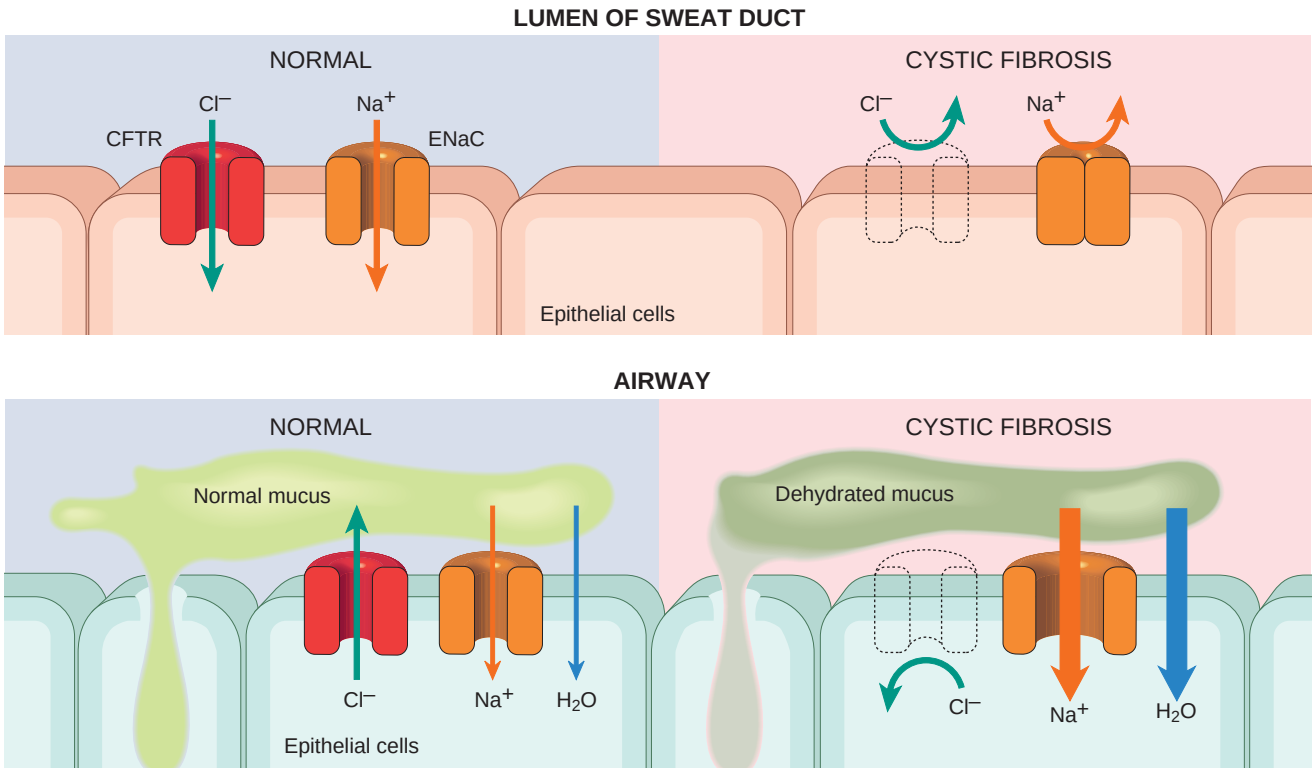

Figure 10-18 Chloride channel defect in the sweat duct *(top)* causes increased chloride and sodium concentration in sweat. In the airway *(bottom)*, patients with cystic fibrosis have decreased chloride secretion and increased sodium and water reabsorption leading to dehydration of the mucus layer coating epithelial cells, defective mucociliary action, and mucus plugging of airways. CFTR, Cystic fibrosis transmembrane conductance regulator; ENaC, epithelial sodium channel.

luminal fluid, rendering it (the luminal fluid) hypotonic. The ENaC is *inhibited* by normally functioning CFTR; hence, *in cystic fibrosis, ENaC activity increases, markedly augmenting sodium uptake across the apical membrane*. The importance of this phenomenon is discussed later in the context of pulmonary and gastrointestinal pathology in cystic fibrosis. The one exception to this rule happens to be the human sweat ducts, where ENaC activity *decreases* as a result of *CFTR* mutations; therefore, a hypertonic luminal fluid containing high sweat sodium chloride (the *sine qua non* of classic cystic fibrosis) is formed. This is the basis for the "salty" sweat that mothers can often detect in their affected infants.

- *The functions of* CFTR *are tissue-specific; therefore, the impact of a mutation in* CFTR *is also tissue-specific.* The major function of CFTR in the *sweat gland ducts* is to reabsorb luminal chloride ions and augment sodium reabsorption via the ENaC (see earlier). Therefore, in the sweat ducts, loss of CFTR function leads to decreased reabsorption of sodium chloride and production of hypertonic sweat (Fig. 10-18). However, in the *respiratory and intestinal epithelium*, the CFTR is one of the most important avenues for *active luminal secretion of chloride.* At these sites, *CFTR* mutations result in loss or reduction of chloride secretion into the lumen (Fig. 10-18). Active luminal sodium absorption is increased (due to loss of inhibition of ENaC activity), and both of these ion changes increase passive water reabsorption from the lumen, *lowering the water content of the surface fluid layer coating mucosal cells.* Thus, unlike the sweat ducts, there is no difference in the salt concentration of the surface fluid layer coating the respiratory and intestinal mucosal cells in normal individuals versus those with cystic fibrosis. Instead, *the pathogenesis of respiratory and intestinal complications in cystic fibrosis seems to stem from an isotonic but low-volume surface fluid layer.* In the lungs, this dehydration leads to defective mucociliary action and the accumulation of hyperconcentrated, viscid secretions that obstruct the air passages and predispose to recurrent pulmonary infections.
- CFTR *regulates transport of bicarbonate ions.* The bicarbonate transport function of CFTR is mediated by reciprocal interactions with a family of anion exchangers called SLC26, which are co-expressed on the apical surface with CFTR. In some *CFTR* mutants chloride transport is completely or substantially preserved, while *bicarbonate transport is markedly abnormal.* Alkaline fluids are secreted by normal tissues, in contrast fluids that are acidic (due to absence of bicarbonate ions) are secreted by epithelia harboring these mutant *CFTR* alleles. The acidity of secretions results in decreased luminal pH that can lead to a variety of adverse effects such as increased mucin precipitation and plugging of ducts, and increased binding of bacteria to plugged mucins. *Pancreatic insufficiency, a feature of classic cystic fibrosis, is virtually always present when there are CFTR mutations with abnormal bicarbonate conductance.*

Cystic Fibrosis Gene: Mutational Spectra and Genotype-Phenotype Correlation. Since the *CFTR* gene was cloned