# Chronic obstructive lung disease

## Clinical treatment and management

EDITED BY
RICHARD E. BRASHEAR
MITCHELL L. RHODES

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**RICHARD E. BRASHEAR, M.D.**

Professor of Medicine and Director, Division of Pulmonary Medicine,
Indiana University School of Medicine, Indianapolis, Indiana;
Fellow, American College of Physicians;
Fellow, American College of Chest Physicians

**MITCHELL L. RHODES, M.D.**

Associate Professor of Medicine, Division of Pulmonary Medicine;
Indiana University School of Medicine, Indianapolis, Indiana;
Fellow, American College of Physicians;
Fellow, American College of Chest Physicians

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# CONTRIBUTORS


**HENRY R. BESCH, Jr., Ph.D.**

Professor of Pharmacology and Medicine and Chairman, Department of Pharmacology, Indiana University School of Medicine, Indianapolis, Indiana

**RICHARD E. BRASHEAR, M.D.**

Professor of Medicine and Director, Division of Pulmonary Medicine, Indiana University School of Medicine, Indianapolis, Indiana

**WALTER J. DALY, M.D.**

Professor of Medicine and Chairman, Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana

**BRIAN G. DANAHER, Ph.D.**

Postdoctoral Research Fellow, Heart Disease Prevention Program, Department of Medicine, Stanford University Medical Center, Stanford, California

**MARK O. FARBER, M.D.**

Associate Professor of Medicine, Division of Pulmonary Medicine, Indiana University School of Medicine, Indianapolis, Indiana

**STEPHEN J. JAY, M.D.**

Associate Professor of Medicine and Chief, Pulmonary Medicine Section, Wishard Memorial Hospital, Indiana University School of Medicine, Indianapolis, Indiana

**LAWRENCE M. LAMPTON, M.D.**

Assistant Professor of Medicine, Division of Pulmonary Medicine, Indiana University School of Medicine, Indianapolis, Indiana

**EDWARD LICHTENSTEIN, Ph.D.**

Professor of Psychology, University of Oregon, Eugene, Oregon

**L. CRAIG MILLER, M.D.**

Assistant Professor of Medicine, Division of Pulmonary Medicine, Indiana University School of Medicine, Indianapolis, Indiana

**MITCHELL L. RHODES, M.D.**

Associate Professor of Medicine, Division of Pulmonary Medicine, Indiana University School of Medicine, Indianapolis, Indiana

**ROBERT B. STONEHILL, M.D.**

Professor of Medicine, Division of Pulmonary Medicine, Indiana University School of Medicine, Indianapolis, Indiana

**ROBERT A. STRAWBRIDGE, M.D.**

Assistant Professor of Medicine, Division of Pulmonary Medicine, Indiana University School of Medicine, Indianapolis, Indiana

**AUGUST M. WATANABE, M.D.**

Associate Professor of Medicine and Pharmacology and Chief, Cardiology Section, Veterans Administration Hospital, Indiana University School of Medicine, Indianapolis, Indiana

**To**

*Diane, Rhoda, and our families*

# PREFACE

In general medical practice, respiratory illness is the most common diagnosis, accounting for 25% of illness episodes.[1] The recent task force report[2] estimates expenditures for chronic obstructive lung diseases during 1977 of $1 billion for direct costs of treatment, $3.8 billion for costs due to morbidity, and $900 million for costs due to mortality. The magnitude of the problem is almost overwhelming.

There were approximately 1.54 million patients newly diagnosed with chronic obstructive lung diseases in 1970.[2] However, thousands of patients with diseases causing airflow obstruction are undiagnosed or misdiagnosed until their disease is far advanced. Once diagnosed, many patients are told they cannot be helped or they may be advised to purchase expensive respiratory therapy equipment of unproved value or treated with useless medications.

In this book we have attempted to provide the physician with a comprehensive approach to the care and management of these many patients with chronic obstructive lung disease. This book is clinically oriented and extensively referenced and may be informative to both generalists and specialists. Where appropriate, the physiology and pathology are discussed but the interested reader is referred to Thurlbeck[3] and Bates and associates[4] for a more thorough discussion of these topics.

The choice of COLD (chronic obstructive lung disease or diseases) in the title was arbitrary. We wished to succinctly express in the title the main theme of the book. This theme should not be lost by attributing too much to semantics. We could easily have settled for COPD (chronic obstructive pulmonary disease or diseases), CAO (chronic airways obstruction), or some other acronym or phrase. All of these expressions have real or imagined deficiencies and we hope our friends and colleagues will allow us some literary license with the use of COLD.

The concept for this book evolved from a continuing medical education course, "Treatment and Management of Chronic Obstructive Lung Disease," in December, 1976. In preparing for this course, we discovered there was no single comprehensive source of information for the practicing physician on treating this illness. With the encouragement of our colleagues in the Division of Pulmonary Medicine, we embarked on rectifying this deficiency. We acknowledge and appreciate the support and encouragement of our friends and colleagues.

Chapters 1, 6, and 8 were thoughtfully and kindly reviewed by Drs. Kaye H. Kilburn, R. Russell Martin, and Henry Yeager, Jr., respectively. The editors gratefully acknowledge the secretarial and editorial assistance of Ms. Debby Thompson and Ms. Vida Boesenberg. The editorial assistance of Ms. Jane Ganter-Neary in the preparation of Chapter 17 was also most helpful.

**Richard E. Brashear**
**Mitchell L. Rhodes**

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# CONTENTS

CHAPTER 1

# Overview of chronic obstructive lung disease

The scope of chronic obstructive lung disease (predominantly chronic bronchitis and emphysema) is immense and difficult to comprehend. For 1967 the estimated cost of morbidity and mortality for bronchitis, emphysema, and bronchiectasis was $1.8 billion. During that year, emphysema and chronic bronchitis probably resulted in 90,000 man-years lost from work. Emphysema and chronic bronchitis represent the most important public health respiratory problems in the United States, both in terms of incidence and cost. The death rate between 1958 and 1967 increased 80% for bronchitis (unqualified) and chronic bronchitis and increased 172% for emphysema.[63] Of all causes of death in 1974, emphysema was the twelfth commonest cause in men and women with 19,907 deaths, the tenth commonest cause of death in men of all ages and the seventh commonest cause of death in men over the age of 54 years.[14]

## ANATOMY

An understanding of lung morphology is essential to understanding these important diseases. The trachea divides into two main bronchi (first order branching), which subsequently give rise to two lobar bronchi on the left and three lobar bronchi on the right (Fig. 1-1). The lobar bronchi give rise to about twenty segmental bronchi (medium size bronchi), which are about 4 to 7 mm in diameter. Small bronchi (0.8 to 4 mm diameter) arise next, followed by bronchioles. Bronchi with an internal diameter of 1 mm occur at about the tenth order of branching. Bronchioles, 0.5 to 0.8 mm in diameter, are devoid of mucus-secreting elements and have no cartilage in their walls. The most distal bronchiole that does not have alveoli originating from its walls is defined as a terminal bronchiole.[35,79] Terminal bronchioles are about the sixteenth order of branching and give rise to respiratory bronchioles (Fig. 1-2).

It is useful to divide the lung into three zones, each with different anatomy and functions (Fig. 1-1). The first zone, the conductive airways, consists of bronchi characterized by cartilage in their walls and smaller (2 mm diameter) bronchioles without cartilage. The last (most distal) conducting airway is called a terminal bronchiole. No alveoli are present, and no gas exchange takes place. The second zone, the transitional airways, consists of respiratory bronchioles distal to the terminal bronchioles and is incompletely lined by increased numbers of alveoli. The third zone, the respiratory airways, is completely lined by alveoli.

The principal site of gas exchange is the acinus distal to a terminal bronchiole. An acinus is defined as the unit of lung structure distal to a single terminal bronchiole and constitutes the functioning unit of the lung (Figs. 1-1 and 1-3). Radiographic visualization of a single, completely filled acinus demonstrates an approximately 7.4 mm diameter spherical structure.[25] Considering the right and left main stem bronchi as the first order of branching, the acinus begins (with wide variation) at about the seventeenth order of branching. The acinus usually consists of three orders of respiratory bronchioles, three or four orders of alveolar ducts, and one order of alveolar sacs.[87] Alveoli, the structure where oxygen and carbon dioxide exchange occurs between the pulmonary capillary bed and the alveolar gas, first sparsely appear on

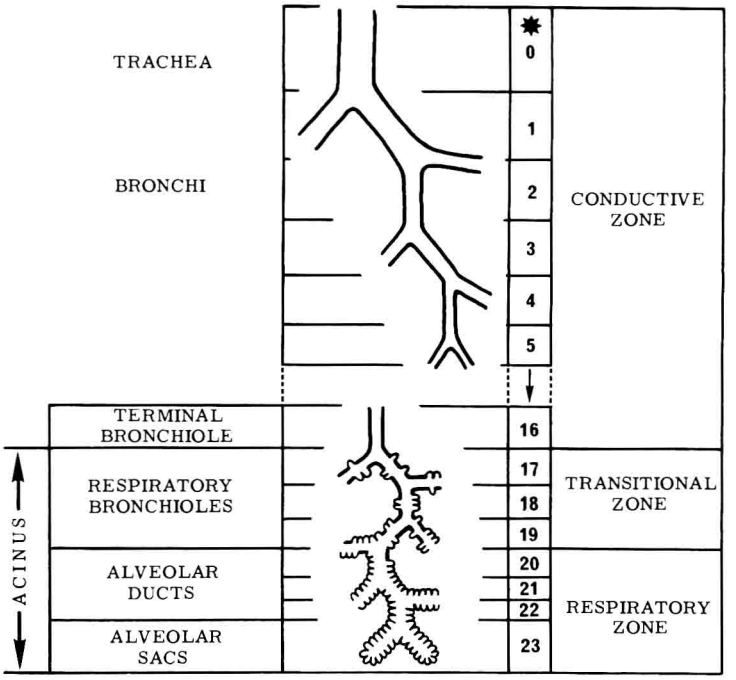


**Fig. 1-1.** Diagrammatic representation of conductive, transitional, and respiratory zones of the airways and components of an acinus. Asterisk designates order of generation of branching. (Modified from Weibel, E. R.: Morphometry of the human lung, Heidelberg, 1963, Springer-Verlag.)

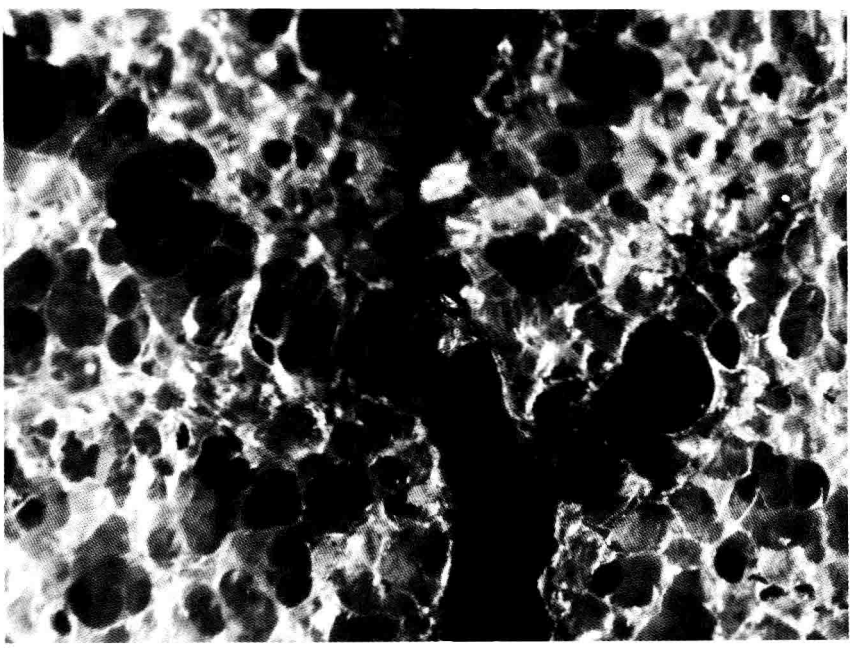

**Fig. 1-2.** A dissecting microscope view of a normal lung. A terminal bronchiole enters the field at the bottom, branches, and becomes a respiratory bronchiole. The membranes appear completely intact. (×25.) (From Pratt, P. C., and Kilburn, K. H.: Hum. Pathol. **1**:443, 1970.)

the first order respiratory bronchioles but rapidly increase in numbers with each subsequent order. Respiratory bronchioles are so named because the alveoli of the bronchiole walls permit gas exchange to occur, in contrast to the more proximal conducting airways. Alveolar ducts are completely surrounded by alveoli. The last generation of alveolar ducts is closed at its distal end by alveoli, and this structure is sometimes termed an alveolar sac.

Approximately five to ten acini comprise a secondary lung lobule (Fig. 1-4), usually a truncated pyramidal structure of 1 to 2 cm diameter.[29,50,91] Reid,[72,73] however, considers that three to five acini constitute a secondary lobule. The periphery of a secondary lobule is imperfectly demarcated by a connective tissue envelope occasionally passing from the lung hilum to the pleural surface.[91] A secondary lung lobule can be considered as a unit or a miniature lung with its own air supply, blood supply, and lymphatic drainage.[29] The respiratory bronchioles of the acini tend to be in the midzone of the secondary lobule, with the alveolar ducts and sacs occupying the more peripheral areas of the secondary lobule near the connective tissue envelope (Fig.

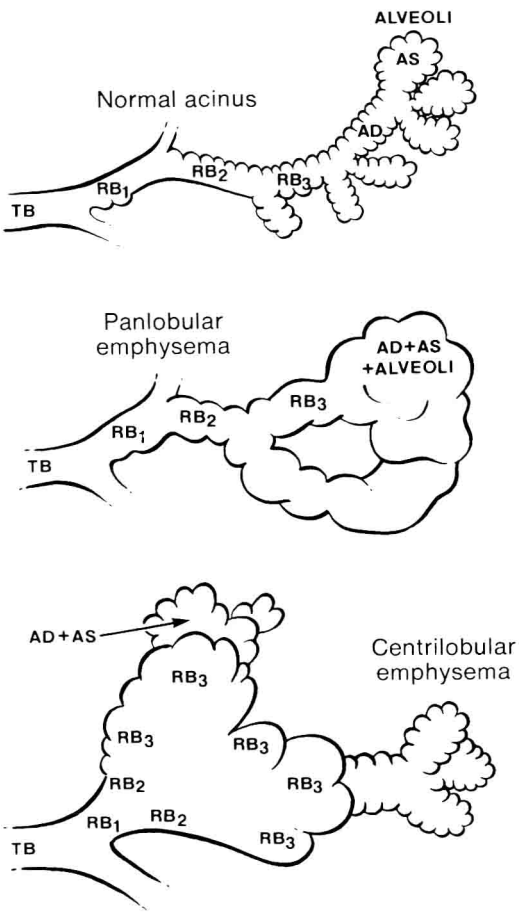


**Fig. 1-3.** Schematic representation of a normal acinus (top), diffuse dilatation of the entire acinus in panlobular/panacinar emphysema (middle), and selective dilatation and destruction of respiratory bronchioles in centrilobular emphysema (bottom). *TB*, Terminal bronchioles; *RB*, respiratory bronchioles; *AD*, alveolar ducts; and *AS*, alveolar sacs. (Modified from Thurlbeck, W. M.: In Sommers, S. C., editor: Pathology Annual 1968. Courtesy Appleton-Century-Crofts, Publishing Division of Prentice-Hall, Inc.)

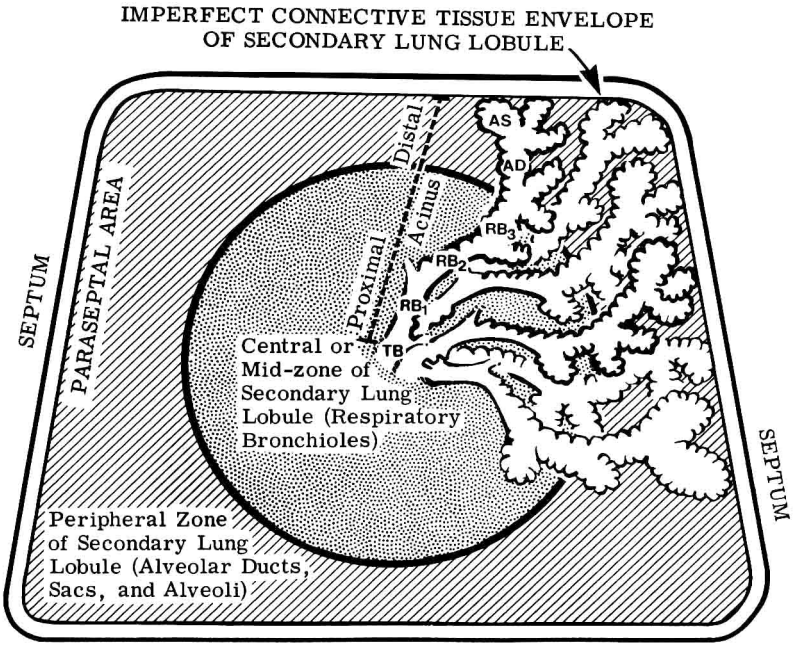


**Fig. 1-4.** Simplified two-dimensional schematic representation of a secondary lung lobule. Note central location of respiratory bronchioles. (Abbreviations as in Fig. 1-3.)

1-4). Since there is variability in the size, structure, and connective tissue septa of a secondary lung lobule, the term has not gained total acceptance. Historically, a primary lung lobule was defined as an alveolar duct with its alveolar sacs and alveoli.[58] Since a primary lung lobule has no specific anatomical or functional meaning, the term has little modern usage.

The trachea has a cross-sectional area of 2 $cm^2$, and the total cross-sectional area progressively increases at each division down the bronchial tree. The total cross-sectional area is 79 $cm^2$ for the terminal bronchioles (approximately sixteenth order of branching) and 281 $cm^2$ for respiratory bronchioles. The large increase in cross-sectional area in the smaller airways results in only 10% to 20% of the total pulmonary resistance to airflow being normally contributed by airways that are 2 mm or less in internal diameter.[35,79]

## EMPHYSEMA

As a general concept, a disease may be defined as those abnormal phenomena observed in a group of people with disturbed function or structure. The group of people may be defined in four ways: descriptive and clinical, functional or physiological, anatomical, or etiological.[81]

In 1958 a group of British investigators met to decide a definition of emphysema. They defined emphysema as a condition of the lung characterized by an increase beyond the normal in the size of air spaces distal to the terminal bronchiole either from dilation or from destruction of their walls.[81]

Subsequently, destruction of respiratory tissue became a requirement for the definition of emphysema. The American Thoracic Society defined emphysema as an anatomical alteration of the lung characterized by an abnormal enlargement of the air spaces distal to the terminal, nonrespiratory bronchiole, accompanied by destructive changes of the alveolar walls.[57] This definition was reaffirmed thirteen years later by a joint committee of the American Thoracic Society and the American College of Chest Physicians.[1] This definition of emphysema is based on a pathological description and precludes, except by lung biopsy, diagnostic certainty during life.

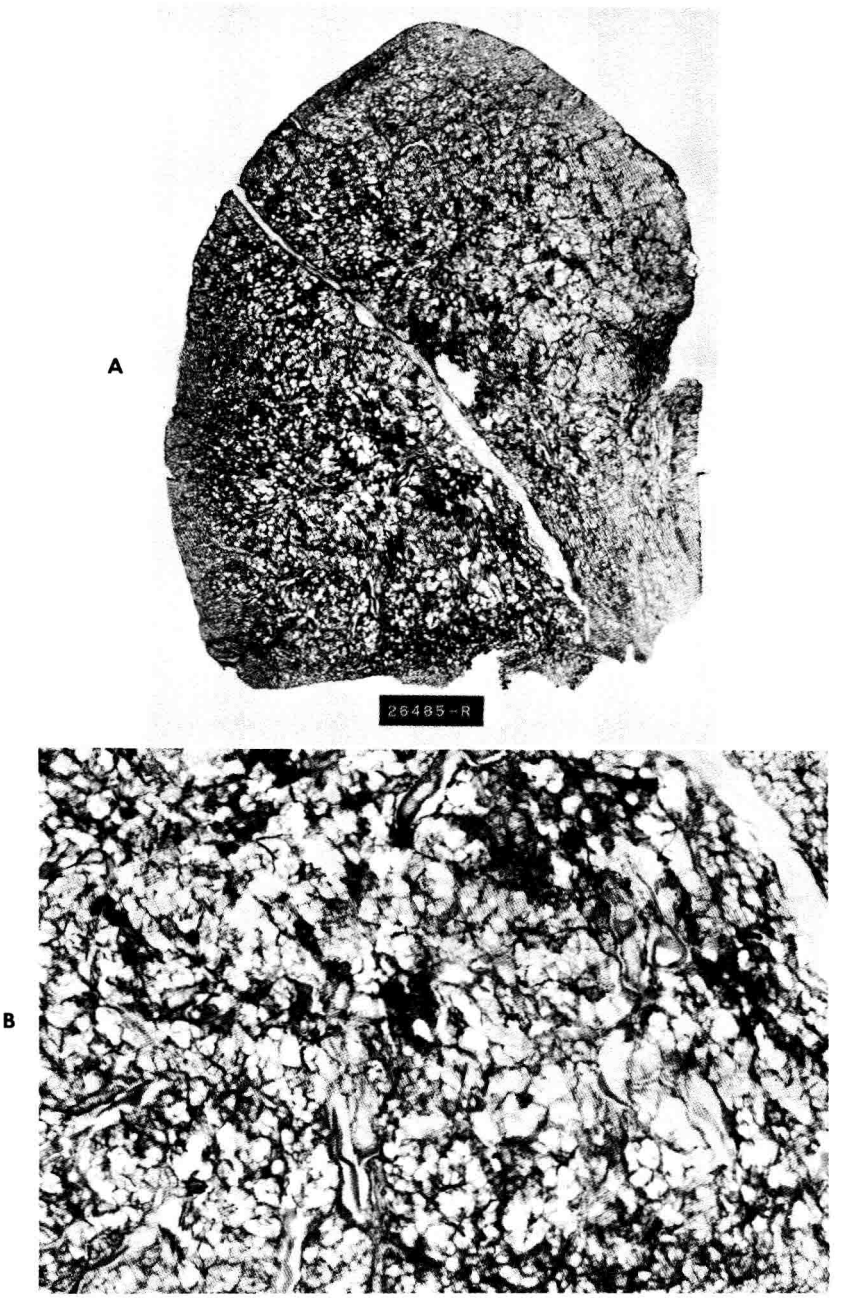


**Fig. 1-5.** An example of widespread, moderately severe panlobular (panacinar) emphysema in an 81-year-old woman with normal alpha$_1$-antitrypsin. (**A**, ×0.5 approximately; **B**, ×1 approximately.) (From Thurlbeck, W. M.: Chronic airflow obstruction in lung disease, Philadelphia, 1976, W. B. Saunders Co.)

There is no uniform agreement on the various radiological and physiological criteria to define emphysema, and the definition provides no reference to etiology.

Adding destruction of alveolar walls to the definition eliminated overinflation, the simple enlargement of air spaces unaccompanied by destruction. The intrathoracic lung tissue remaining after lung resection may undergo enlargement and should be referred to as overinflation rather than compensatory emphysema. The specification of abnormal enlargement of the air spaces excludes the normal changes occurring with age or hyperinflation occurring in some asthmatics.[68,82]

Emphysema is essentially a degenerative process with deterioration and erasure of lung tissue peripheral to terminal bronchioles. Total elastic fiber length and diameter is not altered in mild emphysema.[65] However, with increased involvement with emphysema, elastic fibers in the alveolar walls degenerate, with the appearance of holes with thinning and stretching of the fragile alveolar walls. The alveolar walls degenerate into strands of reticulin or collagen fibers, and the holes or fenestrations gradually increase in size and coalesce until the alveolar wall disappears. The capillaries in the alveolar walls are also erased and disappear. The final re-

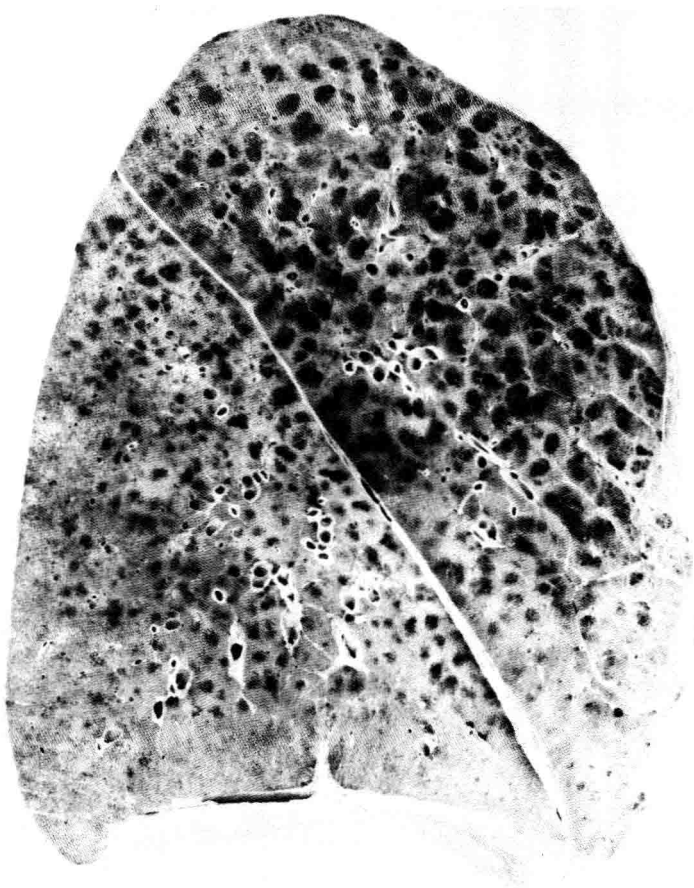

**Fig. 1-6.** A slice of lung impregnated with barium sulfate showing classical centrilobular emphysema which is more severe in the upper lung zones. (×0.5 approximately.) (From Thurlbeck, W. M.: Chronic airflow obstruction in lung disease, Philadelphia, 1976, W. B. Saunders Co.)

sult is the development of enlarged air spaces replacing alveoli.[69,90]

The four major classifications of emphysema are determined by the location and degree of involvement of the acinus. In panacinar emphysema there is a general uniform involvement of the entire acinus. This form is also termed panlobular, since it involves all of a secondary lung lobule (Figs. 1-3 to 1-5). Panlobular emphysema tends to occur diffusely through the lung and is also the type found with familial alpha$_1$-antitrypsin deficiency. Panlobular emphysema is relatively unusual, with not more than 1 individual with panlobular emphysema for every 20 with centrilobular emphysema.[68] Localized, pure panlobular emphysema, which occurs predominantly in women, may be found in patients over the age of 70 years.[83]

Centrilobular (proximal acinar and/or centriacinar) emphysema involves the proximal and central portions (respiratory bronchioles) of the acinus (Fig. 1-3). This is also the midzone or central portion of a secondary lobule, hence the term centrilobular (Figs. 1-4, 1-6, 1-7). There is destruction of the walls of respiratory bronchioles, and the centrilobular spaces represent enlarged and confluent respiratory bronchioles (Fig. 1-8). The distal acinus remains preserved until the process becomes advanced. With increasing destruction of the central zone of a secondary lobule, the destroyed secondary lobule may eventually abut against the peripheral connective tissue envelope with only the envelope remaining. Centrilobular emphysema is the more common form of emphysema and is more severe in the upper lobes.[59] It is frequently associated with inflammatory changes, rarely found in nonsmokers, and is much more common in men than women.[3,50] Simple coal worker's pneumoconiosis (focal emphysema) is characterized by the presence of large amounts of dust around and between the respiratory bronchioles. The severe form of simple pneumoconiosis is essentially indistinguishable from centrilobular emphysema.[68,83]

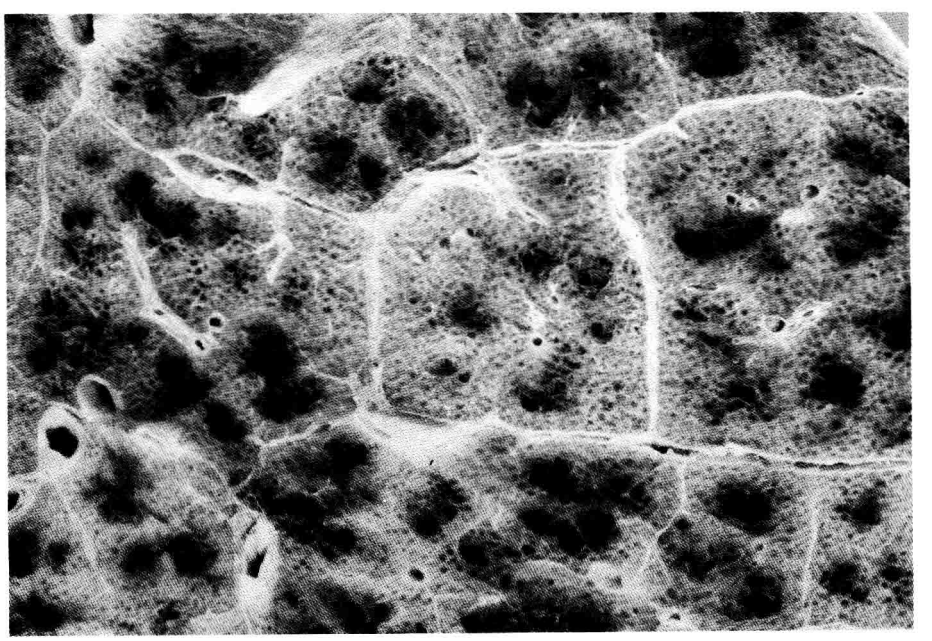

**Fig. 1-7.** Lung with well-demarcated lobular septa. It shows that the centrilobular emphysematous spaces are midway between the center and the periphery of the secondary lung lobule. The emphysematous spaces are separated from each other and from the lobular septa by relatively normal-appearing tissue. (×2.5 approximately.) (From Thurlbeck, W. M.: Chronic airflow obstruction in lung disease, Philadelphia, 1976, W. B. Saunders Co.)

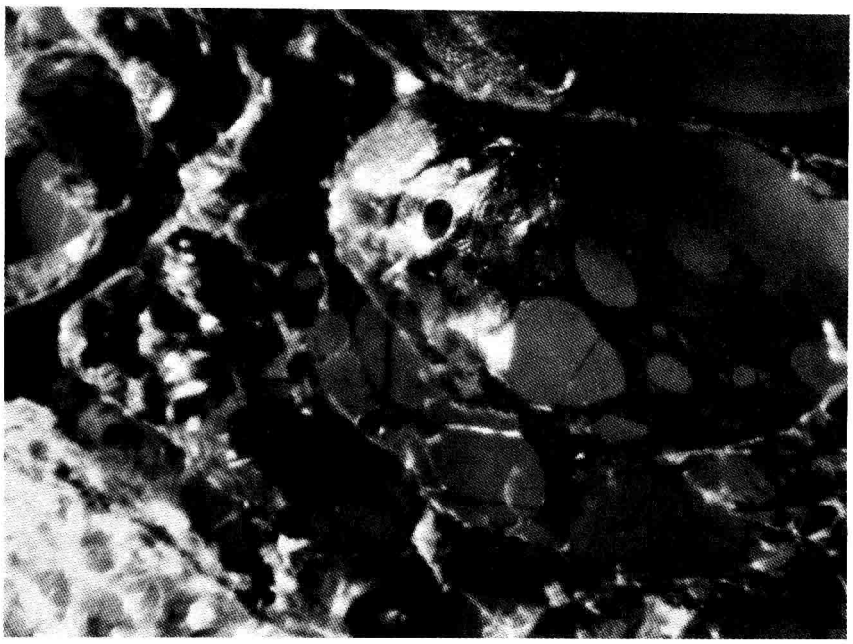

**Fig. 1-8.** A dissecting microscope view of a well-established centrilobular emphysematous bleb. The parent terminal bronchiole enters the field at the left. Note the numerous fenestrations in the membrane composing the wall of the bleb and its communication with adjacent emphysematous tissue. (×25.) (From Pratt, P. C., and Kilburn, K. H.: Hum. Pathol. 1:443, 1970.)

Distal acinar (paraseptal) emphysema involves the distal acinus (alveolar sacs and ducts) near the connective tissue envelope of the secondary lung lobule and is relatively rare. The fourth classification of emphysema is irregular (paracicatricial or scar) emphysema, and the acinus is irregularly involved. The severity of irregular emphysema depends on the extent of the lung damage.

## CHRONIC BRONCHITIS

In 1958 chronic bronchitis was defined as the condition of subjects with chronic or recurrent excessive mucous secretion in the bronchial tree. The definition was clinical and related to cough and expectoration not attributable to other known lung diseases.[81] It included those who cough and swallow sputum and those who produce sputum but deny cough.

The American Thoracic Society later defined chronic bronchitis as a disorder characterized by excessive mucous secretion and chronic or recurrent productive cough. The productive cough should be present for at least three months a year during two consecutive years. Other cardiac or bronchopulmonary diseases must be excluded.[57]

The British concluded that bronchial hypersecretion, usually manifested as a productive cough, was common to all persons with chronic bronchitis. In addition, they frequently noted generalized airways obstruction and bacterial infection resulting in mucopurulent sputum, and adjusted their definition accordingly. Simple chronic bronchitis was defined as a chronic or recurrent increase in the volume of mucoid bronchial secretions sufficient to cause cough and expectoration. Other conditions that might cause expectoration must be excluded. Chronic or recurrent mucopurulent chronic bronchitis was characterized by persistently or intermittently mucopurulent sputum not due to other bronchopulmonary disease. Chronic obstructive bronchitis was defined as chronic bronchitis in which there was persistent, widespread narrowing of the intra-