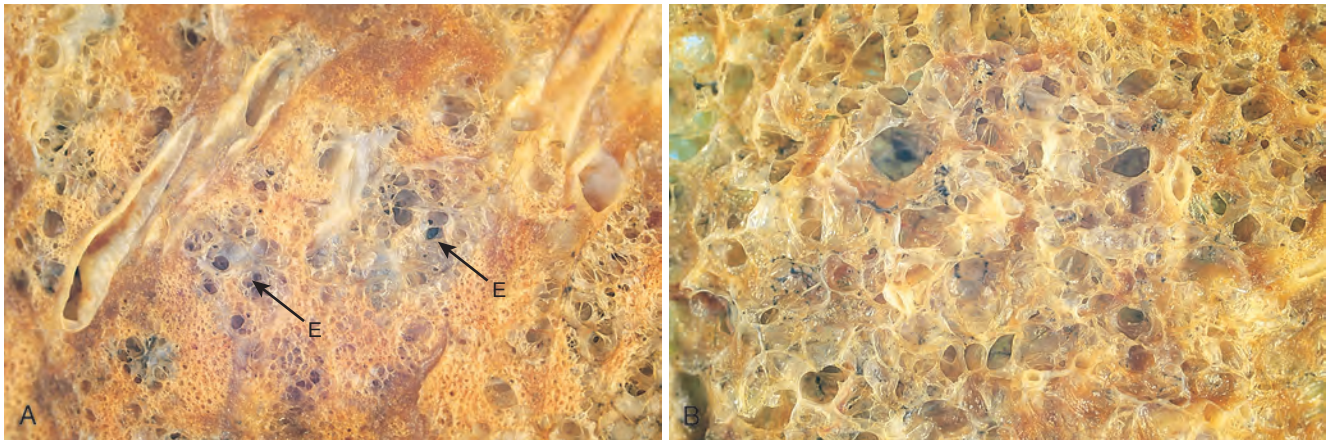

Figure 15-7 A, Centriacinar emphysema. Central areas show marked emphysematous damage (E), surrounded by relatively spared alveolar spaces. **B,** Panacinar emphysema involving the entire pulmonary lobule.

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 findings are of multiple, continuous, enlarged airspaces from less than 0.5 cm to more than 2.0 cm in diameter, sometimes forming cystlike structures. This type of emphysema probably underlies many cases of spontaneous pneumothorax in young adults.

- ***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. Inhaled cigarette smoke and other noxious particles cause lung damage and inflammation, which results in parenchymal destruction (emphysema) and airway disease (bronchiolitis and chronic bronchitis). Factors that influence the development of emphysema include the following (Fig. 15-8):

- *Inflammatory mediators and leukocytes.* A wide variety of mediators have been shown to be increased in the affected parts (including leukotriene B_4, IL-8, TNF, and others) These mediators are released by resident epithelial cells and macrophages, and attract inflammatory cells from the circulation (chemotactic factors), amplify the inflammatory process (proinflammatory cytokines) and induce structural changes (growth factors).
- *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 (further discussed later).
- *Oxidative stress.* Substances in tobacco smoke, alveolar damage, and inflammatory cells all produce oxidants, which may beget more tissue damage and inflammation. The role of oxidants is supported by mouse models in which the *NRF2* gene is inactivated. *NRF2* encodes a transcription factor that serves as a sensor for oxidants in alveolar epithelial cells and many other cells types. Intracellular oxidants activate *NRF2*, which upregulates the expression of multiple 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 a role in the initiation of tissue destruction, bacterial and/or viral infections may exacerbate the associated inflammation and chronic bronchitis.

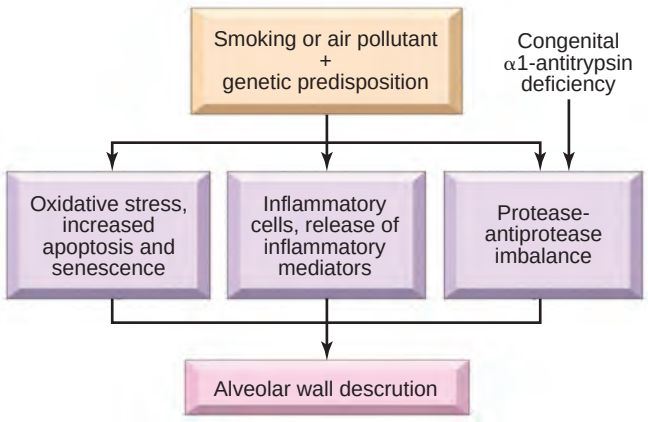

Figure 15-8 Pathogenesis of emphysema. See text for details.

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 pulmonary emphysema, which 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. α_1-antitrypsin is encoded by the proteinase inhibitor *(Pi)* locus on chromosome 14. The *Pi* locus is polymorphic, and approximately 0.012% of the US population is homozygous for the *Z* allele, a genotype that is associated with markedly decreased serum levels of α_1-antitrypsin. More than 80% of these individuals develop symptomatic panacinar emphysema, which occurs at an earlier age and is of greater