VOLUME TWO

Pathology

SIXTH EDITION

Edited by

W. A. D. Anderson

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M.A., M.D., F.A.C.P., F.C.A.P.

Professor of Pathology and Chairman of the Department of Pathology, University of Miami School of Medicine, Miami, Fla.; Director of the Pathology Laboratories, Jackson Memorial Hospital, Miami, Fla.

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Preface

TO SIXTH EDITION

In this new edition of *Pathology,* much of the content has been modified to include new knowledge and concepts in medical sciences. Significant progress in the fields of ultrastructure, cytology, genetics, immunopathology, and biochemistry has led to a merging of the medical sciences—among themselves and with biology. The borderland of pathology has always been both varying and ill-defined, but never more so than now. Thus, the choice of inclusion or exclusion of many subjects must be somewhat arbitrary, although based on subjective judgment aimed at correlating pathology with the total field of medical education and clinical practice.

The entire book has undergone revision. The chapters on inflammation and healing, drug and chemical injury, ophthalmic pathology, upper respiratory tract and ear, lower urinary tract, prostate, and male genitalia, hemopoietic system (reticuloendothelium, spleen, lymph nodes, blood, and bone marrow), thymus, pituitary gland, thyroid gland, parathyroid glands, adrenal glands, and nervous system and skeletal muscle have been completely rewritten. In addition, major changes have been made in the discussions of hypersensitivity diseases and immunopathology, mycotic infections, viral diseases, neoplasms, and diseases of kidney, lung, liver, and pancreas.

The basic nature of disease, and of medical practice, does not change. However, the extent and depth of our knowledge and understanding and of our conceptual and practical approaches are changing rapidly and no doubt will continue to do so. In the life of a student of medicine and a physician, the study of disease must be a continuing program. In these times of core curricula in medical schools, the continuing study and correlation of basic subjects with clinical experience is a necessity. It is hoped that these volumes will continue to be useful in the study of medicine, not only during but also after formal courses, and will assist in the practice of pathology or of other disciplines of medicine.

I am grateful for the patient and helpful cooperation of the contributors to this book and am deeply appreciative of the interest and assistance of my secretaries, Miss Edna Mae Everitt and Mrs. Louise Rhodes.

W. A. D. ANDERSON

Preface

TO FIRST EDITION

Pathology should form the basis of every physician's thinking about his patients. The study of the nature of disease, which constitutes pathology in the broad sense, has many facets. Any science or technique which contributes to our knowledge of the nature and constitution of disease belongs in the broad realm of pathology. Different aspects of a disease may be stressed by the geneticist, the cytologist, the biochemist, the clinical diagnostician, etc., and it is the difficult function of the pathologist to attempt to bring about a synthesis, and to present disease in as whole or as true an aspect as can be done with present knowledge. Pathologists often have been accused, and sometimes justly, of stressing the morphologic changes in disease to the neglect of functional effects. Nevertheless, pathologic anatomy and histology remain as an essential foundation of knowledge about disease, without which basis the concepts of many diseases are easily distorted.

In this volume is brought together the specialized knowledge of a number of pathologists in particular aspects or fields of pathology. A time-tested order of presentation is maintained, both because it has been found logical and effective in teaching medical students and because it facilitates study and reference by graduates. While presented in an order and form to serve as a textbook, yet it is intended also to have sufficient comprehensiveness and completeness to be useful to the practicing or graduate physician. It is hoped that this book will be both a foundation and a useful tool for those who deal with the problems of disease.

For obvious reasons, the nature and effects of radiation have been given unusual relative prominence. The changing order of things, with increase of rapid, world-wide travel and communication, necessitates increased attention to certain viral, protozoal, parasitic, and other conditions often dismissed as "tropical," to bring them nearer their true relative importance. Also, given more than usual attention are diseases of the skin, of the organs of special senses, of the nervous system, and of the skeletal system. These are fields which often have not been given sufficient consideration in accordance with their true relative importance among diseases.

The Editor is highly appreciative of the spirit of the various contributors to this book. They are busy people, who, at the sacrifice of other duties and of leisure, freely cooperated in its production, uncomplainingly tolerated delays and difficulties, and were understanding in their willingness to work together for the good of the book as a whole. Particular thanks are due the directors of the Army Institute of Pathology and the American Registry of Pathology, for making available many illustrations. Dr. G. L. Duff, Strathcona Professor of Pathology, McGill University, Dr. H. A. Edmondson, Department of Pathology of the University of Southern California School of Medicine, Dr. J. S. Hirschboeck, Dean, and Dr. Harry Beckman, Professor of Pharmacology, Marquette University School of Medicine, all generously gave advice and assistance with certain parts.

To the members of the Department of Pathology and Bacteriology at Marquette University, the Editor wishes to express gratitude, both for tolerance and for assistance. Especially valuable has been the help of Dr. R. S. Haukohl, Dr. J. F. Kuzma, Dr. S. B. Pessin, and Dr. H. Everett. A large burden was assumed by the Editor's secretaries, Miss Charlotte Skacel and Miss Ann Cassady. Miss Patricia Blakeslee also assisted at various stages and with the index. To all of these the Editor's thanks, and also to the many others who at some time assisted by helpful and kindly acts, or by words of encouragement or interest.

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Chapter 23

Lung, pleura, and mediastinum

Max Millard

Lung

PULMONARY STRUCTURE AND FUNCTION

The gross and microscopic morphology of the lung as shown by standard methods is altered, so that the true details of pulmonary structure are not always clear. The anatomy of pleurae and of pulmonary lobes and segments is left to specialized texts and the consideration here commences with the branching of the bronchi.[12]

Bronchial branching occurs dichotomously up to twenty-five times, starting from the main bronchus at the hilus of the lung and ending with the terminal bronchiole near the periphery. Between these two points, the airways function as afferent and efferent air-conditioning tubes and play no active role in respiratory exchange. The latter role belongs to the alveoli.

Walls of the *bronchi* consist of mucosa, glands, muscle, and fibrous tissue with cartilage. The mucosa is mainly lined by a pseudostratified ciliated columnar epithelium, with some intervening goblet cells and undifferentiated basal cells. From the latter, the other types are regenerated. The cilia beat rapidly against the undersurface of the covering mucus, moving it upward. The epithelium rests on a prominent continuous, thick, eosinophilic basement membrane, a feature easily seen in large bronchi, although still present in a much thinner form in the small ones. Beneath the mucosa are seromucinous glands, decreasing in number and becoming purely mucous as the bronchi branch. Glands disappear altogether at the level of the terminal bronchioles.

Bronchial muscle, surrounding the mucosa, is not circular but is in the form of a right and a left spiral of smooth muscle that extends up to the level of and into the alveolar ducts. This aids contraction and shortening, or dilatation and lengthening. A loose fibrous tissue sheath surrounds the muscle and allows the bronchial lengths and diameters to alter without affecting tensions in the neighboring alveoli. The hyaline cartilage plates extend, in diminishing size, into the small bronchi.

In large bronchi, the entire circumference is supported by cartilage, whereas in small bronchi, this support is only partial, so that chance section may include no cartilage. Hence, large bronchi have rigidity and can stay patent if there is massive collapse of the lung, in which condition small bronchi also will collapse.

Bronchioles, originally defined as those passages with a diameter of 1 mm or less, are now considered to be those airways distal to the last plate of cartilage and having no mucous glands and few goblet cells. Thus, the mucosa, lined by cuboidal epithelium with few or no cilia, is surrounded by smooth muscle and scanty fibrous tissue. It is important to realize how poor is their ability to drain themselves. There are no glands to secrete and wash away impurities and no cilia to move surface material, but only the few lymphatics and the macrophages of the alveoli and connective tissue.

Investigations of an unusual type of cell described by von Hayek[11] subsequently was recognized as being one of two types of nonciliated bronchiolar epithelial cells called Clara cells. Recognizable only by electron miscroscopy, it is possible that they may secrete surfactant.[5a, 8a, 13a, 17a]

At the end of the bronchiolar tree are the *terminal bronchioles,* the most peripheral bronchioles to have a complete epithelial lining. They come in a cluster of three or five from a final division, the preterminal bronchiole.

Terminal bronchioles give rise to *respiratory bronchioles* of similar caliber to their parent; the maintenance of the original diameter after branching serves to reduce the velocity of the air. Nevertheless, they differ in that a number of alveoli open directly into their muscular walls. In addition, some respiratory bronchioles follow a recurrent path, bringing them back and parallel to their parent terminal bronchiole, with which their alveoli communicate by a narrow channel (Fig. 23-1). This bronchiolar-alveolar anastomosis becomes an important bypass in the event of bronchiolar obstruction. Between the openings of the alveoli, the respiratory bronchiole still has cuboidal epithelium and smooth muscle, the latter surrounding the openings of the alveoli. A respiratory bronchiole will branch several times into further respiratory bronchioles.

The next division is into the *alveolar ducts.* These are elongated passageways that really do not have walls but only the framework of the continuous chain of alveoli opening from them. They therefore have no epithelial lining, but a ring of muscle surrounds the alveolar openings as in the respiratory bronchioles. The knobs of muscle are easily seen where the alveolar septa join the ducts.

Finally, from the alveolar ducts come about four air sacs or *atria*—structures in which muscle fibers end and the greatest number of *alveoli* are formed (Fig. 23-1).

The electron microscope has settled the controversy about *alveolar structure* (Fig. 23-2). It shows a continuous alveolar surface (septal) epithelium, providing a covering to the septal capillary network, only 0.2 μm* thick. This is the type I, or membranous pneumonocyte. It cannot be seen in ordinary sections, but occasional attenuated nuclei are visible (Fig. 23-30). These cells are extremely elastic to conform with respiration. Lying under the epithelium are the alveolar cells. Some drop off to be alveolar macrophages and are replaced by differentiation of alveolar septal fibroblasts.[6] Others, with large nucleus and granular cytoplasm, are thought to secrete pulmonary surfactant (dipalmitoyl lecithin).[9] These are the type II, or granular, pneumonocytes. Hardly recognizable under the light microscope, they are cuboidal with, as seen under the electron microscope, characteristic osmophilic lamellated bodies (Fig. 23-2) which, although associated with surfactant, have not been proved to produce it. In fact, some argue that these cells are phagocytic and that the bronchiolar Clara cells are the source of surfactant.[8a] A filmy surface layer of surfactant lipoprotein covers the alveoli. It helps the elastic recoil of the lung after expansion, and it maintains the alveoli open in expiration. Surfactant is needed throughout life and constantly needs to be replaced (it lasts about three days).[8] Morgan reviews the role played by loss of surfactant in many diseases, drowning, and surgery on the lung.[13a]

The alveolar epithelium has its own basement membrane, continuous with that of the bronchioles, separated from that of the capillaries by an important tissue space containing reticulin and elastic fibers. A thickness of 0.5 μm to 2.5 μm has to be traversed by the respiratory gases.

Preparations of the alveolar septal capillary network indicate that the vessels branch so much that they almost touch each other. An

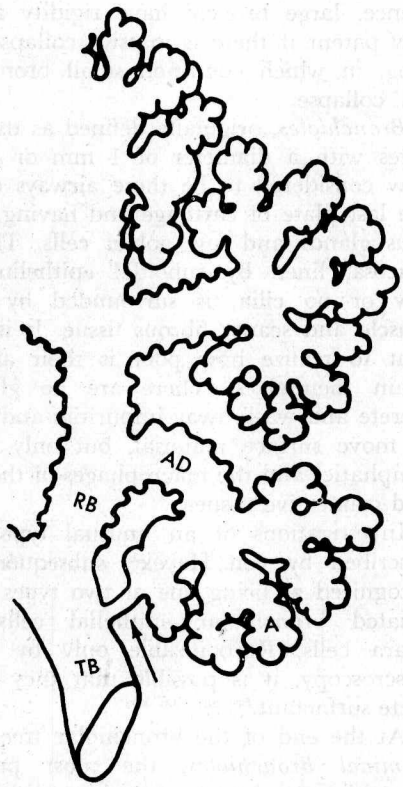

Fig. 23-1 Terminal branches of respiratory tree. **TB,** Terminal bronchiole. **RB,** First-order respiratory bronchiole. **AD,** Alveolar duct. **A,** Atrium with alveoli. Arrow points to bronchiolar-alveolar anastomosis.

*In this chapter, the new nomenclature for a unit of length, micrometer (μm), is used instead of the micron (μ).

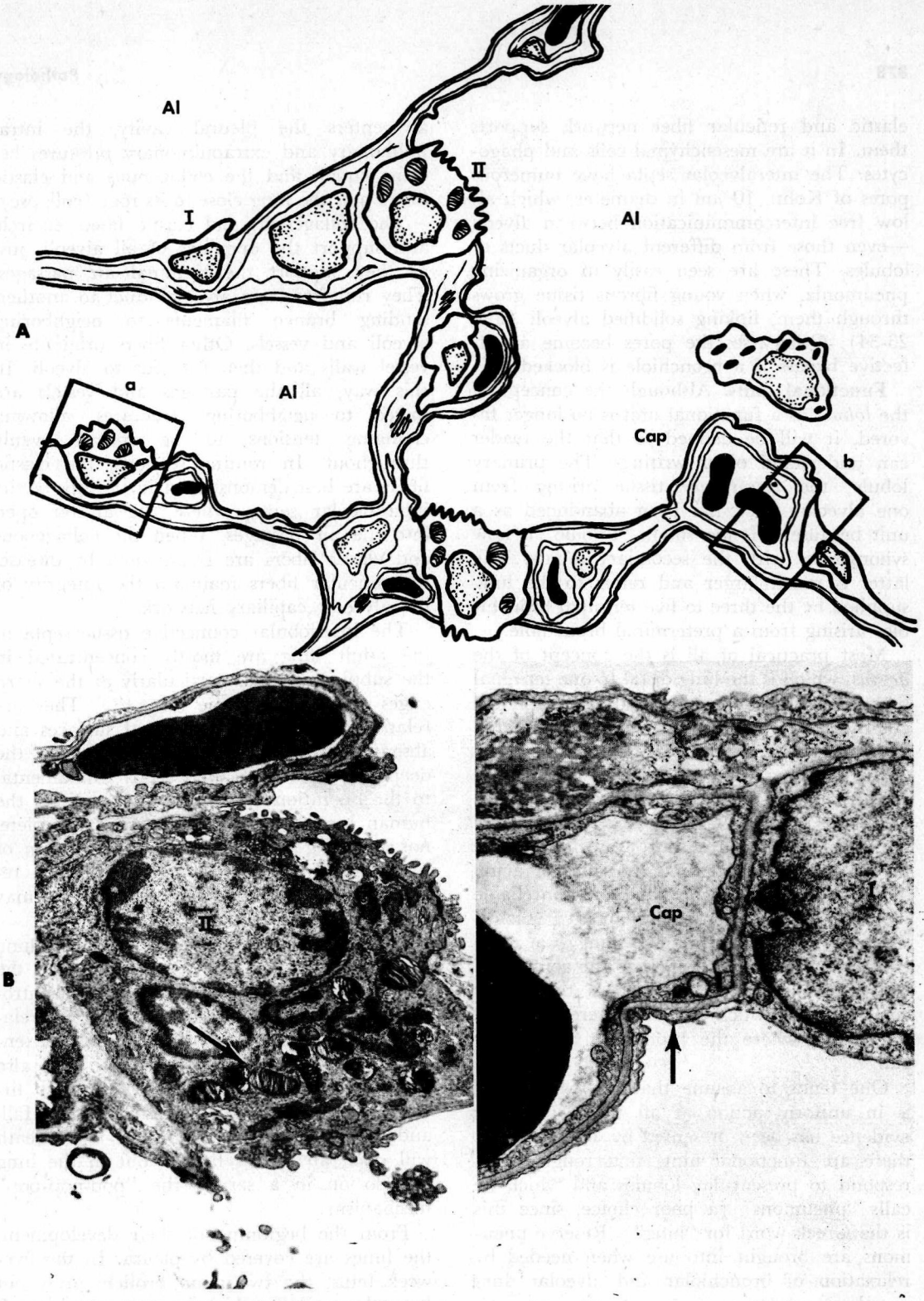

Fig. 23-2 **A,** Normal alveolar wall with type I and type II pneumonocytes. Wall includes capillaries **(Cap),** fibroblasts, collagen, and elastin. Macrophage may be seen free in alveolar space, **Al,** to right. **B,** Type II pneumonocyte as seen at **a** in **A.** Cell has few irregular processes on its free alveolar edge and lamellated bodies (arrow) in its cytoplasm. **C,** Blood-gas barrier, as seen at **b** in **A,** includes epithelial cell and endothelial cell. To right is nucleus of type I cell with thin cytoplasmic flange (at arrow) covering capillary and separated from endothelial cell by their respective basement membranes. Above, space between endothelium and epithelium is wider, since it includes collagen and elastin. (**B,** ×7500; **C,** ×11,000; **A** to **C,** courtesy Miss Barbara Meyrick.)

elastic and reticular fiber network supports them. In it are mesenchymal cells and phagocytes. The interalveolar septa have numerous pores of Kohn, 10 μm in diameter, which allow free intercommunication between alveoli —even those from different alveolar ducts or lobules. These are seen easily in organizing pneumonia, when young fibrous tissue grows through them, linking solidified alveoli (Fig. 23-34). Otherwise, the pores become an effective bypass if a bronchiole is blocked.

Functional units. Although the concept of the *lobule* as a functional unit is no longer favored, it will be defined so that the reader can understand older writings. The primary lobule, the respiratory tissue arising from one alveolar duct, has been abandoned as a unit because it is too small. "Lobule" is now synonymous with the secondary lobule. The latter is much larger and refers to the lung supplied by the three to five terminal bronchioles arising from a preterminal bronchiole.

Most practical of all is the concept of the *acinus,* which is the lung distal to one terminal bronchiole. It is a readily visible unit on the cut surface of a lung perfused with formalin. One lobule is composed of three to five acini. Acini are most easily recognized when black dust is deposited around their central bronchiole (Fig. 23-32). Near the sharp margins of the lungs, septa run a short way in from the pleura, often demarcating the sides of acini. These septa are inconstant and unreliable markers. Even where they are absent (which is the case farther within the lung), a more trustworthy lateral boundary to the acinus can be found—a thin line, which is the acinar vein, a vessel which is always here, never in the center where the bronchiole and artery run.

One tends to assume that the whole lung is in uniform action at all times. Contrary evidence has been presented by Towers[16] that there are functional units that roughly correspond to present-day lobules and which he calls "pneumons" (a poor choice, since this is the Greek word for "lung"). Reserve pneumons are brought into use when needed by relaxation of bronchiolar and alveolar duct muscle.

Supporting structures. Although ordinary microscopic sections do not reveal the mechanism, the lung remains expanded as atmospheric pressure stretches the supporting pulmonary framework of closely linked collagenous and elastic fibers.[12] Reticular fibers have a lesser function in this respect. When air enters the pleural cavity, the intrapulmonary and extrapulmonary pressures become equal, and the collagenous and elastic fibers pull the lung close to its root (collapse).

The collagenous and elastic fibers encircle and support the openings of all alveoli, just as they support the terminal air passages. They run from one alveolar duct to another, sending branch filaments to neighboring alveoli and vessels. Other fibers originate in vessel walls and then run out to alveoli. In this way, all the passages and vessels are linked to neighboring structures, allowing changing tensions to be spread evenly throughout. In routine sections, the elastic fibers are best demonstrated in the tips of the interalveolar septa, where the alveoli open into the air passages. When the collagenous and elastic fibers are fragmented by disease, the reticular fibers maintain the integrity of the alveolar capillary network.

The interlobular connective tissue septa in the adult lung are mostly concentrated in the subpleural zone, particularly at the sharp edges and angles of the lungs.[14, 15] They are relatively scarce over the costal surfaces and absent over the fissural surface and in the deeper parts of the lung. It is fundamental to the operation of collateral air drift in the human lung that these septa are incomplete, not enclosing lobules. The mosaic pattern of subpleural lymphatics bears no constant relationship to the septa, although the two may overlap.[15]

Fetal and neonatal lung. In utero, the lung contains much fluid, but otherwise the alveolar surfaces are generally apposed. Introduction of air by the first breath requires relatively great force to overcome the surface tension in the bronchioles and alveoli and also to move away the fluid.[5] Once the first airways open, their original surface tensions fall, and they tend to stay open. The next breath will open air spaces farther out in the lung and so on in a series (the "pop-pop-pop" mechanism).

From the beginning of their development, the lungs are covered by pleura. In the five-week fetus, the two main bronchi grow out from the trachea, which is, in turn, a bud off the foregut. They subdivide (Fig. 23-3) until, by the sixteenth week, all the airways down to the ends of the terminal bronchioles are created, and no more will be formed. Interlobar septa form very early. A lung in this *"glandular"* or *"bronchial" phase* is recognized by the cuboidal cells lining the airways, which

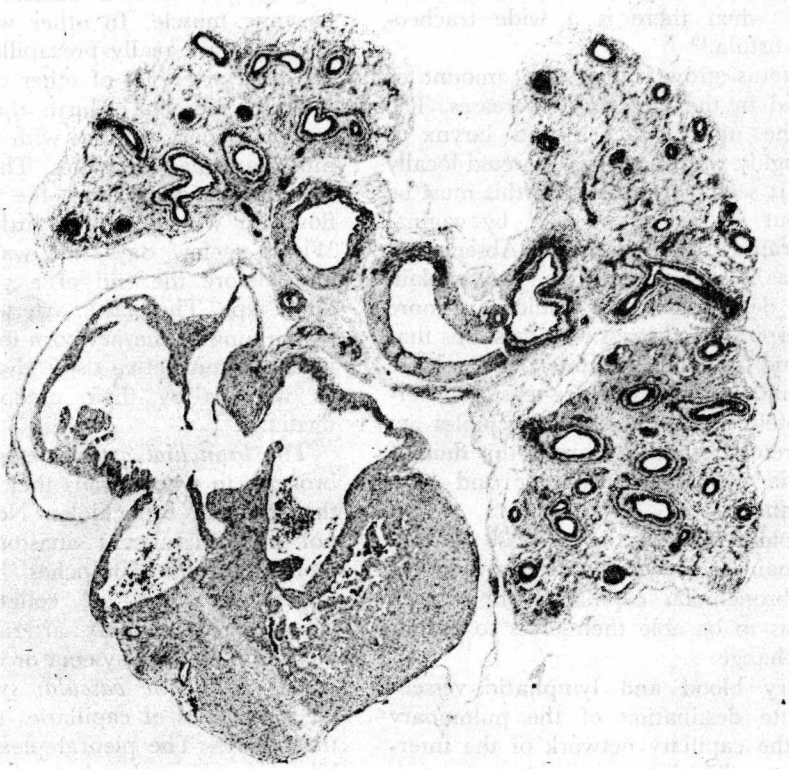

Fig. 23-3 Heart and both lungs in eight-week embryo showing early bronchial tree in undeveloped mesenchyme. (×24.)

are surrounded by mesenchyme. Pulmonary arteries are now in position. The *"canalicular" phase* occupies the sixteenth to twenty-fourth weeks. Rapid proliferation of capillaries between groups of epithelial cells of the air passages converts the epithelium into channels, on the surface of which lie networks of capillaries. A hasty glance at the lungs of a fetus of this age might lead one to believe that these are primitive vascular alveoli lined by cuboidal cells. During this phase, the formation of surfactant commences, and attenuation of the epithelium of the channels begins, allowing the blood to approach closer to the alveolar lumen. Extrauterine life cannot be maintained prior to these events. While this vital opening of the distal airways is proceeding, the mesenchyme is contributing the bronchial cartilage and elastic and collagen fibers.

Not until the twenty-fourth week does the *"alveolar" phase* begin. Fetal alveoli are very shallow evaginations of the primitive bronchiolar walls. Boyden's important wax reconstructions have shown that, from now on, functional lung tissue grows centripetally by the conversion of peripheral terminal bronchioles into respiratory bronchioles.[7] No further airways develop after the sixteenth week.

At birth the full-term infant has twenty million alveoli. They are so small that they barely resemble normal adult alveoli, which are formed only after birth. Boyden prefers to call them saccules.[7] The number increases (with the growth of the thorax) to the adult total of three hundred million by the eighth year, after which they further increase in size.[1] The original plump alveolar lining cell of the alveolar phase very slowly becomes attenuated. Even in an infant, many of them remain visible. Alveolar septa of a newborn infant are thick-walled structures because of the prominent capillaries.

Throughout fetal life, the lower respiratory tract produces a highly complex lung fluid that is held under pressure during later fetal life by sphincterlike contraction of the laryngeal muscles. The resultant positive pressure is considered to be a factor in the expansion and growth of the lung. From time to time, the larynx relaxes and some fluid is released,

to be promptly swallowed. Paralysis of the laryngeal muscles by damage to the vagus will be followed by atelectasis, a condition also found when there is a wide tracheo-esophageal fistula.[16]

As the fetus grows older, the amount of phospholipid in the lung fluid increases. The fluid in the upper trachea and larynx is mainly a highly viscous mucus, secreted locally by glands. It seems probable that this must be squeezed out of the infant (i.e., by vaginal delivery) rather than inspired. Absence of squeezing, as in cesarean section, may explain why babies delivered in this fashion are more prone to respiratory distress.[16] So it seems that the fetal lung functions like an exocrine gland, secreting fluid and the surface-tension-lowering lipoprotein, and that the bronchioles act as the excretory ducts. At birth, the fluid is removed via pulmonary vascular and lymphatic channels.

The viable fetus (i.e., over 1,000 gm) is able to remain alive without true alveoli because the bronchiolar capillaries are so well developed as to be able themselves to permit gaseous exchange.

Pulmonary blood and lymphatic vessels. The ultimate destination of the pulmonary arteries is the capillary network of the interalveolar septa. The return is into the *pulmonary venous system,* which also picks up blood from the bronchial arterial flow and from veins originating from larger bronchi. Other bronchial veins drain the pleural surfaces and the largest bronchi, entering the azygos vein on the right and the hemiazygos or innominate vein on the left.

In the adult, the ill-defined adventitia being omitted from the measurement, elastic *arteries* are said to have an external diameter greater than 1 mm, smaller vessels being muscular arteries. In turn, the transition between these and arterioles is at 0.1 mm.

Orthodox for many years, the foregoing concept is inaccurate because it is based on lungs in which the arteries have not been standardized by injection to their true size.[1] Reid's careful investigations should be consulted to gain understanding of the mechanisms of the pulmonary arterial system.[1] Pulmonary arteries have an internal and an external elastic lamina, whereas in bronchial arteries only the internal elastica is well developed. Even more noticeable in bronchial arteries is an additional muscular layer in the intima, the fibers appearing longitudinal, although most of them follow a spiral course.

It is difficult to tell an arteriole from a venule (unless the former can be traced to an artery), because neither vessel normally has any muscle. In other words, pulmonary arterioles are really precapillaries and do not resemble arterioles of other organs.[17]

At the moment of birth, the full-term infant has pulmonary arteries with thick-walled and muscular small branches. This creates a narrow lumen to cut down the pulmonary blood flow, for which there is little need in utero. Within a few days, the walls become thin, and, before the end of a year, they are of adult type. The elastic arteries are recognized in the lung of the newborn infant by the loose layers of connective tissue that surround them as well as by their predominantly elastic media.

The *bronchial arteries* exist to nourish the bronchi, in whose walls they ramify as far as the terminal bronchioles. Normally, they do not have significant anastomoses with pulmonary arterial branches but can be an important source of collateral circulation when the pulmonary arterial circulation is blocked or in emphysema or diffuse fibrosis.

The *lymphatic vascular system* provides a pleural plexus of capillaries that may outline the lobules. The pleural plexus drains to the hilar lymph nodes but also communicates with the pulmonary lymph vessels, which begin at the respiratory bronchioles.[13] These drain the tissue spaces of the interalveolar septa and the bronchial and vascular trees into the hilar lymph nodes. From here, drainage is to tracheobronchial nodes and eventually to the right lymphatic duct and, on the left, to the thoracic duct. Some lymph also passes to scalene and retroperitoneal lymph nodes.

Lymphoid nodules occur at the bifurcation of bronchi, as far down as the respiratory bronchioles, so that collections of lymphocytes in the muscle coat are not necessarily proof of the presence of chronic inflammation.

CONGENITAL ANOMALIES

Total absence of lungs may occur in anencephalic monsters. Unilateral *atresia,* the absence of a lung, does not endanger life, but serious malformations often accompany it.[28] Usually, there is no trace of the missing lung's bronchus or vessels. Sometimes one lobe or a whole lung is *hypoplastic.* This may be primary or be secondary to the pressure of a large tumor or cyst or to abdominal organs entering the thorax. *Potter's syndrome* is deformity