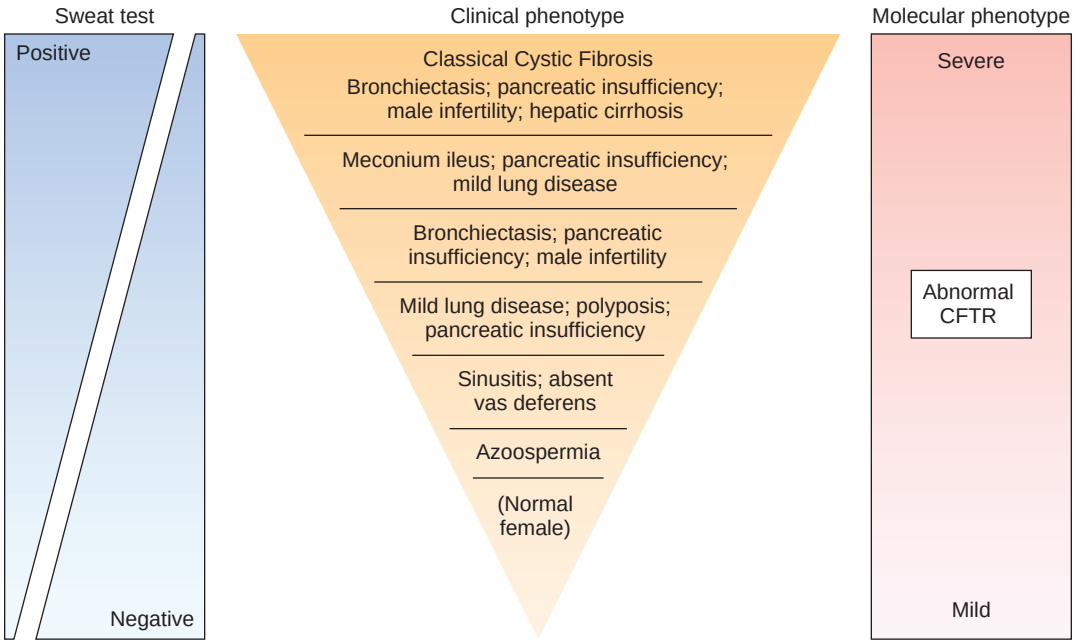

Figure 10-19 The many clinical manifestations of mutations in the cystic fibrosis gene, from most severe to asymptomatic. (Redrawn from Wallis C: Diagnosing cystic fibrosis: blood, sweat, and tears. Arch Dis Child 76:85, 1997.)

in 1989, more than 1800 disease-associated mutations have been identified. The mutations can be grouped into six classes based on their effect on the CFTR protein:

- Class I: *Defective protein synthesis.* These mutations are associated with complete lack of CFTR protein at the apical surface of epithelial cells.
- Class II: *Abnormal protein folding, processing, and trafficking.* These mutations result in defective processing of the protein from the endoplasmic reticulum to the Golgi apparatus; the protein does not become fully folded and glycosylated and is instead degraded before it reaches the cell surface. The most common class II mutation is a deletion of three nucleotides coding for phenylalanine at amino acid position 508 (ΔF508). Worldwide, this mutation can be found in approximately 70% of cystic fibrosis patients. Class II mutations are also associated with complete lack of CFTR protein at the apical surface of epithelial cells.
- Class III: *Defective regulation.* Mutations in this class prevent activation of CFTR by abrogating ATP binding and hydrolysis, an essential prerequisite for ion transport (see earlier). Thus, there is a normal amount of CFTR on the apical surface, but it is nonfunctional.
- Class IV: *Decreased conductance.* These mutations typically occur in the transmembrane domain of *CFTR*, which forms the ionic pore for chloride transport. There is a normal amount of CFTR at the apical membrane, but with reduced function. This class is usually associated with a milder phenotype.
- Class V: *Reduced abundance.* These mutations typically affect intronic splice sites or the *CFTR* promoter, such that there is a reduced amount of normal protein. As discussed subsequently, class V mutations are also associated with a milder phenotype.
- Class VI: *Altered function in regulation of ion channels.* As previously described, CFTR is involved in the regulation of multiple distinct cellular ion channels, of which its role in regulating bicarbonate secretion through relevant apical channels is required for maintaining luminal pH balance. Mutations in this class affect the regulatory role of CFTR. In some cases, a given mutation affects the conductance by CFTR as well as regulation of other ion channels. For example, the ΔF508 mutation is both a class II and class VI mutation.

Because cystic fibrosis is an autosomal recessive disease, affected individuals harbor mutations on both alleles. However, the nature of mutations on each of the two alleles can have a remarkable effect on the overall phenotype, as well as on organ-specific manifestations (Fig. 10-19). Thus, two "severe" mutations (for example, a combination of Class I, II or III mutations in any permutation) that produce virtual absence of membrane CFTR function are associated with the classic cystic fibrosis phenotype (pancreatic insufficiency, sinopulmonary infections, and gastrointestinal symptoms), while the presence of a "mild" (class IV or V) mutation on one or both alleles results in a less severe phenotype. This general dictum of genotype-phenotype correlation is most consistent for pancreatic disease, wherein the presence of one allele with a mild mutation associated with some CFTR activity can prevent the pancreatic insufficiency that is virtually always seen with homozygosity for "severe" mutations. By contrast, genotype-phenotype correlations are far less consistent in pulmonary disease, due to the effect of secondary modifiers (see later). As genetic testing for *CFTR* mutations has expanded, *it has become evident that some patients who present with clinical features apparently unrelated to cystic fibrosis may also harbor* CFTR *mutations.* These include individuals with *idiopathic chronic pancreatitis, late-onset chronic pulmonary disease, idiopathic bronchiectasis*, and *obstructive azoospermia* caused by bilateral absence of the vas deferens (see detailed discussion of individual phenotypes later). Most of these