untreated infants, however, the mental deficit is usually not as severe as that seen in PKU. Accumulation of galactose and galactose-1-phosphate in the kidney impairs amino acid transport, resulting in *aminoaciduria.* There is an increased frequency of fulminant *Escherichia coli septicemia*, possibly arising from depressed neutrophil bactericidal activity. *Hemolysis* and *coagulopathy* in the newborn period can occur as well.

Many of the clinical and morphologic changes of galactosemia can be prevented or ameliorated by early removal of galactose from the diet for at least the first 2 years of life. Control instituted soon after birth prevents the cataracts and liver damage and permits almost normal development. Even with dietary restrictions, however, it is now established that older patients are frequently affected by a speech disorder and gonadal failure (especially premature ovarian failure) and, less commonly, ataxia.

Cystic Fibrosis (Mucoviscidosis)

Cystic fibrosis is an inherited disorder of ion transport that affects fluid secretion in exocrine glands and in the epithelial lining of the respiratory, gastrointestinal, and reproductive tracts. In many individuals this disorder leads to abnormally viscous secretions that obstruct organ passages, resulting in most of the clinical features of this disorder, such as *chronic lung disease secondary to recurrent infections, pancreatic insufficiency, steatorrhea, malnutrition, hepatic cirrhosis, intestinal obstruction, and male infertility.* These manifestations may appear at any point in life from before birth to much later in childhood or even in adolescence.

With an incidence of 1 in 2500 live births, *cystic fibrosis is the most common lethal genetic disease that affects Caucasian populations.* The carrier frequency in the United States is 1 in 20 among Caucasians but significantly lower in African Americans, Asians, and Hispanics. Although cystic fibrosis follows an *autosomal recessive* transmission pattern, recent data suggest that *even heterozygote carriers have a higher incidence of respiratory and pancreatic diseases* as compared with the general population. In addition, despite the classification of cystic fibrosis as a "mendelian" disorder, there is a wide degree of phenotypic variation that results from diverse mutations in the gene associated with cystic fibrosis, the tissue-specific effects of the encoded gene product, and the influence of so-called modifier genes.

Cystic Fibrosis Gene: Normal Structure and Function. In normal duct epithelia, chloride is transported by plasma membrane channels (chloride channels). **The primary defect in cystic fibrosis results from abnormal function of an epithelial chloride channel protein encoded by the cystic fibrosis transmembrane conductance regulator (CFTR) gene on chromosome 7q31.2.** The 1480-amino acid polypeptide encoded by CFTR has two transmembrane domains (each containing six α-helices), two cytoplasmic nucleotide-binding domains (NBDs), and a regulatory domain (R domain) that contains protein kinase A and C phosphorylation sites (Fig. 10-17). The two transmembrane domains form a channel through which chloride passes. Activation of the CFTR channel is mediated by agonist-induced increases in cyclic adenosine monophosphate (cAMP), followed by activation of a protein kinase A that

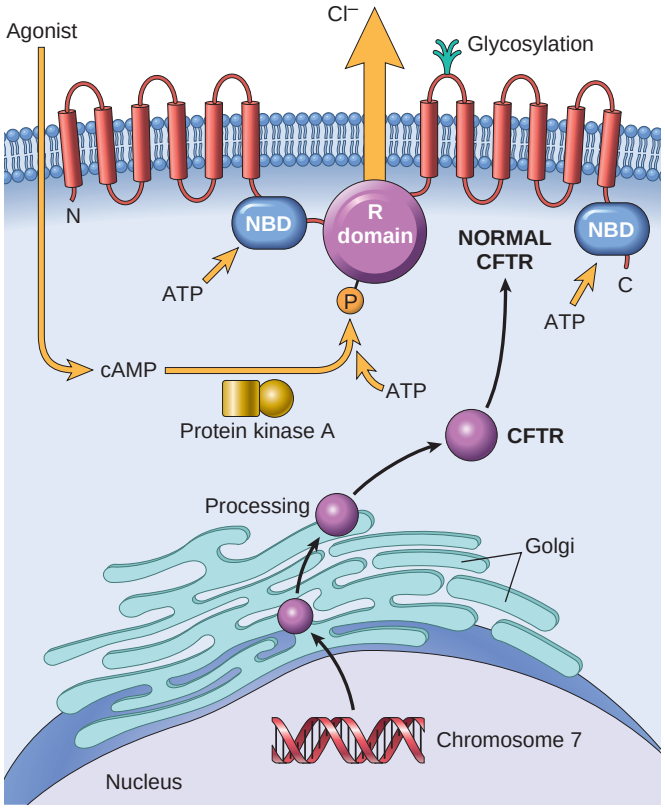

Figure 10-17 *Top*, Normal cystic fibrosis transmembrane conductance regulator (CFTR) structure and activation. CFTR consists of two transmembrane domains, two nucleotide-binding domains (NBDs), and a regulatory R domain. Agonists (e.g., acetylcholine) bind to epithelial cells and increase cyclic adenosine monophosphate (cAMP), which activates protein kinase A, the latter phosphorylating the CFTR at the R domain using ATP. This results in opening of the chloride channel. *Bottom*, CFTR from gene to protein. The most common mutation in the *CFTR* gene results in defective protein folding in the Golgi/endoplasmic reticulum and degradation of CFTR before it reaches the cell surface. Other mutations affect synthesis of CFTR, NBDs, and R domains, as well as membrane-spanning domains. (See text for details.)

phosphorylates the R domain. Adenosine triphosphate (ATP) binding and hydrolysis occurs at the NBD and is essential for the opening and closing of the channel pore in response to cAMP-mediated signaling. Several important facets of CFTR function have emerged in recent years:

- *CFTR regulates multiple additional ion channels and cellular processes.* Although initially characterized as a chloride-conductance channel, it is now recognized that CFTR can regulate multiple ion channels and cellular processes, primarily through interactions involving its NBDs. These include so-called outwardly rectified chloride channels, inwardly rectified potassium channels (Kir6.1), the epithelial sodium channel (ENaC), gap junction channels, and cellular processes involved in ATP transport and mucus secretion. Of these, the interaction of CFTR with the ENaC has possibly the most pathophysiologic relevance in cystic fibrosis. The ENaC is situated on the apical surface of exocrine epithelial cells and is responsible for sodium uptake from the