## KEY CONCEPTS

### Inherited Metabolic Liver Disease

- The inherited metabolic diseases include hemochromatosis, Wilson disease, and $\alpha_1$-antitrypsin deficiency.
- **Hereditary hemochromatosis** is caused by a mutation in the *HFE* gene, whose product is involved in intestinal iron uptake by its effect on hepcidin levels. It is characterized by accumulation of iron in liver and pancreas.
- **Wilson disease** is caused by a mutation in the metal ion transporter *ATP7B*, which results in accumulation of copper in the liver, brain (particularly basal ganglia), and eyes ("Kayser-Fleisher rings").
  - Wilson disease effects on the liver are protean, presenting as acute massive hepatic necrosis, fatty liver disease, or chronic hepatitis and cirrhosis.
- **$\alpha_1$-Antitrypsin deficiency** is a disease of protein misfolding that results in impaired secretion of $\alpha_1$ Antitrypsin into the serum.
  - The Z variant of $\alpha_1$-Antitrypsin is the most likely to impair secretion by hepatocytes and cause disease, particularly when homozygous, that is, the *PiZZ* genotype; the main consequences are pulmonary emphysema caused by increased elastase activity and liver injury caused by the accumulation of abnormal $\alpha_1$-Antitrypsin.

## Cholestatic Diseases

Hepatic bile serves two major functions: (1) the emulsification of dietary fat in the lumen of the gut through the detergent action of bile salts, and (2) the elimination of bilirubin, excess cholesterol, xenobiotics, and other waste products that are insufficiently water-soluble to be excreted into urine. Tissue deposition of bile becomes clinically evident as yellow discoloration of the skin and sclera (*jaundice* and *icterus*, respectively) due to retention of bilirubin, and as *cholestasis*, when there is systemic retention of not only bilirubin but also other solutes eliminated in bile.

**Jaundice occurs when there is bilirubin overproduction, hepatitis, or obstruction of the flow of bile, any of which can disturb the equilibrium between bilirubin production and clearance.** To understand the pathophysiology of jaundice it is important first to become familiar with the major aspects of bile formation and metabolism. The metabolism of bilirubin by the liver consists of four separate but interrelated events: uptake from the circulation; intracellular storage; conjugation with glucuronic acid; and biliary excretion. These are described next.

### Bilirubin and Bile Formation

Bilirubin is the end product of heme degradation (Fig. 18-27). The majority of daily production (0.2 to 0.3 gm, 85%) is derived from breakdown of senescent red cells by the mononuclear phagocytic system, especially in the spleen, liver, and bone marrow. Most of the remainder (15%) of bilirubin is derived from the turnover of hepatic heme or hemoproteins (e.g., the P-450 cytochromes) and from premature destruction of red cell precursors in the bone marrow (Chapter 13). Whatever the source, intracellular heme oxygenase converts heme to biliverdin (step 1 in Fig. 18-27), which is immediately reduced to bilirubin by biliverdin reductase. Bilirubin thus formed outside the liver is released and bound to serum albumin (step 2). Albumin binding is necessary to transport bilirubin because bilirubin is virtually insoluble in aqueous solutions at physiologic pH. Hepatic processing of bilirubin involves carrier-mediated uptake at the sinusoidal membrane (step 3), conjugation with one or two molecules of glucuronic acid by bilirubin uridine diphosphate (UDP)

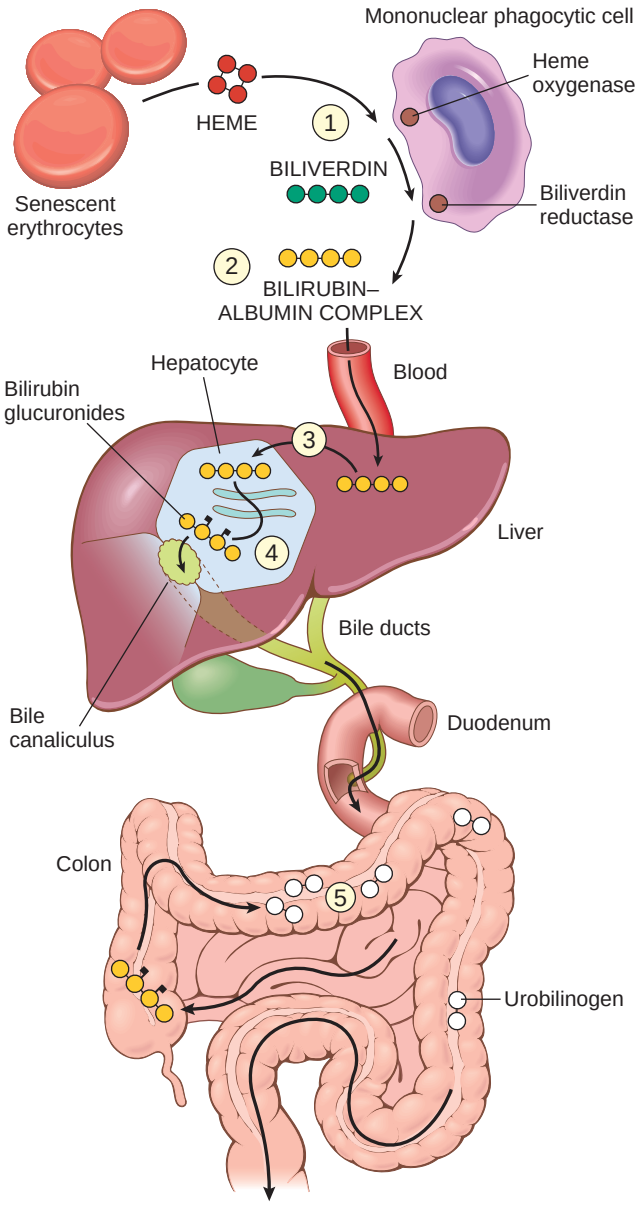


**Figure 18-27** Bilirubin metabolism and elimination. (1) Normal bilirubin production from heme (0.2 to 0.3 gm/day) is derived primarily from the breakdown of senescent circulating erythrocytes. (2) Extrahepatic bilirubin is bound to serum albumin and delivered to the liver. (3) Hepatocellular uptake and (4) glucuronidation in the endoplasmic reticulum generates bilirubin monoglucuronides and diglucuronides, which are water soluble and readily excreted into bile. (5) Gut bacteria deconjugate the bilirubin and degrade it to colorless urobilinogens. The urobilinogens and the residue of intact pigments are excreted in the feces, with some reabsorption and excretion into urine.