Amino Acid Metabolism: Conversion of Amino Acids to Specialized Products

Heme Metabolism

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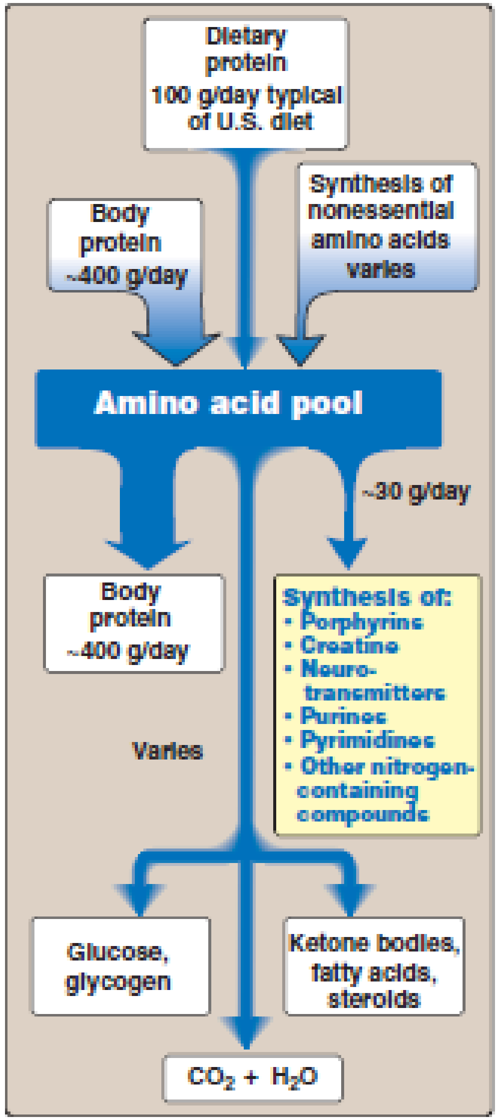
Medical students-First semester

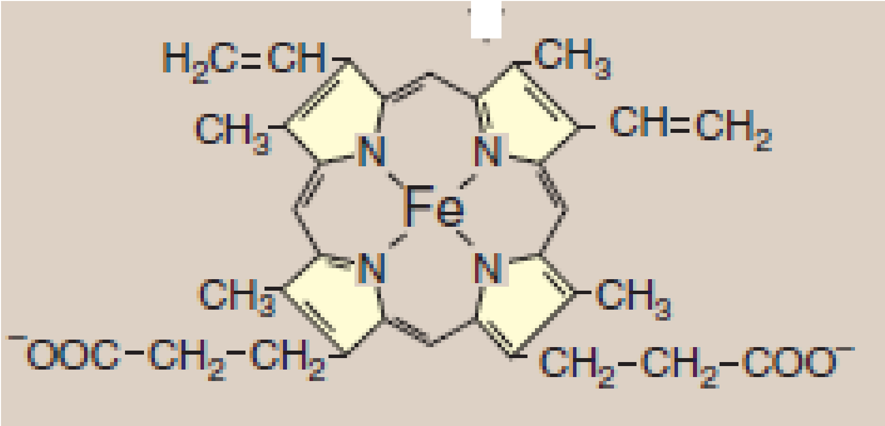
All images are taken from Lippincott's Biochemistry textbook except where noted

Conversion of amino acids to specialized products



PORPHYRIN

Porphyrins are cyclic compounds that readily bind metal ions (Fe^{2+} or Fe^{3+})



The most prevalent metalloporphyrin in humans is heme

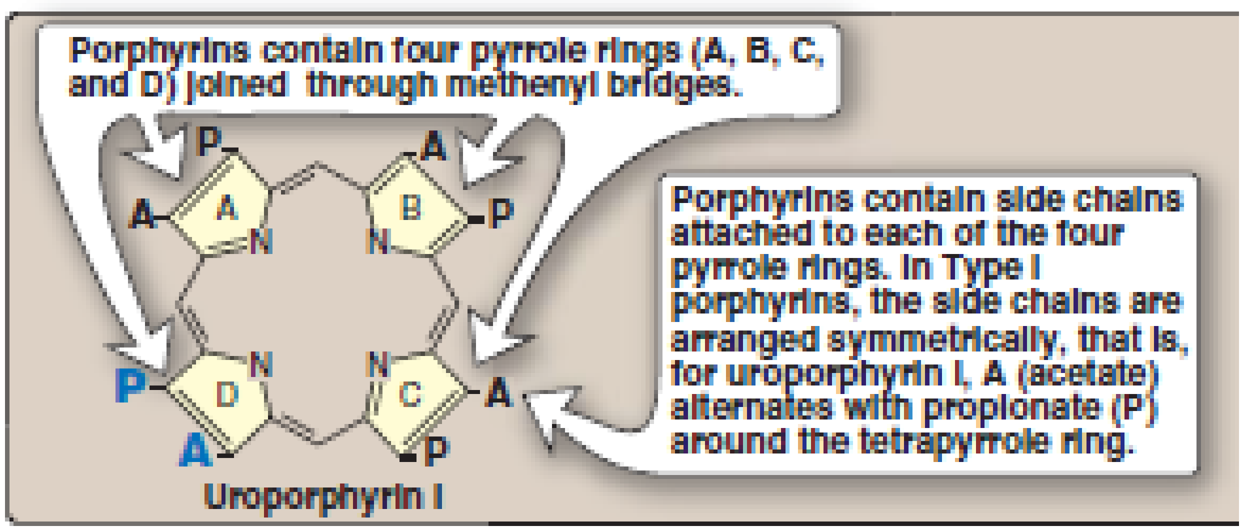
Heme consists of one ferrous (Fe^{2+}) ion in the center of the tetrapyrrole ring of protoporphyrin IX

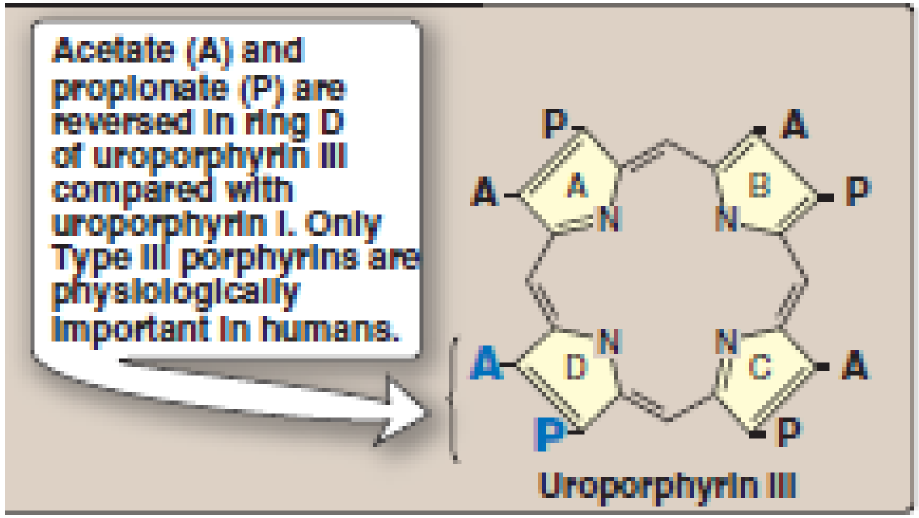
Heme is found in hemoglobin, myoglobin, the cytochromes, catalase, nitric oxide synthase, and peroxidase.

Hemeproteins are rapidly synthesized and degraded

6–7g of hemoglobin are synthesized each day to replace heme lost through the normal turnover of erythrocytes.

Structure of porphyrins

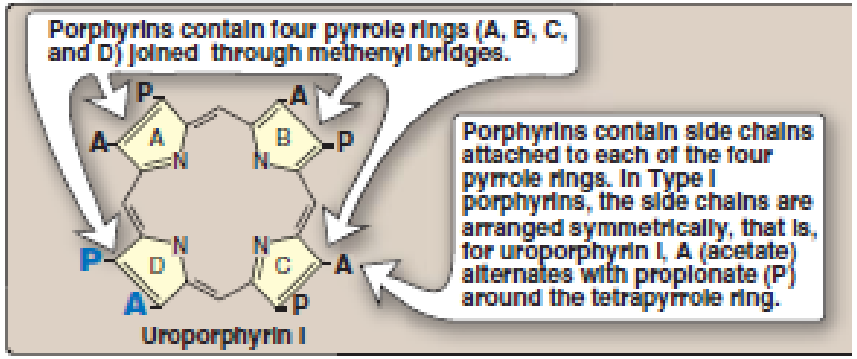


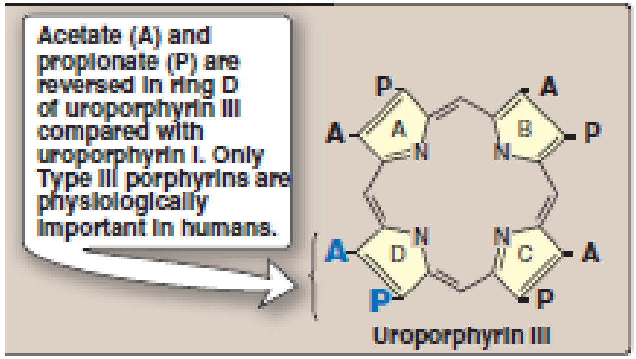


The medical significance of porphyrins is related to the following structural features of these molecules:

1. Nature of the side chains that are attached to each of the four pyrrole rings.
Uroporphyrin contains acetate (–CH2–COO–) and propionate (–CH2–CH2–COO–)
Coproporphyrin contains methyl (–CH3) and propionate groups
Protoporphyrin IX (and heme) contains vinyl (–CH=CH2), methyl, and propionate groups.

Structure of porphyrins





The medical significance of porphyrins is related to the following structural features of these molecules:

2. Distribution of side chains around the tetrapyrrole nucleus. Four different ways (I to IV) Only Type III porphyrins (asymmetric substitution on ring D) are physiologically important in humans.

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

Biosynthesis of heme

The major sites of heme biosynthesis are:

1. Liver (cytochrome P450), variable rate depending on demands for heme proteins

2. Erythrocyte-producing cells of the bone marrow (hemoglobin), more than 85% of all heme synthesis

The initial and last steps in porphyrins formation occur in mitochondria
The intermediate steps occur in the cytosol

Mature RBCs lack mitochondria and are unable to synthesize heme

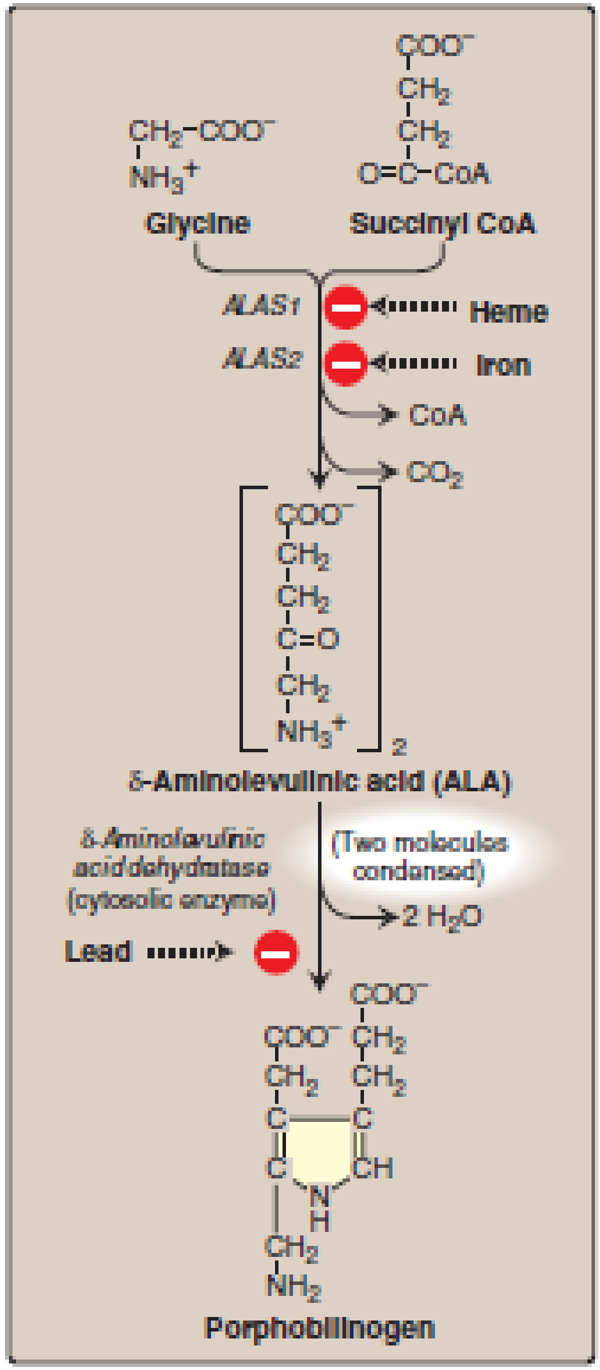
Biosynthesis of Porphyrin-Heme

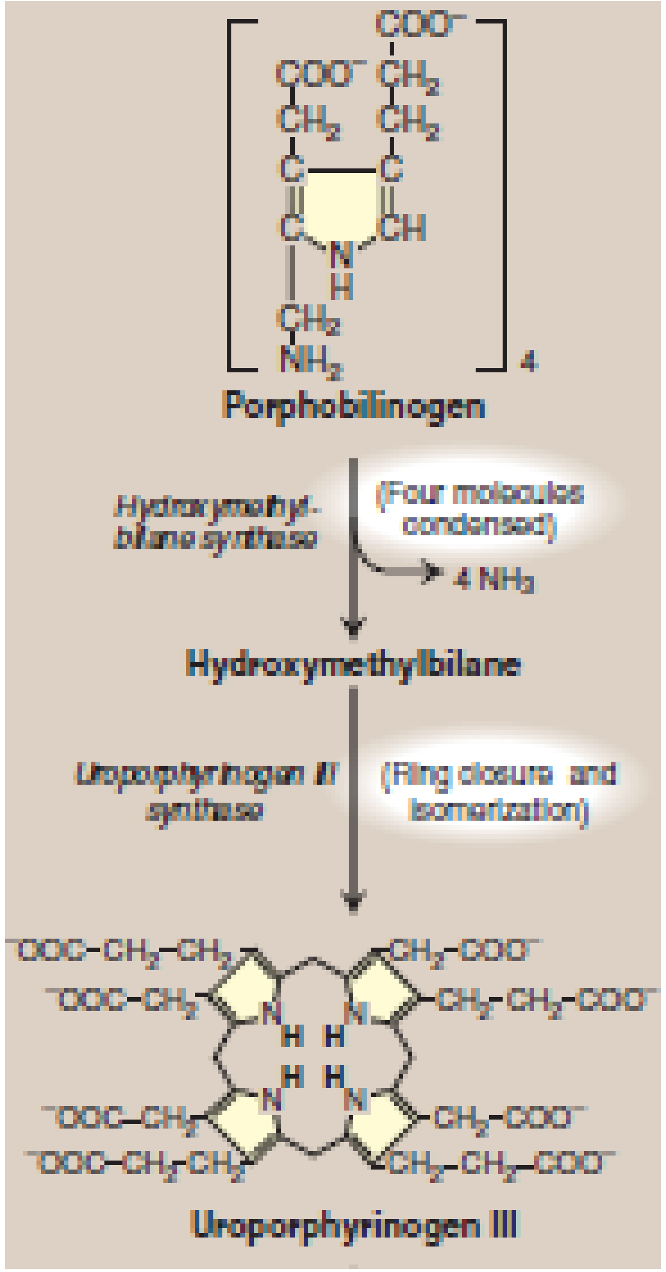
1. Formation of δ-aminolevulinic acid (ALA): All the C and N atoms of the porphyrin are provided by **Gly** (a nonessential AA) and succinyl coenzyme A that condense to form ALA and catalyzed by ALA synthase (ALAS). Coenzyme is pyridoxal phosphate (PLP)

The rate-limiting step in porphyrin synthesis

2. Formation of porphobilinogen: The condensation of two molecules of ALA to form porphobilinogen by Zn-containing ALA dehydratase (porphobilinogen synthase)

ALA is elevated in the anemia seen in lead poisoning.



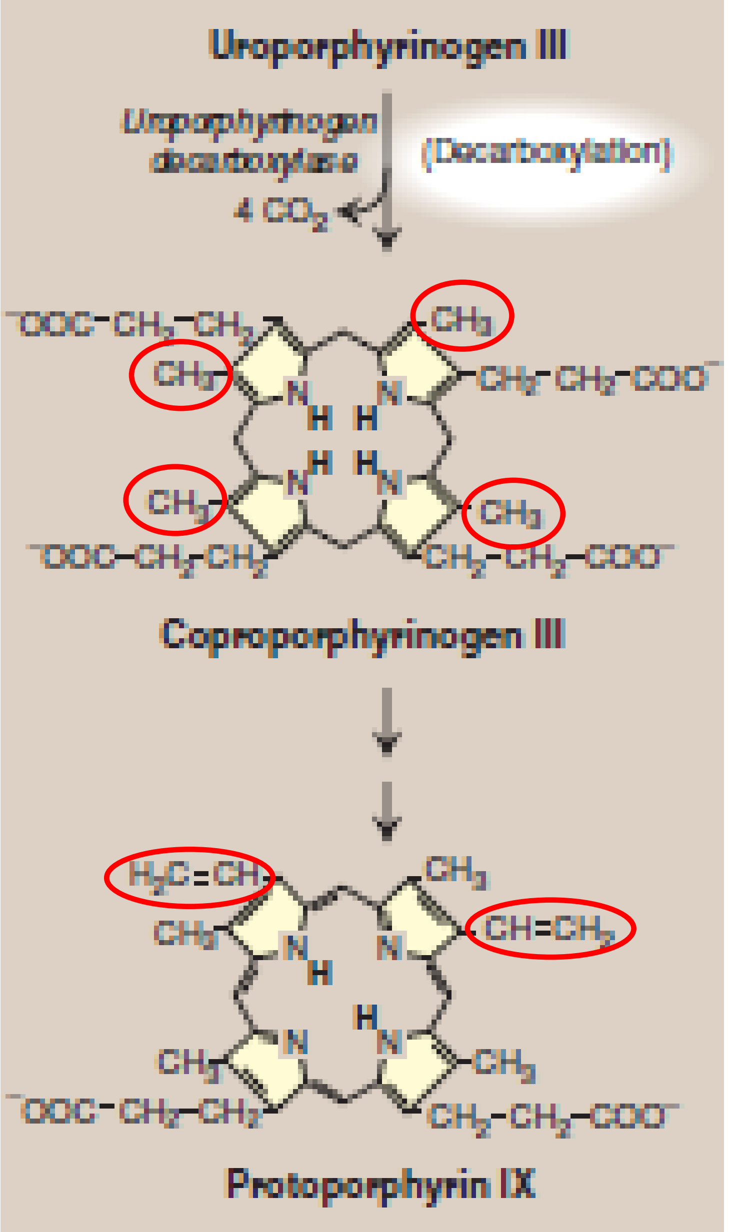


Synthesis of Heme

3. Formation of uroporphyrinogen: The condensation of four porphobilinogens produces the linear tetrapyrrole, hydroxymethyl bilane

Hydroxymethyl bilane is isomerized and cyclized by uroporphyrinogen III synthase to produce the asymmetric uroporphyrinogen III.

These reactions occur in the cytosol.



Cytosol

Mitochondria

Synthesis of Heme

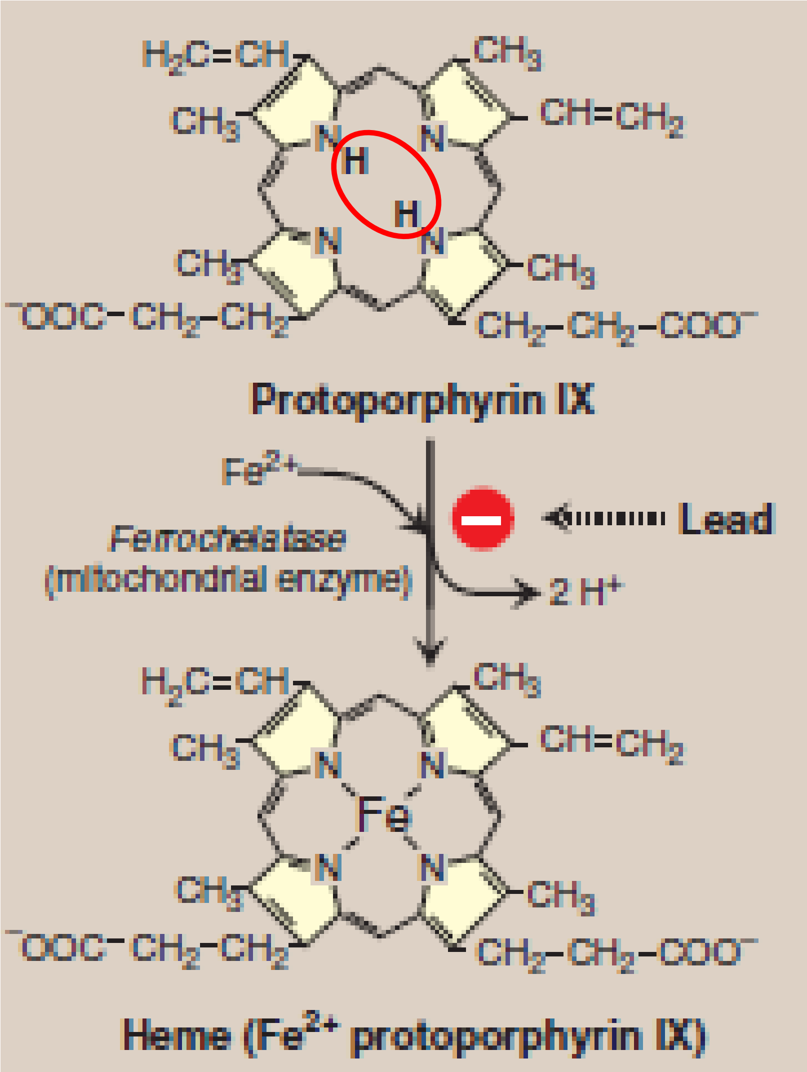
The cyclic hydroxymethyl bilane is decarboxylated (of its acetate groups) generating coproporphyrinogen III

These reactions occur in the cytosol.

Coproporphyrinogen III enters the mitochondrion

Two propionate side chains are decarboxylated to vinyl groups generating protoporphyrinogen IX

Synthesis of Heme



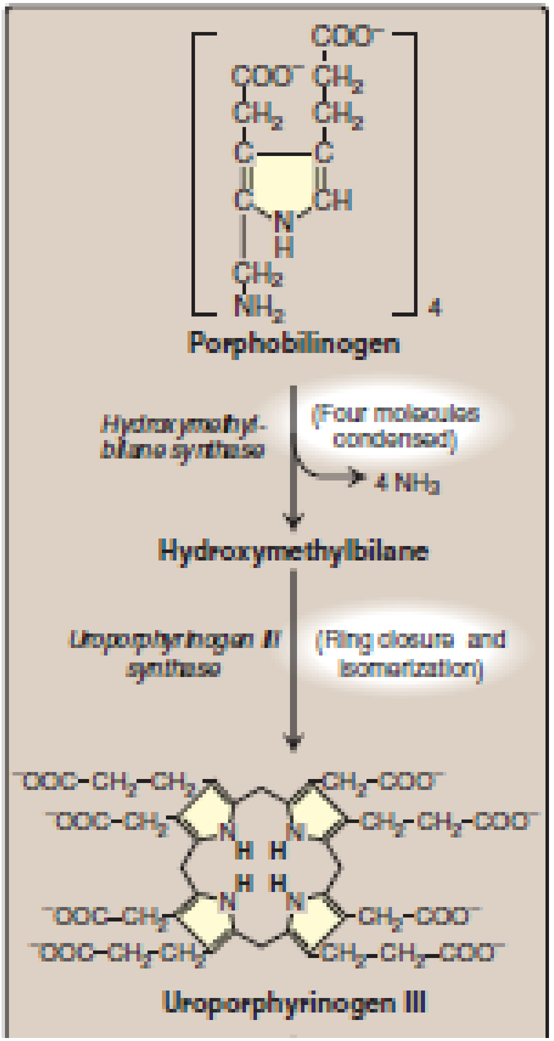
4. Formation of heme:

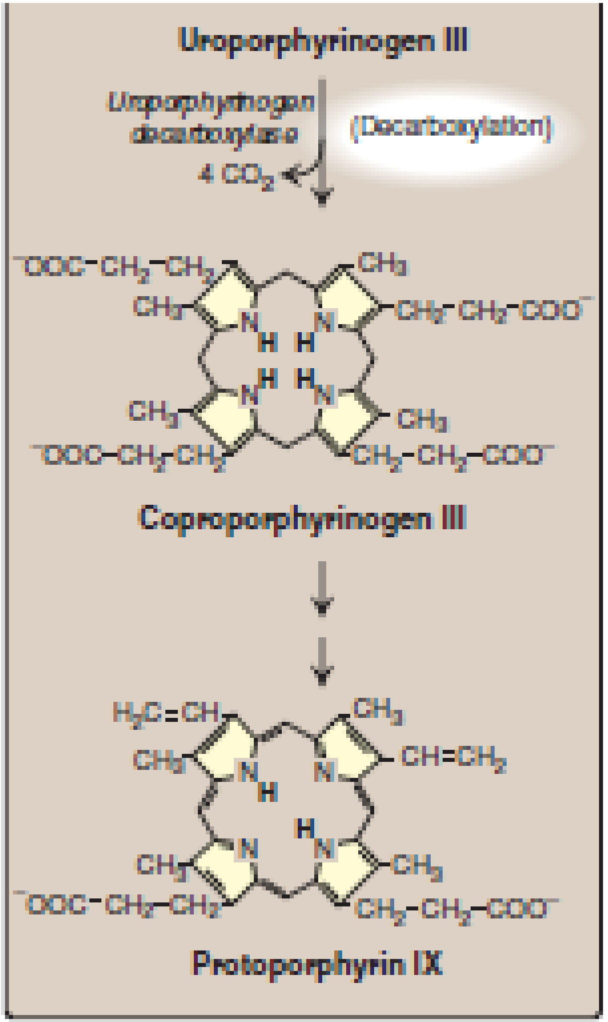
Protoporphyrinogen IX is oxidized to protoporphyrin IX.

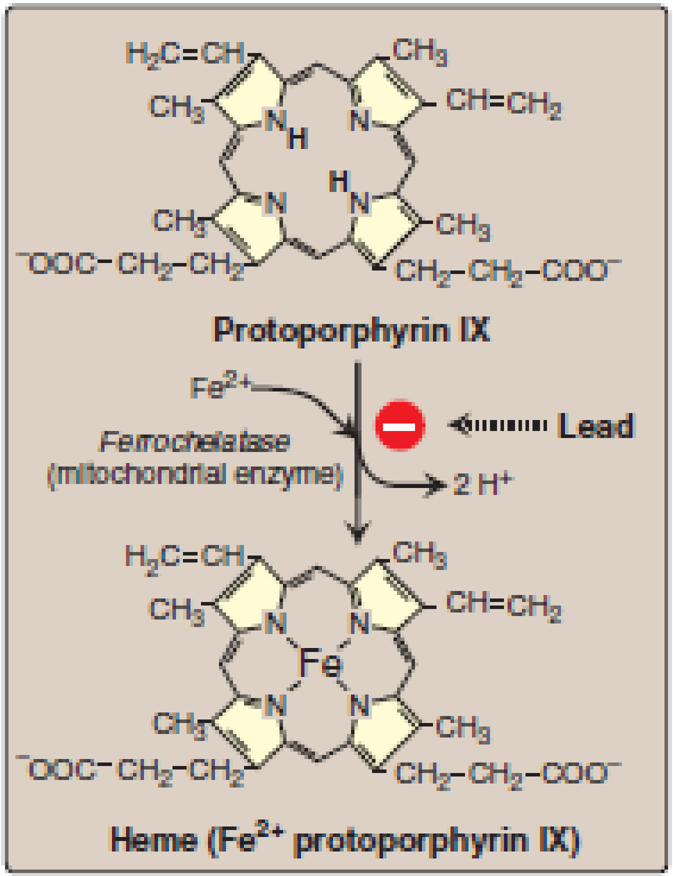
The introduction of iron (as Fe2+) into protoporphyrin IX occurs spontaneously

The rate of Fe addition is enhanced by ferrochelatase (an enzyme that is inhibited by lead)

Synthesis of Porphyrin







Regulation of heme biosynthesis

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 Fe^{2+} to Fe^{3+}

Hemin decreases the activity of **hepatic ALAS1** by reducing its synthesis (mRNA synthesis) and mitochondrial import.

In erythroid cells, **ALAS2** is controlled by the **availability of intracellular iron**.

Effect of drugs on ALA synthase activity:

Many drugs increase hepatic ALAS1 activity. These drugs are metabolized by cytochrome P450 monooxygenase system—a heme protein oxidase system found in the liver

In response to these drugs, the synthesis of cytochrome P450 proteins increases, leading to an enhanced consumption of heme. Low heme concentration increases ALAS1 synthesis

Porphyrias

"Porphyria" refers to the purple color caused by pigment-like porphyrins in the urine of patients

Rare, inherited (or occasionally acquired) defects in heme synthesis

Accumulation and increased excretion of porphyrins or porphyrin precursors

Mutations are heterogenous (not all are at the same DNA locus), and nearly every affected family has its own mutation.

Each porphyria result from a different enzyme deficiency and results in the accumulation of different intermediates

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).

Porphyrias-Biochemical changes and treatment

Biochemical changes: Increased ALA synthase activity and decreased synthesis of heme.

In the liver, heme acts as a repressor of the gene for ALAS1.

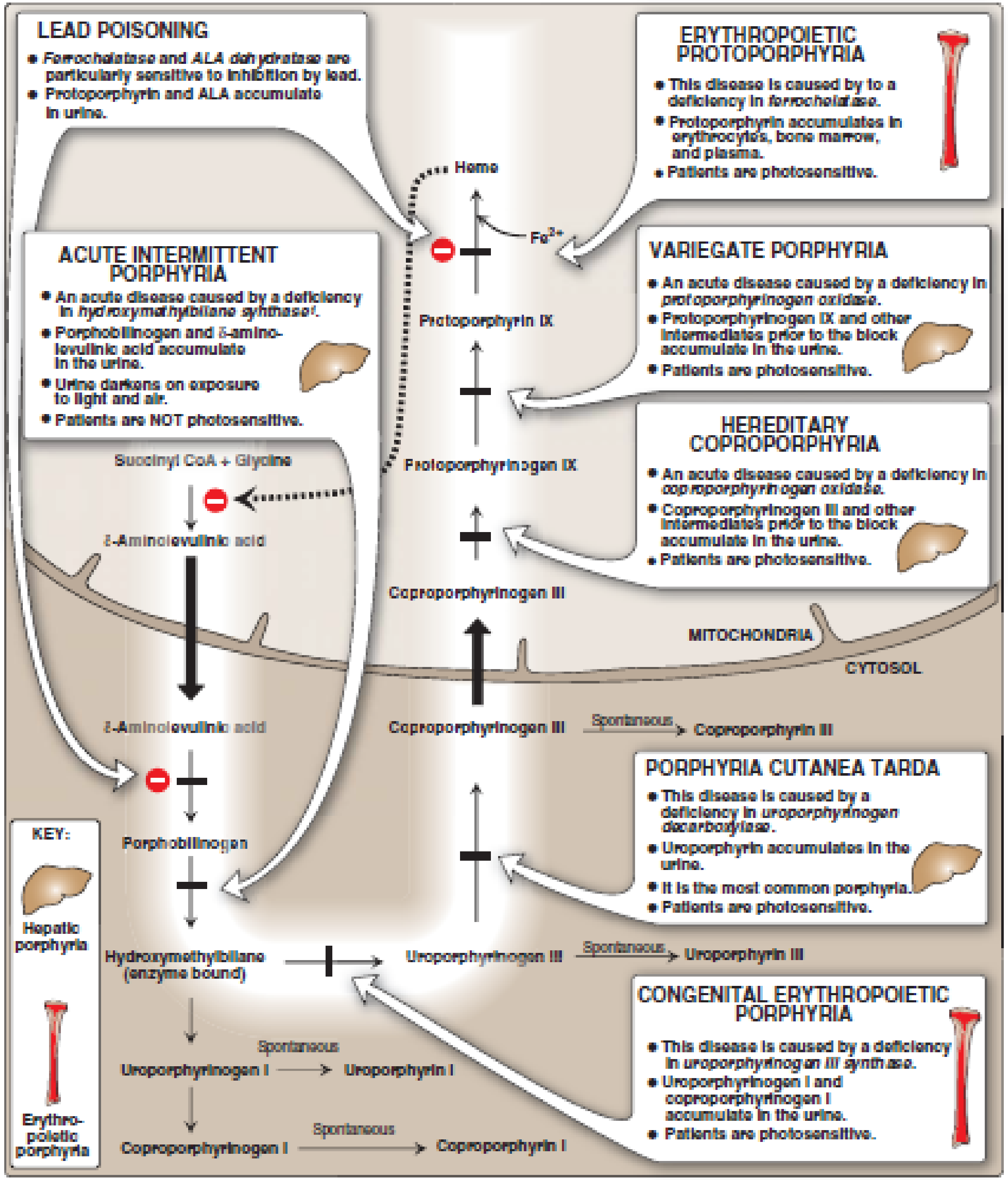
Less heme results in an increased synthesis of ALAS1 and synthesis of intermediates upstream to ALA.

Treatment:
Treatment for pain and vomiting during acute attacks

IV injection of **hemin and glucose**, which **decreases the synthesis of ALAS1**, to reduce symptoms

Ingestion of β-carotene (a free-radical scavenger)

Biosynthesis of heme



Heme Degradation

RBCs are degraded by the reticuloendothelial system (liver and spleen)

~85% of degraded heme comes from senescent RBCs
~15% of degraded heme comes from immature RBCs turnover and cytochromes of nonerythroid tissues.

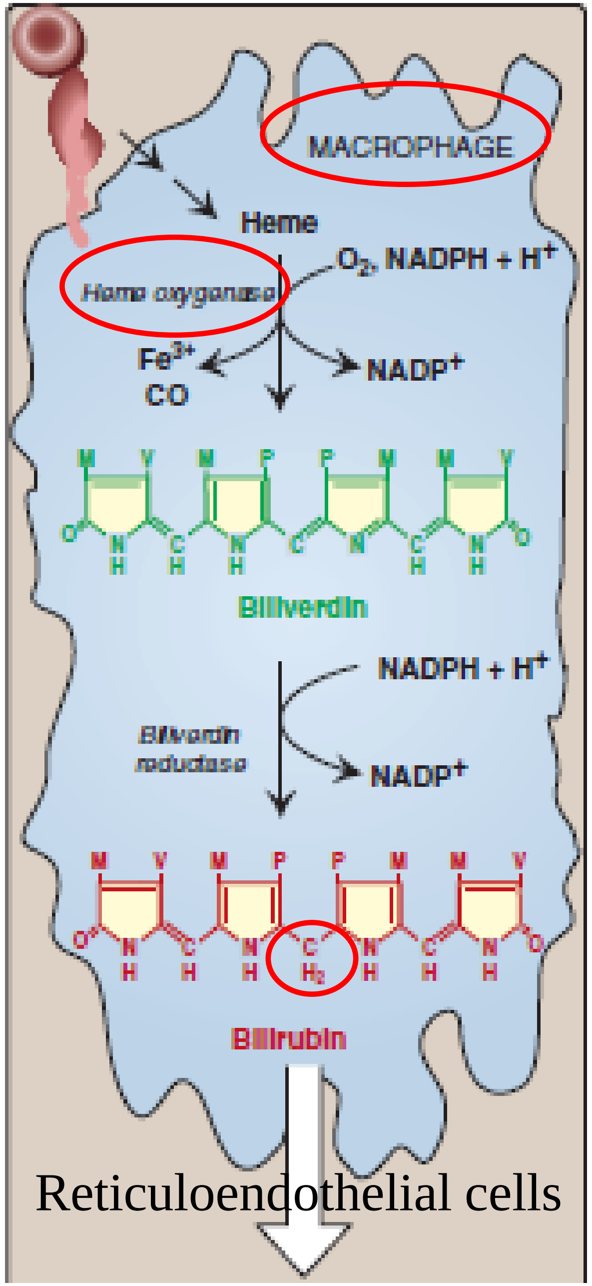
1. Formation of bilirubin:

A. Biliverdin formation by the addition of an OH to the methenyl bridge between two pyrrole rings, and then a second oxidation by the same enzyme system to cleave the porphyrin ring.

Products: the green pigment biliverdin, ferric iron (Fe3+) and CO

B. Biliverdin reduction to bilirubin (redorange)

Bilirubin and its derivatives are called bile pigments.
Bilirubin functions as an antioxidant (oxidized to biliverdin)



Reticuloendothelial cells

Heme Degradation

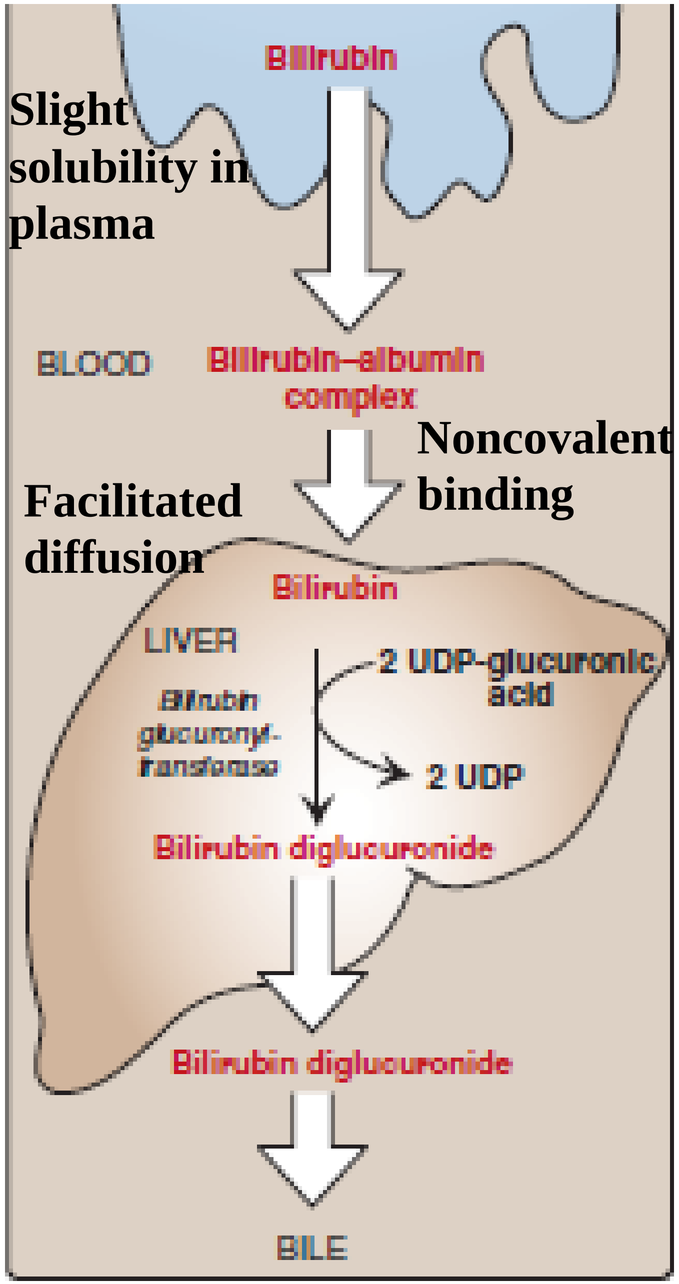
2. Uptake of bilirubin by the liver:

In hepatocytes, bilirubin binds to intracellular proteins, such as, ligandin.

Note: certain anionic drugs, such as salicylates and sulfonamides, can displace bilirubin from albumin, allowing bilirubin to enter the CNS causing a neural damage in infants

3. Formation of bilirubin diglucuronide: two molecules of glucuronic acid are added to increase solubility (conjugation) by microsomal bilirubin glucuronyl-transferase

Deficiency of this enzyme results in Crigler-Najjar I and II (more severe) and Gilbert syndrome.



Heme Degradation

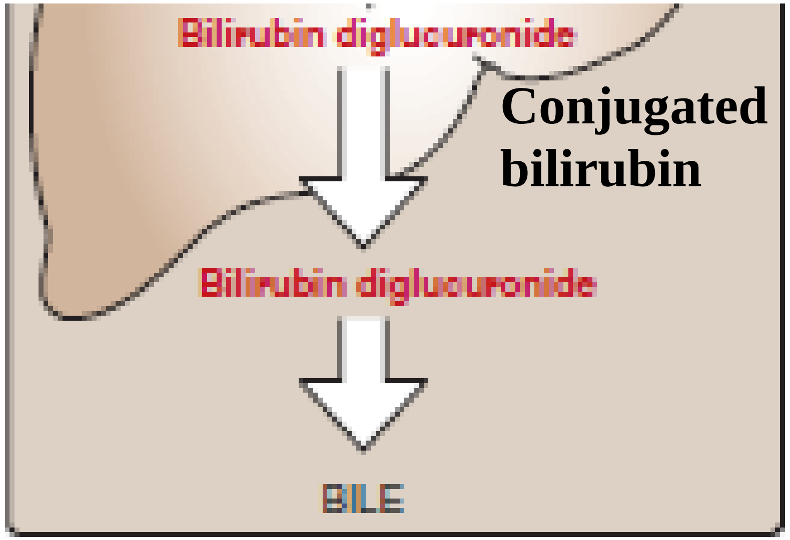
4. Secretion of bilirubin into bile:

Conjugated bilirubin is **actively transported** into the bile canaliculi and then into the bile.

The rate-limiting step (energy-requiring step).

Dubin-Johnson syndrome results from a deficiency in the transport protein of conjugated bilirubin.

Unconjugated bilirubin is normally not secreted.



Heme Degradation

5. Formation of urobilins in the intestine:

Bilirubin diglucuronide is hydrolyzed and reduced by bacteria in the gut to yield urobilinogen (colorless).

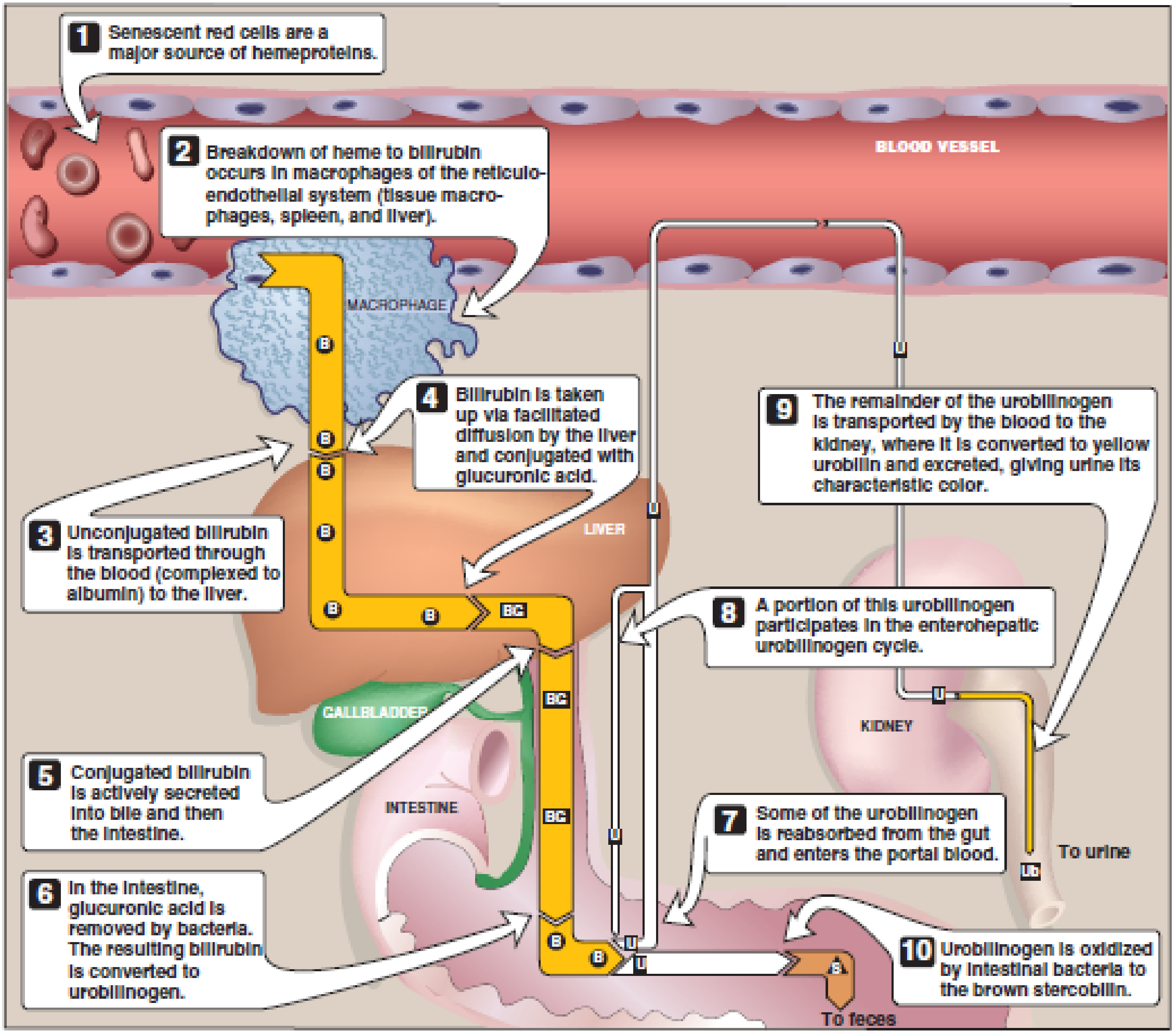
Urobilinogen fates:

1. Oxidation by intestinal bacteria to stercobilin (gives feces the characteristic brown color).

2. Reabsorption from the gut and entrance to the portal blood.

a. Some urobilinogen participates in the enterohepatic urobilinogen cycle where it is taken up by the liver, and then resecreted into the bile.
b. The remainder is transported by the blood to the kidney, where it is converted to yellow urobilin and excreted, giving urine its characteristic color.

Catabolism of heme



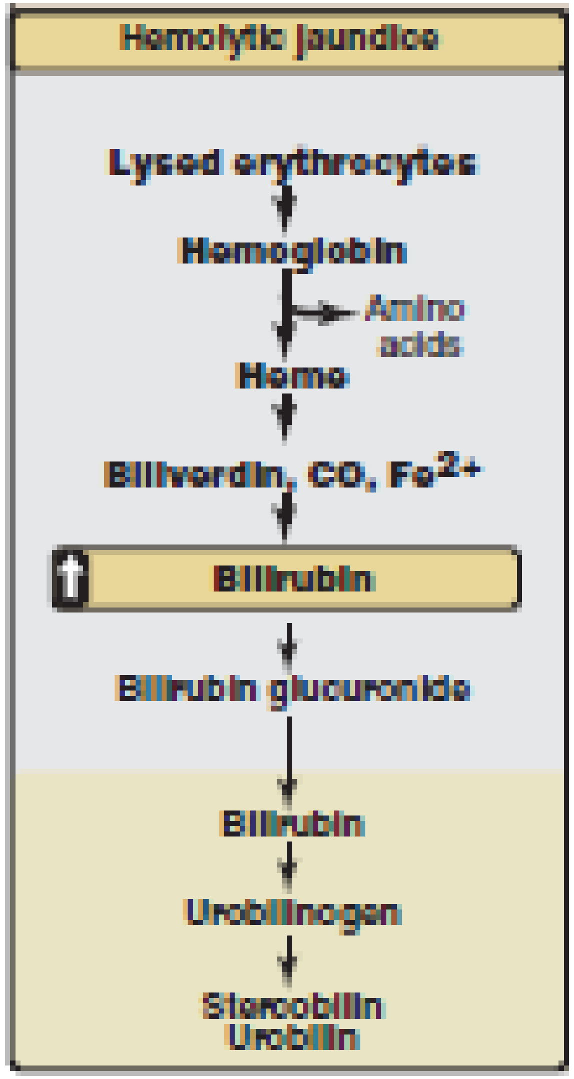
B = bilirubin; BG = bilirubin diglucuronide; U = urobilinogen; Ub = urobilin; S = stercobilin.

Jaundice

Jaundice (or icterus) is the yellow color of skin, nail beds, and sclera due to bilirubin deposition secondary to hyperbilirubinemia

Jaundice is a symptom not a disease

Types of Jaundice

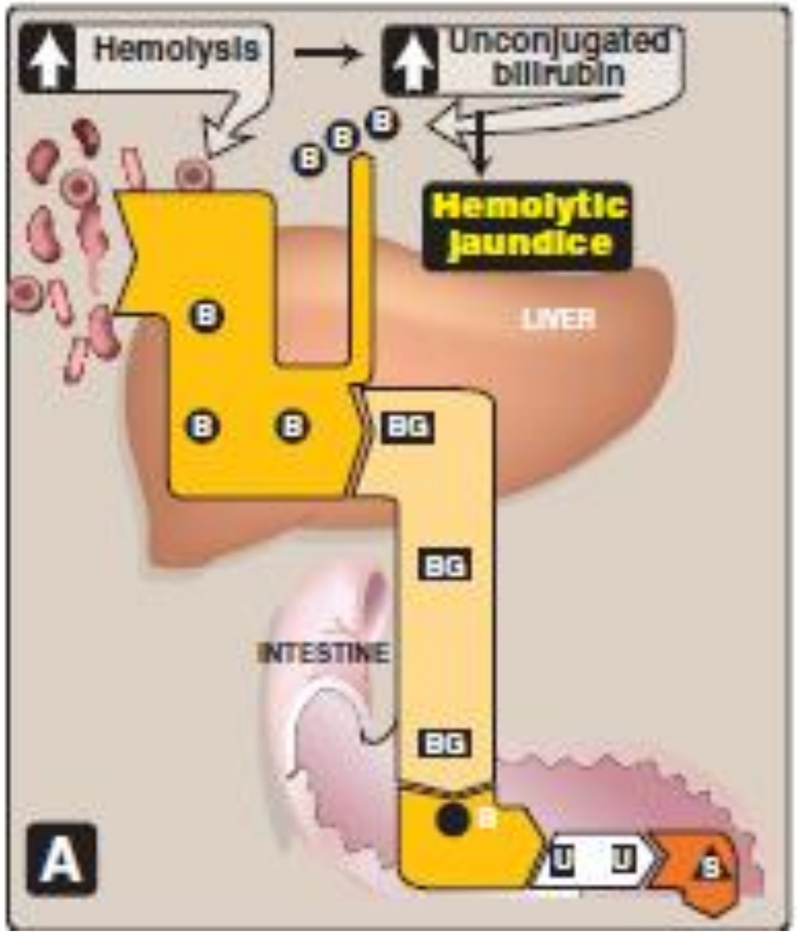


1. **Hemolytic jaundice:**

Bilirubin conjugation and execretion capacity of the liver is >3,000 mg/day

300 mg/day of bilirubin produced

Sickle cell anemia, pyruvate kinase or glucose-6-phosphate dehydrogenase deficiency



BG = bilirubin glucuronide; B = bilirubin; U = urobilinogen; S = stercobilin.

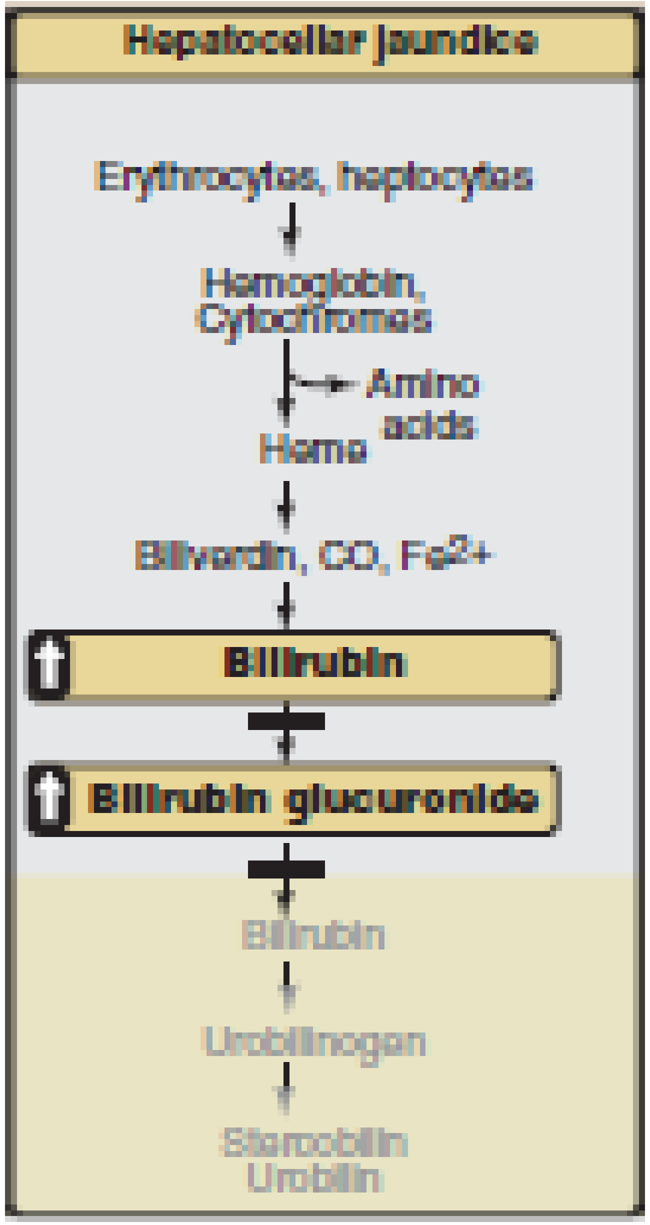
Types of Jaundice-cont

2. Hepatocellular jaundice due to damage to liver cells.

More unconjugated bilirubin levels in the blood

Urobilinogen is increased in the urine (the enterohepatic circulation is reduced) resulting in dark urine.

Stools may have a pale, clay color.



Types of Jaundice-cont

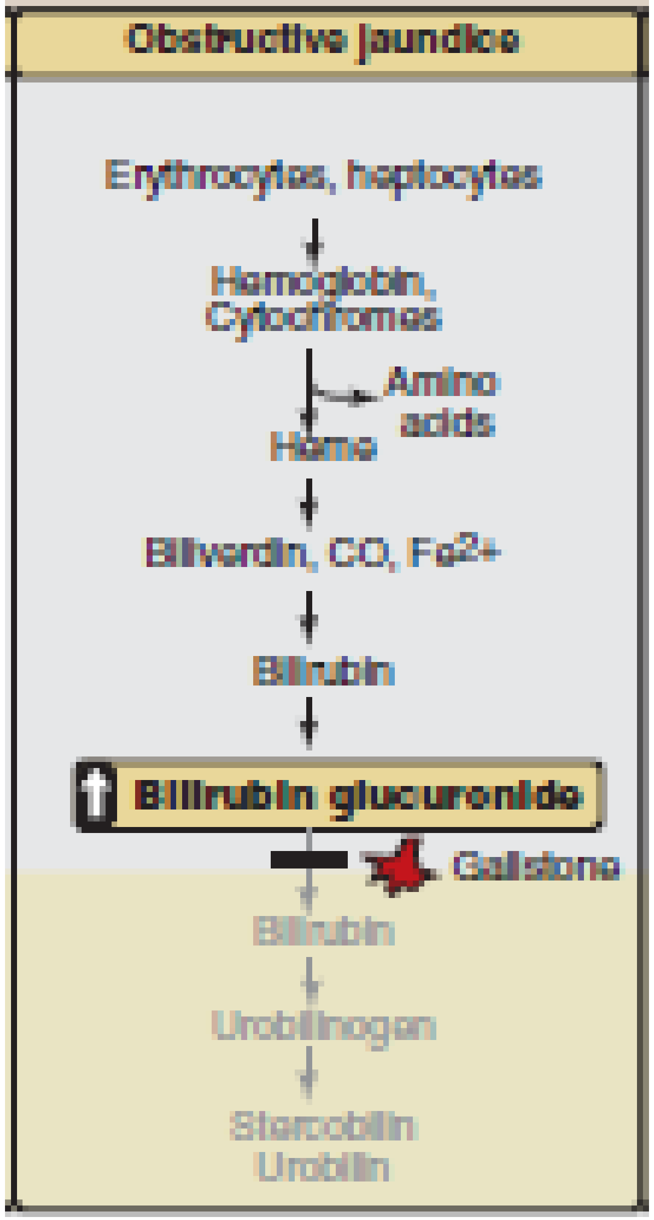
3. Obstructive jaundice: Obstruction of the bile duct (extrahepatic cholestasis) due to a tumor or bile stones, preventing bilirubin passage into the intestine.

No overproduction of bilirubin or decreased conjugation

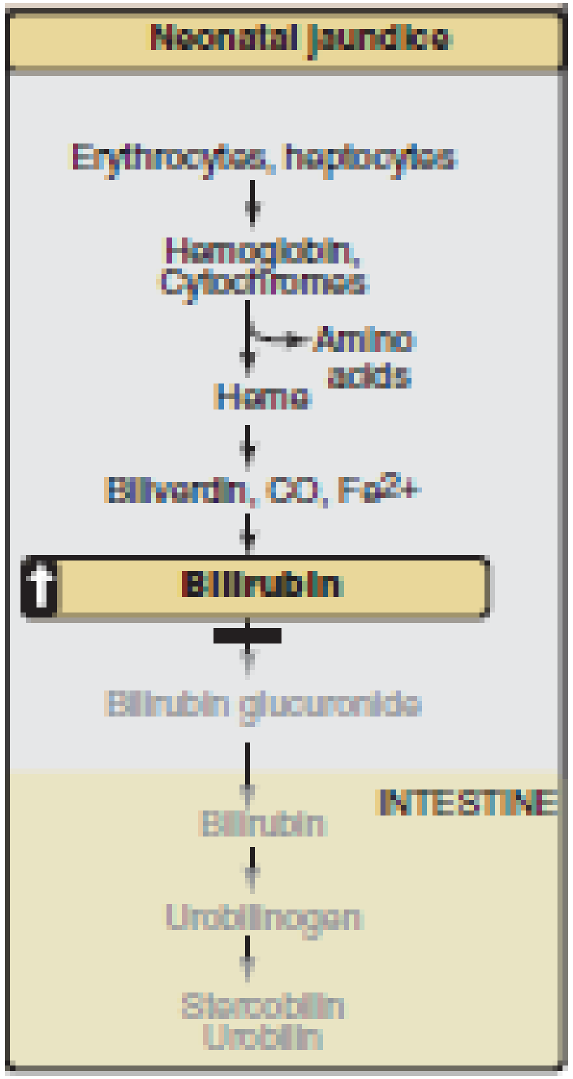
Signs and symptoms: GI pain and nausea, pale clay color stool, and urine that darkens upon standing.

Hyperbilirubinemia, bilirubin execretion in the urine, no urinary urobiloinogen.

Prolonged obstruction of the bile duct can damage the liver and increase unconjugated bilirubin



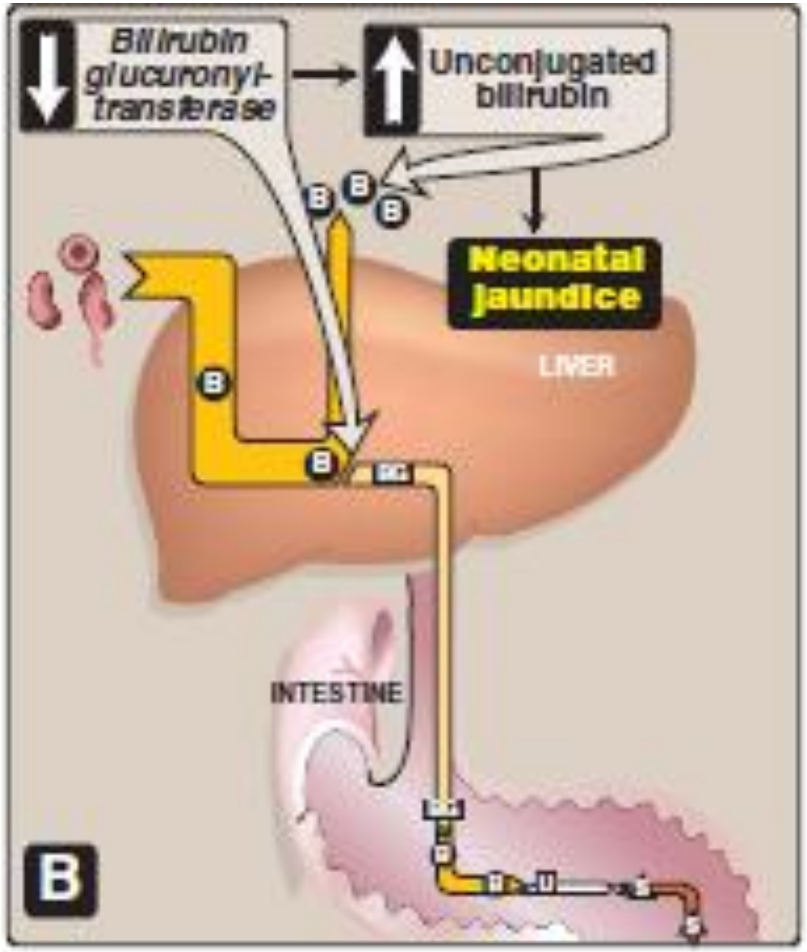
Jaundice in newborns



Newborn infants, particularly if premature, often accumulate bilirubin, because the activity of hepatic bilirubin glucuronyltransferase is low at birth

Enzyme adult levels are reached in ~4 weeks

High bilirubin above the binding capacity of albumin, can diffuse into the basal ganglia and cause toxic encephalopathy (kernicterus).



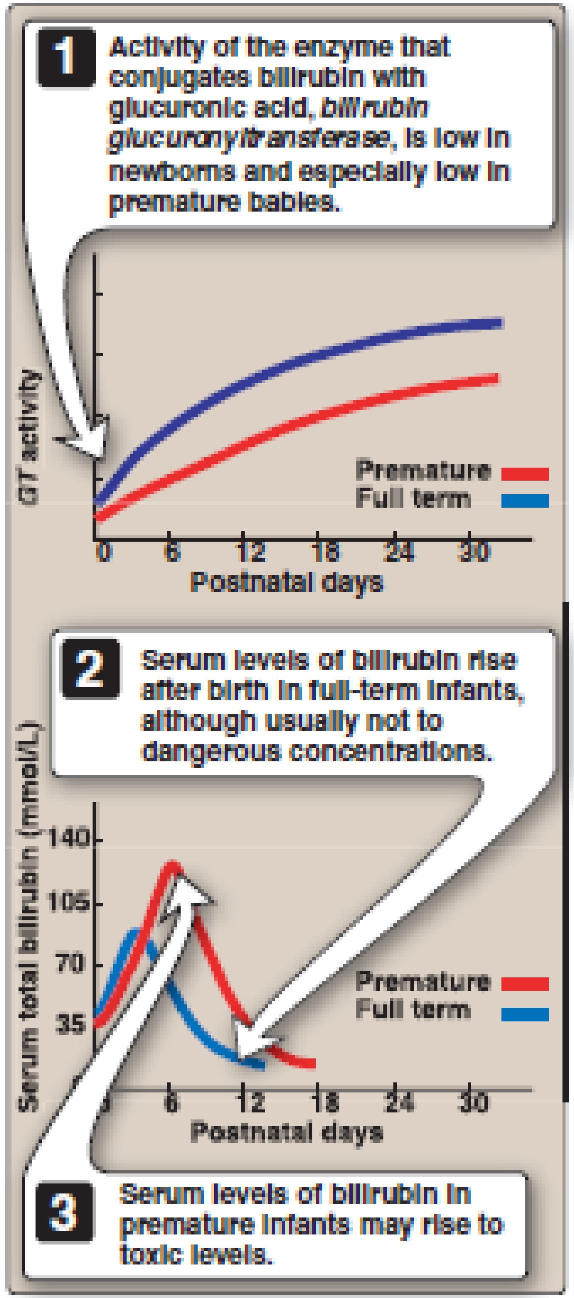
BG = bilirubin glucuronide; B = bilirubin;
U = urobilinogen; S = stercobilin.

Jaundice in newborns

Treatment:

Blue fluorescent light that converts bilirubin to more polar water-soluble isomers.

The resulting photoisomers can be excreted into the bile without conjugation to glucuronic acid.



Determination of bilirubin concentration

The most common way to measure bilirubin uses van den Bergh reaction

Diazotized sulfanilic acid + bilirubin → **Red** azodipyrroles

The color change is measured colorimetrically.

Direct-reacting measurement of **conjugated** bilirubin **(aq)** by rapid reaction with the reactant (within 1 min).

Indirect-reacting measurement of **total** bilirubin **(methanol)** by reaction with the reactant.

Unconjugated bilirubin= total bilirubin - conjugated bilirubin

In normal plasma, only about 4% of the total bilirubin is conjugated or direct-reacting, because most is secreted into bile.