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 emphysema.

Several other genetic variants have been linked to risk of emphysema. Among these are variants associated with the nicotinic acetylcholine receptor, which 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, and the loss of elastic tissue in the walls of alveoli that surround respiratory bronchioles reduces radial traction and thus causes the respiratory bronchioles to collapse during expiration. This leads to functional airflow obstruction despite the absence of mechanical obstruction. In addition, even young smokers often have small airway inflammation associated with the following changes:

- Goblet cell hyperplasia, with mucus plugging of the lumen
- Inflammatory infiltrates in bronchial walls consisting of neutrophils, macrophages, B cells (sometimes forming follicles), and T cells
- Thickening of the bronchiolar wall due to smooth muscle hypertrophy and peribronchial fibrosis

Together these changes narrow the bronchiolar lumen and contribute to airway obstruction.

MORPHOLOGY

Advanced emphysema produces voluminous lungs, often overlapping the heart and hiding it when the anterior chest wall is removed. Generally, the upper two thirds of the lungs are more severely affected. Large apical blebs or bullae are more characteristic of irregular emphysema secondary to scarring and of distal acinar emphysema. Large alveoli can easily be seen on the cut surface of fixed lungs (Fig. 15-7).

Microscopically, abnormally large alveoli are separated by thin septa with only focal centriacinar fibrosis. There is loss of attachments of the alveoli to 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. Prolonged vasoconstriction leads to changes of pulmonary arterial hypertension. 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 were described earlier.

Clinical Course. Symptoms do not appear until at least one third of the functioning pulmonary parenchyma is damaged. *Dyspnea* usually appears first, beginning insidiously but progressing steadily. In some patients, cough or wheezing is the chief complaint, easily confused with asthma. Cough and expectoration are extremely variable and depend on the extent of the associated bronchitis.

Table 15-4 Emphysema and Chronic Bronchitis

	Predominant Bronchitis	Predominant Emphysema
Age (yr)	40-45	50-75
Dyspnea	Mild; late	Severe; early
Cough	Early; copious sputum	Late; scanty sputum
Infections	Common	Occasional
Respiratory insufficiency	Repeated	Terminal
Cor pulmonale	Common	Rare; terminal
Airway resistance	Increased	Normal or slightly increased
Elastic recoil	Normal	Low
Chest radiograph	Prominent vessels; large heart	Hyperinflation; small heart
Appearance	Blue bloater	Pink puffer

Weight loss is common and can be so severe as to suggest an occult cancer. Classically, the patient with severe emphysema is barrel-chested and dyspneic, with obviously prolonged expiration, sits forward in a hunched-over position, and breathes through pursed lips. *Impaired expiratory airflow,* best measured through spirometry, is the key to diagnosis.

In individuals with severe emphysema, cough is often slight, overdistention is severe, diffusion capacity is low, and blood gas values are relatively normal at rest. Such patients may overventilate and remain well oxygenated, and therefore are somewhat ingloriously designated *pink puffers* (Table 15-4). Development of cor pulmonale and eventually congestive heart failure, related to secondary pulmonary hypertension, is associated with a poor prognosis. Death in most patients with emphysema is due to (1) coronary artery disease, (2) respiratory failure, (3) right-sided heart failure, or (4) massive collapse of the lungs secondary to pneumothorax. Treatment options include smoking cessation, oxygen therapy, long-acting bronchodilators with inhaled corticosteroids, physical therapy, bullectomy, and, in selected patients, lung volume reduction surgery and lung transplantation. α_1-AT replacement therapy is being evaluated.

KEY CONCEPTS

Emphysema

- Emphysema is a chronic obstructive airway disease characterized by permanent enlargement of air spaces distal to terminal bronchioles. It is a component of COPD (chronic obstructive pulmonary disease) along with chronic bronchitis.
- Subtypes include centriacinar (most common, smoking related), panacinar (seen in α_1-antitrypsin deficiency), distal acinar and irregular.
- Smoking and inhaled pollutants cause ongoing accumulations of inflammatory cells, releasing elastases and oxidants, which destroy the alveolar walls.
- Most patients with emphysema also have some degree of chronic bronchitis, which is to be expected since cigarette smoking is an underlying risk factor for both.