pro-inflammatory response in this condition. Pro-inflammatory gene expression promotes cytokine production and release, contributing to further inflammatory cell recruitment and activation. Systemic inflammation, triggered by ongoing pulmonary inflammation, may lead to nonpulmonary abnormalities associated with emphysema, including cachexia and skeletal muscle alterations. Finally, increased apoptosis of pneumocytes and endothelial cells has been observed in lungs with emphysema and could contribute to the loss of alveoli.

Understanding of emphysema pathogenesis has improved with the recognition that inflammation, oxidative stress, protease-antiprotease balance, and apoptosis are linked in a complex interaction induced by cigarette smoke. This improved understanding has broadened the range of potential therapies that may be effective in ameliorating the destructive process. To date, however, therapies targeted at molecular pathways involved in emphysema pathogenesis have not been successful in altering disease progression, with the possible exception of α_1-antitrypsin replacement therapy in individuals with α_1-antitrypsin deficiency.

α_1-Antitrypsin, an acute phase reactant, is produced primarily in the liver, from which it travels to the lung. By its effect on elastases in the lung, α_1-antitrypsin prevents the uncontrolled degradation of elastin in the lung parenchyma and protects against the development of emphysema. Individuals with the ZZ genotype of α_1-antitrypsin deficiency produce mutant forms of α_1-antitrypsin that have a tendency to inappropriately polymerize within the hepatocyte, leading to a deficiency in secreted α_1-antitrypsin and, in some cases, collateral damage to the liver caused by accumulation of intracellular misfolded, mutant α_1-antitrypsin. Patients who develop emphysema at a young age (<40 years) should be evaluated for this condition whether or not they smoke, as should patients with bronchiectasis and unexplained liver disease or cirrhosis. Testing shows reduced α_1-antitrypsin levels. Genotyping can reveal specific mutations (most commonly ZZ in severe deficiency). Polymorphisms in various other genes (e.g., *MMP12*) that appear to be relevant to susceptibility to COPD have been uncovered, and other factors contributing to COPD heritability and susceptibility are under active investigation. α_1-Antitrypsin supplementation has been used for patients with α_1-antitrypsin deficiency and appears to result in a decreased loss of lung density (surrogate for emphysema) by computed tomographic measurement (level 1 evidence).

Large and Small Airways Disease in COPD

Chronic bronchitis often coincides with emphysema in patients with COPD, but it may occur independently from either emphysema or COPD and is defined in clinical terms (described earlier). Cigarette smoking is the major cause, although exposure to pollutants such as dusts and smokes may pay a role. Pathologic findings are goblet cell hyperplasia, mucus hypersecretion and plugging, and airway inflammation and fibrosis (Fig. 16-3).

The disease mechanisms involved in the development of emphysema are also important in the pathogenesis of chronic bronchitis. However, in contrast to emphysema, chronic bronchitis is a disease of the large airways and not of the lung parenchyma. Therefore, the relationship of chronic bronchitis to airflow obstruction is less robust than for emphysema, and

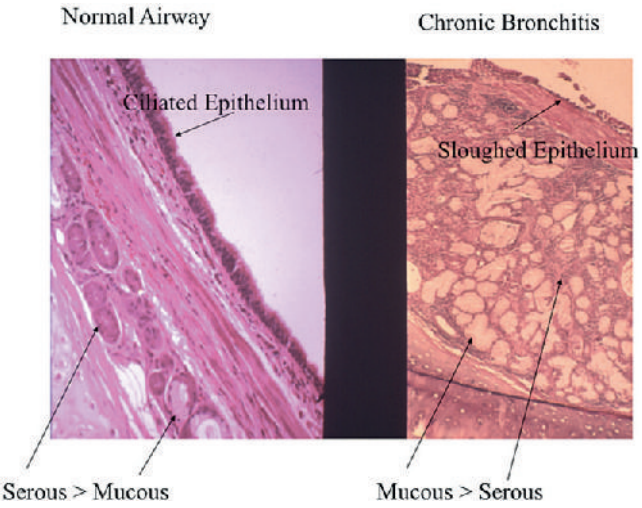

FIGURE 16-3 Pathology of chronic bronchitis: Normally, airway submucosal serous glands outnumber mucous glands and the epithelium includes ciliated cells. In chronic bronchitis, mucous glands are more prevalent than serous glands and the epithelium is abnormal. (Courtesy Dr. Charles Kuhn.)

airflow limitation consistent with COPD in a patient with symptoms of chronic bronchitis may be more reflective of concomitant emphysema and small airways disease. Inflammation in chronic bronchitis leads to effects on the airway epithelium, including excess mucus production and impairment in mucociliary clearance.

Neurogenic stimuli are also important in the pathogenesis of airway obstruction in chronic bronchitis. The conducting airways are surrounded by smooth muscle, which contains adrenergic and cholinergic receptors. Stimulation of β_2-adrenergic receptors by circulating catecholamines dilates airways, whereas stimulation of airway irritant receptors constricts airways through a cholinergic mechanism by means of the vagus nerve. The irritant bronchoconstrictive pathways are normally present to protect against inhalation of noxious agents, but in pathologic states, these pathways may contribute to airway hyperreactivity. A host of endogenous chemical mediators such as proteases, growth factors, and cytokines can also affect airway tone.

By definition, the predominant symptom in chronic bronchitis is sputum production. Bronchospasm may also be prominent. Recurrent bacterial airway infections are typical. As with patients with COPD, the evaluation of patients with chronic bronchitis should include pulmonary function tests and a chest radiograph in addition to standard laboratory testing.

Damage to the small airways (those less than about 2 mm in diameter) is integral to the pathogenesis of COPD. The small airways are the major site of resistance to airflow in COPD. Respiratory bronchiolitis, in which there is an accumulation of pigmented macrophages in and around the bronchioles (E-Fig. 16-5), may be an incidental finding in asymptomatic smokers without COPD. However, as COPD develops, other inflammatory cells are recruited to the small conducting airways, presumably in reaction to ongoing irritation from cigarette smoke or inhaled particles. With inflammation, the small airways in COPD can be affected by remodeling, leading to airway wall thickening and fibrosis, smooth muscle hypertrophy, and airway luminal