Clinical Atlas of Interstitial Lung Disease

Tatjana Peroš-Golubičić, MD, PhD, and
Om P. Sharma, MD, FRCP

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Foreword by Talmadge E. King, Jr., MD

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Tatjana Peroš-Golubičić, MD, PhD
University of Zagreb
Medical School
University Hospital for Lung Diseases "Jordanovac"
Zagreb
Croatia

Om P. Sharma, MD, FRCP
Keck School of Medicine at University of Southern California
Los Angeles, California
USA

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Foreword

The interstitial lung diseases, also called diffuse parenchymal lung diseases, are a diverse group of pulmonary disorders classified together because of similar clinical, roentgenographic, physiologic, or pathologic features. During the past 50 years, we have experienced remarkable advances in the classification, diagnosis, and management of these diseases. Technological advances, particularly high-resolution computed tomography, bronchoalveolar lavage, and video-assisted thoracic surgery, have provided access to information that has vastly improved our understanding of these entities. In addition, genetic medicine, the use of new technologies (e.g., microarrays, mass spectroscopic analysis of proteins, and laser capture microdissection) and the development of animal models have led to better understanding of the pathogenesis of these disorders.

Unfortunately, patients with diffuse parenchymal lung disease continue to present a difficult diagnostic and management challenge to clinicians. A major reason is that the topic of "interstitial lung disease" is vast and difficult to grasp. Some 25 years ago when I first became interested in interstitial lung diseases, there was no ready source of information relating specifically to these processes. Even today, there is a need for a comprehensive, yet easy to read, manual of the key information about the important interstitial lung diseases.

The purpose of this atlas is to provide the clinician, from medical student to lung specialist, with a ready reference helpful in their attempts to master this topic and to provide guidance in their daily practice. The subject of interstitial lung disease is inherently multidisciplinary; consequently, the authors have provided a consistent approach to each entity that includes the key clinical, physiologic, radiologic, and pathologic features.

The *Clinical Atlas of Interstitial Lung Disease* is composed of 37 chapters loosely divided into six sections. The first section provides a historical background to the interstitial lung diseases and an overview of the basis for recognizing the key features that allow a specific diagnosis to be achieved. The second section is dedicated to the interstitial lung diseases of unknown etiology, including sarcoidosis, the idiopathic interstitial pneumonias, and eosinophilic pneumonias. The third section describes interstitial lung diseases of known etiology (e.g., drug-induced, radiation, hypersensitivity pneumonitis, and pneumoconioses). The fourth section addresses interstitial lung diseases associated with the connective tissue diseases and pulmonary vasculitidies. The fifth section deals with a number of specific entities (e.g., alveolar proteinosis, lymphangioleiomyomatosis, and Langerhans cell histiocytosis). The final section devotes several chapters to the pulmonary manifestations of systemic diseases, such as paraproteinemias, liver and gastrointestinal disease, and malignancy.

We owe a debt of gratitude to all those who were involved in producing this *Clinical Atlas of Interstitial Lung Disease*. The authors have succeeded in creating a readable, concise atlas that is up to date and user friendly.

Talmadge E. King, Jr., M.D.
Department of Medicine
University of California San Francisco; and
San Francisco General Hospital
San Francisco, California

Om P. Sharma, MD, FRCP, and Tatjana Peroš-Golubičić, MD, PhD.

Preface

The Oxford English Dictionary defines *atlas* as: "A similar volume containing illustrative plates, large engravings, etc., or the conspectus of any subject arranged in tabular forms; e.g. 'an atlas of anatomical plates,' 'an ethnographical atlas.'" In that vein, the *Clinical Atlas of Interstitial Lung Disease* is a visual representation of common and uncommon interstitial lung diseases.

Is there a need for such an atlas on interstitial lung disease? There has been an unprecedented revision and expansion of scientific and clinical knowledge of interstitial lung disease that now begs for such a volume. Dense, voluminous texts and review manuscripts on the topic grace the shelves of medical libraries and personal collections of many physicians; alas, perusal of these volumes requires considerable time and effort that is not easily available to a practicing clinician. Our aim in writing this atlas has been to produce a compendium that is easy to read, comprehensive, and light enough to be carried in a briefcase or to be enjoyed as a bedside reading. Designed to complement the existing scientific knowledge of interstitial lung disease, it enhances the bedside clinical education of the various disciplines of practitioners who treat patients with interstitial lung disease. It is a true pictorial supplement to the texts available on the topic.

Averill Liebow said, "A man's medical history, and the traces of his habits and his trades are often inscribed upon the lungs—for him who can read." As medical students, we are taught to obtain complete and relevant history and then perform a complete physical examination. This book leads a physician to create appropriate diagnostic patterns by combining the symptoms and signs with radiographic and laboratory findings. Once a clinical pattern or syndrome is successfully recognized and integrated in the memory, it can be conveniently recalled. A student of medical science will never regret mastering this art.

The book opens with a brief description of the relevant history, anatomy of the lung, and definitions of the common terms used. It is followed by a clinical classification of interstitial lung diseases due to known cause and those whose cause is not known.

Each brief chapter deals with the incidence, clinical features, and biochemical and molecular tests. Chest x-ray, HRCT imaging features, and bronchoscopic findings bring to life clinical pictures of the disease. The establishment of a correlation between histological findings and the associated radiographic appearances convey the strong message that the simple chest x-ray and especially the HRCT scan in many interstitial lung diseases have become an invaluable aid to clinical diagnosis. Appropriately placed tables broaden the scope of differential diagnosis. Sarcoidosis, idiopathic interstitial pneumonias, eosinophilic interstitial lung disease (ILD), a group of ILD of known cause, lung in diffuse connective diseases and vasculitis, rare pulmonary diseases, lung manifestations of liver and gastrointestinal diseases, and finally cancer and ILD are the titles of chapters that follow.

This atlas can be best categorized as a manual or handbook with the pictorial images enhancing a concise and practical description of the disease. Medical students, postgraduate trainees, and practitioners of all disciplines will benefit from the book. Because there is no atlas on interstitial lung disease, this will be the first such book on the topic.

Tatjana Peroš-Golubičić
Om. P. Sharma

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It is not possible to acknowledge individually all friends and colleagues who have directly or indirectly contributed to this atlas. We are particularly indebted to our contributors but also to numerous other colleagues. **Mirna Sentić**, MD, clinical immunologist, University Hospital Centre, Department of Internal Medicine, Zagreb, provided Figures 19.1(c), 19.2(a), 20.1, and 20.2(a, b, c); **Branko Malenica**, MD, PhD, Professor, University of Zagreb, Medical school, University Hospital Center, Immunology Lab, Zagreb, Figures 20.4, 21.2(a, b, c), 21.3, 22.4, 23.5, 24.7, 25.3, 26.2, and 27.1; **Igor Petriček**, MD, Ophthalmologist, University Hospital Centre, Department of Eye Diseases, Zagreb, Figures 4.2(a), 23.1(a, b, c), and 23.2(a, c); **Sanja Grle-Popović,** MD, PhD, Pulmonologist, University Hospital for Lung Diseases, Jordanovac, Zagreb, Figures 2.8(a, b), 8.1(d), and 16.2(e); **Vesna Matijević**, MD, Neurologist, University Hospital Centre, Department of Neurologic Diseases, Zagreb, Figure 20.3(b); **Tomislav Jukić**, MD, Ophthalmologist, University Hospital Centre, Department of Eye Diseases, Zagreb, Figures 4.2(c, d), 28.2, and 36.3; **Nenad Vukoja**, MD, Ophthalmologist, University Hospital Centre, Department of Eye Diseases, Zagreb, Figures 4.2(e), 19.2(b), and 28.2(c); **Ivo Sjekavica**, MD, Radiologist, University Hospital Centre, Zagreb, Figures 20.5 and 36.6; **Sonoko Nagai**, MD, Professor, Kyoto University, Japan, Figure 28.3; and **Ivan Dobrić**, MD, PhD, Professor of Dermatology, Department of Dermatology, University Hospital Center, Zagreb, Figures 21.1 and 22.1(c).

Finally, the atlas would never have been completed without the love, support, and patience of our families. Thank you **Maggie**, **Zdravko**, **and Maša**!

Tatjana Peroš-Golubičić
Om. P. Sharma

Contents

Contributors

Tatjana Peroš-Golubičić, MD, PhD
Associate Professor, Pulmonologist
University of Zagreb, Medical School
University Hospital for Lung Diseases
"Jordanovac"
Zagreb, Croatia

Om P. Sharma, MD, FRCP
Professor of Medicine
Keck School of Medicine at University
of Southern California
Los Angeles, California, USA

Jasna Tekavec-Trkanjec, MD, PhD
Pulmonologist and Bronchologist
Department of Pneumonology
University Hospital for Lung Disease
"Jordanovac"
Zagreb, Croatia

Silvana Smojver-Ježek, MD
Clinical Cytologist
Department of Cytology
University Hospital for Lung Disease
"Jordanovac"
Zagreb, Croatia

Šimun Križanac, MD, PhD
Professor of Pathology
Department of Pathology
University of Zagreb, Medical School
Zagreb, Croatia

Marijan Gorečan, MD
Radiologist
Department of Radiology
University Hospital for Lung Disease
"Jordanovac"
Zagreb, Croatia

1

Interstitial Lung Diseases: A Historical Note

> Sophisticated people can hardly understand how vague experience is at bottom, and how truly that vagueness supports whatever clearness is afterwards attained.
>
> George Santayana
> *The Life of Reason*

De morbis artificium diatriba, one of the most influential documents on occupational medicine, written by Bernardino Ramazzini da Capri (1633–1714), (Figure 1.1), surfaced in Padua in 1700. In the chapter "Diseases of Sifters, Measurers, and Handlers of Grain," the author described the occurrence of dry cough, cachexia, asthma, and dropsy in these workers. In addition, he commented on the role of humidity, and suggested that "small worms" not visible to the eye present in the wheat dust might be responsible for the illness. This was the first clinical description of an interstitial lung disease caused by occupational exposure.

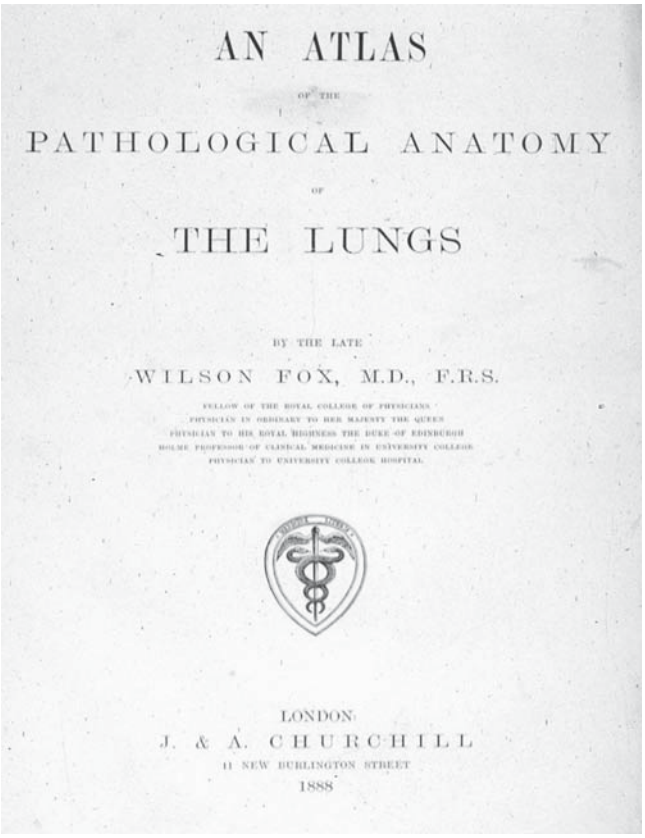
In 1868, Austin Flint described a vague, nondescript lung disease that he called *chronic pneumonitis*. It was characterized by florid inflammatory exudation without pus, and it caused solidification and fibrosis of the lungs. Flint alluded that Carl Freiherr von Rokitansky had described a similar condition in which exudation had occurred into the interlobular and intervesicular areolar tissue. Furthermore, he asserted that the illness was different from florid tuberculosis. A few years earlier, Dominic Corrigan, an Irish cardiologist, called the similar entity *cirrhosis of the lung* because it was analogous, not identical, to cirrhosis of the liver. Although Flint had thought that the condition was rare; two significant observations were made during the period. First, Corrigan described the occurrence of traction bronchiectasis in interstitial pneumonitis. Second, Flint observed that the fingertips of one patient with interstitial pneumonitis had assumed a bulbous appearance, and he therefore became the first to notice the association of clubbing and interstitial pneumonitis/fibrosis.

Two decades later, Wilson Fox, professor of pathological anatomy at the University College, London, recorded the microscopic changes of capillary edema; accumulation of pigmented epithelium in the alveoli; and thickening of the walls of the alveoli and veins in lungs with interstitial pneumonitis. Fox also credited Rokitansky for recognizing the fibrous thickening of the alveoli in this condition (Figure 1.2a, b, c).

In 1892, William Osler, while at Johns Hopkins Hospital, Baltimore, observed, "In one of Charcot's cases . . . death occurred about three months after the onset of the acute disease and the lung was two thirds of the normal size, grayish in color, hard as cartilage. In only case of the kind that has come under my observation, the patient died about a month from the onset of the chill. The lung was uniformly solid and grayish in color. Microscopically these areas showed advanced fibrotic changes and great thickening of the alveolar walls." Osler recommended that the term *cirrhosis* should be applied only to the cases in which a lung was densely fibrosed, whether fibrosis had originated in the parenchyma or the pleura. Additionally, like Flint, Osler advised that this new entity be distinguished from the fibrosis caused by tuberculosis (Figure 1.3).

In 1944, Louis Hamman and Arnold Rich (Figure 1.4), both at the Johns Hopkins University School of Medicine, described four young patients who died of progressive

Figure 1.1. Bernardino Ramazzini (1633–1714).



a

Figure 1.2. Title page: *An Atlas of the Pathological Anatomy* (a). Chronic pneumonitis caused by syphilis (b). Various stages in the development of fibrosis in chronic phthisis (c).
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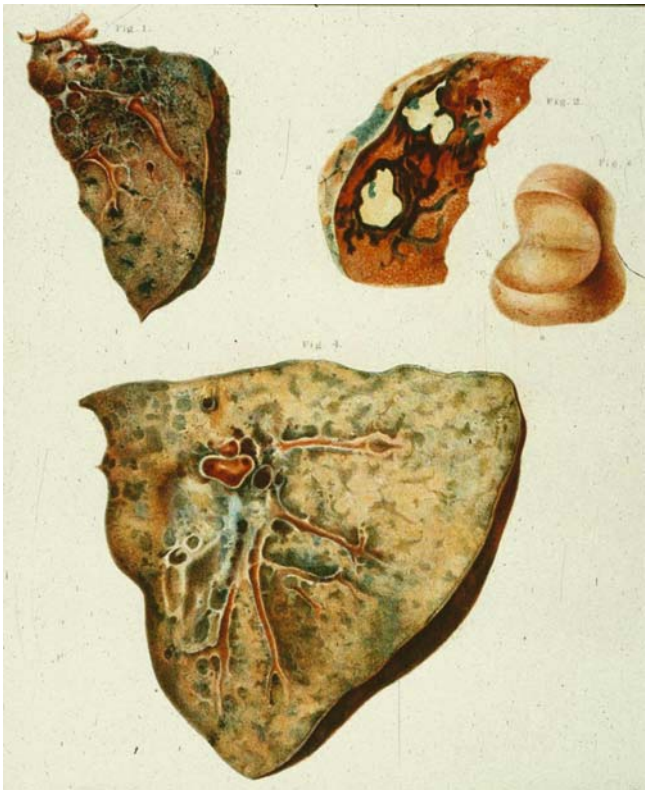

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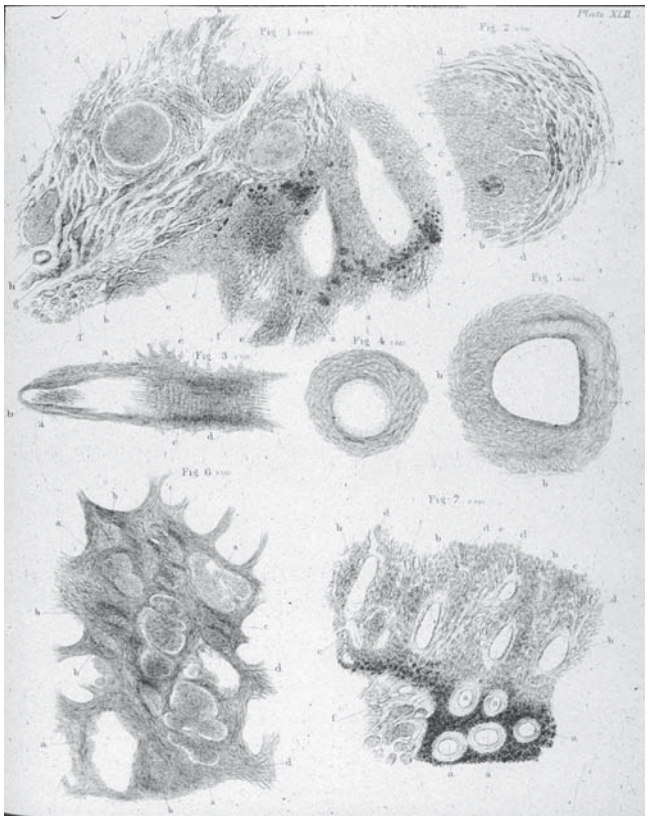

c

Figure 1.2. (continued)

Figure 1.3. Sir William Osler (1849–1919).

Figure 1.4. Louis Hamman and Arnold Rich at Johns Hopkins Medical Center, Baltimore, Maryland.

dyspnea within 6 months of onset. The clinical profile of the illness was similar to that described earlier by Flint, Corrigan, Fox, Charcot, and Osler. The term *Hamman-Rich syndrome* became a synonym for an interstitial pneumonia of unknown cause followed by fulminating pulmonary fibrosis. It was soon apparent that the course of this new disease was not always acute, progressive, or fatal. In 1957, Rubin and Lubliner reviewed 48 cases of the Hamman-Rich syndrome and added 15 cases of their own. From that point on, diffuse interstitial pneumonitis/fibrosis could no longer be considered a rare disease.

In 1960, interstitial pneumonias acquired two new terms: *idiopathic pulmonary fibrosis* and *cryptogenic fibrosing alveolitis*. Scadding and Hinson, working at Brompton Chest Hospital, London, preferred the latter term to define the inflammatory and fibrotic changes in the lung parenchyma. They advised that the word *idiopathic* be dropped in favor of the term *cryptogenic* in describing the illness of unknown cause. *Cryptogenic fibrosing alveolitis* is an accepted term in Europe; whereas, in North America, the usual *interstitial pneumonia* remains a popular description.

Averill Liebow (Figure 1.5), on the basis of his extensive clinical and pathologic sciences, classified interstitial pneumonitis into five different histologic types: usual interstitial pneumonitis (UIP), desquamative interstitial pneumonia (DIP), bronchiolitis obliterans interstitial pneumonia (BIP), lymphoid interstitial pneumonia (LIP), and giant cell interstitial pneumonia (GIP).

The classification of idiopathic or primary interstitial lung disease was further simplified by removing BIP, LIP, and GIP, and by adding nonspecific interstitial

Figure 1.5. Averill Liebow in San Diego, California.

pneumonia (NSIP). The new classification of idiopathic interstitial pneumonia includes UIP and DIP from Liebow's original classification and two new entities, acute interstitial pneumonia (AIP; or Hamman-Rich syndrome) and NSIP. Bronchiolitis obliterans organizing pneumonia (BOOP) was not initially included because it is primarily an intraluminal disease, but later the American Thoracic Society/European Respiratory Society (ATS/ERS) consensus included it again for its similar diagnostic algorithm and clinical behavior as other IIPs. Lymphoid interstitial pneumonias (LIP) were also added to the list. Clinical recognition of these disorders is easier today than it used to be in the early days.

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2

Definition, Classification, and Clinical Features

The term *interstitial lung disease* (ILD), or *diffuse parenchymal lung disease* (DPLD), comprises a number of clinical disorders that affect the alveolar structures, pulmonary interstitium, and small airways (Figures 2.1, 2.2, 2.3a, b, and 2.4a, b). These disorders include bacterial, fungal, viral, protozoal, and parasitic infections or infestations; diffuse connective tissue diseases (systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, ankylosing spondylitis, mixed connective tissue); hypersensitivity pneumonitis or extrinsic allergic alveolitis; pneumoconiosis; drug-induced and iatrogenic syndromes; and disorders of unknown origin (e.g., sarcoidosis, idiopathic pulmonary fibrosis, Langerhans cell histiocytosis, lymphangioleiomyomatosis, and idiopathic interstitial pneumonias) (Figure 2.5). Many of these diseases are benign and self-limiting; others are chronic, progressive, irreversible, and fatal. The lung manifestation may be the one manifestation of a systemic process. Or it may be the only organ affected. All ILDs, however, have certain common clinical, radiologic, and physiologic features that should be recognized.

2.1. Diagnosis of ILD

2.1.1. History

A thorough occupational history of the patient is of paramount importance in evaluating ILD. Every occupation or job experience that the patient ever had should be recorded, including summer and part-time activities. Also, a list should be drawn of the spouse's or live-in partner's occupation because many disorders including asbestosis may be transmitted by dust brought home in clothing. History of recent or past exposure to inorganic or mineral particles or to organic dusts and animal antigens (pets) should be identified. Inquiry should be made for drugs and chemicals known to cause ILD, history of pulmonary infections (particularly HIV), immune disorders, and collagen vascular disorders. A smoking history may alter the diagnostic algorithm because many ILDs, including Langerhans cell histiocytosis, alveolar proteinosis, amiodarone toxicity, idiopathic pulmonary fibrosis, asbestosis, and Goodpasture syndrome are common in smokers, whereas nonsmokers are susceptible to sarcoidosis and hypersensitivity pneumonitis. The country of origin and recent travel history are often critical for establishing the diagnosis. A diffuse nodular interstitial roentgenographic pattern in an Indian patient is highly suggestive of tropical eosinophilia, whereas the similar picture in an Egyptian patient would point toward pulmonary schistosomiasis.

2.1.2. Symptoms

Dyspnea is the most frequent symptom of ILD. At first, dyspnea is evident on exercise; later it progresses to breathlessness at rest. The duration of progressive dyspnea usually

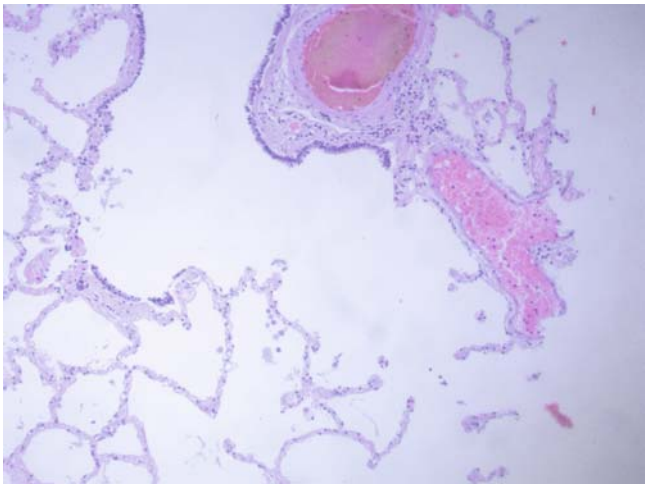


Figure 2.1. The structure of lung parenchyma. Lung parenchyma is composed of structures distal to the terminal bronchioles that include respiratory bronchioli, alveolar ducts, alveolar sacs, and alveolus. Normal lung histology showing terminal bronchiole and alveoli.

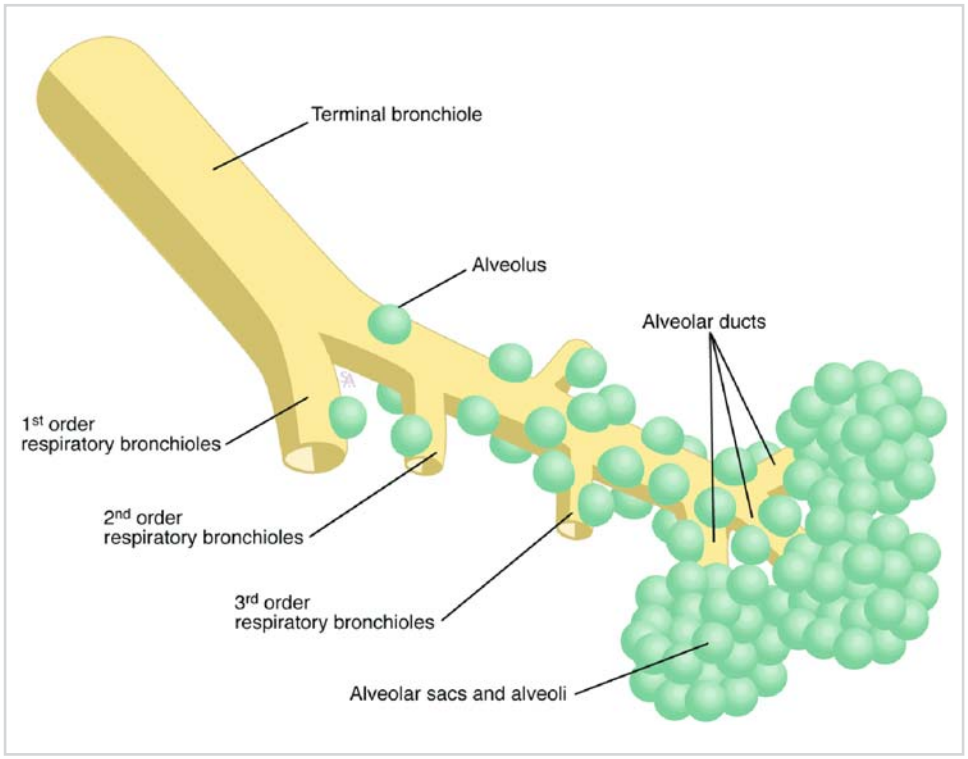


Figure 2.2. The structure of lung parenchyma. Acinus-terminal respiratory unit. The pulmonary acinus is composed of those structures that are distal to the terminal bronchiole.

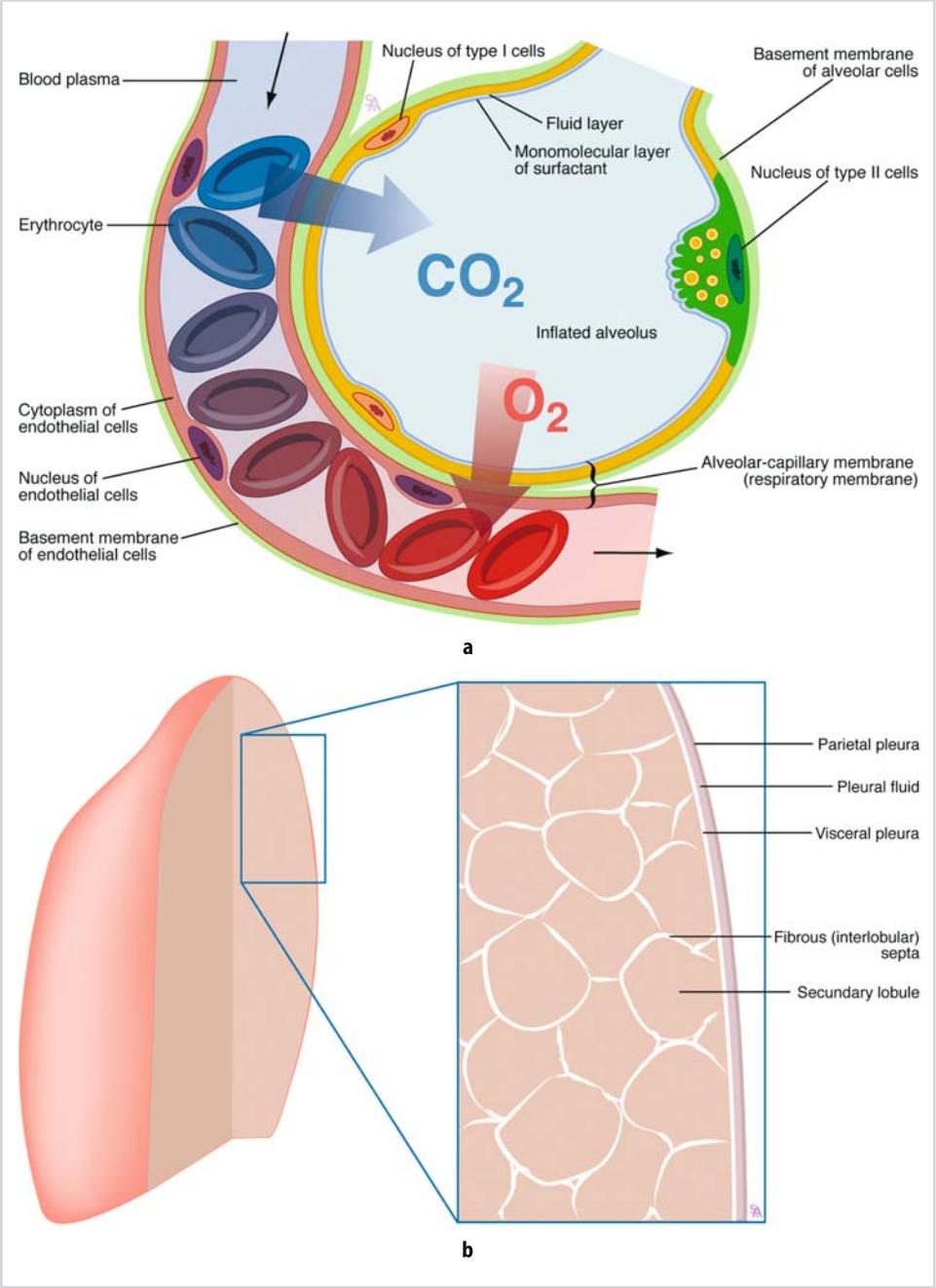
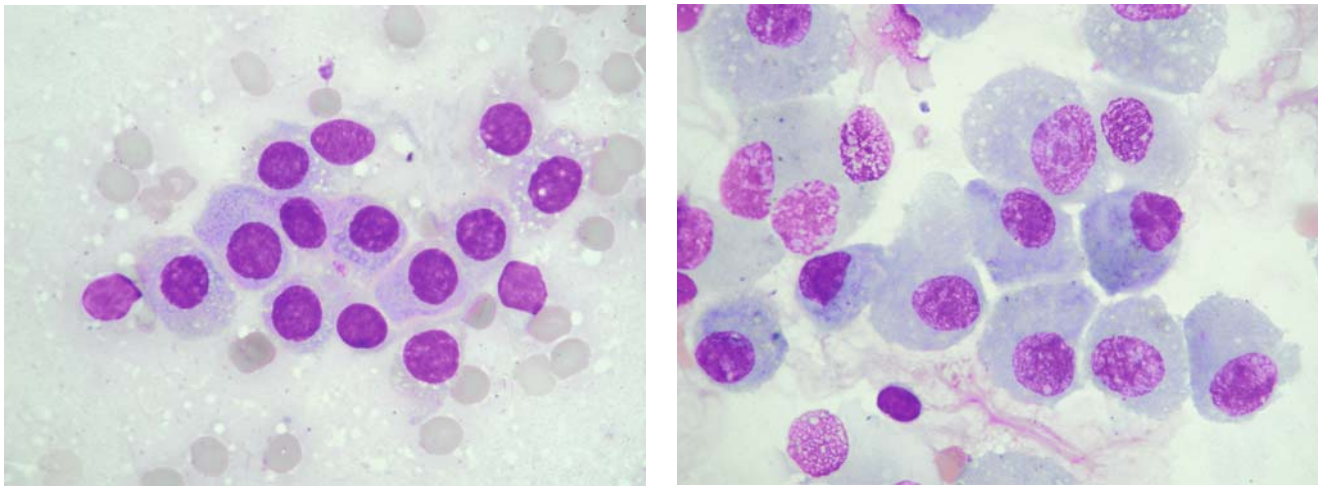


Figure 2.3. The structure of lung parenchyma. Alveolocapillary membrane is composed of capillary endothelium, alveolar epithelium (type I and II pneumocytes), surfactant, epithelial and endothelial basal membranes (a). The extremely thin barrier between air and capillaries allows oxygen to move from the alveoli into the blood and allows carbon dioxide to move from the blood in the capillaries into the alveoli. The pulmonary blood-gas barrier is an extraordinary bioengineering structure because of its vast area but extreme thinness. Interstitium is the integral part of the alveolocapillary membrane. It has been investigated extensively and described in detail by Weibel and associates. It is a continuous structure that runs from the visceral pleura to the hilum and follows the fiber skeleton of the lung (b). The thin alveolar walls comprise alveolar capillaries that are suspended by fiber strands and are covered by type I pneumocytes. Within the alveolar walls is a continuation of the interstitium that is in intimate contact with the alveolar basement membrane, alveolar capillaries, and epithelial cells. It contains matrix of connective tissue, elastic fibers and proteoglycans, but also other cells (fibroblasts and lymphoid cells) and represents a potential space.



a b

Figure 2.4. The structure of lung parenchyma. The numerous types of cells plant the lung parenchyma. These are type I pneumocyte, type II pneumocyte, alveolar macrophage, and neuroendocrine cell. Type II pneumocyte manufactures surfactant. Pneumocyte type II, transbronchial lung biopsy imprint cytology, original magnification ×1000, MGG stain (May-Grünwald-Giemsa) (a). Alveolar macrophages represent the main cellular host defense mechanism in the alveolar space. Cluster of macrophages, BAL fluid cytology, original magnification ×1000, MGG stain (May-Grünwald-Giemsa) (b).

ranged from months to years. Dyspnea is commonly associated with dry cough, particularly on exertion, and fatigue is frequently present. Fever, chills, and weight loss are the main symptoms in interstitial pulmonary infections but may also occur in collagen vascular disorders. The combination of fever, cough, and dyspnea in an immunosuppressed host is often due to *Pneumocystis jiroveci* pneumonitis, cytomegalovirus infection, miliary tuberculosis, or fungal infection. On the other hand, the constellation of fever, cough, chest tightness, and dyspnea that occur 4 to 6 hours after exposure to an organic dust strongly suggests hypersensitivity pneumonitis. Severe dyspnea with weight loss but without fever occurs in lymphangitic carcinomatosis, diffuse connective tissue diseases, and, rarely disseminated tuberculosis.

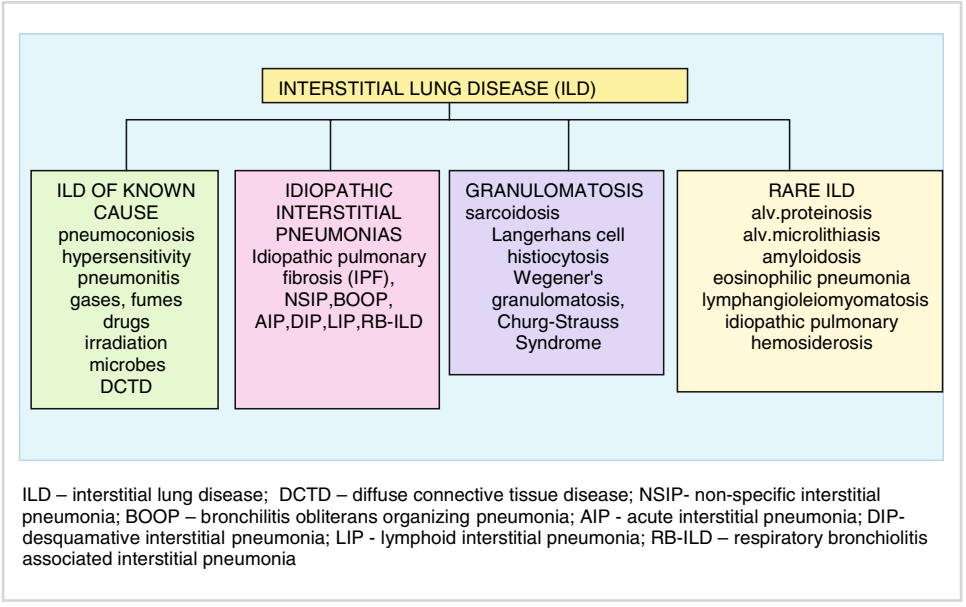


Figure 2.5. Classification of interstitial lung diseases. Reprinted from Classification of Interstitial Lung Disease, ATS/ERS international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. Adapted from data published in ATS/ERS international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2002;165:277–304.

2.1.3. Signs

In 10% to 15% of the patients who have ILD, tachypnea is present. Auscultation of the lungs reveals diffuse, fine end-inspiratory crackles or rales in 60% to 90% of the patients who have idiopathic pulmonary fibrosis (IPF), asbestosis, and acute hypersensitivity. On the other hand, rales are infrequent in sarcoidosis and heard in less than 20% of the patients. Rhonchi or wheezing, present in 20% of the patients with hypersensitivity pneumonitis, are not a feature of IPF. The loud pulmonary second associated with right-sided third sound is often heard in pulmonary hypertension and right heart failure secondary to ILD. Digital clubbing is characteristically common in idiopathic pulmonary fibrosis (IPF) and asbestosis (Figure 2.6).

2.1.4. Extrapulmonary Features of ILD

The combination of erythema nodosum, uveitis, and parotid enlargement is an important feature of sarcoidosis. Multiorgan involvement is present in sarcoidosis, diffuse connective tissue diseases, vasculitis, Langerhans cell histiocytosis, amyloidosis, and neurofibromatosis.

2.1.5. Radiologic Studies

Chest roentgenogram is abnormal in more than 90% of the patients who have ILD. Often the first to be recognized, the radiographic abnormality is of paramount importance in elucidating the diagnosis. It is important to review the past chest x-ray films to assess the course and progression of the disease. Although radiographic features may not always provide the definite diagnosis, certain roentgenographic patterns are highly suggestive (Table 2.1).

In general, parenchymal shadows may be classified into four categories: normal in about 10% of the cases; ground-glass haziness; linear, nodular, reticular, or reticulonodular infiltrate; and honeycombing, representing the end-stage fibrosis (Figure 2.7a, b, c, d, e).

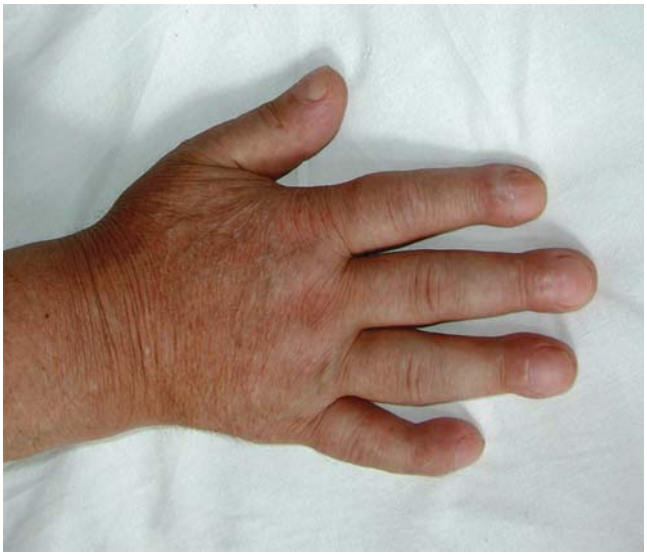


Figure 2.6. The figure depicts finger clubbing. Clubbing is common in IPF. Other pulmonary conditions that cause clubbing of the fingers are carcinoma, asbestosis, cystic fibrosis, and arterio-venous malformation.