291 Cystic Fibrosis

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CLINICAL FEATURES

Cystic fibrosis (CF) is an autosomal recessive exocrinopathy affecting multiple epithelial tissues. The gene product responsible for CF (the cystic fibrosis transmembrane conductance regulator [CFTR]) serves as an anion channel in the apical (luminal) plasma membranes of epithelial cells and regulates volume and composition of exocrine secretion. An increasingly sophisticated understanding of CFTR molecular genetics and membrane protein biochemistry has facilitated CF drug discovery, with a number of recently approved agents that have transformed the clinical outlook for many with the disease.

Respiratory Manifestations The major morbidity and mortality associated with CF is attributable to pulmonary compromise, characterized by copious hyperviscous and adherent secretions that obstruct small and medium-sized airways. CF respiratory secretions are exceedingly difficult to clear, and a complex bacterial flora that includes *Staphylococcus aureus, Haemophilus influenzae*, and *Pseudomonas aeruginosa* (among other pathogens, see below) is routinely cultured from CF sputum. Microbiome analysis has identified dozens of other bacterial species in CF lungs, although a relationship of these less well-characterized organisms to disease progression has not been determined. Robust pulmonary inflammation in the setting of inspissated mucus and chronic bacterial infection leads to collateral tissue injury and further aggravates respiratory decline. Organisms such as *P. aeruginosa* exhibit a stereotypic mode of pathogenesis; a sentinel and early colonization event often engenders lifelong pulmonary infection by the same genetic strain. Over a period of many years, *P. aeruginosa* evolves in CF lungs to adopt a mucoid phenotype (attributable to