States. COPD results in a significant economic burden in terms of health care expenditures and disability. In 2008, there were more than 820,000 inpatient hospital stays for COPD among U.S. adults, and patients with COPD also frequently utilize acute outpatient and emergency room care. Finally, COPD contributes substantially to mortality from chronic disease. According to the World Health Organization, COPD is the fourth leading cause of death worldwide.

COPD is a complex disorder that results from a susceptibility to environmental factors brought about by a genetic predisposition. Cigarette smoking is the major environmental cause of COPD, although other factors may contribute, including outdoor air pollution, dust and fume exposure in the workplace, and indoor air pollution from use of biomass fuels for cooking and heat. Nonsmokers can and do develop COPD, highlighting the role of non–tobacco-related risk factors. A genetic predisposition is implied by the documentation of familial clusters of COPD. However, the only genetic disorder thus far definitively linked to COPD is α_1-antitrypsin deficiency resulting from mutations in *SERPINA1*, which accounts for approximately 1% to 2% of all COPD cases. Recent studies have highlighted other areas of the genome that are also associated with COPD susceptibility.

Several longitudinal studies have defined patterns of age-related decline in lung function and have documented the concept of age-related susceptibility to COPD. These studies showed that most adult nonsmoking men exhibit a decline in FEV_1 of 35 to 40 mL/year. This rate is increased to 45 to 60 mL/year in most cigarette smokers. However, the susceptible smoker may demonstrate losses of 70 to 120 mL/year (Fig. 16-2). This information allows the physician to project the rate of decrease of lung function in patients with COPD and to assess the effects of therapeutic interventions.

Pathology

Various structural changes have been observed in the airways and lungs of individuals with COPD. The current definition of COPD emphasizes the central role of chronic inflammation in the pathogenesis of COPD and in the development of pathologic lung and airway remodeling in the setting of COPD. Structural changes observed in COPD include emphysema and abnormalities of the small and large airways. There is increasing evidence that the small airways are the major site of airflow limitation and a central focus of pathology in COPD.

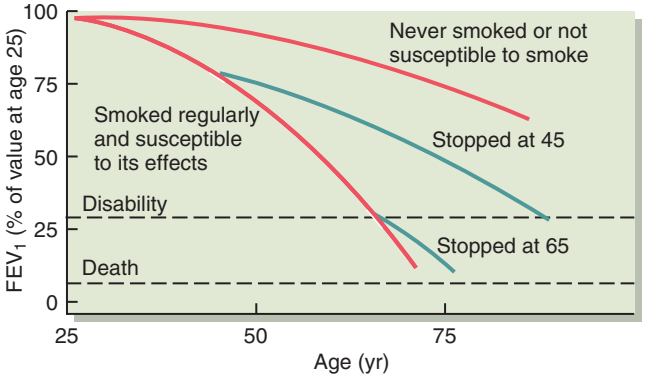

FIGURE 16-2 Pattern of decline in forced expiratory volume in 1 second (FEV_1) with risks for morbidity and mortality from respiratory disease in a susceptible smoker compared with a normal patient and with a nonsusceptible smoker. Although cessation of smoking does not replenish the lung function already lost in a susceptible smoker, it decreases the rate of further decline. (Data from Fletcher C, Peto R: The natural history of chronic airflow obstruction, BMJ 1:1645–1648, 1977.)

Emphysema in COPD

Emphysema is defined as a permanent enlargement of the air spaces distal to the terminal bronchioles (E-Fig. 16-1). This is caused by destruction of the lung parenchyma in the absence of significant fibrosis. These changes result in an abnormal acinus with limited capabilities for gas exchange. Based on thin gross lung sections, emphysema can be classified as either centrilobular and panlobular (E-Figs. 16-2 and 16-3). In centrilobular emphysema, the proximal part of the lobule (the respiratory bronchiole) is affected; this is the most common histologic feature observed in emphysema related to smoking. Panlobular emphysema is seen in α_1-antitrypsin deficiency.

α_1-Antitrypsin is a serine protease inhibitor that deactivates elastase molecules released by inflammatory cells that are capable of degrading connective tissue matrices. The observations that this enzyme was associated with emphysema and that emphysema could be reproduced in experimental models by the instillation of papain (a protease) into the lungs led to the hypothesis that emphysema is caused by an imbalance between protease and antiprotease systems in the lung. This theorized imbalance would favor proteolytic destruction of lung connective tissue, resulting in emphysema (the protease-antiprotease hypothesis). Research has focused on neutrophil elastase and its role in the destruction of lung elastin. Neutrophil elastase is the main target for inactivation by α_1-antitrypsin and has relatively unopposed effects. However, evidence for a primary role of this enzyme in cigarette smoke–induced emphysema is less clear, so the focus has broadened to include examination of the role of the matrix metalloproteinases (MMPs), produced by macrophages and other cells, in emphysema. Transgenic mice that are deficient in the *MMP12* gene are resistant to the development of emphysema, and a single nucleotide polymorphism in the *MMP12* gene is associated with a reduced risk for development of COPD, supporting a role for this enzyme in mediating lung connective tissue loss leading to emphysema.

The inflammation induced by cigarette smoke is a trigger of the cycle of protease release and lung destruction resulting in emphysema (E-Fig. 16-4). Macrophages are activated by cigarette smoke and recruit neutrophils and other inflammatory cells to the lung, leading to the release of elastase and MMPs. The destruction of elastin and other connective tissue elements in the lungs by these proteases leads over time to the loss of elastic recoil and destruction of alveolar structures characteristic of emphysema.

Cigarette smoke contains many oxidant molecules capable of inducing oxidative stress in the lung. Oxidative stress has diverse effects, including the oxidative inactivation of antiproteases in the lung and the acetylation of specific histones in the chromatin of lung cells and macrophages, allowing the expression of various pro-inflammatory genes. Histone deacetylase activity is reduced in COPD, and this in turn may result in an inability to control the