

# Conversion of Amino Acids to Specialized Products

# 21

## I. OVERVIEW

In addition to serving as building blocks for proteins, amino acids are precursors of many nitrogen-containing compounds that have important physiologic functions (Figure 21.1). These molecules include porphyrins, neurotransmitters, hormones, purines, and pyrimidines.

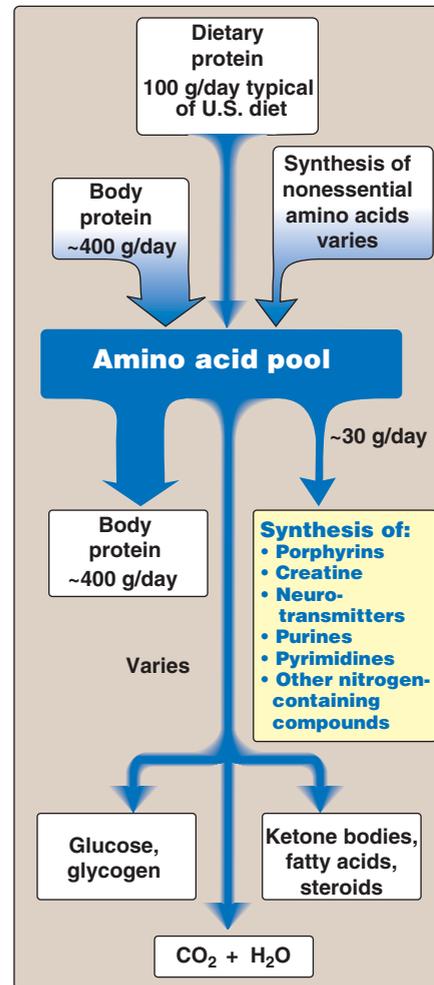
## II. PORPHYRIN METABOLISM

Porphyrins are cyclic compounds that readily bind metal ions—usually  $\text{Fe}^{2+}$  or  $\text{Fe}^{3+}$ . The most prevalent metalloporphyrin in humans is heme, which consists of one ferrous ( $\text{Fe}^{2+}$ ) iron ion coordinated in the center of the tetrapyrrole ring of protoporphyrin IX (see p. 280). Heme is the prosthetic group for hemoglobin, myoglobin, the cytochromes, *catalase*, *nitric oxide synthase*, and *peroxidase*. These heme proteins are rapidly synthesized and degraded. For example, 6–7 g of hemoglobin are synthesized each day to replace heme lost through the normal turnover of erythrocytes. Coordinated with the turnover of heme proteins is the simultaneous synthesis and degradation of the associated porphyrins, and recycling of the bound iron ions.

### 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.

- Side chains:** Different porphyrins vary in the nature of the side chains that are attached to each of the four pyrrole rings. Uroporphyrin contains acetate ( $-\text{CH}_2-\text{COO}^-$ ) and propionate ( $-\text{CH}_2-\text{CH}_2-\text{COO}^-$ ) side chains, coproporphyrin contains methyl ( $-\text{CH}_3$ ) and propionate groups, and protoporphyrin IX (and heme) contains vinyl ( $-\text{CH}=\text{CH}_2$ ), methyl, and propionate groups. [Note: The methyl and vinyl groups are produced by decarboxylation of acetate and propionate side chains, respectively.]



**Figure 21.1**

Amino acids as precursors of nitrogen-containing compounds.

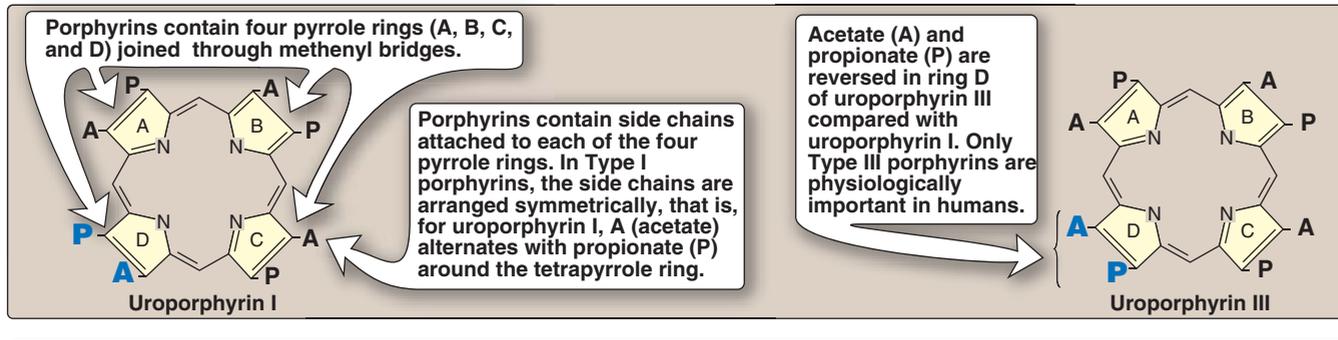


Figure 21.2

Structures of uroporphyrin I and uroporphyrin III. A = acetate and P = propionate.

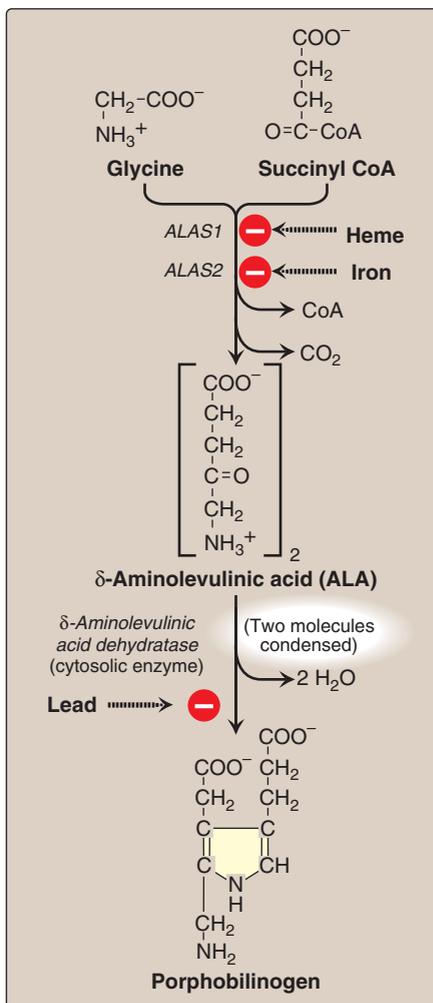


Figure 21.3

Pathway of porphyrin synthesis: Formation of porphobilinogen. ALAS = δ-aminolevulinic acid synthase. (Continued in Figures 21.4 and 21.5.)

**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 I to IV. Only Type III porphyrins, which contain an asymmetric substitution on ring D (see Figure 21.2), are physiologically important in humans. [Note: Protoporphyrin IX is a member of the Type III series.]

**3. Porphyrinogens:** These porphyrin precursors (for example, uroporphyrinogen) exist in a chemically reduced, colorless form, and serve as intermediates between porphobilinogen and the oxidized, colored protoporphyrins in heme biosynthesis.

## B. Biosynthesis of heme

The major sites of heme biosynthesis are the liver, which synthesizes a number of heme proteins (particularly cytochrome P450 proteins), and the erythrocyte-producing cells of the bone marrow, which are active in hemoglobin synthesis. [Note: Over 85% of all heme synthesis occurs in erythroid tissue.] In the liver, the rate of heme synthesis is highly variable, responding to alterations in the cellular heme pool caused by fluctuating demands for heme proteins. In contrast, heme synthesis in erythroid cells is relatively constant, and is matched to the rate of globin 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 Figure 21.8). [Note: Mature red blood cells lack mitochondria and are unable to synthesize heme.]

**1. Formation of δ-aminolevulinic acid (ALA):** All the carbon and nitrogen atoms of the porphyrin molecule are provided by glycine (a nonessential amino acid) and succinyl coenzyme A (an intermediate in the citric acid cycle) that condense to form ALA in a reaction catalyzed by *ALA synthase (ALAS)* (Figure 21.3) This reaction requires pyridoxal phosphate (PLP) as a coenzyme, and is the committed and rate-limiting step in porphyrin biosynthesis. [Note: There are two isoforms of ALAS, 1 and 2, each controlled by different mechanisms. Erythroid tissue produces only ALAS2, the gene for which is located on the X-chromosome. Loss of function mutations in ALAS2 result in X-linked sideroblastic anemia.]

**a. End-product inhibition of ALAS1 by hemin:** When porphyrin production exceeds the availability of the apoproteins that

require it, heme accumulates and is converted to hemin by the oxidation of  $\text{Fe}^{2+}$  to  $\text{Fe}^{3+}$ . Hemin decreases the activity of hepatic *ALAS1* by causing decreased synthesis of the enzyme, through inhibition of mRNA synthesis and use (heme decreases stability of the mRNA), and by inhibiting mitochondrial import of the enzyme. [Note: In erythroid cells, *ALAS2* is controlled by the availability of intracellular iron.]

**b. Effect of drugs on ALA synthase activity:** Administration of any of a large number of drugs results in a significant increase in hepatic *ALAS1* activity. These drugs are metabolized by the *microsomal cytochrome P450 monooxygenase* system—a heme protein *oxidase* system found in the liver (see p. 149). In response to these drugs, the synthesis of cytochrome P450 proteins increases, leading to an enhanced consumption of heme—a component of cytochrome P450 proteins. This, in turn, causes a decrease in the concentration of heme in liver cells. The lower intracellular heme concentration leads to an increase in the synthesis of *ALAS1* (derepression), and prompts a corresponding increase in ALA synthesis.

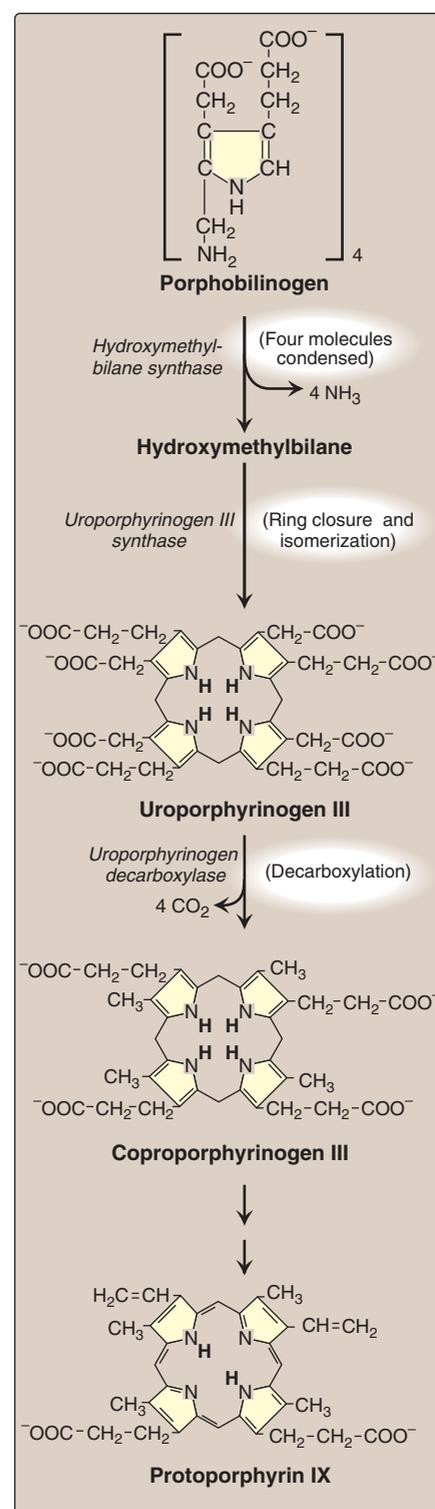
**2. Formation of porphobilinogen:** The condensation of two molecules of ALA to form porphobilinogen by Zn-containing *ALA dehydratase* (*porphobilinogen synthase*) is extremely sensitive to inhibition by heavy metal ions, for example, lead that replace the zinc (see Figure 21.3). This inhibition is, in part, responsible for the elevation in ALA and the anemia seen in lead poisoning.

**3. Formation of uroporphyrinogen:** The condensation of four porphobilinogens produces the linear tetrapyrrole, hydroxymethylbilane, which is isomerized and cyclized by *uroporphyrinogen III synthase* to produce the asymmetric uroporphyrinogen III. This cyclic tetrapyrrole undergoes decarboxylation of its acetate groups, generating coproporphyrinogen III (Figure 21.4). These reactions occur in the cytosol.

**4. Formation of heme:** Coproporphyrinogen III enters the mitochondrion, and two propionate side chains are decarboxylated to vinyl groups generating protoporphyrinogen IX, which is oxidized to protoporphyrin IX. The introduction of iron (as  $\text{Fe}^{2+}$ ) into protoporphyrin IX occurs spontaneously, but the rate is enhanced by *ferrochelatase*, an enzyme that, like *ALA dehydratase*, is inhibited by lead (Figure 21.5).

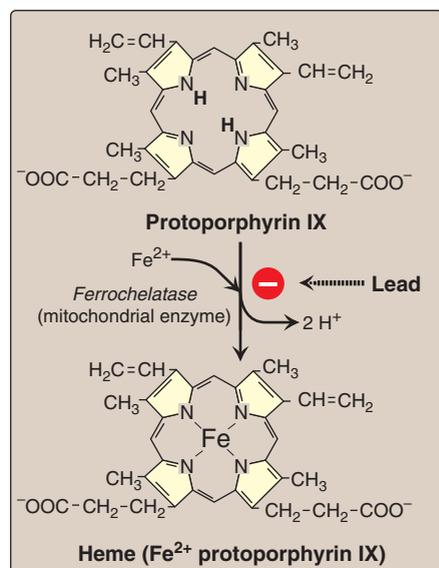
### C. Porphyrins

Porphyrias are rare, inherited (or occasionally acquired) defects in heme synthesis, resulting in the accumulation and increased excretion of porphyrins or porphyrin precursors (see Figure 21.8). [Note: With few exceptions, porphyrias are inherited as autosomal dominant disorders.] The mutations that cause the porphyrias are heterogeneous (not all are at the same DNA locus), and nearly every affected family has its own mutation. Each porphyria results in the accumulation of a unique pattern of intermediates caused by the deficiency of an enzyme in the heme synthetic pathway. [Note: “Porphyria” refers to the purple color caused by pigment-like porphyrins in the urine of some patients with defects in heme synthesis.]



**Figure 21.4**

Pathway of porphyrin synthesis: Formation of protoporphyrin IX. (Continued from Figure 21.3.)

**Figure 21.5**

Pathway of porphyrin synthesis:  
Formation of heme. (Continued  
from Figures 21.3 and 21.4)

**Figure 21.6**

Skin eruptions in a patient with  
porphyria cutanea tarda.

**Figure 21.7**

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

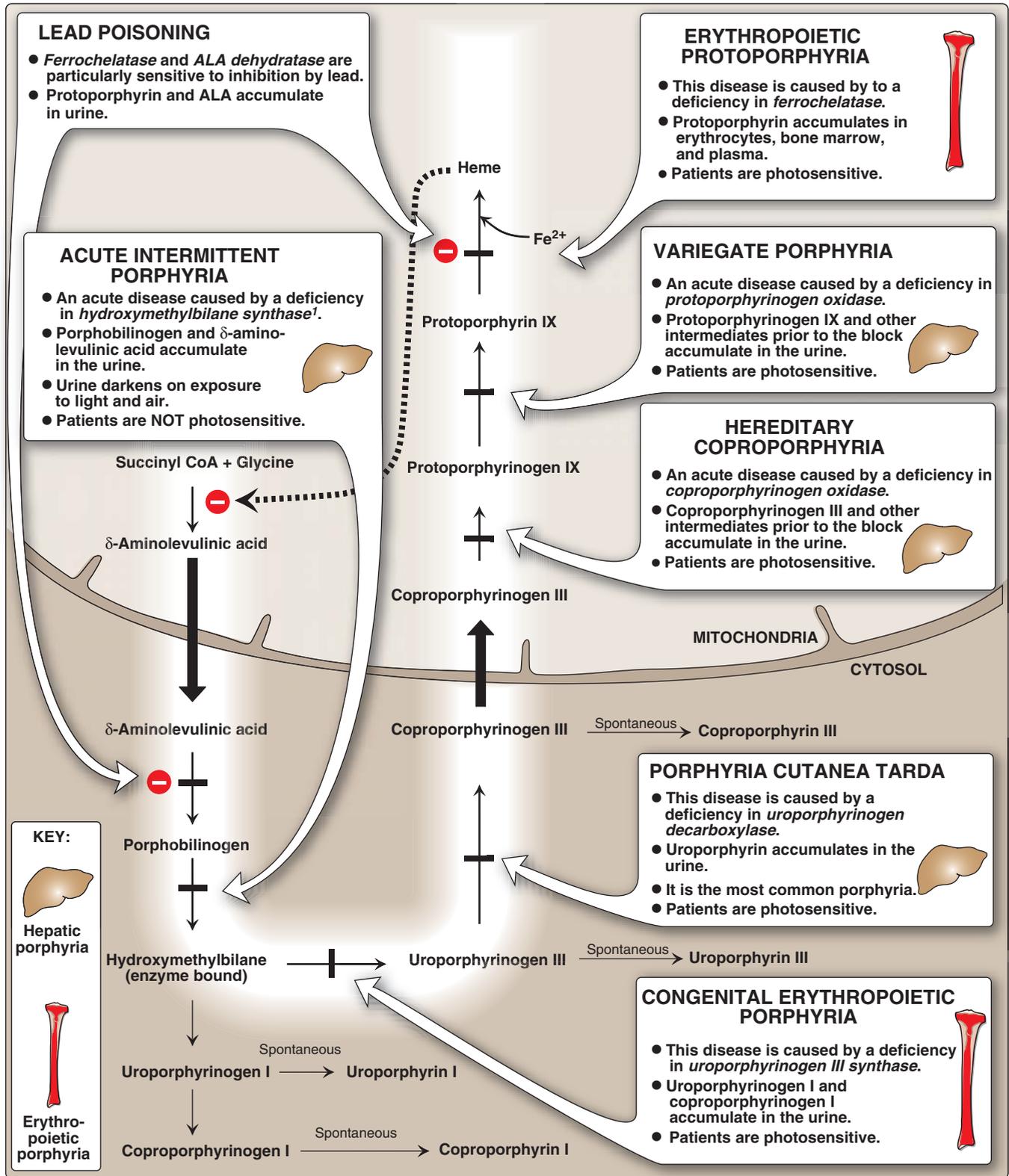
**1. Clinical manifestations:** The porphyrias are classified as erythropoietic or hepatic, depending on whether the enzyme deficiency occurs in the erythropoietic cells of the bone marrow or in the liver. Hepatic porphyrias can be further classified as chronic or acute. In general, individuals with an enzyme defect prior to the synthesis of the tetrapyrroles manifest abdominal and neuropsychiatric signs, whereas those with enzyme defects leading to the accumulation of tetrapyrrole intermediates show photosensitivity—that is, their skin itches and burns (pruritus) when exposed to visible light. [Note: Photosensitivity is a result of the oxidation of colorless porphyrinogens to colored porphyrins, which are photosensitizing molecules that are thought to participate in the formation of superoxide radicals from oxygen. These reactive oxygen species can oxidatively damage membranes, and cause the release of destructive enzymes from lysosomes.]

**a. Chronic hepatic porphyria:** Porphyria cutanea tarda, the most common porphyria, is a chronic disease of the liver. 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, alcohol ingestion, and the presence of hepatitis B or C, or HIV infections. Clinical onset is typically during the fourth or fifth decade of life. Porphyrin accumulation leads to cutaneous symptoms (Figure 21.6), and urine that is red to brown in natural light (Figure 21.7), and pink to red in fluorescent light.

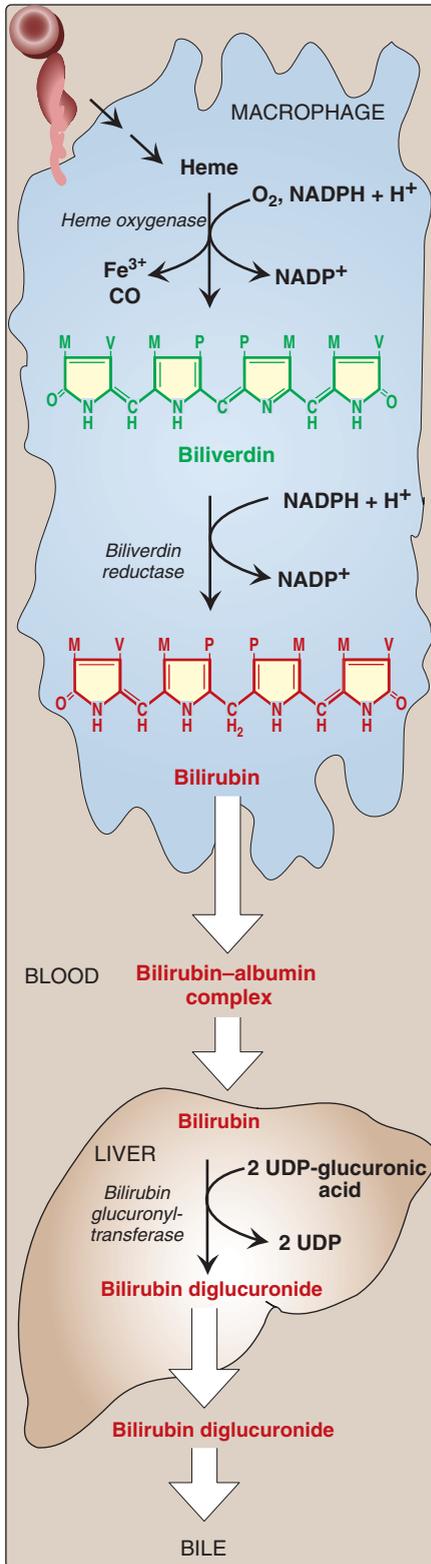
**b. Acute hepatic porphyrias:** Acute hepatic porphyrias (*ALA dehydratase* deficiency, acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria) are characterized by acute attacks of gastrointestinal, neuropsychiatric, and motor symptoms that may be accompanied by photosensitivity. Porphyrias leading to accumulation of ALA and porphobilinogen, such as acute intermittent porphyria, cause abdominal pain and neuropsychiatric disturbances, ranging from anxiety to delirium. Symptoms of the acute hepatic porphyrias are often precipitated by administration of drugs such as barbiturates and ethanol, which induce the synthesis of the heme-containing cytochrome P450 microsomal drug oxidation system. This further decreases the amount of available heme, which, in turn, promotes the increased synthesis of *ALAS1*.

**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 the gene for *ALAS1*. Therefore, the absence of this end product results in an increase in the synthesis of *ALA synthase1* (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.



**Figure 21.8** Summary of heme synthesis. <sup>1</sup>Also referred to as *porphobilinogen deaminase*.



**Figure 21.9**  
Formation of bilirubin from heme.  
UDP = uridine diphosphate.

**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 heme and glucose, which decreases the synthesis of *ALAS1*. Avoidance of sunlight and ingestion of  $\beta$ -carotene (a free-radical scavenger) are helpful in porphyrias with photosensitivity.

#### D. Degradation of heme

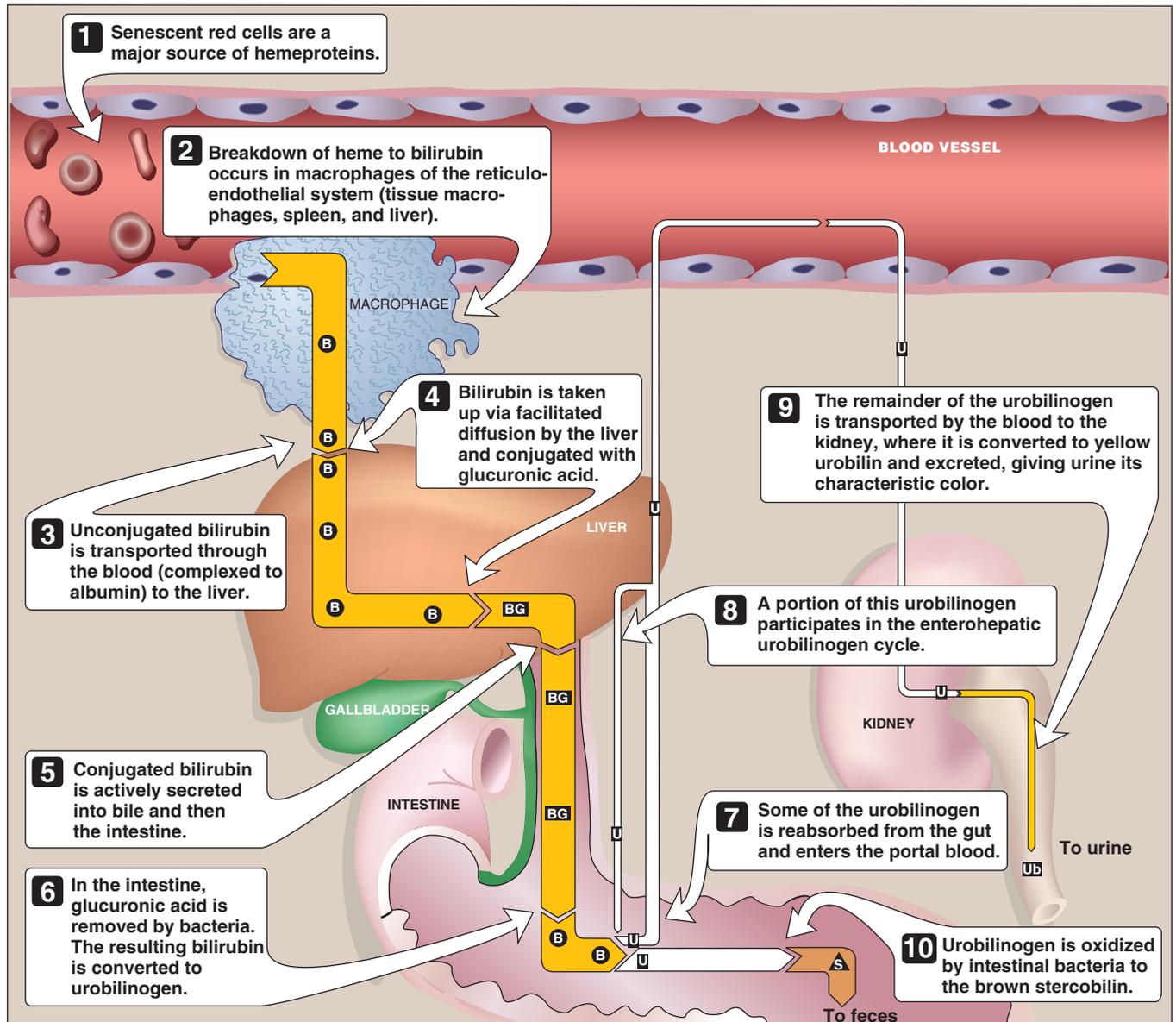
After approximately 120 days in the circulation, red blood cells are taken up and degraded by the reticuloendothelial system, particularly in the liver and spleen (Figure 21.9). Approximately 85% of heme destined for degradation comes from senescent red blood cells, and 15% is from turnover of immature red blood cells and cytochromes from nonerythroid tissues.

**1. Formation of bilirubin:** The first step in the degradation of heme is catalyzed by the microsomal *heme oxygenase* system of the reticuloendothelial cells. In the presence of NADPH and O<sub>2</sub>, the enzyme adds a hydroxyl group to the methenyl bridge between two pyrrole rings, with a concomitant oxidation of ferrous iron to Fe<sup>3+</sup>. A second oxidation by the same enzyme system results in cleavage of the porphyrin ring. The green pigment biliverdin is produced as ferric iron and CO are released (see Figure 21.9). [Note: The CO has biologic function, acting as a signaling molecule and vasodilator.] Biliverdin is reduced, forming the red-orange bilirubin. Bilirubin and its derivatives are collectively termed bile pigments. [Note: The changing colors of a bruise reflect the varying pattern of intermediates that occurs during heme degradation.]

||| Bilirubin, unique to mammals, appears to function as an antioxidant. In this role, it is oxidized to biliverdin, which is then reduced by *biliverdin reductase*, regenerating bilirubin.

**2. Uptake of bilirubin by the liver:** Bilirubin is only slightly soluble in plasma and, therefore, is transported to the liver by binding non-covalently to albumin. [Note: Certain anionic drugs, such as salicylates and sulfonamides, can displace bilirubin from albumin, permitting bilirubin to enter the central nervous system. This causes the potential for neural damage in infants.] Bilirubin dissociates from the carrier albumin molecule, enters a hepatocyte via facilitated diffusion, and 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 microsomal *bilirubin glucuronyl-transferase* using uridine diphosphate-glucuronic acid as the glucuronate donor. [Note: Varying degrees of deficiency of this enzyme result in Crigler-Najjar I and II and Gilbert syndrome, with Crigler-Najjar I being the most severe deficiency.]



**Figure 21.10**

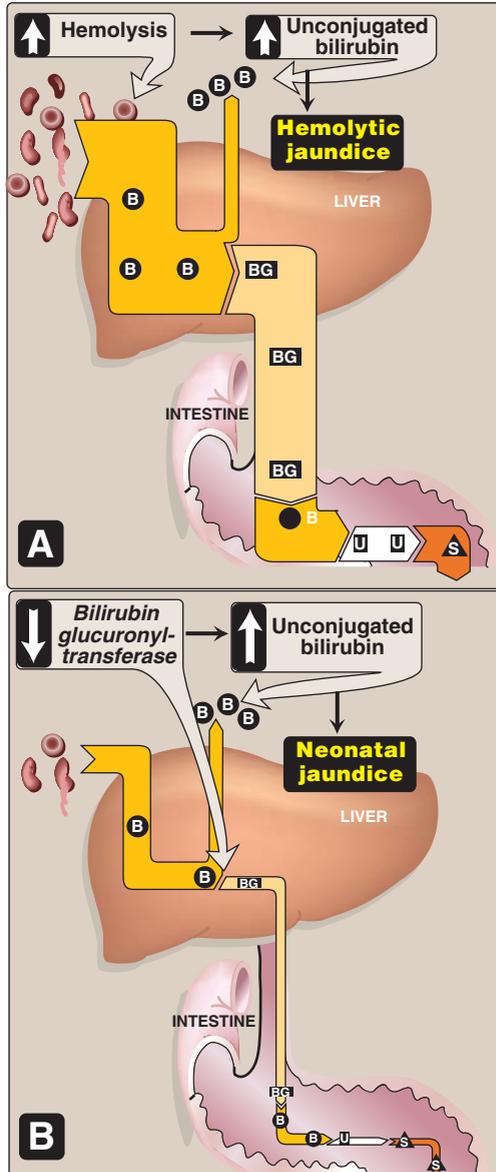
Catabolism of heme **B** = bilirubin; **BG** = bilirubin diglucuronide; **U** = urobilinogen; **Ub** = urobilin; **S** = stercobilin.

4. **Secretion of bilirubin into bile:** Bilirubin diglucuronide (conjugated bilirubin) is actively transported against a concentration gradient into the bile canaliculi and then into the bile. This energy-dependent, rate-limiting step is susceptible to impairment in liver disease. [Note: A deficiency in the protein required for transport of conjugated bilirubin out of the liver results in Dubin-Johnson syndrome.] Unconjugated bilirubin is normally not secreted.
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. However, some of the urobilinogen is reabsorbed from the gut and enters the portal blood. A portion of



**Figure 21.11**

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



**Figure 21.12**

Alterations in the metabolism of heme.  
 A. Hemolytic jaundice. B. Neonatal jaundice.  
 BG = bilirubin glucuronide; B = bilirubin;  
 U = urobilinogen; S = stercobilin.

this urobilinogen participates in the enterohepatic urobilinogen cycle in which it is taken up by the liver, and then resecreted into the bile. 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. The metabolism of bilirubin is summarized in Figure 21.10.

### 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, secondary to increased bilirubin levels in the blood (hyperbilirubinemia, Figure 21.11). Although not a disease, jaundice is usually a symptom of an underlying disorder.

**1. 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.

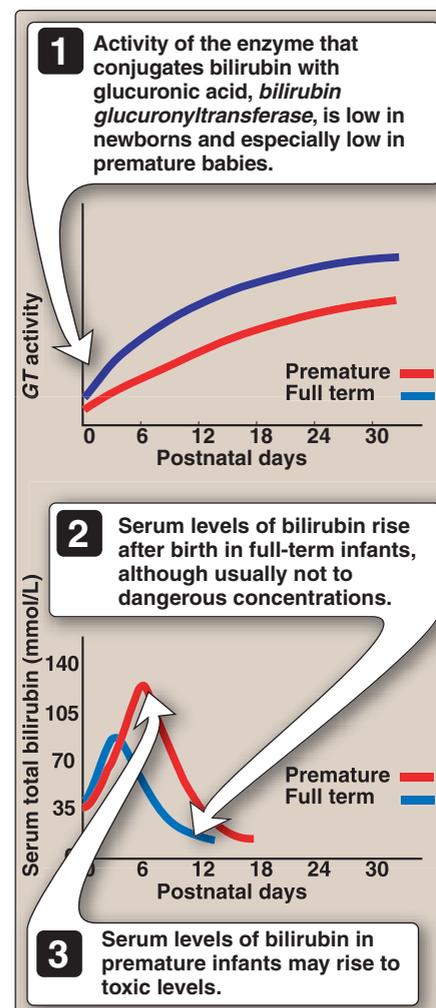
**a. Hemolytic jaundice:** The liver has the capacity to conjugate and excrete over 3,000 mg of bilirubin per day, whereas the normal production of bilirubin is only 300 mg/day. This excess capacity allows the liver to respond to increased heme degradation with a corresponding increase in conjugation and secretion of bilirubin diglucuronide. However, massive lysis of red blood cells (for example, in patients with sickle cell anemia, *pyruvate kinase* or *glucose 6-phosphate dehydrogenase* deficiency) may produce bilirubin faster than it can be conjugated. Unconjugated bilirubin levels in the blood become elevated, causing jaundice (Figure 21.12A). [Note: More conjugated bilirubin is excreted into the bile, the amount of urobilinogen entering the enterohepatic circulation is increased, and urinary urobilinogen is increased.]

**b. Hepatocellular jaundice:** Damage to liver cells (for example, in patients with cirrhosis or hepatitis) can cause unconjugated bilirubin levels in the blood to increase as a result of decreased conjugation. Urobilinogen is increased in the urine because hepatic damage decreases the enterohepatic circulation of this compound, allowing more to enter the blood, from which it is filtered into the urine. The urine thus darkens, whereas stools may be a pale, clay color. Plasma levels of *AST* and *ALT* (see p. 251) are elevated. [Note: If conjugated bilirubin is not efficiently secreted from the liver into bile (intrahepatic cholestasis), it can diffuse (“leak”) into the blood, causing a conjugated hyperbilirubinemia.]

**c. Obstructive jaundice:** In this instance, jaundice is not caused by overproduction of bilirubin or decreased conjugation, but instead results from obstruction of the bile duct (extrahepatic cholestasis). For example, the presence of a 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, and urine that darkens upon standing. The liver “regurgitates” conjugated bilirubin into the blood

(hyperbilirubinemia). The compound is eventually excreted in the urine. Urinary urobilinogen is absent. [Note: Prolonged obstruction of the bile duct can lead to liver damage and a subsequent rise in unconjugated bilirubin.]

- 2. Jaundice in newborns:** Newborn infants, particularly if premature, often accumulate bilirubin, because the activity of hepatic *bilirubin glucuronyltransferase* is low at birth—it reaches adult levels in about 4 weeks (Figures 21.12B and 21.13). Elevated bilirubin, in excess of the binding capacity of albumin, can diffuse into the basal ganglia and cause toxic encephalopathy (kernicterus). Thus, newborns with significantly elevated bilirubin levels are treated with blue fluorescent light (Figure 21.14), which converts bilirubin to more polar and, hence, water-soluble isomers. These photoisomers can be excreted into the bile without conjugation to glucuronic acid.
- 3. Determination of bilirubin concentration:** Bilirubin is most commonly determined by the van den Bergh reaction, in which diazotized sulfanilic acid reacts with bilirubin to form red azodipyrrroles that are measured colorimetrically. In aqueous solution, the water-soluble, conjugated bilirubin reacts rapidly with the reagent (within one minute), and is said to be “direct-reacting.” The unconjugated bilirubin, which is much less soluble in aqueous solution, reacts more slowly. However, when the reaction is carried out in methanol, both conjugated and unconjugated bilirubin are soluble and react with the reagent, providing the total bilirubin value. The “indirect-reacting” bilirubin, which corresponds to the unconjugated bilirubin, is obtained by subtracting the direct-reacting bilirubin from the total bilirubin. [Note: In normal plasma, only about 4% of the total bilirubin is conjugated or direct-reacting, because most is secreted into bile.]



**Figure 21.13**  
Neonatal jaundice. *GT* = *glucuronyltransferase*.

### III. OTHER NITROGEN-CONTAINING COMPOUNDS

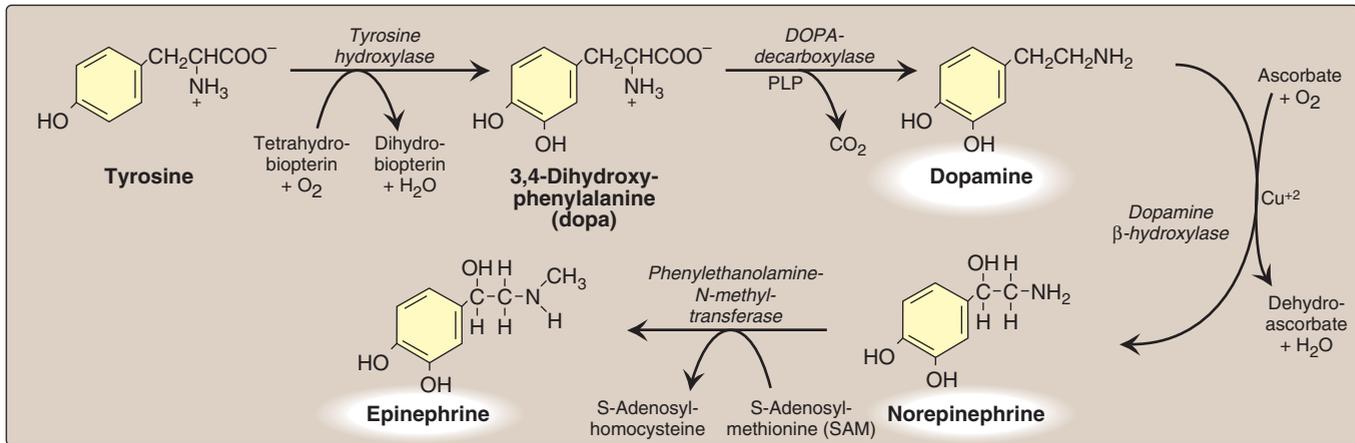
#### A. Catecholamines

Dopamine, norepinephrine, and epinephrine are biologically active (biogenic) amines that are collectively termed catecholamines. Dopamine and norepinephrine are synthesized in the brain and function as neurotransmitters. Norepinephrine is also synthesized in the adrenal medulla, as is epinephrine.

- 1. Function:** Outside the nervous system, norepinephrine and its methylated derivative, epinephrine, are hormone regulators of carbohydrate and lipid metabolism. Norepinephrine and epinephrine are released from storage vesicles in the adrenal medulla in response to fright, exercise, cold, and low levels of blood glucose. They increase the degradation of glycogen and triacylglycerol, as well as increase blood pressure and the output of the heart. These effects are part of a coordinated response to prepare the individual for stress, and are often called the “fight-or-flight” reactions.
- 2. Synthesis of catecholamines:** The catecholamines are synthesized from tyrosine, as shown in Figure 21.15. Tyrosine is first hydroxylated by *tyrosine hydroxylase* to form 3,4-dihydroxyphenyl-



**Figure 21.14**  
Phototherapy in neonatal jaundice

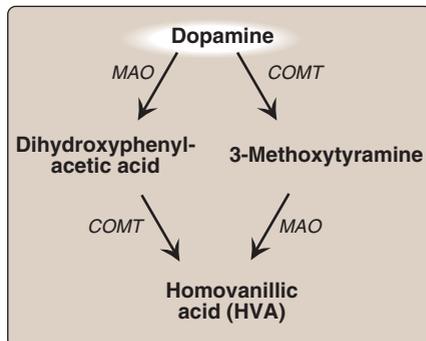
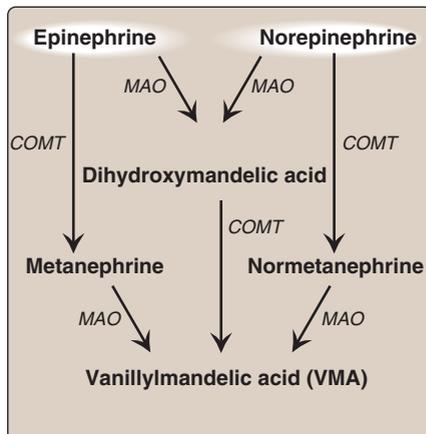


**Figure 21.15**

Synthesis of catecholamines. PLP = pyridoxal phosphate.

alanine (DOPA) in a reaction analogous to that described for the hydroxylation of phenylalanine (see p. 268). The tetrahydrobiopterin (BH<sub>4</sub>)-requiring enzyme is abundant in the central nervous system, the sympathetic ganglia, and the adrenal medulla, and is the rate-limiting step of the pathway. DOPA is decarboxylated in a reaction requiring pyridoxal phosphate (PLP, see p. 378) to form dopamine, which is hydroxylated by *dopamine β-hydroxylase* to yield norepinephrine in a reaction that requires ascorbate (vitamin C) and copper. Epinephrine is formed from norepinephrine by an N-methylation reaction using S-adenosylmethionine (SAM) as the methyl donor (see p. 264).

|| Parkinson disease, a neurodegenerative movement disorder, is due to insufficient dopamine production as a result of the idiopathic loss of dopamine-producing cells in the brain. Administration of L-DOPA (levodopa) is the most common treatment.



**Figure 21.16**

Metabolism of the catecholamines by *catechol-O-methyltransferase* (COMT) and *monoamine oxidase* (MAO).

**3. Degradation of catecholamines:** The catecholamines are inactivated by oxidative deamination catalyzed by *monoamine oxidase* (MAO), and by O-methylation carried out by *catechol-O-methyltransferase* using SAM as the methyl donor (Figure 21.16). The two reactions can occur in either order. The aldehyde products of the MAO reaction are oxidized to the corresponding acids. The metabolic products of these reactions are excreted in the urine as vanillylmandelic acid (VMA) from epinephrine and norepinephrine, and homovanillic acid from dopamine. [Note: VMA is increased with pheochromocytomas, tumors of the adrenal characterized by excessive production of catecholamines.]

**4. MAO inhibitors:** MAO is found in neural and other tissues, such as the intestine and liver. In the neuron, this enzyme oxidatively deaminates and inactivates any excess neurotransmitter molecules (norepinephrine, dopamine, or serotonin) that may

leak out of synaptic vesicles when the neuron is at rest. MAO inhibitors may irreversibly or reversibly inactivate the enzyme, permitting neurotransmitter molecules to escape degradation and, therefore, to both accumulate within the presynaptic neuron and to leak into the synaptic space. This causes activation of norepinephrine and serotonin receptors, and may be responsible for the antidepressant action of these drugs.

### B. Histamine

Histamine is a chemical messenger that mediates a wide range of cellular responses, including allergic and inflammatory reactions, gastric acid secretion, and possibly neurotransmission in parts of the brain. A powerful vasodilator, histamine is formed by decarboxylation of histidine in a reaction requiring PLP (Figure 21.17). It is secreted by mast cells as a result of allergic reactions or trauma. Histamine has no clinical applications, but agents that interfere with the action of histamine have important therapeutic applications.

### C. Serotonin

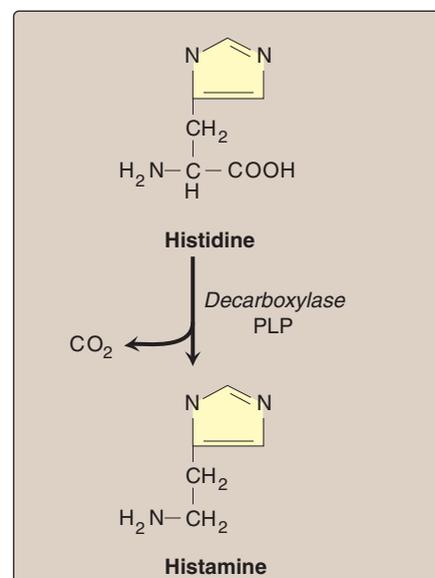
Serotonin, also called 5-hydroxytryptamine (5HT), is synthesized and stored at several sites in the body (Figure 21.18). By far the largest amount of serotonin is found in cells of the intestinal mucosa. Smaller amounts occur in the central nervous system, where it functions as a neurotransmitter, and in platelets. Serotonin is synthesized from tryptophan, which is hydroxylated in a  $BH_4$ -requiring reaction analogous to that catalyzed by *phenylalanine hydroxylase*. The product, 5-hydroxytryptophan, is decarboxylated to serotonin, which is also degraded by MAO. Serotonin has multiple physiologic roles, including pain perception, regulation of sleep, appetite, temperature, blood pressure, cognitive functions, and mood (causes a feeling of well-being). [Note: Serotonin is converted to melatonin in the pineal gland via acetylation and methylation.]

### D. Creatine

Creatine phosphate (also called phosphocreatine), the phosphorylated derivative of creatine found in muscle, is a high-energy compound that provides a small but rapidly mobilized reserve of high-energy phosphates that can be reversibly transferred to ADP (Figure 21.9) to maintain the intracellular level of ATP during the first few minutes of intense muscular contraction. [Note: The amount of creatine phosphate in the body is proportional to the muscle mass.]

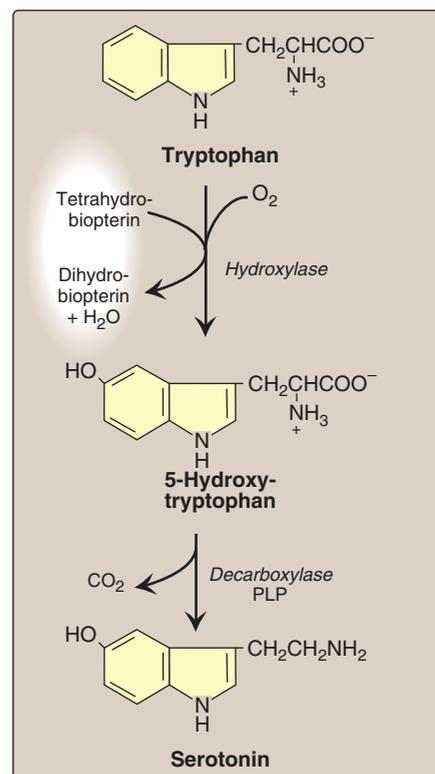
**1. Synthesis:** Creatine is synthesized from glycine and the guanidino group of arginine, plus a methyl group from SAM (see Figure 21.19). Creatine is reversibly phosphorylated to creatine phosphate by *creatine kinase*, using ATP as the phosphate donor. [Note: The presence of *creatine kinase* (MB isozyme) in the plasma is indicative of heart damage, and is used in the diagnosis of myocardial infarction (see p. 65).]

**2. Degradation:** Creatine and creatine phosphate spontaneously cyclize at a slow but constant rate to form creatinine, which is excreted in the urine. The amount of creatinine excreted is propor-



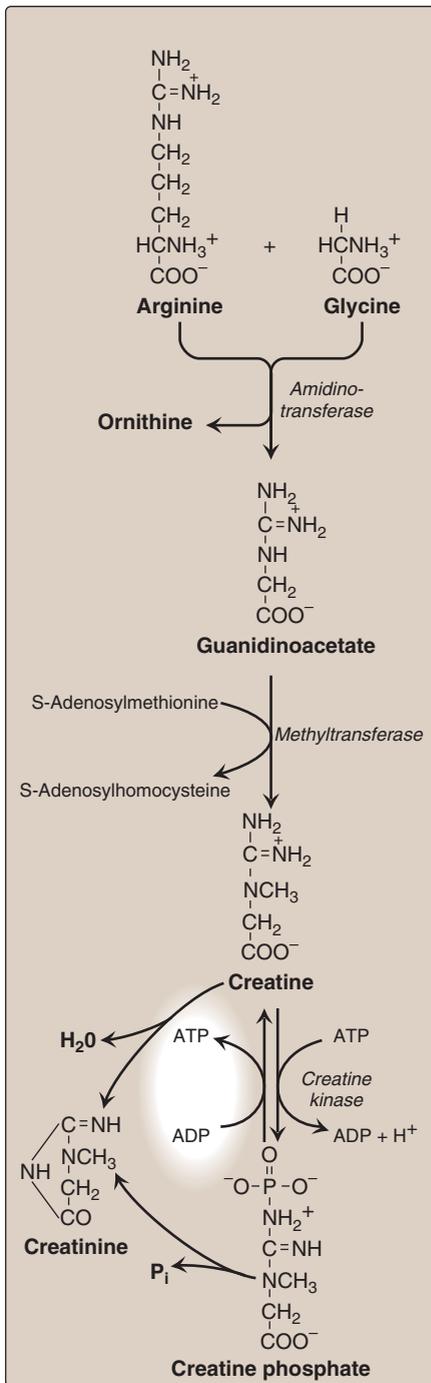
**Figure 21.17**

Biosynthesis of histamine. PLP = pyridoxal phosphate.



**Figure 21.18**

Synthesis of serotonin. PLP = pyridoxal phosphate.



**Figure 21.19**  
Synthesis of creatine.

tional to the total creatine phosphate content of the body, and thus can be used to estimate muscle mass. When muscle mass decreases for any reason (for example, from paralysis or muscular dystrophy), the creatinine content of the urine falls. In addition, any rise in blood creatinine is a sensitive indicator of kidney malfunction, because creatinine normally is rapidly removed from the blood and excreted. A typical adult male excretes about 15 mmol of creatinine per day.

### E. Melanin

Melanin is a pigment that occurs in several tissues, particularly the eye, hair, and skin. It is synthesized from tyrosine in the epidermis by pigment-forming cells called melanocytes. Its function is to protect underlying cells from the harmful effects of sunlight. [Note: A defect in melanin production results in albinism, the most common form being due to defects in copper-containing *tyrosinase* (see p. 273).]

## IV. CHAPTER SUMMARY

Amino acids are precursors of many nitrogen-containing compounds including **porphyrins**, which, in combination with ferrous ( $\text{Fe}^{2+}$ ) iron, form **heme** (Figure 21.20). 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. In the liver, the rate of heme synthesis is highly variable, responding to alterations in the cellular heme pool caused by fluctuating demands for heme proteins. In contrast, heme synthesis in erythroid cells is relatively constant, and is matched to the rate of globin synthesis. **Porphyryn synthesis** start with **glycine** and **succinyl CoA**. The **committed step** in heme synthesis is the formation of  $\delta$ -aminolevulinic acid (ALA). This reaction is catalyzed by **ALA synthase-1** in liver (inhibited by hemin, the oxidized form of heme that accumulates in the cell when heme is being underutilized) and ALA synthase-2 in erythroid tissues (regulated by iron). **Porphyrias** are caused by inherited or acquired defects in heme synthesis, resulting in the accumulation and increased excretion of porphyrins or porphyrin precursors. With few exceptions, **porphyrias** are inherited as **autosomal dominant** disorders. **Degradation** of hemoproteins occurs in the **reticuloendothelial system**, particularly in the **liver** and **spleen**. The first step in the degradation of heme is the production of the green pigment **biliverdin**, which is subsequently reduced to **bilirubin**. Bilirubin is transported to the liver, where its solubility is increased by the addition of two molecules of **glucuronic acid**. Bilirubin diglucuronide is transported into the **bile canaliculi**, where it is first hydrolyzed and reduced by bacteria in the gut to yield **urobilinogen**, then oxidized by intestinal bacteria to **stercobilin**. **Jaundice** refers to the yellow color of the skin and sclera that is caused by deposition of bilirubin, secondary to increased bilirubin levels in the blood. Three commonly encountered type of jaundice are **hemolytic jaundice**, **obstructive jaundice**, and **hepatocellular jaundice**. Other important N-containing compounds derived from amino acids include the **catecholamines** (dopamine, norepinephrine, and epinephrine), **creatine**, **histamine**, **serotonin**, and **melanin**.

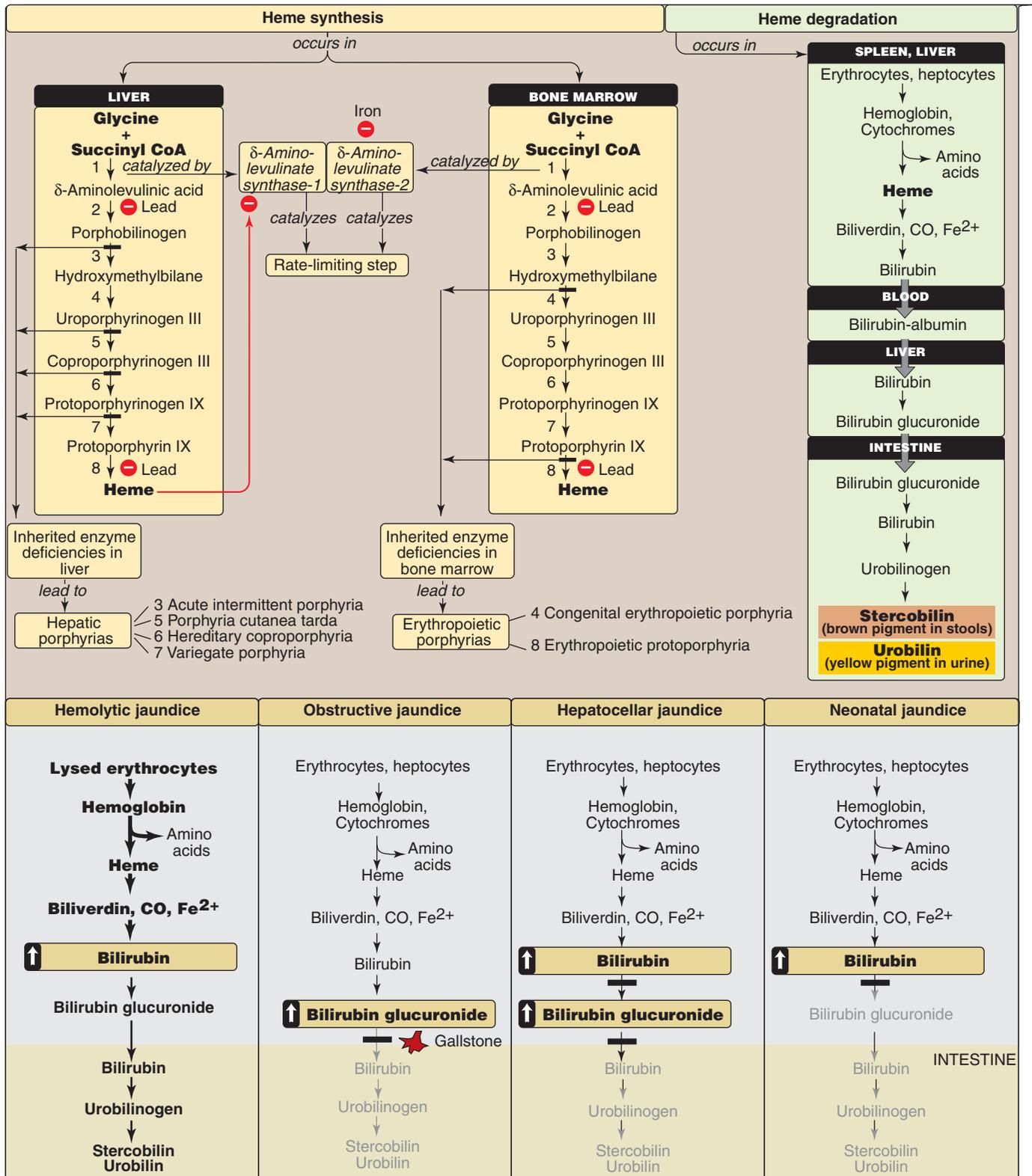


Figure 21.20

Key concept map for heme metabolism. — = Block in the pathway.

## Study Questions

Choose the ONE best answer.

21.1  $\delta$ -Aminolevulinic acid synthase activity:

- A. in liver is frequently decreased in individuals treated with drugs, such as the barbiturate phenobarbital.
- B. catalyzes a rate-limiting reaction in porphyrin biosynthesis.
- C. requires the coenzyme biotin.
- D. is strongly inhibited by heavy metal ions such as lead.
- E. occurs in the cytosol.

21.2 The catabolism of hemoglobin:

- A. occurs in red blood cells.
- B. involves the oxidative cleavage of the porphyrin ring.
- C. results in the liberation of carbon dioxide.
- D. results in the formation of protoporphyrinogen.
- E. is the sole source of bilirubin.

21.3 A 50-year-old man presented with painful blisters on the backs of his hands. He was a golf instructor, and indicated that the blisters had erupted shortly after the golfing season began. He did not have recent exposure to poison ivy or sumac, new soaps or detergents, or new medications. He denied having previous episodes of blistering. He had partial complex seizure disorder that had begun about three years earlier after a head injury. The patient had been taking phenytoin—his only medication—since the onset of the seizure disorder. He admitted to an average weekly ethanol intake of about eighteen 12-oz cans of beer. The patient's urine was reddish orange. Cultures obtained from skin lesions failed to grow organisms. A 24-hour urine collection showed elevated uroporphyrin (1,000 mg; normal, <27mg). The most likely presumptive diagnosis is:

- A. porphyria cutanea tarda.
- B. acute intermittent porphyria.
- C. hereditary coproporphyrin.
- D. congenital erythropoietic porphyria.
- E. erythropoietic protoporphyria.

21.4 A 10-year-old boy is referred to a specialist because of skin that blisters easily, urine that darkens on standing, and stained teeth. Lab studies are remarkable for high levels of uroporphyrin I and coproporphyrin I in plasma, with uroporphyrin I being present in the urine. The most likely biochemical pathology in this case is:

- A. deficiency of ALA synthase.
- B. deficiency of bilirubin glucuronyltransferase.
- C. deficiency of uroporphyrinogen III synthase.
- D. down-regulation of tyrosinase.
- E. inhibition of ALA dehydratase by lead.

Correct answer = B. The activity of  $\delta$ -aminolevulinic acid synthase controls the rate of porphyrin synthesis. The hepatic form of the enzyme is increased in patients treated with certain drugs, and requires pyridoxal phosphate as a coenzyme. Another enzyme in the pathway ( $\delta$ -aminolevulinic acid dehydratase) is extremely sensitive to the presence of heavy metals.

Correct answer = B. The cyclic heme molecule is oxidatively cleaved to form biliverdin. The catabolism occurs in the cells of the reticulo-endothelial system, particularly the spleen, and results in the liberation of carbon monoxide. Protoporphyrinogen is an intermediate in the synthesis, not degradation, of heme. Cytochromes and other non-hemoglobin heme-proteins are also precursors of bilirubin.

Correct answer = A. The disease is associated with a deficiency in uroporphyrinogen decarboxylase, but clinical expression of the enzyme deficiency is influenced by hepatic injury caused by iron overload, chronic ethanol consumption, and the presence of hepatitis B or C and HIV infections. Exposure to sunlight can also be a precipitating factor. Clinical onset is typically during the fourth or fifth decade of life. Porphyrin accumulation leads to cutaneous symptoms and urine that is red to brown. Treatment of the patient's seizure disorder with phenytoin caused increased synthesis of ALA synthase, and, therefore, of uroporphyrinogen, the substrate of the deficient enzyme. The laboratory and clinical findings are inconsistent with other porphyrias.

Correct answer = C. A deficiency of uroporphyrinogen III synthase results in accumulation of hydroxymethylbilane and the spontaneous conversion of this substrate to porphyrins of the Type I series. A deficiency of ALA synthase or inhibition of ALA dehydratase by lead would not allow the synthesis of porphobilinogen, the first pyrrole product in the heme biosynthetic pathway, and thus would not result in uro- or coproporphyrin synthesis. Deficiency of the glucuronyltransferase would not present with the systems described, and lab studies would be remarkable for an elevation of unconjugated bilirubin. Down-regulation of tyrosinase would result in decreased pigmentation.