Clinical Features

Profound dyspnea and tachypnea herald ALI/ARDS, followed by increasing respiratory failure, hypoxemia, cyanosis, and the appearance of diffuse bilateral infiltrates on radiographic examination. Hypoxemia may be refractory to oxygen therapy due to ventilation-perfusion mismatch, and respiratory acidosis can develop. Early in the course, the lungs become stiff due to loss of functional surfactant, leading to the need for intubation and high ventilatory pressures to maintain adequate gas exchange.

There are no proven specific treatments for ARDS, which is common in acutely ill patients and continues to take a high toll, even in patients receiving state-of-the-art supportive care. In a 2016 study of intensive care units in 50 countries, the incidence of ARDS was 10.4%, and mortality rates were 35% for mild, 40% for moderate, and 46% for severe ARDS. The majority of deaths are attributable to sepsis, multiorgan failure, or severe lung injury. Most survivors recover pulmonary function, but in a minority of patients, the lung damage results in interstitial fibrosis and chronic pulmonary disease.

KEY CONCEPTS

ACUTE RESPIRATORY DISTRESS SYNDROME

- ARDS is a clinical syndrome of progressive respiratory insufficiency caused by diffuse alveolar damage in the setting of sepsis, severe trauma, or diffuse pulmonary infection.
- Damage to endothelial and alveolar epithelial cells and secondary inflammation are the key initiating events and the basis of lung damage.
- The characteristic histologic finding is hyaline membranes lining alveolar walls, accompanied by edema, scattered neutrophils and macrophages, and epithelial necrosis.

OBSTRUCTIVE AND RESTRICTIVE LUNG DISEASES

Obstructive lung diseases are characterized by an increase in resistance to airflow due to diffuse airway disease, which may affect any level of the respiratory tract. These are contrasted with restrictive diseases, which are characterized by reduced expansion of lung parenchyma and decreased total lung capacity. The clinical distinction between these diseases is based primarily on pulmonary function tests. In individuals with diffuse obstructive disorders, pulmonary function tests show decreased maximal airflow rates during forced expiration, usually expressed as forced expiratory volume at 1 second (FEV_1) over forced ventilatory capacity (FVC). An FEV_1/FVC ratio of less than 0.7 generally indicates obstructive disease. Expiratory airflow obstruction may be caused by a variety of conditions (Table 15.3), each with characteristic pathologic changes and different mechanisms of airflow obstruction. As discussed later, however, the divisions between these entities are not "clean," and many patients have diseases with overlapping features. By contrast, restrictive diseases are associated with proportionate decreases in both total lung capacity and FEV_1, such that the FEV_1/FVC ratio remains normal. Restrictive defects occur in two broad kinds of conditions: (1) *chest wall disorders* (e.g., severe obesity, pleural diseases, kyphoscoliosis, and neuromuscular diseases such as poliomyelitis) and (2) *chronic interstitial and infiltrative diseases,* such as pneumoconioses and interstitial fibrosis.

OBSTRUCTIVE LUNG DISEASES

Common obstructive lung diseases include chronic obstructive pulmonary disease (COPD), asthma, and bronchiectasis (Table 15.3). COPD has two major clinicopathologic manifestations, emphysema and chronic bronchitis, which are often found together in the same patient, almost certainly because they share the same major etiologic factor—cigarette smoking. While asthma is distinguished from chronic bronchitis and emphysema by the presence of reversible bronchospasm, some patients with otherwise typical asthma also develop an irreversible component (Fig. 15.5). Conversely, some patients with otherwise typical COPD have a reversible component. Clinicians commonly label such patients as having COPD/asthma.

Chronic Obstructive Pulmonary Disease

COPD, a major public health problem, is defined by the World Health Organization (WHO) as "a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities caused by exposure to noxious particles or gases." It is currently the fourth

Table 15.3 Disorders Associated With Airflow Obstruction: The Spectrum of Chronic Obstructive Pulmonary Disease

Clinical Term	Anatomic Site	Major Pathologic Changes	Etiology	Signs/Symptoms
Chronic bronchitis	Bronchus	Mucous gland hyperplasia, hypersecretion	Tobacco smoke, air pollutants	Cough, sputum production
Bronchiectasis	Bronchus	Airway dilation and scarring	Persistent or severe infections	Cough, purulent sputum, fever
Asthma	Bronchus	Smooth muscle hyperplasia, excess mucus, inflammation	Immunologic or undefined causes	Episodic wheezing, cough, dyspnea
Emphysema	Acinus	Airspace enlargement; wall destruction	Tobacco smoke	Dyspnea
Small airways disease, bronchiolitis[a]	Bronchiole	Inflammatory scarring/obliteration	Tobacco smoke, air pollutants, miscellaneous	Cough, dyspnea

[a]Can be seen with any form of obstructive lung disease or as an isolated finding.

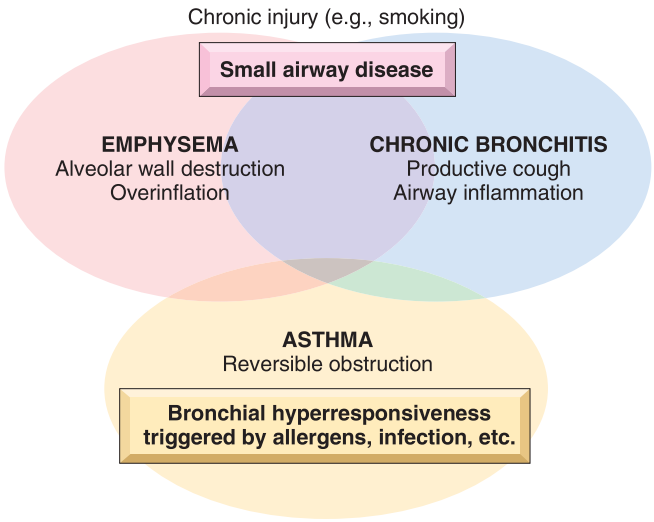

Figure 15.5 Schematic representation of overlap between chronic obstructive lung diseases.

leading cause of death in the world and is projected to rank third by 2020 due to increases in cigarette smoking in countries such as China. There is a strong association between heavy cigarette smoking and COPD. Overall, 35% to 50% of heavy smokers develop COPD; conversely about 80% of COPD is attributable to smoking. Women and African Americans who smoke heavily are more susceptible than other groups. Additional risk factors include poor lung development early in life, exposure to environmental and occupational pollutants, airway hyperresponsiveness, and certain genetic polymorphisms.

Recognizing that emphysema and chronic bronchitis often occur together in patients with COPD, it is still useful to discuss these patterns of lung injury and associated functional abnormalities individually to highlight the pathophysiologic basis of different causes of airflow obstruction. We will finish our discussion by returning to the clinical features of COPD.

Emphysema

Emphysema is defined by irreversible enlargement of the airspaces distal to the terminal bronchiole, accompanied by destruction of their walls. Subtle but functionally important small airway fibrosis (distinct from chronic bronchitis) is also present and is a significant contributor to airflow obstruction. Emphysema is classified according to its anatomic distribution within the lobule. Recall that the lobule is a cluster of acini, the terminal respiratory units. Based on the segments of the respiratory units that are involved, emphysema is subdivided into four major types: (1) *centriacinar,* (2) *panacinar,* (3) *paraseptal,* and (4) *irregular.* Of these, only the first two cause clinically significant airflow obstruction (Fig. 15.6).

- *Centriacinar (centrilobular) emphysema.* Centriacinar emphysema is the most common form, constituting more than 95% of clinically significant cases. It occurs predominantly in heavy smokers with COPD. In this type of emphysema the central or proximal parts of the acini, formed by respiratory bronchioles, are affected, whereas distal alveoli are spared (Figs. 15.6B and 15.7A). Thus, both emphysematous and normal airspaces exist within the same acinus and lobule. The lesions are more common and usually more pronounced in the upper lobes, particularly in the apical segments. In severe centriacinar emphysema, the distal acinus may also be involved, making differentiation from panacinar emphysema difficult.
- *Panacinar (panlobular) emphysema.* Panacinar emphysema is associated with *α1-antitrypsin deficiency* (Chapter 18) and is exacerbated by smoking. In this type the acini are uniformly enlarged from the level of the respiratory bronchiole to the terminal blind alveoli (Figs. 15.6C and 15.7B). In contrast to centriacinar emphysema, panacinar emphysema tends to occur more commonly in the lower zones and in the anterior margins of the lung, and it is usually most severe at the bases.
- *Distal acinar (paraseptal) emphysema.* Distal acinar emphysema probably underlies many cases of spontaneous pneumothorax in young adults. In this type the proximal portion of the acinus is normal, and the distal part is predominantly involved. The emphysema is more striking adjacent to the pleura, along the lobular connective tissue septa, and at the margins of the lobules. It occurs adjacent to areas of fibrosis, scarring, or atelectasis and is usually more severe in the upper half of the lungs. The characteristic finding is multiple enlarged airspaces, ranging from less than 0.5 cm to more than 2.0 cm in diameter, which sometimes form cyst-like structures.

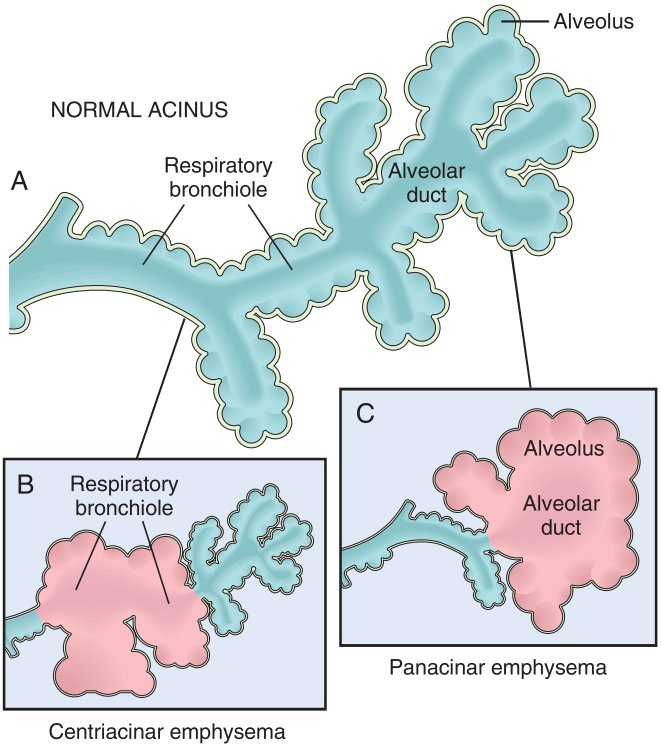

Figure 15.6 Clinically significant patterns of emphysema. (A) Structure of the normal acinus. (B) Centriacinar emphysema with dilation that initially affects the respiratory bronchioles. (C) Panacinar emphysema with initial distention of the alveolus and alveolar duct.

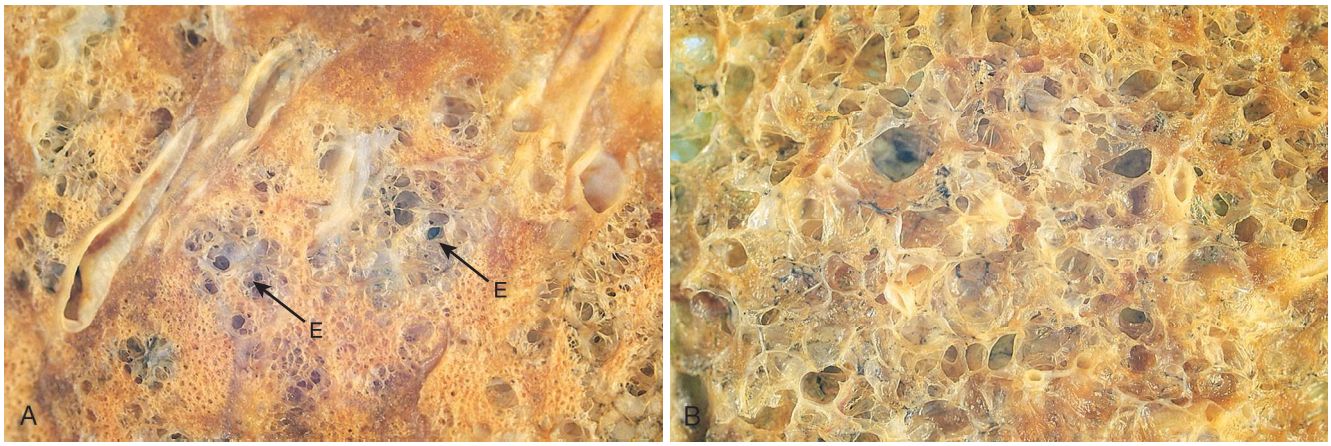

Figure 15.7 (A) Centriacinar emphysema. Central areas show marked emphysematous damage *(E)* surrounded by relatively spared alveolar spaces. (B) Panacinar emphysema involving the entire pulmonary lobule.

- *Airspace enlargement with fibrosis (irregular emphysema).* Irregular emphysema, so named because the acinus is irregularly involved, is almost invariably associated with scarring. In most instances it occurs in small foci and is clinically insignificant.

Pathogenesis

Clinically significant emphysema is largely confined to smokers and to patients with α_1-antitrypsin deficiency, highlighting the importance of these two etiologic factors. Mechanisms relating to these factors that contribute to the development of emphysema include the following (Fig. 15.8):

- *Toxic injury and inflammation.* Inhaled cigarette smoke and other noxious particles damage respiratory epithelium and cause inflammation, which results in variable degrees of parenchymal destruction. A wide variety of inflammatory mediators (including leukotriene B_4, interleukin [IL]-8, TNF, and others) are increased in the affected parts of the lung. These mediators are released by resident epithelial cells and macrophages and variously attract inflammatory cells from the circulation (chemotactic factors), amplify the inflammatory process (proinflammatory cytokines), and induce structural changes (growth factors). Chronic inflammation also leads to the accumulation of T and B cells in affected parts of the lung, but the role of adaptive immunity in emphysema is currently uncertain.
- *Protease-antiprotease imbalance.* Several proteases are released from the inflammatory cells and epithelial cells that break down connective tissue components. In patients who develop emphysema, there is a relative deficiency of protective antiproteases, which in some instances has a genetic basis (discussed later).
- *Oxidative stress.* Substances in tobacco smoke, alveolar damage, and inflammatory cells all produce oxidants, which may beget tissue damage, endothelial dysfunction, and inflammation. The role of oxidants is supported by studies of mice in which the *NRF2* gene is inactivated. NRF2 is a transcription factor that serves as a sensor for oxidants in many cell types including alveolar epithelial cells. Intracellular oxidants activate *NRF2,* which upregulates the expression of genes that protect cells from oxidant damage. Mice without *NRF2* are significantly more sensitive to tobacco smoke than normal mice, and genetic variants in *NRF2, NRF2* regulators, and *NRF2* target genes are all associated with smoking-related lung disease in humans.
- *Infection.* Although infection is not thought to play an initiating role in the tissue destruction, bacterial and/or viral infections may acutely exacerbate existing disease.

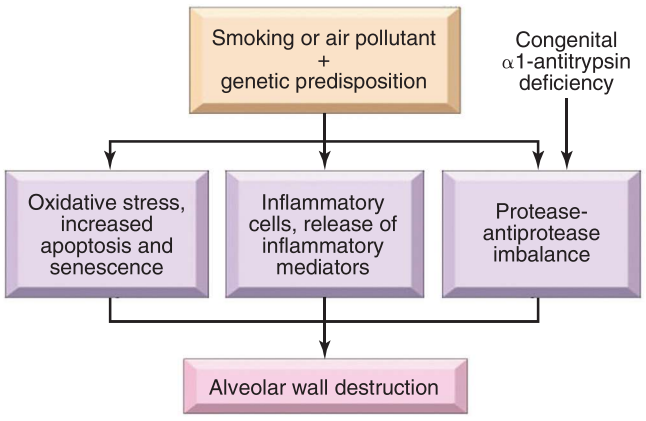

Figure 15.8 Pathogenesis of emphysema. See text for details.

The idea that proteases are important is based in part on the observation that patients with a genetic deficiency of the antiprotease α_1-antitrypsin have a markedly enhanced tendency to develop emphysema that is compounded by smoking. About 1% of all patients with emphysema have this defect. α_1-Antitrypsin, normally present in serum, tissue fluids, and macrophages, is a major inhibitor of proteases (particularly elastase) secreted by neutrophils during inflammation. It is encoded by the proteinase inhibitor *(Pi)* locus on chromosome 14. The *Pi* locus is polymorphic, and approximately 0.012% of the U.S. population is homozygous for the *Z* allele, a genotype associated with very low serum levels of α_1-antitrypsin. More than 80% of *ZZ* individuals develop symptomatic panacinar emphysema, which occurs at an earlier age and is of greater severity if the individual smokes. It is postulated that any injury (e.g., that induced by smoking) that increases the activation and influx of

neutrophils into the lung leads to local release of proteases, which in the absence of α_1-antitrypsin activity result in excessive digestion of elastic tissue and, with time, emphysema.

Several other genetic variants have also been linked to risk of emphysema. Among these are variants of the nicotinic acetylcholine receptor that are hypothesized to influence the addictiveness of tobacco smoke and thus the behavior of smokers. Not surprisingly, the same variants are also linked to lung cancer risk, emphasizing the importance of smoking in both of these diseases.

A number of factors contribute to airway obstruction in emphysema. Small airways are normally held open by the elastic recoil of the lung parenchyma. The loss of elastic tissue in the walls of alveoli that surround respiratory bronchioles reduces radial traction, leading to collapse of respiratory bronchioles during expiration and functional airflow obstruction in the absence of mechanical obstruction. In addition, even young smokers often have changes related to small airway inflammation that also contribute to airway narrowing and obstruction (described later).

MORPHOLOGY

Advanced emphysema produces voluminous lungs, often overlapping the heart anteriorly. Generally, in patients with smoking-related disease, the upper two-thirds of the lungs are more severely affected. Large alveoli can easily be seen on the cut surface of fixed lungs (see Fig. 15.7). Apical blebs or bullae characteristic of irregular emphysema may appear in patients with advanced disease.

Microscopically, abnormally large alveoli are separated by thin septa with focal centriacinar fibrosis. There is loss of attachments between alveoli and the outer wall of small airways. The pores of Kohn are so large that septa appear to be floating or protrude blindly into alveolar spaces with a club-shaped end. As alveolar walls are destroyed, there is a decrease in the capillary bed area. With advanced disease, there are even larger abnormal airspaces and possibly blebs or bullae, which often deform and compress the respiratory bronchioles and vasculature of the lung. Inflammatory changes in small airways are often superimposed (described next under chronic bronchitis), as are vascular changes related to pulmonary hypertension stemming from local hypoxemia and loss of capillary beds.

Chronic Bronchitis

Chronic bronchitis is defined clinically as persistent cough with sputum production for at least 3 months in at least 2 consecutive years in the absence of any other identifiable cause. Longstanding chronic bronchitis is associated with progressive lung dysfunction, which may be so severe as to lead to hypoxemia, pulmonary hypertension, and cor pulmonale.

Pathogenesis

The primary or initiating factor in the genesis of chronic bronchitis is exposure to noxious or irritating inhaled substances such as tobacco smoke (90% of those affected are smokers) and dust from grain, cotton, and silica. Several factors contribute to its pathogenesis.

- *Mucus hypersecretion.* The earliest feature of chronic bronchitis is hypersecretion of mucus in the large airways, associated with enlargement of the submucosal glands in the trachea and bronchi. The basis for mucus hypersecretion is incompletely understood, but it appears to involve inflammatory mediators such as histamine and IL-13. With time, there is also a marked increase in goblet cells in small airways—small bronchi and bronchioles—leading to excessive mucus production that contributes to airway obstruction. It is thought that both the enlargement of submucosal glands and the increase in numbers of goblet cells are protective reactions against tobacco smoke or other pollutants (e.g., sulfur dioxide and nitrogen dioxide).
- *Acquired cystic fibrosis transmembrane conductance regulator (CFTR) dysfunction.* There is substantial evidence that smoking leads to acquired CFTR dysfunction, which in turn causes the secretion of abnormal, dehydrated mucus that exacerbates the severity of chronic bronchitis.
- *Inflammation.* Inhalants that induce chronic bronchitis cause cellular damage, eliciting both acute and chronic inflammatory responses involving neutrophils, lymphocytes, and macrophages. Long-standing inflammation and accompanying fibrosis involving small airways (small bronchi and bronchioles, less than 2 to 3 mm in diameter) can also lead to chronic airway obstruction.
- *Infection.* Infection does not initiate chronic bronchitis, but is probably significant in maintaining it and may be critical in producing acute exacerbations.

Cigarette smoke predisposes to chronic bronchitis in several ways. Not only does it damage airway-lining cells, leading to chronic inflammation, but it also interferes with the ciliary action of the respiratory epithelium, preventing the clearance of mucus and increasing the risk of infection.

MORPHOLOGY

Grossly, there is hyperemia, swelling, and edema of the mucous membranes, frequently accompanied by excessive mucinous or mucopurulent secretions. Sometimes, heavy casts of secretions and pus fill the bronchi and bronchioles. The characteristic microscopic features are chronic inflammation of the airways (predominantly lymphocytes and macrophages); thickening of the bronchiolar wall due to smooth muscle hypertrophy, deposition of extracellular matrix in the muscle layer, and peribronchial fibrosis; goblet cell hyperplasia; and enlargement of the mucus-secreting glands of the trachea and bronchi. Of these, the most striking change is an increase in the size of the mucous glands. This increase can be assessed by the ratio of the thickness of the mucous gland layer to the thickness of the wall between the epithelium and the cartilage **(Reid index)**. The Reid index (normally 0.4) is increased in chronic bronchitis, usually in proportion to the severity and duration of the disease. The mucus plugging, inflammation, and fibrosis may lead to marked narrowing of bronchioles, and in the most severe cases, there may be obliteration of lumen due to fibrosis **(bronchiolitis obliterans)**. The bronchial epithelium may also exhibit squamous metaplasia and dysplasia due to the irritating and mutagenic effects of substances in tobacco smoke.

Clinical Features of COPD

Most affected patients have a smoking history of 40 pack-years or greater. COPD often presents insidiously with slowly

Table 15.4 Predominant Features of Emphysema and Chronic Bronchitis

	Bronchitis	Emphysema
Age, years	40–45	50–75
Dyspnea	Mild; late	Severe; early
Cough	Early; copious sputum	Late; scanty sputum
Infections	Common	Occasional
Respiratory insufficiency	Early, periodic	End-stage
Cor pulmonale	Common	Uncommon, end-stage
Airway resistance	Increased	Normal or slightly increased
Elastic recoil	Normal	Low
Chest radiograph	Prominent vessels; large heart size	Hyperinflation; normal heart size
Appearance	Blue bloater	Pink puffer

increasing dyspnea on exertion and chronic cough with sputum production, slight at first but increasing over time. Other patients present with exacerbations caused by superimposed infection that can lead to confusion with other disorders, such as asthma (due to wheezing). The most important diagnostic test is spirometry, which typically shows an FEV_1/FVC ratio of less than 0.7.

Once COPD appears, symptoms often wax and wane over time and are generally worse in the morning. The clinical picture varies according to the severity of the disease and the relative contributions of emphysematous and bronchitic changes (Table 15.4). At one extreme end of the spectrum lie *"pink puffers,"* patients in whom emphysema dominates. Classically, the patient is barrel-chested and dyspneic, with obviously prolonged expiration, sits forward in a hunched-over position, and breathes through pursed lips. Cough is often slight, overdistention of the lungs is severe, diffusion capacity is low, and blood gas values are relatively normal at rest. Weight loss is common and can be so severe as to suggest an occult cancer. At the other end lie patients with pure chronic bronchitis, ingloriously referred to as *"blue bloaters."* Their cardinal symptom is a persistent cough productive of sputum, coupled with hypercapnia, hypoxemia, and mild cyanosis. Most patients are somewhere in the middle, with signs and symptoms stemming from both bronchitic and emphysematous changes.

Treatment options include smoking cessation, oxygen therapy, long-acting bronchodilators with inhaled corticosteroids, antibiotics, physical therapy, bullectomy, and, in selected patients, lung volume reduction surgery and lung transplantation. Even with intervention, however, COPD often progresses and frequently proves fatal. Long-standing COPD, particularly in patients with a bronchitic component, commonly leads to pulmonary hypertension, cor pulmonale, and death due to heart failure. Death may also result from acute respiratory failure due to acute infections superimposed on COPD. In patients with emphysematous changes, subpleural blebs may rupture, leading to fatal pneumothorax. The best hope for a major change in this dire picture is more effective programs aimed at prevention of smoking and other environmental exposures.

KEY CONCEPTS

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

- Most common in long-standing tobacco smokers (typically >40 pack-years); air pollutants also contribute.
- Underlying pulmonary pathology usually includes both chronic bronchitis and emphysema.
- Often fatal due to development of heart failure or of respiratory failure due to superimposed infection.

Emphysema

- In COPD, usually follows a centroacinar distribution characterized by permanent enlargement of airspaces distal to terminal bronchioles.
- Particularly severe in patients with α_1-antitrypsin deficiency, in which a panacinar pattern of emphysematous change may be seen.
- Tissue destruction is caused by elastases and oxidants released from inflammatory cells, particularly neutrophils, which are responding to cellular injury caused by tobacco smoke and pollutants.

Chronic Bronchitis

- Defined as persistent productive cough for at least 3 consecutive months in at least 2 consecutive years.
- Dominant pathologic features are mucus hypersecretion due to enlargement of mucus-secreting glands and chronic inflammation associated with bronchiolar wall fibrosis.

Other Forms of Emphysema

In addition to emphysema occurring in the setting of COPD, several other conditions may be associated with lung overinflation or focal emphysematous change and are mentioned here in brief.

- *Compensatory hyperinflation.* This term is used to designate dilation of alveoli in response to loss of lung substance elsewhere, for example, following surgical removal of a lung or lobe with cancer.
- *Obstructive overinflation.* In this condition the lung expands because air is trapped within it. A common cause is subtotal obstruction of an airway by a tumor or foreign object. In infants, it may be caused by *congenital lobar overinflation*, which most often results from hypoplasia of bronchial cartilage. Overinflation occurs either (1) because of an obstruction that acts as ball valve, allowing air to enter on inspiration while preventing its exodus on expiration, or (2) because collaterals bring in air behind the obstruction. These collaterals consist of the *pores of Kohn* and other direct accessory bronchioloalveolar connections (the *canals of Lambert*). Obstructive overinflation can be life-threatening if the affected portion distends sufficiently to compress the adjacent uninvolved lung.
- *Bullous emphysema.* This is a descriptive term for large subpleural blebs or bullae (spaces greater than 1 cm in diameter in the distended state) that can occur in any form of emphysema (Fig. 15.9), often near the apex. Rupture of the bullae may give rise to pneumothorax.
- *Interstitial emphysema.* Entrance of air into the connective tissue stroma of the lung, mediastinum, or subcutaneous