
Secret Getaway


بسم الله الرحمن الرحيم

SYNTHESIS AND DEGRADATION OF PORPHYRINS

BY

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Amino acids, in addition to serving as building blocks for proteins, are precursors of many nitrogen-containing compounds that have important physiologic functions.

- **These functions include:**

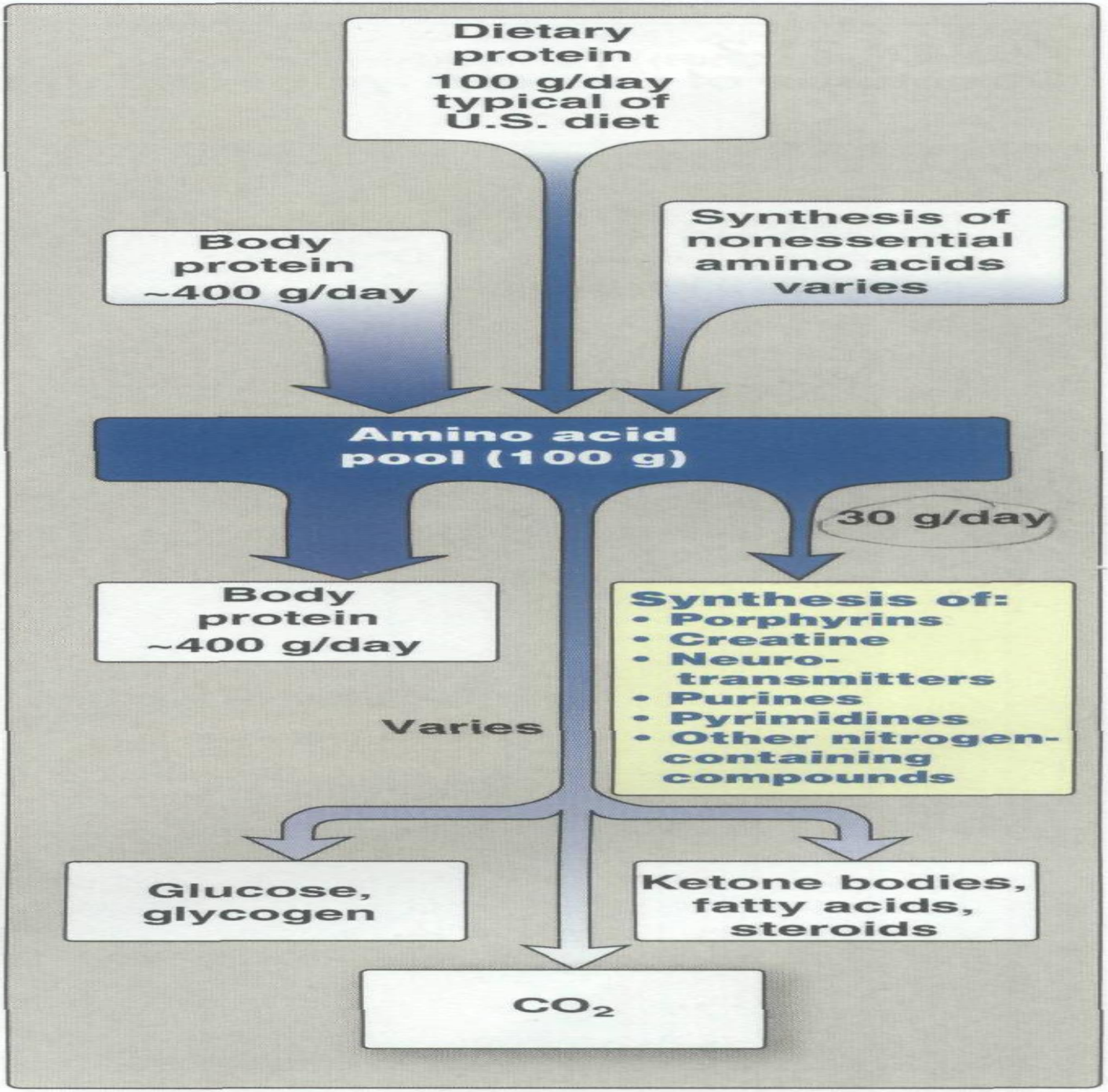
✓Porphyrins.

✓Neurotransmitters.

✓Hormones.

✓Purines.

✓Pyrimidines.


Dietary protein
100 g/day typical of U.S. diet
Body protein ~400 g/day
Synthesis of nonessential amino acids varies
Amino acid pool (100 g)
30 g/day
Body protein ~400 g/day
Varies
Synthesis of:
• Porphyrins
• Creatine
• Neuro-transmitters
• Purines
• Pyrimidines
• Other nitrogen-containing compounds
Glucose, glycogen
Ketone bodies, fatty acids, steroids
CO_2

- **Porphyrins** are cyclic compounds that readily bind metal ions, usually Fe^{2+} or Fe^{3+}.

  The most prevalent metalloporphyrin in humans is heme, which is the prosthetic group for:

- Hemoglobin.
- Myoglobin.
- Cytochromes.
- Catalase.
- Tryptophan pyrrolase.

Table 31–1. Examples of Some Important Human and Animal Hemoproteins.[1]	
Protein	**Function**
Hemoglobin	Transport of oxygen in blood
Myoglobin	Storage of oxygen in muscle
Cytochrome *c*	Involvement in electron transport chain
Cytochrome P450	Hydroxylation of xenobiotics
Catalase	Degradation of hydrogen peroxide
Tryptophan pyrrolase	Oxidation of tryptophan

- ✓These hemeproteins are constantly being rapidly synthesized and degraded.

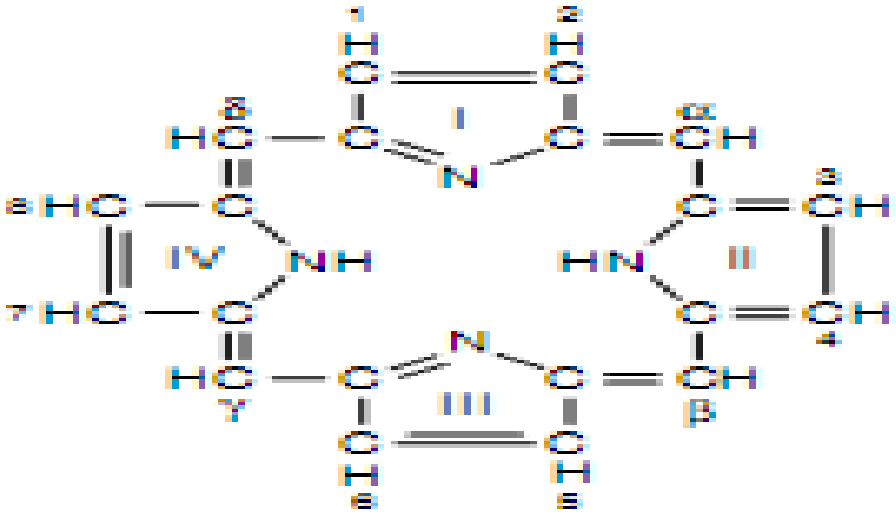
- ✓ For example, six to seven gm of hemoglobin are synthesized each day to replace heme lost through catabolism.

Structure of porphyrins

Ring structure:

The Porphyrins are complex structures consisting of 4 pyrrole rings united by "methenyl" bridges or (methylidene bridges) (A, B, C, D) .

Pyrrole



Porphin
($C_{20}H_{14}N_4$)

Side chains:

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

For example:

- Uroporphyrin contains acetate (-CH2-COO-) and propionate (-CH2-CH2-COO-) side chains.
- Coproporphyrin, shown at left, is substituted with methyl (-CH3) and propionate groups.

* Porphyrins *

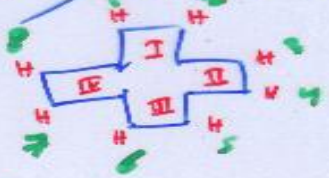
* cyclic compound formed from 4 pyrrole rings. (I, II, III & IV) Combined together through 4 methyline bridges (α, β, γ & δ).

* the compound produced from such 4 pyrrole rings is called → "porphin"

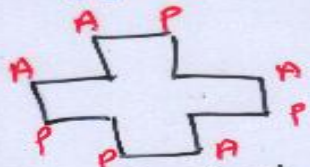
Pyrrole ring

* Porphyrin derivatives:-

* If 8 hydrogen atoms replaced by certain chemical groups → new compounds called porphyrin derivatives are produced as follows:



Uroporphyrin I



Uroporphyrin III

A → CH_2-CO_2H

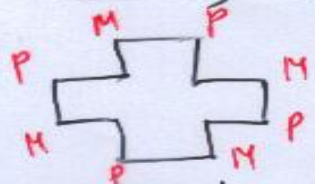
P → $CH_2-CH_2-CO_2H$

→ first isolated from urine

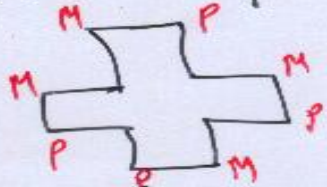
* If CH_2-CO_2H → CO_2 → CH_3 (M)

Acetic group — methyl group

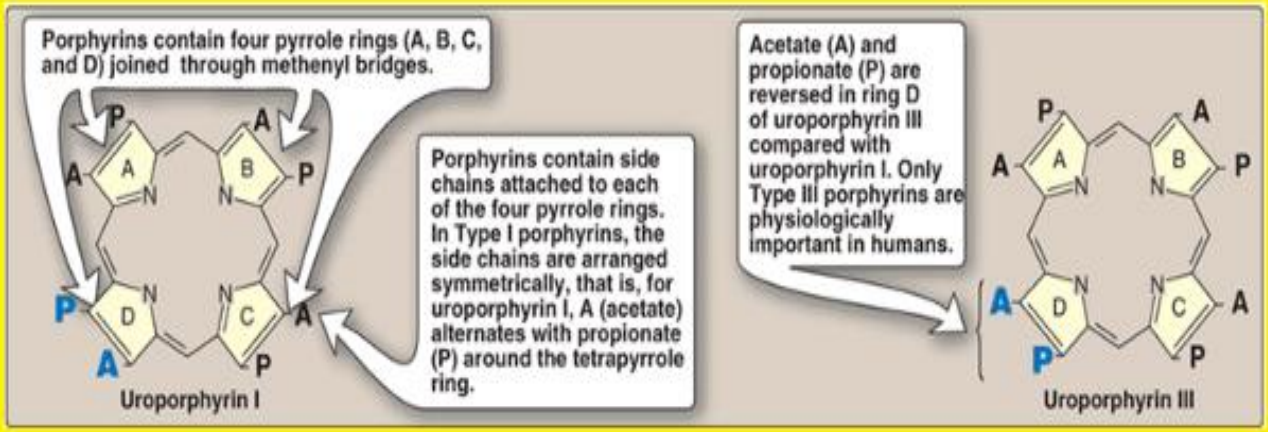
Coproporphyrins are produced (isolated from stool)



Coproporphyrin I



Coproporphyrin III

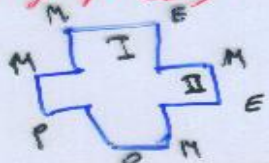


Structures of uroporphyrin I and uroporphyrin III. A = acetate and P = propionate.

D- if the propionic groups (ring I & II) of Coproporphyrin III → decarboxylated → ethyl group produced → forming mesoporphyrin III

$CH_2-CH_2-COOH \xrightarrow{-CO_2} CH_2-CH_3$

propionic group → ethyl group (E)

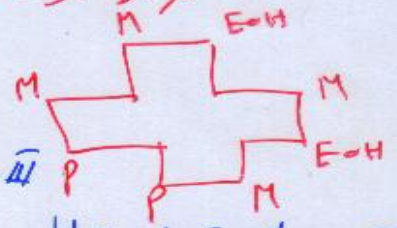


Mesoporphyrin III

E- if the ethyl group are oxidised → hydroxy ethyl groups → produced and → hematoporphyrin III is formed.

$CH_2-CH_3 \xrightarrow{O} CHe-CHe-OH$ (E-OH)

ethyl group → hydroxy ethyl group

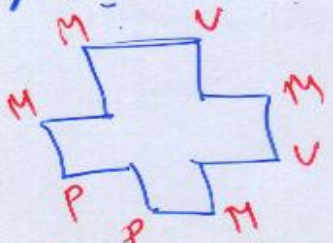


Hematoporphyrin III

D- if the hydroxy ethyl group is dehydrated → vinyl groups are formed → protoporphyrin III is produced.

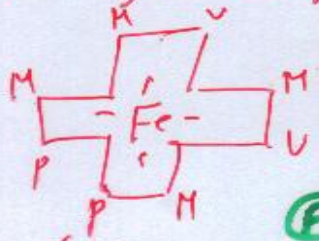
$CH_3-CH_2-OH \xrightarrow{-H_2O} CH=CH_2$

vinyl group (V)



Protoporphyrin III

E- Iron can be added forming → Heme



Heme

F- 4 molecules of heme combine with one molecule of globin → hemoglobin.

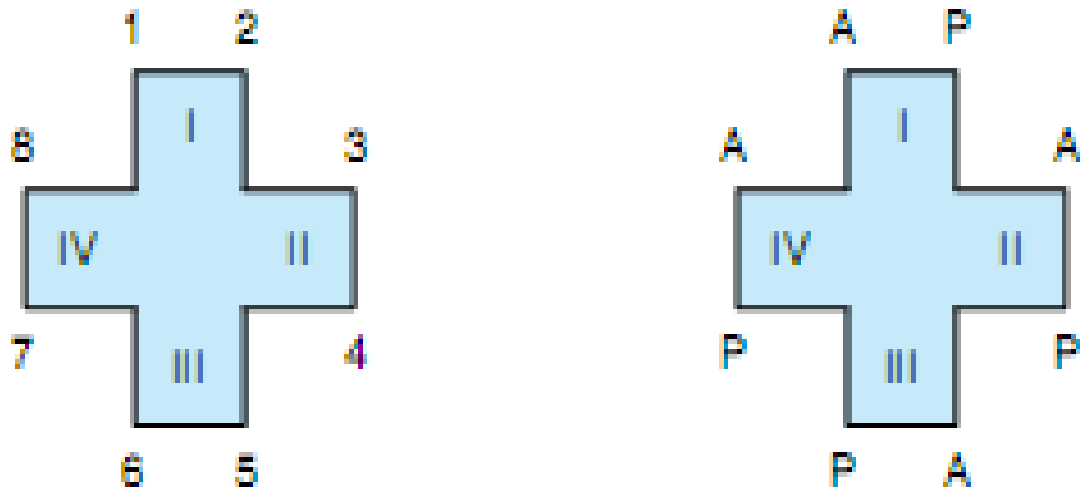


Figure 32–2. Uroporphyrin III. A (acetate) = —CH_2COOH; P (propionate) = —CH_2CH_2COOH.

Uroporphyrins were first found in the urine, but they are not restricted to urine.

Coproporphyrins were first isolated from feces, but they are also found in urine.

Figure 32–3. Uroporphyrins and coproporphyrins. A (acetate); P (propionate); M (methyl) = —CH_3; V (vinyl) = —CH—CH_2.

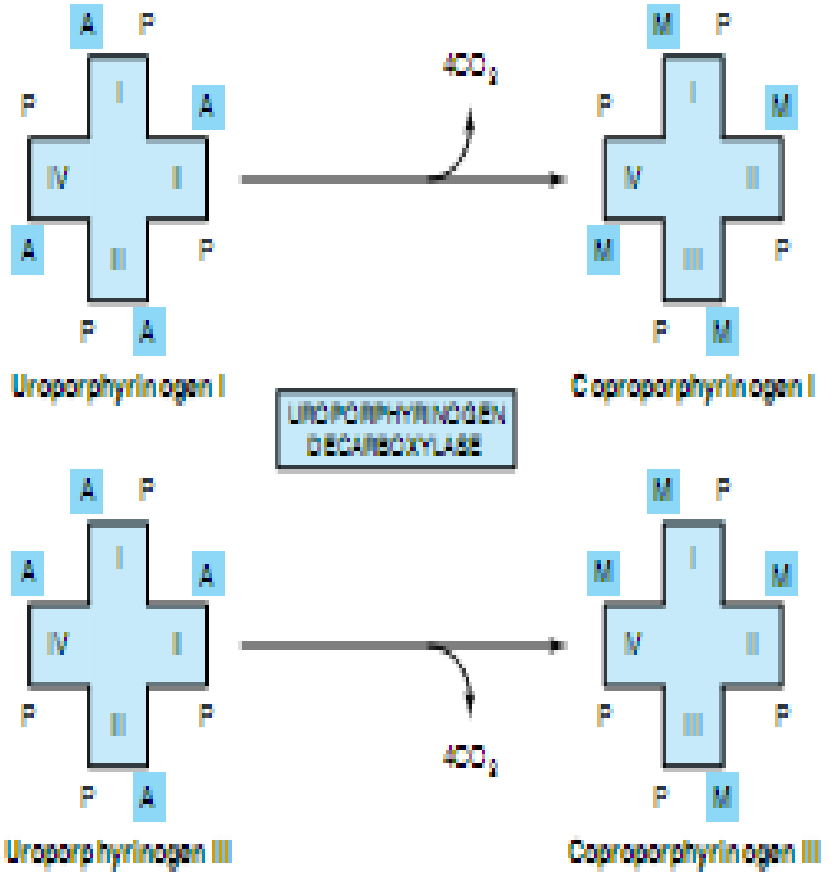


Figure 32–7. Decarboxylation of uroporphyrinogens to coproporphyrinogens in cytosol. (A, acetyl; M, methyl; P, propionyl.)

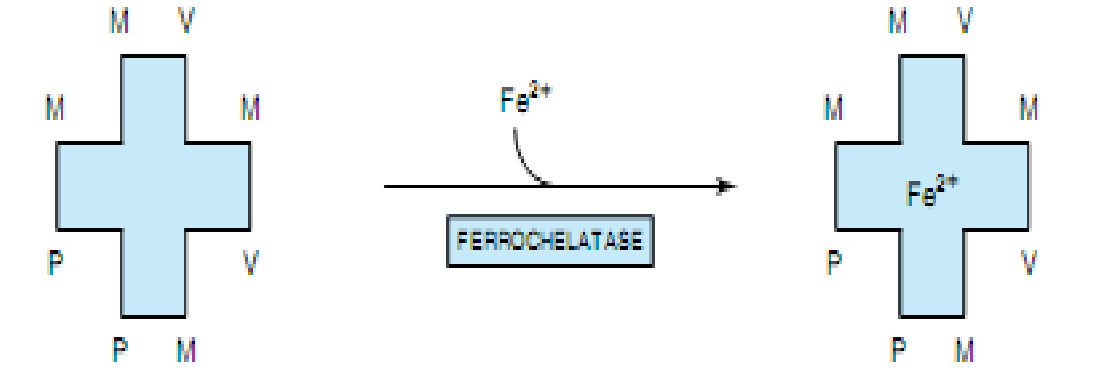


Figure 32–4. Addition of iron to protoporphyrin to form heme.

Biosynthesis of porphyrins

- **Site:**

➢ The major sites of heme biosynthesis are the liver.

➢ The ***Initial reaction and the last three steps*** in the formation of porphyrins occur in mitochondria.

➢ The ***intermediate steps*** of the biosynthetic pathway occur in the cytosol.

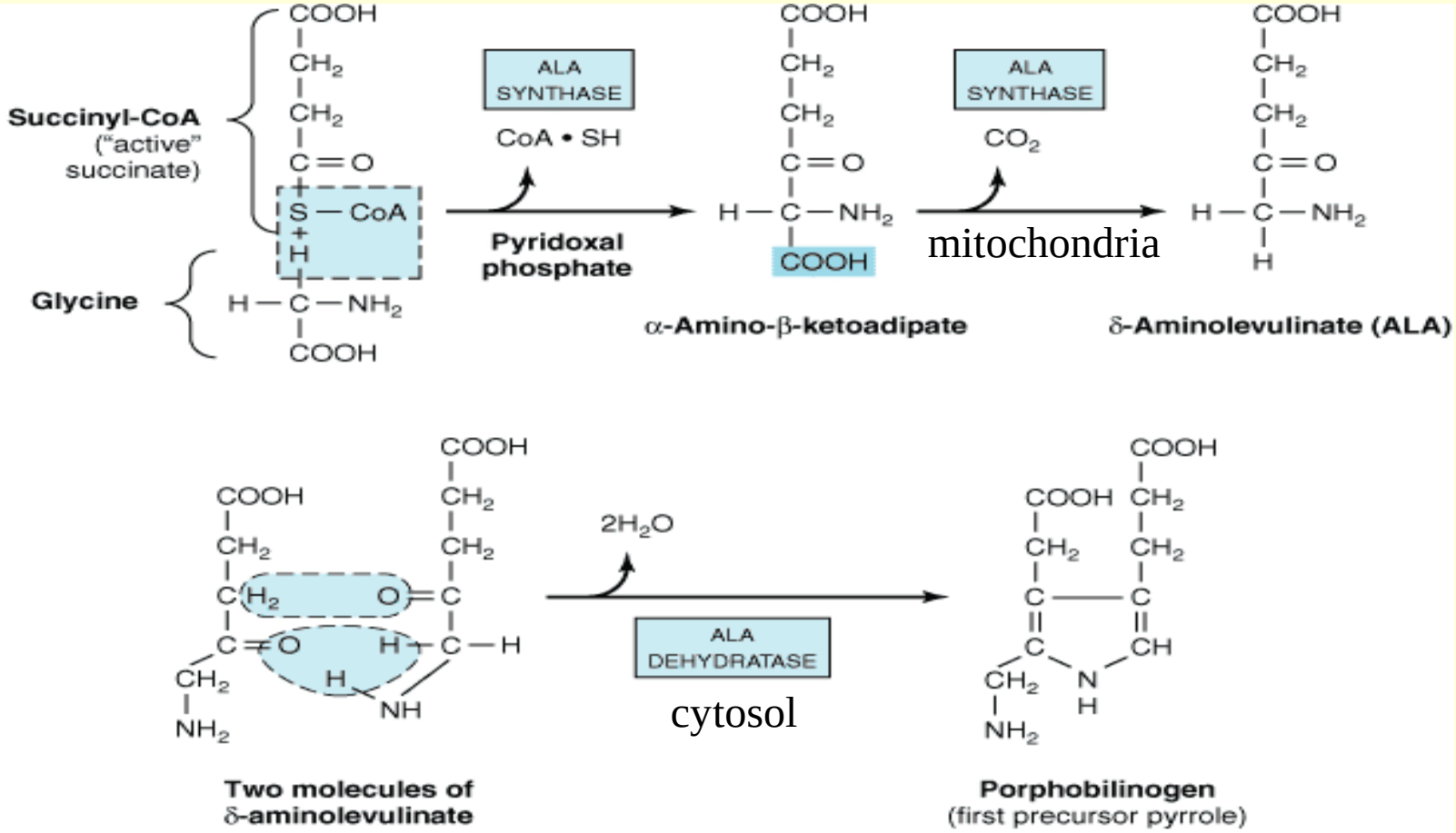
- **Note:** Mature red blood cells lack mitochondria and are unable to synthesize heme.

1. Formation of δ-aminolevulinic acid (ALA):

- All the carbon and nitrogen atoms of the porphyrin molecule are provided by two simple building blocks:

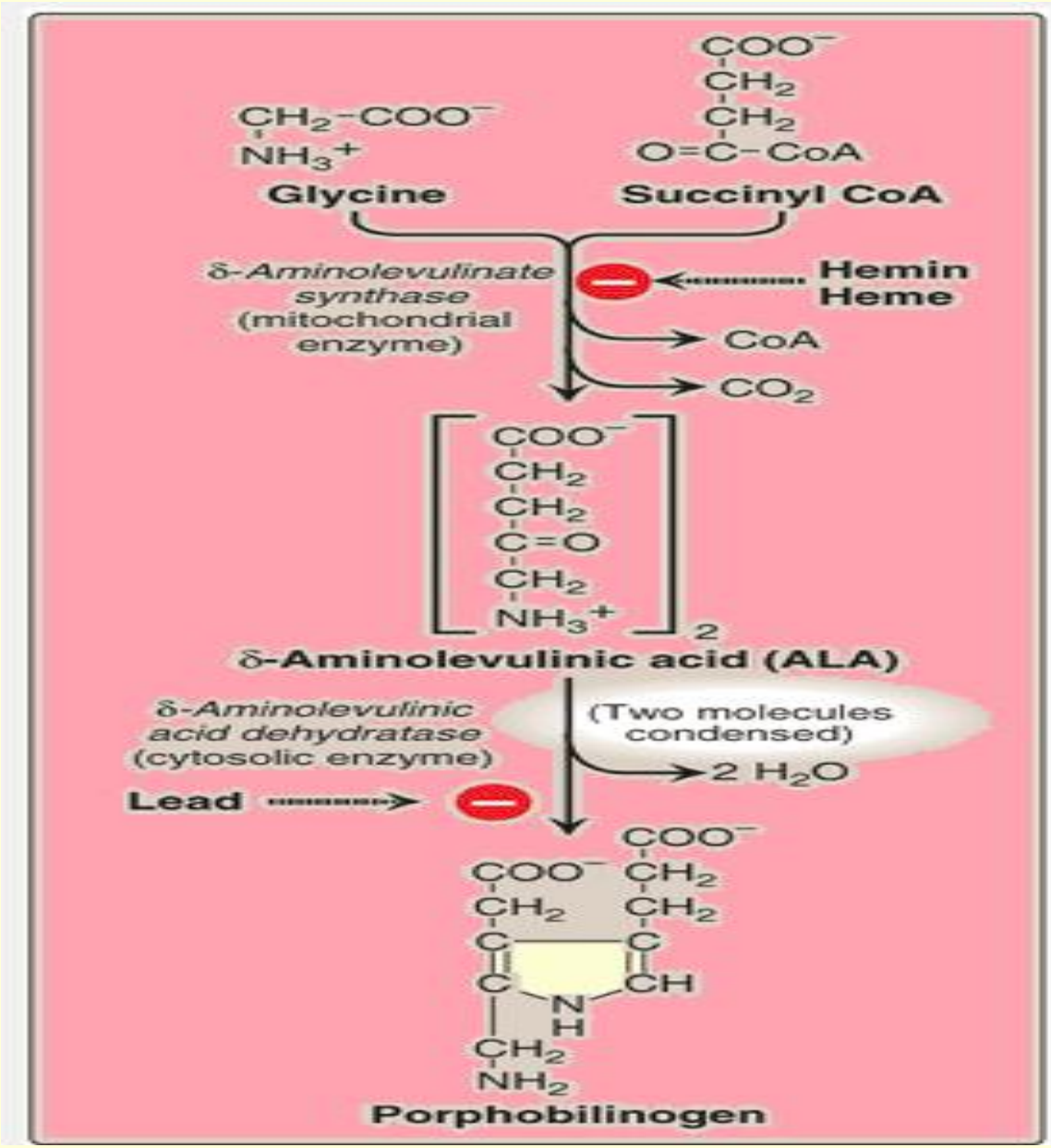
1. Glycine (a non essential amino acid).
2. Succinyl CoA (an intermediate in the citric acid cycle).

- ✓ Glycine and succinyl CoA condense to form ALA in a reaction catalyzed by ALA synthase.
- ✓ This reaction requires pyridoxal phosphate as a coenzyme.
- ✓ It is a rate-controlling step in porphyrin biosynthesis.



a. End product inhibition by hemin:

- The activity of ALA synthase is decreased by elevated concentrations of hemin, which is derived from heme by the oxidation of Fe^{2+} to Fe^{3+}.
- When porphyrin production exceeds the availability of globin or other Apo proteins, heme accumulates and is oxidized to hemin.
- This end product inhibition causes the decreased synthesis of ALA synthase.


Glycine
Succinyl CoA
δ-Aminolevulinate synthase (mitochondrial enzyme)
Hemin
Heme
CoA
CO2
2
δ-Aminolevulinic acid (ALA)
δ-Aminolevulinic acid dehydratase (cytosolic enzyme)
(Two molecules condensed)
2 H2O
Lead
Porphobilinogen

b. Effect of drugs on ALA synthase activity:

- Administration of drugs, such as phenobarbital, results in a marked increase in hepatic ALA synthase activity.
- These drugs are metabolized by microsomal cytochrome P**450** mono-oxygenase system, a hemeprotein oxidase system found in the liver .

- In response to these drugs the synthesis of cytochrome P**450** increases, leading to an enhanced consumption of heme, a component of cytochrome P**450**.
- This causes a decrease in the concentration of heme in liver cells.
- The lower intracellular heme concentration leads to an increase in the synthesis of ALA synthase (derepression) and prompts a corresponding increase in ALA synthesis.

2. Formation of porphobilinogen:

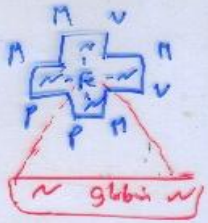
- The dehydration of two molecules of ALA to form porphobilinogen by δ-aminolevulinic acid dehydrase.
- **It is inhibited by heavy metal ions like lead.**
- This inhibition is responsible for the elevation in ALA and the anemia seen in **lead poisoning.**

(h)

Hemoglobin

oxygenated Hb

Reduced Hb.

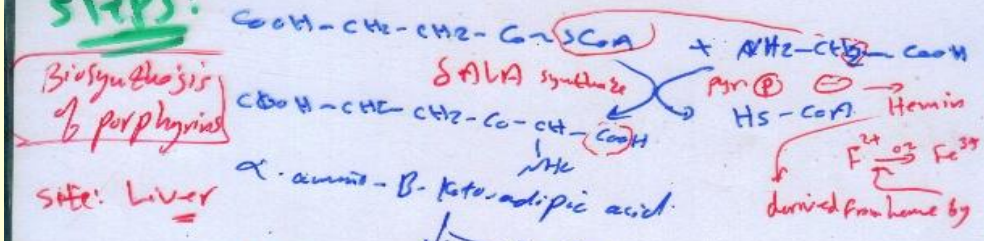


* globin is simple protein
* having high histidine & lysine
* small amount of tolurene.

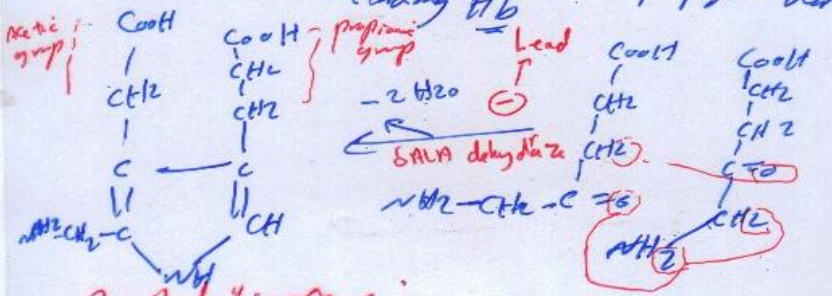
STEPS:

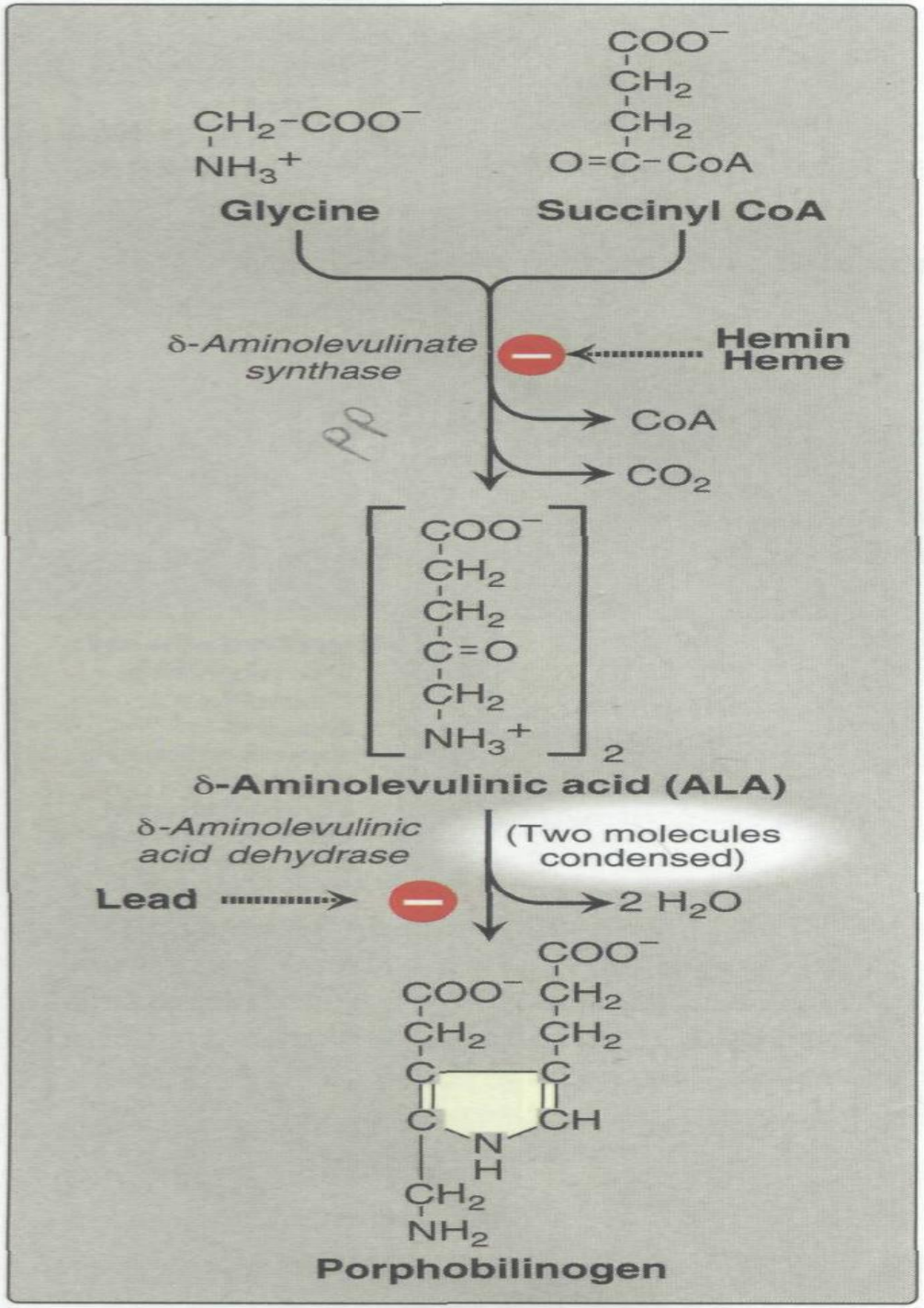
Biosynthesis of porphyrins

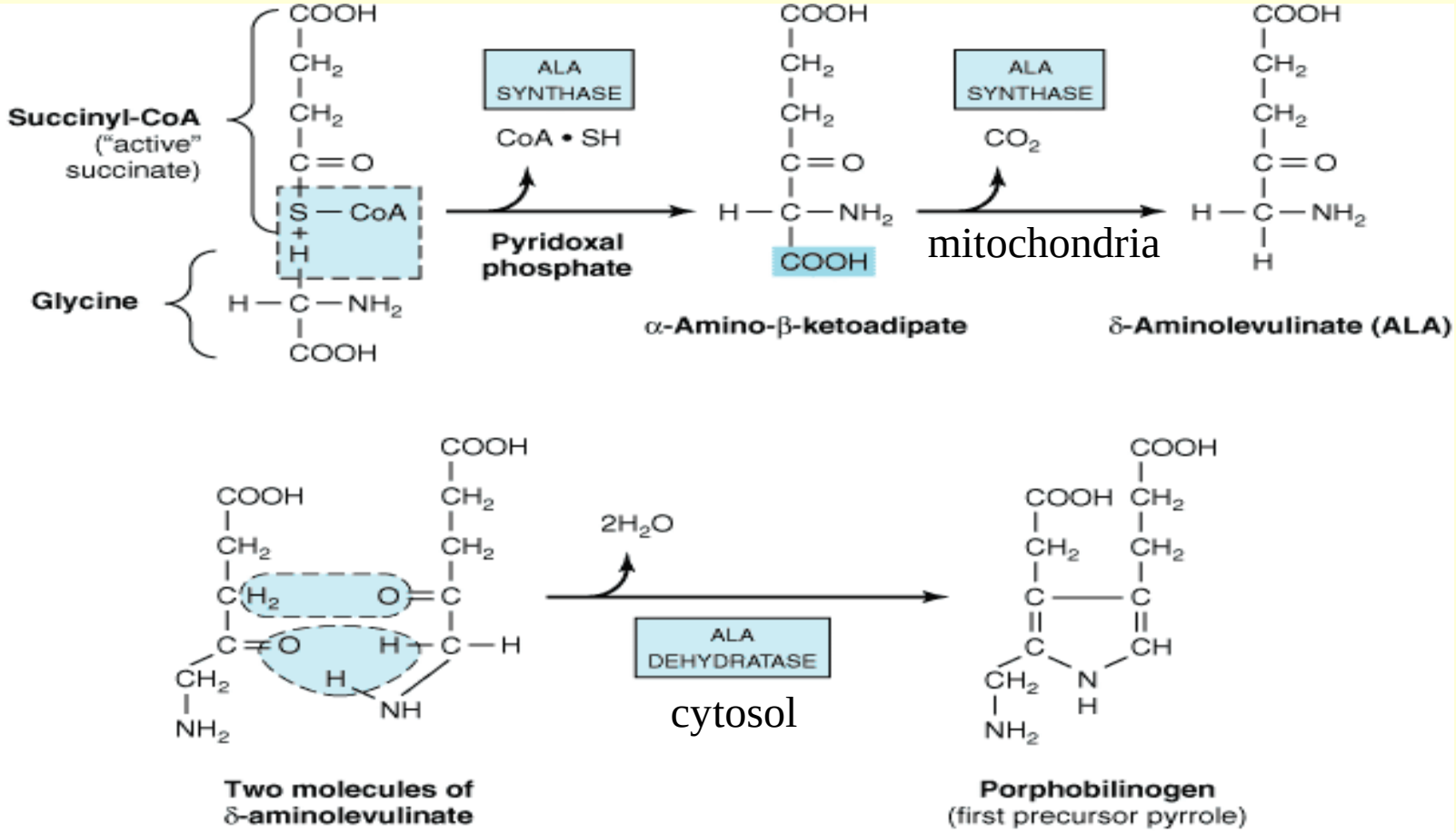
Site: Liver



* Two molecules of δALA condense together with loss of 2 molecules of H_2O → the precursors of all porphyrin derivatives including Hb → Porphobilinogen




Glycine
Succinyl CoA
δ-Aminolevulinate synthase
Hemin
Heme
CoA
CO_2
2
δ-Aminolevulinic acid (ALA)
δ-Aminolevulinic acid dehydrase
Lead
(Two molecules condensed)
2 H_2O
Porphobilinogen



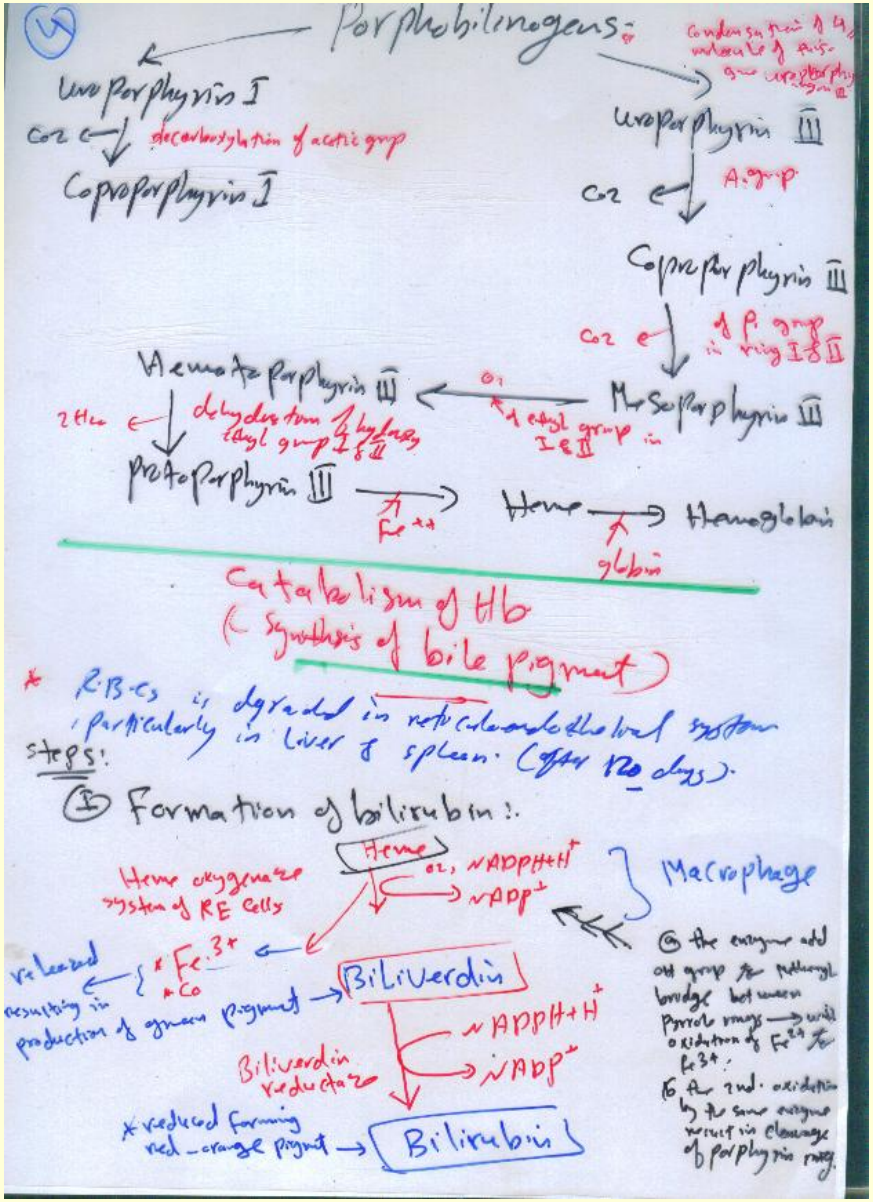
3. Formation of uroporphyrinogen:

- ✓ **The condensation of four molecules of porphobilinogen results in the formation of uroporphyrinogen III.**

- ✓ **The reaction requires uroporphyrinogen I synthetase (which form uroporphyrinogen I), and uroporphyrinogen III cosynthetase (which produces uroporphyrinogen III).**

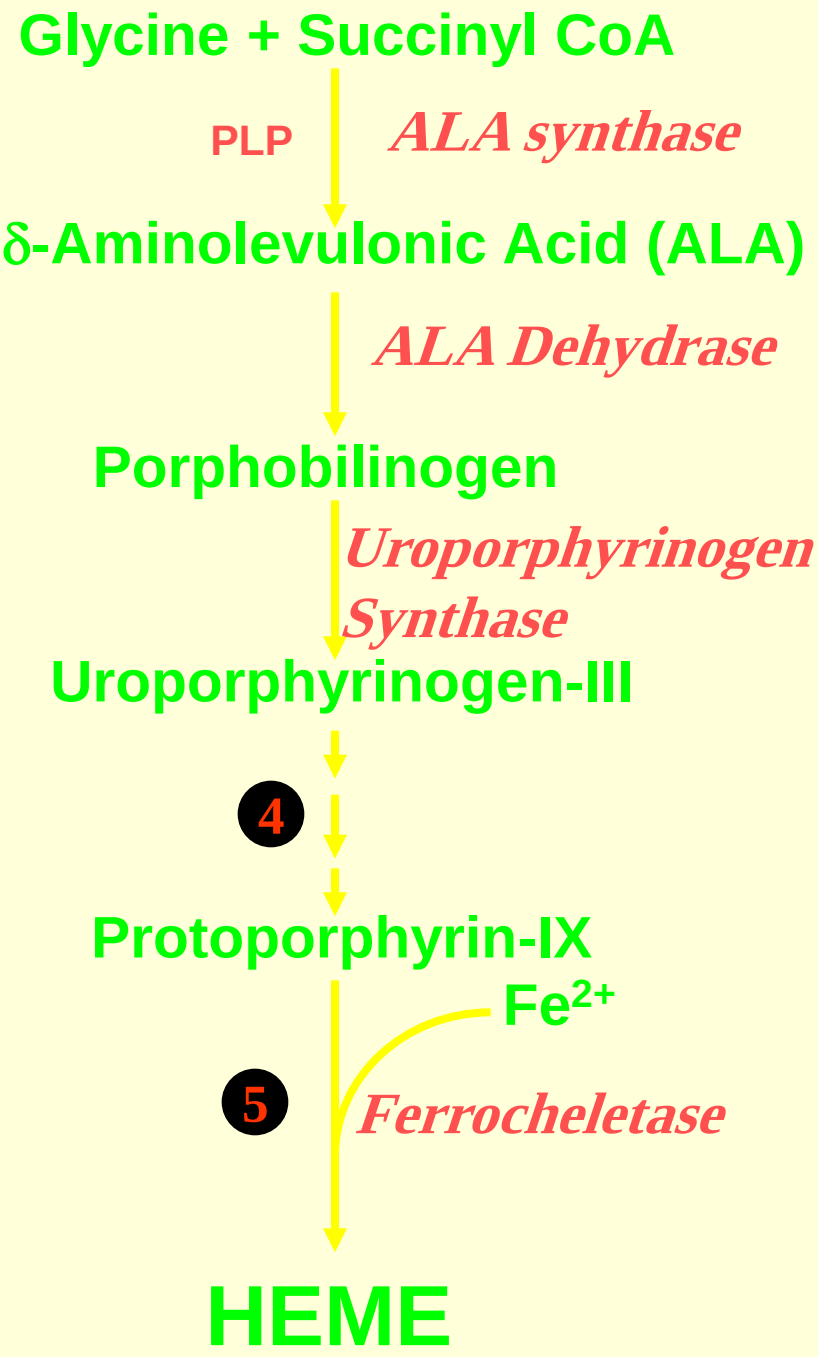
4. Formation of heme:

- **Uroporphyrinogen III is converted to heme by a series of decarboxylations and oxidations.**
- **The introduction of Fe2+ into protoporphyrin IX occurs spontaneously, and the rate is enhanced by the enzyme ferrochelatase, (inhibited by lead).**

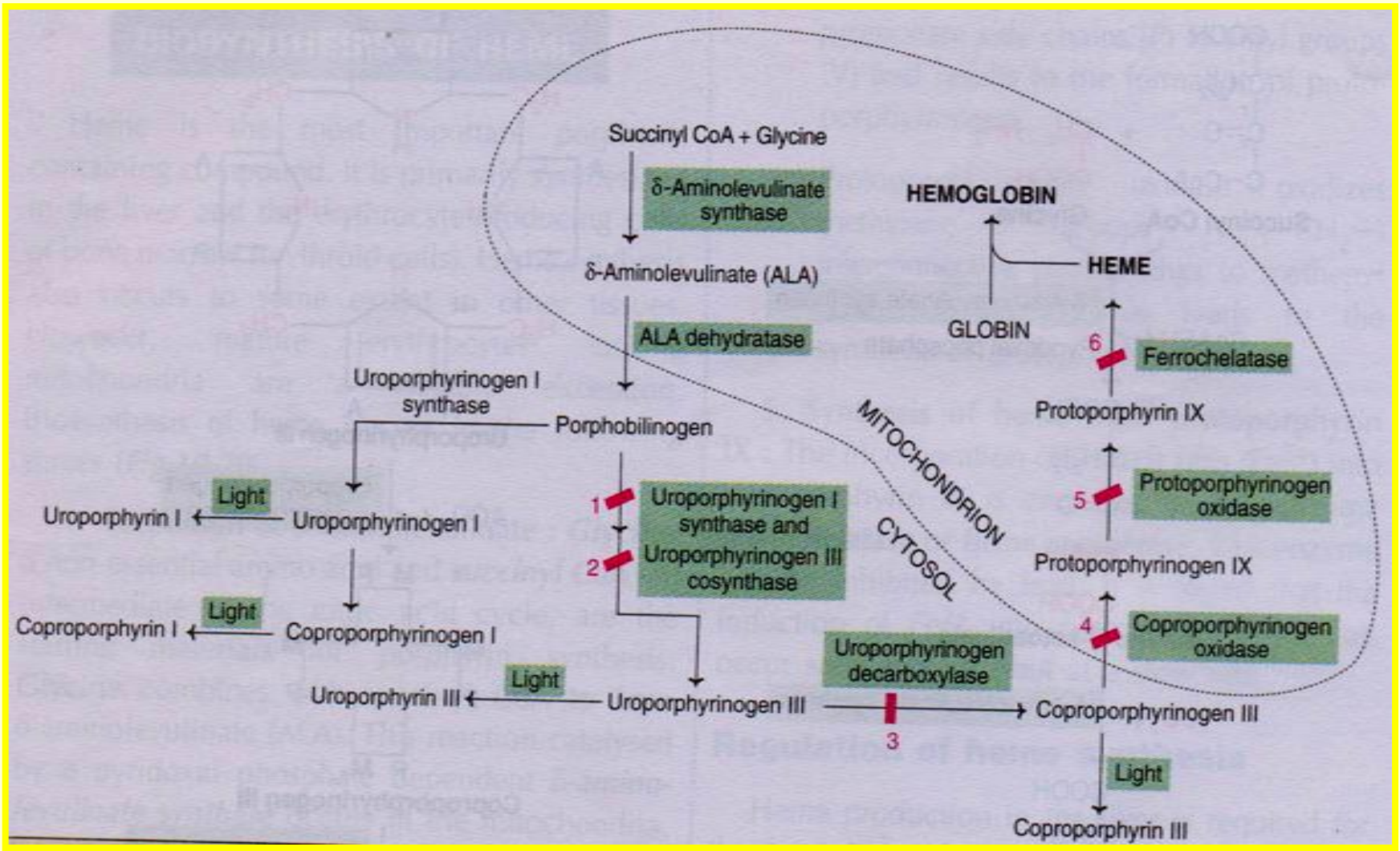

Porphobilinogens
Uroporphyrin I
CO2
decarboxylation of acetic grp
Coproporphyrin I
Uroporphyrin III
A grp
Coproporphyrin III
P grp in ring I & II
Mesoporphyrin III
Oxidation
Ethyl group in I & II
Hemato Porphyrin III
2H
dehydration of hydroxy ethyl group I & III
Proto Porphyrin III
Fe++
Heme
Globin
Hemoglobin
Catabolism of Hb
(Synthesis of bile pigment)
RBCs is degraded in reticuloendothelial system particularly in liver & spleen. (after 120 days).
Steps:
1 Formation of bilirubin:
Heme
Heme oxygenase system of RE cells
O2, NADPH+H+
NADP+
Macrophage
Fe3+
Co
released resulting in production of green pigment
Biliverdin
NADPH+H+
NADP+
Biliverdin reductase
reduced forming red-orange pigment
Bilirubin
the enzyme add OH group to methenyl bridge between pyrrol rings → with oxidation of Fe2+ to Fe3+.
2nd oxidation by the same enzyme result in cleavage of porphyrin ring.

4. Conversion of uroporphyrinogen III to protoporphyrin IX: This is catalysed by a series of reactions

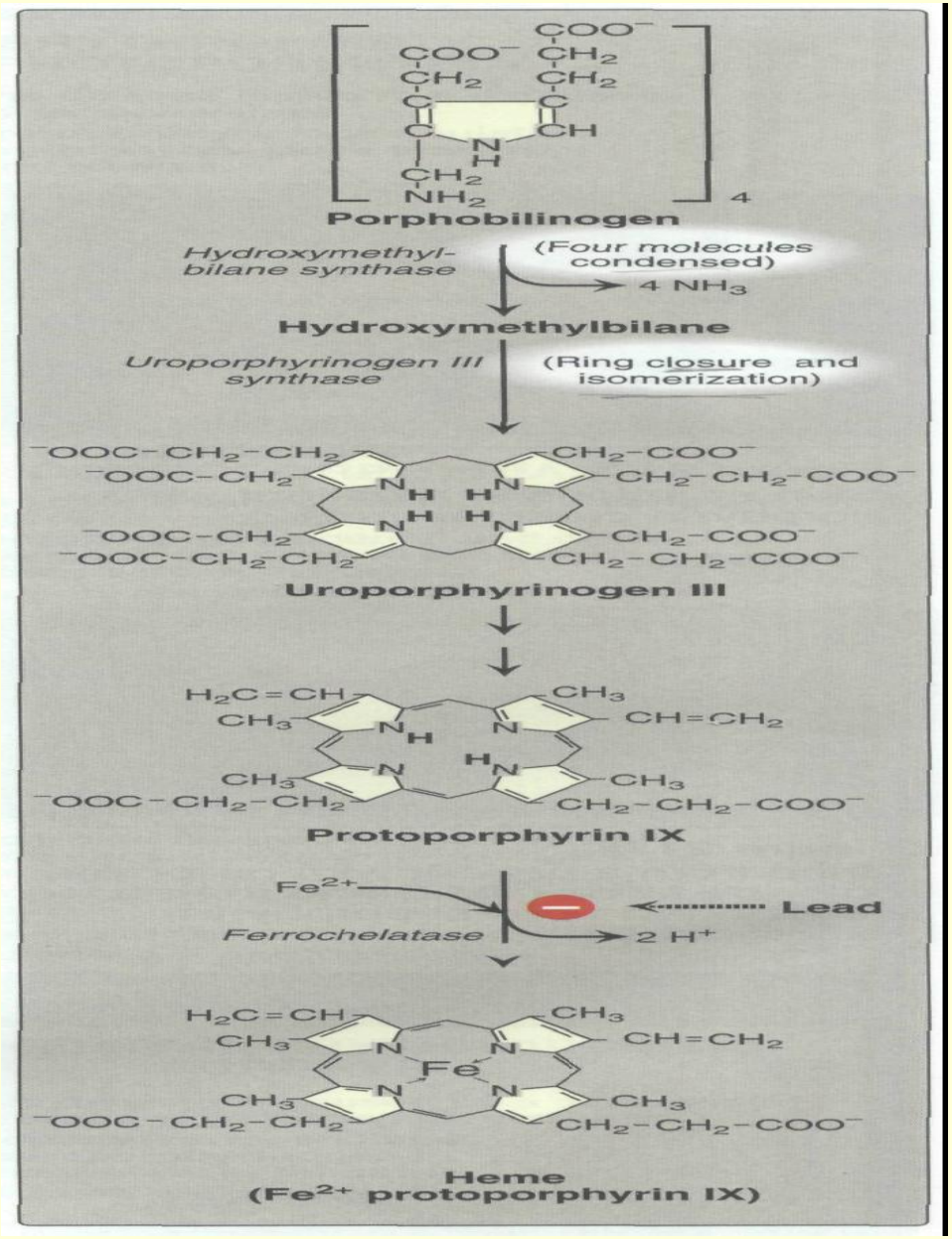
5. Synthesis of heme from protoporphyrin IX: The incorporation of ferrous iron (Fe^{2+}) into protoporphyrin IX is catalysed by the enzyme *ferrochelatase.* This enzyme is inhibited by lead.

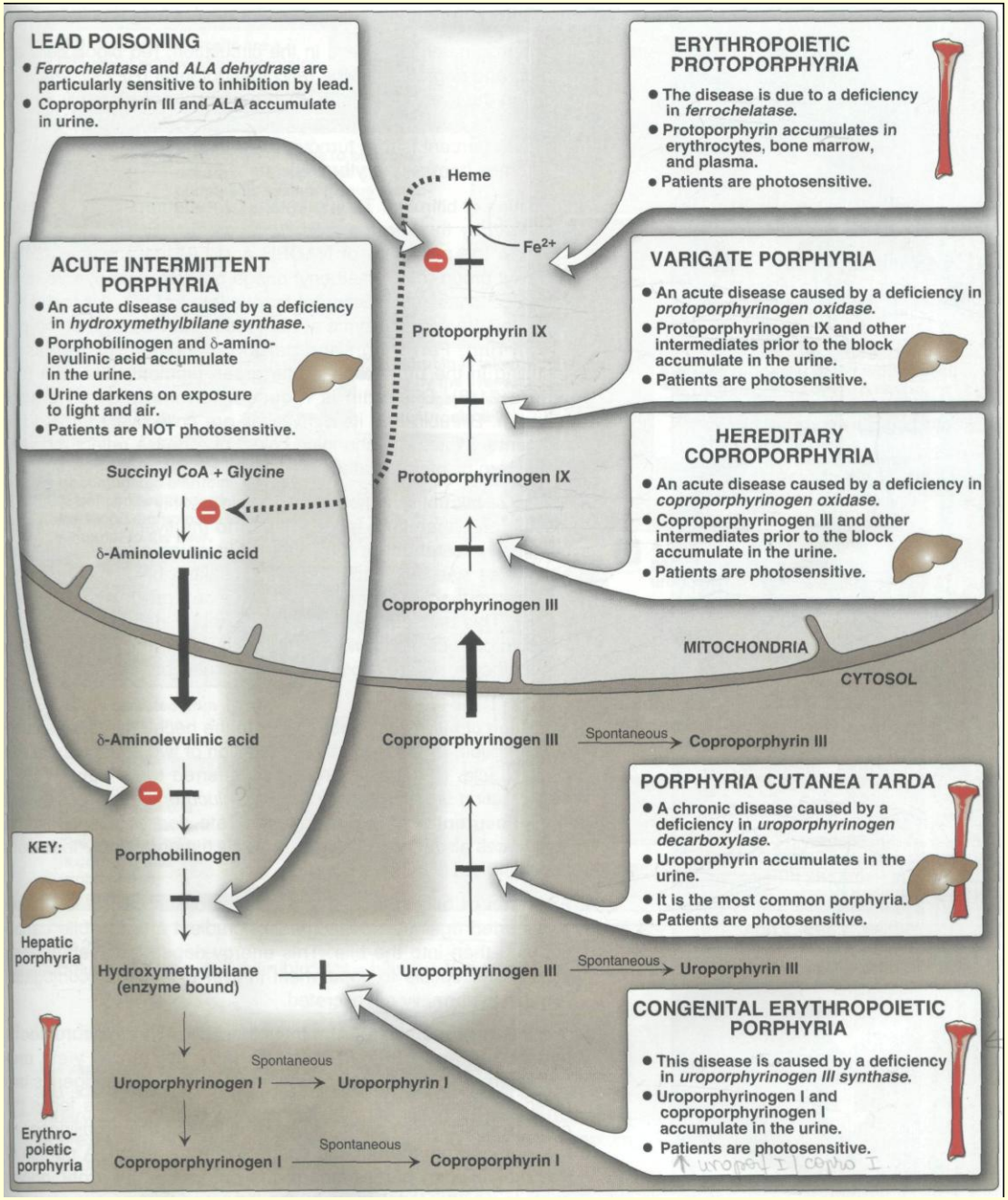


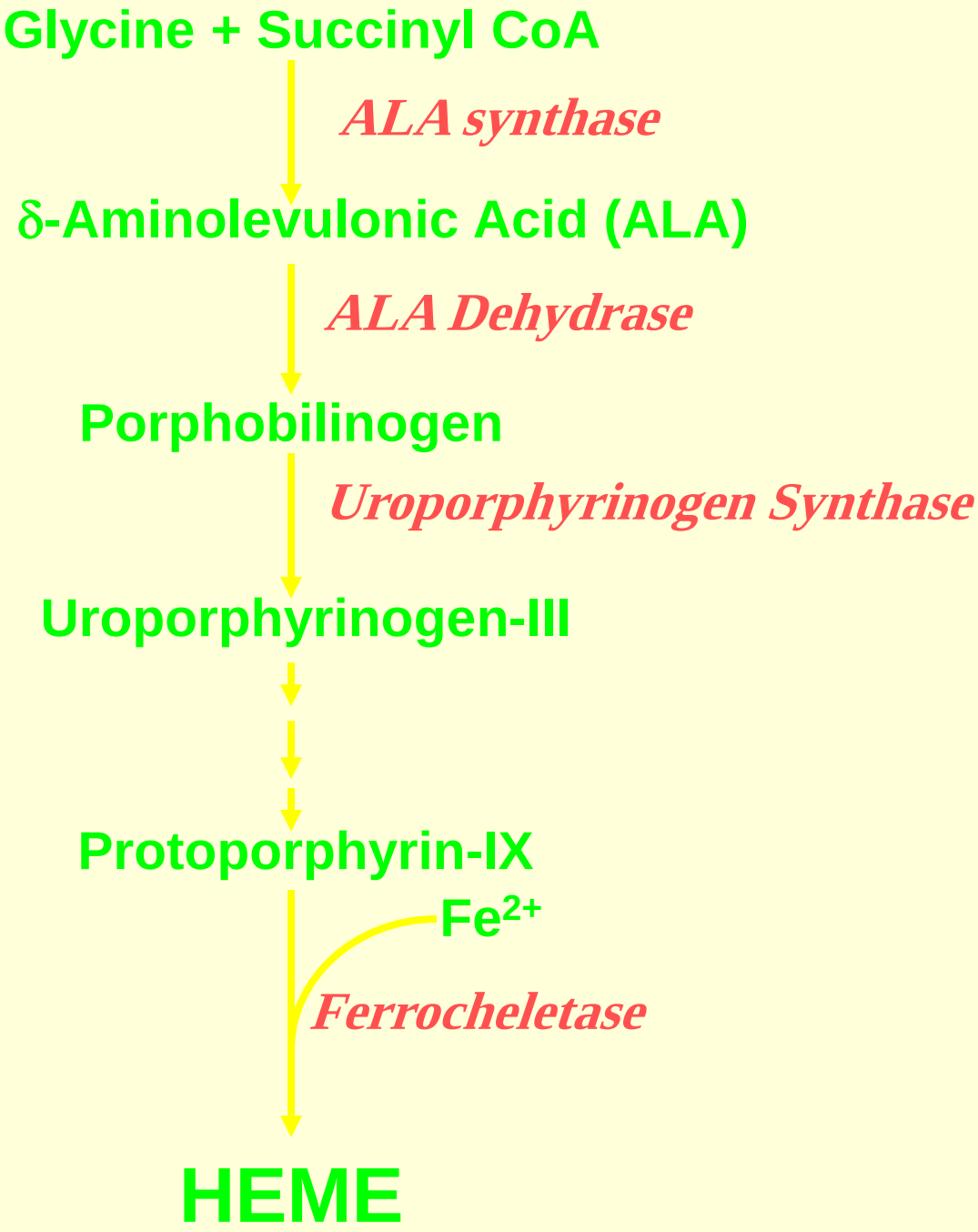
BIOSYNTHESIS OF HEME



Formation of heme




LEAD POISONING
• Ferrochelatase and ALA dehydrase are particularly sensitive to inhibition by lead.
• Coproporphyrin III and ALA accumulate in urine.
ERYTHROPOIETIC PROTOPORPHYRIA
• The disease is due to a deficiency in ferrochelatase.
• Protoporphyrin accumulates in erythrocytes, bone marrow, and plasma.
• Patients are photosensitive.
Heme
Fe2+
ACUTE INTERMITTENT PORPHYRIA
• An acute disease caused by a deficiency in hydroxymethylbilane synthase.
• Porphobilinogen and δ-amino-levulinic acid accumulate in the urine.
• Urine darkens on exposure to light and air.
• Patients are NOT photosensitive.
Protoporphyrin IX
VARIGATE PORPHYRIA
• An acute disease caused by a deficiency in protoporphyrinogen oxidase.
• Protoporphyrinogen IX and other intermediates prior to the block accumulate in the urine.
• Patients are photosensitive.
Protoporphyrinogen IX
HEREDITARY COPROPORPHYRIA
• An acute disease caused by a deficiency in coproporphyrinogen oxidase.
• Coproporphyrinogen III and other intermediates prior to the block accumulate in the urine.
• Patients are photosensitive.
Succinyl CoA + Glycine
δ-Aminolevulinic acid
Coproporphyrinogen III
MITOCHONDRIA
CYTOSOL
δ-Aminolevulinic acid
Coproporphyrinogen III
Spontaneous
Coproporphyrin III
PORPHYRIA CUTANEA TARDA
• A chronic disease caused by a deficiency in uroporphyrinogen decarboxylase.
• Uroporphyrin accumulates in the urine.
• It is the most common porphyria.
• Patients are photosensitive.
KEY:
Hepatic porphyria
Erythro-poietic porphyria
Porphobilinogen
Hydroxymethylbilane (enzyme bound)
Uroporphyrinogen III
Spontaneous
Uroporphyrin III
CONGENITAL ERYTHROPOIETIC PORPHYRIA
• This disease is caused by a deficiency in uroporphyrinogen III synthase.
• Uroporphyrinogen I and coproporphyrinogen I accumulate in the urine.
• Patients are photosensitive.
Spontaneous
Uroporphyrinogen I
Uroporphyrin I
Spontaneous
Coproporphyrinogen I
Coproporphyrin I


Glycine + Succinyl CoA
ALA synthase
δ-Aminolevulonic Acid (ALA)
ALA Dehydrase
Porphobilinogen
Uroporphyrinogen Synthase
Uroporphyrinogen-III
Protoporphyrin-IX
Fe2+
Ferrocheletase
HEME

Degradation of heme

- ✓After 120 days in the circulation, red blood cells are degraded by the reticuloendothelial (RE) system, particularly in the liver and spleen.
- ✓Approximately 85% of heme destined for degradation comes from red blood cells, and 15% from turnover of immature red blood cells and cytochromes from extraerythroid tissues.

1. Formation of bilirubin

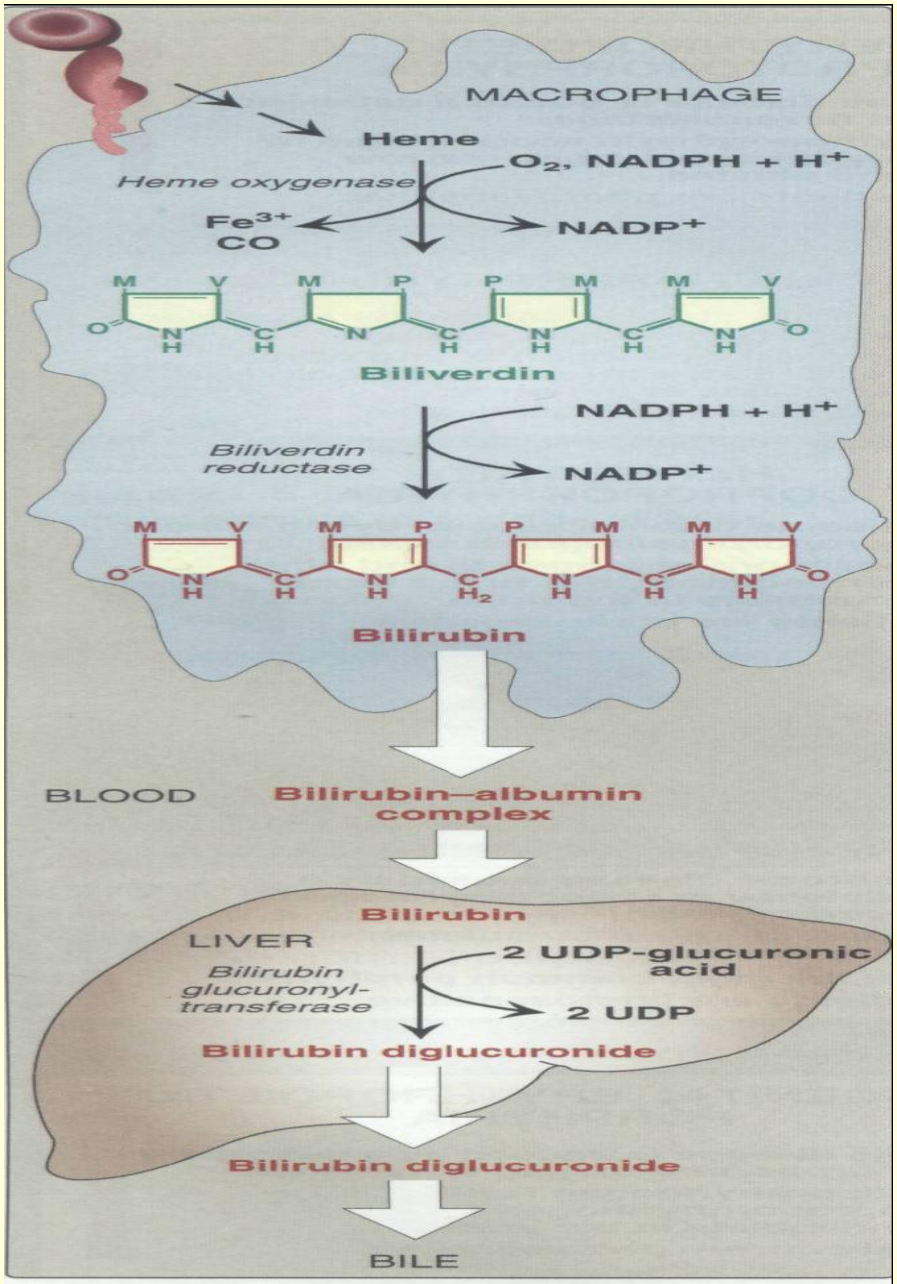
I. The first step of degradation catalyzed by:

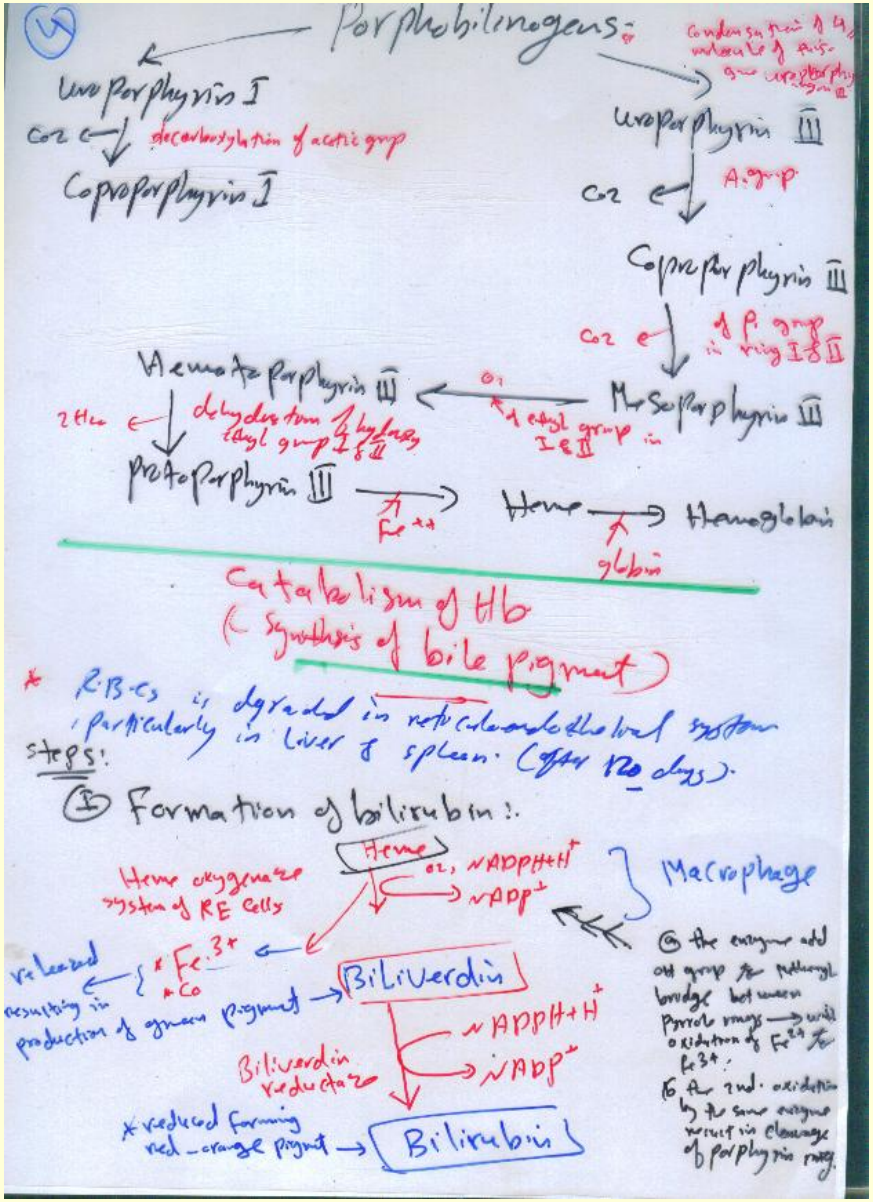
- Microsomal heme oxygenase system of the RE cells. In the presence of NADPH and O2.
- The enzyme adds a hydroxyl group to the methenyl bridge between two pyrrole rings with a concomitant oxidation of ferrous iron to Fe3+.

II. A second oxidation by the same enzyme system results in cleavage of the porphyrin ring.

- Ferric iron and carbon monoxide are released, resulting in production of green pigment biliverdin.
- Biliverdin is reduced, forming red-orange bilirubin.
- Bilirubin and its derivatives are collectively termed bile pigments.

Formation of bilirubin from heme




Porphobilinogens
Uroporphyrin I
CO2
decarboxylation of acetic grp
Coproporphyrin I
Uroporphyrin III
A grp
Coproporphyrin III
P grp in ring I & II
Mesoporphyrin III
Oxidation
Ethyl group in I & II
Hemato Porphyrin III
2H
dehydration of hydroxy ethyl group I & III
Proto Porphyrin III
Fe++
Heme
Globin
Hemoglobin
Catabolism of Hb
(Synthesis of bile pigment)
RBCs is degraded in reticuloendothelial system particularly in liver & spleen. (after 120 days).
Steps:
1 Formation of bilirubin:
Heme
Heme oxygenase system of RE cells
O2, NADPH+H+
NADP+
Macrophage
Fe3+
Co
released resulting in production of green pigment
Biliverdin
NADPH+H+
NADP+
Biliverdin reductase
reduced forming red-orange pigment
Bilirubin
the enzyme add OH group to methenyl bridge between pyrrol rings → with oxidation of Fe2+ to Fe3+.
2nd oxidation by the same enzyme result in cleavage of porphyrin ring.

2. Uptake of bilirubin by the liver

- Bilirubin is slightly soluble in plasma and transported to the liver by binding to albumin (Bilirubin-Albumin Complex).
- Bilirubin dissociates from the carrier albumin molecule and enters a hepatocyte, it binds to intracellular proteins, called ligandin.

Bilirubin → Transport to Liver by binding to albumin (in blood forming → Bilirubin-albumin complex)

Blood

Bilirubin

↓

Bilirubin – albumin Complex

→ bilirubin dissociated from carrier albumin & enters a hepatocytes → which it binds to intracellular proteins called "Ligandin"

(3) Formation of bilirubin diglucuronide :-

Bilirubin-albumin complex

Liver

bilirubin glucuronyl transferase

2 UDP-glucuronic acid

2 UDP

Bilirubin diglucuronide.

(4 Excretion of bilirubin into bile.

Bilirubin diglucuronide → Transport into bile

(5 Formation of urobilin in the intestine:

Bilirubin diglucuronide → hydrolysed & reduced by bacteria in the gut → urobilinogen

some reabsorbed from the gut into the portal blood and transported to the kidney

converted to yellow urobilin → excreted in urine → gives urine its characteristic colour

oxidation by intestinal bacteria → stercobilin → gives brown colour of stool

3. Formation of bilirubin diglucuronide

In the hepatocyte the solubility of bilirubin is increased by the addition of two molecules of glucuronic acid, catalyzed by bilirubin glucuronyltransferase using UDP-glucuronic acid as the glucuronate donor.

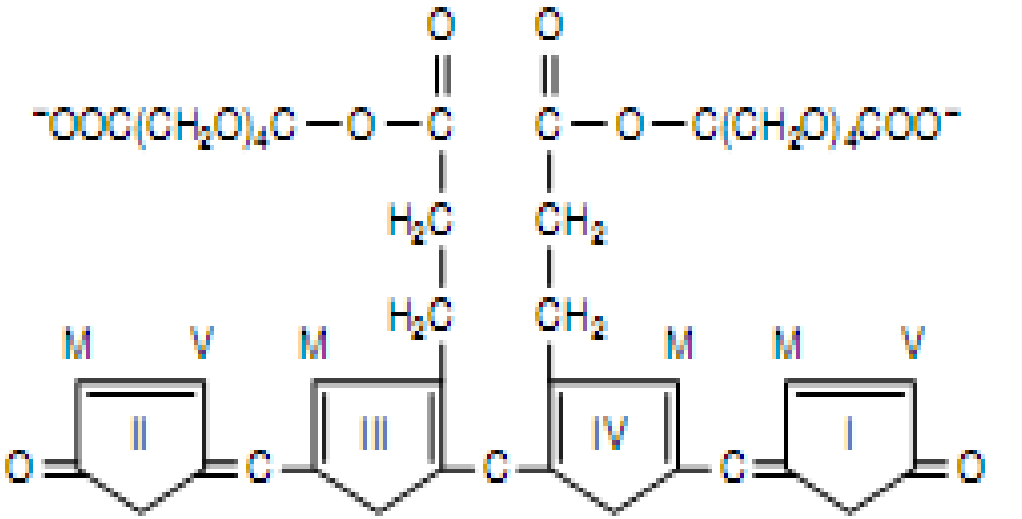


Figure 32–13. Structure of bilirubin diglucuronide (conjugated, "direct-reacting" bilirubin). Glucuronic acid is attached via ester linkage to the two propionic acid groups of bilirubin to form an acylglucuronide.

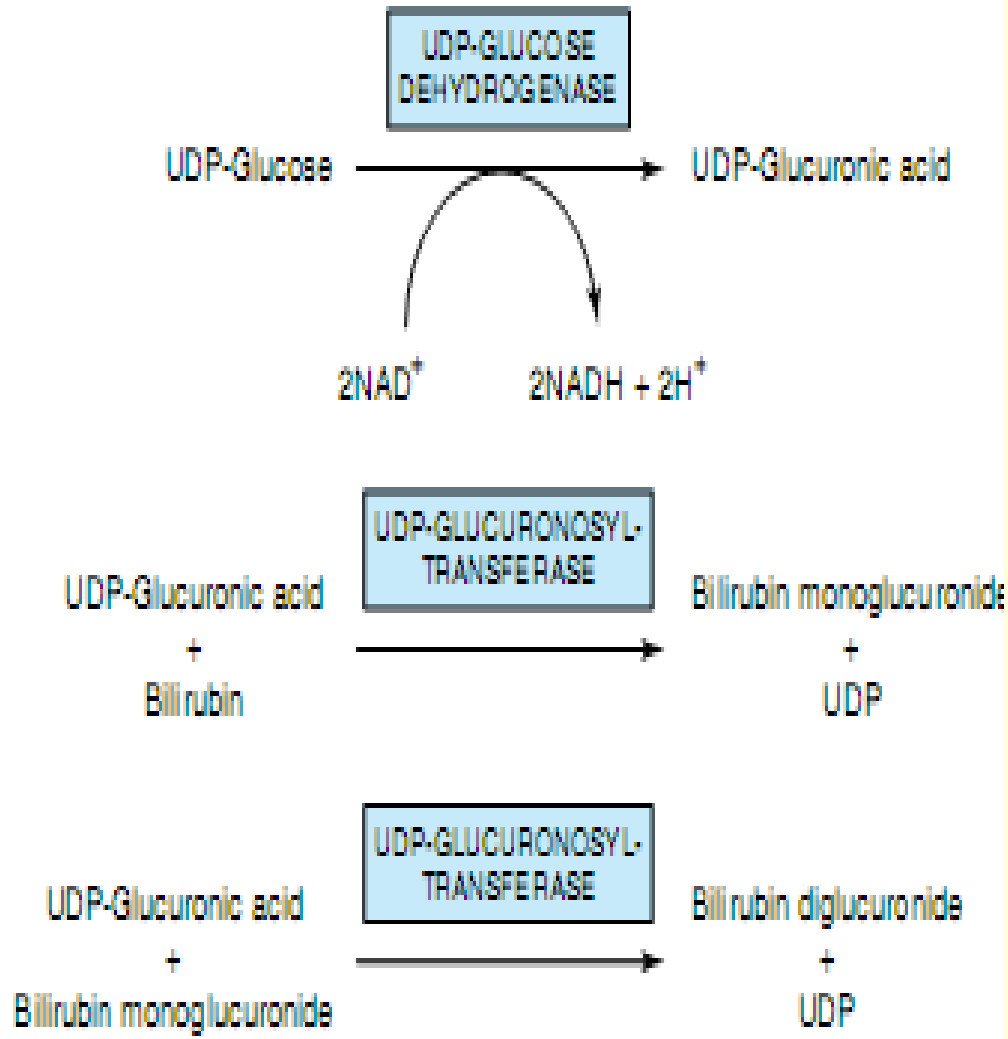


Figure 32–14. Conjugation of bilirubin with glucuronic acid. The glucuronate donor, UDP-glucuronic acid, is formed from UDP-glucose as depicted. The UDP-glucuronosyl-transferase is also called bilirubin-UGT.

4. Excretion of bilirubin into bile

- **Bilirubin diglucuronide is actively transported into the bile canaliculi and then into the bile.**
- **Unconjugated bilirubin is normally not excreted.**

5. Formation of urobilins in the intestine

- Bilirubin diglucuronide hydrolyzed and reduced by bacteria in the gut to a colorless compound urobilinogen.

A. Some urobilinogen is reabsorbed from the gut into portal blood and transported to the kidney where it is converted to the yellow urobilin and excreted, giving urine its characteristic color.

B. Most of urobilinogens of the feces are oxidized by intestinal bacteria to stercobilin which gives stools their characteristic brown color.

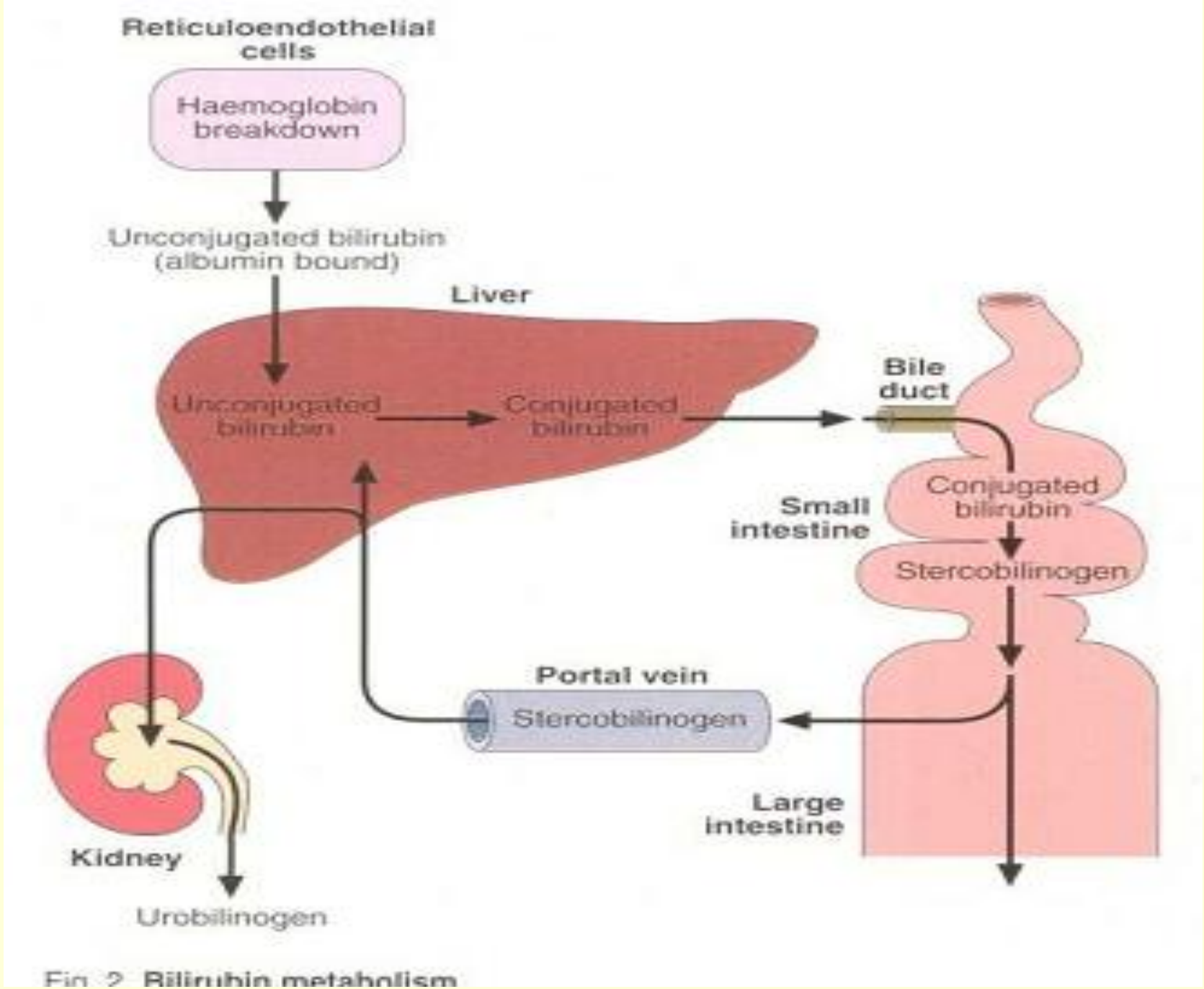
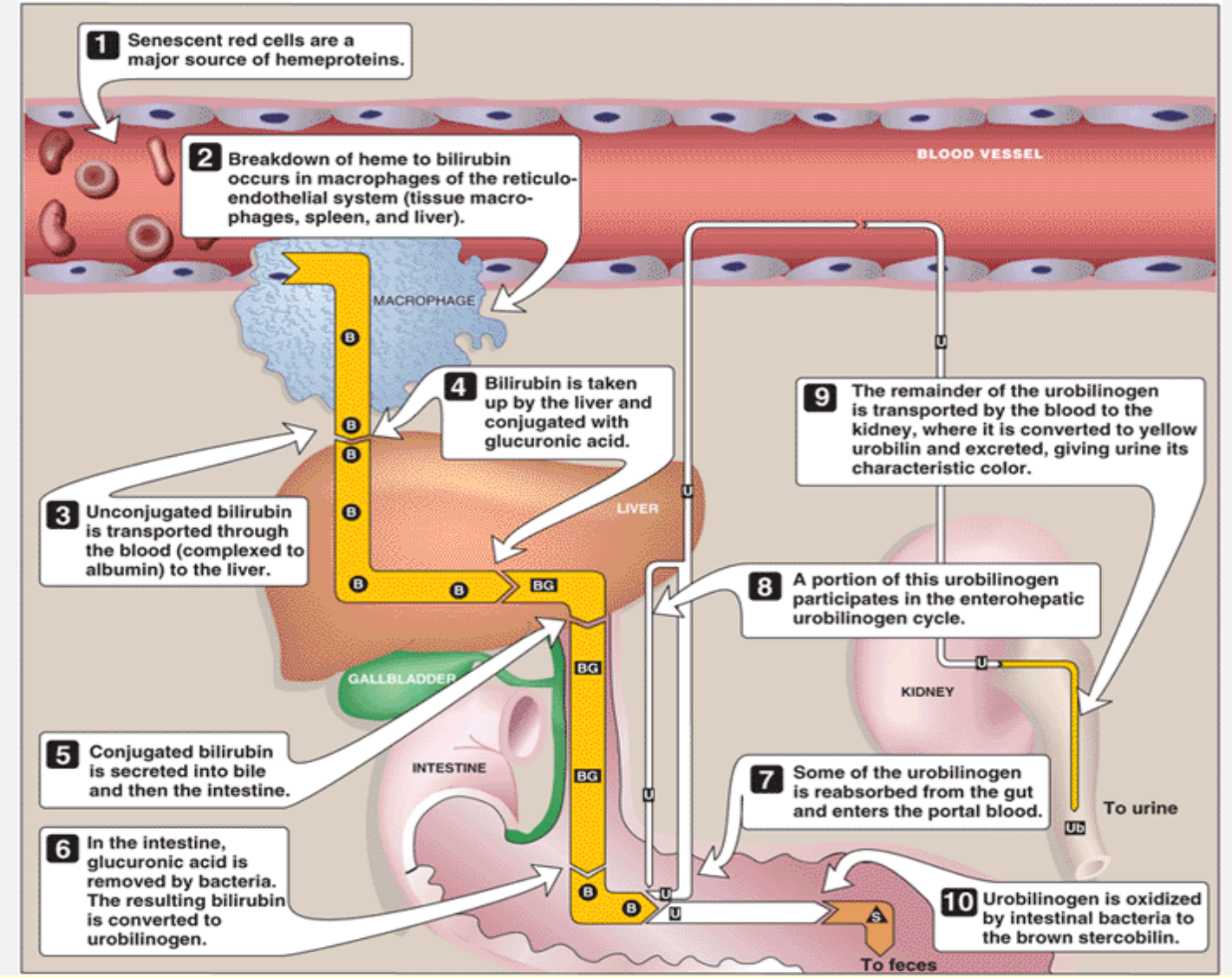


Fig. 2. Bilirubin metabolism

Catabolism of heme

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