Lippincott® Illustrated Reviews: Biochemistry, 8e >

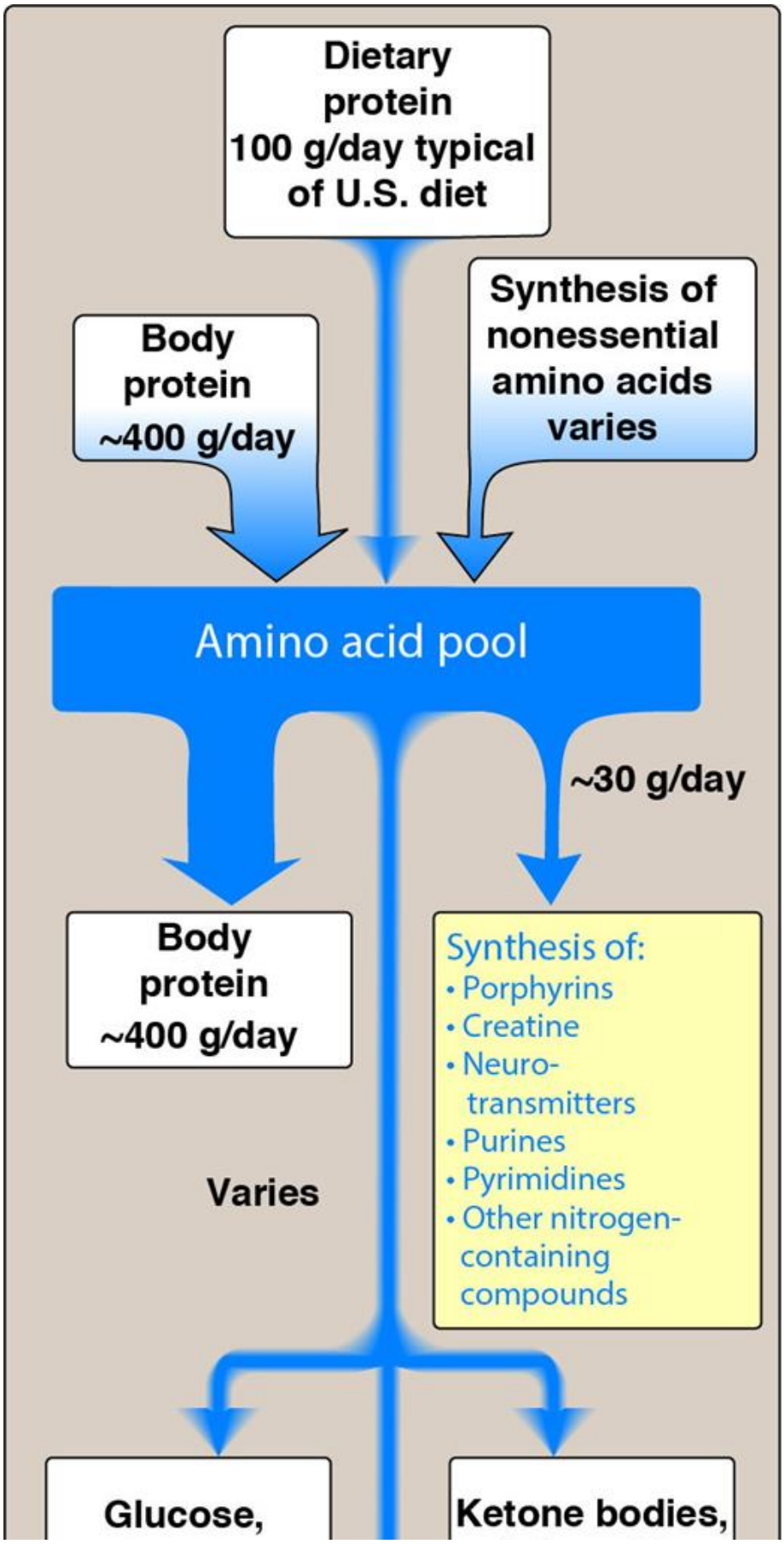
21: Amino Acids: Conversion to Specialized Products

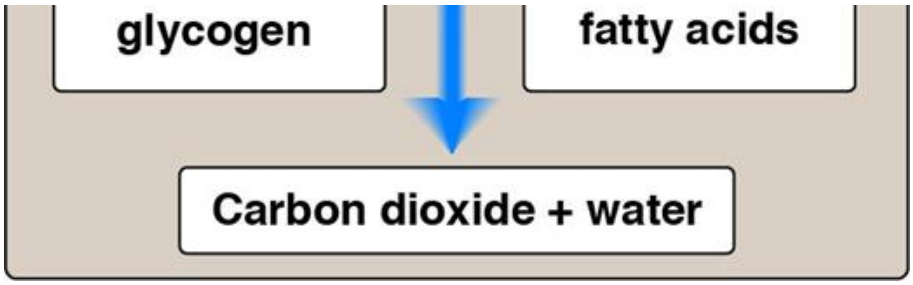
Overview

In addition to serving as building blocks for proteins, amino acids are precursors of many nitrogen (N)-containing compounds that have important physiologic functions (Fig. 21.1). These molecules include porphyrins, neurotransmitters, hormones, purines, and pyrimidines. (Note: See p. 166 for the synthesis of nitric oxide from arginine.)

FIGURE 21.1

Amino acids as precursors of nitrogen-containing compounds.





Porphyrin Metabolism

Porphyrins are cyclic compounds that readily bind metal ions, usually ferrous (Fe^{2+}) or ferric (Fe^{3+}) iron. The most prevalent metalloporphyrin in humans is heme, which consists of one Fe^{2+} coordinated in the center of the tetrapyrrole ring of protoporphyrin IX (see p. 310). Heme is the prosthetic group for hemoglobin (Hb), myoglobin, the cytochromes, including the cytochrome P450 (CYP) monooxygenase system, catalase, nitric oxide synthase, and peroxidase. These heme proteins are rapidly synthesized and degraded. For example, 6 to 7 g of Hb is synthesized each day to replace heme lost through the normal turnover of erythrocytes. The synthesis and degradation of the associated porphyrins and recycling of the iron are coordinated with the turnover of heme proteins.

Structure

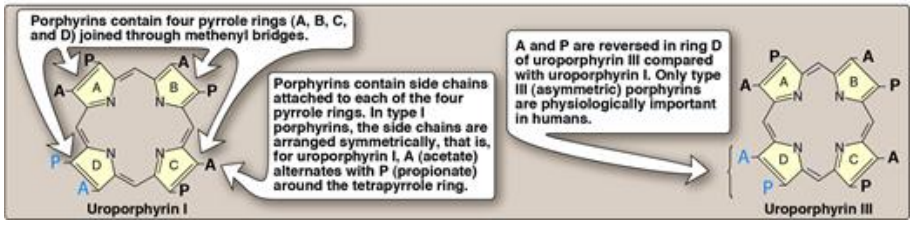
Porphyrins are cyclic planar molecules formed by the linkage of four pyrrole rings through methenyl bridges (Fig. 21.2). Three structural features of these molecules are relevant to understanding their medical significance.

Side chains

Different porphyrins vary in the nature of the side chains attached to each of the four pyrrole rings. Uroporphyrin contains acetate ($-CH_2-COO-$) and propionate ($-CH_2-CH_2-COO-$) side chains; coproporphyrin contains methyl ($-CH_3$) and propionate groups; and protoporphyrin IX (and heme b, the most common heme) contains vinyl ($-CH = CH_2$), methyl, and propionate groups. (Note: The methyl and vinyl groups are produced by decarboxylation of acetate and propionate side chains, respectively.)

FIGURE 21.2

Structures of uroporphyrin I and uroporphyrin III.



Side chain distribution

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 (Fig. 21.2), are physiologically important in humans. (Note: Protoporphyrin IX is a member of the type III series.)

Porphyrinogens

These porphyrin precursors (e.g., uroporphyrinogen) exist in a chemically reduced, colorless form and serve as intermediates between porphobilinogen (PBG) and the oxidized, colored protoporphyrins in heme biosynthesis.

Heme biosynthesis

The major sites of heme biosynthesis are the liver and the erythrocyte-producing cells of the bone marrow. In the liver, which synthesizes a number of heme proteins (particularly the CYP proteins), 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, which are active in Hb synthesis, is relatively constant and is matched to the rate of globin synthesis. (Note: Over 85% of all heme synthesis occurs in erythroid tissue. Mature red blood cells (RBCs) lack mitochondria and are unable to synthesize heme.) 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. (Note: Fig. 21.8 summarizes heme synthesis.)

δ-Aminolevulinic acid formation

All the carbon and nitrogen atoms of the porphyrin molecule are provided by glycine (a nonessential amino acid) and succinyl coenzyme A (a tricarboxylic acid cycle intermediate) that condense to form δ-aminolevulinic acid (ALA) in a reaction catalyzed by ALA synthase ([ALAS], Fig. 21.3). This reaction requires pyridoxal phosphate ([PLP], see p. 428) as a coenzyme and is the committed and rate-limiting step in porphyrin biosynthesis. (Note: There are two ALAS isoforms, each produced by different genes and controlled by different mechanisms. ALAS1 is found in all tissues, whereas ALAS2 is erythroid specific. Loss-of-function mutations in ALAS2 result in X-linked sideroblastic anemia and iron overload.)

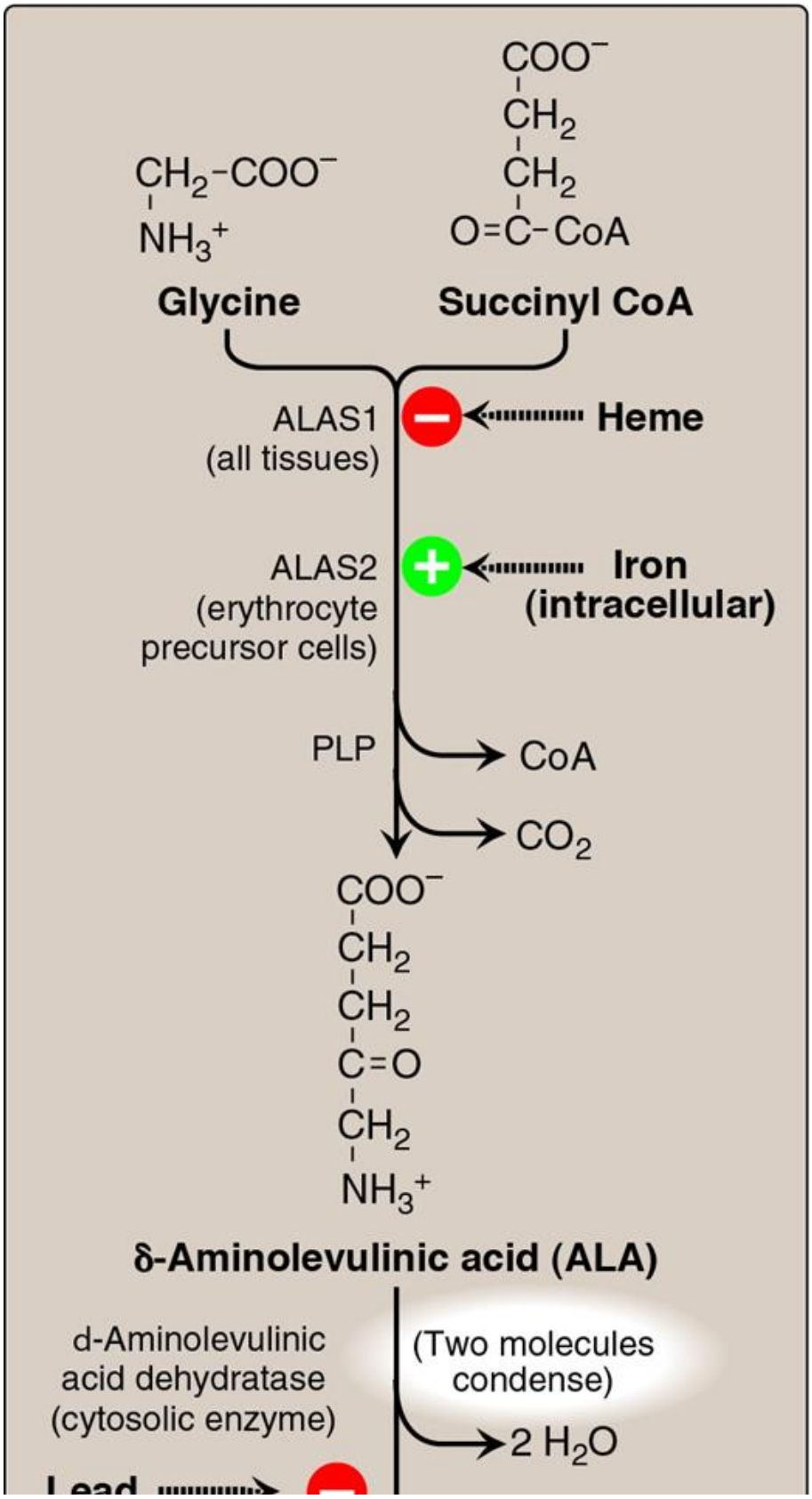
Heme (hemin) effects

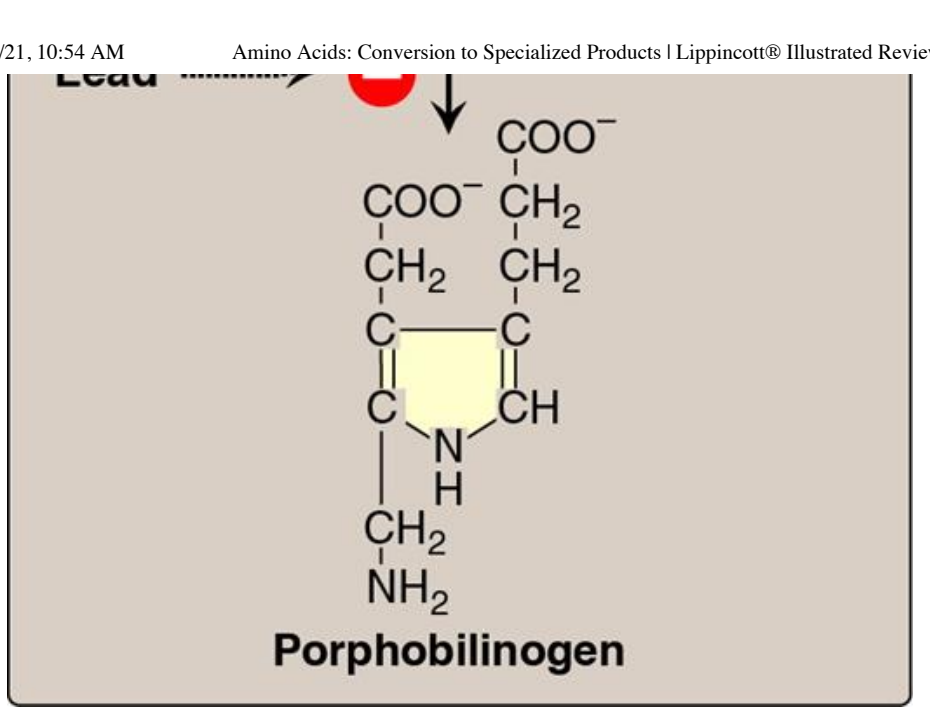
When porphyrin production exceeds the availability of the apoproteins that require it, heme accumulates and is converted to hemin by the oxidation of Fe^{2+} to Fe^{3+}. Hemin decreases the amount (and, thus, the activity) of ALAS1 by repressing transcription of its gene, increasing degradation of its messenger RNA, and decreasing import of the enzyme into mitochondria. (Note: In erythroid cells, ALAS2 is controlled by the availability of intracellular iron [see p. 525].)

FIGURE 21.3

Pathway of porphyrin synthesis: Formation of porphobilinogen.

(Note: ALAS1 is regulated by heme; ALAS2 is regulated by iron.) ALAS, δ-aminolevulinic acid synthase; CoA, coenzyme A; CO_2, carbon dioxide; PLP, pyridoxal phosphate. (Continued in Figs. 21.4 and 21.5.)





Drug effects

Administration of any of a large number of drugs (and various environmental xenobiotic chemicals, present in certain foods, cosmetics, and commercial products) results in a significant increase in hepatic ALAS1 activity. These molecules are metabolized by the microsomal CYP monooxygenase system, a heme protein oxidase system found in the liver (see p. 164). In response to these drugs, the synthesis of CYP proteins increases, leading to an enhanced consumption of heme, a component of these proteins. This, in turn, causes a decrease in the concentration of free or unbound heme in liver cells. The lower intracellular concentration of unbound heme leads to an increase in the synthesis of ALAS1 and prompts a corresponding increase in the synthesis of ALA.

Porphobilinogen formation

The cytosolic condensation of two ALA to form PBG by zinc-containing ALA dehydratase (PBG synthase) is extremely sensitive to inhibition by heavy metal ions (e.g., lead) that replace the zinc (Fig. 21.3). This inhibition is, in part, responsible for the elevation in ALA and the anemia caused by lead poisoning.

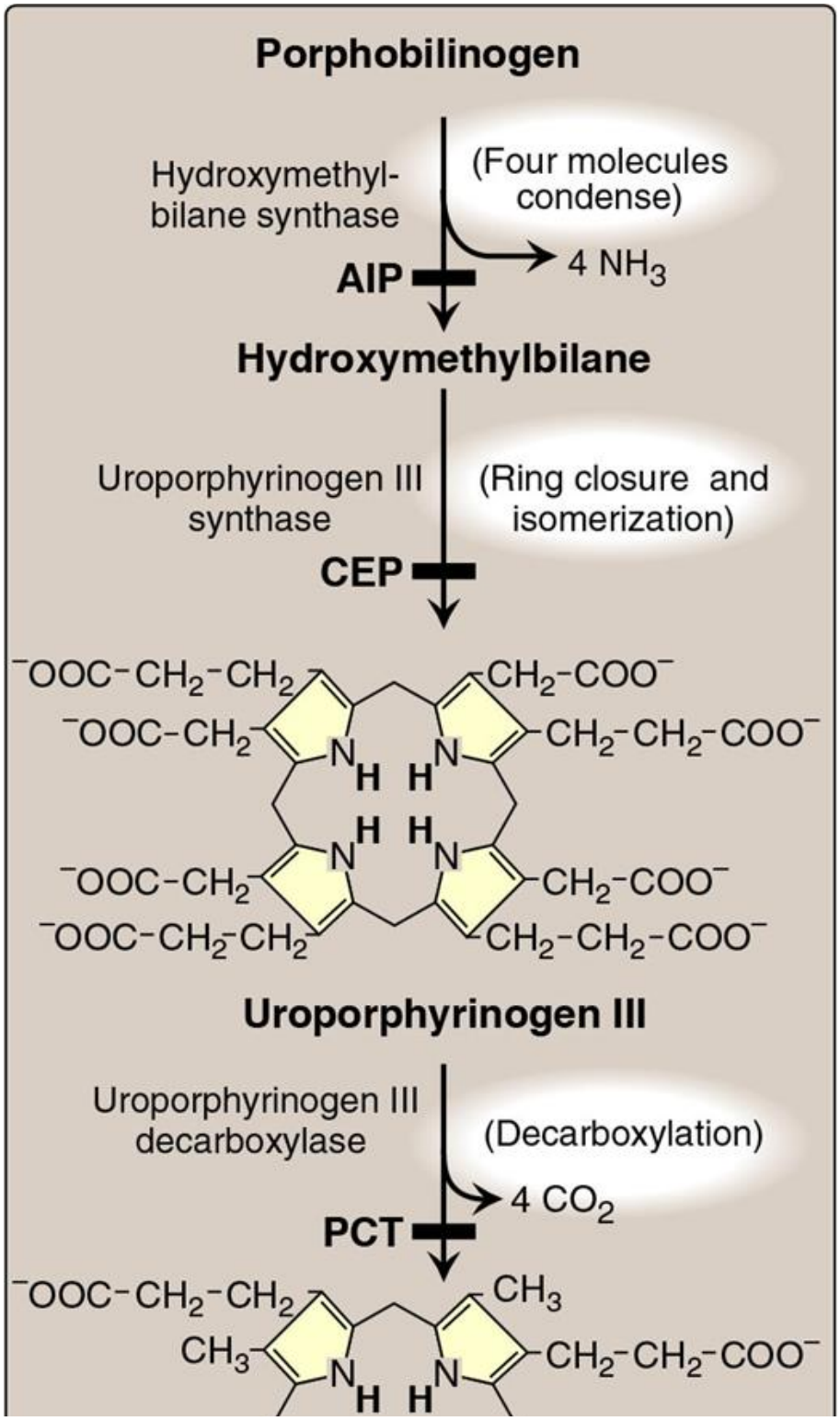
Uroporphyrinogen formation

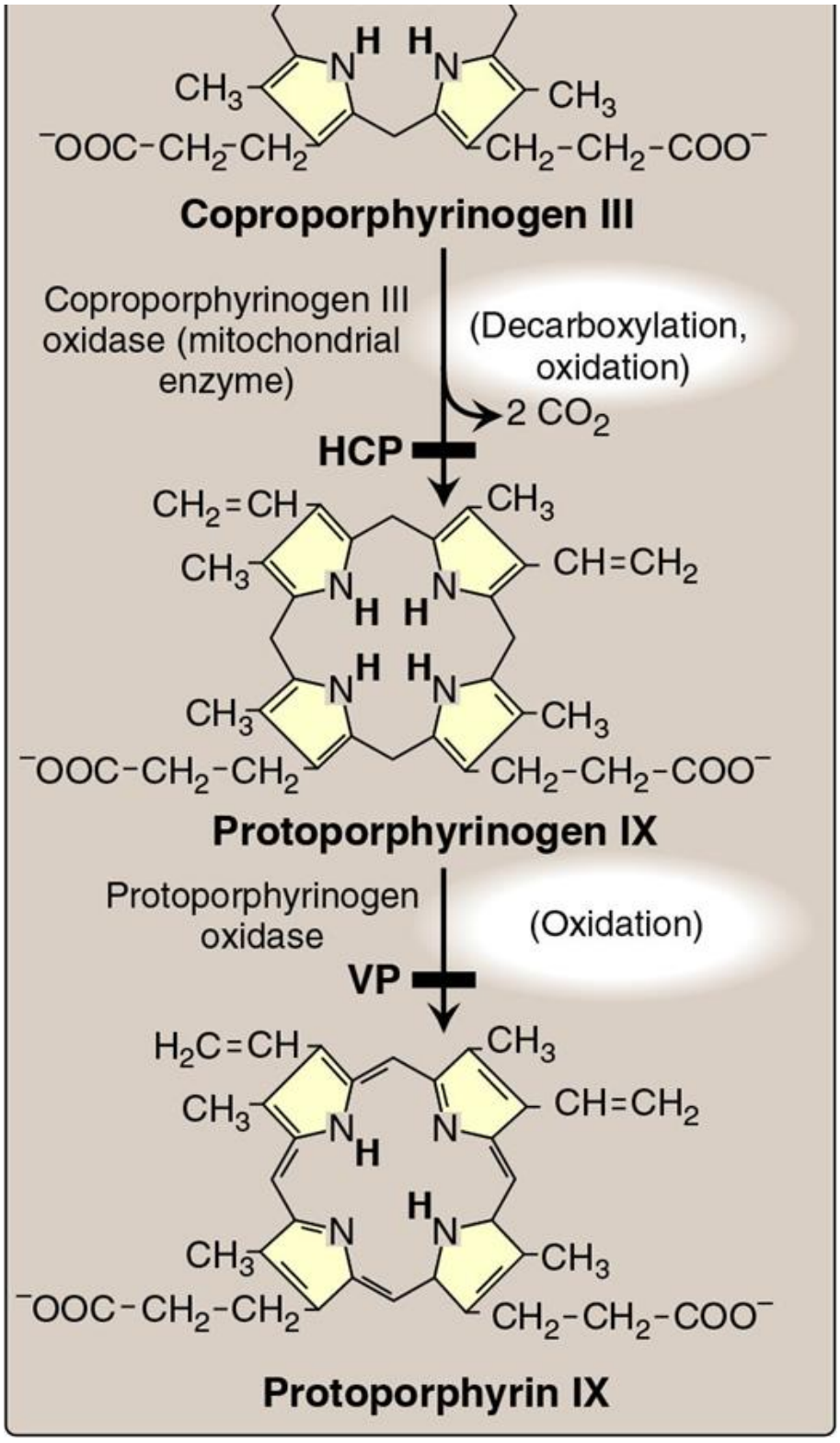
Condensation of four PBG molecules, catalyzed by hydroxymethylbilane synthase, produces the linear tetrapyrrole hydroxymethylbilane. A deficiency in this enzyme results in acute intermittent porphyria (AIP, Fig. 21.4, also see p. 313 and 21.8 for more details for different forms of porphyrias). Uroporphyrinogen III synthase cyclizes and isomerizes hydroxymethylbilane to produce the asymmetric uroporphyrinogen III. A deficiency in this enzyme results in congenital erythropoietic porphyria (CEP). Uroporphyrinogen III undergoes decarboxylation of its acetate groups by uroporphyrinogen III decarboxylase (UROD), generating coproporphyrinogen III. A deficiency in this enzyme results in porphyria cutanea tarda (PCT). These three reactions occur in the cytosol.

FIGURE 21.4

Pathway of porphyrin synthesis: formation of protoporphyrin IX.

(Continued from Fig. 21.3.) The prefixes uro- (urine) and copro- (feces) reflect initial sites of discovery. Enzyme deficiencies in porphyrias are indicated with black bars. AIP = acute intermittent porphyria; CEP = congenital erythropoietic porphyria; PCT = porphyria cutanea tarda; HCP = hereditary coproporphyria; VP = variegate porphyria. (Note: Deficiency in uroporphyrinogen III synthase prevents isomerization but not ring closure, resulting in production of type I porphyrins.)





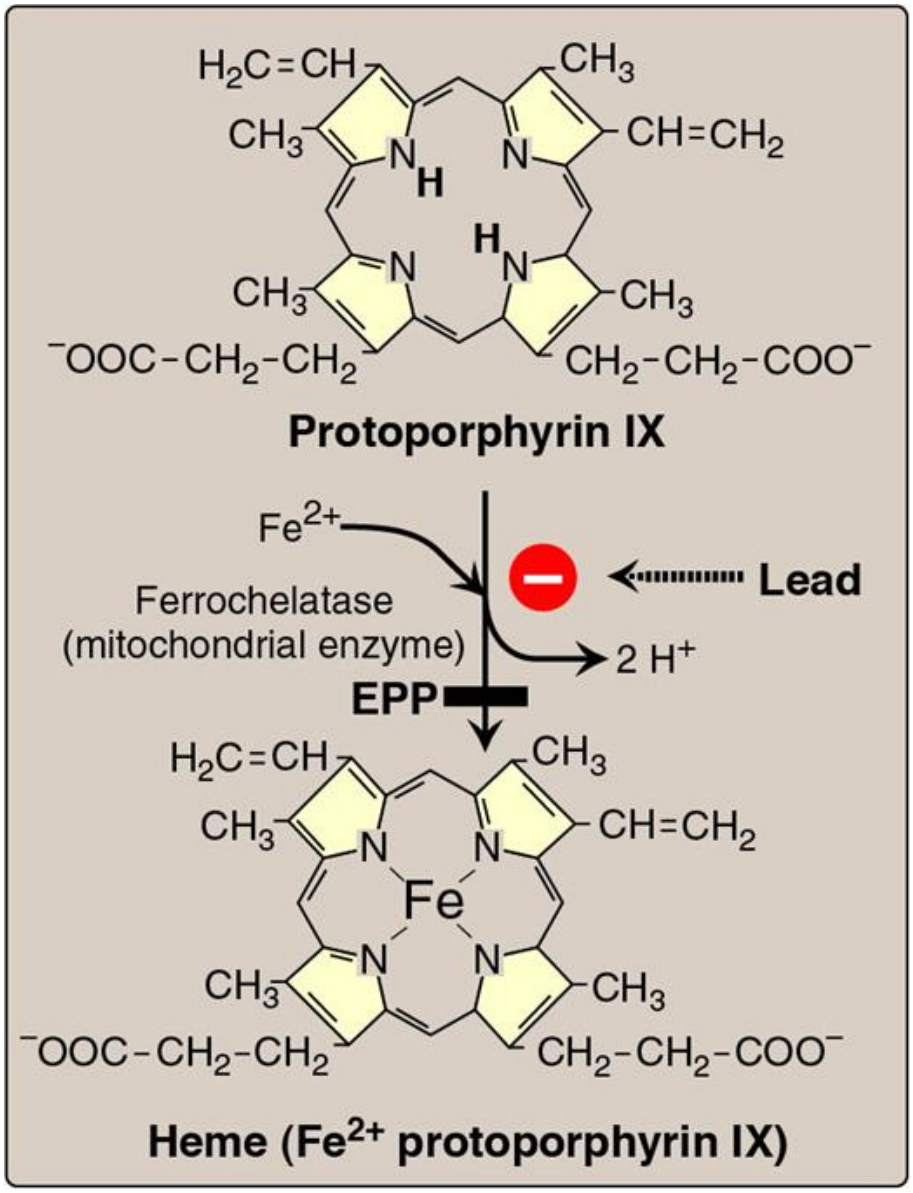
Heme formation

Coproporphyrinogen III enters the mitochondrion, and two propionate side chains are decarboxylated by coproporphyrinogen III oxidase to vinyl groups generating protoporphyrinogen IX. A deficiency in this enzyme results in hereditary coproporphyria (HCP). Protoporphyrinogen IX is oxidized by protoporphyrinogen oxidase to protoporphyrin IX. A deficiency in this enzyme results in variegate porphyria (VP). The introduction of iron (as Fe^{2+}) into protoporphyrin IX produces heme. This step can occur spontaneously, but the rate is enhanced by ferrochelatase, an enzyme that, like ALA dehydratase, is inhibited by lead (Fig. 21.5). A deficiency in this enzyme results in erythropoietic protoporphyria (EPP).

FIGURE 21.5

Pathway of porphyrin synthesis: formation of heme b.

(Continued from Figs. 21.3 and 21.4.) Fe^{2+} = ferrous iron. Enzyme deficiency in porphyria is indicated with *black bar*; EPP = erythropoietic protoporphyria.



CLINICAL APPLICATION 21.1

Lead Poisoning

Lead poisoning is a buildup of lead in the body over a period of months to years. Common sources for lead include exposure to lead-based paints and paint dust or flakes common in older buildings; lead in household plumbing pipes may also contaminate drinking water. Exposure can occur through inhalation, contact with the skin or mucous membranes, or ingestion. Lead has a sweet taste, and ingestion exposure is of special concern for infants and toddlers. Symptoms of lead poisoning may include developmental delays, learning disabilities and low IQ, abdominal pain, constipation, neurologic changes, and irritability. Very high lead levels can be fatal. Lead inhibits ALA dehydratase and ferrochelatase, both enzymes involved in the synthesis of heme, and therefore causes a decrease in heme synthesis. Further, high levels of lead impair iron utilization. This results in increased use of zinc (instead of iron) as substrate for chelation to protoporphyrin IX by ferrochelatase. Consequently, patients with lead poisoning may present with anemia and elevated levels of zinc protoporphyrin. The increase in ALA can be toxic to neurons. Lead can also cross the blood–brain barrier and is neurotoxic. The usual treatment is to remove the source of exposure to the lead contaminant, but in cases of severe lead poisoning (greater than 45 µg/dl measured in the serum), divalent chelators such as succimer (DMSA, 2,3-dimercaptosuccinic acid), calcium disodium ethylenediaminetetraacetic acid (EDTA) or others may be used to remove excess lead ions from the blood.

Porphyrias

Porphyrias are rare, inherited (or sometimes acquired) defects in heme synthesis, resulting in the accumulation and increased excretion of porphyrins or porphyrin precursors (Fig. 21.8). (Note: Inherited porphyrias are autosomal-dominant (AD) or autosomal-recessive (AR) disorders.) 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, derived from the Greek for purple, refers to the red-blue color caused by pigment-like porphyrins in the urine of some patients with defects in heme synthesis.)

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 (i.e., their skin itches and burns [pruritus] when exposed to sunlight). (Note: Photosensitivity is a result of the oxidation of colorless porphyrinogens to colored porphyrins, which are photosensitizing molecules thought to participate in the formation of superoxide radicals from oxygen. These radicals can oxidatively damage membranes and cause the release of destructive enzymes from lysosomes.)

Chronic hepatic porphyria

PCT, the most common porphyria, is a chronic disease of the liver. The disease is associated with severe deficiency of UROD, but clinical expression of the deficiency is influenced by various factors, such as hepatic iron overload, exposure to sunlight, alcohol ingestion, estrogen therapy, and the presence of hepatitis B or C or HIV infections. (Note: Mutations to UROD are found in only 20% of affected individuals. Inheritance is AD.) Clinical onset is typically during the fourth or fifth decade of life. Porphyrin accumulation leads to cutaneous symptoms (Fig. 21.6) as well as urine that is red to brown in natural light (Fig. 21.7) and pink to red in fluorescent light.

FIGURE 21.6

Skin eruptions in a patient with porphyria cutanea tarda.

Image provided by Stedman's.

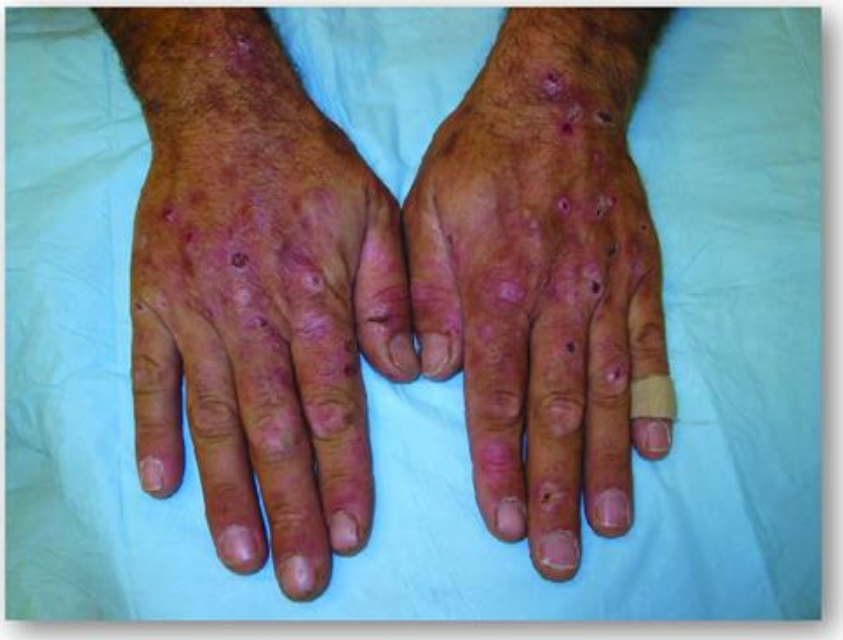
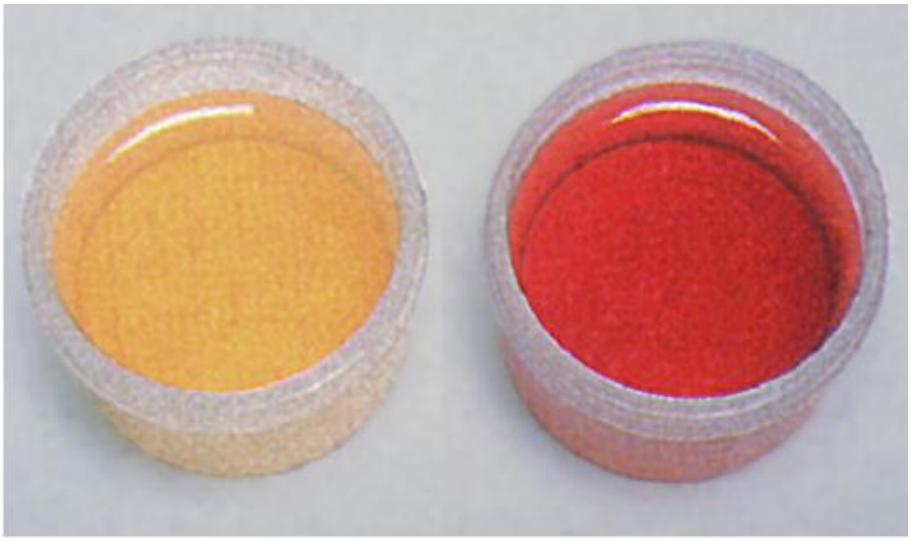


FIGURE 21.7

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

Rich MW. Porphyria cutanea tarda. *Postgrad Med*. 1999;105:208–214.



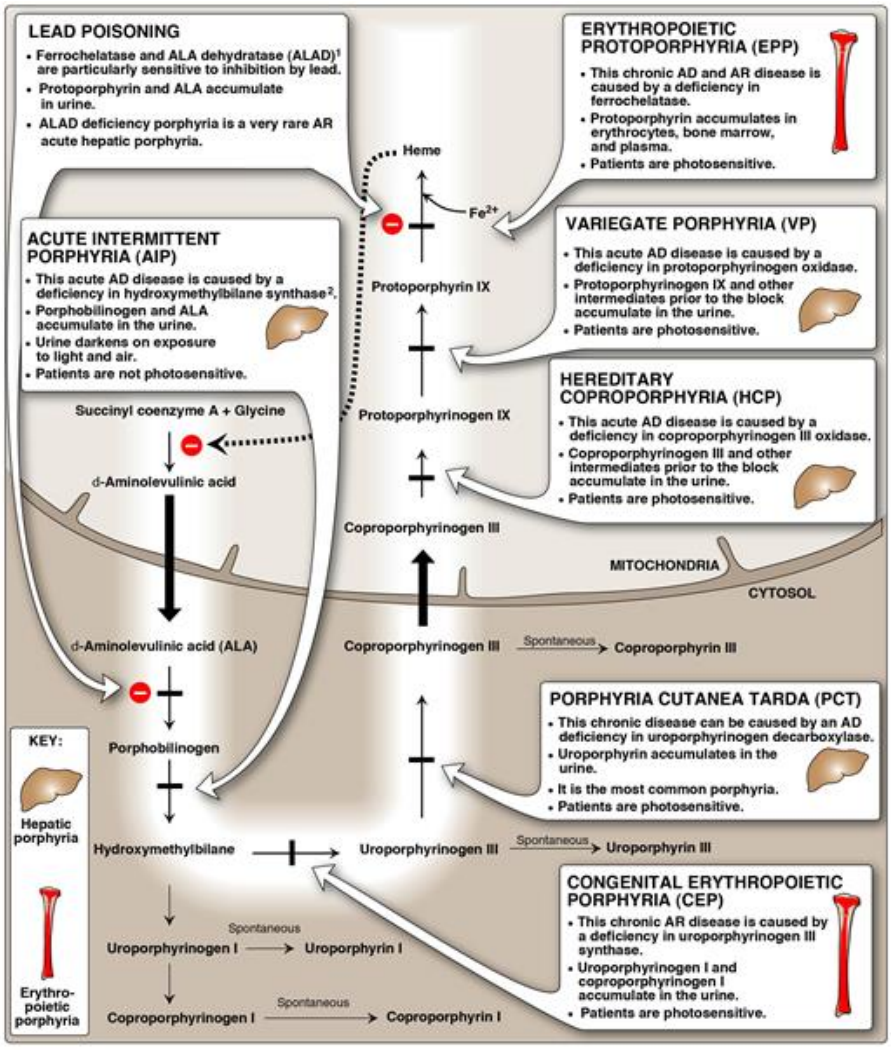
Acute hepatic porphyrias

Acute hepatic porphyrias (ALA dehydratase–deficiency porphyria, AIP, HCP, and VP) are characterized by acute attacks of gastrointestinal (GI), neuropsychiatric, and motor symptoms that may be accompanied by photosensitivity (Fig. 21.8). Porphyrias leading to accumulation of ALA and PBG, such as AIP, cause abdominal pain and neuropsychiatric disturbances, ranging from anxiety to delirium. Symptoms of the acute hepatic porphyrias are often precipitated by use of drugs, such as barbiturates and ethanol, which induce the synthesis of the heme-containing CYP microsomal drug-oxidation system. This further decreases the amount of available heme, which, in turn, promotes increased synthesis of ALAS1.

FIGURE 21.8

Summary of heme synthesis.

[1]Also referred to as porphobilinogen synthase. [2]Also referred to as porphobilinogen deaminase. (Note: Symptomatic deficiencies in ALA synthase-1 [ALAS1] are unknown. Deficiencies in X-linked ALAS2 result in an anemia.) ALA = δ-aminolevulinic acid; AD = autosomal dominant; AR = autosomal recessive; Fe = iron.



Erythropoietic porphyrias

The chronic erythropoietic porphyrias (CEP and EPP) cause photosensitivity characterized by skin rashes and blisters that appear in early childhood (Fig. 21.8).

Increased δ-aminolevulinic acid synthase activity

One common feature of the hepatic porphyrias is decreased synthesis of heme. In the liver, heme normally functions as a repressor of the ALAS1 gene. Therefore, the absence of this end product results in an increase in the synthesis of ALAS1 (derepression/activation). 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.

Treatment

During acute porphyria attacks, patients require medical support, particularly treatment for pain and vomiting. The severity of acute symptoms of the porphyrias can be diminished by intravenous injection of hemin and glucose. Hemin consists of a protoporphyrin structure with a ferric iron (Fe^{3+}) coordinated with a chloride ion. Hemin administration reduces the deficit of porphyrins. This in turn decreases the synthesis of ALAS1 and minimizes the production of toxic porphyrin intermediates. High doses of glucose can also decrease porphyrin biosynthesis in the liver. These treatments are particularly effective to treat AIP and other acute porphyrias. Protection from sunlight, ingestion of β-carotene (provitamin A; see p. 432) that scavenges free radicals, and phlebotomy (removes porphyrins) are helpful in porphyrias with photosensitivity.

Heme degradation

After ~120 days in the circulation, RBCs are taken up and degraded by the mononuclear phagocyte system (MPS), particularly in the liver and spleen (Fig. 21.9). Approximately 85% of heme destined for degradation comes from senescent RBCs (Fig. 21.10). The remainder is from the degradation of heme proteins other than Hb.

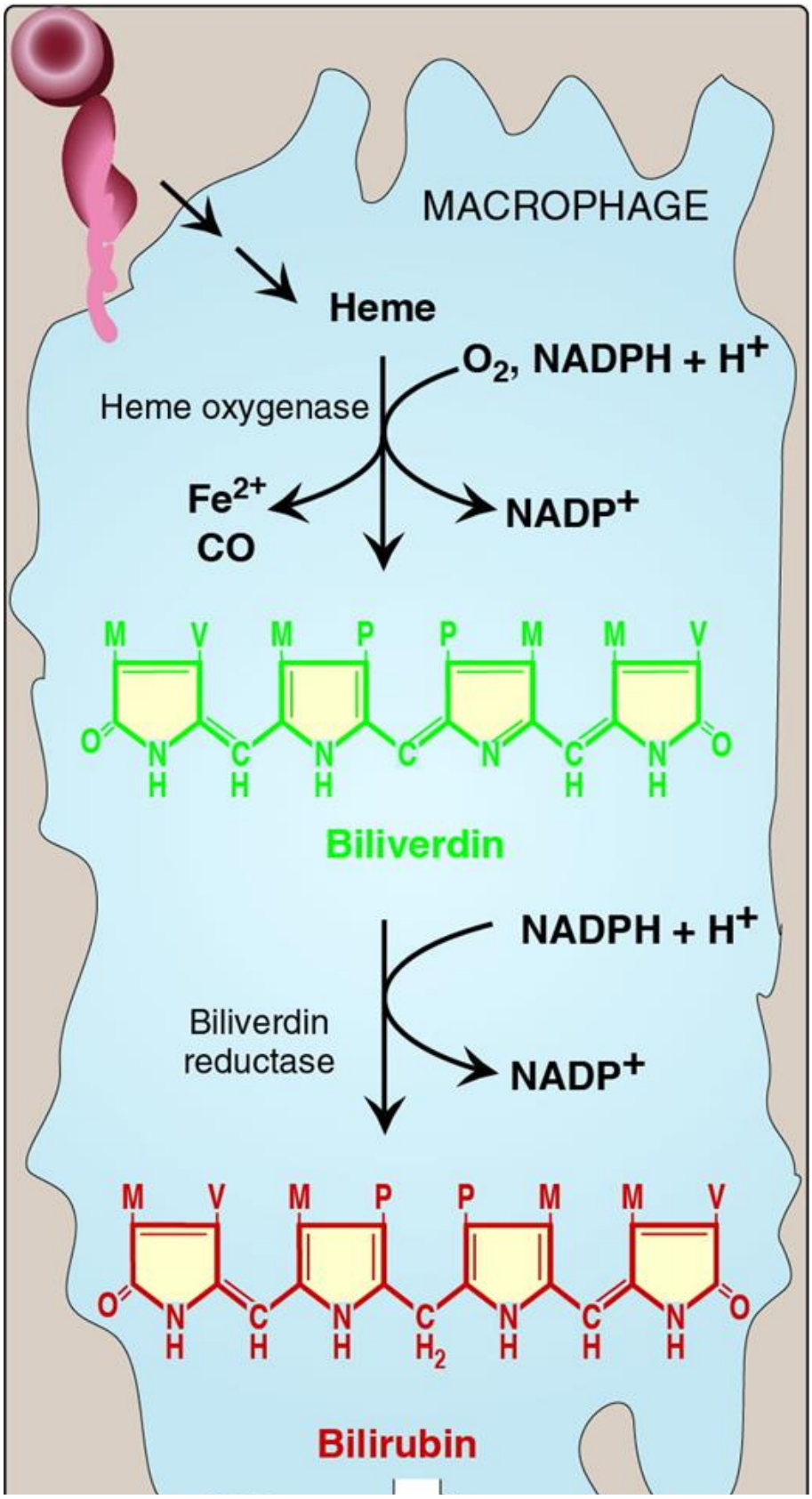
Bilirubin formation

The first step in the degradation of heme is catalyzed by microsomal heme oxygenase in macrophages of the MPS. In the presence of nicotinamide adenine dinucleotide phosphate and oxygen, the enzyme catalyzes three successive oxygenations that result in opening of the porphyrin ring (converting cyclic heme to linear biliverdin), production of carbon monoxide (CO), and release of Fe^{2+} (Fig. 21.9). (Note: The CO has biologic function, acting as a signaling molecule and anti-inflammatory. Iron is discussed in Chapter 29.) Biliverdin, a green pigment, 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.)

FIGURE 21.9

Formation of bilirubin from heme and its conversion to bilirubin diglucuronide.

UDP = uridine diphosphate; Fe = iron; CO = carbon monoxide; NADP(H) = nicotinamide adenine dinucleotide phosphate.



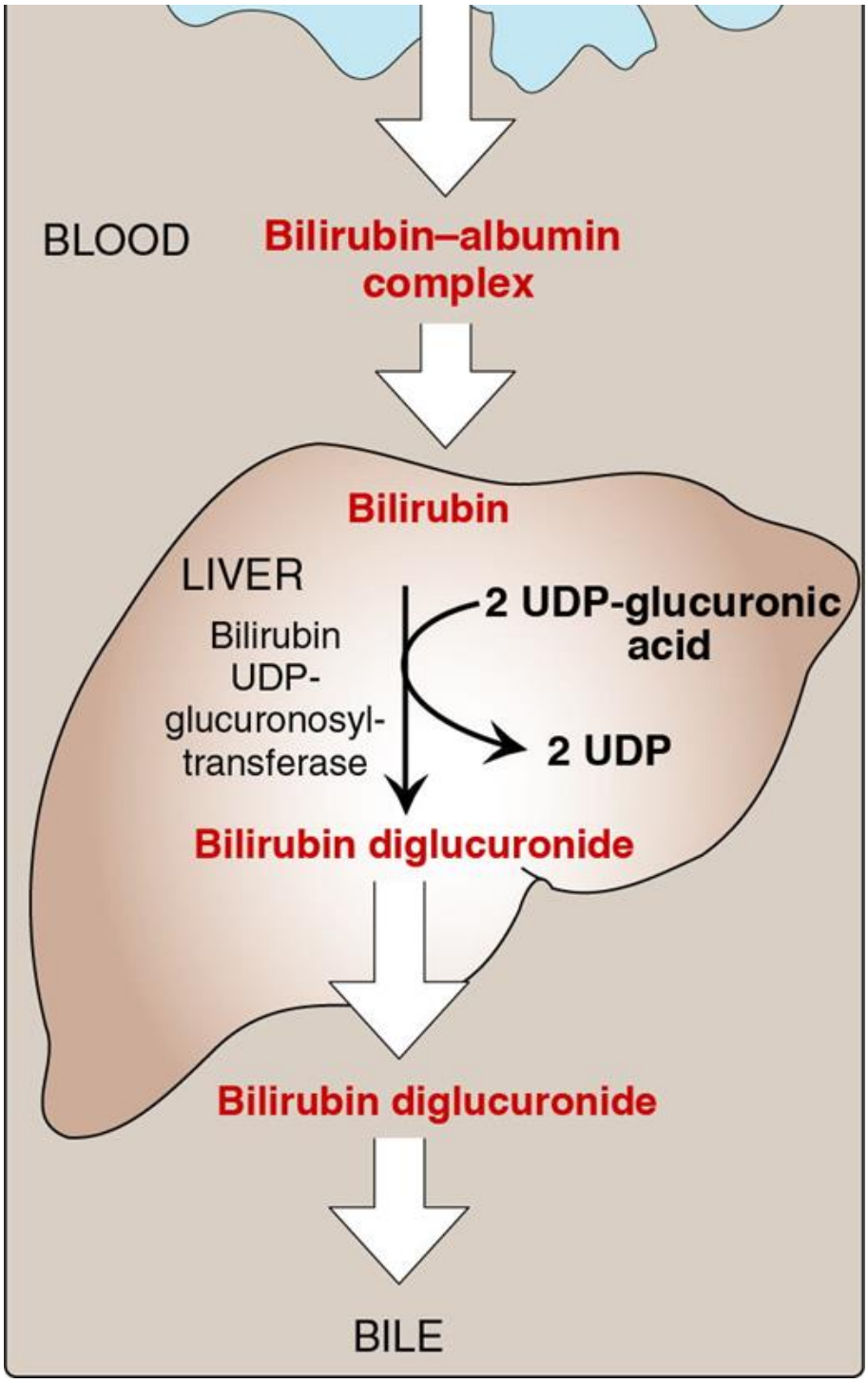
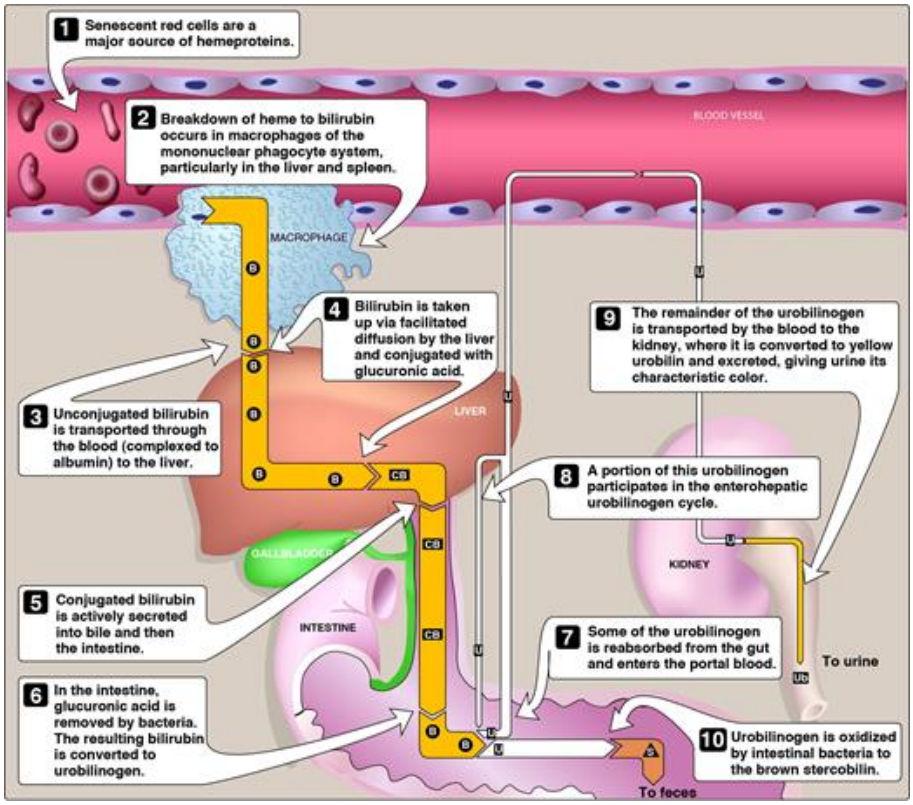

BLOOD
Bilirubin–albumin complex
Bilirubin
LIVER
Bilirubin UDP-glucuronosyl-transferase
2 UDP-glucuronic acid
2 UDP
Bilirubin diglucuronide
Bilirubin diglucuronide
BILE

FIGURE 21.10

Catabolism of heme.

B = bilirubin; CB = conjugated bilirubin; U = urobilinogen; Ub = urobilin; S = stercobilin.



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

Bilirubin uptake by the liver

Because bilirubin is only slightly soluble in plasma, it is transported through blood to the liver by binding noncovalently to albumin. (Note: Certain anionic drugs, such as salicylates and sulfonamides, can displace bilirubin from albumin, permitting bilirubin to enter the central nervous system [CNS]. This causes the potential for neural damage in infants [see p. 317].) Bilirubin dissociates from the carrier albumin molecule, enters a hepatocyte via facilitated diffusion, and binds to intracellular proteins, particularly the protein ligandin.

Bilirubin diglucuronide formation

In the hepatocyte, bilirubin solubility is increased by the sequential addition of two molecules of glucuronic acid in a process called conjugation. The reactions are catalyzed by microsomal bilirubin UDP-glucuronosyltransferase (bilirubin UGT) using uridine diphosphate (UDP)-glucuronic acid as the glucuronate donor. The bilirubin diglucuronide product is referred to as conjugated bilirubin (CB). (Note: Varying degrees of deficiency of bilirubin UGT result in Crigler–Najjar I and II and Gilbert syndrome, with Crigler–Najjar I being the most severe.)

Bilirubin secretion into bile

CB 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 rare deficiency in the protein required for transport of CB out of the liver results in Dubin–Johnson syndrome.) Unconjugated bilirubin (UCB) is normally not secreted into bile.

Urobilin formation in the intestine

CB is hydrolyzed and reduced by gut bacteria to yield urobilinogen, a colorless compound. Most of the urobilinogen is further oxidized by bacteria to stercobilin, which gives feces the characteristic brown color. However, some is reabsorbed from the gut and enters the portal blood. A portion of 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.

Jaundice

Jaundice (or, icterus) refers to the yellow color of skin, nail beds, and sclerae (whites of the eyes) caused by bilirubin deposition, secondary to increased bilirubin levels in the blood (hyperbilirubinemia) as shown in Figure 21.11. Although not a disease, jaundice is usually a symptom of an underlying disorder. (Note: Blood bilirubin levels are normally ≤1 mg/dl. Jaundice is seen at 2 to 3 mg/dl.)

Types

Jaundice can be classified into three major types 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 (prehepatic)

The liver has the capacity to conjugate and excrete >3,000 mg of bilirubin/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 CB. However, extensive hemolysis (e.g., in patients with sickle cell anemia or deficiency of pyruvate kinase or glucose 6-phosphate dehydrogenase) may produce bilirubin faster than it can be conjugated. UCB levels in the blood become elevated (unconjugated hyperbilirubinemia), causing jaundice (Fig. 21.12A). Due to hemolysis, CB levels may be greatly elevated to the upper most range of normal hepatic capacity and excreted into the bile. The amount of urobilinogen entering the enterohepatic circulation is also increased, as well as urinary urobilinogen. Still, CB, urobilinogen, stercobilin, and urobilin levels are seen at the higher side of their normal ranges. In hemolytic jaundice, only UCB levels are abnormally high in the blood.

FIGURE 21.11

Jaundiced patient with the sclerae of his eyes appearing yellow.

From Zay Nyi Nyi/Shutterstock.com.

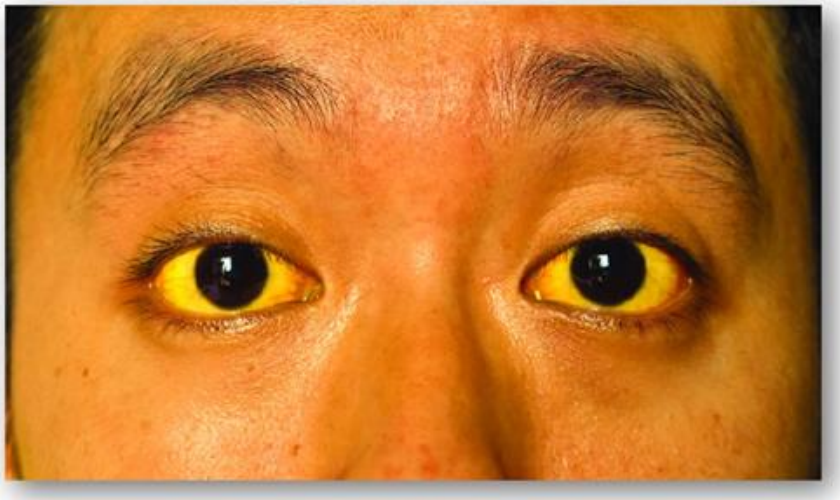
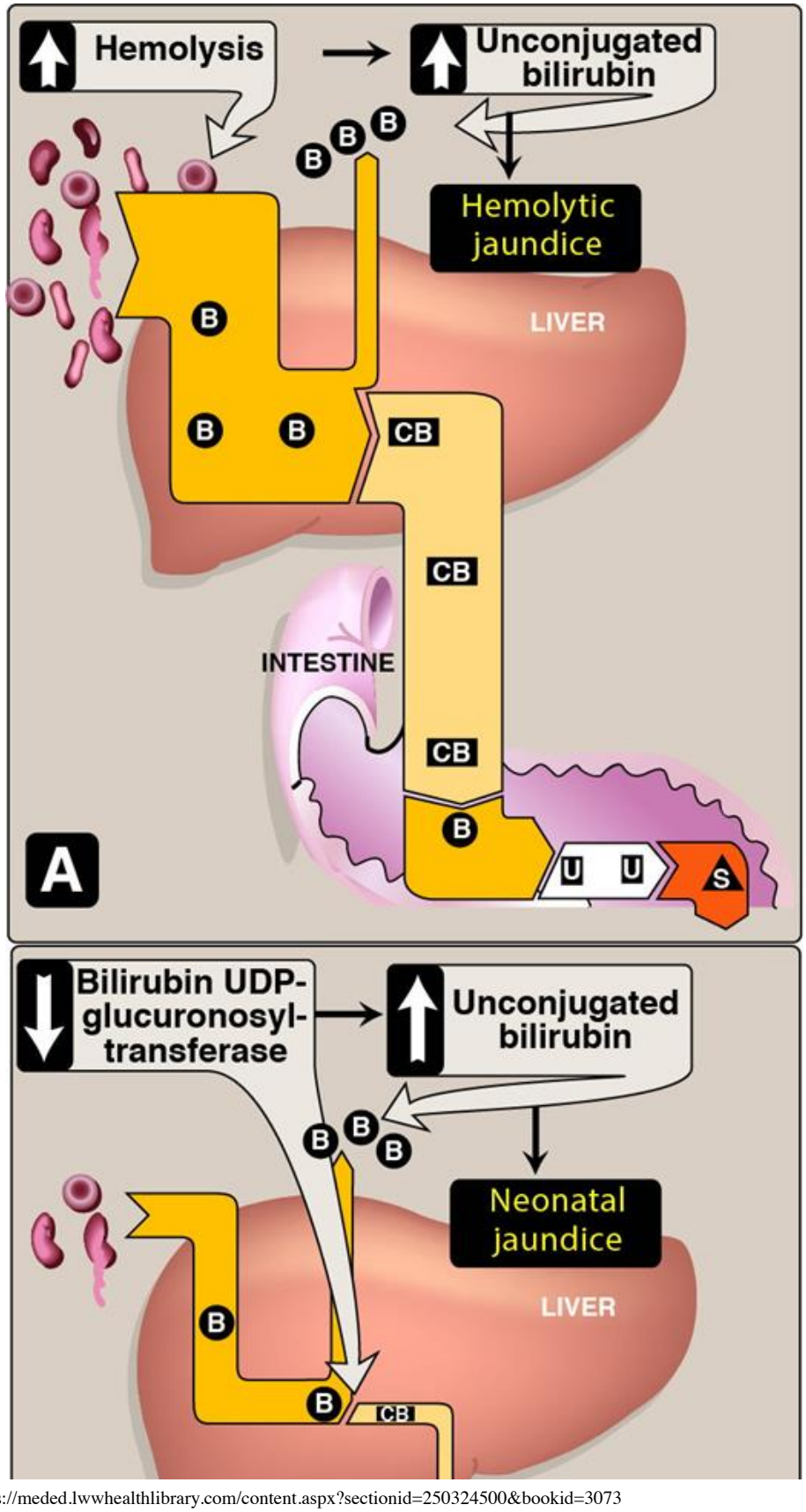
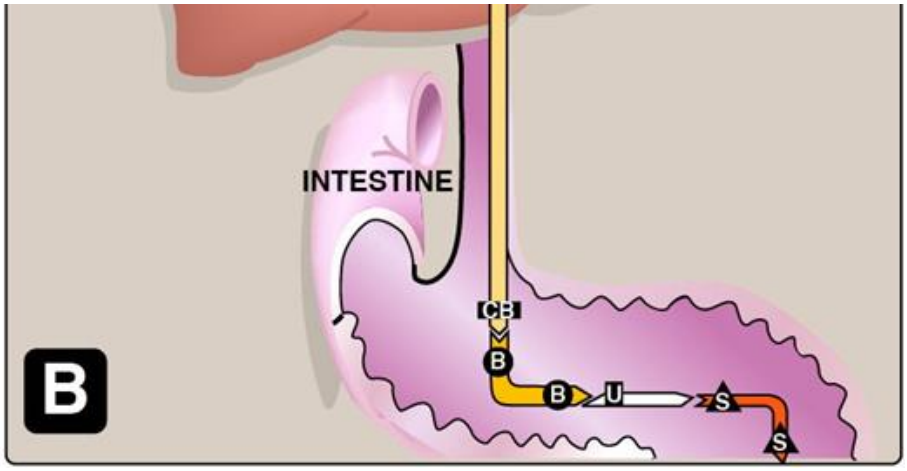


FIGURE 21.12

Alterations in the metabolism of heme.

A: Hemolytic jaundice. **B** : Neonatal jaundice. CB = conjugated bilirubin; B = bilirubin; U = urobilinogen; S = stercobilin; UDP = uridine diphosphate.





Hepatocellular (hepatic)

Damage to liver cells (e.g., in patients with cirrhosis or hepatitis) can cause unconjugated hyperbilirubinemia 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 consequently darkens, whereas stools may be a pale, clay color. Plasma levels of alanine and aspartate transaminases (ALT and AST, respectively; see p. 276) are elevated. If CB is made but is not efficiently secreted from the liver into bile (intrahepatic cholestasis), it can leak into the blood (regurgitation), causing a conjugated hyperbilirubinemia. In hepatic jaundice, both UCB and CB levels are abnormally elevated in the blood.

Obstructive (posthepatic)

In this instance, jaundice is not caused by overproduction of bilirubin or decreased conjugation but, instead, results from obstruction of the common bile duct (extrahepatic cholestasis). For example, the presence of a tumor or bile stones may block the duct, preventing passage of CB into the intestine. Patients with obstructive jaundice experience GI pain and nausea and produce stools that are a pale, clay color. The CB regurgitates into the blood (conjugated hyperbilirubinemia). The CB is eventually excreted in the urine (which darkens over time) and is referred to as urinary bilirubin. Urinary urobilinogen is absent.

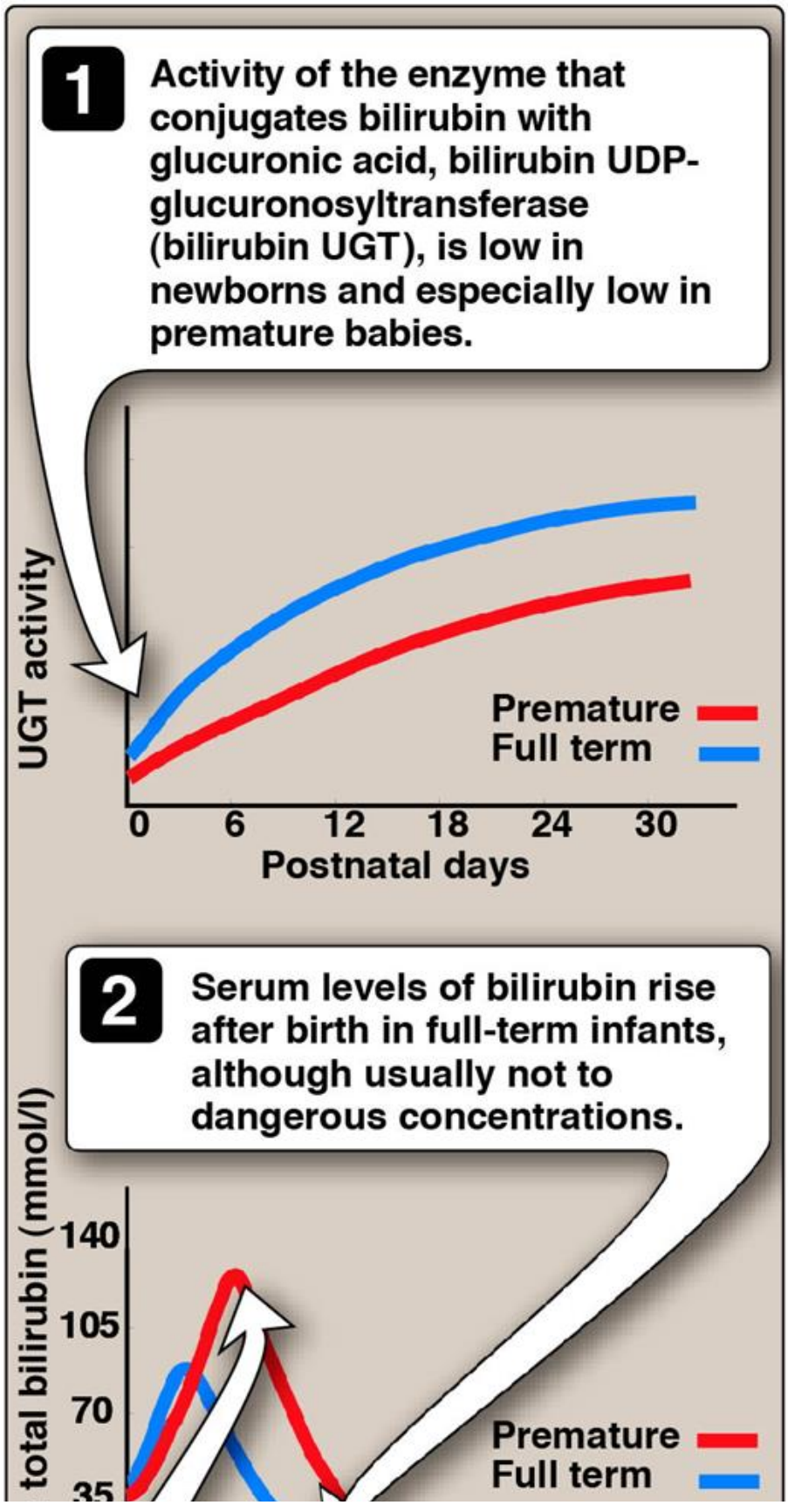
Jaundice in newborns

Most newborn infants (60% of full term and 80% of preterm) show a rise in UCB in the first postnatal week (and a transient, physiologic jaundice) because the activity of hepatic bilirubin UGT is low at birth (it reaches adult levels in about 4 weeks), as shown in Figures 21.12B and Figure 21.13. Elevated UCB, in excess of the binding capacity of albumin (20 to 25 mg/dl), can diffuse into the basal ganglia, causing toxic encephalopathy (kernicterus) and a pathologic jaundice. Therefore, newborns with significantly elevated bilirubin levels are treated with blue fluorescent light (phototherapy), as shown in Figure 21.14, which converts bilirubin to more polar and, therefore, water-soluble isomers. These photoisomers can be excreted into the bile without conjugation to glucuronic acid. (Note: Because of solubility differences, only UCB crosses the blood–brain barrier, and only CB appears in urine.)

FIGURE 21.13

Neonatal jaundice.

UDP = uridine diphosphate.



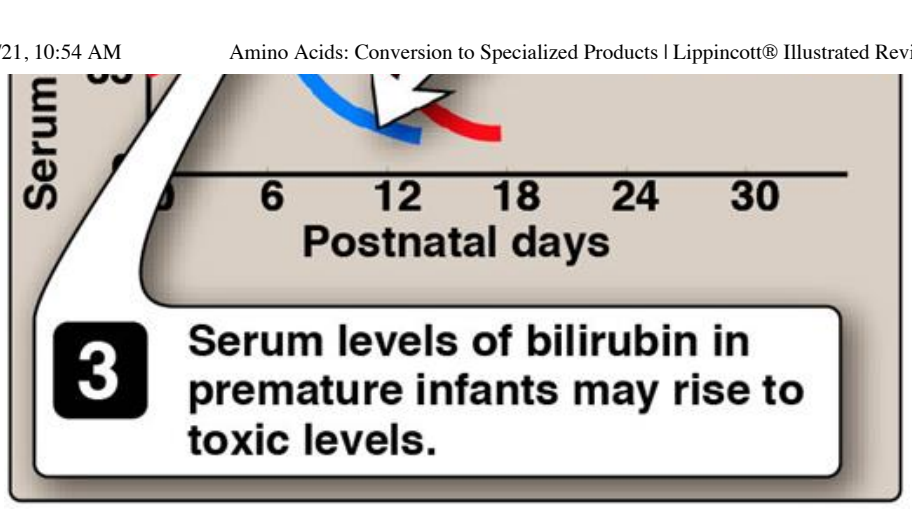
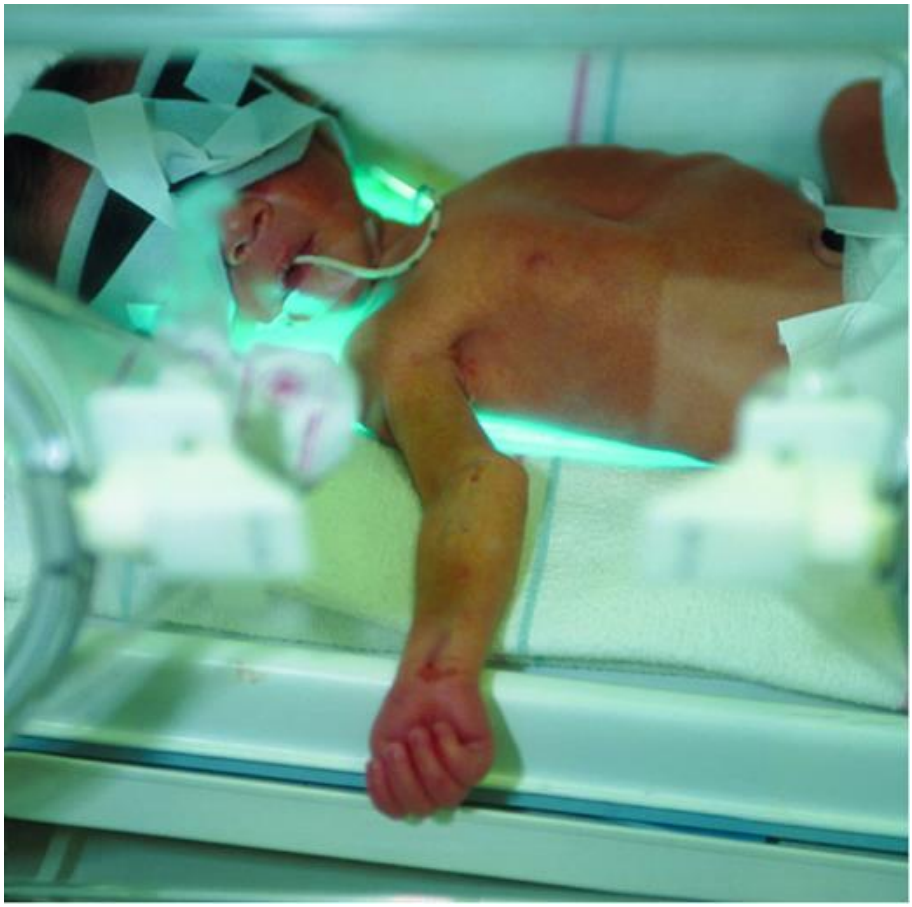


FIGURE 21.14

Phototherapy in neonatal jaundice.

Phototake.



Bilirubin measurement

Bilirubin is commonly measured by the van den Bergh reaction, in which diazotized sulfanilic acid reacts with bilirubin to form red azodipyrroles that are measured colorimetrically. In aqueous solution, the water-soluble CB reacts rapidly with the reagent (within 1 minute) and is said to be direct reacting. The UCB, which is much less soluble in aqueous solution, reacts more slowly. However, when the reaction is carried out in methanol, both CB and UCB are soluble and react with the reagent, providing the total bilirubin value. The indirect-reacting bilirubin, which corresponds to the UCB, is obtained by subtracting the direct-reacting bilirubin from the total bilirubin. (Note: In normal plasma, only ~4% of the total bilirubin is conjugated, or direct reacting, because most is secreted into bile.)

Other Nitrogen-Containing Compounds

Catecholamines

Dopamine, norepinephrine (NE), and epinephrine (or, adrenaline) are biologically active (biogenic) amines that are collectively termed catecholamines. Dopamine and NE are synthesized in the brain and function as neurotransmitters. Epinephrine is synthesized from NE in the adrenal medulla.

Function

Outside the CNS, NE and its methylated derivative, epinephrine, are hormone regulators of carbohydrate and lipid metabolism. NE 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.

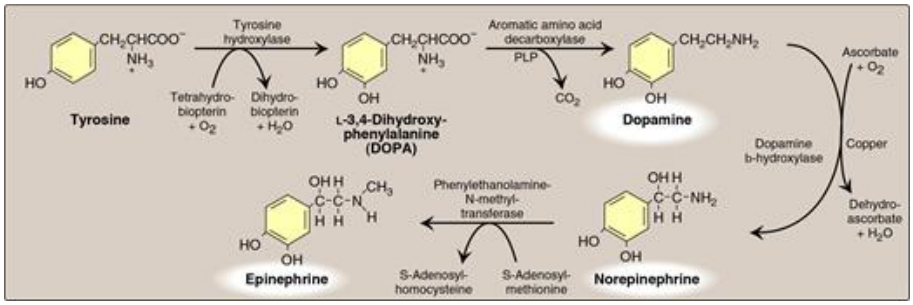
Synthesis

The catecholamines are synthesized from tyrosine, as shown in Figure 21.15. Tyrosine is first hydroxylated by tyrosine hydroxylase to form L-3,4-dihydroxyphenylalanine (DOPA, a catechol) in a reaction analogous to that described for the hydroxylation of phenylalanine (see p. 292). The tetrahydrobiopterin (BH_4)-requiring enzyme is abundant in the CNS, the sympathetic ganglia, and the adrenal medulla, and it catalyzes the rate-limiting step of the pathway. DOPA is then decarboxylated in a reaction catalyzed by DOPA decarboxylase (DDC) and requiring PLP to form dopamine (the first catecholamine in the pathway). Dopamine is next hydroxylated by dopamine β-hydroxylase to yield NE in a reaction that requires ascorbic acid (vitamin C) and copper. Epinephrine is formed from NE by an N-methylation reaction using S-adenosylmethionine (SAM) as the methyl donor (see p. 293).

FIGURE 21.15

Synthesis of catecholamines.

(Note: Catechols have two adjacent hydroxyl groups.) PLP = pyridoxal phosphate.



CLINICAL APPLICATION 21.2

Parkinson Disease

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 levodopa (L-DOPA) is the most common treatment, because dopamine cannot cross the blood–brain barrier. Carbidopa is a drug that inhibits DDC activity, preventing the conversion of L-DOPA to dopamine in the peripheral nervous system. Since carbidopa cannot cross the blood–brain barrier, when used in tandem with L-DOPA, it allows more peripheral L-DOPA to cross the blood–brain barrier, to reach a more therapeutic range in the CNS. In the case of a BH_4-deficiency, L-DOPA may be given as a neurotransmitter supplement to produce dopamine, NE, and epinephrine.

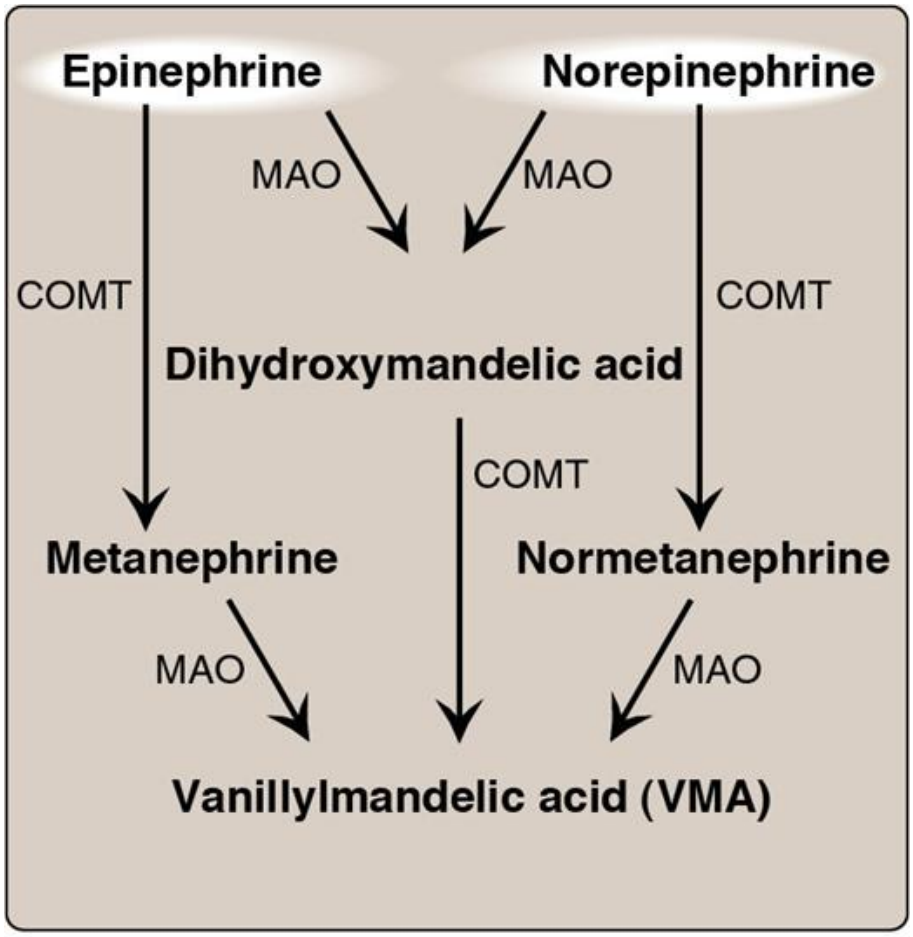
Degradation

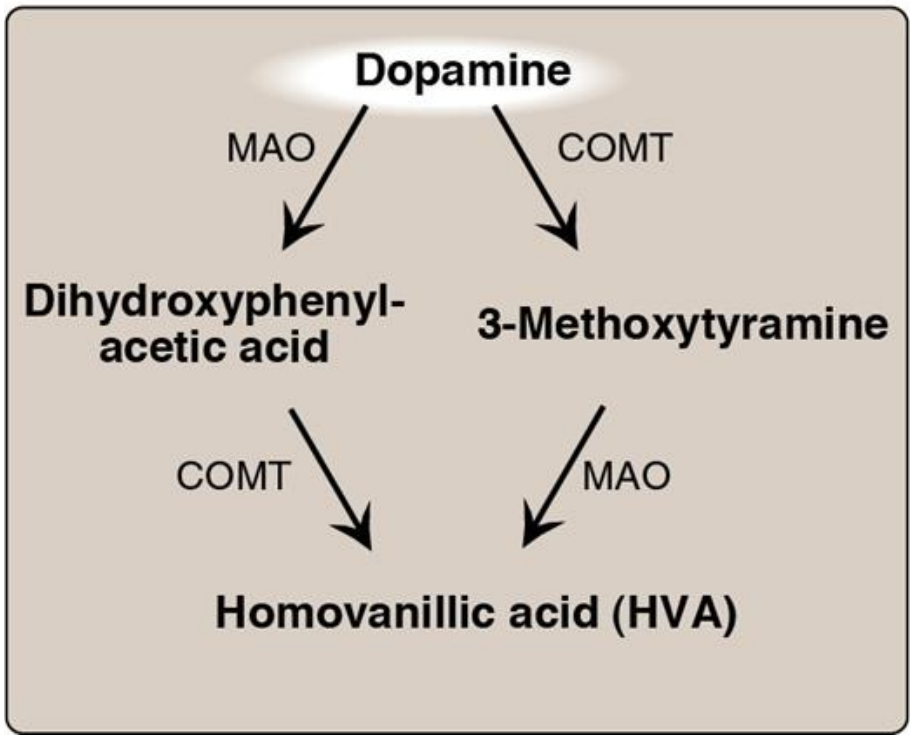
The catecholamines are inactivated by oxidative deamination catalyzed by monoamine oxidase (MAO) and by O-methylation catalyzed by catechol-O-methyltransferase (COMT) using SAM as the methyl donor (Fig. 21.16). The reactions can occur in either order. The aldehyde products of the MAO reaction are oxidized to the corresponding acids. The products of these reactions are excreted in the urine as vanillylmandelic acid (VMA) from epinephrine and NE and homovanillic acid (HVA) from dopamine. (Note: VMA and the metanephrines are increased with pheochromocytomas, rare tumors of the adrenal gland characterized by excessive production of catecholamines.)

FIGURE 21.16

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

(Note: COMT requires S-adenosylmethionine.)





Monoamine oxidase 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 (NE, dopamine, or serotonin) that may leak out of synaptic vesicles when the neuron is at rest. MAO inhibitors (MAOI) may irreversibly or reversibly inactivate the enzyme, permitting neurotransmitter molecules to escape degradation and, therefore, both to accumulate within the presynaptic neuron and to leak into the synaptic space. This causes activation of NE and serotonin receptors and may be responsible for the antidepressant action of MAOI. (Note: The interaction of MAOI with tyramine-containing foods is discussed in p. 418.)

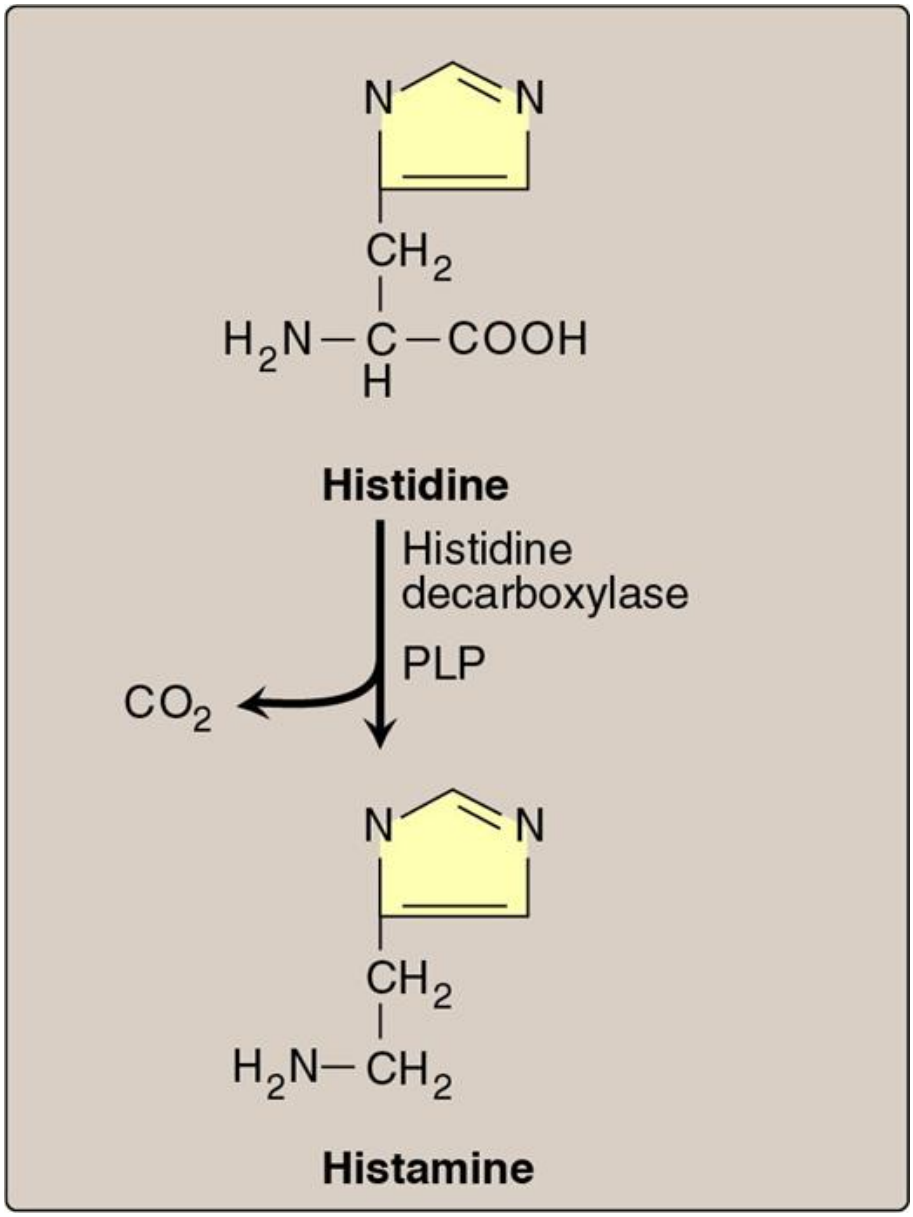
Histamine

Histamine is a chemical messenger that mediates a wide range of cellular responses, including allergic and inflammatory reactions and gastric acid secretion. A powerful vasodilator, histamine is formed by decarboxylation of histidine in a reaction catalyzed by histidine decarboxylase and requiring PLP as a cofactor (Fig. 21.17). It is secreted by mast cells as a result of allergic reactions or trauma. Histamine has no clinical applications, but antihistamines that interfere with the action of histamine have important therapeutic applications. Antihistamines are generally histamine analogs that block histamine binding to its receptors to reduce histamine responses.

FIGURE 21.17

Biosynthesis of histamine.

PLP = pyridoxal phosphate.



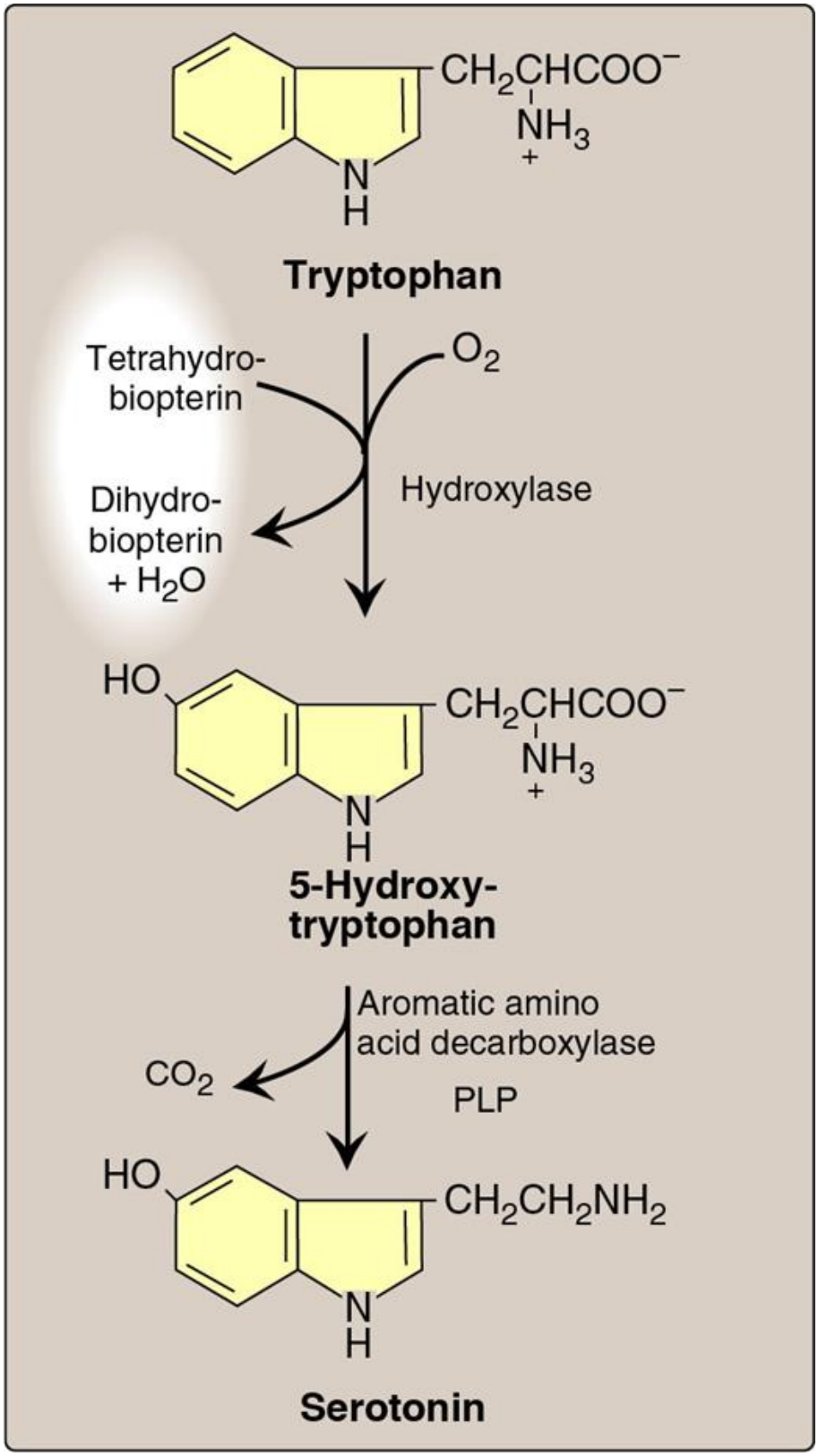
Serotonin

Serotonin, also called 5-hydroxytryptamine (5-HT), is synthesized and/or stored at several sites in the body (Fig. 21.18). The largest amount by far is found in the intestinal mucosa. Smaller amounts occur in the CNS, where it functions as a neurotransmitter, and in platelets (see online Chapter 35). 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 5-HT. In the case of a BH_4-deficiency, 5-hydroxytryptophan may be given as a neurotransmitter supplement to produce serotonin. Serotonin has multiple physiologic roles including pain perception and regulation of sleep, appetite, temperature, blood pressure, cognitive functions, and mood (causes a feeling of well-being). (Note: Selective serotonin reuptake inhibitors [SSRIs] maintain serotonin levels, thereby functioning as antidepressants.) Serotonin is degraded by MAO to 5-hydroxy-3-indoleacetic acid (5-HIAA).

FIGURE 21.18

Synthesis of serotonin.

(Note: Serotonin is converted to melatonin, a regulator of circadian rhythm, in the pineal gland.) PLP = pyridoxal phosphate; CO_2 = carbon dioxide.



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 adenosine diphosphate (Fig. 21.19) 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.)

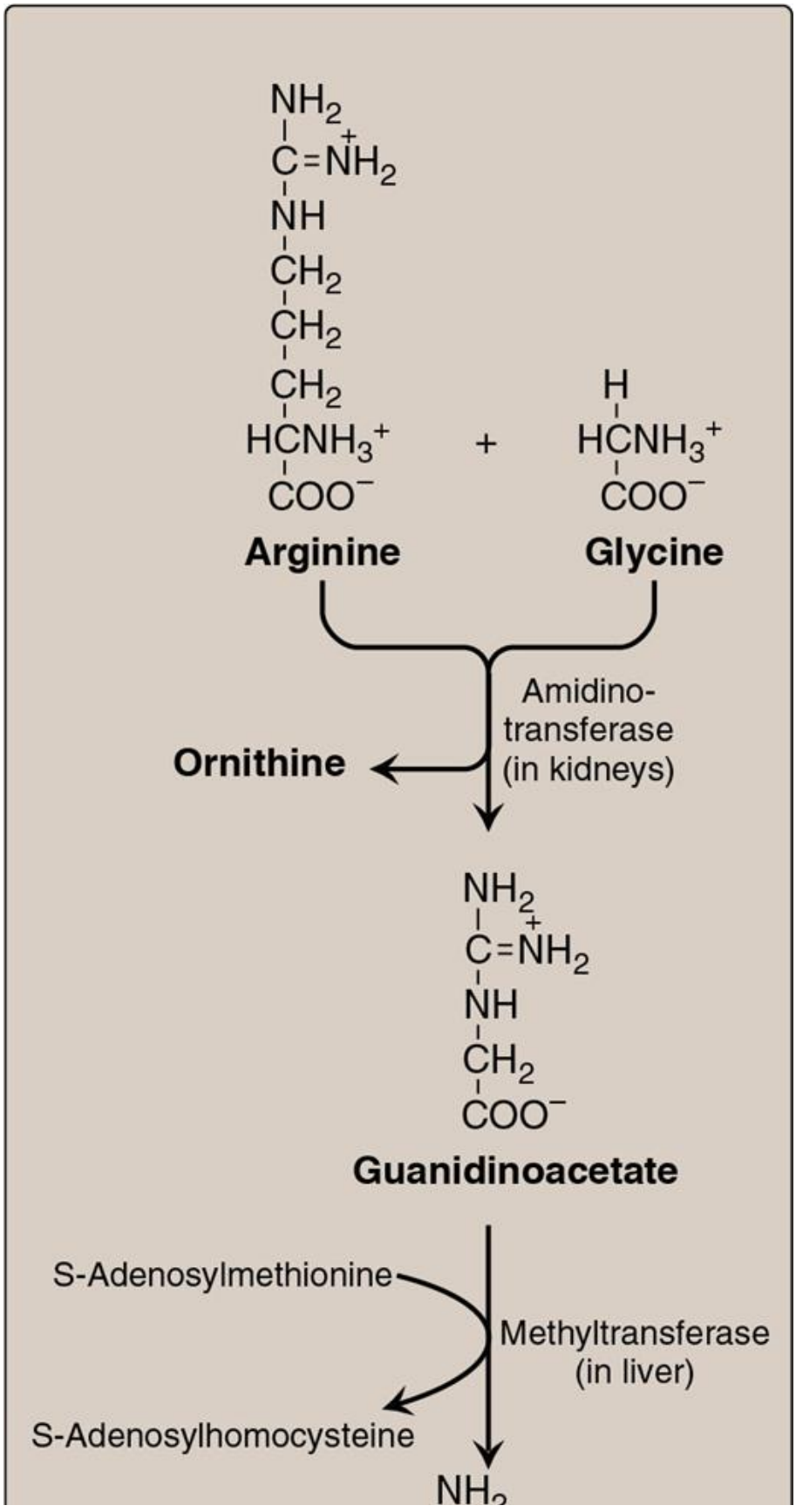
Synthesis

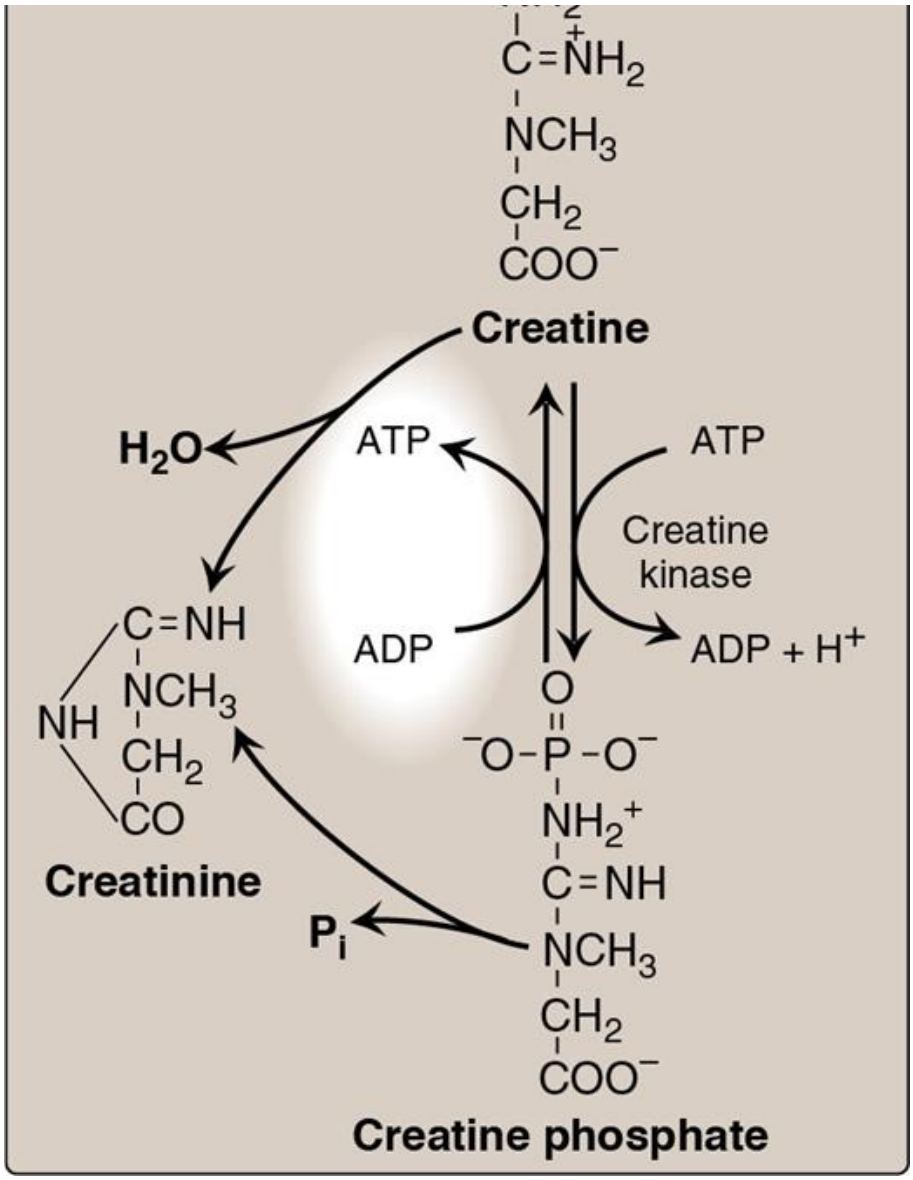
Creatine is synthesized in the liver and kidneys from glycine and the guanidino group of arginine, plus a methyl group from SAM (Fig. 21.19). Animal products are dietary sources. Creatine is reversibly phosphorylated to creatine phosphate by creatine kinase, using ATP as the phosphate donor. (Note: The 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. 70].)

FIGURE 21.19

Synthesis of creatine.

ADP = adenosine diphosphate; P_i = inorganic phosphate.





Degradation

Creatine and creatine phosphate spontaneously cyclize at a slow but constant rate to form creatinine, which is excreted in the urine. The amount excreted is proportional to the total creatine phosphate content of the body and, therefore, can be used to estimate muscle mass. When muscle mass decreases for any reason (e.g., from paralysis or muscular dystrophy), the creatinine content of the urine falls. In addition, a rise in blood creatinine is a sensitive indicator of kidney malfunction, because creatinine normally is rapidly cleared from the blood and excreted. A typical adult male excretes ~1 to 2 g of creatinine/day.

Melanin

Melanin is a pigment that occurs in several tissues, particularly the eye, hair, and skin. It is synthesized from tyrosine in melanocytes (pigment-forming cells) of the epidermis. It functions to protect underlying cells from the harmful effects of sunlight. A defect in melanin production results in oculocutaneous albinism, the most common type being due to defects in copper-containing tyrosinase (see p. 303).

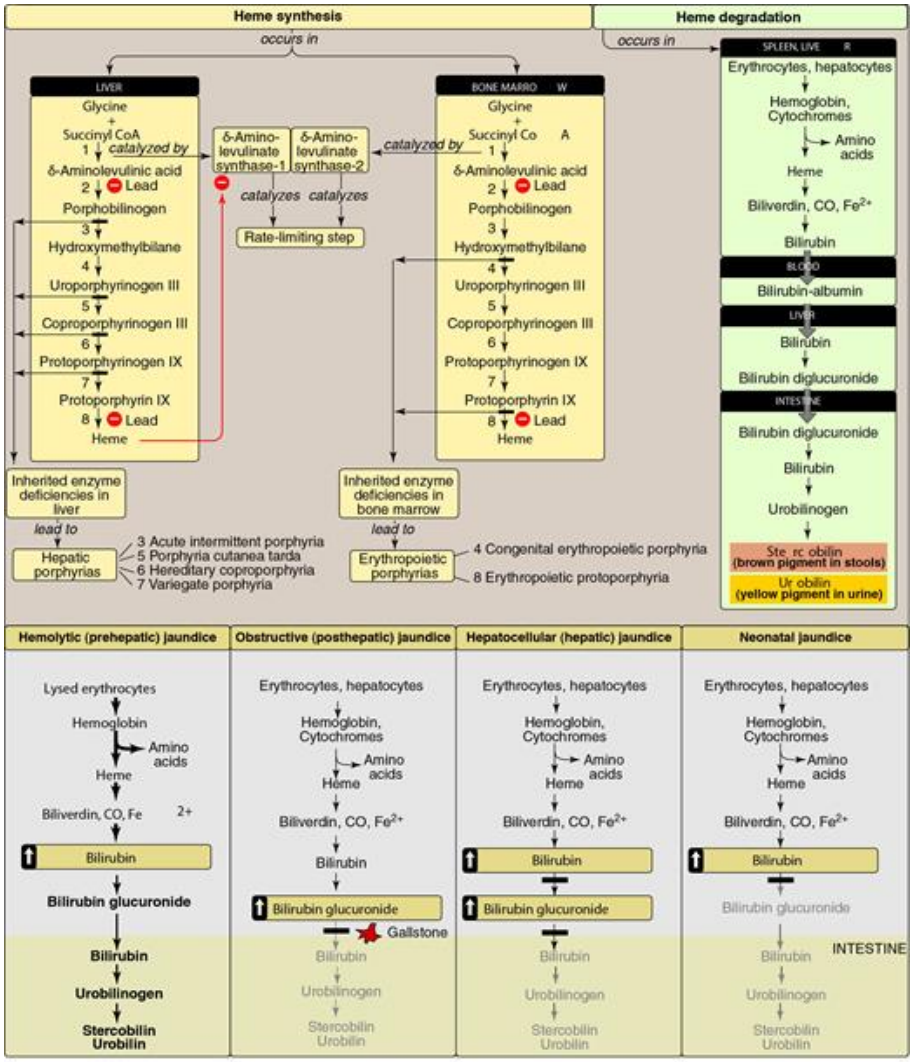
Chapter Summary

- **Amino acids** are **precursors** of many N-containing compounds including **porphyrins**, which, in combination with **Fe^{2+} iron**, form **heme** (Fig. 21.20).

FIGURE 21.20

Key concept map for heme metabolism.

[redacted] = Block in the pathway. (Note: Hepatocellular jaundice can be caused by decreased conjugation of bilirubin or decreased secretion of conjugated bilirubin from the liver into bile.) CoA = coenzyme A; CO = carbon monoxide; Fe = iron.



- The major sites of **heme biosynthesis** are the **liver** and the **erythrocyte-producing cells** of the bone marrow. 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 (particularly **CYP enzymes**). In contrast, heme synthesis in erythroid cells is relatively constant and is matched to the rate of Hb synthesis.
- Heme synthesis starts with **glycine** and **succinyl coenzyme A**. The **committed step** is the formation of **δ-ALA**. This mitochondrial reaction is catalyzed by **ALAS1** in the liver (inhibited by **hemin**, the oxidized form of heme that accumulates when heme is being underutilized) and **ALAS2** in erythroid tissues (regulated by iron).

- **Porphyrias** are caused by inherited or acquired (**lead poisoning**) defects in heme synthesis, resulting in the accumulation and increased excretion of porphyrins or porphyrin precursors. Enzyme defects early in the pathway cause **abdominal pain** and **neuropsychiatric symptoms**, whereas later defects cause **photosensitivity**.
- **Degradation** of heme occurs in the **MPS**, particularly in the **liver** and **spleen**. The first step is the production by **heme oxygenase** of **biliverdin**, which is subsequently reduced to **bilirubin**. Bilirubin is transported by **albumin** to the liver, where its solubility is increased by the addition of two molecules of **glucuronic acid** by **bilirubin UGT**. **Bilirubin diglucuronide** (**CB**) is transported into the **bile canaliculi**, where it is first hydrolyzed and reduced by gut bacteria to yield **urobilinogen**, which is further oxidized by bacteria to **stercobilin**.
- **Jaundice** (**icterus**) refers to the yellow color of the skin and sclerae that is caused by deposition of bilirubin, secondary to increased bilirubin levels in the blood. Three commonly encountered types of jaundice are **hemolytic** (**prehepatic**), **obstructive** (**posthepatic**), and **hepatocellular** (**hepatic**) (see Fig. 21.20).
- Other important N-containing compounds derived from amino acids include the **catecholamines** (**dopamine**, **NE**, and **epinephrine**), **creatine**, **histamine**, **serotonin**, **melanin**, and **nitric oxide**.

Study Questions

Choose the ONE best answer.

21.1. δ-Aminolevulinic acid synthase activity:

A. Catalyzes the committed step in porphyrin biosynthesis.

B. Is decreased by iron in erythrocytes.

C. Is decreased in the liver in individuals treated with certain drugs such as the barbiturate phenobarbital.

D. Occurs in the cytosol.

E. Requires tetrahydrobiopterin as a coenzyme.

Correct answer = A. δ-Aminolevulinic acid synthase is mitochondrial and catalyzes the rate-limiting and regulated step of porphyrin synthesis. It requires pyridoxal phosphate as a coenzyme. Iron increases production of the erythroid isozyme. The hepatic isozyme is increased in patients treated with certain drugs.

21.2. A 50-year-old male 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 common skin irritants. He had partial complex seizure disorder that had begun ~3 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 ~18 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, <27 mg). The most likely diagnosis is:

A. acute intermittent porphyria.

B. congenital erythropoietic porphyria.

C. erythropoietic protoporphyria.

D. hereditary coproporphyria.

E. porphyria cutanea tarda.

Correct answer = E. The disease is associated with a deficiency in uroporphyrinogen III decarboxylase (UROD), but clinical expression of the enzyme deficiency is influenced by hepatic injury caused by environmental (e.g., ethanol) and infectious (e.g., hepatitis B virus) agents. 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 δ-aminolevulinic acid synthase and, therefore, of uroporphyrinogen, the substrate of the deficient UROD. The laboratory and clinical findings are inconsistent with other porphyrias.

21.3. A patient presents with jaundice, abdominal pain, and nausea. Clinical laboratory results are shown below:

Plasma bilirubin	Urine urobilinogen	Urinary bilirubin
Increase in conjugated bilirubin (CB)	Not present	Present

What is the most likely cause of the jaundice?

A. Decreased hepatic conjugation of bilirubin

B. Decreased hepatic uptake of bilirubin

C. Decreased secretion of bile into the intestine

D. Increased hemolysis

Correct answer = C. The data are consistent with an obstructive jaundice, in which a block in the common bile duct decreases the secretion of bile-containing CB into the intestine (stool will be pale in color). The CB regurgitates into the blood (conjugated hyperbilirubinemia). The CB is excreted in the urine (which darkens) and is referred to as urinary bilirubin. Urinary urobilinogen is not present because its source is intestinal urobilinogen, which is low. The other choices do not match the data.

21.4. A 2-year-old child was brought to his pediatrician for evaluation of gastrointestinal problems. The parents report that the boy has been listless for the last few weeks. Lab tests reveal a microcytic, hypochromic anemia. Blood lead levels are elevated. Which of the enzymes listed below is most likely to have higher-than-normal activity in the liver of this child?

A. δ-Aminolevulinic acid synthase

B. Bilirubin UDP glucuronosyltransferase

C. Ferrochelatase

D. Heme oxygenase

E. Porphobilinogen synthase

Correct answer = A. This child has the acquired porphyria of lead poisoning. Lead inhibits both δ-aminolevulinic acid dehydratase and ferrochelatase and, consequently, heme synthesis. The decrease in heme derepresses δ-aminolevulinic acid synthase-1 (the hepatic isozyme), resulting in an increase in its activity. The decrease in heme also results in decreased hemoglobin synthesis, and anemia is seen. Ferrochelatase is directly inhibited by lead. The other choices are enzymes of heme degradation.

21.5. A 50-year-old male presents with hand tremors, a slow unsteady gait, and stiffness. After neurologic scans and additional testing, the patient is diagnosed with Parkinson disease. Which one of the following treatments listed below would be most effective in this patient?

A. Biopterin

B. β-Carotene

C. Hemin

D. Levodopa–carbidopa

E. Serotonin reuptake inhibitors

Correct answer = D. Levodopa (L-DOPA) can cross the blood–brain barrier to be used as a substrate for DOPA decarboxylase to increase dopamine levels in the central nervous system. Carbidopa cannot cross the blood–brain barrier and inhibits peripheral DOPA decarboxylase. This provides higher therapeutic L-DOPA levels for the central nervous system. Biopterin can be provided as a useful therapeutic agent for aromatic amino acid hydroxylase reactions when the cofactor is deficient. β-Carotene is an antioxidant, which can scavenge free radicals. Along with phlebotomy, it can help with photosensitivity in acute porphyria cases. Hemin reduces the deficit of porphyrins. This in turn decreases the synthesis of ALAS1 and minimizes the production of toxic porphyrin intermediates. Serotonin reuptake inhibitors help maintain serotonin levels, and function as antidepressants.

21.6. Kidney malfunction in a patient may be indicated by which one of the following lab tests?

A. Increased blood creatine kinase MB isoenzyme levels

B. Increased urine vanillylmandelic acid and metanephrine levels

C. Increased blood bilirubin diglucuronide levels

D. Decreased urine creatinine levels

E. Increased blood creatinine levels

Correct answer = E. Creatinine is normally very rapidly cleared from the blood by the kidneys and excreted in the urine. An increase in blood creatinine concentration levels indicates renal malfunction. Increased blood creatine kinase MB isoenzyme levels would be indicative of heart damage and/or myocardial infarction. Increased urine vanillylmandelic acid and metanephrine levels would be indicative of tumors of the adrenal gland, characterized by increased production of catecholamines. Increased blood bilirubin diglucuronide levels would be indicative of obstructive jaundice. Decreased urine creatinine levels would be indicative of decreased muscle mass, such as muscle atrophy from paralysis or muscular dystrophy.