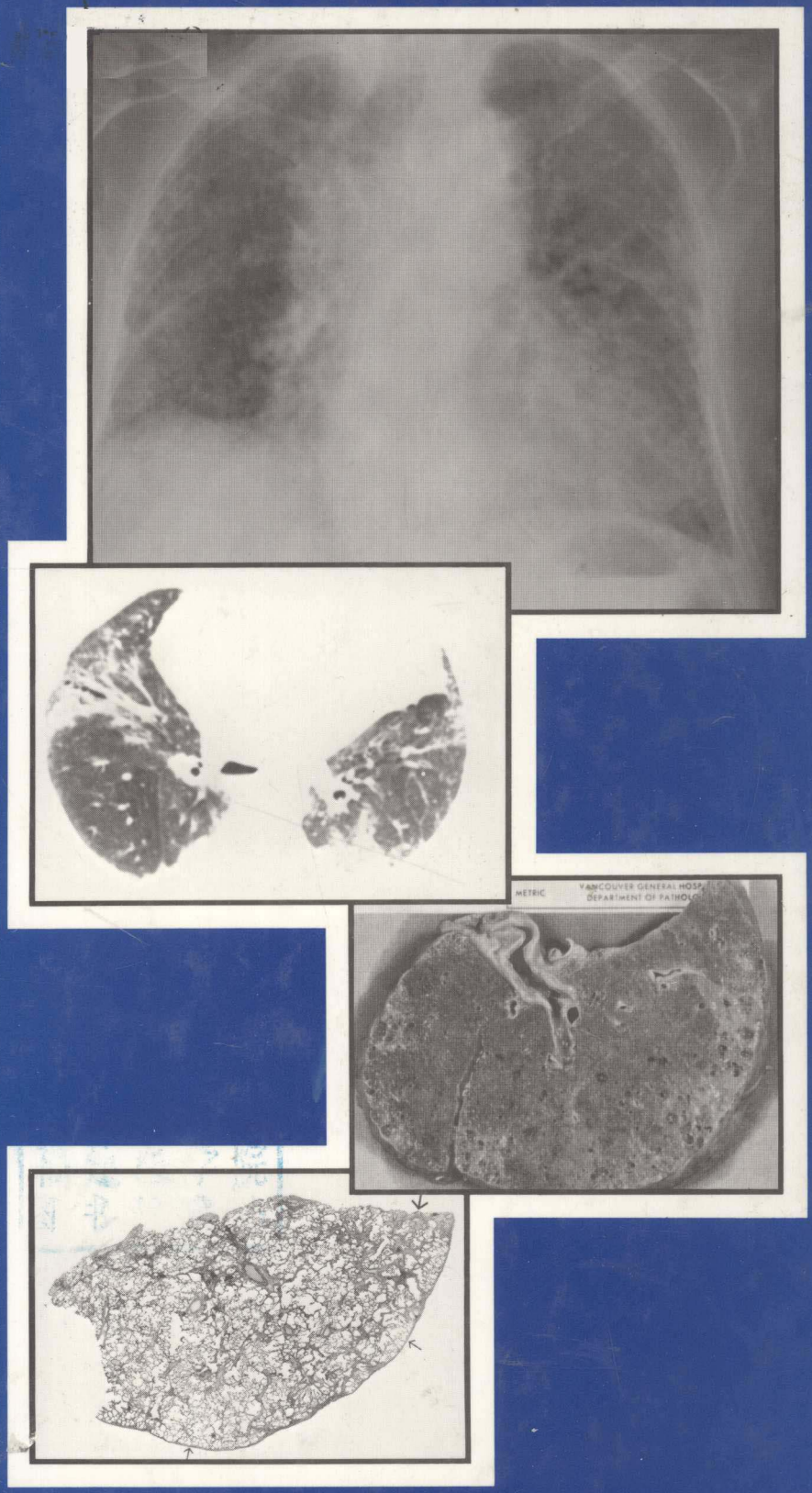
Diffuse Diseases of the Lung

A Team Approach



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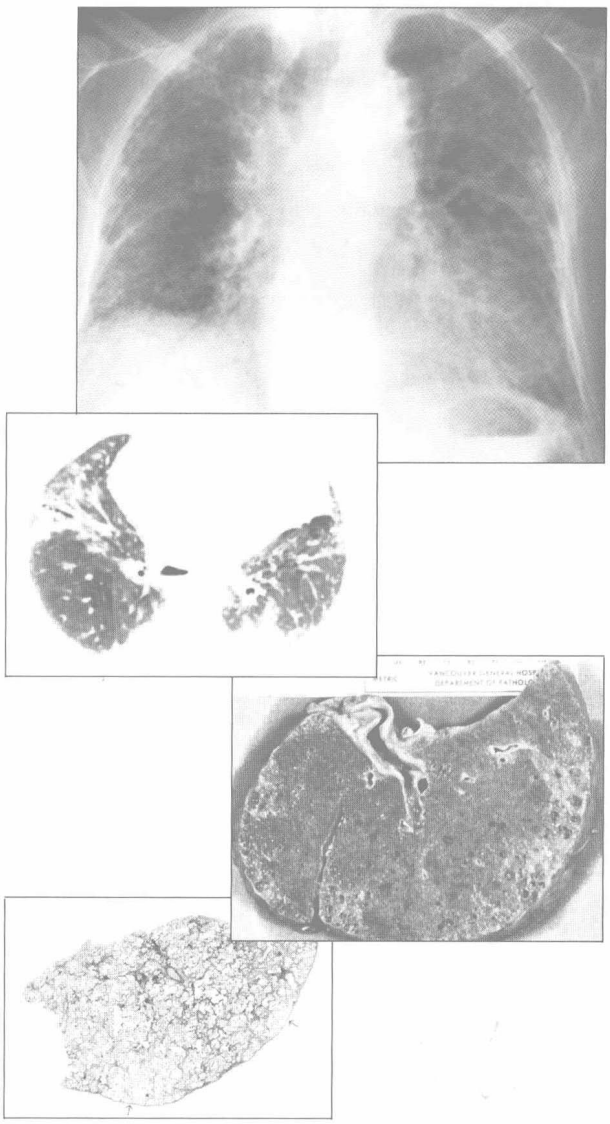
Diffuse Diseases of the Lung



A Team Approach

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To our children

Chris and Luca Miller
Alison and Phillip Müller
Sheryl Lynn and Scott Edward Rosenow
Sarah Margaret, David William,
and Alison Mary Thurlbeck

Preface

This book is the product of two unlikely parents. Two of us (RRM, WMT) contributed a chapter entitled "Diffuse Diseases of the Lungs" in Steve Silverberg's *Principles and Practice of Surgical Pathology* (2nd Ed, Churchill Livingstone 1990). While we were pleased with our product, it had a number of defects; it was written with only practicing surgical pathologists in mind and had no radiologic and little clinical information, and it also suffered from understandable space and illustration constraints. The other parent is the weekly Chest Rounds at the Vancouver General Hospital, where two of the authors (RRM, NLM) are active participants and another (WMT) is an enthusiastic observer. The observer's enthusiasm is derived from the fact that actual active cases are discussed. These are chosen with no preparation ahead of time, and they represent spontaneous presentation of cases. What was apparent to the observer was the high degree of interaction between internist, surgeon, radiologist, and pathologist and that each member of the team knew the details of all the aspects of the case, not merely from his or her particular discipline.

Both surgical and medical cases are discussed in this book, but the need for intermember team cooperation is most apparent in the case of biopsy for diffuse lung disease. We had difficulty selecting the title because, for example, emphysema and pulmonary edema are diffuse lung diseases, as are some pleural diseases. We did not wish to limit the content to infiltrative or interstitial lung disease. Further, neither of these terms is suitably precise. What the conditions presented here have in common is that they frequently come to biopsy for diagnostic purposes.

The outcome and the diagnosis depend very much on interdepartmental cooperation. Because the site of the lung biopsy is usually dictated by computed tomography, the surgeon must be aware of the findings so that

he or she can take a representative and adequate biopsy or biopsies. The pathologist in the final analysis needs to know the clinical data. For example, a previously known lymphoma or malignant tumor (and its site) may be important information. The internist must be able to understand the limitations of biopsy diagnosis in general and, in that case, in particular. Hence the subtitle "A Team Approach." In this monograph all authors have contributed to and edited all chapters and have worked interactively on many occasions.

It became apparent that there was a danger of parochialism because of the close communication among authors associated with the same institution. Therefore, we believe that the contributions of a distinguished chest physician (ECR, III) from another institution with a somewhat different attitude and type of practice would be welcome. The difference is best illustrated in the handling of open lung biopsies in the immunocompromised host, where the Mayo Clinic approach is to follow a specific protocol. In contrast, the approach at Vancouver General Hospital is more individualistic depending on the pathologist's knowledge of the clinical, radiologic, and gross findings in the case. Also, all the biopsies are handled by one pathologist.

The monograph starts with a series of chapters on normal structure, function, and imaging, followed by sections on "how to" or practical background information. Then the topics are presented in chapters based primarily on clinical groupings. As indicated in the various chapters, it is not possible to impose a rigid division of all diseases into special chapters and within this caveat we have done our best.

William M. Thurlbeck, M.B., FRCP(C)

Contents

CHAPTER 1

NORMAL STRUCTURE AND FUNCTION OF THE LUNG

This chapter describes the normal histology relevant to the subject of this book, arbitrarily considered to be that of bronchioles, the gas-exchanging units of the lung, and the pulmonary vessels. The review is brief; excellent, more extensive reviews of lung structure are available (Breeze and Wheeldon, 1976; Kuhn, 1976, 1978, 1988; Reid, 1979).

Bronchi are defined as airways that have cartilage in their walls; the airways distal to them, without alveoli in their walls, are referred to as membranous bronchioles or, simply, bronchioles. Bronchioles have an irregular dichotomous branching pattern, except for their distal three orders, which show regular dichotomy (Horsfield and Cumming, 1968). An important feature is that while each succeeding generation has a smaller diameter than the preceding one, the total cross-sectional area increases with succeeding generations (Weibel, 1963), since the daughter bronchioles are more than half the diameter of the parent one (Fig. 1-1). It is this increase in total cross-sectional area, which becomes rapid distally, that accounts for the fact that there is little resistance to flow in the peripheral airways (see "Chronic Airflow Obstruction," chapter 12). Bronchiolar mucosa lacks the compound mucus-secreting subepithelial glands so characteristic of bronchi. The lining epithelium of the largest bronchioles when fully distended loses some of the pseudostratified appearance of bronchi (Fig. 1-2). The great majority of the cells lining the bronchioles are ciliated cells (see Fig. 1-2). Their nuclei are basal, rather square in shape, and are arranged in a single row in the smaller bronchioles and mostly pseudostratified in larger bronchioles. Scattered basal cells with elongated nuclei lie deep to the nuclei of the ciliated cells (see Fig. 1-2). Mucus-secreting cells are extremely scanty in nonsmokers. When these cells are distended with mucus they are referred to as goblet cells (Fig. 1-3).

Neuroendocrine cells ("K cells," Kulchitsky cells) of the lung occur either singly or in clusters, the latter generally referred to as neuroepithelial bodies. With hematoxylin and eosin (H&E) staining, these cells have a clear or slightly eosinophilic cytoplasm; with appropriate silver stains, they may be argyrophilic. They are considerably more numerous in fetal lungs than adult lungs and are distributed mostly in the epithelium of subsegmental bronchi. They are a part of the APUD (*A*mine *P*recursor *U*ptake and *D*ecarboxylation) cell system throughout the body and ultrastructurally contain characteristic dense core cytoplasmic granules. Normally they may be shown to contain gastrin-releasing peptide (bombesin), leu-enkephalin, calcitonin, serotonin, and neuron-specific enolase, although the precise role of these substances in the regulation of growth,

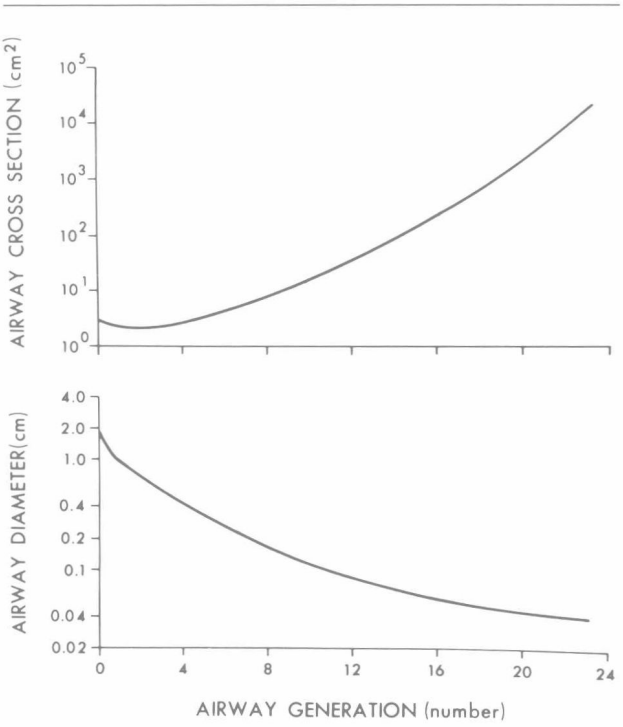
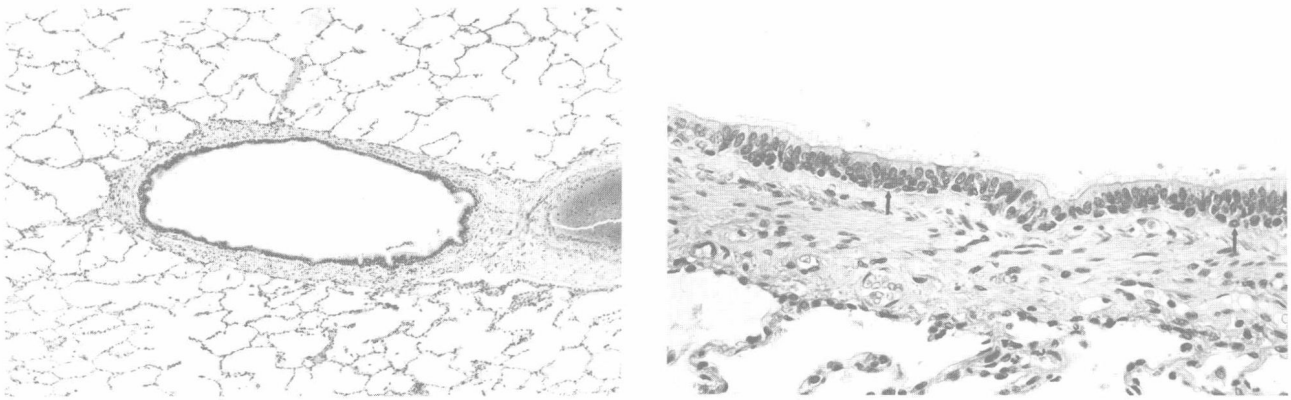


Figure 1–1 The cross-sectional area of individual generations (*bottom*) and the summed cross-sectional area of generations (*top*) are shown. In this model generation 0 is the trachea, and symmetric dichotomy is assumed. Proceeding peripherally, the total cross-sectional area increases dramatically (note that the cross-sectional area is expressed on a logarithmic scale). The end of the bronchial tree corresponds approximately to generation 7 and terminal bronchioles are generation 16. (Reprinted with permission from Weibel ER. Morphometry of the human lung. Berlin: Springer Verlag, 1963.)

development, and gas exchange is still uncertain. Carcinoid tumors and small-cell carcinomas show differentiation toward neuroendocrine cells. In addition to bombesin and other indigenous peptides, hormones, such as ACTH and antidiuretic hormone (ADH), which are not demonstrable in normal lung epithelium may also be produced by these tumors. (Gail and Lenfant, 1983; Gould et al, 1983).

The columnar, nonciliated secretory cell (Clara cell) is inconspicuous in humans compared with small laboratory animals. Characteristically, the cells are taller than other epithelial cells, projecting into the lumen of the bronchioles. The function of these cells is not known with certainty. Some consider them to be the major source of pulmonary surfactant. Others consider them to secrete the hypophase of protein and liquid on which surfactant lies. In laboratory animals, Clara cells are the progenitor cells of the



A B

Figure 1–2 Large (membranous) bronchiole, approximately 2 mm in diameter. *A*, Cartilage and compound mucus-secreting glands are not present in the walls of the bronchiole (H&E, × 63). *B*, Most of the cells of the epithelium are ciliated. Flattened basal cell nuclei are also seen (*arrows*). Mucus-secreting (goblet) and nonciliated columnar (Clara) cells are not apparent. The basal lamina is thin (H&E, × 400).

bronchioles and may differentiate into other Clara cells, ciliated cells, or mucus-secreting cells. The epithelial basal lamina is very thin (see Fig. 1-2), and it is the collagen associated with the basal lamina that makes the basement membrane visible by light microscopy. An elastic tissue net is closely applied to the basal lamina (Fig. 1-4). The muscle of the bronchioles is arranged in a geodesic pattern, which in smaller bronchioles leads to an appearance of an incomplete muscular layer (see Fig. 1-4). A few mononuclear inflammatory cells are present in most bronchioles, but even a modest collection of cells and any neutrophils should be regarded as abnormal. Outside of the muscular layer the arteries and bronchioles share a common adventitia. There is loose connective tissue outside this, forming part of the lung interstitium. The surrounding connective tissue becomes progressively more scanty in the smallest bronchioles.

The last purely conducting bronchiole, without alveoli in its walls, is the terminal bronchiole. Distal to it is the gas-exchanging unit of the lung, known as the acinus. In order, it comprises respiratory bronchioles, alveolar ducts, and sacs. Respiratory bronchioles have both alveolated and nonalveolated walls (Fig. 1-5). Nonalveolated walls have epithelium like that of bronchioles, except that the cells are flatter. The majority of the cells are still ciliated. There is a relatively abrupt transition between the ciliated cells and flattened epithelium, resembling that of the

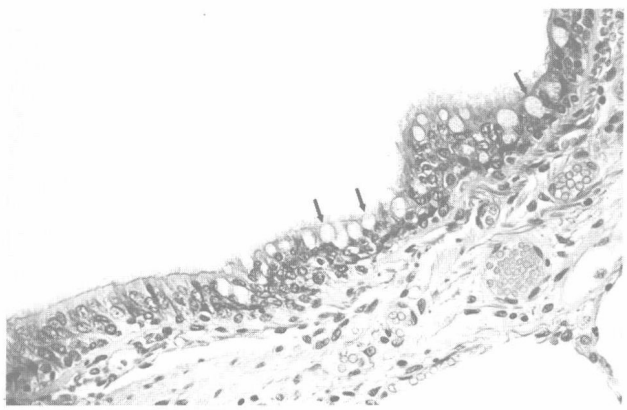


Figure 1–3 Bronchiole comparable in size to Figure 1–2 from a cigarette smoker. Note goblet cells (*arrows*) (H&E, × 400).

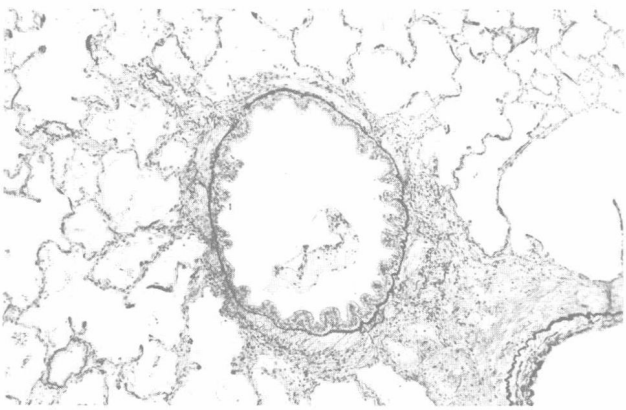


Figure 1–4 Subepithelial elastic layer is closely adherent to the epithelium, with underlying interrupted smooth muscle (VVG, × 100).

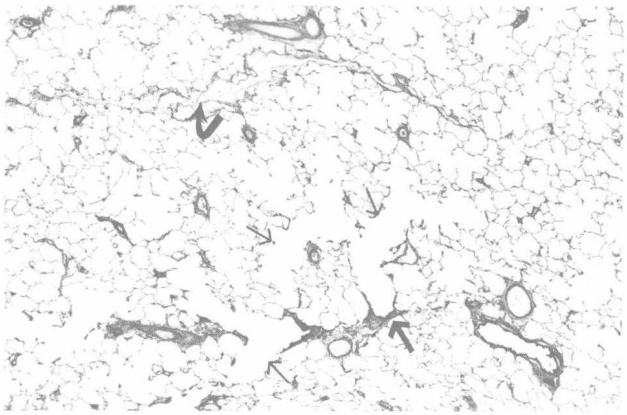


Figure 1–5 Acinus, showing respiratory bronchioles (*large arrow*), alveolar ducts (*small arrows*), and lobular septum (*curved arrow*) (H&E, × 25).

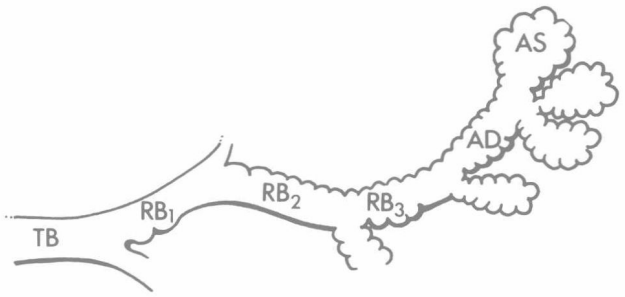


Figure 1–6 Diagrammatic representation of the acinus shows the terminal bronchiole (TB); three orders of respiratory bronchioles (RB) with increasing numbers of alveoli in their walls; a single order of alveolar duct (AD), whose wall is entirely alveolated; and the terminal structure, the alveolar sac (AS).

alveoli. A simplified model of the acinus is shown in Figure 1-6. Respiratory bronchioles have more alveoli in their walls in succeeding generations and are succeeded by alveolar ducts, entirely alveolated conducting structures. The terminal unit of the acinus is the alveolar sac, which is likewise entirely alveolated. The acinus is important as the gas-exchanging unit of the lung, and it is this structure that is enlarged and its walls destroyed in emphysema.

A traditional structural unit of the lung is the lobule. Sheets of connective tissue containing veins and lymphatics subdivide the lung into macroscopic units, and the smallest units surrounded by (lobular) septa are referred to as lobules. The problem is that lobular septa are quite variable in extent, being more obvious in the upper lobe than the lower lobe and more obvious in infants than adults (Fig. 1-7). Also there are quite considerable differences between individuals. Thus the size of lobules is variable and different lobules contain different numbers of acini. While the boundaries of lobules are easier to identify morphologically (i.e., interlobular septa), the acinus is a more useful unit.

The surface of human alveoli is lined by type-I and type-II epithelial cells. The majority of the surface is covered by the thin, greatly extended cytoplasm of type-I epithelial cells, which contain few organelles. There are actually more type-II epithelial cells but, because they are columnar, they cover only about 5 percent of the surface of the alveoli. They are characteristically situated in the angles of the alveoli and are thus sometimes called corner cells or niche cells. They contain large numbers of organelles and the characteristic osmiophilic lamellar bodies (Fig. 1-8), which, when secreted into the alveolus, constitute the surface-active material essential for alveolar stability. Type-II cells have another vital function, that of being the progenitor cell of alveolar epithelium. They have the ability to divide and produce two type-II cells; this happens during lung development and following injury. Alternatively they can divide to form one type-II cell and one type-I cell; this is a normal process in mature lungs and in the recovery phase of lung injury. Type-I and type-II cells are joined by tight junctions and thus represent the major barrier to passage of large molecules from the capillary lumen to the airspace.

Alveolar macrophages play a major role in the lung's defense mechanism, but the source of these cells is controversial. Some consider that they are mainly derived from the monocytes of the bone marrow and undergo a maturation division in the alveolar interstitium before passing into the airspaces.

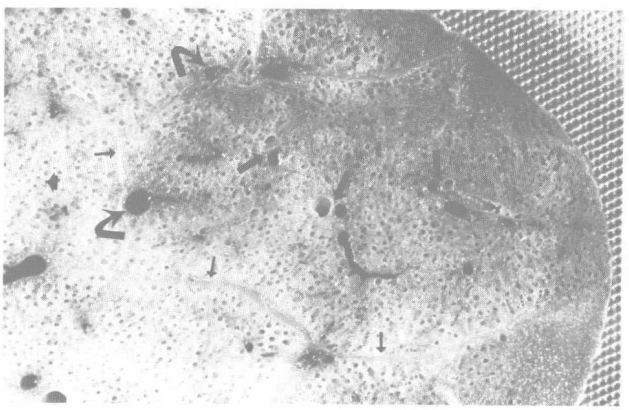


Figure 1–7 Gross view of lobules, showing centrilobular bronchovascular structures (*large arrows*), septa (*small arrows*) and veins within septa (*curved arrows*).

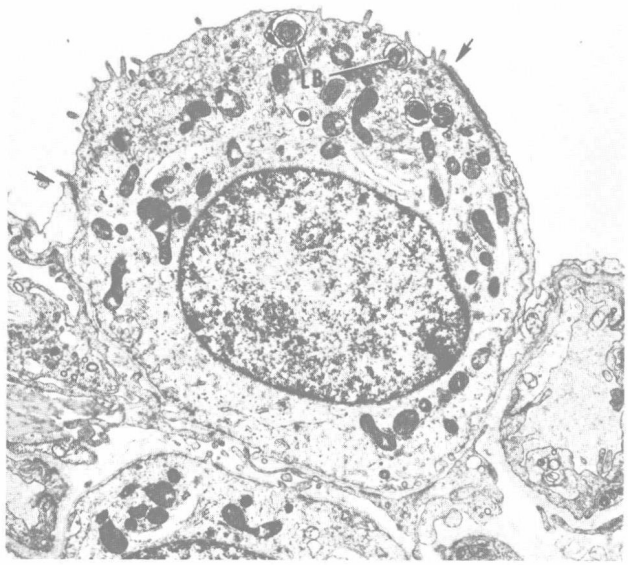


Figure 1–8 A type-II cell contains many lamellar bodies (LB). The type-II cell is partially covered by extensions of type-I cells, extending up to the intercellular junctions (*arrows*). Microvilli are present on the exposed apical surface. (Reprinted with permission from Kuhn C III. Normal anatomy and histology. In Thurlbeck WM, ed. Pathology of the lung. New York: Thieme, 1988.)

Considerable multiplication of alveolar macrophages also may occur within airspaces especially in the neonatal period (Evans et al, 1987). They differ from peritoneal macrophages in that alveolar macrophages are more dependent on aerobic metabolism.

The alveolar wall contains capillaries, collagen fibers, elastic fibers, glycosaminoglycans, and interstitial cells. The latter include mast cells, smooth muscle cells, occasional lymphocytes, pericytes, and connective tissue cells. The last type of cells are usually referred to as fibroblasts, but they appear quiescent and have few organelles. Bundles of filaments identified as actin and myosin have been noted in these cells, and it has been suggested that they may have a contractile role and may control perfusion in the lung. Capillary endothelial cells are joined by tight or "semitight" junctions. The latter are relatively sparse but permit the passage of large molecules. Endothelial cells are metabolically active and metabolize serotonin, norepinephrine, acetylcholine, adenine monophosphate, adenine triphosphate, bradykinin, angiotensin I, very low density lipoproteins, and prostaglandins E_1, E_2, and F_2. Cells of the alveoli differ in their susceptibility to injury. The type-I cell is the most sensitive, with damage leading to increased permeability and alveolar edema. The capillary endothelial cells are the next most sensitive, followed by the type-II cell. The alveolar wall has a "thin" and a "thick" side (Fig. 1-9). On the thin side the basal lamina of epithelial cells and that of endothelial cells fuse, and gas exchange is most easily accomplished here. On the thick side the basal laminae are separate, and in this space lies another part of the interstitium of the lung with the components noted above. There is a single capillary layer in the alveolar wall, with capillaries winding from one side of the alveolar wall to the other.

The pulmonary arterial tree is a high-capacitance system, with the resistance vessels being the muscular pulmonary arteries. These arteries accompany the airways, and it is usual to refer to this arrangement together with the common adventitia as the bronchovascular bundle. Age-dependent structural differences exist in the pulmonary arterial system, with increased intimal thickening occurring with age. In the adult, the elastic arteries (Fig. 1-10A), which have more than two elastic laminae, are larger than 1000 μm in diameter, whereas arteries between 100 and 200 μm are muscular, in which the muscle is enclosed by an internal and an external elastic lamina (Fig. 1-10B). Smaller vessels may be muscular, partially muscular (when the muscle is spirally arranged around the vessel so that parts of the wall appear muscular and parts nonmuscular), and nonmuscular. The two elastic laminae fuse where muscle is absent, and a single fragmented elastic lamina separates the intima from the adventitia (Fig. 1-10C). The term "pulmonary arteriole" (arterial vessels less

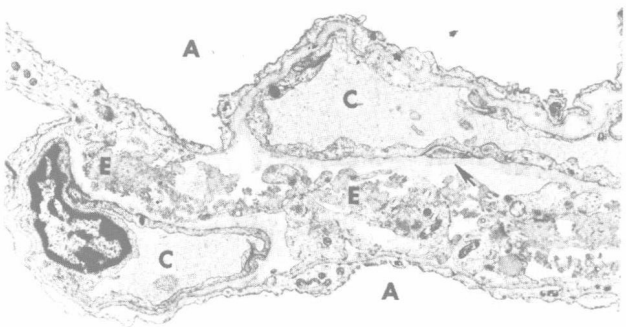


Figure 1–9 Electron micrograph of alveolar wall showing alveolar space (A), capillary (C), and elastic tissue (E). Note that the basal lamina of endothelium and epithelium are joined on the thin side of the alveolar wall (*top right*). On the thick side of the alveolar wall the basal lamina of the capillary (*arrow*) is separated from the basal lamina of a type-I epithelial cell (*lower right*). In the space, elastic tissue can be seen as well as cytoplasm of an interstitial cell. (Reprinted with permission from Kuhn C III. Normal anatomy and histology. In Thurlbeck WM, ed. Pathology of the lung. New York: Thieme, 1988.)

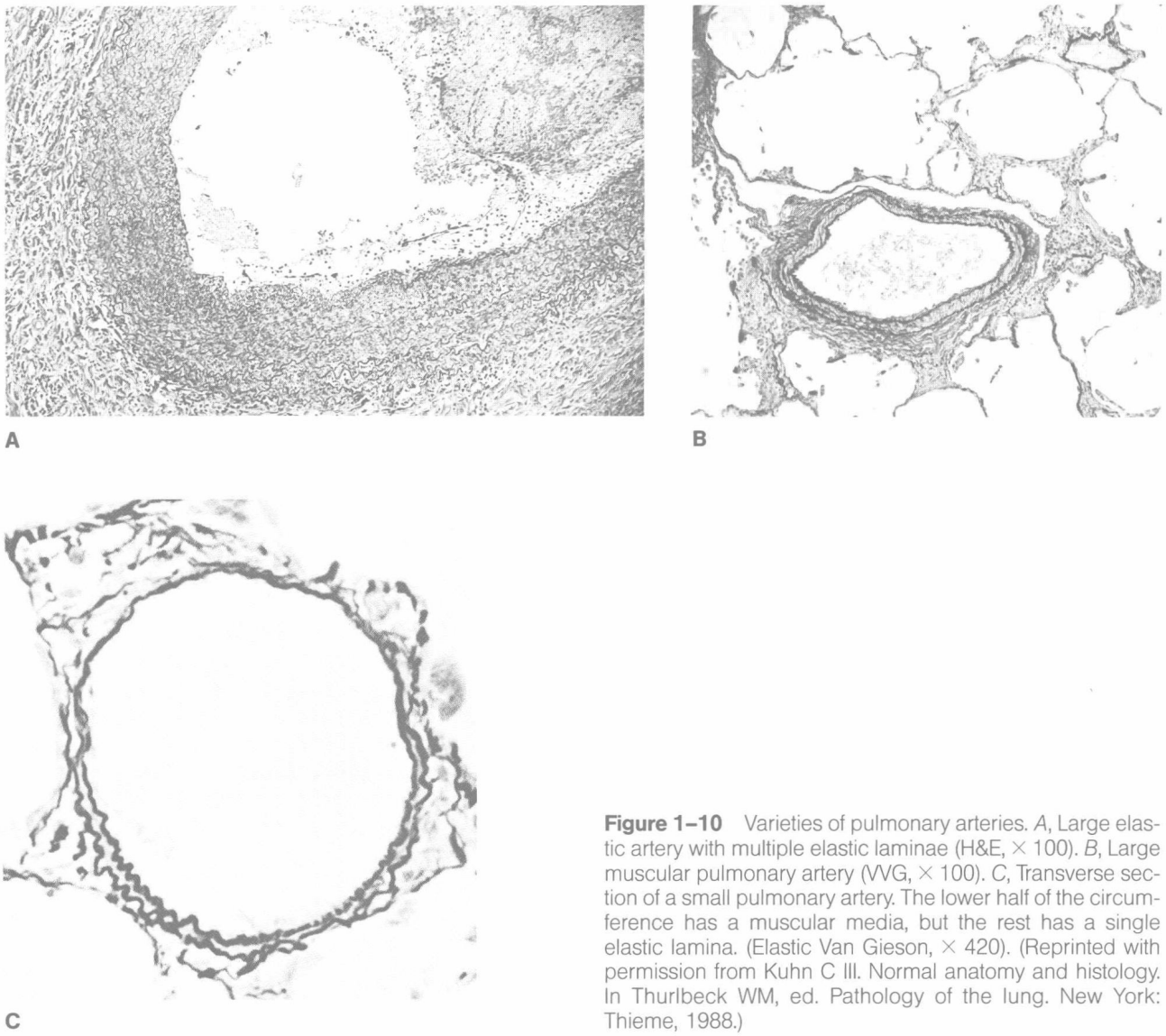


Figure 1–10 Varieties of pulmonary arteries. *A*, Large elastic artery with multiple elastic laminae (H&E, × 100). *B*, Large muscular pulmonary artery (VVG, × 100). *C*, Transverse section of a small pulmonary artery. The lower half of the circumference has a muscular media, but the rest has a single elastic lamina. (Elastic Van Gieson, × 420). (Reprinted with permission from Kuhn C III. Normal anatomy and histology. In Thurlbeck WM, ed. Pathology of the lung. New York: Thieme, 1988.)

than 100 μm in diameter) has become obsolete. The appearance, in terms of vessel size, is surprisingly similar in adults, children, and fetuses (Reid, 1979), but this is because vessels of similar size represent different generations of artery in infants compared with adults. When compared by position in the lung, the structure of vessels is quite different at different ages. In the fetus and soon after birth, the intra-acinar arteries are all nonmuscular. There is increasing muscularity of the intra-acinar arteries during childhood, but even at age 11 this process is not complete, with muscle extending only to the level of the alveolar ducts. In the adult, arterial muscle reaches as far as the alveoli. The ratio of arterial wall thickness to external arterial diameter is a useful parameter to assess abnormality, but it should be noted that the values for arteries distended with contrast medium are lower when high pressures are used to distend the vessel. In undistended muscular arteries, the ratio of medial thickness to external arterial diameter is about 5 percent (3 to 7 percent).

Pulmonary veins commence at the distal end of alveolar capillaries and proceed in the interstitium of the lung toward the lobular septa. Small pulmonary veins are indistinguishable from nonmuscular pulmonary arteries by histology, but the distinction can be made by the juxta-airway position of pulmonary arteries. The veins drain centrally in the septa and then form larger structures that lie separate from arteries and airways. The walls of veins are much thinner than arteries and, in general, have a single, poorly formed external elastic lamina and no muscle

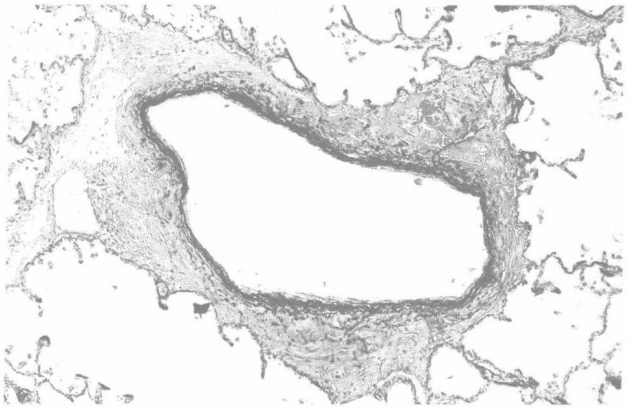


Figure 1–11 Medium-sized pulmonary vein with several incomplete elastic laminae, and virtually no muscle (VVG, × 100).

(Fig. 1-11). Larger veins may contain more than one elastic lamina, also poorly formed; muscle is scanty.

Bronchial arteries arise from the aorta or the intercostobrachial trunk, and course with the airways and pulmonary arteries in the bronchovascular tree. They are usually two to four in number. The bronchial arteries have the structure of systemic arteries, i.e., have a relatively thick media and supply the structures in the interstitium. The bronchial arteries extend as far as the terminal bronchiole and then anastomose with branches of the pulmonary artery at this point and beyond. Bronchial veins arise from the bronchial capillaries and drain into the bronchovascular bundle to join the azygos and hemiazygos veins. The bronchial vessels that have precapillary, capillary and postcapillary anastomoses with the pulmonary arteries drain into the pulmonary vein. The bronchial arteries also supply the medial and diaphragmatic visceral pleura and the tracheal, carinal, hilar, and intrapulmonary lymph nodes.

Pulmonary lymphatics are not present between alveolar walls but start where alveoli are juxtaposed to lobular septa and the bronchovascular bundles. These vessels have walls that are quite thin with a lining of endothelial cells lying on a basal lamina, embedded in a loose connective-tissue matrix. They contain valves that direct the flow of lymph. Lymphatics proceed centrally with the bronchovascular tree, in lobular septa and with veins, and also to the pleural surface. Pleural lymphatics course in the visceral pleura and send numerous connections into the interior of the lung to anastomose with perivenous lymphatics.

The interstitium of the lung is an important concept (Fig. 1-12). It has never been officially defined, but our understanding is that it is tissue between structures concerned with gas exchange. It is thus the loose connective tissue outside airways and arteries, outside veins and lymphatics, and the tissue between the capillary and epithelium on the thick side of the alveolar wall.

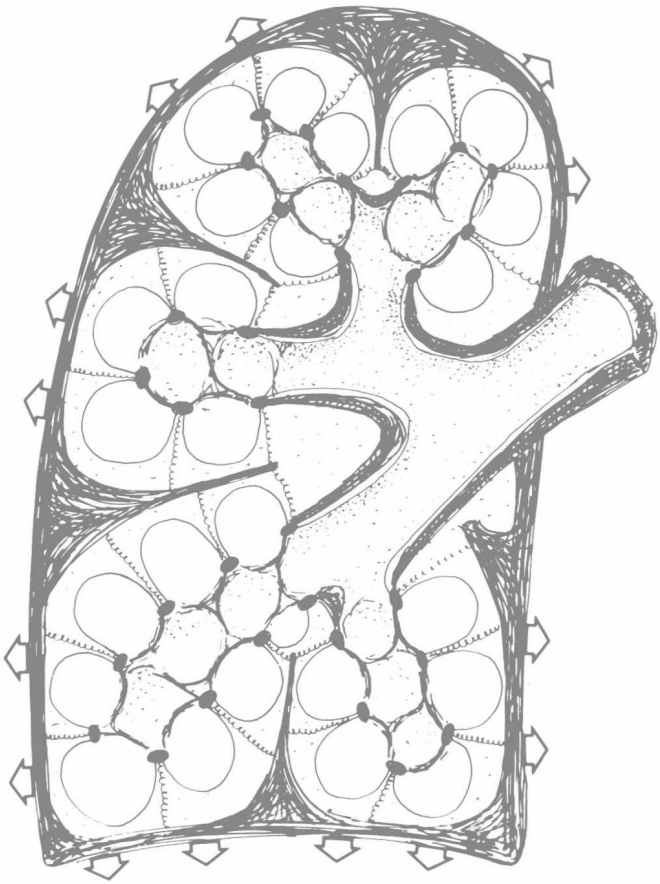


Figure 1–12 The interstitium of the lung represents a continuum of connective tissue. It extends around airways (and arteries) to the walls of alveoli, represented as circles. In addition, the interstitium extends from alveolar walls to lobular septa (deep indentations from pleura), in which veins are found in the pleura. Lymphatics are also found in the interstitium which has its blood supply from the bronchial arteries. (Reprinted with permission from Weibel ER, Gil J. Structure-function relationships at the alveolar level. In West JB, ed. Bioengineering aspects of the lung. New York: Marcel Dekker, 1977.)

RADIOLOGY

Chest Radiograph

A properly exposed chest radiograph allows visualization of small blood vessels in the lung periphery, and faint visualization of the intervertebral disk

spaces, ribs, and blood vessels behind the heart. As any degree of rotation will result in changes in density of one lung as compared with the other, the position of the patient should be assessed. On a well-centered radiograph, the medial aspect of the clavicles is equidistant to the spinous processes. Provided that the individual is not rotated, normally the density of the right lung is similar to that of the left.

Analysis of the chest radiograph may be made by a free global search, a directed search, or preferably a combination of both methods (Fraser et al, 1988). Up to 70 percent of abnormalities can be detected within 0.2 second by a global overview, or gestalt, of the radiograph (Kundel and Nodine, 1975). However, detection of more subtle abnormalities requires an orderly, directed search that includes analysis of the extrathoracic soft tissues, bony thorax, diaphragm, pleura, mediastinum, as well as the lungs. The lungs are inspected most easily by comparing right and left lungs from apex to base. Approximately 15 percent of the lung is hidden behind the diaphragm and the cardiothoracic structures.

On the normal radiograph, the visualized shadows in the lung parenchyma are made up almost exclusively by the pulmonary vessels. The right hilar vessels are 1 to 3 cm lower than the left hilum in 97 percent of individuals and seem to extend farther out than the left because a portion of the left hilum is obscured by the heart. The vessels branch and taper, and on high-quality radiographs may be seen to extend to the periphery of the lungs. The pulmonary circulation is a low-pressure system, the vessel walls being thin and readily distensible. Because the pulmonary arterial pressure is low, blood flow to the different lung regions is markedly influenced by changes in posture. In the upright individual, there is a gradient in hydrostatic pressure of approximately 30 cm H_2O from the lung apices to the lung bases. As a consequence, the blood flow to the bases is normally severalfold greater than that to the apices. On the radiograph, the increased hydrostatic pressure is reflected by the greater caliber of the lower-lobe vessels as compared with that of the upper-lobe vessels. In the supine individual, although flow to the upper lobe increases, because of the larger anteroposterior diameter in the lung bases, blood flow and blood-vessel diameter are still greater in the lower lobes.

Apart from the interlobar pulmonary arteries, the superior and inferior pulmonary veins, and perhaps their major branches, it is usually not possible to determine which of these vessels are arteries and which are veins. This, however, is not of much consequence, as arteries and veins usually change in caliber equally (Trapnell, 1983). Thus, in left-sided heart failure, the prominent upper-lobe vessels do not represent "engorged veins" but rather redistribution of blood flow to the upper lobes.

Apart from the vessels, the only normal structures seen are the major bronchi and interlobar fissures. The walls of the segmental bronchi are often seen end-on and are normally about 1 mm thick.

The normal interstitium, including the interlobular septa, is not visualized.

Computed Tomography

Computed tomography (CT) scan images should be analyzed systematically, taking into consideration the findings on the images immediately above and below. As on the radiograph, the main structures seen on CT are the pulmonary vessels (Fig. 1-13). Vessels equal to or greater than 0.8 mm in diameter can be clearly visualized (Zerhouni et al, 1985). Bronchi are much better seen on CT than on the radiograph. The lobar and segmental bronchi coursing vertically or horizontally are clearly identified. Their walls normally measure approximately 1 mm in thickness. Subsegmental bronchi can often be seen as small lucencies adjacent to pulmonary arteries. The middle lobe and lingular bronchi course obliquely and are well seen on routine 1-cm collimation scans in about 75 percent of patients, but can be visualized in almost all individuals with 1.5-mm collimation scans.

The major fissures appear on 10-mm collimation scans as white lines or as ill-defined bands of increased or decreased density (Frija et al, 1982). On 1.5-mm collimation scans, they are almost always seen as thin white lines. The minor fissure is seen as

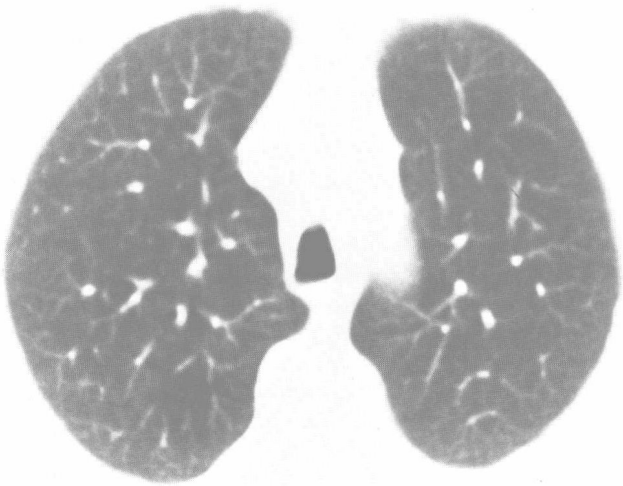


Figure 1–13 Normal 10-mm collimation CT scan through the upper lobes. The vessels can be seen as branching structures.

a hypovascular triangle, circle, or oval on 10-mm collimation scans and as a white line on 1.5-mm scans.

There is normally a density (attenuation) gradient between lung apex and base, and between dependent and nondependent portions of lung related to the influence of gravity on blood flow. Often a localized band of increased density is seen in the dependent lung. The nature of this is not clear, but presumably it is related to airway closure. These gravity-dependent changes can hinder the assessment of subtle parenchymal abnormalities. The problem can be solved, however, by rescanning the area of interest with the patient prone.

CT scans are routinely done using 10-mm collimation. This leads to volume averaging of the structures within that thickness and allows for clear identification of vessels as they course through the thickness of the slice and thus, usually, easy distinction of vessels from nodules (see Fig. 1-13). However, volume averaging also results in lower spatial resolution. Therefore, in the assessment of diffuse lung disease, the conventional CT should be supplemented with 1.5-mm collimation scans (thin-section CT). These images may be further optimized by using a high-spatial-frequency reconstruction algorithm ("bone algorithm" on the GE 9800 scanner) and a smaller field of view. The bone algorithm and the smaller field of view improve the spatial resolution and give a sharper image (Fig. 1-14). These high-resolution images, known as high-resolution CT scans, allow identification of smaller parenchymal structures including secondary pulmonary lobules. These lobules are identified by the centrally situated artery and accompanying bronchus and by the surrounding interlobular septa (Fig. 1-15). The septa can also often be identified in the lung periphery as thin lines extending to the pleural surface.

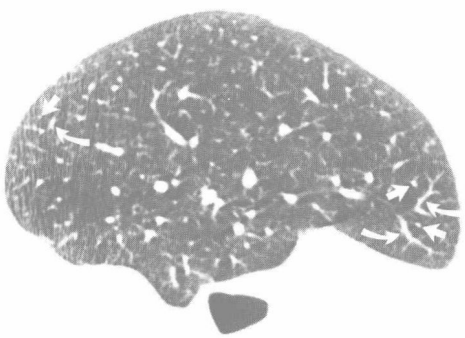


Figure 1–14 A 1.5-mm collimation scan targeted to the right lung at the same level as Figure 1–13 and reconstructed using a high-spatial-frequency algorithm (high-resolution CT) allows much better assessment of parenchymal detail. However, as most vessels appear as nodular densities, it would be easy to miss small nodules. In some areas, veins in the interlobular septa (*curved arrows*) can be seen as well as the centrilobular artery and bronchiole (*straight arrows*).

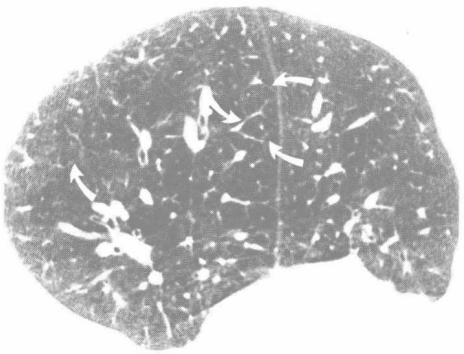


Figure 1–15 Normal high-resolution CT through the right lower lung zone allows identification of secondary pulmonary lobules. The pulmonary veins in the septa appear as polygonal lines (*curved arrows*), and the artery and the accompanying bronchiole are seen as dots near the center of the lobule.

Other modalities of lung imaging and their application are discussed in Chapter 3.

PULMONARY FUNCTION TESTS

Standard tests of pulmonary function often play an important role in the diagnosis of lung disease. Even a moderately brief review of pulmonary physiology is inappropriate for this book, but an outline of standard tests of pulmonary function may be useful, as they will be referred to repeatedly.

Subdivisions of Lung Volumes

During quiet breathing the diaphragm and intercostal muscles contract to produce inspiration. The amount of air breathed in is referred to as the tidal volume or V_T (Fig. 1-16). Expiration results from the elastic recoil of the lungs and occurs passively. Expiration ceases when the elastic recoil of the lungs inward is equal to the outward elastic recoil of the chest wall. This is the functional residual capacity (FRC) and is the amount of air in the lung at the end of a normal quiet expiration. Residual volume (RV) is the amount of air left in the lung at the end of the

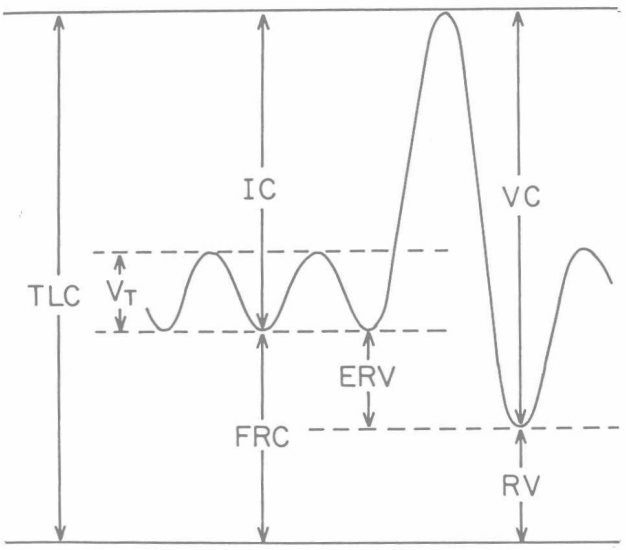


Figure 1–16 Subdivisions of lung volume: total lung capacity (TLC), vital capacity (VC), residual volume (RV), tidal volume (V_T), expiratory reserve volume (ERV), functional residual capacity (FRC), and inspiratory reserve capacity (IC). (From Bates DV, Christie TRV. Respiratory function in disease. 3rd ed. Philadelphia: WB Saunders, 1989.)

deepest possible expiration. If the lungs are normal, this point is determined by the chest wall because at low lung volumes the chest wall becomes very stiff and can move no further inward. Residual volume is also in part determined by airway closure. In young subjects airway closure plays a very small part, but in middle-aged or older subjects airways close before maximum chest wall stiffness is reached, so that RV increases with age. The amount of air in the lung at the end of a maximum inspiration is called total lung capacity (TLC). It represents the dissipation of forces applied to the chest wall on the lungs and is limited primarily by the lungs because they become very noncompliant as they approach full inspiration. Vital capacity (VC) is the maximum amount of air that can be exhaled following full inspiration and thus represents the volume of air between TLC and RV. Two subdivisions of lung volume are seldom used clinically: expiratory reserve volume (ERV), which is the difference between FRC and RV, and inspiratory capacity (IC), the difference between FRC and TLC. By convention, the term "capacity" means a sum of two or more volumes: e.g.,

$$VC = IC + V_T + ERV.$$

Lung volume and its subdivisions are determined by stature, sex, and age, with stature being the most important. Even prediction data using these variables have a wide range of normal, usually considered ± 20 percent of predicted normal.

Expiratory Flow

Tests of expiratory flow are mainly related to airflow resistance within the airways. However, this measurement is not easily made and thus airway resistance is usually measured indirectly. The most common and most popular test is the forced expiratory volume in one second (FEV_1). This is the amount of air that is expired in the first second of forced expiration from TLC and is decreased when expiratory flow resistance is increased. It is volume differentiated by time, and therefore represents a measurement of flow. One of the difficulties is that like lung volumes, the FEV_1 is stature, sex, age, and effort dependent. One way of correcting for this is to express it as a percentage of the forced vital capacity (FVC), which is likewise stature, age, sex, and effort dependent. Thus the FEV_1/FVC ratio is body size independent and reduction indicates airflow obstruction.

Formerly it was believed that the peripheral ("small") airways contributed very little to total flow resistance, and it has been argued that considerable disease could occur in these airways without the FEV_1 being abnormal. Thus a large number of tests had a great vogue 10 to 15 years ago. These included measurements of flow at low lung volumes (which reflect flow in the peripheral airways). Another popular test is the single-breath nitrogen test (SBNT), which is largely a reflection of airway narrowing at low lung volumes and airway closure. The slope of phase III of the SBNT reflects irregular airway closure, and closing volume (CV) represents a volume at which airways close.

Gas Exchange

The transfer of gas from alveolar air to blood is referred to as the transfer factor or diffusing capacity. This is measured by assessing the ability of very dilute carbon monoxide inspired into the airspaces to transfer itself into the blood (diffusing capacity for carbon monoxide [D_LCO]). It has two components: the membrane component, which reflects the transfer of gas from alveolar air to the intravascular space, and the capillary component, which reflects the amount of available blood. Most commonly these are expressed together as the D_LCO. The most important, but relatively insensitive, measurements of gas exchange are the partial pressure of oxygen in the arterial blood (PaO_2) and the partial pressure of carbon dioxide in the arterial blood ($PaCO_2$).