PATHOLOGY OF THE LUNG

THIRD EDITION

VOLUME 1

SPENCER

PATHOLOGY OF THE LUNG

(Excluding Pulmonary Tuberculosis

Third Edition

IN TWO VOLUMES

H. SPENCER

M.D.(Lond.), Ph.D., F.R.C.S.Eng., F.R.C.P., F.R.C.Path.

Professor of Morbid Anatomy in the University of London at St. Thomas's Hospital Medical School and Honorary Consultant Pathologist to St. Thomas's Hospital, London

With a Foreword by

AVERILL A. LIEBOW, M.D.

Formerly Professor of Pathology, Yale University School of Medicine, and Emeritus Chairman and Professor of Pathology, University of California, San Diego, La Jolla, California

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Preface to the Third Edition

SINCE the publication of the second edition the growth in knowledge of the physiology, anatomy and the pathology of the lung has led to new concepts about several lung diseases. Several new diseases has been identified and others better understood. The greatly increased use of electron microscopy and the introduction of methods for the identification of trace amounts of hormone substances have provided a new insight into the inter-relationship and nature of such lung tumours as bronchial carcinoids and oat-cell lung cancer. Other disorders previously regarded as diseases *sui generis* such as desquamative interstitial pneumonia and alveolar lipoproteinosis are now more generally regarded as forms of lung reaction to a wide variety of injurious agents. The identification of new forms of pulmonary angeitides and the relationship of these diseases to each other, to immunological disturbances and to the development of lymphomas is one of the more fascinating problems of pulmonary pathology and one also of great biological interest. Also it has become more widely appreciated that some viruses may cause continuing damage to the lung while others may persist in a latent, inactive form but are stimulated to re-awakened activity following disturbances of cellular immunity.

Many additions and extensive alterations have been made throughout this edition to almost every chapter and in all sections references have been updated. Among the additions and major alterations are included accounts of the microanatomy of the lung, the Gram-negative bacterial pneumonias, the virus pneumonias, adiaspiromycosis, the respiratory distress syndrome of the new born and the related Wilson-Mikity syndrome, pulmonary venous thrombosis, the pathergic pulmonary angeitides, eosinophilic pneumonia and the related bronchocentric granulomatosis, shock lung and some of the lesser known and newly described pulmonary tumours. As in previous editions emphasis has been laid whenever possible on the aetiology and pathogenesis of the disease.

It is again the author's pleasure to gratefully acknowledge the unstinted and continuing help that he has received from so many pathologists and friends throughout the world who have provided material and illustrations as indicated in the legends. As previously a great debt of gratitude is owed to Mr. A. E. Clark for his help in preparing many of the new photomicrographs, to Miss J. Ring for her help in the preparation of the typescript, to my publishers the Pergamon Press for their unfailing courtesy and help and especially to my wife for her continued help and support without which this edition would not have been completed.

H. SPENCER

London

Foreword

AT FIRST glance the lungs may seem uncomplicated, but many wise men have gone astray in their labyrinths. When apparently "simplified" as in emphysema, they have remained refractory to analysis. Disease commonly results in a profound but variable revision of their architecture. Their tumors form a bewildering array and some exert profound metabolic effects unsuspected until recently. Blood comes to the lungs from both sides of the heart, in a proportion that may deviate considerably from the norm under particular conditions. The vessels reflect alterations in hemodynamics, and when themselves changed, they can profoundly affect the work of the heart. The pulmonary capillaries, lying as a filter astride the venous outflow of all other organs, must often suffer the consequences. With each breath, also, the innermost recesses of the respiratory tract are brought very much into contact with a sometimes hostile external environment. The lungs are thus vulnerable from all sides. That we are not more often disabled we owe to their marvellous capacity to recover from injury and to their large reserve.

A man's medical history and the traces of his habits and his trade are often inscribed upon the lungs—for him who can read. Not since the monumental contribution of Fischer in the Handbook of Henke-Lubarsch have the lungs been so thoroughly or so well read, and the reading so well recorded as in this volume. Recent years have witnessed the identification, and even the introduction, of many new agents of pulmonary disease. Many other conditions such as "eosinophilic granuloma", while still of unknown etiology, have been defined in anatomical terms. Cardiopulmonary disease in the broadest sense is now much better understood than it was twenty years ago. The intelligent use of the cardiac catheter in man and in many ingenious experiments in animals and the development of cardiac surgery have greatly broadened our comprehension of this subject. Although the current exponential increase in knowledge indicates how much there is yet to learn, the time is surely ripe for a sound and comprehensive statement of what is now known. Professor Spencer has supplied this need admirably, and with a fine sense of history. Only a rare concurrence of meticulous scholarship and discernment could have enabled the condensation of so much information into so little space. This work will long be of interest and value to all students of disease.

AVERILL A. LIEBOW

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Volume 1

CHAPTER 1

Embryology of the Lung

A KNOWLEDGE of the development of the lung and of its vascular supply and drainage is essential if the many congenital abnormalities occurring in the organ are to be understood.

Intrauterine Development

The respiratory anlage or laryngo-tracheal groove first appears as a median, ventral groove in the floor of the gut caudal to the pharyngeal pouches at about the 3·0 mm (20 somite stage), 24 days after ovulation. At this stage of growth the oesophagus and stomach have not yet differentiated and the laryngo-tracheal depression lies just proximal to the liver diverticulum.

As development proceeds the larynx and trachea grow as a ventral diverticulum in a caudal direction, separated from the foregut by a spur of entoderm and later by mesenchyme which grows between the two structures. The ingrowth of the mesenchyme, which surrounds the foregut, commences at the distal end of the tracheal bud and spreads cranially to where the two structures join at the distal part of the pharynx.

The caudal end of the trachea divides into two bronchial buds at about the 5·0 mm (4th week) stage and each of these proceeds to form the main (primary) bronchi. The further growth of the bronchi is asymmetric, the right being the larger as it grows caudally and dorsally, whilst the left assumes a more horizontal position. Each main bronchus and its branches end in flask-shaped swellings. The right bronchus first buds a ventral branch, which is soon followed by a lateral division situated more proximally, which is destined to become the eparterial bronchus.

By the 8–10 mm (32–35 days) stage, the buds of the lobar (secondary) bronchi have appeared, and each bud with its surrounding mesenchyme will later form a lobe of the lung. A further burst of rapid growth during the 9–11 mm (35–45 days) stage leads to the formation of the segmental and subsegmental bronchial buds (Boyden, 1955a). At this stage the developing lung buds have become well separated ventrally from the elongating oesophagus due to the ingrowth of investing mesenchyme. From this time onwards the lungs gradually grow and assume their adult form, but the main bronchi supplying the lower lobes remain the axial continuations of the original main bronchi. All the bronchi are branches of the primary bronchus up to the 50 mm (12 weeks) stage (Fig. 1.1). The further development of the segmental and subsegmental bronchi was described by Bucher and Reid (1961a) and the ensuing account is based largely on their observations. They found that the period of greatest growth in the subsegmental bronchi took place during the 50–120 mm (12th–16th weeks) stage when about 70 per cent of the full-term bronchial tree was formed. They counted the number of epithelialized branches arising in each of the eighteen segmental bronchi starting from the segmental bronchus and counting distally, but selected for detailed examination certain of the largest axial bronchi. Some of the bronchi selected for such examination were found initially to run outwards to the pleural surface whereupon they bent at right angles to continue their further course and branching, lying subjacent and parallel to the pleural surface. In the upper right and left anterior axillary segmental bronchi they found on average 17 and 18 branches respectively. In the medial bronchus supplying the right middle

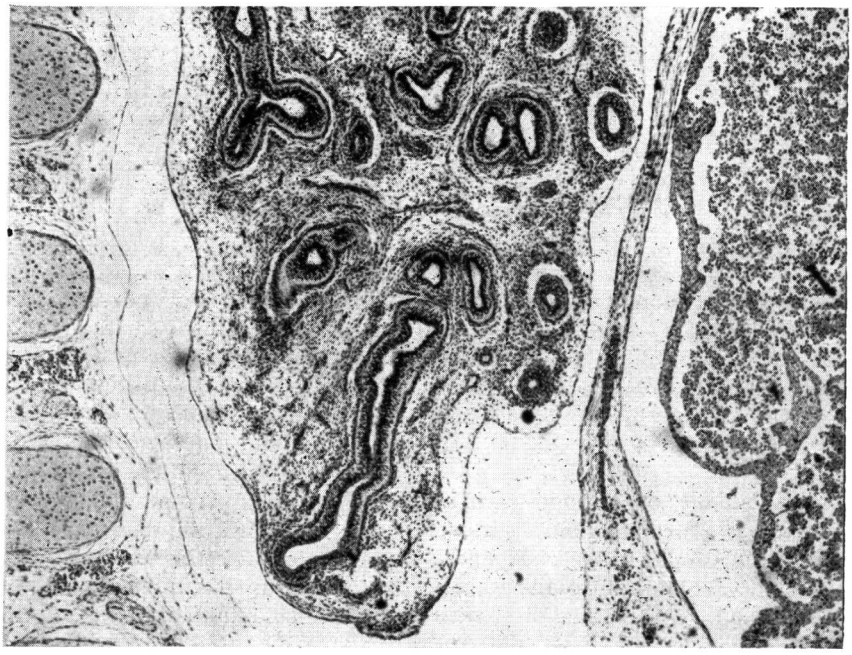

FIG. 1.1. Developing lung 20 mm stage showing bronchial tubes but as yet no attempt to form alveolar tissue. × 40.

lobe they found an average of 23 branches and in the left lingula bronchus 22 branches. In the anterior basal bronchi in both lower lobes there were on average 19 branches, and 21 along the posterior basal bronchi. The number of branches arising from the middle lobe bronchi was in close agreement with the figure quoted by Boyden and Tompsett (1962) in a full-term infant, thus proving that little further development of the bronchi occurs after the end of the 16th week of foetal life.

Boyden (1955a) had earlier found that up to about the 56 mm (12th week) stage, one to five more post-segmental branches were present on average along the axial bronchi in the right than the left lung, but after about the 70 mm (14th week) stage little difference in growth rate occurred. This finding was confirmed by Bucher and Reid (1961a). Although the burst of bronchial growth activity that occurs during the 40–120 mm (10–16 weeks) stage involves all segments of the lungs, the growth rate may not be uniform, and is normally greatest in the lower lobe basal segments as the general growth of both lungs proceeds more in a caudal than cephalic direction. This tendency to greater continued growth in the caudal parts of the lungs results in a greater number of branches along the segmental bronchi in the lower lobes in full term infants.

By 16 weeks the number of bronchial generations in the lower lobes may exceed the number found in the adult lung. This excess of distal air passages later becomes transformed into alveolated tissues.

Until the 150 mm (18th week) stage the lung consists only of branching bronchi surrounded by mesenchyme and it shows no differentiation into alveolar tissue before about the 180 mm (20 weeks) stage (Fig. 1.2).

After the 180 mm (20th week) stage the number of fully epithelialized segmental bronchial branches may appear to decrease as some of the most distal air passages begin to partly lose their light visible epithelium following capillary ingrowth and conversion of the tubes

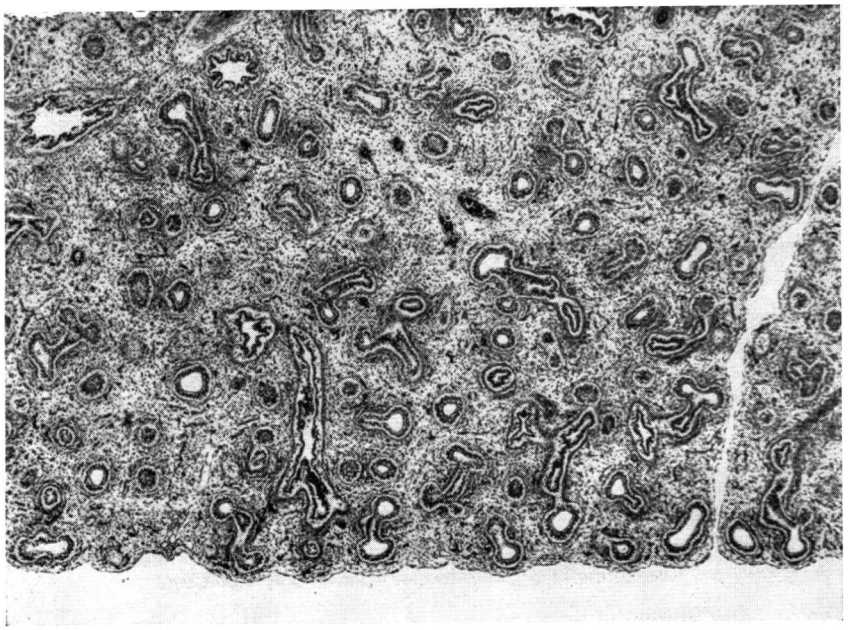

FIG. 1.2. A slightly later stage of pulmonary development 60 mm stage showing more extensive branching of the bronchial tubes but still no attempt to form alveoli. × 40.

into partly epithelialized, partly alveolated respiratory bronchioles. During the 180–300 mm (20–24th weeks) stage the most distal air passages end in clumps of cells which begin to cannulate to form alveoli (Fig. 1.3). After the 300 mm (24 weeks) stage the terminal bronchioles develop up to four generations of smooth non-alveolated bronchioles destined later to become respiratory bronchioles. Each generation of these future respiratory bronchioles gives rise to two or three branches. The most distal generation of respiratory bronchioles terminate in two clusters of very thin-walled saccules which are the precursors and immature forms of future alveoli (Boyden, 1972). The distal generations of respiratory bronchioles are themselves lined by flattened epithelium and were referred to by Boyden (1967) as transitional ducts. The alveolar saccules at the time of birth further subdivide into four lobules and immature shallow depressions appear in their walls which are very primitive alveoli. The knob-like clumps of cells forming the saccules resemble acini as they cannulate, and were referred to as pneumoneres by Farber and Wilson (1933). Although the saccules are very immature respiratory structures they suffice for adequate gas exchange in many prematurely born infants.

Coincident with the first appearance of the alveoli the lung septa begin to appear (Reid and Rubino, 1959). The septa are best developed beneath the sharp margins and apices of the lungs but do not isolate one portion of lung from another as they are only incomplete septa. As Boyden (1955b) and Reid (1954) showed, the pleural fissures between lobes are very variable and are often incomplete, often failing to extend to the hilum. Communication between lobes may therefore occur and may account for translobar spread of pneumonia in adult life. A distinct sheath forms around the larger bronchi and vessels central to the lobules.

The development of the lung saccules (acini) is accompanied by considerable vascular proliferation throughout the growing lung and the newly formed alveoli are invaded by capillaries.

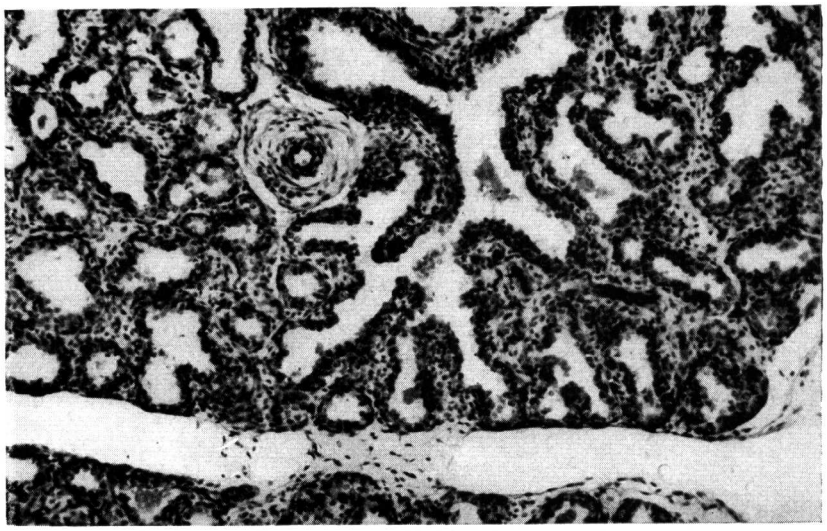

FIG. 1.3. Foetal lung of between 22–25 weeks of age. Note the development of rudimentary alveolar ducts and the beginning of alveolar development. × 100 H and E.

The developing alveolar epithelial lining attenuates and appears to be partly disrupted by the underlying capillaries (Fig. 1.4). This appearance led to the erroneous conclusion reached by Barnard and Day (1937) that there was no continuous alveolar epithelial lining. The further intrauterine development of the lung leads to further attenuation of the alveolar epithelium until at full-term only a few alveolar epithelial cell nuclei are still visible lying in spaces between the alveolar capillaries. After birth the respiratory movements lead to still further thinning of the cytoplasm of the alveolar epithelium which assumes its post-natal inconspicuous appearance. The existence of such alveolar epithelial cells in normal postnatal lung was finally proved by Low (1953) following the introduction of the electron microscope. The mode of growth of alveoli both *in utero* and after birth is uncertain. Loosli and Potter (1951) considered they grew as a result of septal division within existing saccules. Macklin (1936), however, regarded alveoli as being analogous to interstitial emphysematous spaces in which the lung mesenchyme split and allowed the capillaries to come into intimate contact with fluid and later air contained in the alveolar spaces.

In the adult lung the number of segmental bronchial branches along axial bronchi may again increase compared with the number found in the full-term infant. This has been attributed by both Engel (1947) and Bucher and Reid (1961a) to conversion once again of respiratory bronchioles into fully epithelialized terminal bronchioles during childhood. This process was observed by Willson (1928) to occur in mice and by Bremer (1935) in cats. Boyden (1965), as stated previously, however, believed the reverse process occurs, namely that terminal bronchioles are converted into respiratory bronchioles. The further course of post-natal lung growth is considered separately. The mode of bronchial division is still disputed, some regarding all growth as proceeding from the growing tip, others considering that lateral branching takes place proximal to the tip. According to Arey (1946), both methods occur. The failure of bronchial growth is responsible for the absence of lobes, segments or smaller volumes of lung in the future organ, and its cessation at an early stage can be responsible for the later development of congenital bronchiectasis.

The evolution of the asymmetric adult bronchial pattern has excited much interest, but

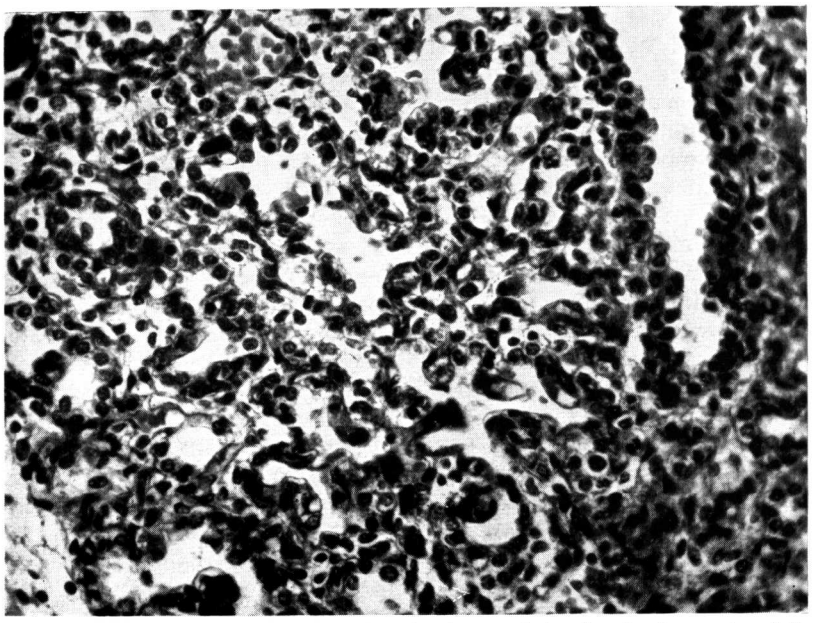

FIG. 1.4. Lung tissue from a 30-week-old foetus showing the degree of alveolar development and the still prominent alveolar epithelium. × 280 H and E.

is probably caused by the laevo-rotation of the heart, and the persistence of the left dorsal aorta and fourth left aortic arch to form the arch of the aorta. In aquatic mammals with a central heart, such as the cetacea and pinnipedia, the lungs exhibit a symmetrical pattern and in hippopotami both lungs possess eparterial bronchi. Aeby (1880) considered that the left eparterial bronchus had become suppressed in man, but according to the **migration theory,** first propounded by Willach (1888), the bronchi were originally arranged symmetrically but migrated from their primary sites of origin from main bronchi to become attached to branch bronchi. Huntington (1920) strongly refutes this latter view, adding "comparative anatomy if correctly interpreted absolutely negatives the migratory theory, and teaches that a branch budding from any point of the bronchial tree develops at the site of its first inception".

The **selection theory** of bronchial development maintains that the eventual size of the lung, and therefore the growth of the bronchi, is ultimately dependent on the amount of coelomic space available to accommodate it. The later cessation of branching along the axial segmental bronchi in the lower lobes, referred to above, is probably due to the fact that the lungs do not fill the available pleural (coelomic) space during the earlier weeks of foetal development, and growth may therefore continue in a caudal direction for a longer time in the lower lobes. This view is the one now most widely accepted.

It has usually been accepted that both the conducting bronchi (the lobar down to the terminal bronchioles) and respiratory components (respiratory bronchioles, alveolar ducts, air sacs and alveoli) were derived by repeated division of the original entodermal bronchial bud, but Waddell (1949), as a result of histochemical studies and transplantation experiments, has cast doubt on the classical view. He believes that whilst the conducting portion of the respiratory tree is of entodermal origin, the distal respiratory portion is formed from pulmonary mesenchyme which, as already stated above, condenses about the tips of the growing bronchi. He claims to have shown that