# West's Pulmonary Pathophysiology

## The Essentials

NINTH EDITION

John B. West
Andrew M. Luks

Wolters Kluwer

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# WEST'S PULMONARY PATHOPHYSIOLOGY

## THE ESSENTIALS


John B. West, MD, PhD

Distinguished Professor of Medicine and Physiology
University of California, San Diego
School of Medicine
San Diego, California

Andrew M. Luks, MD

Professor of Medicine
University of Washington School of Medicine
Seattle, Washington



Wolters Kluwer

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Ninth Edition



First Edition, 1977
Second Edition, 1982
Third Edition, 1987
Fourth Edition, 1992
Fifth Edition, 1998
Sixth Edition, 2003
Seventh Edition, 2008
Eighth Edition, 2013



9 8 7 6 5 4 3 2 1

Printed in China

**Library of Congress Cataloging-in-Publication Data**
Names: West, John B. (John Burnard), author. | Luks, Andrew, author. | Complemented by (expression): West, John B. (John Burnard). West's respiratory physiology. 10th edition.
Title: West's pulmonary pathophysiology : the essentials / John B. West, Andrew M. Luks.
Other titles: Pulmonary pathophysiology
Description: Ninth edition. | Philadelphia : Wolters Kluwer, [2017] | Preceded by Pulmonary pathophysiology : the essentials / John B. West. 8th ed. 2013. | Complemented by West's respiratory physiology / John B. West, Andrew M. Luks. 10th ed. 2016. | Includes bibliographical references and index.
Identifiers: LCCN 2016046551 | ISBN 9781496339447
Subjects: | MESH: Lung Diseases—physiopathology | Respiratory Function Tests | Lung—pathology
Classification: LCC RC711 | NLM WF 600 | DDC 616.2/407—dc23 LC record available at https://lccn.loc.gov/2016046551



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Obstructive diseases of the lung are extremely common and remain an important cause of morbidity and mortality. While the distinctions among the various types of obstructive disease are blurred, giving rise to difficulties in definition and diagnosis, all of these diseases are characterized by airway obstruction.

## AIRWAY OBSTRUCTION

Increased resistance to airflow can be caused by conditions (1) inside the lumen, (2) in the wall of the airway, and (3) in the peribronchial region **(Figure 4.1)**:

1. The lumen may be partially occluded by excessive secretions, such as in chronic bronchitis. Partial obstruction can also occur acutely in pulmonary edema or after aspiration of foreign material and, postoperatively, with retained secretions. Inhaled foreign bodies may cause localized partial or complete obstruction.
2. Causes in the wall of the airway include contraction of bronchial smooth muscle, as in asthma; hypertrophy of the mucous glands, as in chronic bronchitis (see Figure 4.6); and inflammation and edema of the wall, as in bronchitis and asthma.
3. Outside the airway, destruction of lung parenchyma may cause loss of radial traction and consequent narrowing, as in emphysema. A bronchus may also be compressed locally by an enlarged lymph node or neoplasm. Peribronchial edema can also cause narrowing (see Figure 6.5).

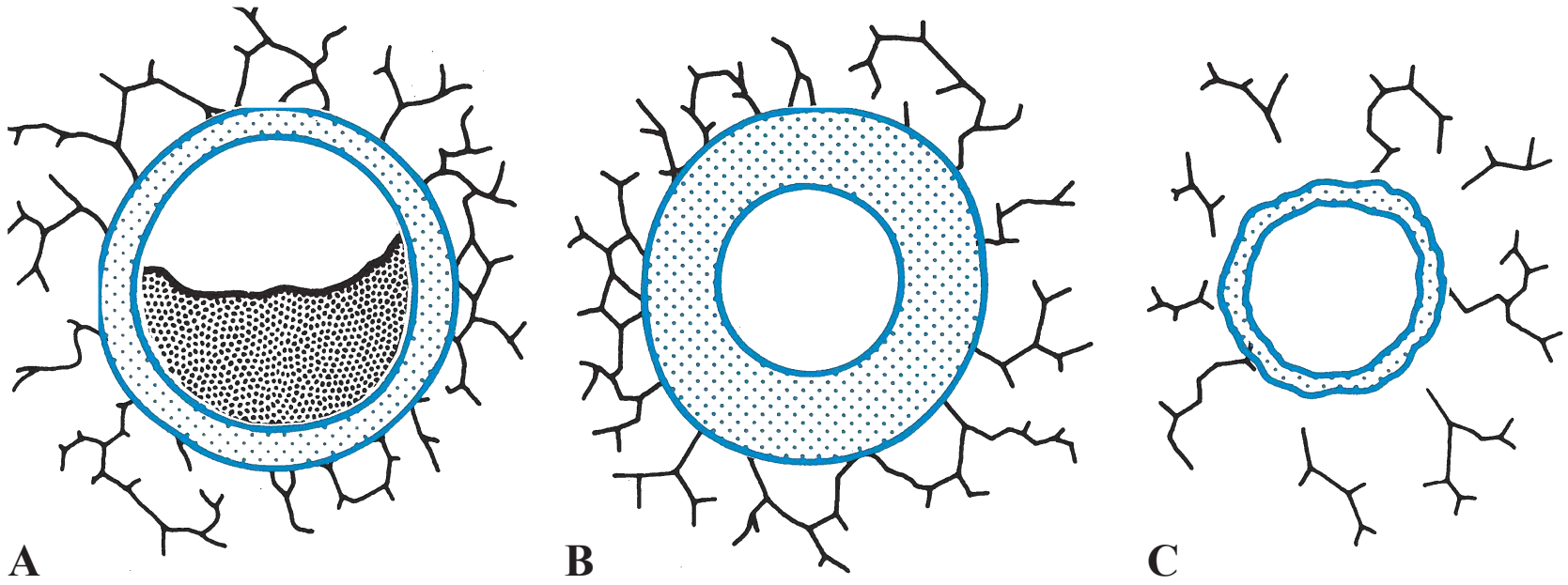


Figure 4.1. **Mechanisms of airway obstruction. A.** The lumen is partly blocked, for example, by excessive secretions. **B.** The airway wall is thickened, for example, by edema or hypertrophy of smooth muscle. **C.** The abnormality is outside the airway; in this example, the lung parenchyma is partly destroyed and the airway has narrowed because of the loss of radial traction.

# CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease (COPD) is caused by emphysema, chronic bronchitis, or a mixture of the two and is defined by the presence of airflow obstruction. Patients typically have increasing shortness of breath over several years, chronic cough, impaired exercise tolerance, as well as overinflated lungs and impaired gas exchange. It can often be difficult to determine to what extent patients have emphysema or chronic bronchitis, and the term "chronic obstructive pulmonary disease" is a convenient, non-descript label that avoids making an unwarranted diagnosis with inadequate data.

## Emphysema

*Emphysema is characterized by enlargement of the air spaces distal to the terminal bronchiole, with destruction of their walls. Note that this is an anatomic definition; in other words, the diagnosis is presumptive and based largely on radiologic findings in the living patient.*

### Pathology

A typical histologic appearance is shown in **Figure 4.2B**. Note that in contrast to the normal lung section in **Figure 4.2A**, the emphysematous lung shows loss of alveolar walls with consequent destruction of parts of the capillary bed. Strands of parenchyma that contain blood vessels can sometimes be seen coursing across large dilated airspaces. The small airways (less than 2 mm wide) are narrowed, tortuous, and reduced in number. In addition, they have thin, atrophied walls. There is also some loss of larger airways. The structural changes are well seen with the naked eye or hand lens in large slices of lung **(Figure 4.3)**.

### Types

Various types of emphysema are recognized. The definition given earlier indicates that the disease affects the parenchyma distal to the terminal bronchiole. This unit is the *acinus*, but it may not be damaged uniformly. In *centriacinar emphysema*, the destruction is limited to the central part of the acinus, and the peripheral alveolar ducts and alveoli may escape unscathed **(Figure 4.4)**. By contrast, *panacinar emphysema* shows distension and destruction of the whole acinus. Occasionally, the disease is most marked in the lung adjacent to interlobular septa (paraseptal emphysema), while in other patients, large cystic areas or bullae develop (bullous emphysema).

Centriacinar and panacinar emphysema tend to have different topographic distributions. The former is typically most marked in the apex of the upper

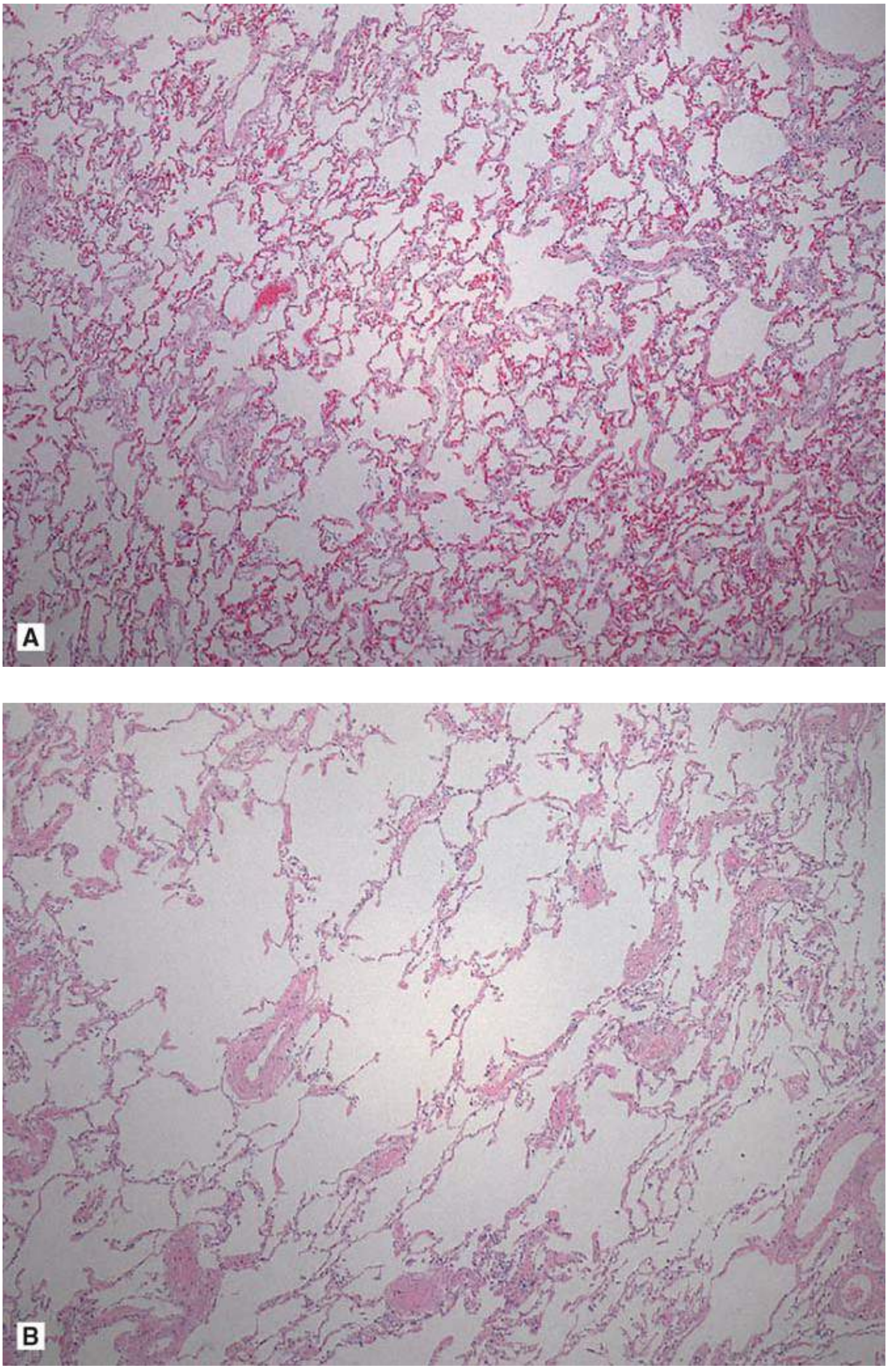


Figure 4.2. **Microscopic appearance of emphysematous lung. A.** Normal lung. **B.** Loss of alveolar walls and consequent enlargement of airspaces (×4). (Image courtesy of Corinne Fligner, MD.)

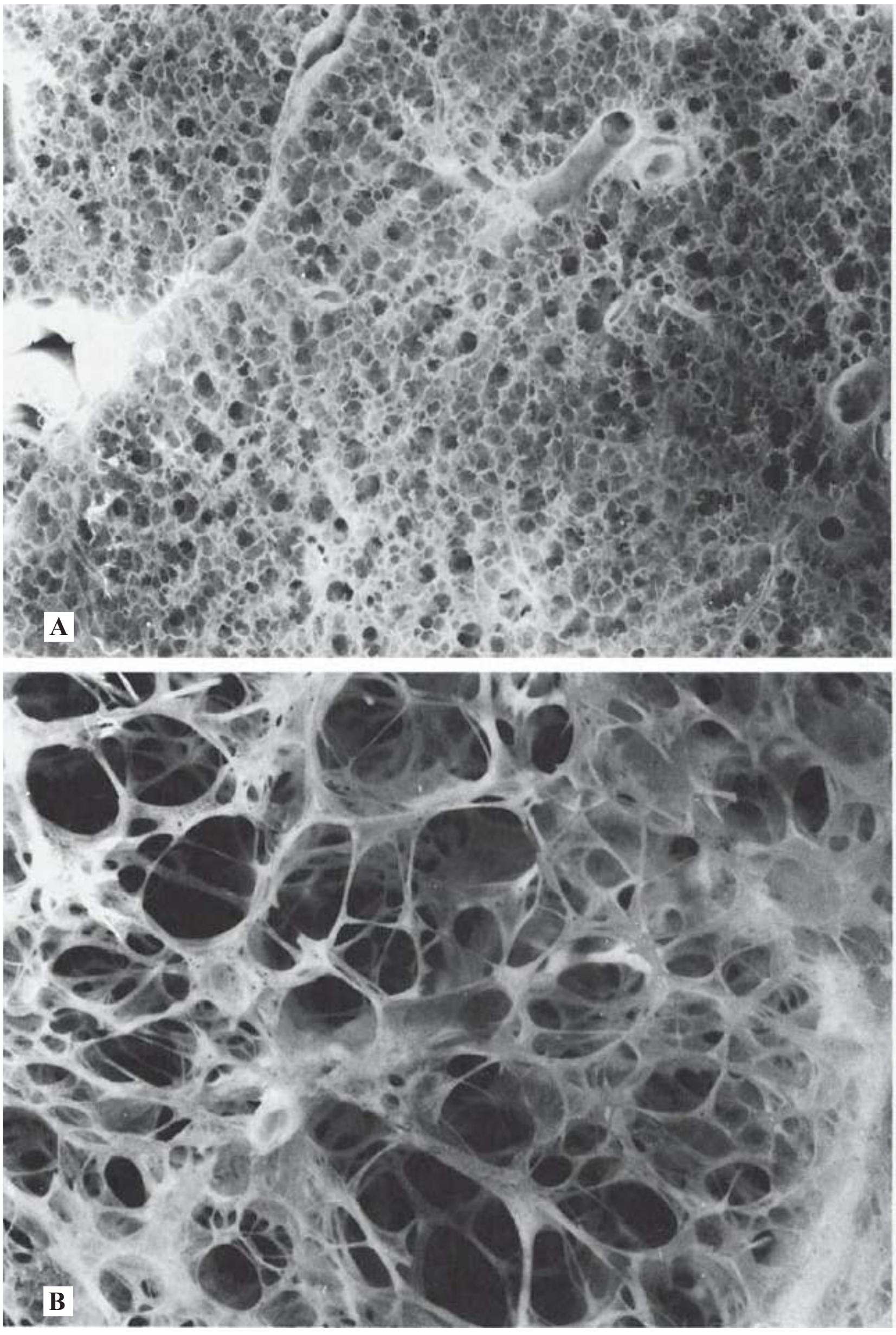


Figure 4.3. **Appearance of slices of normal and emphysematous lung. A.** Normal. **B.** Panacinar emphysema (barium sulfate impregnation, ×14). (From Heard BE. Pathology of Chronic Bronchitis and Emphysema. London, UK: Churchill, 1969.)

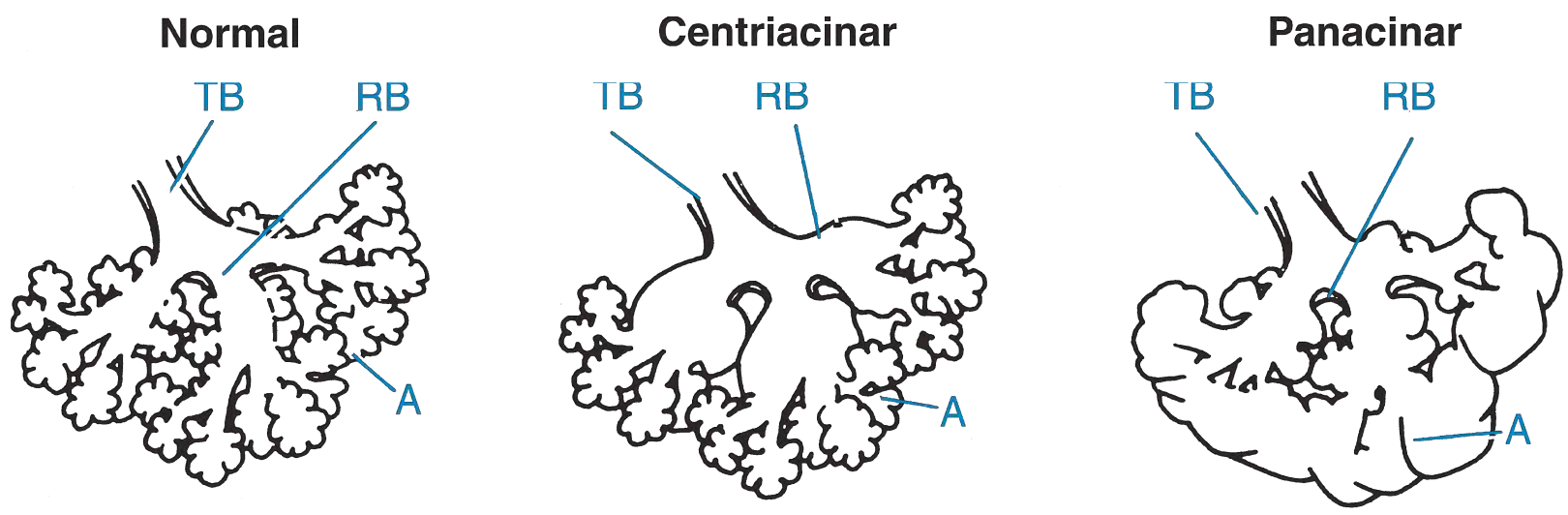


Figure 4.4. **Centriacinar and panacinar emphysema.** In centriacinar emphysema, the destruction is confined to the terminal and respiratory bronchioles (TB and RB). In panacinar emphysema, the peripheral alveoli (A) are also involved.

lobe but spreads down the lung as the disease progresses **(Figure 4.5A)**. The predilection for the apex might reflect the higher mechanical stresses (see Figure 3.4), which predispose to structural failure of the alveolar walls. By contrast, panacinar emphysema has no regional preference or, possibly, is more common in the lower lobes. When emphysema is severe, it is difficult to distinguish the two types, and these may coexist in one lung. The centriacinar form is a very common form and is most often due to long-standing exposure to cigarette smoke. Mild forms apparently cause no dysfunction.

A severe form of panacinar emphysema can be seen in $\alpha_1$-antitrypsin deficiency **(Figure 4.5B)**. The disease, which usually begins in the lower lobes, may become evident by the age of 40 years in patients who are homozygous for the Z gene, particularly in those who also smoke. Extrapulmonary manifestations may also be present in the liver, bowel, kidneys, and other organs. Therapy by replacement of $\alpha_1$-antitrypsin is now available. Heterozygotes do not seem to be at risk, although this is not certain. Other variants of emphysema include unilateral emphysema (MacLeod's or Swyer-James syndrome), which causes a unilaterally hyperlucent chest radiograph.

## Pathogenesis

One hypothesis is that excessive amounts of the enzyme lysosomal elastase are released from the neutrophils in the lung. This results in the destruction of elastin, an important structural protein of the lung. Neutrophil elastase also cleaves type IV collagen, and this molecule is important in determining the strength of the thin side of the pulmonary capillary and therefore the integrity of the alveolar wall. Animals that have had neutrophil elastase instilled into their airways develop histologic changes that are similar in many ways to emphysema.

Cigarette smoking is an important pathogenic factor and may work by stimulating macrophages to release neutrophil chemoattractants, such as C5a, or by reducing the activity of elastase inhibitors. In addition, many neutrophils are normally marginated (trapped) in the lung, and this process is exaggerated by cigarette smoking, which also activates trapped leucocytes.

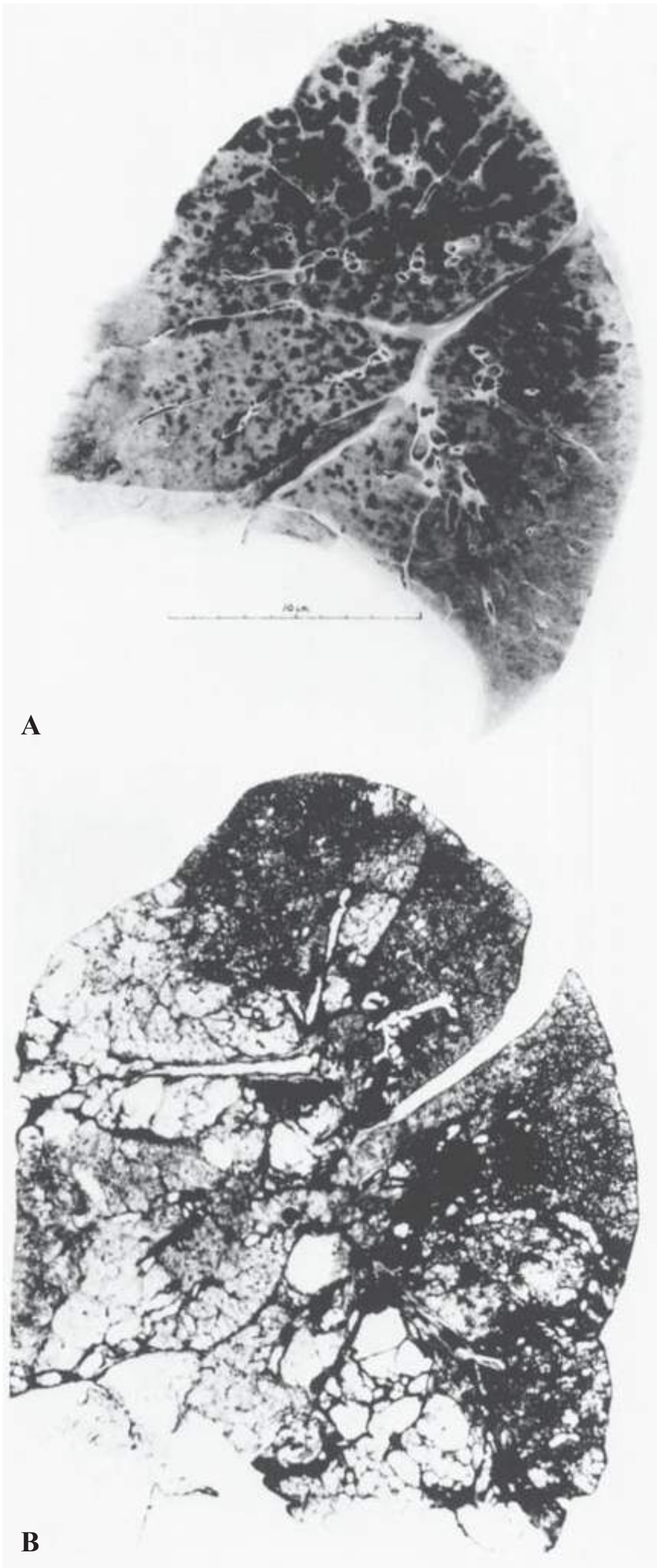


Figure 4.5. **Topographic distribution of emphysema. A.** The typical upper zone preference of centriacinar emphysema. **B.** The typical lower zone preference of emphysema caused by $\alpha_1$-antitrypsin deficiency. (From Heard BE. Pathology of Chronic Bronchitis and Emphysema. London, UK: Churchill, 1969.)

This hypothesis puts the etiology on the same footing as that for the emphysema of $\alpha_1$-antitrypsin deficiency, in which the mechanism is the lack of the antiprotease that normally inhibits elastase. One puzzle is why some heavy smokers do not develop the disease. Air pollution may play a role, as may hereditary factors, which are clearly important in $\alpha_1$-antitrypsin deficiency. Smoke pollution from fuels, for example, from use of poorly ventilated wood-burning stoves indoors, is now also recognized as an important cause of COPD worldwide.

## Chronic Bronchitis

*This disease is characterized by excessive mucus production in the bronchial tree, sufficient to cause excessive expectoration of sputum. Note that this is a clinical definition (unlike the definition of emphysema). In practice, criteria for excessive expectoration are often laid down, for example, expectoration on most days for at least 3 months in the year for at least 2 successive years.*

### Pathology

The hallmark is hypertrophy of mucous glands in the large bronchi **(Figure 4.6)** and evidence of chronic inflammatory changes in the small airways. The mucous gland enlargement may be expressed as the gland–wall ratio, which is normally less than 0.4 but may exceed 0.7 in severe chronic bronchitis. This is known as the "Reid index" **(Figure 4.7)**. Excessive amounts of mucus are found in the airways, and semisolid plugs of mucus may occlude some small bronchi.

In addition, the small airways are narrowed and show inflammatory changes, including cellular infiltration and edema of the walls. Granulation tissue is present, bronchial smooth muscle increases, and peribronchial fibrosis may develop. There is evidence that the initial pathologic changes are in the small airways and that these progress to the larger bronchi.

### Pathogenesis

Again, cigarette smoking is the chief culprit. Repeated exposure to this inhaled irritant results in chronic inflammation. If you hear a patient give a moist, fruity (or gurgling) cough, you can safely bet that he is a smoker. Air pollution caused by smog or industrial smoke is another definite factor.

## Clinical Features of Chronic Obstructive Pulmonary Disease

As we have seen, chronic bronchitis is a clinical definition, and the diagnosis in the living patient can therefore be made confidently. However, a definitive diagnosis of emphysema requires histologic confirmation that is usually not available during life, although a combination of history, physical

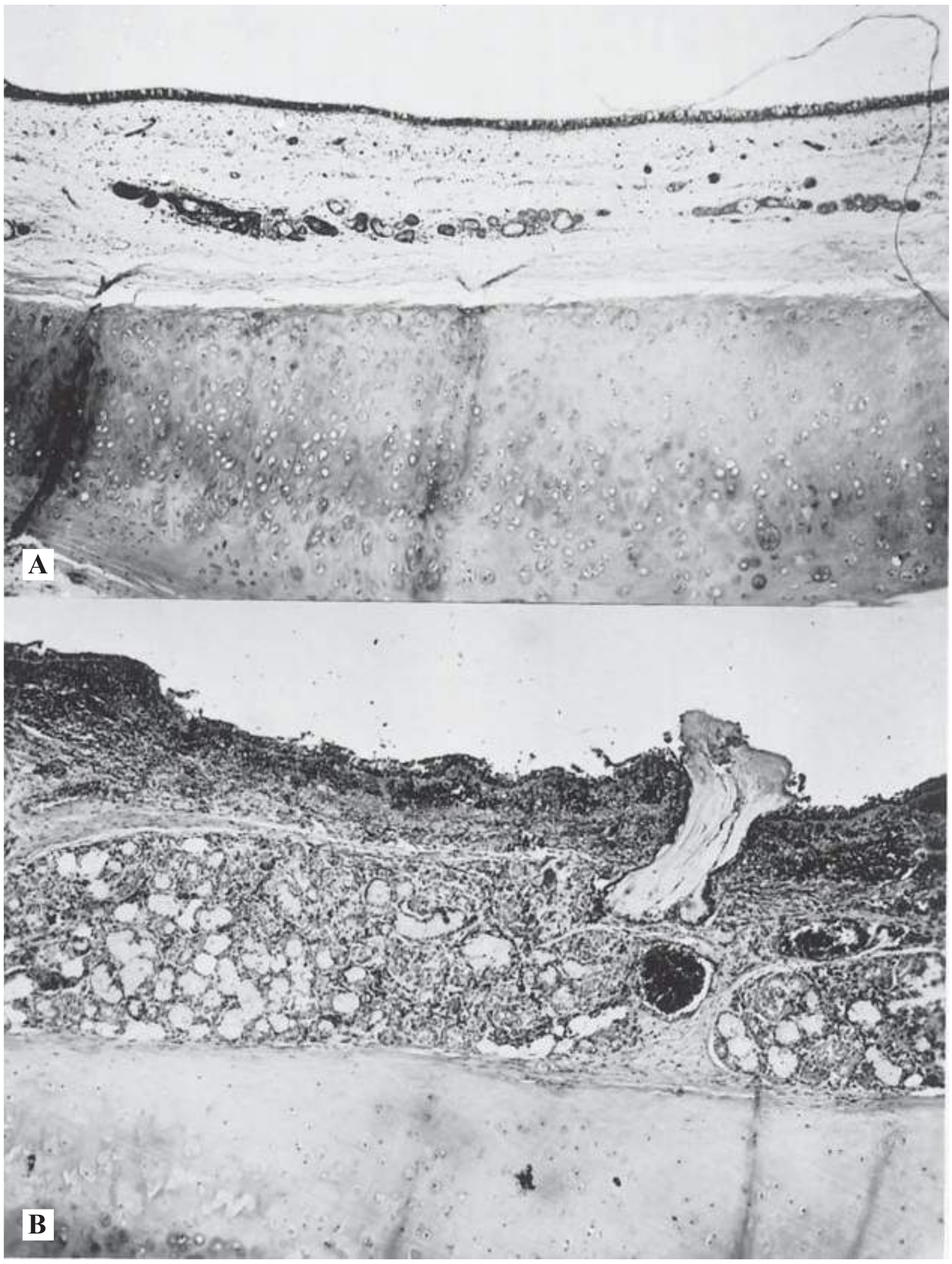


Figure 4.6. **Histologic changes in chronic bronchitis. A.** A normal bronchial wall. **B.** Bronchial wall of a patient with chronic bronchitis. Note the great hypertrophy of the mucous glands, the thickened submucosa, and the cellular infiltration (3× 60). Compare with the diagram of the bronchial wall in Figure 4.7. (From Thurlbeck WM. Chronic Air*fl*ow Obstruction in Lung Disease. Philadelphia, PA: WB Saunders, 1976.)

examination, and radiology (especially computed tomography [CT]) can give a high probability of the diagnosis. It follows that the amount of emphysema in a given patient is uncertain. This is why COPD remains a useful term.

Within the spectrum of COPD, two extremes of clinical presentation are recognized: type A and type B. At one time, it was thought that these types correlated

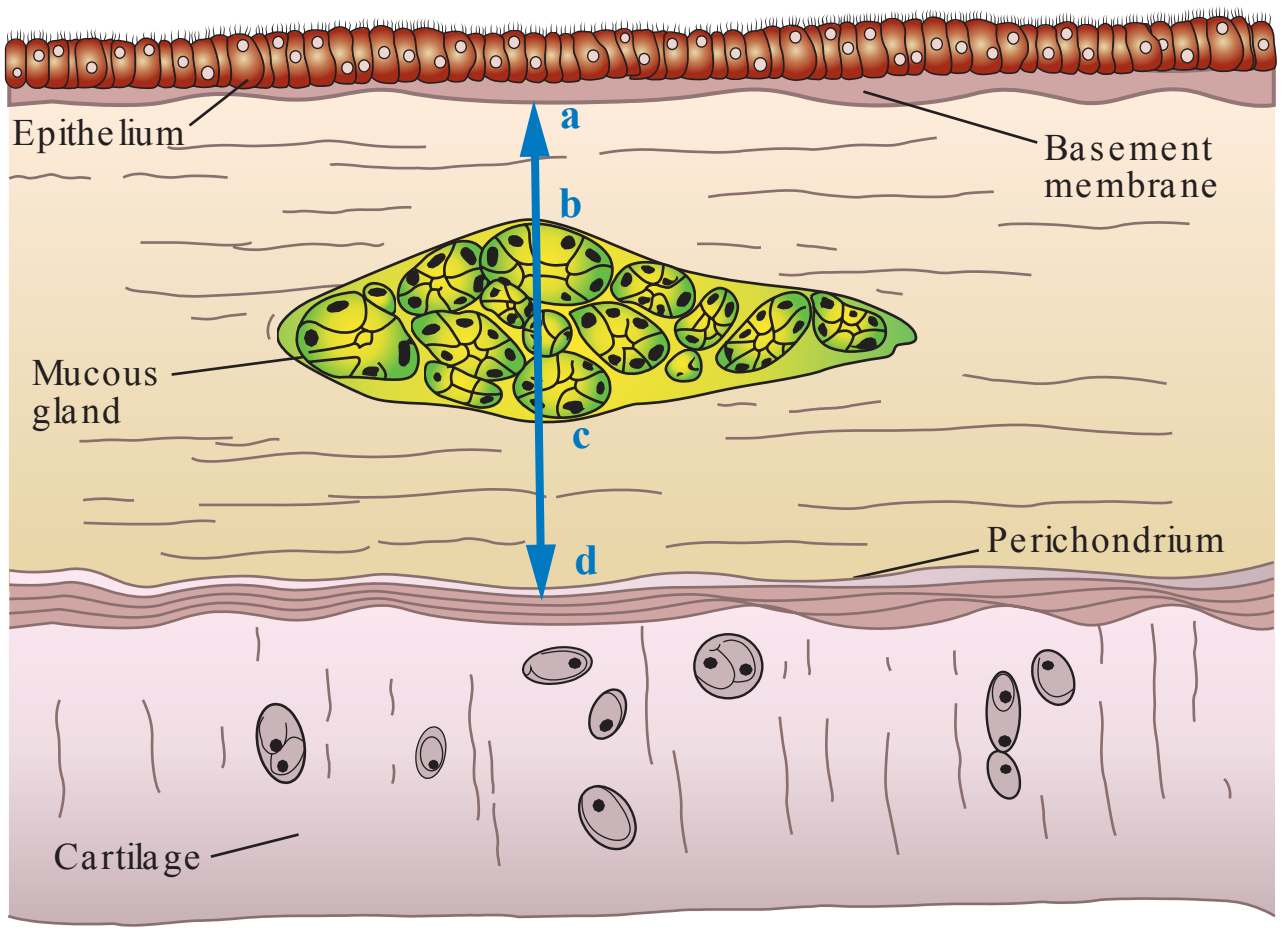


Figure 4.7. **Structure of a normal bronchial wall.** In chronic bronchitis, the thickness of the mucous glands increases and can be expressed as the Reid index given by (b–c)/(a–d). (From Thurlbeck WM. Chronic Air*fl*ow Obstruction in Lung Disease. Philadelphia, PA: WB Saunders, 1976.)

to some extent with the relative amounts of emphysema and chronic bronchitis, respectively, in the lung, but this view has been challenged. Nevertheless, it is still useful to describe two patterns of clinical presentation because they represent different pathophysiologies. In practice, most patients have features of both.

### Type A

A typical presentation would be a man in his middle 50s who has had increasing shortness of breath for the last 3 or 4 years. Cough may be absent or may produce little white sputum. Physical examination reveals an asthenic build with evidence of recent weight loss. There is no cyanosis. The chest is overexpanded with quiet breath sounds and no adventitious sounds. The radiograph **(Figure 4.8B)** confirms the overinflation with low and flattened diaphragms, narrow mediastinum, and increased retrosternal translucency (between the sternum and the heart on the lateral view). In addition, the radiograph shows increased lucency, particularly in the apical lung zones, due to attenuation and narrowing of the peripheral pulmonary vessels. Additional information is available from computer tomography (CT). **Figure 4.9A** shows a normal lung using this imaging technique. **Figure 4.9B** shows an axial section of a lung from a patient with emphysema. Holes scattered throughout the lung can be seen. These patients have been dubbed "pink puffers."

### Type B

A typical presentation would be a man in his 50s with a history of chronic cough with expectoration for several years. This expectoration has gradually increased in severity, being present only in the winter months initially

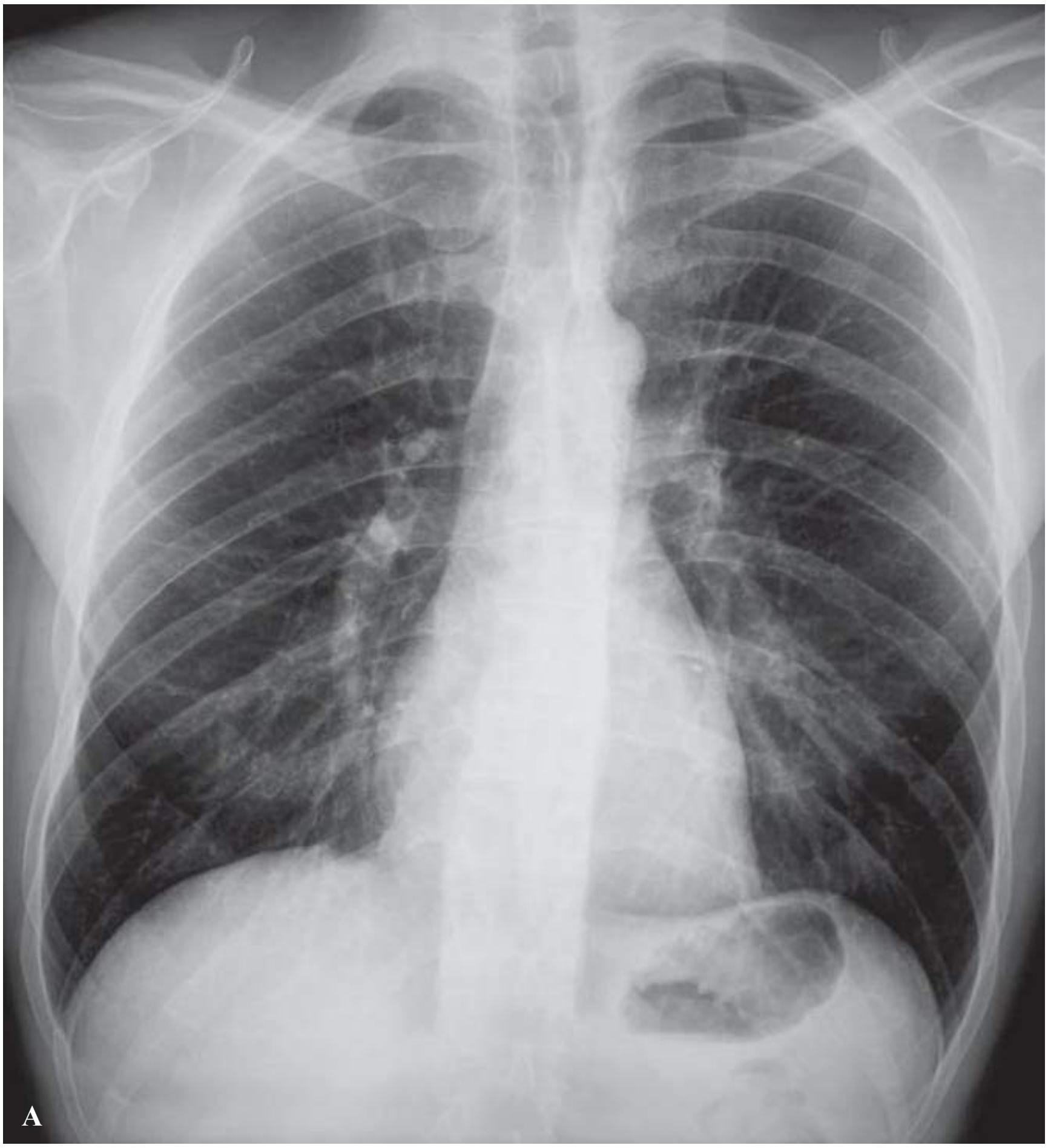


Figure 4.8. **Radiographic appearances in the normal lung and in emphysema.**
**A.** Normal lung.

but, more recently, lasting most of the year. Acute exacerbations with frankly purulent sputum have become more common. Shortness of breath on exertion has gradually worsened, with progressively limiting exercise tolerance. The patient is almost invariably a cigarette smoker of many years' duration. This can be quantified as the number of cigarette packs a day multiplied by the number of years of smoking to give the "pack-years."

On examination, the patient has a stocky build with a plethoric complexion and some cyanosis. Auscultation reveals scattered rales (crackles) and rhonchi (whistles). There may be signs of fluid retention with a raised jugular venous pressure and ankle edema. The chest radiograph shows some cardiac

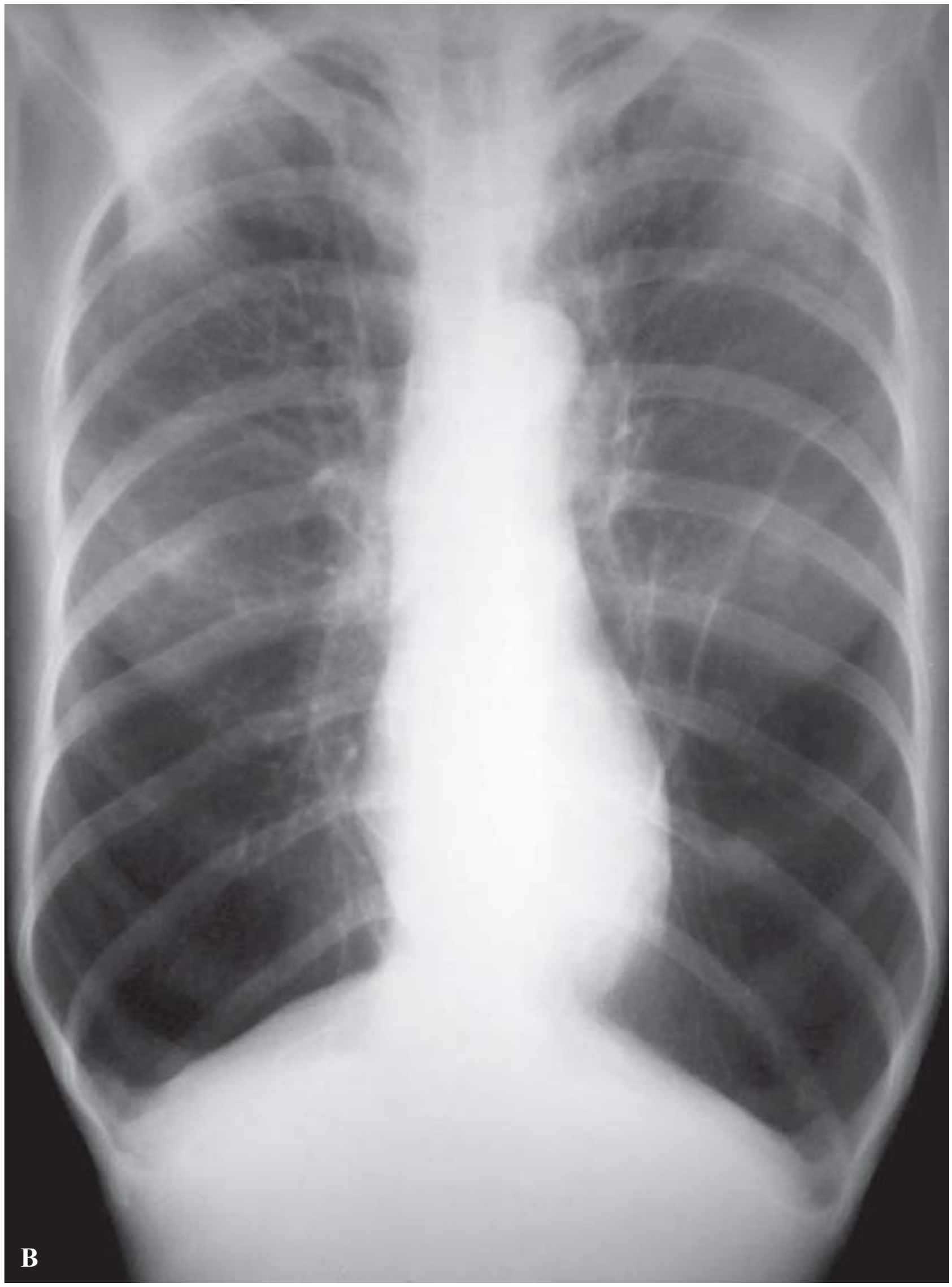


Figure 4.8. (Continued) **B.** The pattern of overinflation, with low diaphragms, narrow mediastinum, and increased translucency that is seen in emphysema. The emphysema is particularly prominent in the lower regions of the lung.

enlargement, congested lung fields, and increased markings attributable to old infection. Parallel lines (tram lines) may be seen, probably caused by the thickened walls of inflamed bronchi. At autopsy, chronic inflammatory changes in the bronchi are the rule if the patient had severe bronchitis, but there may be severe emphysema as well. These patients are sometimes called "blue bloaters."

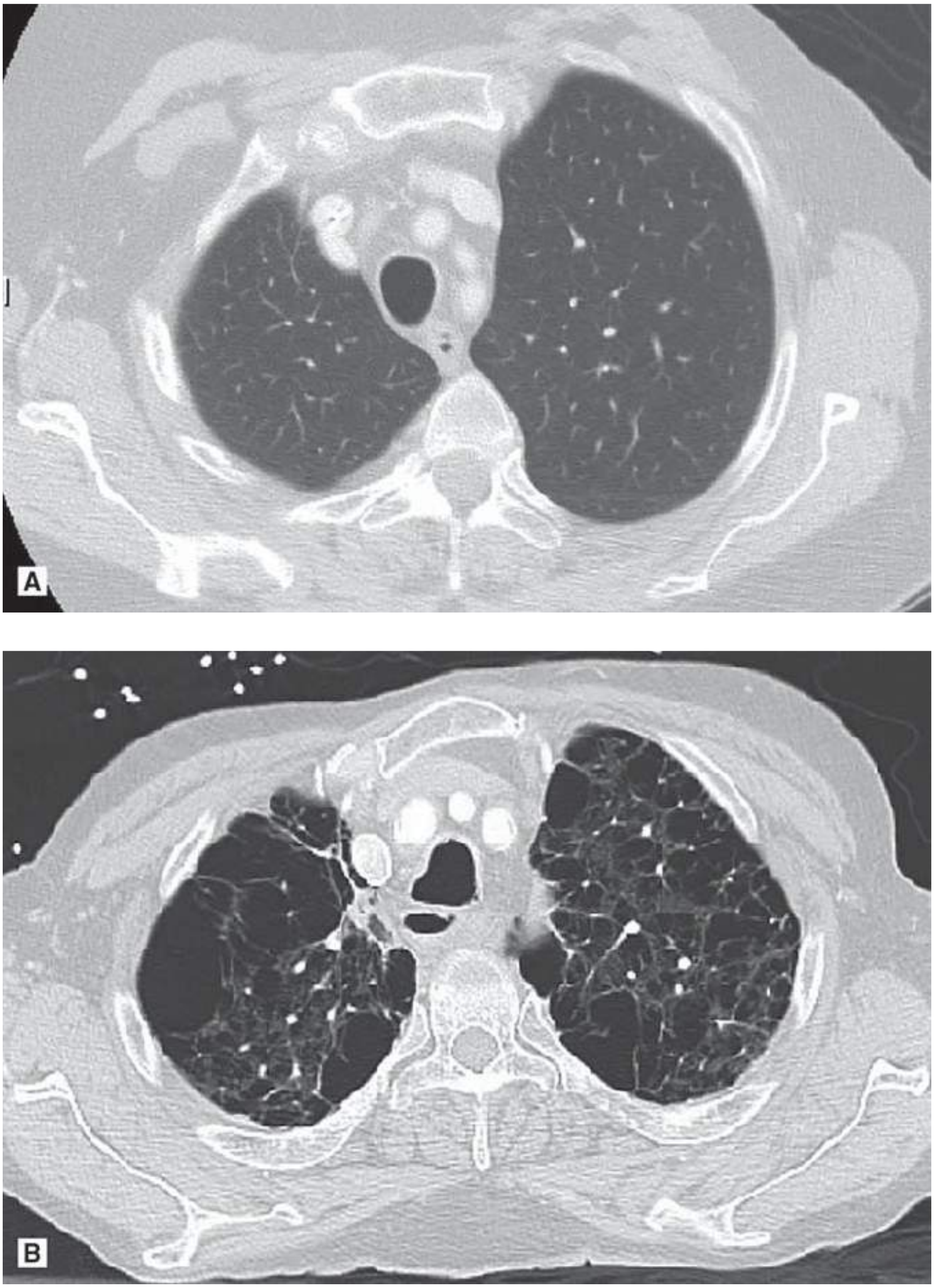


Figure 4.9. **A.** Appearance of normal lung on CT scan of the chest. **B.** CT scan of the lungs of a patient with emphysema. Holes can be seen scattered throughout the lung.

Some physicians believe that the essential difference between the two types is in the control of breathing. They suggest that the more severe hypoxemia and consequent higher incidence of cor pulmonale in the type B patients can be attributed to a reduced ventilatory drive, especially during sleep.

**Features of Type A and Type B Presentations in COPD**

| Type A—"Pink Puffer" | Type B—"Blue Bloater" |
|---|---|
| Increasing dyspnea over years | Increasing dyspnea over years |
| Little or no cough | Frequent cough with sputum |
| Marked chest overexpansion | Moderate or no increase in chest volume |
| No cyanosis | Often cyanosis |
| Quiet breath sounds | Rales and rhonchi |
| Normal jugular venous pressure | Raised jugular venous pressure |
| No peripheral edema | Peripheral edema |
| Arterial $P_{O_2}$ only moderately depressed | $P_{O_2}$ often very low |
| Arterial $P_{CO_2}$ normal | $P_{CO_2}$ often raised |

## Pulmonary Function

Most of the features of disordered function in COPD follow from the pathologic features discussed earlier and illustrated in **Figures 4.2** to **4.7**.

### Ventilatory Capacity and Mechanics

The forced expiratory volume in 1 second ($FEV_1$), forced vital capacity (FVC), forced expiratory volume as a percentage of vital capacity (FEV/FVC), forced expiratory flow ($FEF_{25-75\%}$), and maximum expiratory flow at 50% and 75% of exhaled vital capacity ($\dot{V}max_{50\%}$ and $\dot{V}max_{75\%}$) are all reduced. All of these measurements reflect the airway obstruction, whether caused by excessive mucus in the lumen, thickening of the wall by inflammatory changes (see **Figure 4.1A and B**) or by the loss of radial traction (see **Figure 4.1C**). The FVC is reduced because the airways close prematurely during expiration at an abnormally high lung volume, giving an increased residual volume (RV). Again, all three mechanisms of **Figure 4.1** may be contributing factors.

Examination of the spirogram shows that the flow rate over most of the forced expiration is greatly reduced and the *expiratory time* is much increased. Indeed, some physicians regard this prolonged time as a useful simple bedside index of obstruction. Often, the maneuver is terminated by breathlessness when the patient is still exhaling. The low flow rate over most of the forced expiration partly reflects the reduced elastic recoil of the emphysematous lung, which generates the pressure responsible for flow under these conditions of dynamic compression (see Figure 1.6). Typically, the $FEV_1$ may be reduced to less than 0.8 liters in severe disease, whereas healthy young individuals may have values at or above 4 liters depending on their age, height, and gender (see Appendix A).

In some patients, the $FEV_1$, FVC, and FEV/FVC may increase significantly after the administration of a bronchodilator aerosol (e.g., 0.5% albuterol by nebulizer for 3 minutes), although the airflow obstruction is incompletely reversible. Significant response to bronchodilators over a period of weeks suggests asthma, and this disease may overlap with chronic bronchitis (asthmatic bronchitis).

The expiratory flow–volume curve is grossly abnormal in severe disease. Figure 1.8 shows that after a brief interval of moderately high flow, flow is strikingly reduced as the airways collapse, and flow limitation by dynamic compression occurs. The graphed curve often has a scooped-out appearance. Flow is greatly reduced in relation to lung volume and ceases at a high lung volume because of premature airway closure (see Figure 1.5B). However, the inspiratory flow–volume curve may be normal or nearly so (see Figure 1.9) as the airways are tethered open by radial traction exerted by the surrounding alveolar walls during inhalation.

The total lung capacity (TLC), functional residual capacity (FRC), and RV are all typically increased in emphysema. Often, the RV/TLC may exceed 40% (less than 30% in young healthy patients). There is often a striking discrepancy between the FRC determined by the body plethysmograph and by the gas dilution techniques (helium equilibration), the former being higher by 1 liter or more. This may be caused by regions of uncommunicating lung behind grossly distorted airways. However, the disparity more often reflects the slow equilibration process in poorly ventilated areas. These static lung volumes are also often abnormal in patients with chronic bronchitis, although the increases in volume are generally less marked.

Elastic recoil of the lung is reduced in emphysema (see Figure 3.1), the pressure–volume curve being displaced up and to the left. This change reflects the disorganization and loss of elastic tissue as a result of the destruction of alveolar walls. The transpulmonary pressure at TLC is low. In uncomplicated chronic bronchitis in the absence of emphysema, the pressure–volume curve may be nearly normal because the parenchyma is little affected.

Airway resistance (related to lung volume) is increased in COPD. All the factors shown in Figure 4.1 may be responsible. However, it is possible to distinguish between an increased resistance caused by intrinsic narrowing of the airway or debris in the lumen (Figure 4.1A and B) and the loss of elastic recoil and radial traction (Figure 4.1C). This can be done by relating resistance to the static elastic recoil.

**Figure 4.10** shows airway conductance (reciprocal of resistance) plotted against static transpulmonary pressure in a series of 10 healthy patients, 10 patients with emphysema (without bronchitis), and 10 asthmatics. The measurements were made during a quiet, unforced expiration. Note that the relationship between conductance and transpulmonary pressure for the patients with emphysema was almost normal. In other words, we can ascribe their reduced ventilatory capacity almost entirely to the effects of the smaller elastic recoil pressure of the lung. This not only reduces the effective driving pressure during

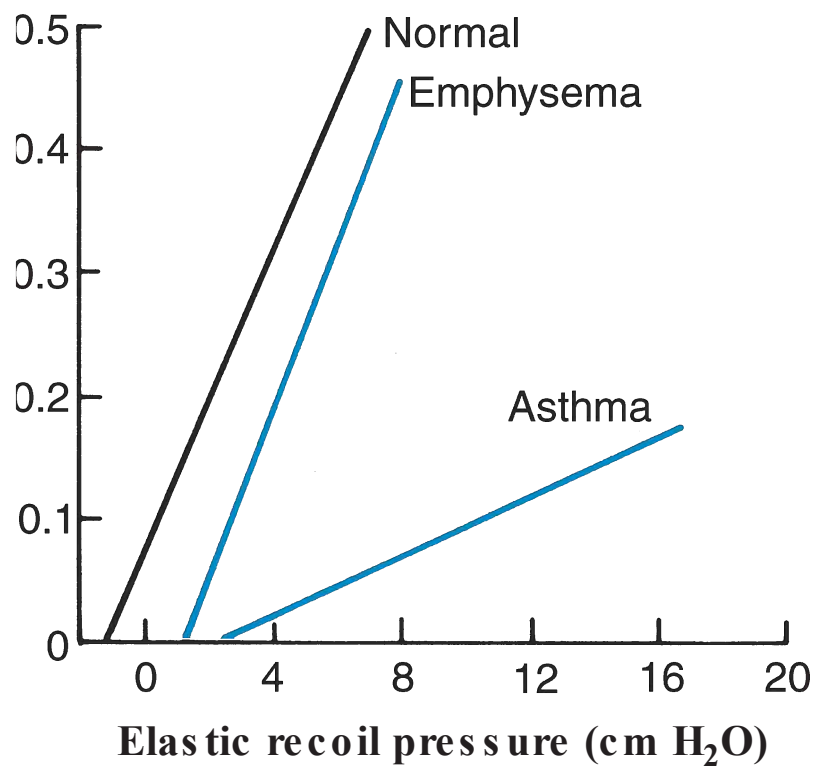


Figure 4.10. **Relationships between airway conductance and elastic recoil pressure in obstructive pulmonary disease.** Note that the line for emphysema lies close to the normal line. It is evident that any increase in airway resistance is chiefly caused by the smaller elastic recoil of the lung. By contrast, in asthma, the line is markedly abnormal due to the intrinsic narrowing of the airways. (From Colebatch HJH, Finucane KE, Smith MM. Pulmonary conductance and elastic recoil relationships in asthma and emphysema. J Appl Physiol 1973;34:143–153.)

a forced expiration but also allows the airways to collapse more easily because of the loss of radial traction. The small displacement of the emphysematous line to the right probably reflects the distortion and loss of airways in this disease.

By contrast, the line for the asthmatics shows that the airway conductance was greatly reduced at a given recoil pressure. Thus, the higher resistance in these patients can be ascribed to intrinsic narrowing of the airways caused by contraction of smooth muscle and inflammatory changes in the airways. After inhalation of a bronchodilator drug, isoproterenol, the asthmatic line moved toward the normal position (not shown in Figure 4.10). Comparable data are not available for a group of patients with chronic bronchitis without emphysema because it is virtually impossible to select such a group during life. However, Figure 4.10 clarifies the behavior of different types of airway obstruction.

## Gas Exchange

Ventilation–perfusion inequality is inevitable in COPD and leads to hypoxemia with or without $CO_2$ retention. Typically, the type A patient has only moderate hypoxemia ($P_{O_2}$ often in the high 60s or 70s), and the arterial $P_{CO_2}$ is normal. By contrast, the type B patient often has severe hypoxemia ($P_{O_2}$ often in the 50s or 40s) with an increased $P_{CO_2}$, especially in advanced disease.

The alveolar–arterial difference for $P_{O_2}$ is always increased, especially in patients with severe bronchitis. An analysis based on the concept of the ideal point (see Figure 2.7) reveals increases in both physiologic dead space and physiologic shunt. The dead space is particularly increased in emphysema, whereas high values for physiologic shunt are especially common in bronchitis.

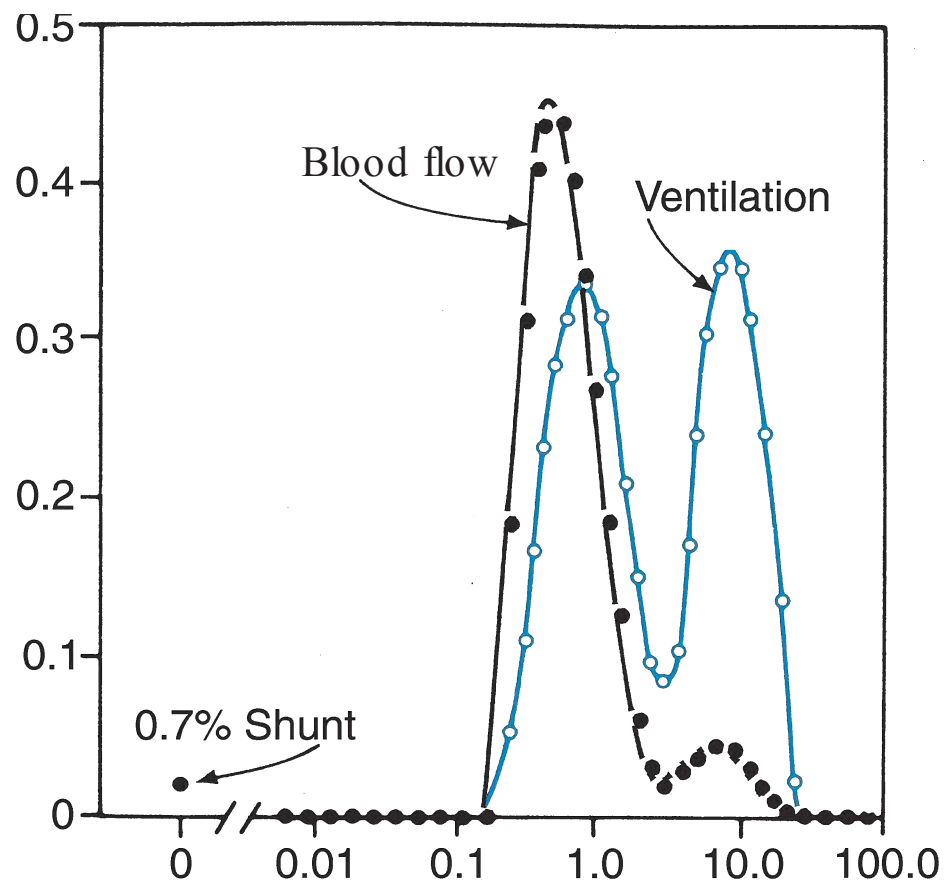


Figure 4.11. **Distribution of ventilation–perfusion ratios in a patient with type A COPD.** Note the large amount of ventilation to units with high ventilation–perfusion ratios (physiologic dead space). (From Wagner PD, Dantzker DR, Dueck R, et al. Ventilation–perfusion inequality in chronic pulmonary disease. J Clin Invest 1977;59:203–206.)

The reasons for these differences are clarified by the results obtained with the inert gas elimination technique. First, review Figure 2.8, which shows a typical pattern in a normal subject. By contrast, **Figure 4.11** shows a typical distribution in a patient with advanced type A disease. This 76-year-old man had a history of increasing dyspnea over several years. The chest radiograph showed hyperinflation with attenuated small pulmonary vessels. The arterial $P_{O_2}$ and $P_{CO_2}$ were 68 and 39 mm Hg, respectively.

The distribution shows that a large amount of ventilation went to lung units with high ventilation–perfusion ratios ($\dot{V}_A / \dot{Q}$) (compare Figure 2.8). This would be shown as physiologic dead space in the ideal point analysis, and the excessive ventilation is largely wasted from the point of view of gas exchange. By contrast, there is little blood flow to units with an abnormally low $\dot{V}_A / \dot{Q}$. This explains the relatively mild degree of hypoxemia in the patient and the fact that the calculated physiologic shunt was only slightly increased.

These findings can be contrasted with those shown in **Figure 4.12**, which shows the distribution in a 47-year-old man with advanced chronic bronchitis and type B disease. He was a heavy smoker and had had a productive cough for many years. The arterial $P_{O_2}$ and $P_{CO_2}$ were 47 and 50 mm Hg, respectively. Note that there was some increase in ventilation to high $\dot{V}_A / \dot{Q}$ units (physiologic dead space). However, the distribution chiefly shows large amounts of blood flow to low $\dot{V}_A / \dot{Q}$ units (physiologic shunt), accounting for his severe hypoxemia. It is remarkable that there was no blood flow to unventilated alveoli (true shunt). Indeed, true shunts of more than a few percent are uncommon in COPD. Note that although the patterns shown in Figures 4.11 and 4.12 are typical, considerable variation is seen in patients with COPD.

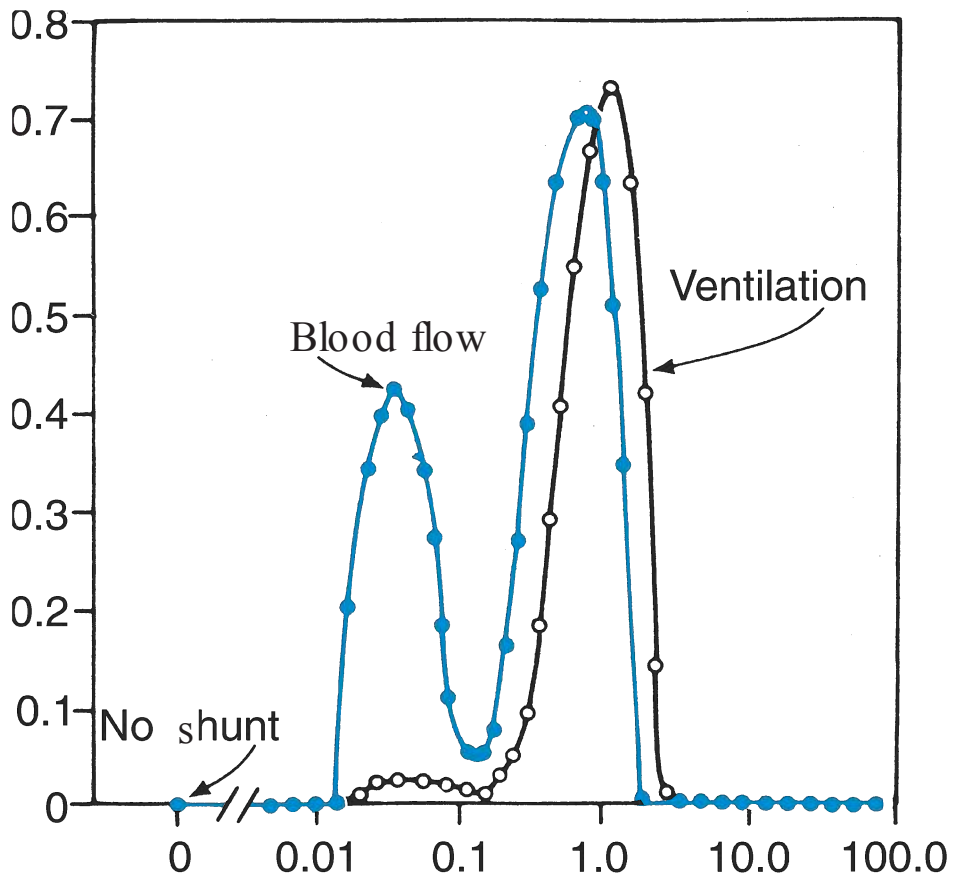


Figure 4.12. **Distribution of ventilation–perfusion ratios in a patient with type B COPD.** There is a large amount of blood flow to units with low ventilation–perfusion ratios (physiologic shunt). (From Wagner PD, Dantzker DR, Dueck R, et al. Ventilation–perfusion inequality in chronic pulmonary disease. J Clin Invest 1977;59:203–206.)

On exercise, the arterial $P_{O_2}$ may fall or rise depending on the response of the ventilation and the cardiac output and the changes in the distribution of ventilation and blood flow. In some patients at least, the main factor in the fall of $P_{O_2}$ is the limited cardiac output, which, in the presence of ventilation–perfusion inequality, exaggerates any hypoxemia. Patients with $CO_2$ retention often show higher $P_{CO_2}$ values on exercise because of their limited ventilatory response.

The reasons for the ventilation–perfusion inequality are clear when we consider the disorganization of the lung architecture in emphysema (Figures 4.2 and 4.3) and the abnormalities in airways in chronic bronchitis (Figure 4.6). There is ample evidence of uneven ventilation as determined by the single-breath nitrogen washout (see Figure 1.10). In addition, topographic measurements with radioactive materials show regional inequality of both ventilation and blood flow. The blood flow inequality is largely caused by the destruction of portions of the capillary bed.

The deleterious effects of airway obstruction on gas exchange are reduced by collateral ventilation that occurs in these patients. Communicating channels normally exist between adjacent alveoli and between neighboring small airways, and there have been many experimental demonstrations of these. The fact that there is so little blood flow to unventilated units in these patients (Figures 4.11 and 4.12) emphasizes the effectiveness of collateral ventilation because some airways must presumably be completely obstructed, especially in severe bronchitis (see Figure 1.12).

Another factor that reduces the amount of ventilation–perfusion inequality is hypoxic vasoconstriction. (See *West's Respiratory Physiology: The Essentials*. 10th ed. p. 52.) This local response to a low alveolar $P_{O_2}$ reduces the blood flow to poorly ventilated and unventilated regions, minimizing the arterial

hypoxemia. When patients with COPD are given bronchodilators, for example, albuterol, they sometimes develop a slight fall in arterial $P_{O_2}$. This is probably caused by the vasodilator action of these β-adrenergic drugs, increasing the blood flow to poorly ventilated areas. This finding is more marked in asthma (see Figures 4.17 and 4.18).

The arterial $P_{CO_2}$ is often normal in patients with mild to moderate COPD despite their ventilation–perfusion inequality. Any tendency for the arterial $P_{CO_2}$ to rise stimulates the chemoreceptors, thus increasing ventilation to the alveoli (see Figure 2.9). As disease becomes more severe, the arterial $P_{CO_2}$ may rise. This is particularly likely to occur in type B patients. The increased work of breathing is an important factor, but there is also evidence that the sensitivity of the respiratory center to $CO_2$ is reduced in some of these patients.

If the arterial $P_{CO_2}$ rises, the pH tends to fall, resulting in respiratory acidosis. In some patients, the $P_{CO_2}$ rises so slowly that the kidney is able to compensate adequately by retaining bicarbonate, and the pH remains almost constant (compensated respiratory acidosis). The $P_{CO_2}$ may rise more suddenly during COPD exacerbations or acute chest infections, leading to acute respiratory acidosis (see Chapter 8, Respiratory Failure).

Additional information about gas exchange in these patients can be obtained by measuring the diffusing capacity (transfer factor) for carbon monoxide (see Figure 2.11). The diffusing capacity as measured by the single-breath method is particularly likely to be reduced in patients with severe emphysema. By contrast, patients with chronic bronchitis but little parenchymal destruction may have normal values.

### Pulmonary Circulation

The pulmonary artery pressure frequently rises in patients with COPD as their disease progresses. Several factors are responsible. In emphysema, large portions of the capillary bed are destroyed, thus increasing vascular resistance. Hypoxic vasoconstriction also raises the pulmonary arterial pressure, and often, an exacerbation of chest infection causes an additional transient increase as the alveolar hypoxia worsens. Acidosis may exaggerate the hypoxic vasoconstriction. In advanced disease, histologic changes in the walls of the small arteries occur. Finally, these patients often develop polycythemia as a response to the hypoxemia, thus increasing blood viscosity. This occurs most commonly in patients with severe bronchitis, who tend to have the lowest arterial $P_{O_2}$.

Fluid retention with dependent edema and engorged neck veins may occur, especially in type B patients. The right heart often enlarges with characteristic radiologic and electrocardiographic appearances. The term “cor pulmonale” is given to this condition, but whether it should be regarded as right heart failure is disputed. The output of the heart is normally increased because it is operating high on the Starling curve, and the output can rise further on exercise.

## Control of Ventilation

As indicated previously, some patients with COPD, particularly those with severe chronic bronchitis, develop $CO_2$ retention because they do not sufficiently increase the ventilation to their alveoli. The reasons why some patients behave in this way and some do not are not completely understood. One factor is the increased work of breathing as a result of the high airway resistance. As a consequence, the $O_2$ cost of breathing may be enormous **(Figure 4.13)**. Normal subjects have an abnormally small ventilatory response to inhaled $CO_2$ if they are asked to breathe through a high resistance. Thus, a patient with a severely limited $O_2$ consumption may be willing to forgo a normal arterial $P_{CO_2}$ to obtain the advantage of a reduced work of breathing and a correspondingly reduced $O_2$ cost. However, the correlation between airway resistance and arterial $P_{CO_2}$ is sufficiently poor that some other factor must be involved.

Measurements of the ventilatory response to inhaled $CO_2$ show that there are significant differences among normal subjects. These differences are partly caused by genetic factors. Some patients have a reduced respiratory center output in response to inhaled $CO_2$, many have a mechanical obstruction to ventilation, and some patients have both. Thus, it is possible that the ventilatory response of a patient in the face of severe ventilation–perfusion inequality and increased work of breathing is predetermined to some extent by these factors.

## Changes in Early Disease

So far, we have been concerned mainly with pulmonary function in patients with well-established disease. However, relatively little can be done to reverse the disease process in this group, and the treatment is limited chiefly to symptom relief with bronchodilators, prevention and control of infection, and rehabilitative programs. There is a great deal of interest in identifying patients with early disease in the hope that the changes can be arrested or

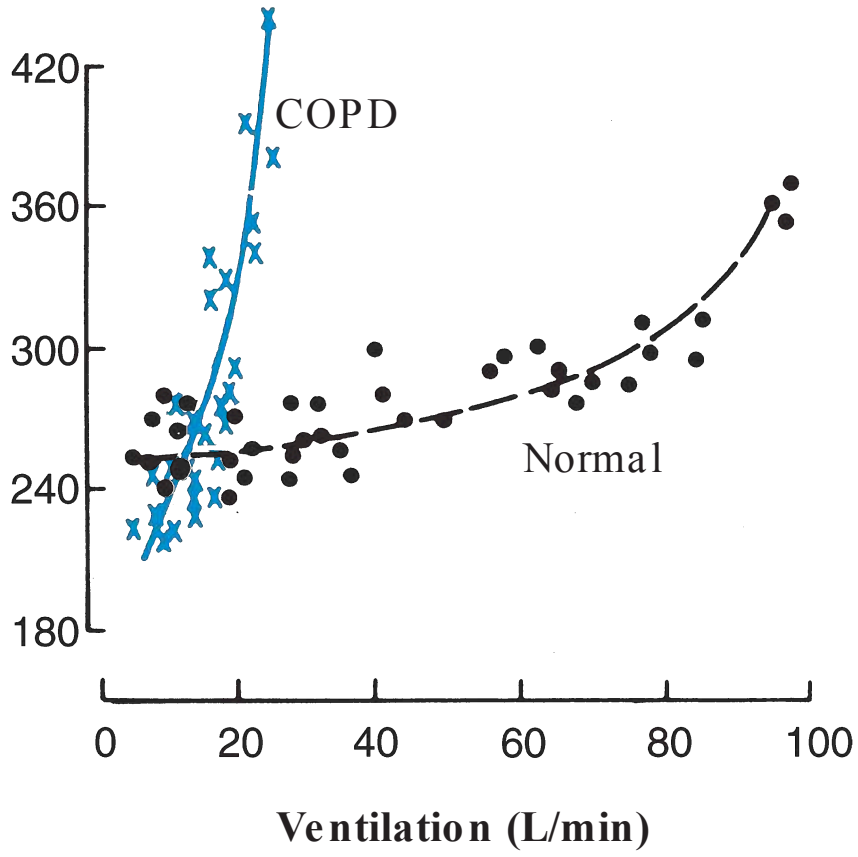


Figure 4.13. **Oxygen uptake during voluntary hyperventilation in patients with COPD.** Note the high values compared with those of the normal subjects. (From Cherniack RM, Cherniack L, Naimark A. Respiration in Health and Disease. 2nd ed. Philadelphia, PA: WB Saunders, 1972.)

reversed by elimination of smoking or other risk factors such as exposure to pollution.

It was emphasized in Chapter 1 that because relatively little of the airway resistance resides in small airways (less than 2 mm wide), pathophysiologic changes there may go unnoticed by the usual function tests. There is some evidence that the earliest changes in COPD occur in these small airways. Interest has focused on whether changes in $FEV_1$, $FEF_{25-75\%}$, $\dot{V}\,max_{50\%}$, $\dot{V}\,max_{75\%}$, and closing volume can be used to identify early disease but their practical value for clinical purposes remains uncertain.

## Treatment of Patients with COPD

Smoking cessation is the most critical step for most patients as this is the one intervention that can slow the rate of decline in lung function over time. Exposure to occupational and atmospheric pollution should also be reduced as far as possible. Bronchodilator therapy, including β-agonists and anticholinergics, is the mainstay of therapy for all COPD patients, with the intensity of use varying depending on the severity of the patient's airflow obstruction, functional limitation, and frequency of exacerbations. Inhaled corticosteroids are also used in many patients but are generally reserved for those with more severe disease and/or frequent exacerbations, while the macrolide antibiotic, azithromycin, is now being used on a chronic basis in patients who suffer from frequent exacerbations. Pulmonary rehabilitation can be prescribed to patients with stable disease of any severity and has been shown to quality of life and exercise capacity. Administration of continuous supplemental oxygen to patients with sufficient degrees of chronic hypoxemia is associated with improved survival in such patients. One benefit of this intervention is an increase in the average alveolar $P_{O_2}$, which lessens hypoxic pulmonary vasoconstriction and partially alleviates the pulmonary hypertension that can occur in severe cases and worsen prognosis.

## Lung Volume Reduction Surgery

Surgery to reduce the volume of the overexpanded lung can be valuable in selected cases. The physiologic basis is that reducing the volume increases the radial traction on the airways and therefore helps to limit dynamic compression. In addition, the inspiratory muscles, particularly the diaphragm, are shortened with consequent improvement in their mechanical efficiency. Initially, the emphasis was on resecting bullae, but now, good results can be obtained in patients with more diffuse emphysema. The aim is to remove emphysematous and avascular areas and to preserve the nearly normal regions. Criteria for surgery usually include an $FEV_1$ of less than 45% predicted, lung volume measurements consistent with air-trapping and hyperinflation, upper lobe predominant emphysema demonstrated by CT scan, and low exercise capacity following a pulmonary rehabilitation program. In properly selected patients, LVRS is associated with improvements in spirometry, lung volumes, quality of life, and dyspnea and, in a small set of patients, improved survival.