Table 18-9 Hereditary Hyperbilirubinemias

Disorder	Inheritance	Defects in Bilirubin Metabolism	Liver Pathology	Clinical Course
Unconjugated Hyperbilirubinemia				
Crigler-Najjar syndrome type I	Autosomal recessive	Absent UGT1A1 activity	None	Fatal in neonatal period
Crigler-Najjar syndrome type II	Autosomal dominant with variable penetrance	Decreased UGT1A1 activity	None	Generally mild, occasional kernicterus
Gilbert syndrome	Autosomal recessive	Decreased UGT1A1 activity	None	Innocuous
Conjugated Hyperbilirubinemia				
Dubin-Johnson syndrome	Autosomal recessive	Impaired biliary excretion of bilirubin glucuronides due to mutation in canalicular multidrug resistance protein 2 (MRP2)	Pigmented cytoplasmic globules	Innocuous
Rotor syndrome	Autosomal recessive	Decreased hepatic uptake and storage? Decreased biliary excretion?	None	Innocuous

UGT1A1, Uridine diphosphate-glucuronyltransferase family, peptide A1

cholesterol), or symptoms related to intestinal malabsorption, including nutritional deficiencies of the fat-soluble vitamins A, D, or K. A characteristic laboratory finding is elevated serum alkaline phosphatase and γ-glutamyl transpeptidase (GGT), enzymes present on the apical (canalicular) membranes of hepatocytes and bile duct epithelial cells.

MORPHOLOGY

The morphologic features of cholestasis depend on its severity, duration, and underlying cause. Common to both obstructive and nonobstructive cholestasis is the accumulation of bile pigment within the hepatic parenchyma (Fig. 18-28*A, B*). Elongated green-brown plugs of bile are visible in dilated bile canaliculi (Fig. 18-28*C*). Rupture of canaliculi leads to extravasation of bile, which is quickly phagocytosed by Kupffer cells. Droplets of bile pigment also accumulate within hepatocytes, which can take on a fine, foamy appearance, so called "feathery degeneration."

Large Bile Duct Obstruction

The most common cause of bile duct obstruction in adults is extrahepatic cholelithiasis (gallstones) followed by malignancies of the biliary tree or head of the pancreas, and strictures resulting from previous surgical procedures. Obstructive conditions in children include biliary atresia, cystic fibrosis, choledochal cysts and syndromes in which there are insufficient intrahepatic bile ducts. The initial morphologic features of cholestasis (described below) are entirely reversible with correction of the obstruction. Prolonged obstruction can lead to biliary cirrhosis, described later.

Subtotal or intermittent obstruction may promote *ascending cholangitis*, a secondary bacterial infection of the biliary tree that aggravates the inflammatory injury. Enteric organisms such as coliforms and enterococci are common culprits. Cholangitis usually presents with fever, chills, abdominal pain, and jaundice. *The most severe form of cholangitis is suppurative cholangitis, in which purulent bile fills and distends bile ducts.* Since sepsis rather than cholestasis tends to dominate this potentially grave process, prompt diagnostic evaluation and intervention are imperative.

MORPHOLOGY

Acute biliary obstruction, either intrahepatic or extrahepatic, causes distention of upstream bile ducts, which often become dilated. In addition, bile ductules proliferate at the portal-parenchymal interface, accompanied by stromal edema and infiltrating neutrophils (Fig. 18-28*B* and 18-29). These labyrinthine ductules reabsorb secreted bile salts, serving to protect the downstream obstructed bile ducts from their toxic detergent action. Indeed, **the histologic hallmark of ascending cholangitis is the influx of these periductular neutrophils directly into the bile duct epithelium and lumen** (Fig. 18-30)**.**

Left uncorrected, secondary inflammation resulting from **chronic biliary obstruction** and ductular reactions initiate periportal fibrosis, eventually leading to hepatic scarring and nodule formation, generating **secondary or obstructive biliary cirrhosis** (Fig. 18-31). Cholestatic features in the parenchyma may be severe, with extensive **feathery degeneration of periportal hepatocytes**, cytoplasmic swelling often with **Mallory-Denk bodies** (differing from those in alcohol-induced liver disease and non-alcoholic fatty liver disease by their periportal predominance), and formation of **bile infarcts** from detergent effects of extravasated bile. However, once regenerative nodules have formed, bile stasis may become less conspicuous. **Ascending cholangitis may be superimposed on this chronic process as well, sometimes triggering acute-on-chronic liver failure.**

Since extrahepatic biliary obstruction is frequently amenable to surgical alleviation, correct and prompt diagnosis is imperative. In contrast, cholestasis due to diseases of the intrahepatic biliary tree or hepatocellular secretory failure (collectively termed intrahepatic cholestasis) is not benefited by surgery (short of transplantation), and the patient's condition may be worsened by an operative procedure. *There is thus some urgency in making a correct diagnosis of the cause of jaundice and cholestasis.*

Cholestasis of Sepsis

Sepsis may affect the liver by several mechanisms (1) through direct effects of intrahepatic bacterial infection (e.g., abscess formation or bacterial cholangitis), (2)