glucuronyl transferase (UGT1A1, step 4) in the endoplasmic reticulum, and excretion of the water-soluble, nontoxic bilirubin glucuronides into bile. Most bilirubin glucuronides are deconjugated in the gut lumen by bacterial β-glucuronidases and degraded to colorless urobilinogens (step 5). The urobilinogens and the residue of intact pigment are largely excreted in feces. Approximately 20% of the urobilinogens formed are reabsorbed in the ileum and colon, returned to the liver, and reexcreted into bile. A small amount of reabsorbed urobilinogen is excreted in the urine.

Two thirds of the organic materials in bile are bile salts, which are formed by the conjugation of bile acids with taurine or glycine. Bile acids, the major catabolic products of cholesterol, are a family of water-soluble sterols with carboxylated side chains. The primary human bile acids are cholic acid and chenodeoxycholic acid. Bile acids in bile salts are highly effective detergents. Their primary physiologic role is to solubilize water-insoluble lipids secreted by hepatocytes into bile, and also to solubilize dietary lipids in the gut lumen. Ninety-five percent of secreted bile acids, conjugated or unconjugated, are reabsorbed from the gut lumen and recirculate to the liver *(enterohepatic circulation),* thus helping to maintain a large endogenous pool of bile acids for digestive and excretory purposes.

Pathophysiology of Jaundice

Both unconjugated bilirubin and conjugated bilirubin (bilirubin glucuronides) may accumulate systemically. There are two important pathophysiologic differences between the two forms of bilirubin. Unconjugated bilirubin is virtually insoluble in water at physiologic pH and exists in tight complexes with serum albumin. This form cannot be excreted in the urine even when blood levels are high. Normally, a very small amount of unconjugated bilirubin is present as an albumin-free anion in plasma. This fraction of unbound bilirubin may diffuse into tissues, particularly the brain in infants, and produce toxic injury. The unbound plasma fraction may increase in severe hemolytic disease or when drugs displace bilirubin from albumin. Hence, hemolytic disease of the newborn (erythroblastosis fetalis) may lead to accumulation of unconjugated bilirubin in the brain, which can cause severe neurologic damage, referred to as *kernicterus* (Chapter 10). In contrast, conjugated bilirubin is water-soluble, nontoxic, and only loosely bound to albumin. Because of its solubility and weak association with albumin, excess conjugated bilirubin in plasma can be excreted in urine.

Serum bilirubin levels in the normal adult vary between 0.3 and 1.2 mg/dL, and the rate of systemic bilirubin production is equal to the rates of hepatic uptake, conjugation, and biliary excretion. Jaundice becomes evident when the serum bilirubin levels rise above 2 to 2.5 mg/dL; levels as high as 30 to 40 mg/dL can occur with severe disease. Mechanisms underlying jaundice are summarized in Table 18-8. Although more than one mechanism may be operative, generally one predominates, so knowledge of the major form of plasma bilirubin is of value in evaluating possible causes of hyperbilirubinemia.

The following two conditions result from specific defects in hepatocellular bilirubin metabolism.

Table 18-8 Causes of Jaundice

Predominantly Unconjugated Hyperbilirubinemia
Excess production of bilirubin
Hemolytic anemias
Resorption of blood from internal hemorrhage (e.g., alimentary tract bleeding, hematomas)
Ineffective erythropoiesis (e.g., pernicious anemia, thalassemia)
Reduced hepatic uptake
Drug interference with membrane carrier systems
Some cases of Gilbert syndrome
Impaired bilirubin conjugation
Physiologic jaundice of the newborn (decreased UGT1A1 activity, decreased excretion)
Breast milk jaundice (β-glucuronidases in milk)
Genetic deficiency of UGT1A1 activity (Crigler-Najjar syndrome types I and II)
Gilbert syndrome
Diffuse hepatocellular disease (e.g., viral or drug-induced hepatitis, cirrhosis)
Predominantly Conjugated Hyperbilirubinemia
Deficiency of canalicular membrane transporters (Dubin-Johnson syndrome, Rotor syndrome)
Impaired bile flow from duct obstruction or autoimmune cholangiopathies

UGT1A1, Uridine diphosphate-glucuronyltransferase family, peptide A1

Neonatal Jaundice. Because the hepatic machinery for conjugating and excreting bilirubin does not fully mature until about 2 weeks of age, almost every newborn develops transient and mild unconjugated hyperbilirubinemia, termed neonatal jaundice or *physiologic jaundice of the newborn*. This may be exacerbated by breastfeeding, as a result of the presence of bilirubin-deconjugating enzymes in breast milk. Nevertheless, sustained jaundice in the newborn is abnormal (discussed later).

Hereditary Hyperbilirubinemias. Multiple genetic mutations can cause hereditary hyperbilirubinemia (Table 18-9). For example, the hepatic conjugating enzyme UGT1A1 is a product of the *UGT1A1* gene located on chromosome 2q37. It is a member of a family of enzymes that catalyze the glucuronidation of an array of substrates such as steroid hormones, carcinogens, and drugs. In humans, UGT1A1, generated from the *UGT1A1* gene, is the only isoform responsible for bilirubin glucuronidation. Mutations of *UGT1A1* cause hereditary unconjugated hyperbilirubinemias: *Crigler-Najjar syndrome types I and II* and *Gilbert syndrome*. Crigler-Najjar syndrome type 1 is caused by severe UGT1A1 deficiency and is fatal around the time of birth, while in Crigler-Najjar type II and Gilbert syndrome there is some UGT1A1 activity and the phenotypes are much milder. In contrast, *Dubin-Johnson syndrome* and *Rotor syndrome* result from other defects that lead to conjugated hyperbilirubinemia. Both are autosomal recessive disorders and innocuous.

Cholestasis

Cholestasis is caused by impaired bile formation and bile flow that gives rise to accumulation of bile pigment in the hepatic parenchyma. It can be caused by extrahepatic or intrahepatic obstruction of bile channels, or by defects in hepatocyte bile secretion. Patients may have jaundice, pruritus, skin xanthomas (focal accumulation of