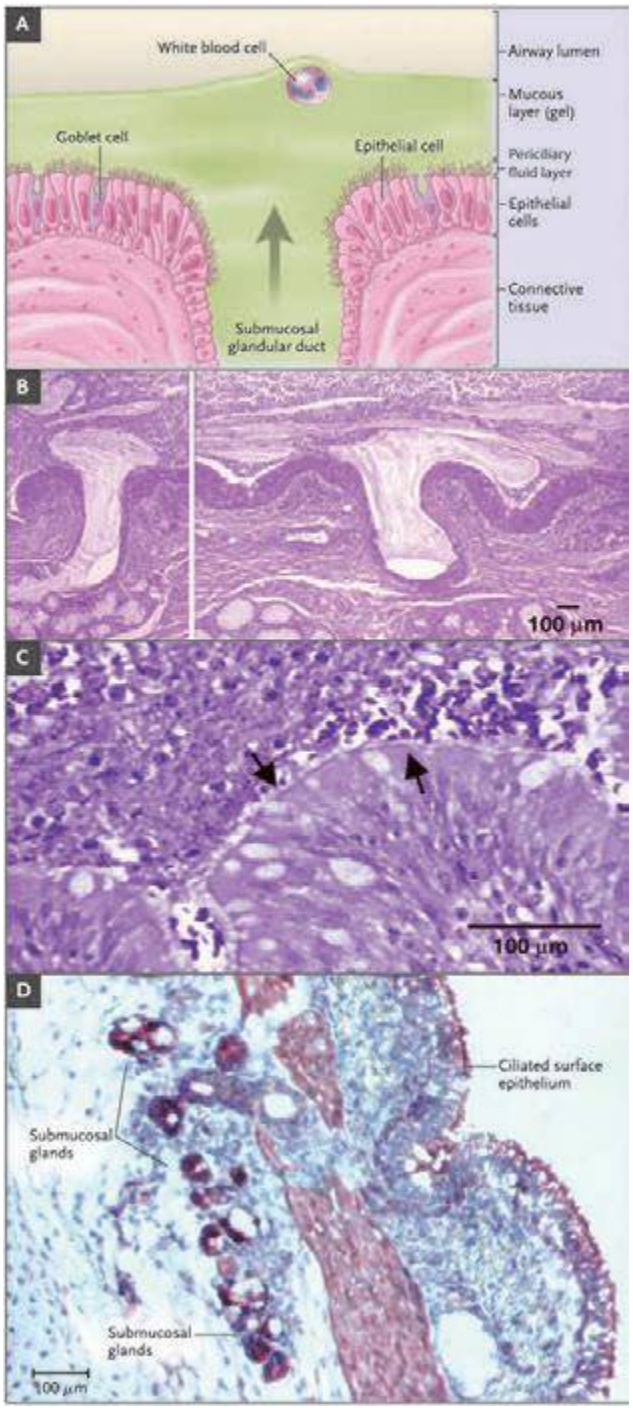

FIGURE 313-1 Extrusion of mucus secretion onto the epithelial surface of airways in cystic fibrosis. ***A.*** Schematic of the surface epithelium and supporting glandular structure of the human airway. ***B.*** The submucosal glands of a patient with cystic fibrosis are filled with mucus, and mucopurulent debris overlies the airway surfaces, essentially burying the epithelium. ***C.*** A higher magnification view of a mucus plug tightly adhering to the airway surface, with *arrows* indicating the interface between infected and inflamed secretions and the underlying epithelium to which the secretions adhere. (Both ***B*** and ***C*** were stained with hematoxylin and eosin, with the colors modified to highlight structures.) Infected secretions obstruct airways and, over time, dramatically disrupt the normal architecture of the lung. ***D.*** CFTR is expressed in surface epithelium and serous cells at the base of submucosal glands in a porcine lung sample, as shown by the dark staining, signifying binding by CFTR antibodies to epithelial structures (aminoethylcarbazole detection of horseradish peroxidase with hematoxylin counterstain). *(From SM Rowe, S Miller, EJ Sorscher: N Engl J Med 352:1992, 2005.)*

approximately 90% of individuals with CF carry at least one F508del mutation.

Other gene defects include CFTR ion channels properly trafficked to the apical cell surface but unable to open and/or gate. Such channel proteins include G551D (a glycine to aspartic acid replacement at CFTR position 551), which leads to an inability to transport Cl^- or HCO_3^- in the presence of ATP (a class III abnormality). Individuals with at least one G551D allele represent 4–5% of CF patients in North America. *CFTR* nonsense alleles such as G542X, R553X, and W1282X (premature termination codon replaces glycine, arginine, or tryptophan at positions 542, 553, or 1282, respectively) are among the common class I defects, in addition to large deletions or other major disruptions of the gene. The W1282X mutation, for example, is prevalent among individuals of Ashkenazi descent and is a predominant CF genotype in Israel. Additional categories of *CFTR* mutation include defects in the ion channel pore (class IV), RNA splicing (class V), and increased plasma membrane turnover (class VI) **(Fig. 313-2)**.

DIAGNOSIS

The diagnosis of CF is based in part on clinical symptoms, family history, or positive newborn screening. *CFTR* mutation analysis together with sweat electrolyte measurements represent cardinal diagnostic tests. DNA-based evaluation typically surveys numerous disease-associated mutations; panels that identify 20–80 gene defects are

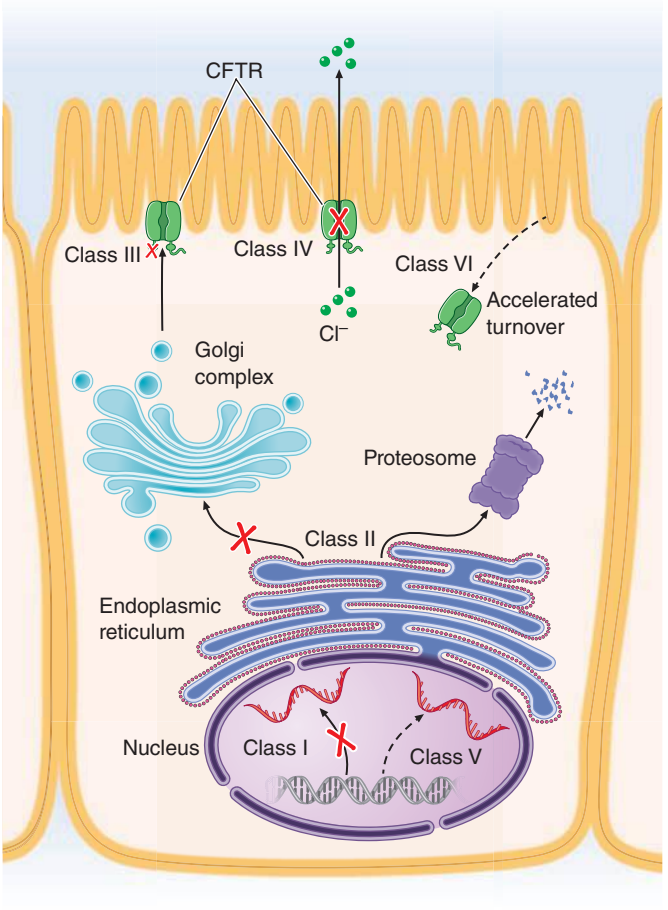

FIGURE 313-2 Categories of *CFTR* mutations. Classes of defects in the *CFTR* gene include the absence of synthesis (class I); defective protein maturation and premature degradation (class II); disordered gating/regulation, such as diminished adenosine triphosphate (ATP) binding and hydrolysis (class III); defective conductance through the ion channel pore (class IV); a reduced number of *CFTR* transcripts due to a promoter or splicing abnormality (class V); and accelerated turnover from the cell surface (class VI). *(From SM Rowe, S Miller, EJ Sorscher: N Engl J Med 352:1992, 2005.)*