

canalicular bicarbonate secretion. For most of these transporters, genetic defects have been identified that are associated with various forms of cholestasis or defects of biliary excretion. FIC1 (ATP8B1) is defective in progressive familial intrahepatic cholestasis type 1 (PFIC1) and benign recurrent intrahepatic cholestasis type 1 (BRIC1) and results in ablation of all other ATP-dependent transporter functions. BSEP (ABCB11) is defective in PFIC2 and BRIC2. Mutations of MRP2 (ABCC2) cause the Dubin-Johnson syndrome, an inherited form of conjugated hyperbilirubinemia ([Chap. 338](#)). A defective MDR3 (ABCB4) results in PFIC3. ABCG5/G8, the canalicular half transporters for cholesterol and other neutral sterols, are defective in sitosterolemia. The cystic fibrosis transmembrane regulator (CFTR, ABCC7), located on bile duct epithelial cells but not on canalicular membranes, is defective in cystic fibrosis, which is associated with impaired cholangiocyte pH regulation during ductular bile formation and chronic cholestatic liver disease, occasionally resulting in biliary cirrhosis.

■ THE BILE ACIDS

The primary bile acids, cholic acid and chenodeoxycholic acid (CDCA), are synthesized in hepatocytes from cholesterol, conjugated with glycine or taurine, and secreted into the bile canaliculus. Secondary bile acids, including deoxycholate and lithocholate, are formed in the colon as bacterial metabolites of the primary bile acids. However, lithocholic acid is much less efficiently absorbed from the colon than deoxycholic acid. Another secondary bile acid, found in low concentration, is ursodeoxycholic acid (UDCA), a stereoisomer of CDCA. In healthy subjects, the ratio of glycine to taurine conjugates in bile is ~3:1.

Bile acids are detergent-like molecules that in aqueous solutions and above a critical concentration of ~2 mM form molecular aggregates called *micelles*. Cholesterol alone is sparingly soluble in aqueous environments, and its solubility in bile depends on both the total lipid concentration and the relative molar percentages of bile acids and lecithin. Normal ratios of these constituents favor the formation of solubilizing *mixed micelles*, while abnormal ratios