Porphyrin

In addition to serving as building blocks for proteins, amino acids are precursors of many nitrogen-containing compounds that have important physiologic functions. These molecules include porphyrins.

PORPHYRIN METABOLISM

Porphyrins are cyclic compounds that readily bind metal ions—usually Fe2+ Fe3+. The most prevalent metalloporphyrin in humans is heme, which consists of one ferrous (Fe2+) iron atom coordinated in the center of the tetrapyrrole ring of protoporphyrin IX.

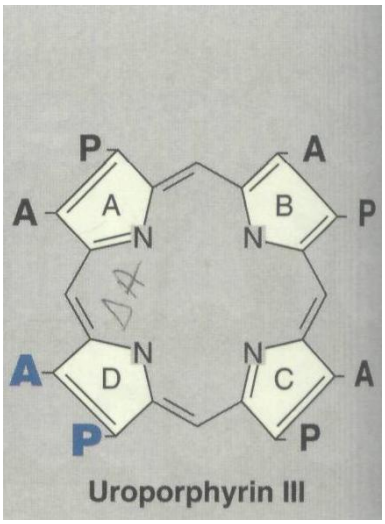
A. Structure of porphyrins

Porphyrins are cyclic molecules formed by the linkage of four pyrrole rings through methenyl bridges (Figure 21.2). Three structural features of these molecules are relevant to understanding their medical significance.

1. Side chains: Different porphyrins vary in the nature of the side chains that are attached to each of the four pyrrole rings.

2. Distribution of side chains: The side chains of porphyrins can be ordered around the tetrapyrrole nucleus in four different ways, designated by Roman numerals from I to IV.

3. Porphyrinogens: Porphyrin precursors exist in the chemically reduced form called porphyrinogens.



B. Biosynthesis of heme

The major sites of heme biosynthesis are the liver, which synthesizes a number of heme proteins (particularly, cytochrome P450), and the erythrocyte-producing cells of the bone marrow, which are active in hemoglobin synthesis. The initial reaction and the last three steps in the formation of porphyrins occur in mitochondria, whereas the intermediate steps of the biosynthetic pathway occur in the cytosol (see Summary Figure 21.7). [Note: Mature red blood cells lack mitochondria and are unable to synthesize heme.]

1. Formation of aminolevulinic acid (ALA): all the carbon and nitrogen atoms of the porphyrin molecule are provided by two simple building blocks: glycine (a nonessential amino acid) and succinyl CoA (an intermediate in the citric acid cycle). Glycine and succinyl CoA condense to form ALA in a reaction catalyzed by *ALA synthase* (Figure 21.3). This reaction requires pyridoxal phosphate as a coenzyme, and is the rate-controlling step hepatic porphyrin biosynthesis.

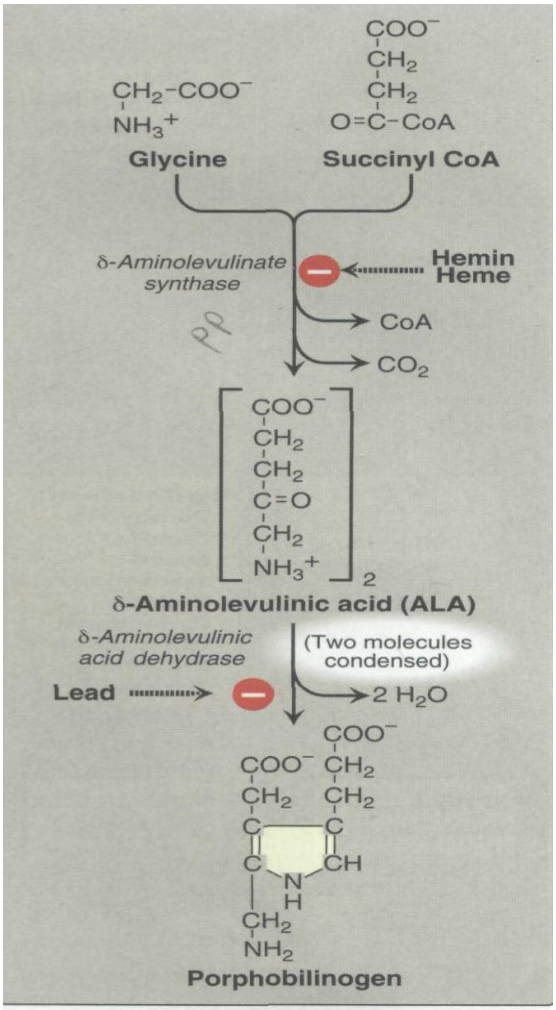


Figure 21.3
Pathway of porphyrin synthesis: formation of porphobilinogen.

a)End product inhibition by hemin: When porphyrin production exceeds the availability of globin, heme accumulates and is converted to hemin by the oxidation of Fe^{2+} to Fe^{3+}. Hemin decreases the activity of hepatic *ALA synthase by* causing decreased synthesis of the enzyme. [Note: in erythroid cells, heme synthesis is under the control of erythropoietin and the availability of intracellular iron.]

b)Effect of drugs on ALA synthase activity: Administration of any of a large number of drugs, such as phenobarbital, griseofulvinor hydantoins, results in a significant increase in hepatic ALA synthase activity.

2.Formation of porphobilinogen: The dehydration of two molecules of ALA to form porphobilinogen by *S-aminolevulinic acid dehydrase* is extremely sensitive to inhibition by heavy metal ions. This inhibition is, in part, responsible for the elevation in ALA and the anemia seen in **lead poisoning.**

3. Formation of uroporphyrinogen: The condensation of four molecules of porphobilinogen results in the formation of uroporphyrinogen III.

4. Formation of heme: Uroporphyrinogen III is converted to heme by a series of decarboxylations and oxidations The introduction of Fe^{2+} into protoporphyrin IX occurs spontaneously, but the rate is enhanced by the enzyme *ferrochelatase*—an enzyme that is inhibited by lead.

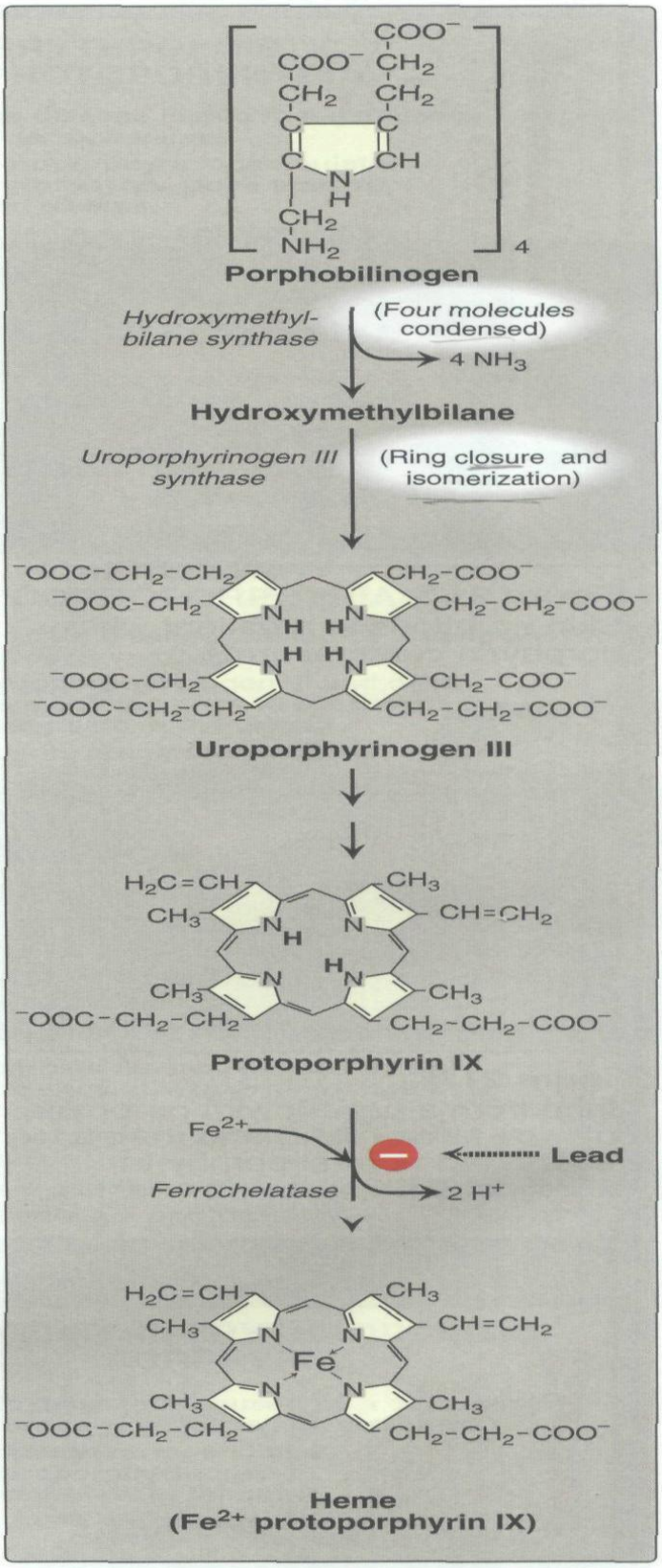


Figure 21.4
Pathway of porphyrin synthesis: formation of heme. (Continued from Figure 21.3.)

Porphyrias

Porphyrias are caused by inherited (or occasionally acquired) defects in heme synthesis, resulting in the accumulation and increased excretion of porphyrins or porphyrin precursors.
Each porphyria results in the accumulation of a unique pattern of intermediates caused by the deficiency of an enzyme in the heme synthetic pathway.

1. Clinical manifestations:
The porphyrias are classified as **erythropoietic** or **hepatic,** depending on whether the enzyme deficiency occurs in the erythropoietic cells of the bone marrow or in the liver. Hepatic porphyrias can be further classified as acute or chronic. Individuals with an enzyme defect leading to the accumulation of tetrapyrrole Intermediates show **photosensitivity**—that is, their skin itches and burns **(pruritis)** when exposed to visible light.

[Note: These symptoms are thought to be a result of the porphyrin-mediated formation of superoxide radicals from oxygen. These reactive oxygen species can oxidatively damage membranes, and cause the release of destructive enzymes from lysosomes. Destruction of cellular components leads to the photosensitivity]

a. Chronic porphyria: Porphyria cutanea tarda, the most common porphyria, is a chronic disease of the liver and erythroid tissues. The disease is associated with a deficiency in uroporphyrinogen decarboxylase, but clinical expression of the enzyme deficiency is influenced by various factors, such as hepatic iron overload, exposure to sunlight, and the presence of hepatitis B or C, or HIV infections. Porphyrin accumulation leads to cutaneous symptoms, and urine that is red to brown in natural light (Figure 20.6), and pink to red in fluorescent light.

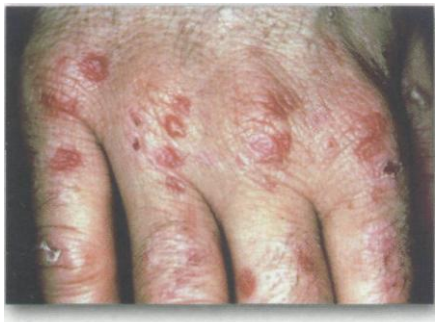


Figure 21.5
Skin eruptions in a patient with porphyria cutanea tarda.

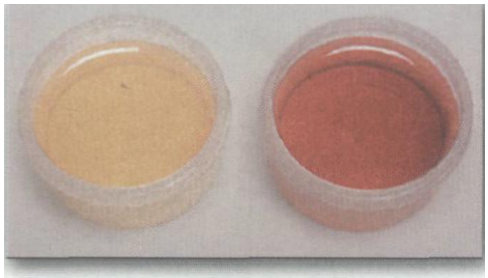


Figure 21.6
Urine from a patient with porphyria cutanea tarda (right) and from a patient with normal porphyrin excretion (left).

b. Acute hepatic porphyrias: Acute hepatic porphyrias (acute **intermittent porphyria, hereditary coproporphyria,** and **varigate porphyria)** are characterized by acute attacks of gastrointestinal, neurologic/psychiatric, and cardiovascular symptoms. Porphyrias leading to accumulation of ALA and porphobilinogen, such as acute intermittent porphyria, cause abdominal pain and neuropsychiatric disturbances.

c. Erythropoietic porphyrias: The erythropoietic porphyrias **(congenital erythropoietic porphyria** and **erythropoietic protoporphyria)** are characterized by skin rashes and blisters that appear in early childhood. The diseases are complicated by cholestatic liver cirrhosis and progressive hepatic failure.

2. Increased ALA synthase activity: One common feature of the porphyrias is a decreased synthesis of heme. In the liver, heme normally functions as a repressor of *ALA synthase.* Therefore, the absence of this end product results in an increase in the synthesis of *ALA synthase* (derepression). This causes an increased synthesis of intermediates that occur prior to the genetic block. The accumulation of these toxic intermediates is the major pathophysiology of the porphyrias.

3. Treatment: During acute porphyria attacks, patients require medical support, particularly treatment for pain and vomiting. The severity of symptoms of the porphyrias can be diminished by intravenous injection of hemin, which decreases the synthesis of *ALA synthase.* Avoidance of sunlight and ingestion of β-carotene (a free-radical scavenger) are also helpful.

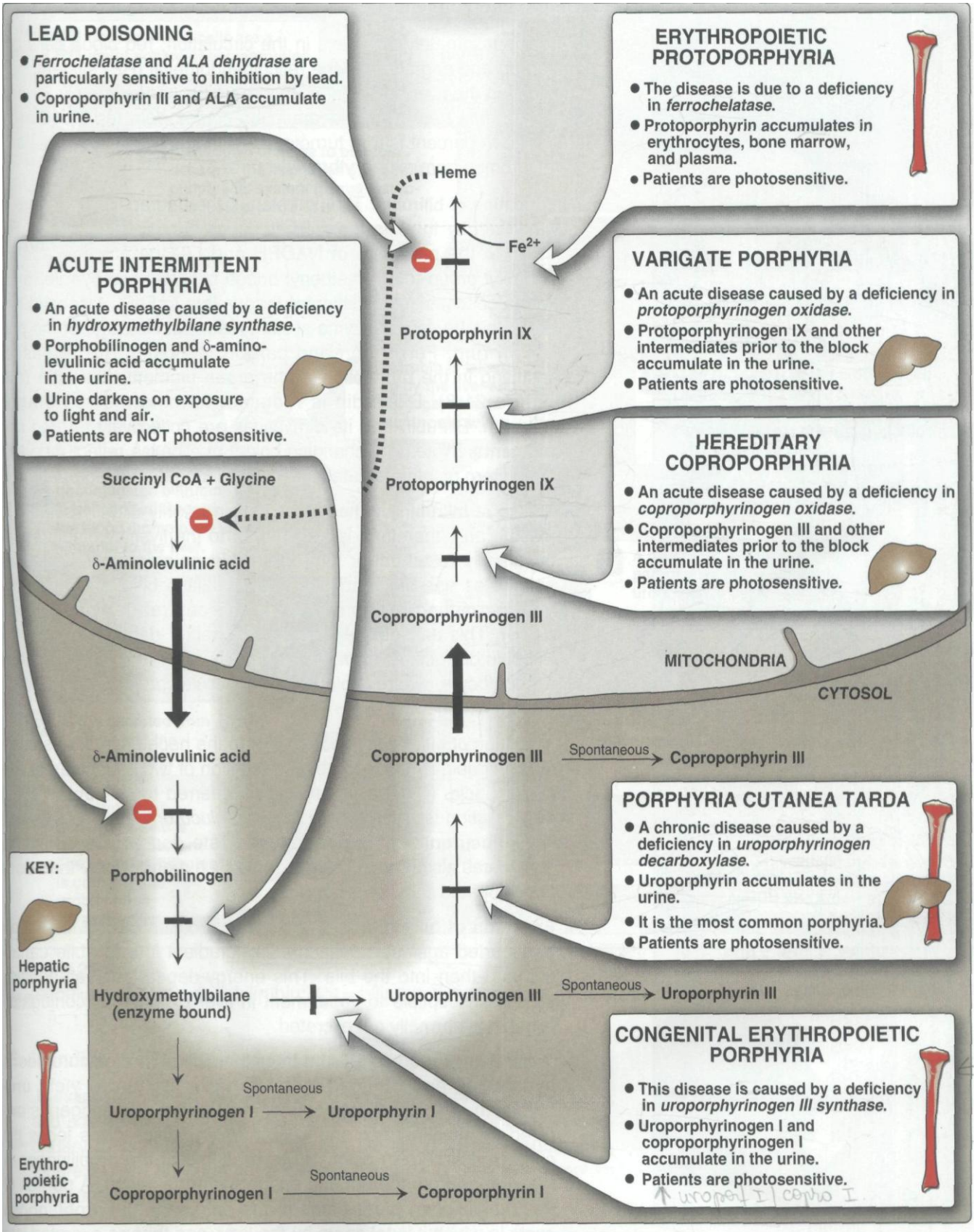


Figure 21.7
Summary of heme synthesis.

all are AD, except congenital erytho

D. Degradation of heme

After approximately 120 days in the circulation, red blood cells are taken up and degraded by the reticuloendothelial (RE) system, particularly in the liver and spleen (Figure 21.8). Approximately 85 percent of heme destined for degradation comes from red blood cells, and fifteen percent is from turnover of immature red blood cells and cytochromes from extra erythroid tissues.

1. **Formation of bilirubin:** The first step in the degradation of heme is catalyzed by the microsomal *heme oxygenase* system of the RE cells. In the presence of NADPH and O2, the enzyme adds a hydroxyl group to the methenyl bridge between two pyrrole rings, with a concomitant oxidation of ferrous iron to Fe3+. A second oxidation by the same enzyme system results in cleavage of the porphyrin ring. Ferric iron and carbon monoxide are released, resulting in the production of the green pigment **biliverdin** (see Figure 21.8). Biliverdin is reduced, forming the red-orange **bilirubin.** Bilirubin and its derivatives are collectively termed bile **pigments.**
2. **Uptake of bilirubin by the liver:** Bilirubin is only slightly soluble in plasma and, therefore, is transported to the liver by binding to albumin. [Note: Certain anionic drugs, such as salicylates and sulfonamides,[1] can displace bilirubin from albumin, permitting bilirubin to enter the central nervous system (CNS). This causes the potential for neural damage in infants.] Bilirubin dissociates from the carrier albumin molecule and enters a hepatocyte, where it binds to intracellular proteins, particularly the protein ligandin.

3. **Formation of bilirubin diglucuronide:** in the hepatocyte, the solubility of bilirubin is increased by the addition of two molecules of glucuronic acid. [Note: This process is referred to as conjugation.] The reaction is catalyzed by bilirubin glucuronyltransferase using UDP-glucuronic acid as the glucuronate donor.

4. **Excretion of bilirubin into bile:** Bilirubin diglucuronide is actively transported into the bile canaliculi and then into the bile. This energy-dependent, rate-limiting step is susceptible to impairment in liver disease. Unconjugated bilirubin is normally not excreted.

5. **Formation of urobilins in the intestine:** Bilirubin diglucuronide is hydrolyzed and reduced by bacteria in the gut to yield urobilinogen, a colorless compound. Most of the urobilinogen is oxidized by intestinal bacteria to **stercobilin,** which gives feces the characteristic brown color. The remainder of the urobilinogen is transported by the blood to the kidney, where it is converted to yellow **urobilin** and excreted, giving urine its characteristic color.

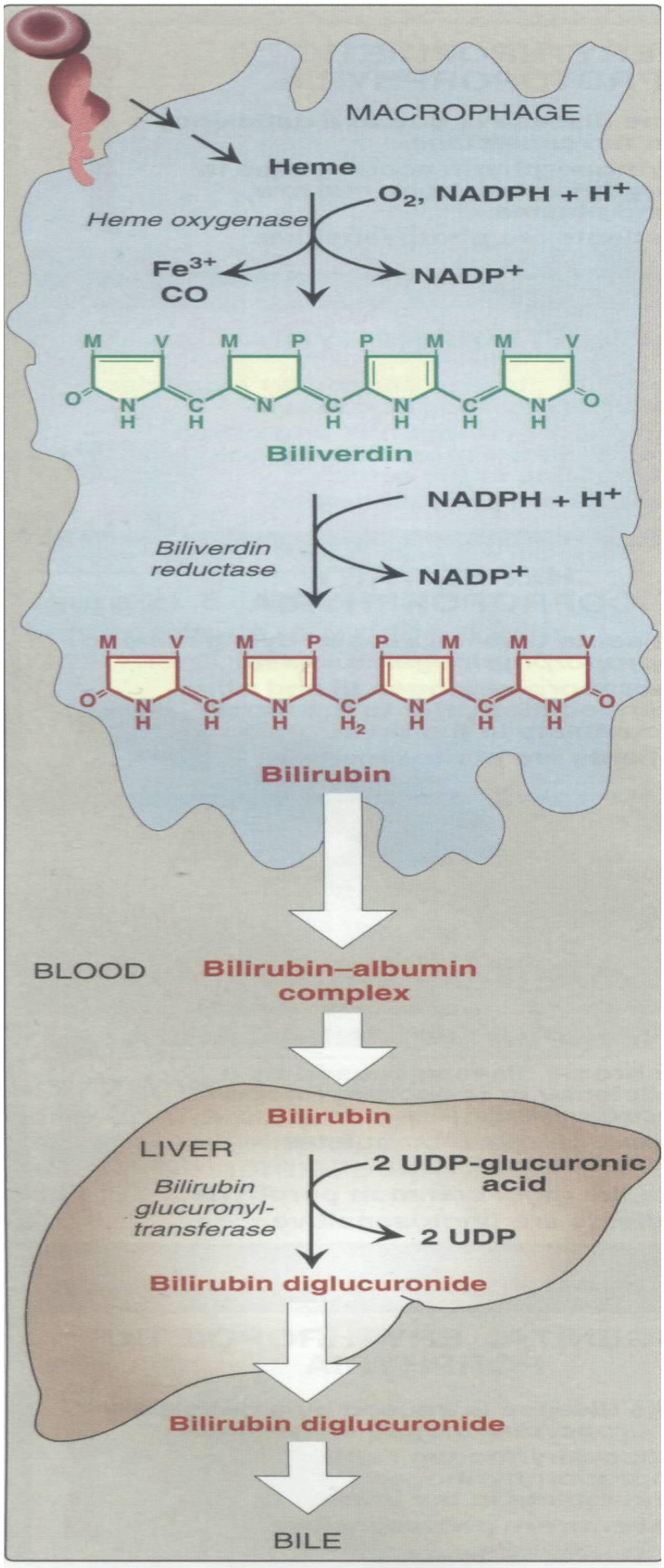


Figure 21.8
Formation of bilirubin from heme.

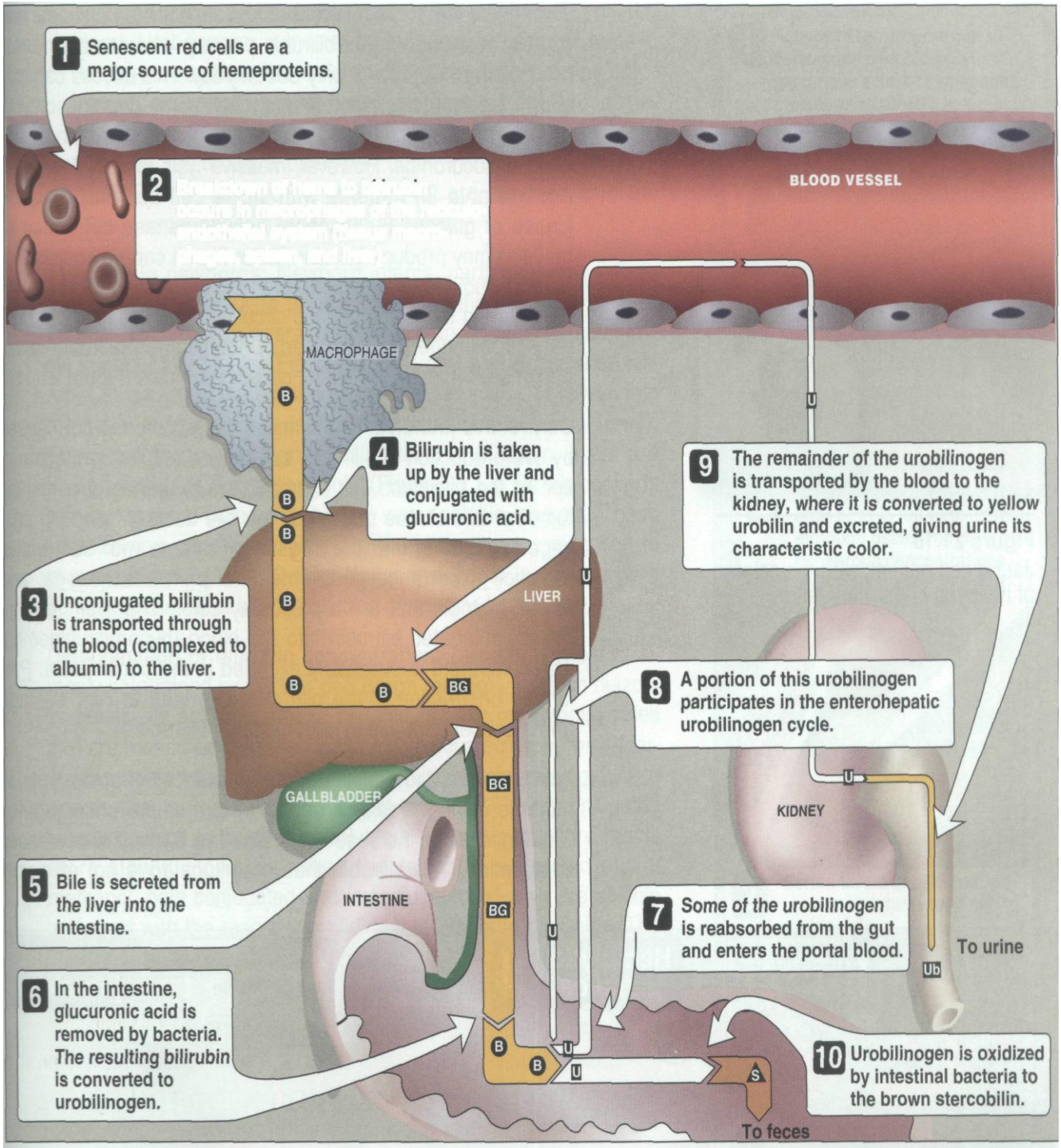


Figure 21.9
Catabolism of heme B = bilirubin; BG = bilirubin diglucuronide; U = urobilinogen; Ub = urobilin; S = stercobilin.

E. Jaundice : Jaundice (also called **icterus**) refers to the yellow color of skin, nail beds, and sclerae (whites of the eyes) caused by deposition of bilirubin.

Types of jaundice: Jaundice can be classified into three major forms described below. However, in clinical practice, jaundice is often more complex than indicated in this simple classification. For example, the accumulation of bilirubin may be a result of defects at more than one step in its metabolism.

#Hemolytic jaundice: The liver has the capacity to conjugate and excrete over 3000 mg of bilirubin per day, whereas the normal production of bilirubin is only 300 mg/day. However, massive lysis of red blood cells (for example, in patients with sickle cell anemia, pyruvate kinase or glucose 6-phosphate dehydrogenase deficiency, malaria) may produce bilirubin faster than it can be conjugated, More bilirubin is excreted into the bile, the amount of urobilinogin entering the enterohepatic circulation is increased, and urinary urobilinogen is increased. Unconjugated bilirubin levels become elevated in the blood, causing jaundice (Figure21.11).

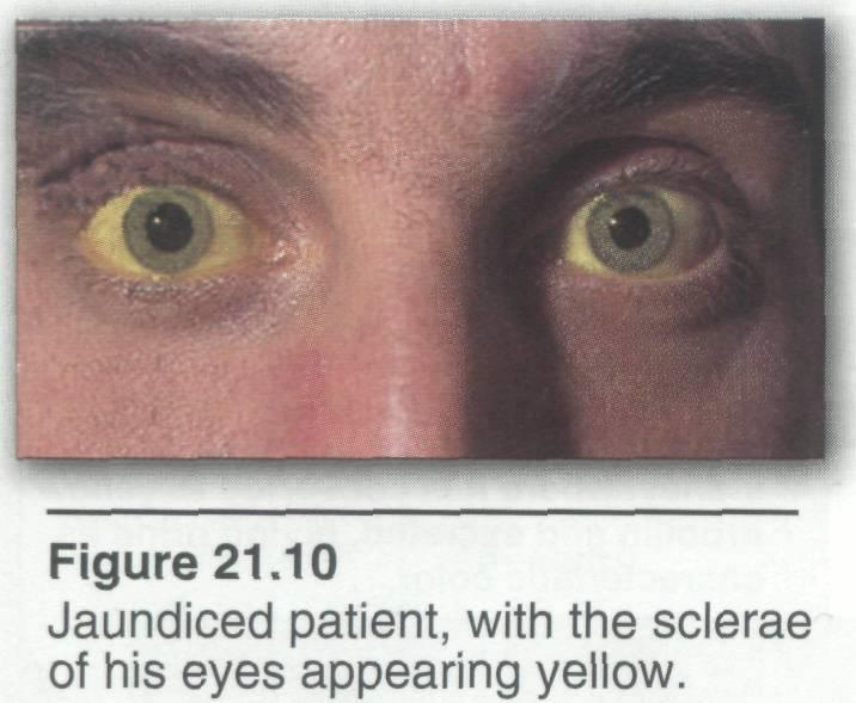


Figure 21.10
Jaundiced patient, with the sclerae of his eyes appearing yellow.

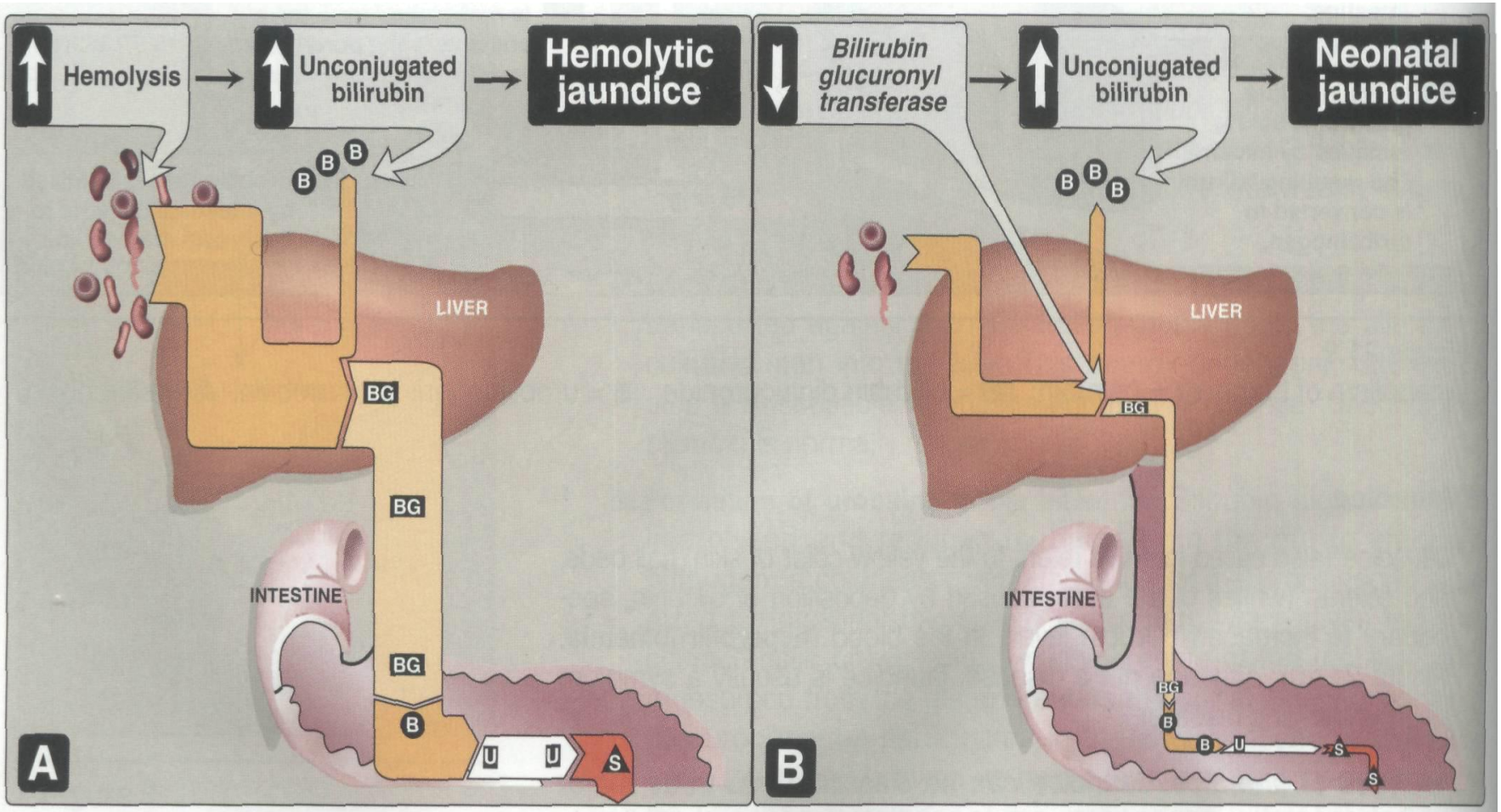


Figure 21.11

Alterations in the metabolism of heme. A. Hemolytic jaundice. B. Neonatal jaundice. [Note: The enterohepatic circulation of urobilinogen is omitted for simplicity.] BG = bilirubin glucuronide; B = bilirubin; U = urobilinogen; S = stercobilin.

#Obstructive jaundice: in this instance, jaundice is not caused by overproduction of bilirubin, but instead results from obstruction of the bile duct. For example, the presence of a hepatic tumor or bile stones may block the bile ducts, preventing passage of bilirubin into the intestine. Patients with obstructive jaundice experience gastrointestinal pain and nausea, and produce stools that are a pale, clay color. The liver "regurgitates" conjugated bilirubin into the blood (hyperbilirubinemia). The compound is eventually excreted in the urine. [Note: Prolonged obstruction of the bile duct can lead to liver damage and a subsequent rise in unconjugated bilirubin.].

#Hepatocellular jaundice: Damage to liver cells (for example, in patients with cirrhosis or hepatitis) can cause unconjugated bilirubin levels to increase in the blood as a result of decreased conjugation. Plasma levels of AST (SGOT) and ALT (SGPT, see p. 249) are elevated, and the patient experiences nausea and anorexia.

Jaundice in newborns: Newborn infants, particularly premature babies, often accumulate bilirubin, because the activity of hepatic *bilirubin glucuronyl transferase* is low at birth, it reaches adult levels in about four weeks. Elevated bilirubin, in excess of the binding capacity of albumin, can diffuse into the basal ganglia and cause toxic encephalopathy. Thus, newborns with significantly elevated bilirubin levels are treated with blue fluorescent light (Figure 21.13), which converts bilirubin to more polar and, hence, water-soluble isomers. These photoisomers can be excreted into the bile without conjugation to glucuronic acid. [Note: **Crigler-Najjar syndrome** is caused by a genetic deficiency of hepatic *bilirubin glucuronyl transferase.]*

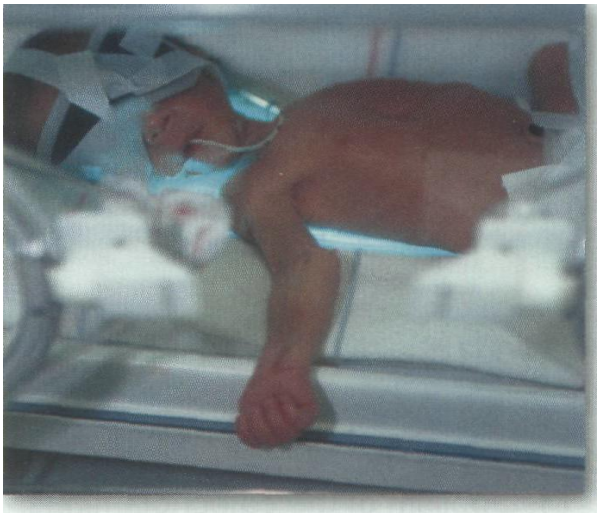


Figure 21.13
Phototherapy in neonatal jaundice.