PEDIATRIC PULMONARY DISEASE

Edited by

J. Thomas Stocker

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Dedicated to my wife, Patricia, and my children, Rick, David, and Meg, whose love and encouragement make all the efforts worthwhile.

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Preface

This volume, the second in the Aspen Seminars on Pediatric Disease series, was derived in part from a seminar presented at the Society for Pediatric Pathology meeting in Chicago in March 1987. The faculty members at this symposium, Drs. C. Langston, J. T. Stocker, F. B. Askin, V. V. Joshi, L. P. Dehner, and C. A. Wagenvoort, have each contributed a chapter to this text, and by invitation, Drs. E. F. Gilbert and J. M. Opitz have graciously prepared a chapter entitled "Malformations and Genetic Disorders of the Respiratory Tract."

Pulmonary disease, in its varied manifestations, accounts for many of the illnesses in infants and children. This book describes the clinical and pathological features of congenital pulmonary malformations and many of the acquired pulmonary diseases in the pediatric patient. An appreciation of the problems encountered in the neonate, particularly the premature infant, requires an understanding of the structure of the lung and its various stages of development. Langston describes the morphogenesis of the lung along with one of its major abnormalities, pulmonary hypoplasia, emphasizing the multiple methods available to determine the degree of hypoplasia.

Gilbert and Opitz enumerate the wide range of congenital malformations of the respiratory tract, including those of the nasopharynx, larynx, trachea, lung, chest wall, and diaphragm. Special attention is given to the genetic aspects of many of the malformations.

Bronchopulmonary dysplasia, a disease seen in immature infants and produced by barotrauma, high oxygen tensions, inflammation, pulmonary edema, and nutritional deficiencies is described, along with its sequel, long-standing "healed" bronchopulmonary dysplasia. Askin presents the pathological features of interstitial pulmonary emphysema, another complication of mechanical ventilation.

Lesions of pulmonary veins and lymphatics, frequently overlooked by the pathologist, are described by Wagenvoort. Joshi and coauthors present the most detailed description to date of the unique pulmonary features of acquired immunodeficiency

syndrome in children. These primarily lymphoid lesions are divided into three types: pulmonary lymphoid hyperplasia; lymphoid interstitial pneumonitis; and pulmonary polyclonal, polymorphic, B-cell, lymphoproliferative disorders.

Dehner reviews the clinical and pathological features of tumors and tumor-like lesions of the lung and chest wall, defining the broad spectrum of neoplasms in children.

The Aspen Seminars on Pediatric Disease are sponsored by the Institute for Pediatric Medical Education, a Colorado-based nonprofit organization founded in 1981 to encourage a multidisciplinary approach to the study of diseases in children. The Institute presents the Aspen Conferences on Pediatric Disease, initiated in 1979 and held at the Gant in Aspen, Colorado, each summer with topics including pediatric liver and renal disease, pediatric gastroenterology, surgical pathology of pediatric tumors, and bronchopulmonary dysplasia, the subject of the first volume of the Aspen Seminars on Pediatric Disease. The conferences bring together participants for an in-depth discussion on the clinical and pathological features of a disease process and an examination of the current status of research in that area. Participants usually include basic laboratory scientists, practicing subspecialists, specialists, and other interested medical personnel.

I thank the faculty of the 1987 Society for Pediatric Pathology seminar and the authors of the chapters for their expertise and diligent efforts in the preparation of this text. My thanks also to my colleagues at the Armed Forces Institute of Pathology, especially Drs. Robert F. Karnei, Vernon Armbrustmacher, and Florabel G. Mullick, whose understanding and support contribute to the continuation of this series. Special thanks to Mrs. Connie H. Hickerson for her incomparable secretarial and organizational skills and her enthusiastic personality. I would also like to acknowledge the continuous support of my family in organizing and running the Aspen Conferences. My wife, Patricia, and children, Rick, Dave, and Meg have been of invaluable help over the 10 years the seminars have been held.

J. Thomas Stocker

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Chapter One

Prenatal Lung Growth and Pulmonary Hypoplasia

Claire Langston

Structural development of the lung is of at least equal importance as functional development for viability as an independent organism. Not only must the surfactant system of the alveolar lining mature to permit alveolar stability with air breathing, but the alveolar wall and vascular supply must develop adequately to provide enough sites for gas exchange, and the neuromuscular system must develop to permit control of respiratory function.

MORPHOLOGIC DEVELOPMENT

Lung development throughout gestation is divided into five phases, each marked by a major structural landmark (Table 1). In the first stage, the embryonic period, the proximal airways are formed. Initially the laryngotracheal groove forms as an outpouching of the foregut at about the fourth week of gestation, and a single lung bud forms at its caudal end.[1] This single bud divides to form the two main bronchial buds. These further divide during the fifth week to form the lobar bronchi, and the lung buds begin to grow laterally into the walls of the pericardioperitoneal canal. Segmental bronchi form during the sixth week, establishing the bronchopulmonary segments. At the same time as the major proximal airways are formed, the basic pattern of the pulmonary vasculature is established.[2] The sixth bronchial arches appear at 32 days.

Table 1 Normal Human Lung Growth

Phase	Timing	Major development
Embryonic	4–6 weeks' gestation	Proximal airways
Pseudoglandular	7–16 weeks' gestation	Conducting airways
Canalicular	17–27 weeks' gestation	Acinus
Saccular	28–35 weeks' gestation	Gas-exchanging sites
Alveolar	36 weeks' gestation to 2 years	Surface area

They form connections with a preformed vascular plexus around the proximal airways in the developing lung buds. While this plexus initially connects to systemic veins, it soon joins the developing pulmonary veins, which become connected to the left atrium, establishing the pulmonary circulation.

Branching morphogenesis of the bronchial system is more extensive in the pseudoglandular period. This stage from weeks 7 through 16 is marked by the formation of all conducting airways.[3] Airway development during this period is by a process of terminal branching from the growing bronchial buds. Pulmonary arterial development follows bronchial development very closely and is complete in its main outlines shortly after the completion of bronchial branching. The major pulmonary arteries branch with the bronchial system and follow its course. The arteries along this bronchial pathway are termed "conventional" arteries. There are additional arteries, termed "supernumerary" arteries, which arise as side branches of conventional arteries and directly enter the developing tissues, bypassing the bronchial pathway.[4] During this period the developing lung has a glandular appearance with the epithelial lined tubules of the conducting airways disposed in abundant poorly vascularized mesenchyma (Fig. 1). The respiratory epithelium begins its differentiation as goblet cells, basal cells, and ciliated and nonciliated cells appear from the primitive simple columnar epithelium. The cartilage associated with airways also appears. These changes all begin proximally in the airways and spread distally.

While the next period is known as the canalicular period, it is the time of acinar development. Prior to this period, the airways have been the focus of development. Now with their formation complete, the acinus, the site of gas exchange, begins its development. From this time on, developmental events are focused on the gas-exchanging portions of the lung. In the canalicular period, the basic structure of the acinus appears, and small blood vessels canalize the acinar mesenchyma. The mesenchyma of the acinar rim is altered, and the outlines of individual pulmonary lobules appear. Early in the canalicular period, the internal configuration of the developing potential air spaces is simple. Formed by terminal budding and branching, they first appear as smooth-walled, blind-ending channels (Fig. 2). These channels are lined by uniform cuboidal epithelium and are separated by a thick but sparsely cellular interstitium in which there are scattered capillaries. As the developing air spaces elongate and divide, their internal configuration becomes less smooth and more undulant, and their simple cuboidal epithelium begins to differentiate (Fig. 3). At about 20 weeks the lamellar and multivesicular bodies associated with surfactant synthesis first appear in these cells which take on the ultrastructural characteristics of type II alveolar epithelial cells.[5] Type I cells develop from type II cells by mitotic division and cytoplasmic

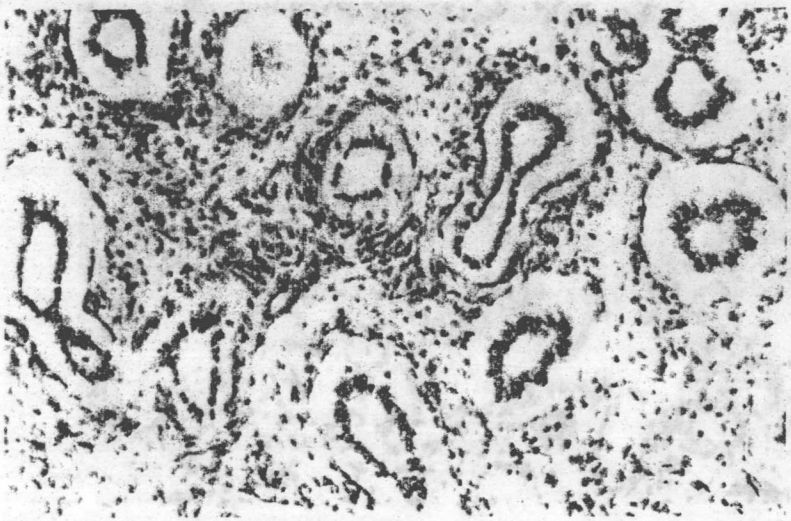

Figure 1 Lung at 14 weeks' gestation, pseudoglandular period. H&E ×160.

flattening.[6] This process, too, begins proximally in the acinus and spreads distally. Supernumerary arteries form as the acinus appears. Capillaries become more numerous in the interstitium and are aligned to the epithelial surfaces of the potential air spaces. This alignment, together with the epithelial thinning inherent in type I cell differentiation, results in the formation of narrow air-blood barriers. Late in this period there are sufficient numbers of these for independent extrauterine existence to become a possibility.

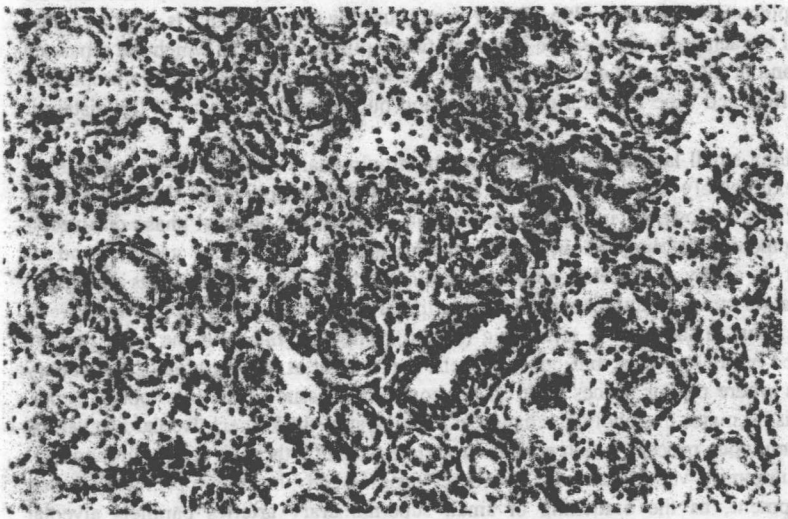

Figure 2 Lung at 18 weeks' gestation, early canalicular period. H&E ×160.

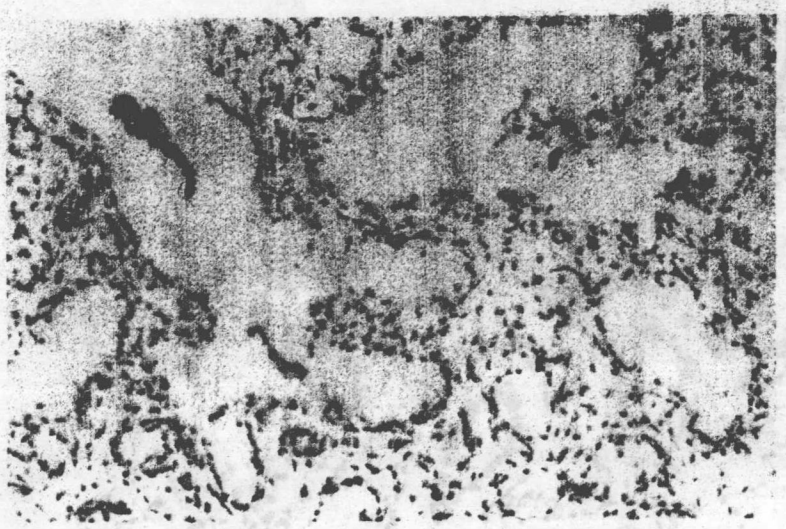

Figure 3 Lung at 24 weeks' gestation, late canalicular period. H&E ×160.

The next period, the saccular, begins at about 28 weeks' gestation and is marked by an abrupt change in the appearance of the lung. The mesenchymal tissue present between the developing air spaces becomes much less prominent, and air space walls become narrower and more compact (Fig. 4). This alteration decreases the distance between the capillaries and the potential gas-exchanging surface. In addition, lateral projections called secondary crests arise from the air space walls and begin to subdivide the primitive air spaces or saccules into smaller units. The saccular walls and the developing crests have a double capillary configuration (Fig. 5)—that is, capillaries are aligned to each epithelial surface and form two capillary networks which are separated by a band of interstitial tissue. Cuboidal epithelial cells decrease in relative proportion to the flattened type I cells during this period but remain prominent in the distal air spaces.

Many small laboratory animals, in which pulmonary developmental events have been extensively studied, are born during this period and only develop alveoli postnatally.[7,8] However, in the human there is an extensive prenatal phase of alveolar development. Alveoli appear in some fetal lungs as early as 32 weeks' gestation and are present in all by 36 weeks' gestation.[9] Alveoli can be characterized as polygonal terminal air space structures with a single capillary network in their thin walls. Alveoli are plentiful in the normal term lung (Fig. 6). They are lined for the most part by flattened epithelial cells, but cuboidal cells are evident at the margins of pulmonary lobules where the air spaces abut on the connective tissue of the interlobular septa. There is no major morphologic change in the lung at birth. Rather, alveolar acquisition is a continuous process which extends from late gestation through early childhood.[9-11] The pulmonary vasculature, too, becomes progressively more complex with acinar development, as the branching of small supernumerary arteries parallels alveolar proliferation. The relatively thick main pulmonary trunk of the fetus has many elastic

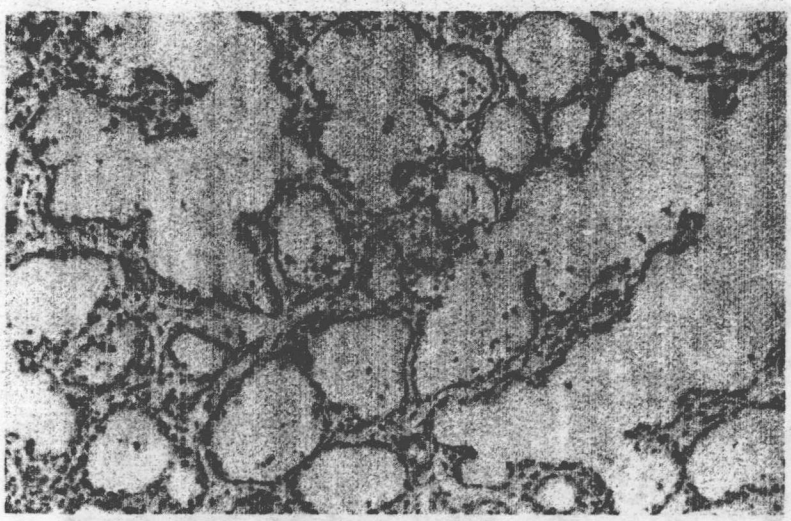

Figure 4 Lung at 28 weeks' gestation, early saccular period. H&E ×160.

lamina, much like the fetal aorta. Pulmonary arteries beyond this main trunk have decreasing numbers of elastic lamina until they reach a diameter of about 1000 μm. They then become muscular arteries with only internal and external elastic lamina. Along the "conventional" pathway, there is a gradual transition between artery types and a gradual change in diameter.[12] These changes are abrupt at the origin of the supernumerary arteries. As the lung grows after midgestation, the airways and their

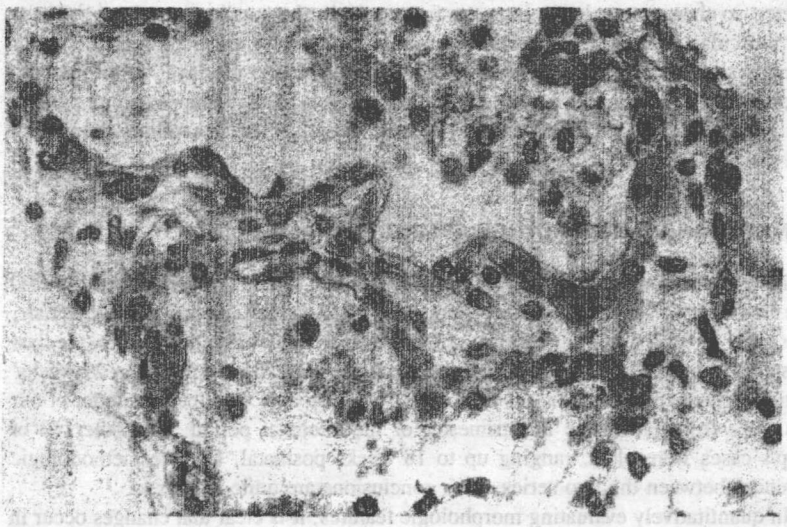

Figure 5 Double capillary saccular walls at 29 weeks' gestation. H&E ×500.

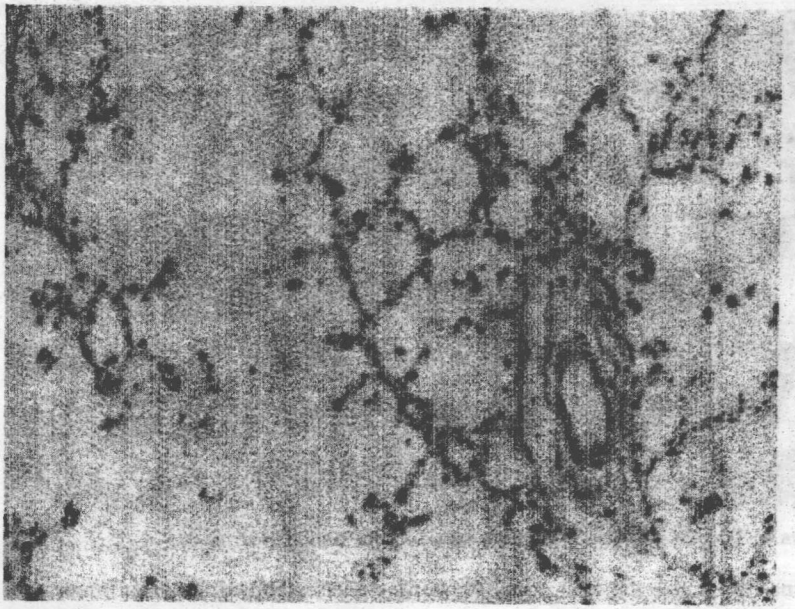

Figure 6 Lung at term with numerous alveoli. H&E ×160.

accompanying arteries grow in length, but it is the elastic vessels that lengthen more while the muscular artery segment remains nearly constant.[12] As the muscular arteries decrease in diameter to about 100 μm, the amount of muscle decreases less than the diameter, so there is a relative increase in muscle in the smallest arteries.[4,13] These small muscular arteries lie adjacent to terminal bronchioles and represent the major resistance sites within the pulmonary vasculature. The muscle layer is present peripherally as a discontinuous spiral muscle layer which finally disappears completely. The nonmuscularized arteries that follow connect directly with the capillary network of the alveoli.

QUANTITATION OF MORPHOLOGIC CHANGES

Morphometric examination of the normally developing human lung has been limited. There are only two series of any size—our series of 42 cases[10] and that of Hislop et al., comprising 29 cases.[14] The majority of cases examined have been from the last trimester of gestation. Of the 42 cases we examined, only 15 were less than 29 weeks' gestation. Nineteen of the 29 cases examined by Hislop et al. and the remainder of our series were from either the last trimester or the neonatal period. The other 10 of Hislop's cases were older, ranging up to 18 weeks postnatal. Despite methodologic differences between the two series, their conclusions are quite similar.

In quantitatively evaluating morphologic features, it is clear that changes occur in different parameters during different phases of lung development.[10] During the latter