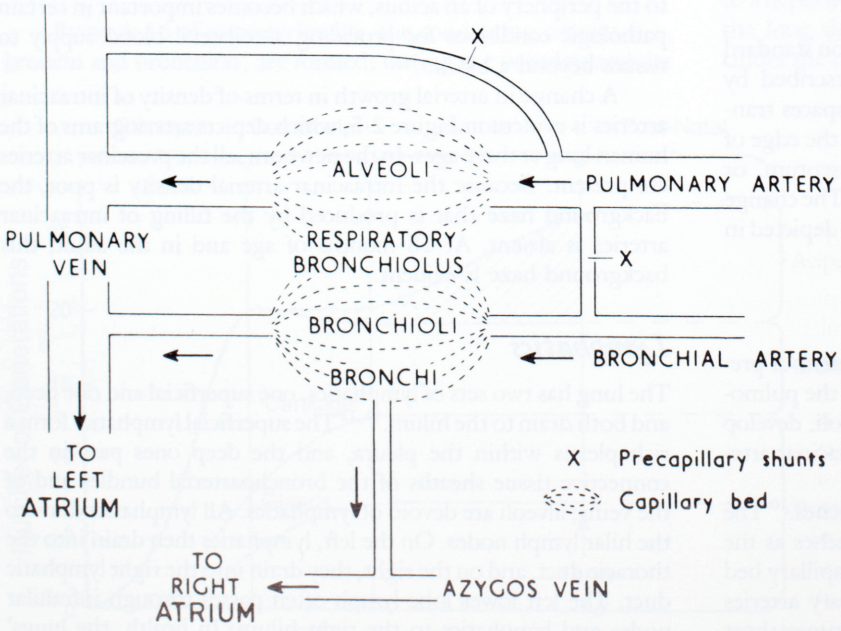

FIGURE 2-6. The double arterial and venous systems of the lung. The bronchial artery supplies the capillary bed of the bronchi and the pulmonary artery of the respiratory region. The pulmonary veins drain both regions, but the true bronchial veins drain only the hilar bronchi and perihilar structures and drain to the azygos system. (From Reid L, Fried R, Geggel R, Langleben D. Anatomy of pulmonary hypertensive states. In: Bergofsky EH, ed. Abnormal pulmonary circulation. New York: Churchill-Livingstone, 1986:221.)

TABLE 2-1
Development of Blood Vessels to the Lung

Week of Gestation	Airway	Blood Vessels
4	Main	Primitive ventral aorta; PV links to heart; 6th arch supplies lung; paired systemic arteries from dorsal aorta
5	Lobar	Only blood from RV to PA
6	Segmental	Systemic arteries disappear
9–12		Bronchial arteries enter peribronchial plexus

PA, pulmonary artery; PV, pulmonary vein; RV, right ventricle.

surface of the main bronchi.[16] Within the lung, these arteries induce communication with the existing capillary network in the walls of the airway. In some developmental anomalies, the primitive bronchial arteries persist. They can be identified by their origin near the celiac axis below the diaphragm. These are the arteries that commonly supply pulmonary sequestrations.

Perinatal Adaptation

To prepare the lung for its function of gas exchange, a series of changes start just before labor and continue during labor and into the early postnatal period. In sheep 2 to 3 days before spontaneous birth, secretion of lung liquid into the fetal trachea decreases.[17,18] Investigators have demonstrated an elevation in the fetal plasma epinephrine concentration in sheep and changes in plasma concentration of several hormones just before labor in several species.[19,20] These changes promote the absorption of lung liquid from alveolar and tissue spaces and probably aid in increasing distensibility of pulmonary arteries, producing a fall in pulmonary artery pressure and vascular resistance.

Distensibility refers to the increase in external diameter and the drop in wall thickness of a vessel at a given intraluminal pressure.[21] The reduction in pulmonary artery pressure occurs by dilatation of the arterial bed and an increase in the distensibility of the smallest resistance arteries.

POSTNATAL DEVELOPMENT

Postnatal Growth

Postnatal growth includes a general increase in size and weight of lung, which probably reflects pituitary, thyroid, and insulinlike growth factor activity. Little is known regarding the interactions between the various hormones and other peptide-regulating factors from these and other sources, and the lungs' cells and tissues.

The postnatal growth of lung includes several important shifts in template. Superimposed on the striking increase in total alveolar number is an increase in the density of arteries per unit volume of lung. In the rat, an increase in alveolar density occurs several days before an increase in the concentration of alveolar wall vessels, which more than compensates for the increased alveolar density. For convenience, this is expressed as an alveolus-to-artery ratio, because the ratio is in whole numbers. As this ratio falls, the density of arteries increases relative to alveoli. These two shifts are dissociated, and sometimes, especially in cases of congenital heart disease, alveolar growth occurs without arterial growth. The arterial system is less dense than normal and more restricted compared with lung volume.[22]

Compensatory Overgrowth

Questions about the nature of compensatory growth of the residual lung after resection are often addressed to the pathologist. The literature contains seemingly conflicting results about whether in the residual lung there is an increase in the number of alveoli. This conflict is resolved if the age of the experimental animal and the duration of the experiment are considered. If the effect of pneumonectomy in 6- to 10-week-old or 1-year-old beagle dogs is assessed after a 5-year postoperative recovery, a normal total alveolar number is found in the remaining right lung in both groups. Resection in the adult leads to some increase in weight and DNA content, but does not increase alveolar number; resection during the period of alveolar multiplication does not increase the final number, but a spurt of multiplication occurs soon after resection.[23] This explains the finding a few weeks after resection that the alveolar number is higher than in controls. If the animals survive to adulthood, this is not apparent.

Lung resection causes an increase in lung weight and DNA. It seems that stretch provides the stimulus; neither the surgical procedure nor the blood flow mediate the increase.[24] Increased concentration of insulinlike growth factors in the residual lung has been demonstrated. In some species, an increase is seen in the volume of circulating blood. Intriguing questions remain to be answered concerning the control of organ size and the signals for compensatory growth.

MECHANISMS OF GROWTH AND MATURATION

At various stages of development, a variety of cellular events occur, and each has its special pathways of control. The major biologic events include cell migration, adhesion, and chemotactic attraction; cell proliferation and programmed death; and a switch in phenotype.

Mediator research offers insights into the way critical cellular events could occur. Only the application of the equivalent of Koch's postulates for infectious agents can validate their biologic role. Prevention of an *in vivo* event by use of the appropriate antagonist is key evidence. Relatively few of the examples given here have passed this critical test.

Airway Branching

The branching of the bronchial tree, complete by 16 weeks of intrauterine life, is a story of mesenchyme and epithelium interaction (see Figs. 2-3 and 2-4). At the distal branching points of the hollow blind tubes, multiplication and necrosis of the epithelial layer are balanced. At these sites, increased synthesis and lysis of the basement membrane occur. In the mesenchymal fibroblast, the signal for epidermal growth factor increases, as does the epithelial signal for fibroblast growth factor. The tissue also includes inhibitors of the metalloproteinases that provide a negative feedback mechanism, and an increase in these inhibitors leads to stability of the connective tissues.

Normal metabolic resources are essential to the normal functioning of growth factors. In the mouse, administration of a proline analog that selectively inhibits collagen biosynthesis alters lung morphogenesis *in vitro* by differential modification of the rate of epithelial growth and airway branching.[25] This effect illustrates a mechanism whereby mesenchyme controls the spatial organization of the airway and points to the essential role of collagen in achieving a normal and complete branching pattern. At a critical stage in lung development, the kidney is a source of proline, explaining the association between kidney maldevelopment and impaired airway branching as in the Potter syndrome.

In development of the numerous central conducting airways, branching represents division of one hollow tube into two (*i.e.*, a dichotomy). Over the length of the distal epithelium, there is a spatial distribution of stability and activity. The two emerging buds represent sites of activity, and the carina between them represents a site of stability. Collagen type IV is concentrated at the tip of the carina or crest between the buds.[26] In the mouse, it seems that collagen IV is the critical component. In a mutant mouse with a nonfunctional gene for collagen type I, branching morphogenesis is normal until the mouses's death during the middle of gestation.[27]

Neuroendocrine cells produce a wide range of bioactive agents. These cells are more numerous during intrauterine growth, and at least for bombesin, the message is highest early *in utero*, although toward term, when the message is reduced, the intracellular product increases.[28] The presence of the protein does not indicate its biologic activity or significance.

Vascular Development

Two types of activity produce the blood vessels of the lung: branching from central vessels and the development of vascular lakes within the pulmonary mesenchyme.[29] Central and peripheral channels then connect with each other. Within a lobe, the appropriate spatial arrangement develops (*i.e.*, a central bronchoarterial bundle with peripheral veins). Directed branching of arteries is important even before the alveolar region is present, because both conventional branches of the pulmonary artery (*i.e.*, those that run with airways) and the supernumerary arteries (*i.e.*, those that supply the cuff of alveoli around the artery) develop contemporaneously as airways divide during the pseudoglandular phase.

The vascular channels develop from mesenchyme. The endothelial cell, the smooth muscle cell or its precursors, and the fibroblast are each responsible for one vessel: the intima, media, and adventitia, respectively. Receptor differences establish different patterns of response. Elastin production is a significant feature of vascular growth and differentiation. The gene for tropoelastin is expressed in all three cell types.[30] In the rat fetus, the degree of expression is high and greater in the artery than in the vein. After birth, it gradually decreases, selectively in the arteries, so that by postnatal day 21, its expression is stronger in veins than arteries. In the adult, it is not apparent, although in certain models of injury, increased elastin production indicates that the gene is again expressed at higher levels.

Alveolar Differentiation

Alveolar differentiation includes an increase in surface area and development of saccules, sculpting of the blood-gas barrier, and maturation of the surfactant system.

When the time for airway branching is finished, although the full normal complement of branches has not necessarily been achieved, development shifts. This shift focuses on the distal few airway branches along any pathway, whether it is close to the hilum or to the pleura. The new template is not for dichotomous branching, even or uneven, but for developing outpouchings that by their walls define open spaces. Epithelium, with its basement membrane, mesenchyme, and blood vessels, is still a player. The volume of the mesenchyme matrix reduces, although its vascular components increase.

Over the distal few generations, laminin and type IV collagen show a discontinuous pattern in the basement membrane.[26,31] The epithelial cells become motile and change shape. They seem to invade and stretch the surface area to produce thin tubes lined by flattened epithelium. The epithelial cells multiply, causing localized lateral expansion of the space with increased luminal volume. A saccular structure becomes apparent. Within this simple structure, further subdivision by outpouching occurs.

At this point in human lung proliferation, two types of interstitial fibroblast are apparent; one is lipid filled and is seen for a relatively short time.[32,33] Both types make contact with overlying epithelial cells. Noguchi and colleagues described in the rat a messenger RNA for tropoelastin at day 17 of gestation.[34] Less is known about growth factors at this later stage than for earlier periods.

A complex pattern of intercellular reactions has been identified. The scene is set for the development of the blood-gas barrier.[35–38] The mechanisms responsible for this are not understood, but a feature of the program in alveolar wall morphogenesis is apparent. The capillary expands or migrates toward the epithelium, which it contacts. The epithelium thins, and the capillary bulges into the alveolar space. The epithelial layer is no longer apparent by light microscopy but only by electron microscopy. The basement membranes of the epithelial and endothelial cells fuse. At first, the alveolar wall is thick enough to give the impression of a double capillary network, one for each alveolar surface. The alveolar wall thins, and this appearance is lost. At approximately 19 weeks of gestation, the blood-gas barrier is achieved and is the same thickness as that in the adult.[38] In alveolar capillary dysplasia, this part of the program does not occur.[39–41] In an experimental model of diabetes, it is delayed.[42]

Formation of the blood-gas barrier is the first requirement for viability. Cellular and biochemical maturation of the surfactant system proceeds by a complex pattern of intercellular reactions, apparently mediated by the fibroblast.[43]

CHARACTERISTICS OF THE AGING LUNG

Changes in the biochemistry, morphologic appearance, and function of the lung characterize its aging.[44] These changes do not cause disability, and vigorous exercise is still possible. In the absence of lung disease, an elderly person breathes effortlessly and comfortably.

Morphologic Changes

The diameters of the trachea and central airways increase, expanding the anatomic dead space. Tracheal cartilage may calcify, but proteoglycan and collagen contents are not altered. Alveoli and

alveolar ducts increase in volume, decreasing the lung surface area. Even a doubling in alveolar diameter means that the volume of an alveolus increases eightfold (2^3). Although this seems considerable, it is far below the loss of surface area in symptomatic panacinar emphysema.

Reduced elasticity results in somewhat earlier closure of small airways than in the young lung, and this increases functional residual capacity, with air trapping, particularly in the apices. The extent to which reduced chest wall compliance contributes to the air trapping is a subject of controversy. Aging does not alter the ability of the lung to recruit blood vessels when blood flow increases. Large pulmonary arteries can develop atherosclerotic plaques, and the stiffness of medium sized vessels increases. In small vessels, fibrosis of the intima is common. These changes contribute to an overall increase in vascular resistance.

Functional Changes

Aging results in a loss of elastic recoil, an increase in closing volume, changes in the subdivisions of lung volume, and a decrease in maximal expiratory flows. These changes are mild compared with those caused by disease processes. Because of the closure of small airways, there is a ventilation-perfusion inequality that contributes to decreased arterial oxygen tension.

Biochemical Changes

Collagen, the predominant protein in mammalian lung that constitutes as much as 20% of the dry weight, has been difficult to analyze because of its low solubility. Conflicting results, including no change, increase, and decrease in collagen levels, have been reported. As in skin and tendon, the physical properties of collagen, including cross-linking, are probably altered. Lung elastin content comprises as much as 30% of dry weight and increases with age, although there is a loss of elastic recoil.

The propensity of the aged patient to aspirate or inhale foreign material into the tracheobronchial tree results from uncoordinated deglutition, not from an intrinsic aging effect in the lung. The foreign material can elicit a chemical or infectious pneumonia. Although the aging lung undergoes some structural remodeling and functional change, it adequately fulfills its gas-exchange function.

RESPONSE TO INJURY

Injury represents disturbance of homeostasis. Systems for neutralizing injury are effective at maintaining homeostasis; when they are ineffective, injury and destruction of tissue and overaction of the repair process occur. The protective or repair function often amplifies the injury. The protective systems of the body include cellular or humoral immunologic, phagocytic, thrombotic, and thrombolytic mechanisms.

The body typically becomes tolerant to a continuing injurious challenge. For example, exposure to hyperoxia causes necrosis, but continuing exposure to the same level produces a certain tolerance because the debris clears quickly, and although necrosis continues, it is not on the initial scale.

In the organism, the homeostatic mechanisms work through hemodynamic and temperature regulation, chemotaxis for inflammatory cells, and the modulation of the endocrine and nervous systems. The manifestations of local injury can be considered inflammation. Cells act locally through growth factors, cytokines, and other mediators. The characters in the drama are often difficult to separate. Disturbed homeostasis can return to equilibrium with virtual resolution, although an injury always leaves its imprint, even long after healing seems to have occurred.[45,46] Structural normality may be restored, but function remains disturbed. For example, the speed or intensity of response to a repeat challenge is usually different from a first response. The healing process usually includes some scarring, with structural distortion of the tissues. In the airways, an epithelial injury with an intact basement membrane represents a different degree of injury from that with an interrupted basement membrane.

Epithelial Loss With an Intact Basement Membrane

Epithelial loss with an intact basement membrane is produced typically by viral infections such as influenza or by a chemical burn. The surface recovers itself quickly as epithelial cells grow in from the mouths of glands in the trachea and bronchi, from the edge of the lesion, and from surviving isolated cells attached, albeit tenuously, to the basement membrane. These cells multiply, migrate, and change shape to cover the surface with first a single and then a multilayer of cells. The cells become stratified and, although they do not have squamous cell interconnections, resemble a squamous epithelium. This squamous epithelium is a stage in healing.

The cells change shape once again, rearrange themselves, and differentiate into the full complement of cell types typical of respiratory epithelium. In the trachea and the large airways, these constitute a pseudostratified ciliated epithelium, in which all cells attach to the basement membrane, although not all reach the lumen; in bronchioli and smaller bronchi, a simpler mix of more cuboidal or flatter cells develop.

Epithelial Loss With Ulceration of the Basement Membrane

Epithelial loss with ulceration of the basement membrane involves stimulation of connective tissues and inflammatory cells deeper in the wall with formation of granulation tissue (*i.e.*, a mixture of new blood vessels and interstitial cells, particularly fibroblasts) that erupts into the floor of an ulcer, recreating a surface over which epithelium can grow and differentiate as described previously.

This healing process varies in its effectiveness. Although healing in the case of an intact basement membrane produces resolution, healing after ulceration is often associated with scarring. The seriousness of scarring varies, depending on the size of the ulcer and the size and content of the airway. In the trachea, the scarring produced by pressure ulceration of an intratracheal tube or a tracheostomy are serious complications of otherwise lifesaving treatments. The telltale pucker of a ruptured caseous tuberculous node used to be common in hilar airways.

In small airways, the healing by scar leads typically to stenosis and obliteration. This may be localized to one level along the length of an airway, and the distal and proximal parts show less than complete obliteration. The diagnosis of obliterating or obliterative bronchiolitis is a serious one, and a biopsy often is performed because this diagnosis is suspected. Any small airway injury associated with scarring is safely put in this category. From

the few airways in one biopsy section, the pathologist cannot tell the full extent of the airway injury, but at least the clinician can be alerted to estimate the functional significance of a scarring disease. In a microscopic section of an airway during the acute phase of this injury, pockets of epithelium are often found deep in the granulation tissue (see Chap. 30).

Bronchiolitis Obliterans of Immune Suppression

In bronchiolitis obliterans of immune suppression, the chronic inflammatory injury is associated with the infiltration of activated inflammatory and immune cells.[47] It represents a fibrosing lesion in which the injurious cells penetrate from the adventitia (*i.e.*, injury occurs from outside to within). Cell injury to the wall and epithelium is the result of the mediators produced by these protective cells. This reaction can cause a fatal stenosing and obliterating lesion, but if treatment suppresses the mediators of cell injury, healing can occur, usually with scar. The wall may appear intact but with subepithelial fibrosis in plaques between the epithelium and smooth muscle. Typically these plaques are irregularly distributed around the wall.[48]

Peribronchiolar fibrosis is seen in rheumatoid arthritis, typically in small airways and external to muscle.[49]

After lung transplantation, the line of tracheal or large bronchial suture is prone to dehiscence.[50] These airways move and slide within the surrounding tissues, and their connections to neighboring structures are flimsy. With a single arterial supply and so much avascular cartilage in their walls, the bronchi are at special risk of necrosis.[51] The complication is much less frequent now that surgical technique includes drawing up omentum from the peritoneal cavity and wrapping it around the suture line (see Chap. 71).

In the alveoli, the problem is similar to the airway in that the depth of the surface injury or erosion is critical.[52] Bacterial or viral pneumonia, chemical inhalation, or the secondary lung injury of adult respiratory distress syndrome after systemic sepsis and endotoxemia are examples of alveolar injury. Inflammation can be confined to the alveolar wall, so that the saga of inflammatory cell infiltration, mediator release, fluid exudation, and resolution by fibrosis effectively runs its course within the alveolar wall (Fig. 2-7; see Chaps. 14 and 15).

If the epithelial barrier is breached, alveolar consolidation is produced by cells and high-protein fluid, which must be lysed and resorbed. In pneumococcal pneumonia, this occurs with resolution; in other types of injury, this is not always the case. With severe epithelial injury, granulation tissue invades the alveolar exudate. The balance of epithelial survival and fibrotic aggression are probably critical to the ultimate outcome, but their interaction is incompletely understood.

Sometimes healing is by fibrosis effacing the lungs' architecture and sometimes by reorganization with granulation tissue drawing back to leave a space within the alveolus (see Fig. 2-7); as it does so, it forms the bouton of Masson, which is a knot of granulation tissue covered by epithelium. In the ultimate outcome, another balance is important: that between the capillaries of the granulation tissue, which would be expected to be absorbed, and those of the original tissue, which unfortunately disappear as part of the original injury or the general closing down of the capillary bed during healing. Although the alveolar space may be reformed, the capillary bed is usually less dense after injury.

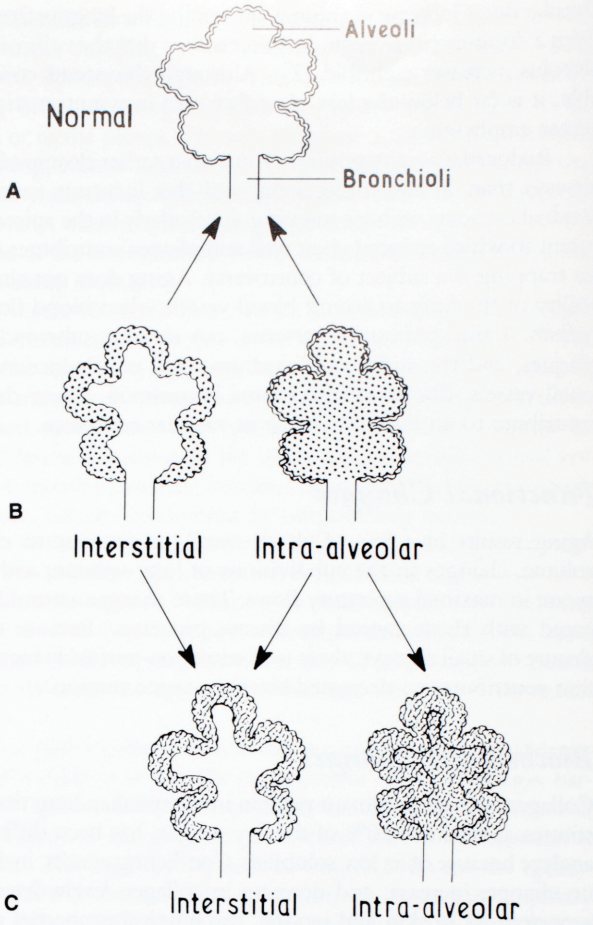

FIGURE 2-7. The evolution of interstitial and intralobular injury. (**A**) Resolution with return to normalcy has occurred. (**B**) An exudate of inflammatory cells and fluid (*dotted areas*) is usually present in both the alveolar wall or space, but the alveolar architecture is intact. (**C**) The injury has progressed to fibrosis. (From Reid LM. The pathology of pulmonary inflammation. In: Bray MA, Anderson WH, eds. Lung biology in health and disease. New York: Marcel Dekker, 1991:1.)

Restoration and Obliteration of Alveolar Architecture

The mixture of restoration and obliteration of alveolar architecture is the basis for the honeycomb lung (Fig. 2-8). Even within the smallest unit of lung, the acinus, the fate of the alveoli varies, producing a mixture of scarring and patent alveoli. Scar retracts, and the alveoli it includes condense into a smaller volume, probably leaving adjacent alveoli with damaged walls to overexpand into the new volume. The small airways are affected in a similar way, and the cystic spaces in a honeycomb lung can represent a bronchiolus or an alveolus (see Fig. 2-8; see Chap. 31).

A similar focal pattern that occurs during injury to the growing lung (*e.g.*, bronchopulmonary dysplasia) has implications for subsequent growth, and the outcome depends on the relatively normal parts of the lung.[53] It is unlikely that alveolar multiplication compensates for the loss of tissue, and the more normal regions of lung are often ultimately emphysematous (see Chap. 11).

The restoration of alveolar epithelium is paradoxic. The once accepted generalization was that during growth it is the simple

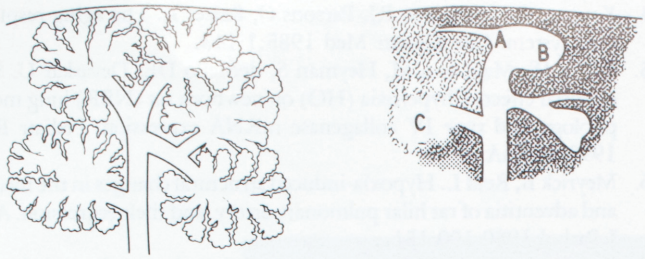

FIGURE 2-8. The pathogenesis of the honeycomb lung consists of a patchy distribution of obliterative and interstitial fibrosis with overdistention of the intervening regions. (A, obliterated bronchiolus; B, bronchiolar cyst; C, alveolar cyst; from Reid LM. The pathology of pulmonary inflammation. In: Bray MA, Anderson WH, eds. Lung biology in health and disease. New York: Marcel Dekker, 1991:1.)

cells that multiply and later differentiate. After a continuous alveolar epithelial layer was identified by electron microscopy, it was the type I pneumocyte that looked like the undifferentiated cell.[54] It looks like a fried egg sunny side up, with the nucleus as the yolk and the egg white as the long flat expanse of cell cytoplasm, uninteresting in its sparse endowment with organelles. The chunky type II cell in its alveolar corner with differentiated and elegant organelles was thought to be the more advanced cell, implying that the type I cell was the simple progenitor of the type II. This is not so. The stages of injury and healing produce an army of type II cells that line the injured alveoli. Recovery represents differentiation of the type II to the type I cell. The type I pneumocyte certainly deserves a fan club as inspired and devoted as that for the type II (see Chap. 1).

There is a type III pneumocyte in the alveolar epithelium, which is little studied in normal tissue and almost not at all in disease.[55] It resembles a brush cell of the gut, and although it constitutes only a few percent of the cells of the alveolar lining, it is tantalizing because its function is not known.

Bronchiolitis obliterans organizing pneumonia represents an inflammation of peripheral air spaces, including small airways and alveoli, at the stage of consolidation.[56] It seems to justify a separate name because of its favorable outcome. Presumably, the consolidation is associated with an intact alveolar structure. After obliteration of alveolar architecture by scar occurs, it is too late for anatomic resolution. The pathologist can only say what is seen on one biopsy section, discuss the likely outcome, and include a caveat if the sample is not representative (see Chap. 33).

REFERENCES

1. Hislop A, Reid L. Growth and development of the respiratory system—anatomical development. In: Davis JA, Dobbing J, eds. Scientific foundations of pediatrics. London: William Heinemann Medical Books, 1974:214.
2. Bucher UG, Reid L. Development of the intrasegmental bronchial tree: the pattern of branching and development of cartilage at various stages of intrauterine life. Thorax 1961;16:207.
3. Hislop A, Reid L. Development of the acinus in the human lung. Thorax 1974;29:90.
4. Boyden EA. The mode of origin of pulmonary acini and respiratory bronchioles in the fetal lung. Am J Anat 1974;141:317.
5. Davies GM, Reid L. Growth of the alveoli and pulmonary arteries in childhood. Thorax 1970;25:669.
6. Emery JL, Mithal A. The number of alveoli in the terminal respiratory unit of man during late intrauterine life and childhood. Arch Dis Child 1960;35:544.
7. Hislop A, Reid L. Intrapulmonary arterial development during fetal life—branching pattern and structure. Am J Anat 1972;113:35.
8. Elliott FM, Reid L. Some new facts about the pulmonary artery and its branching pattern. Clin Radiol 1965;16:193.
9. Hislop A, Reid L. Pulmonary arterial development during childhood—branching pattern and structure. Thorax 1973;28A:129.
10. deMello DE, Reid LM. Arteries and veins. In: Crystal RG, West JB, Barnes PJ, Cherniak NS, Weibel ER, eds. The lung: scientific foundations. New York: Raven Press, 1991:767.
11. Miller WS. The lung. 2nd ed. Springfield, IL: Charles C Thomas, 1947:89.
12. Nagaishi C. Functional anatomy and histology of the lung. Baltimore: University Park Press, 1972:148.
13. Drake RE, Lauie GA, Allen SJ, Katz J, Gabel J. A model of the lung interstitial-lymphatic system. Microvasc Res 1987;34:96.
14. Casey-Smith JR. Are the initial lymphatics normally pulled open by the anchoring filaments? Lymphology 1980;13:120.
15. deMello DE, Gashi-Luci L, Hu LM, Davies P, Reid LM. Effect of hypoxia on post-natal vascular adaptation in the newborn rabbit. FASEB J 1988;2:A1181.
16. Boyden EA. The developing bronchial arteries in a fetus of the 12th week. Am J Anat 1970;129:357.
17. Kitterman JA. Fetal lung development. J Dev Physiol 1984;6:67.
18. Kitterman JA, Ballard PL, Clements JA, Mescher EJ, Tooley WH. Tracheal fluid in fetal lambs: spontaneous decrease prior to birth. J Appl Physiol 1979;47:985.
19. Bland RD, Nielson DW. Developmental changes in lung epithelial transport and liquid movement. Ann Rev Physiol 1992;54:373.
20. Strang LB. Fetal lung liquid: secretion and reabsorption. Physiol Rev 1991;71:991.
21. Meyrick B, Reid L. Pulmonary arterial and alveolar development in normal postnatal rat lung. Am Rev Respir Dis 1982;125:468.
22. Haworth SG, Sauer U, Buhlmeyer K, Reid L. Development of the pulmonary circulation in ventricular septal defect: a quantitative structural study. Am J Cardiol 1977;40:781.
23. Davies P, McBride J, Murray GF, Wilcox BR, Shallal JA, Reid LR. Structural changes in the canine lung and pulmonary arteries after pneumonectomy. J Appl Physiol Respir Environ Exercise Physiol 1982;53:859.
24. McBride JT, Kirchner KK, Epstein V. Influence of lung distension on lung cell proliferation after unilateral pneumonectomy. Am Rev Respir Dis 1992;145A:A122.
25. Alescio T. Effect of a proline analogue, azetidine-2-carboxylic acid on the morphogenesis *in vitro* of mouse embryonic lung. J Embryol Exp Morphol 1973;29:439.
26. Chen J-M, Little CD. Cellular events associated with lung branching morphogenesis including the deposition of collagen type IV. Dev Biol 1987;120:311.
27. Kratochwil K, Dziadek M, Lohler J, Harbers K, Jaenisch R. Normal epithelial branching morphogenesis in the absence of collagen I. Dev Biol 1986;117:596.
28. Spindel ER, Sunday ME, Hofler H, Wolfe JF, Habener JF, Chin WW. Transient elevation of mRNAs encoding gastrin releasing peptide (GRP), a putative pulmonary growth factor, in human fetal lung. J Clin Invest 1987;80:1172.
29. Noden DM. Embryonic origins and assemblying of blood vessels. Am Rev Respir Dis 1989;140:1097.
30. Noguchi A, Samaha H, deMello DE. Tropoelastin gene expression in the rat pulmonary vasculature: a developmental study. Pediatr Res 1992;31:280.
31. Bernfield M, Bannerjee SD, Koda JE, Rapraeger AC. Remodeling of

the basement membrane as a mechanism of morphogenetic tissue interaction. In: Trelstad RL, ed. The role of extracellular matrix in development. New York: Allen R Liss, 1984:545.
32. Brody JS, Kaplan NB. Proliferation of alveolar interstitial cells during post-natal lung growth. Evidence for two distinct populations of pulmonary fibroblasts. Am Rev Respir Dis 1983;127:763.
33. Vaccaro C, Brody JS. Ultrastructure of developing alveoli. 1. Role of the interstitial fibroblast. Anat Rec 1979;192:467.
34. Noguchi A, Samaha H. Developmental changes in tropoelastin gene expression in the rat lung studied by in situ hybridization. Am J Respir Cell Mol Biol 1991;5:571.
35. Weibel ER. Morphological basis of alveolar capillary gas exchange. Physic Rev 1973;53:419.
36. Dimaio M, Gil J, Ciurea D, Katten M. Structural maturation of the human fetal lung: a morphometric study of the development of air-blood barriers. Pediatr Res 1989;26:88.
37. Campiche MA, Gautier A, Hernandez EI, Reymond A. An electron microscopic study of the fetal development of human lung. Pediatrics 1963;32:976.
38. Meyrick B, Reid L. The blood/gas barrier including its ultrastructure. In: Hatzfeld C, ed. Distribution of pulmonary gas exchange. Les colloques de INSERM/SEPCR, Sept 1975. Paris: INSERM, 1976: 145.
39. Janney CG, Askin FB, Kuhn C. Congenital alveolar capillary dysplasia—an unusual cause of respiratory distress in the newborn. Am J Clin Pathol 1981;76:722.
40. Cater G, Thibeault DW, Beatty EC, Kilbride HW, Huntrakoon M. Misalignment of lung vessels and alveolar capillary dysplasia: a cause of persistent pulmonary hypertension. J Pediatr 1989;114:293.
41. Wagenvoort CA. Misalignment of lung vessels: a syndrome causing persistent neonatal pulmonary hypertension. Human Pathol 1986; 17:727.
42. Sosenko IRS, Frantz ID III, Roberts RJ, Meyrick B. Morphologic disturbance of lung maturation in fetuses of alloxan diabetic rabbits. Am Rev Respir Dis 1980;122:687.
43. Van Golde LMG, Batenburg JJ, Robertson B. The pulmonary surfactant system: biochemical aspects and functional significance. Physiol Rev 1988;68:374.
44. Krumpe PE, Knudson RJ, Parsons G, Reiser K. The aging respiratory system. Clin Geriatr Med 1985;1:143.
45. Taylor W, Malicdem M, Heyman S, deMello DE, Devaskar U. Sequential effect of hyperoxia (HO) on newborn rat (NBR) lung morphology and type IV collagenase mRNA expression. Pediatr Res 1992;31:54A.
46. Meyrick B, Reid L. Hypoxia-induced structural changes in the media and adventitia of rat hilar pulmonary artery, and their regression. Am J Pathol 1980;100:151.
47. Yousem SA, Burke CM, Billingham ME. Pathologic pulmonary alterations in long-term human heart-lung transplantation. Human Pathol 1985;16:911.
48. Marchevsky A, Hartman G, Walts A, Ross D, Koerner S, Waters P. Lung transplantation: the pathologic diagnosis of pulmonary complications. Mod Pathol 1991;4:133.
49. Geddes DM, Corrin B, Brewerton DA, Davies RJ, Turner-Warrick M. Progressive airway obliteration in adults and its association with rheumatic disease. Q J Med 1977;46:427.
50. Veith F, Sinha S, Blumcke S, et al. Nature and evolution of lung allograft rejection with and without immunosuppression. J Thorac Cardiovasc Surg 1972;63:509.
51. Yousem SA, Dauber JH, Griffith BP. Bronchial cartilage alterations in lung transplantation. Chest 1990;98:1121.
52. Reid LM. The pathology of pulmonary inflammation. In: Bray MA, Anderson WH, eds. Lung biology in health and disease. New York: Marcel Dekker, 1991:1.
53. Tomashefski J, Vawter G, Reid L. Pathologic observations on infants who do not survive the respiratory distress syndrome. In: Nelson GH, Lenfant C, eds. Pulmonary development transition from intrauterine to extrauterine life. Lung biology in health and disease. vol. 27. New York: Marcel Dekker, 1985:387.
54. Brody JS, Williams MC. Pulmonary alveolar epithelial cell differentiation. Annu Rev Physiol 1992;54:351.
55. Meyrick B, Reid L. The alveolar brush cell in rat lung—a third pneumocyte. J Ultrastruct Res 1968;23:71.
56. Epler GR, Colby TV, McLoud TC, Carrington CB, Gaensler EA. Bronchiolitis obliterans organizing pneumonia. N Engl J Med 1985; 312:152.