Understanding Pulmonary Pathology

Applying Pathological Findings in Therapeutic Decision-Making

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125 London Wall, London EC2Y 5AS, United Kingdom
525 B Street, Suite 1800, San Diego, CA 92101-4495, United States
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, United Kingdom

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Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

ISBN: 978-0-12-801304-5

Publisher: Mica Haley
Acquisition Editor: Stacy Masucci
Editorial Project Manager: Samuel Young
Production Project Manager: Edward Taylor
Designer: Matthew Limbert

Typeset by TNQ Books and Journals

Acknowledgments

I wish to acknowledge the people who have helped in the production of this textbook. The medical artwork was done by S. Cashman, M. Forrestall-Lee, and S. Conley. L. Arini assisted in the compilation of the text.

My career could not have taken its unique path without the support of my early mentors, including the late R.T. McCluskey, a former Chairman of MGH Pathology, H. Kazemi, the former Chairman of the MGH Pulmonary and Critical Care Unit, and R.B. Colvin, a former Chairman of MGH Pathology and my research mentor in immunopathology.

Introduction

This text is an attempt to bridge the practices of pulmonary medicine and pulmonary pathology. Although in the past, it was common for clinicians to be engaged directly in the study of pathology, this is no longer the case. For many reasons, the practices of clinical medicine and pathology have diverged. But clinical medicine and pathology provide cogent and complementary perspectives on disease. The information gleaned by clinicians is based on empirical observation of the patient at the macroscopic level, whereas the surgical pathologist primarily examines disease at the microscopic scale.

Translating microscopic images into words is not a simple exercise, especially in the practice of medical pathology. A detailed description of a lung biopsy would require pages of words, far more information than the clinician wants or needs to know. Detailed descriptive diagnoses tend to confuse clinicians who are largely unacquainted with the jargon of pathology. How to formulate a pathological diagnosis succinctly is an art as well as a goal that is often only achieved after a long career.

When formulating diagnoses, it is important to recognize what may be lost in translation. Consider the following example: Two people are attempting to have a conversation when neither understands the other's language. In this case, sophisticated discourse is impossible, and the conversationalists might have to revert to signing to make their point.

Next, let's assume that both individuals speak similar languages, e.g., Spanish and Italian, but neither is fluent in the other. In this scenario, elements of the conversation will be understood, whereas others will not be. In fact, this is comparable to what occurs when pathologists and clinicians converse. Although they share a basic medical education, their respective languages have diverged sufficiently due to their specific training that the details of the conversation are no longer fully comprehended.

Based on my experience as both a pulmonologist and pulmonary pathologist, I am convinced that the difficulties involved in conveying detailed information from one discipline to another have currently become great enough to detract from patient care. Although a standard medical school education continues to include introductions to pathology, the time allotted to its teaching has diminished. Medical subspecialties do not routinely attend autopsy conferences or study specimens through the microscope. In the United States, pathologists-in-training are no longer required to participate in direct patient care beyond medical school. Consequently, there has been an emergence of "medical dialects" that interfere with communication.

As a medical resident, I thought of diseases as distinct entities as they are presented in most medical textbooks. However, after training in pathology, I realized that my conceptions of disease had been artificial. Although certain diseases, like cancer, can be diagnosed by widely accepted criteria, the nonneoplastic medical diseases, which make up the bulk of disorders addressed by medical subspecialists, are difficult to define with precision. Their pathologies are frequently nonspecific, so that clinicopathological correlation is often required, if an accurate diagnosis is to be established, and even then, the diagnosis may remain in doubt.

In addition, there are many pathological findings that I had never encountered in clinical training. These represent the *esoterica* of pathology, i.e., entities recognized by pathologists, but unknown to clinicians. Pathologists may choose not to reveal these observations as efforts at communicating them to clinicians tend to produce undesirable confusion. Clinicians may experience the same frustration in describing certain clinical facets of disease to pathologists, who for the most part are no longer conversant with the subtleties of physiology and therapeutics.

The unintended result is the insularity of medical specialties. For pathologists, this has resulted in an increased inclination to focus primarily on the diagnosis of neoplastic diseases, as this is the pathologist's area of greatest expertise vis-à-vis medical internists. As pathologists may have difficulties in interpreting biopsies of nonneoplastic diseases and in recognizing the implications of their diagnoses, they frequently choose to defer to the clinical impressions of the medical subspecialist in interpreting their pathological findings.

Furthermore, pathological observations are too often ignored by medical researchers who lack training in pathology. Creative researchers can develop some very interesting theories concerning the pathogenesis of disease, but which have

little bearing on disease as it appears under the microscope. I have reviewed research articles for prestigious medical research journals in which the published images of an animal model did not actually show what they were purported to, or lacked any resemblance to the disease being investigated. A substantial amount of funded research is ill conceived for this reason.

So how does one convey information concerning the pathology of lung disease to pulmonologists and vice versa? Routinely attending mandatory clinico-pathological conferences is a good first step. I have personally come to know my medical colleagues' understanding of pathology. I make a concerted effort at these conferences to be certain that pathological diagnoses are clearly explained, with respect to their specificities. When I sense that a pathological diagnosis is perhaps being misconstrued, I will guide my colleagues back to the reality at hand. Although it may be difficult to rein in a clinician's diagnosis, optimal patient care may require it.

There tends to be a dichotomous appreciation of pathologists among clinicians. Some expect that pathologists know all, others that they know next to nothing. As in most things, the correct answer is somewhere in between.

Another challenge is a widespread confusion among pulmonologists concerning who, when, and how to harvest lung samples. There are multiple reasons for this problem. Pulmonologists do not understand the challenges that face pathologists in the diagnosis of medical lung disease. The findings in the lung may be patchy, as in pulmonary vascular disease, or complex and multifocal, as in autoimmune disorders. In such cases, a transbronchial biopsy is likely to be a low yield procedure with respect to establishing an accurate diagnosis. Some pulmonologists are routinely hesitant to pursue larger thoracoscopic biopsies and tend to default to less invasive procedures that they can control. However, routinely opting for a low diagnostic yield procedure with the idea that a larger procedure can subsequently be pursued can be inappropriate and put the patient through unnecessary discomfort.

It is likely that the nuances of both pulmonary medicine and pathology can only be optimally synthesized by a single mind. Understandably, this is rarely possible, yet a deep knowledge of lung anatomy and microscopic anatomy is an absolute requirement for understanding pulmonary disease. I often wish that pulmonologists would spend more time formally learning lung pathology, but it is unreasonable to expect them to become experts. Instead, it is my hope that they will use this text to foster diagnostic acumen. They should also use this text to learn which questions are important to pose to their colleagues in pathology, to achieve sophistication in diagnosis, therapy, and research.

Although this project was originally aimed at educating pulmonologists, pathologists will find that this text will enhance their appreciation of lung disease, a field that many find challenging.

A chapter on the radiology of common lung diseases authored by Dr. S. Digumarthy has been included as an integral part of the text as it will certainly help both clinicians and pathologists approach lung pathology in practice.

As access to references is widely available on the Internet, I have chosen not to provide a detailed bibliography. Instead, I have cited a number of articles that should provide the reader with a broad overview of the topics presented here. Some of the ideas presented in this text represent my own perspectives on lung pathology and have never been published. However, as they represent the observations made over a long career engaged in the study of lung disease, I am confident that they will be confirmed by others in practice.

Finally, I have included a glossary of terms widely used by pulmonary pathologists that lead to considerable confusion among pulmonologists. This was at the suggestion of the editors, and I fully agree that it will be of substantial value to the reader. Most of these terms that appear in the text are in italics.

Richard L. Kradin

Chapter 1

Approach to the Sampling of the Lung

The basics of lung pathology include how to optimally harvest and process lung samples. There are currently a variety of options available for obtaining lung cells, fluids, and tissue, and they differ with respect to their potential diagnostic yield. Specialty training and individual can bias which approach is taken, but this may not always be optimal for establishing an accurate diagnosis.

Determining which approach to take depends on a variety of factors. Most important is whether the patient can tolerate the procedure. Seriously hypoxemic patients in respiratory distress are not able to tolerate bronchoscopic procedures. Patients with tenuous cardiovascular status may not be candidates for anesthesia. Severe pulmonary hypertension is a contraindication for most invasive procedures. Coagulopathies must be corrected before considering either a lung biopsy or a bronchoscopic brushing. Each patient presents a different decision matrix.

If the patient is judged sufficiently healthy to undergo either an endoscopic or a surgical biopsy, the next concern should be the diagnostic yield. A variety of disorders can potentially be diagnosed via bronchoalveolar lavage (Table 1.1). This includes most infections, as well as malignancy, the presence of diffuse pulmonary hemorrhage, alveolar proteinosis, eosinophilic pneumonia, and Langerhans' cell histiocytosis.

If one opts for a bronchoalveolar lavage (BAL), the question should arise as to whether to perform a concomitant endoscopic biopsy. In a diffuse pulmonary disease, transbronchial biopsy generally adds little morbidity to the procedure and tends to enhance the diagnostic yield. Central endobronchial lesions can readily be visualized and biopsied. Endoscopic ultrasound-guided biopsies and transpulmonary needle biopsies increase the diagnostic yield for sarcoidosis and malignancy and can be helpful in staging lung cancers as potentially inoperable.

Malignant pulmonary nodules that are peripherally located can be accurately sampled via fine needle aspirate biopsies and this may be the optimal approach especially if the likelihood of infection and additional information from a BAL is low. However, nonmalignant nodules are rarely definitively diagnosed by minimal sampling, with the exception of infectious granulomatous disease. Severe emphysema is a contraindication for fine needle aspiration (FNA) due to the increased risk of pneumothorax, and certain nodules cannot be sampled due to their location.

Thoracoscopic biopsies are the gold standard for the diagnosis of diffuse interstitial pneumonias and benign nodular diseases. The diagnosis of interstitial disease requires that the pathologist be provided sufficient tissue with which to achieve a diagnosis. Many disorders are patchy and cannot be reliably sampled by a transbronchial approach. Ideally, in diffuse interstitial disease wedge biopsies should be harvested via the thoracoscope from all lobes of the lung and for benign nodular diseases, from areas showing radiographic abnormalities.

TABLE 1.1 Diagnosis by Bronchoalveolar Lavage (BAL)

Infection (viral, bacterial, mycobacterial, helminths)	Culture, PCR, electron microscopy (EM)
Malignancy	Cytology, EM
Pulmonary alveolar proteinosis	Gross inspection, EM
Langerhans' cell histiocytosis	Immunostains for CD1a, and S-100, EM
Eosinophilic pneumonia (PNA)	Eosinophil count
Diffuse alveolar hemorrhage	Blood, hemosiderin-laden macrophages
Lipid aspiration	Oil-Red O stain
Asbestosis	Asbestos bodies

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TABLE 1.2 Diagnoses that Generally Require a Video-Assisted Thoracoscopic (VATS) or Open Lung Biopsy Procedure

Usual interstitial pneumonia/idiopathic pulmonary fibrosis
Nonspecific interstitial pneumonia
Hypersensitivity pneumonitis (subacute/chronic)
Organizing pneumonia
Rheumatoid nodules
Langerhans' cell histiocytosis
Erdheim–Chester disease
Rosai–Dorfman disease
Drug-induced pneumonitis
Vasculitis
Nodular infections
Pulmonary veno-occlusive disease
Pulmonary capillary hemangiomatosis
Sclerosing hemangioma
IgG4 disease
Amyloidosis
Isolated scars

The tip of the right middle lobe and the lingula can show nonspecific chronic changes and these areas should not be sampled. The surgeon should avoid areas of lung with features of end-stage lung, as these may not be diagnostic (Table 1.2).

Cryobiopsies increase the amount of lung tissue that can be sampled and may in the future decrease the need for thoracoscopic biopsies. But at present, there have been untoward hemorrhagic complications in patients and this approach requires further evaluation.

Perhaps the most critical question is whether an invasive sampling approach will influence treatment. This is a difficult subject to discuss out of context. For example, there are many inflammatory medical disorders that respond well to corticosteroids and it can be argued that a biopsy is unlikely to add much to an empiric therapeutic approach. Although there is merit to this argument, especially if a patient is not a good candidate for a procedure or is reticent to undergo one, obtaining a biopsy can foster confidence in adopting a therapeutic approach and may ultimately reassure patients. As will be discussed, characterizing the histological features of the inflammatory response may assist in guiding therapy. Finally, research into disease must be based in part on pathological observations. For all of these reasons, biopsies should be pursued, ideally in the early stage of the disease, whenever there is doubt concerning the diagnosis, assuming that the benefits outweigh the actual risks.

How best to approach the diagnosis of noninfectious pulmonary disorders merits a detailed explaination. Endobronchial biopsies will generally suffice for the diagnosis of intraluminal neoplasia, both benign and malignant, when sampling is adequate. But the ability of transbronchial biopsies to yield an accurate diagnosis is limited to diffuse diseases with a lymphangitic pattern of spread, including lymphangitic carcinoma, lymphoma, and sarcoidosis, and they can generally be diagnosed by this approach if approximately five samples are retrieved. The pulmonary lymphatics course adjacent to the small airways and therefore are readily sampled. Peribronchiolar and diffuse diseases can also be diagnosed in some cases. Transbronchial biopsy (TBB) is a reasonable first choice when the differential diagnosis, based on an in-depth appreciation of the clinical and radiographic findings, includes eosinophilic pneumonia, organizing pneumonia, hypersensitivity pneumonitis, Langerhans' cell histiocytosis, desquamative interstitial pneumonitis (DIP), and respiratory bronchiolitis. All published series on the role of TBB tend to include a variety of diagnoses but the level of reproducibility for some is poor (Table 1.3).

Finally, pulmonologists must be cautious in their interpretation of the results of certain procedures. For example, the finding of *Aspergillus* spp. in a BAL specimen does not mean that a peripheral nodule in the lung is necessarily caused

TABLE 1.3 Biopsies Established by Endobronchial/Transbronchial Biopsy

Malignant
Endobronchial and lymphangitic malignant tumor
Lepidic adenocarcinoma
Carcinoid
Granular cell myoblastoma
Adenoid cystic carcinoma
Granular cell tumor
Squamous papilloma
Benign
Sarcoidosis
Amyloidosis (airway)
Granulomatous polyangiitis (airway)
Eosinophilic pneumonia
Diffuse alveolar damage/acute interstitial pneumonia
Acute panbronchiolitis
Infection (if nodular or localized[a])
Hypersensitivity pneumonitis
Organizing pneumonia[a]
Drug-induced pneumonia
Obliterative bronchiolitis[a]
Langerhans' cell histiocytosis[a]
[a]*Diagnosis most often requires a VATS or an open biopsy.*

by the fungus. In such a case, and in the absence of immunosuppression, it would be wise to obtain a tissue biopsy. Certain findings, for example, organizing pneumonia in a small biopsy, may reflect a nonspecific change adjacent to a tumor or abscess. In the same vein, a diagnosis of organizing pneumonia does not mean that the disease is cryptogenic and the pulmonologist must consider a list of possible causes. The diagnostic process should not stop after a biopsy diagnosis has been rendered until all etiologies have been excluded. On the other hand, a diagnosis of malignancy made with a high degree of confidence, even in a small sample, is rarely an error, and additional diagnostic approaches are rarely required.

Ultimately, the choice of biopsy depends on a thoughtfully considered differential diagnosis. If there is doubt concerning which approach to pursue, the question should be discussed with the diagnosing pathologist who ultimately will have to make the diagnosis and may have a clearer idea as to what type of sampling is optimal.

HANDLING OF THE SAMPLES

Bronchoalveolar lavage fluids should be divided into samples for cytological, hematologic, biochemical, and microbiological examination. Cell counts and differential counts can be extremely helpful in assessing infection. In autoimmune disorders, serological testing can help establish the correct diagnosis. In cases in which a diagnosis of alveolar proteinosis is a consideration the milky opaque appearance of the fluid can be diagnostic and a small aliquot can be centrifuged and processed for electron microscopy. If lymphoproliferative disease is being considered, fluids should be examined by cytofluorimetry.

Specific questions should be posed directly to the hospital cytologist who may be inclined to comment solely on the presence or absence of malignancy. If there is a question of Langerhans' cell histiocytosis, the cytologist should be asked to apply appropriate immunostains and/or process the fluid for electron microscopy. If there is a question of pulmonary

TABLE 1.4 Commonly Histochemical Stains Applied in the Diagnosis of Pulmonary Disease

Stain	Purpose
Hematoxylin and eosin	Standard stain for assessing histopathology. Most forms of inflammation, microorganisms, and tumors can be identified accurately with this single combination stain
Elastic stains	Determine underlying architecture, evaluate vascular disease, identify obliterated airways, and determine invasion by tumor or fungi
Trichrome stains	Detects and distinguishes new (gray) from established collagen (dark blue) deposition. Distinguishes muscle (red) from collagen. Distinguishes fibrin (red) from collagen
Periodic acid Schiff	Detects glycogen and glycogenated proteins. Helpful in distinguishing alveolar lipoproteinosis from pulmonary edema and in the diagnosis of certain tumors
Iron stain	Detects hemosiderin, a breakdown product of red cell hemoglobin, and can be used to diagnose early and chronic pulmonary hemorrhage. Asbestos bodies are easily detected with iron stains
Congo red	Used to detect amyloid fibers. True amyloid stains red and is apple green when examined under polarizing light

hemorrhage, which may be seen in diffuse alveolar hemorrhage (DAH), lymphangioleiomyomatosis (LAM), or pulmonary veno-occlusive disease (PVOD), the cytologist should be asked to note the presence of hemosiderin-laden macrophages.

The pulmonologist should be aware that in most centers, the standard approach to handling tissue by surgeons and surgical pathologists is to place it directly into buffered formalin prior to processing it for microscope slide production. However, this approach may be suboptimal. When infectious disease is a consideration, tissue should first be cultured and saved or frozen for the possible application of PCR. Frozen tissue is also required if direct immunofluorescence is to be applied, if there is a question of immune complex disease, or for research purposes.

In some cases, especially certain unusual malignancies, infections, or storage diseases, tissue should be harvested for ultrastructural examination, which requires glutaraldehyde fixation and appropriate buffering, as formaldehyde is a suboptimal fixative for ultrastructural examination.

HISTOCHEMICAL STAINS

The standard histochemical stain applied to biopsies in pathology is the hematoxylin and eosin stain. It allows the pathologist to diagnose most disorders. However, a host of other stains may be required to optimize the diagnosis of lung diseases (Table 1.4).

IMMUNOSTAINS

Various immunological antibodies have been commercially developed for the detection of cell-associated antigens. These are important in the diagnosis and subclassification of malignancies but they also play a role in the diagnosis of nonmalignant disorders. Other techniques including in situ hybridization and molecular phenotyping play an important role in the diagnosis of malignant and benign lung disorders.

FURTHER READING

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Chapter 2

Anatomy of the Lung

The practice of surgical pathology is based on "morbid anatomy," i.e., the interpretation of changes in normal lung structure. The lung develops from the embryonic *foregut*. The developing lung in the first trimester of gestation consists of epithelial-lined tubules that course within undifferentiated *mesenchyme*. This is referred to as the *pseudoglandular* phase of development (Fig. 2.1). With increasing gestational age, branching tubular precursors of what will ultimately become the conducting airways invade the *mesenchyme* to produce the *canalicular* phase. In the late third trimester, the process of alveolarization occurs and does not fully mature until term. This *alveolar* phase includes the differentiation of the gas-exchanging units of the lung.

At birth, the fetal lung is normally filled with amniotic fluid but must inflate without collapsing as it enters the gaseous medium of the ambient air. Surfactant lipoproteins produced by mature pulmonary alveolar epithelial cells reduce surface tension according to the *Laplace equation* ($P = 2T/R$; i.e., intra-alveolar pressure = 2 × tension/radius of the alveolus) and surfactants prevent the inflated alveoli from collapsing. When surfactant production is deficient due to prematurity or congenital abnormalities, ventilation and gas exchange may be reduced leading to the neonatal *respiratory distress syndrome*. After birth, the thickened blood vessels of the fetal circulation become progressively thin walled as they mature into a high-capacity, low-pressure, system for the conduction of pulmonary blood flow.

GROSS PULMONARY ANATOMY

The lungs are located in the chest cavities on either side of the heart and other mediastinal structures. The right lung is larger and normally has three lobes, whereas the left lung has two lobes (Fig. 2.2). The right lung includes 10 segments, the left lung 8 (Fig. 2.3). These segmental bronchi can be identified by the bronchoscopist (Table 2.1). Fibrous *major fissures* separate the upper from lower lobes of both the right and left lungs and an additional *minor fissure* partitions the right middle lobe (Fig. 2.2). These fissures may be anatomically complete or incomplete. This is potentially important as air can move from one segment or lobe to another via collateral ventilation if fissures are incomplete.

AIRWAY ANATOMY

Lung structure determines lung function (Table 2.2). The airways serve different physiological activities depending on their caliber. The larger conducting airways consist of ~15 orders of fractal-like, asymmetric, dichotomously branching, cartilaginous tubes that efficiently carry air to and from the lung (Fig. 2.4A and B). The conducting airways represent the normal anatomic *dead space* of the lung (~150 mL), as they do not participate directly in gas exchange.

The large airways are lined by a complex pseudostratified ciliated columnar epithelium (Fig. 2.5A and B) that secretes serous and mucinous glycoproteins, which defend against microbial invasion and injury due to inhaled particulates.

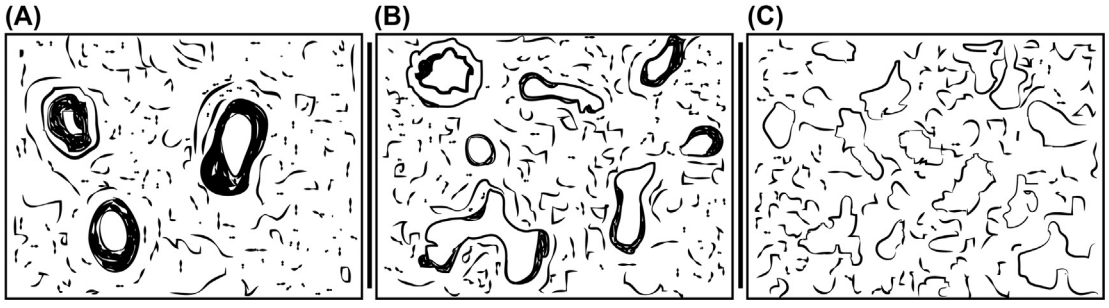

FIGURE 2.1 Development of the embryonic lung: (A) the pseudoglandular phase, (B) the canalicular phase, and (C) the alveolar phase.

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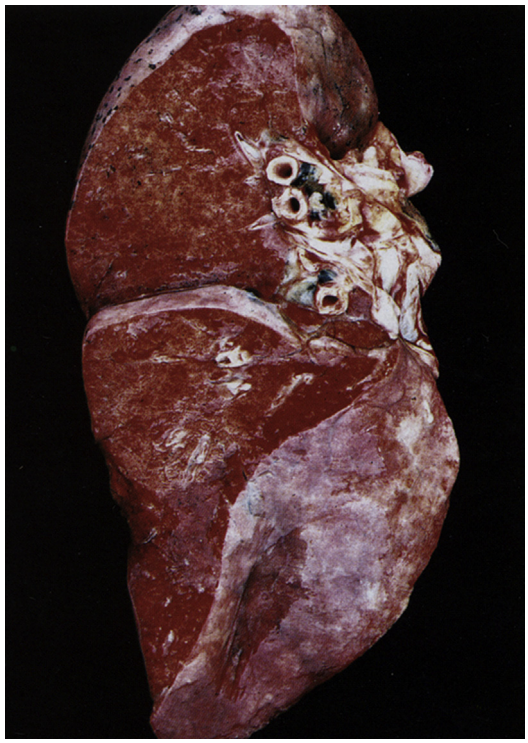

FIGURE 2.2 The adult right lung has three lobes separated by a major and minor fissure.

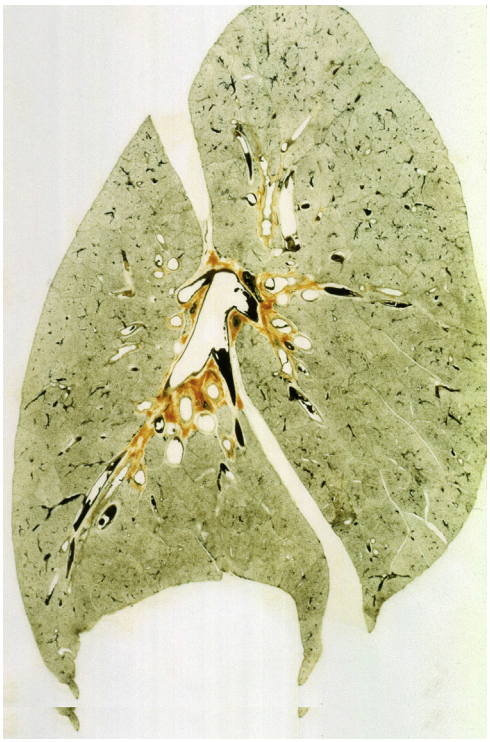

FIGURE 2.3 A thin Gough section of the adult left lung showing its major fissure.

TABLE 2.1 Gross Lung Lobar and Segmental Anatomy

Right Lung	Left Lung

• Upper lobe
  ◦ Apical
  ◦ Anterior
  ◦ Posterior
	• Upper lobe
	  ◦ Apical-posterior
	  ◦ Anterior
	  ◦ Superior
	  ◦ Inferior

• Middle lobe
  ◦ Medial
  ◦ Lateral	

• Lower lobe
  ◦ Superior
  ◦ Anterior basal
  ◦ Lateral basal
  ◦ Medial basal
  ◦ Posterior basal
	• Lower lobe
	  ◦ Superior
	  ◦ Antero-medial basal
	  ◦ Lateral basal
	  ◦ Posterior basal

TABLE 2.2 Essential Aspects of Pulmonary Microanatomy

Bronchi are cartilaginous airways, bronchioles lack cartilage
The acinus is an idealized unit of gas exchange that includes all airway structures distal to the terminal bronchiole
Airways course with pulmonary arteries to the level of the terminal bronchiole
Pulmonary veins run in the interlobular septa
Lymphatics run adjacent to bronchovascular septa, interlobular septa, and both visceral and parietal pleura
The visceral pleura reflects along the chest wall as the parietal pleura

Secreted mucus mobilized by ciliated epithelial cells acts as a *mucociliary escalator* that sweeps inhaled particulates adorally toward the mouth to be expectorated or swallowed.

The airways course together with the pulmonary arteries within fibrous bronchovascular septa to the level of the terminal bronchiole (Fig. 2.6). The terminal bronchioles enter the lung at the center of the secondary *pulmonary lobule*, a hexagonal lung tissue unit subtended by adjacent interlobular septa. The pulmonary veins course within these septa. The interlobular septa can be visualized by computed tomography scanning and with the naked eye (Fig. 2.7).

The location of disease within the pulmonary lobule is an important feature in diagnosis. Airway disease tends to be located at the center of lobules, whereas certain forms of pulmonary fibrosis are located peripherally. Diseases associated with the microcirculation are randomly distributed in the pulmonary lobule. For this reason, biopsy samples that do not adequately sample the pulmonary lobule are often inadequate for diagnostic purposes.

Cartilage in the trachea normally forms a continuous semicircle with a membranous posterior membrane, whereas the bronchial cartilage is segmented. The distribution of cartilage in the airways is irregularly identified in airways that are less than ~2 mm in diameter. Serial sectioning of a small caliber airway at this level can reveal cartilage in some sections but not in others. For this reason, they are best referred to generically, both anatomically and physiologically, as *small airways*.

Bronchioles by definition lack cartilaginous investment. The membranous *terminal bronchioles* ramify into three to five pulmonary acini that include the gas-exchanging surfaces of the lung (Fig. 2.8). The acinus is an idealized structure with (1) approximately three orders of branching respiratory bronchioles that are partially alveolated and contribute to gas exchange; (2) the alveolar duct that has the highest O_2 tension within the acinus; and (3) the terminal alveolar sacs (Fig. 2.9). However, what can actually be seen radiographically or with the naked eye is the *pulmonary lobule* and not the acinus.

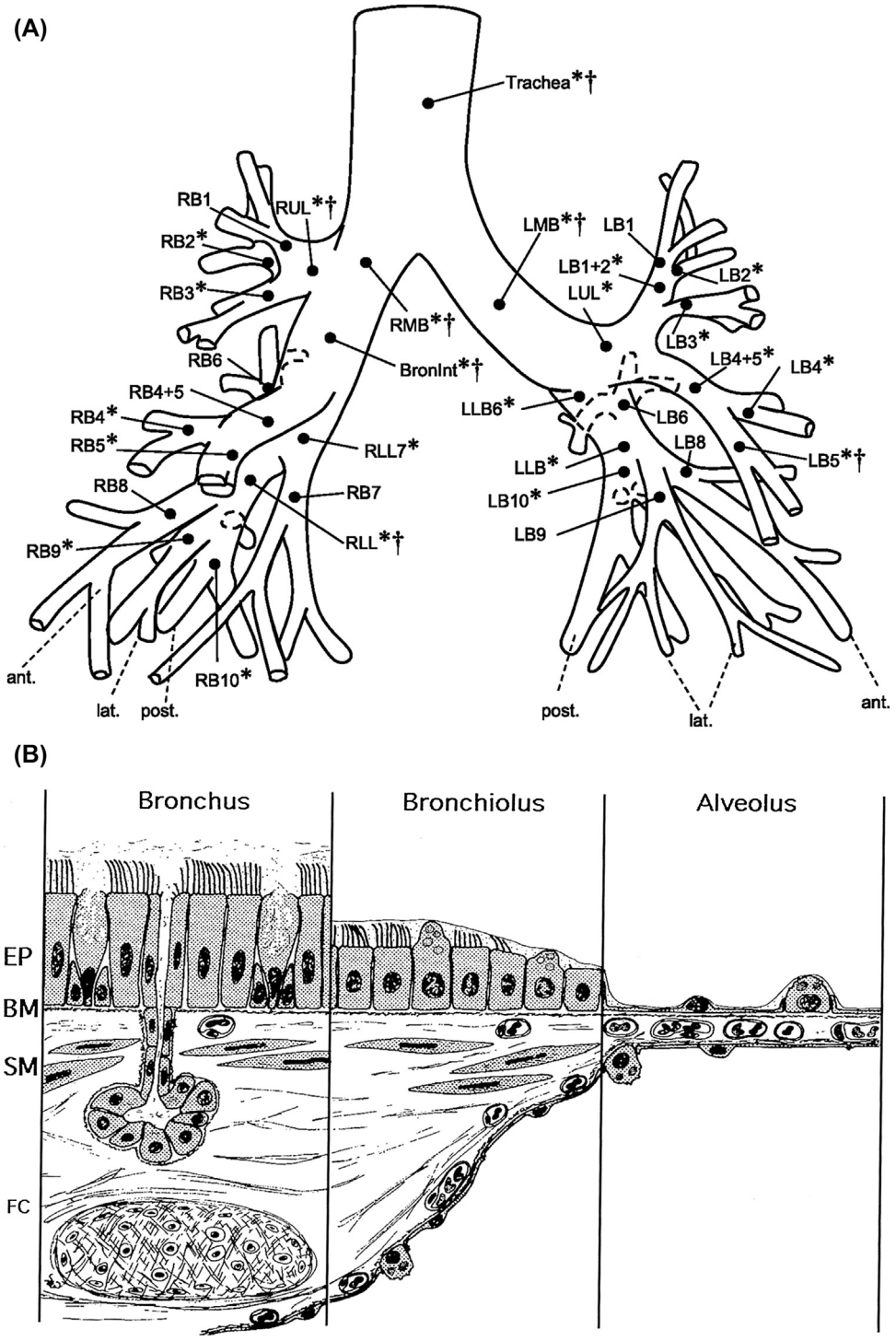

FIGURE 2.4 (A) The branching segmental anatomy of the normal airways, (B) diagram of airway structure moving from proximal to distal. *BM*, basement membrane; *EP*, epithelium; *F*, fibrocartilage; *SM*, smooth muscle.

The alveolar wall is lined by a flattened squamous alveolar type I cell that can only be visualized with the electron microscope (Fig. 2.10) and by alveolar type II cells that secrete surfactant (Fig. 2.11). The latter proliferate nonspecifically during inflammation, and an increase in the number of alveolar epithelial cells is a nonspecific indicator of alveolar injury.

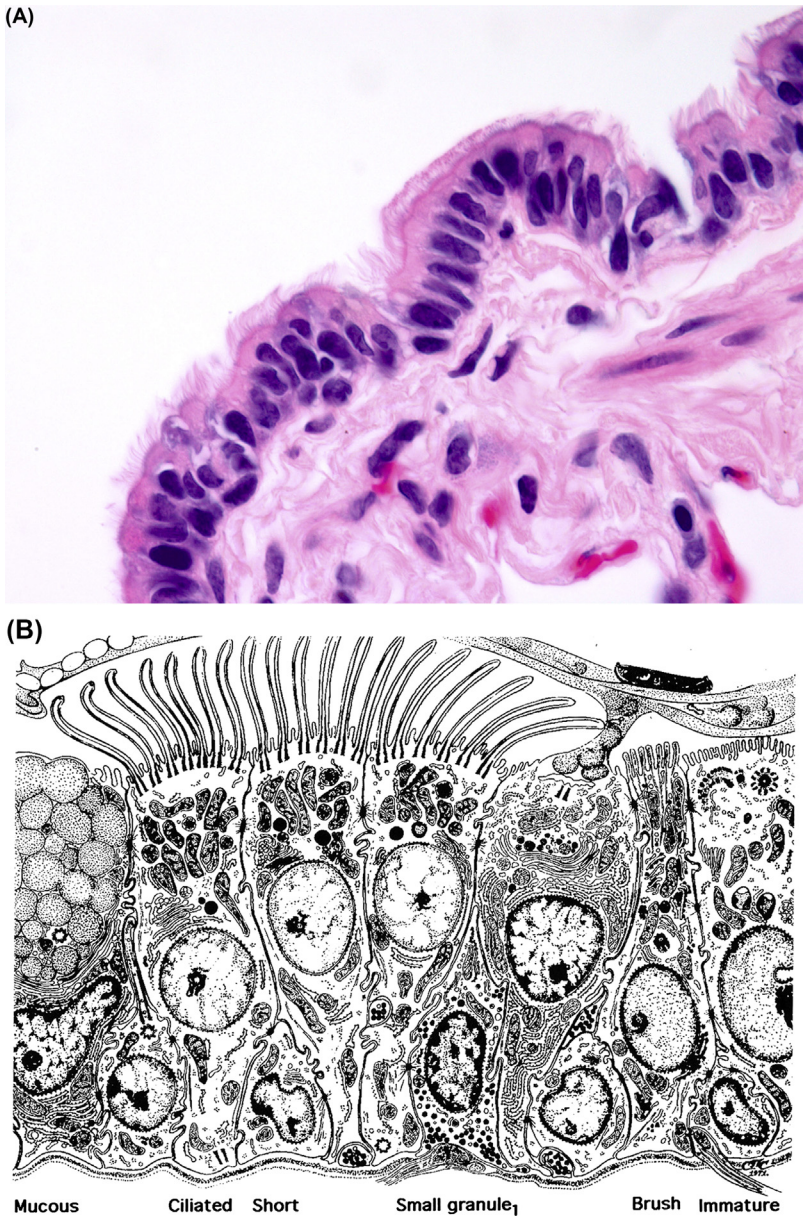

FIGURE 2.5 (A) Normal pseudostratified ciliated respiratory epithelium, (B) diagram of respiratory epithelium.

Gas exchange takes place across the basement membrane shared by the alveolar type I cell and the alveolar endothelial cell (Fig. 2.10). The nongas exchanging surface of the alveolus includes matrix-producing cells and elastin fibers, and it serves as a potential space for the accumulation of fluid and inflammatory cells.

PULMONARY VESSELS

The main pulmonary artery arises from the right cardiac ventricle and immediately branches into two trunks that carry deoxygenated blood to each lung. As noted, the pulmonary arteries course in fibrous septa with their accompanying airways. This allows pathologists to landmark these structures with the light microscope. The pulmonary artery is generally ~15% smaller in luminal diameter than its accompanying airway. Changes in their relative size suggest underlying pathology due to either airway or vascular disease. The pulmonary arteries distal to the terminal bronchiole diverge as they enter the pulmonary lobule to supply the pulmonary alveolar capillaries, where the bulk of the gas exchange occurs between inhaled O_2 and circulating CO_2.

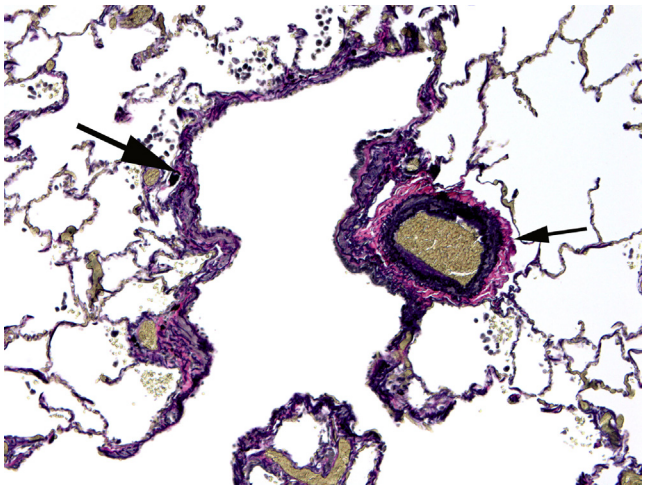

FIGURE 2.6 A pulmonary airway (*large arrow*) and artery (*small arrow*) course together in the fibrous bronchovascular septa (elastic stain).

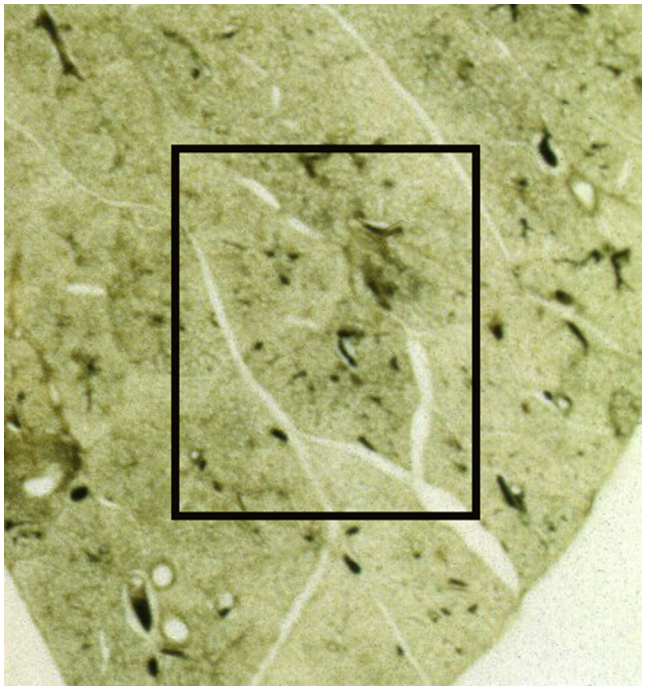

FIGURE 2.7 A secondary pulmonary lobule (box) is delineated by the interlobular septae.

Hypoxemia, i.e., decreased partial pressures of O_2 (pO_2) in the systemic arterial blood is a cardinal feature of lung disease (Table 2.3). The physiological causes of hypoxemia include (1) hypoventilation, (2) V/Q abnormalities in which there is suboptimal matching of ventilation and pulmonary blood flow, (3) the shunting of deoxygenated blood, which can reflect (a) an intracardiac shunt of deoxygenated blood from the right into the left ventricle, (b) shunting by blood vessels in the lung, or (c) areas of lung that are receiving blood but not ventilated (atelectatic lung), and (4) a block to the normal diffusion of O_2 across the alveolar wall. Carbon monoxide reduces O_2 saturation by competing with O_2 for binding sites on hemoglobin. Methemoglobin induced by certain drugs and foods (fava beans) in patients with glucose 6-phosphate dehydrogenase (G6PDH) deficiency and can also produce hypoxemia.

An elevated pCO_2 in the arterial blood (Table 2.4) *always* indicates hypoventilation due to (1) decreased pulmonary bellows function, (2) decreased central ventilatory drive, or (3) increased peripheral CO_2 production due to hypermetabolism, e.g., fever, when unmatched by an adaptive increase in ventilation. The level of arterial pCO_2 is a function of the