Porphyrins and bile pigments: metabolism and disorders

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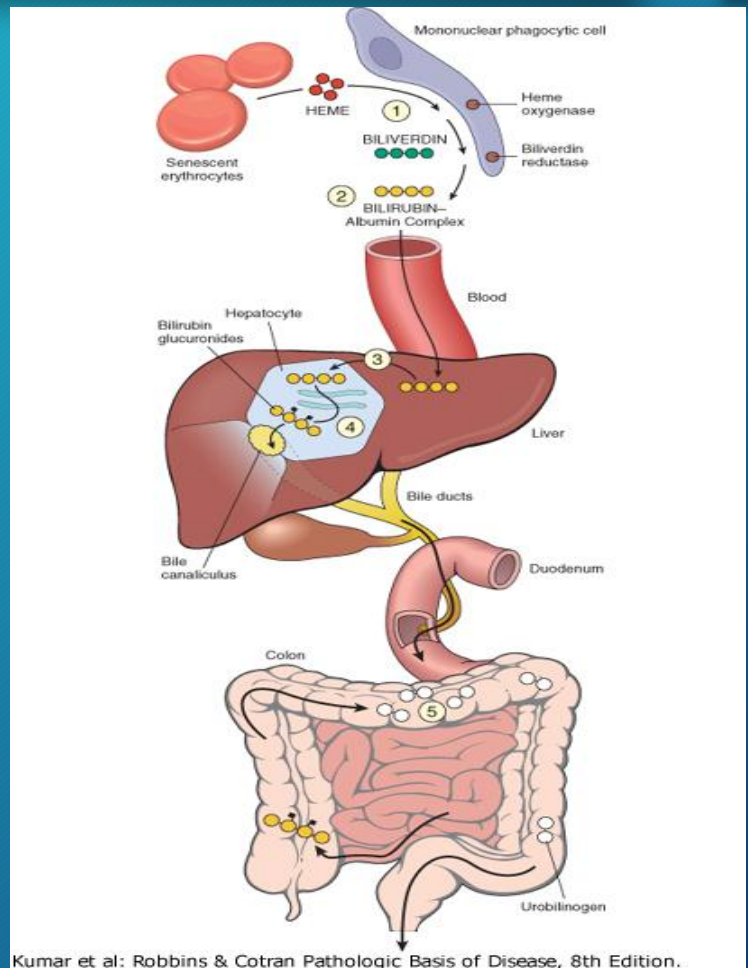
Porphyrins

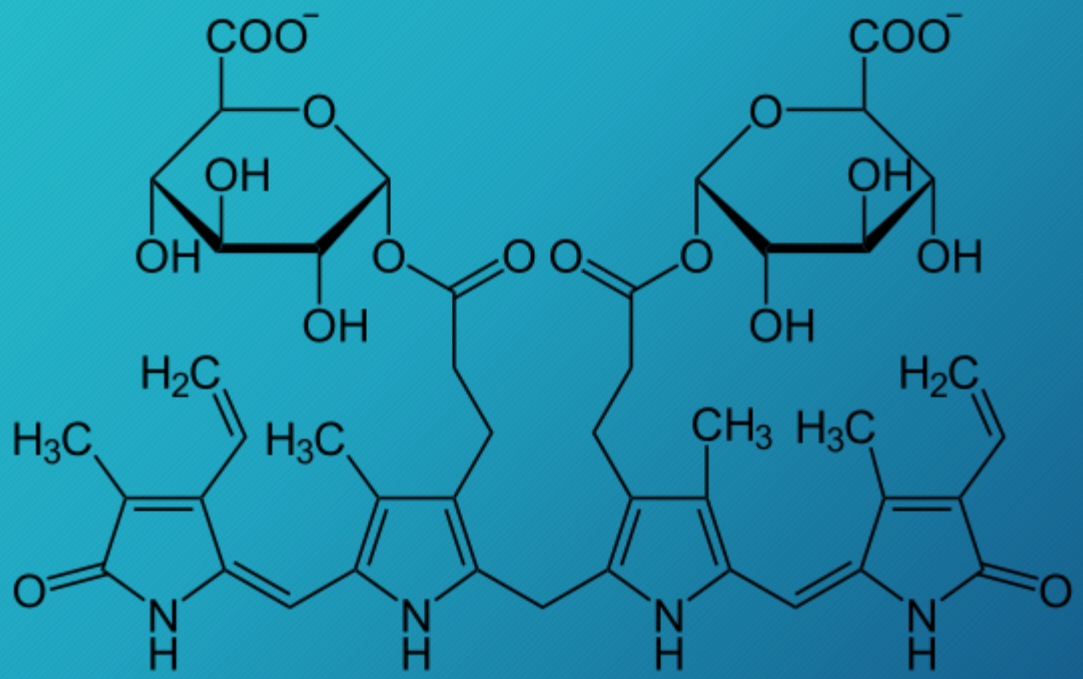
- Porphyrins are cyclic compounds formed by the linkage of four pyrrole rings through methyne (ÓHC—) bridges.In the naturally occurring porphyrins, various side chains replace the eight numbered hydrogen atoms of the pyrroles.
- Porphyrins have had different structures depend on side chains that are attached to each of the four pyrrole rings. For example; Uroporphyrin, coporporphyyrin and protoporphyrin IX (heme).
- The most prevalent metalloporphyrin in humans is heme, which consists of one ferrous (Fe2+) iron ion coordinated at the center of the tetrapyrrole ring of protoporphyrin IX.

What is bilirubin?

- Bilirubin is a yellowish pigment found in bile, a fluid made by the liver.
- The breakdown product of Hgb from injured RBCs and other heme containing proteins.
- Produced by reticuloendothelial system
- Released to plasma bound to albumin
- Hepatocytes conjugate it and excrete through bile channels into small intestine.

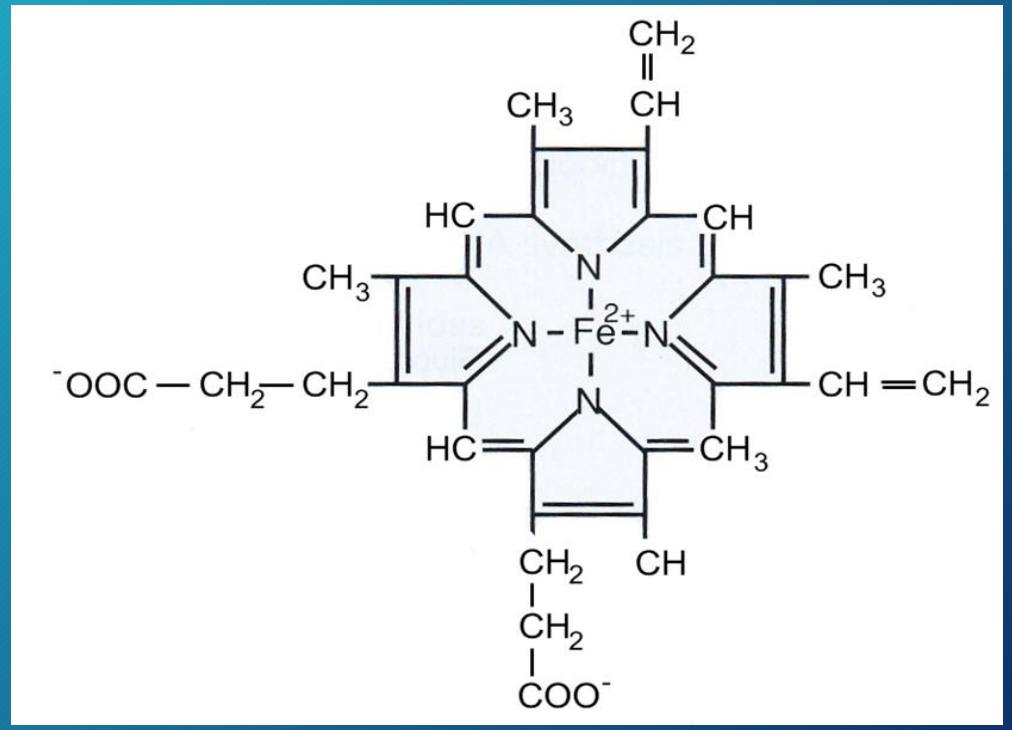


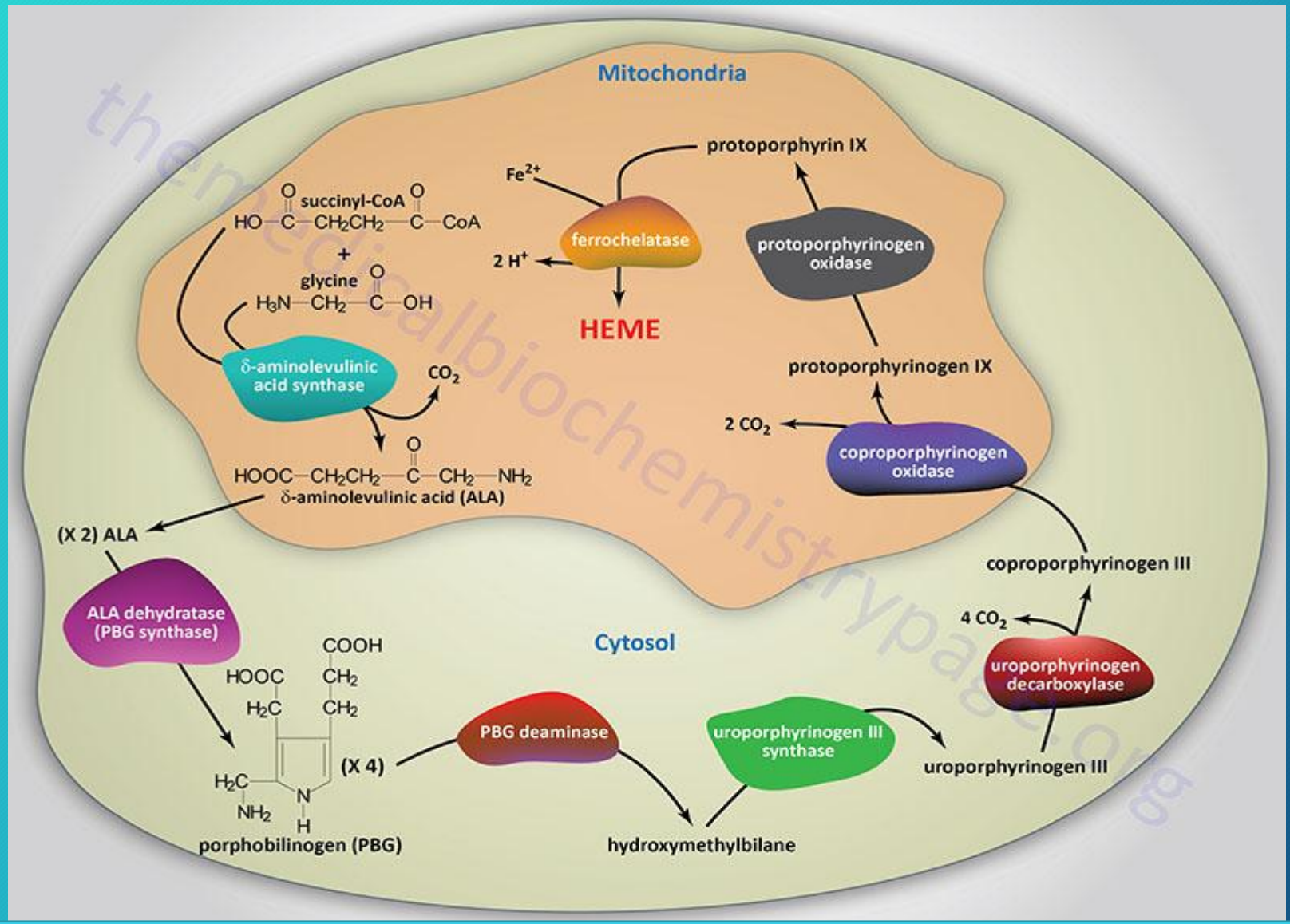
Bilirubin di-glucoronid



Structure of heme:

- **Heme structure:**
  - ➢ a porphyrin ring coordinated with an atom of iron
  - ➢ side chains: methyl, vinyl, propionyl
- **Heme is complexed with proteins to form:**
- Hemoglobin, myoglobin and cytochromes



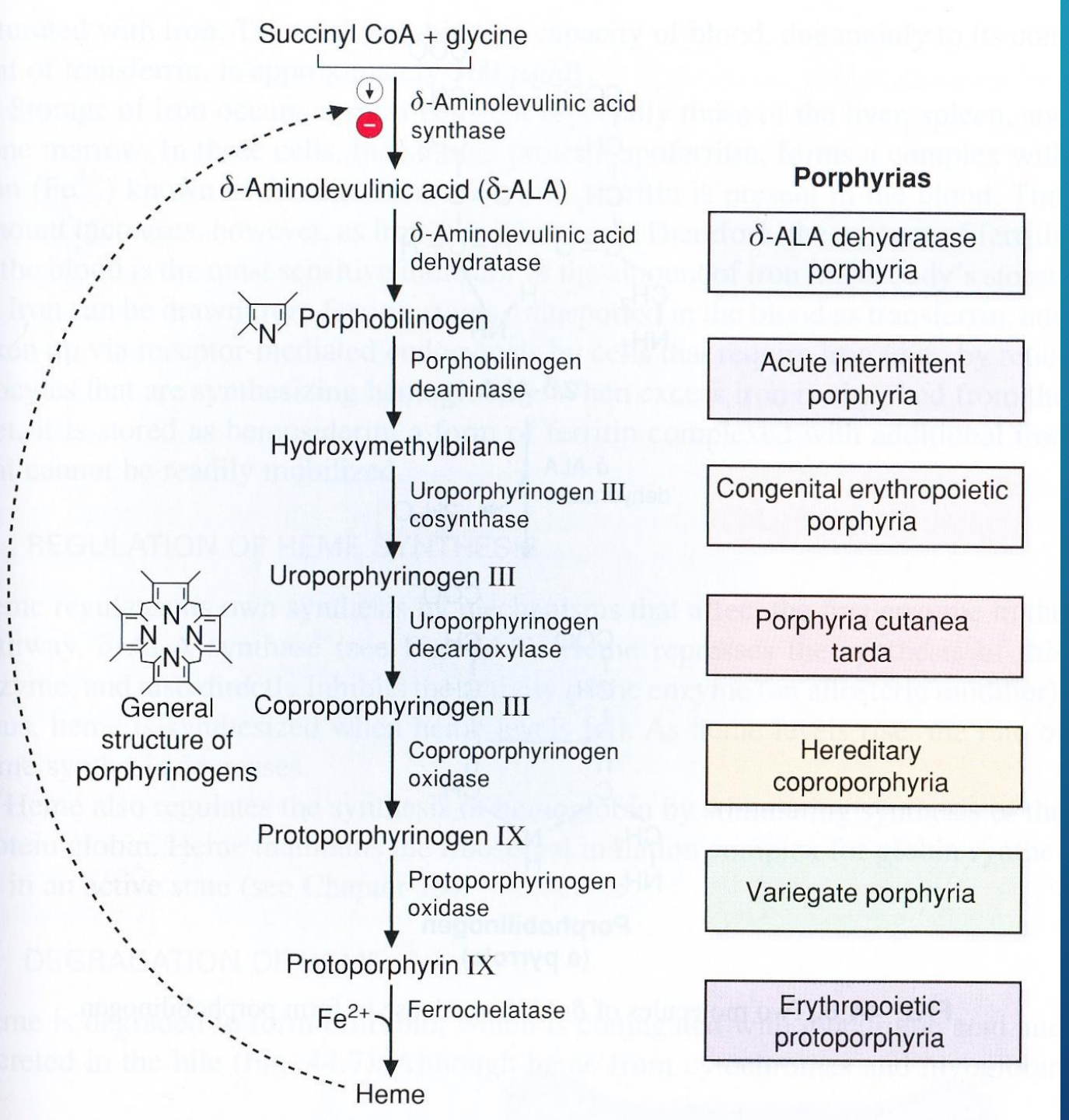


Pathway of Heme Biosynthesis. Heme biosynthesis begins in the mitochondria from glycine and succinyl-CoA, continues in the cytosol, and ultimately is completed within the mitochondria. The heme that it produced by this biosynthetic pathway is identified as heme *b*. PBG: porphobilinogen; ALA: δ-aminolevulinic acid

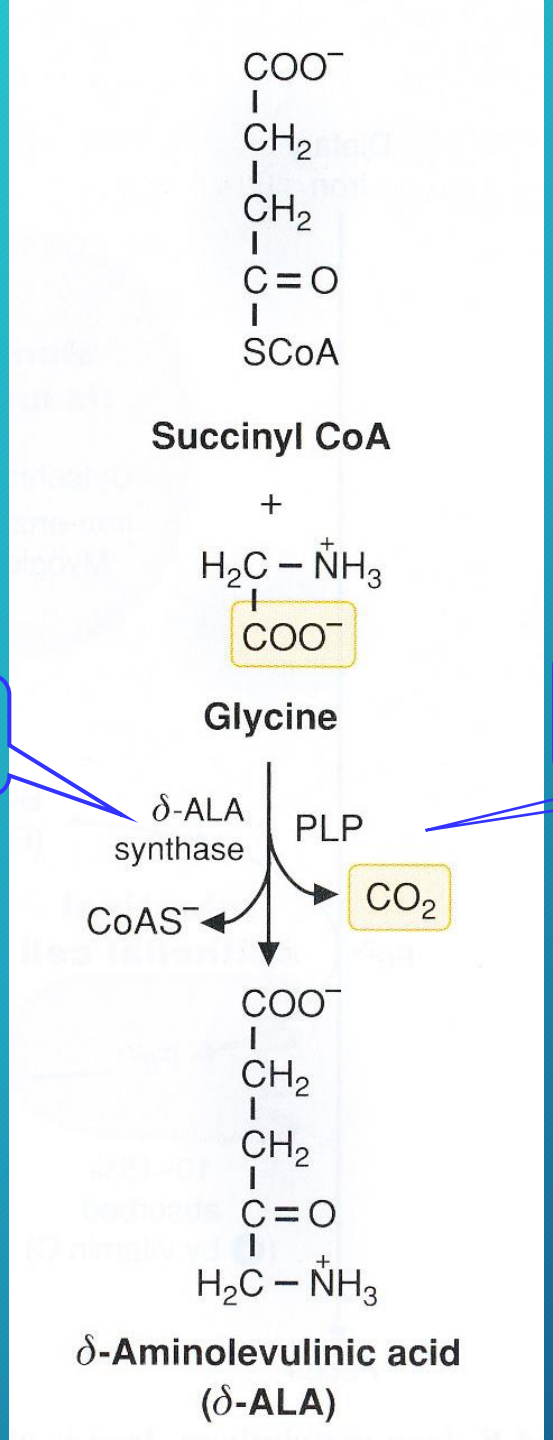
Mitochondria

Cytosol

Mitochondria



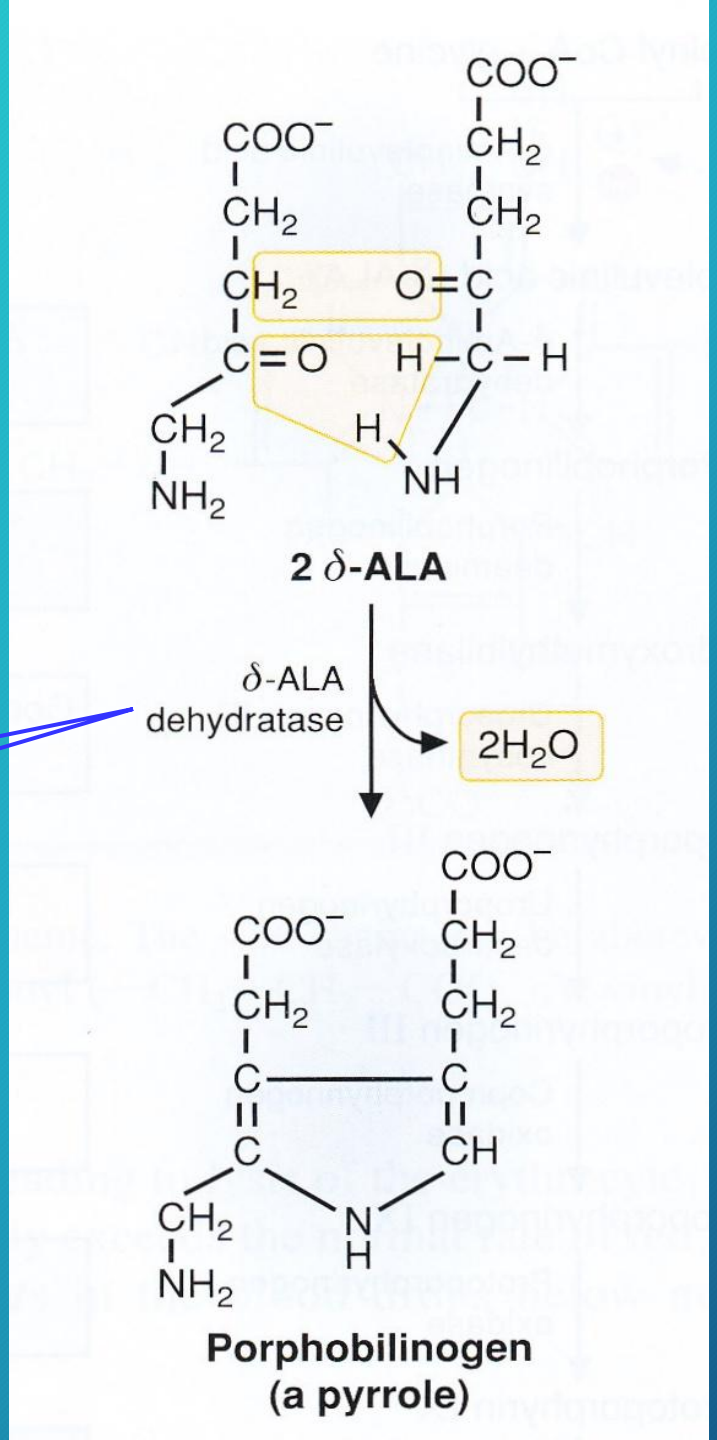
Synthesis of δ-aminolevulinic acid:



induced by: drugs (barbiturates), oral contraceptive pills

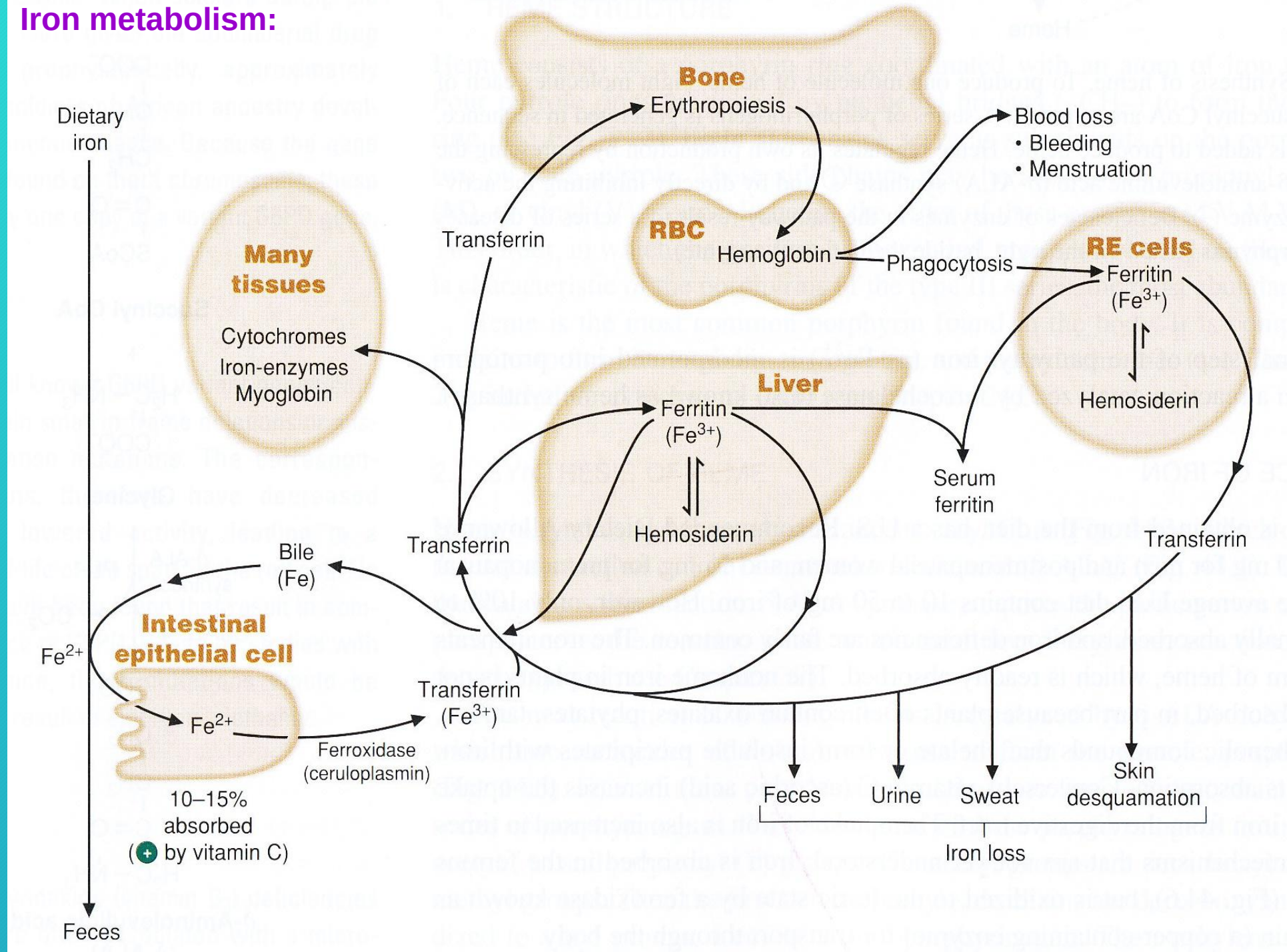
Pyridoxal phosphate (vit. B_6)

Formation of porphobilinogen:



inhibited by lead

Iron metabolism:



Iron metabolism:

- Recommended dietary allowance 10-15 mg (only 10-15% is normally absorbed)

Iron distribution:

	g	%
Hemoglobin	2,5	68
Myoglobin	0,15	4
Transferrin	0,003	0,1
Ferritin, tissue	1,0	27
Ferritin, serum	0,0001	0,004
Enzymes	0,02	0,6
Total	**3,7**	**100**

Intestinal absorption of iron:

- in the duodenum
- regulation (by the synthesis of apoferritin within mucosal cells)

1. The heme iron (unknown mechanism)
2. The nonheme iron
   - is not readily absorbed (chelates with oxalates, phytates, etc.)
   - vit. C increases the uptake

Iron transport:

- **Transferrin** (Fe^{3+}) $Transferrin + Fe^{3+} + CO_3^{2-} \rightarrow Transferrin \bullet 2(Fe^{3+}CO_3^{2-})$
  - only one third saturated with iron
  - unsaturated transferrin protects againsts infections (iron overload and infection)
- **Lactoferrin**
  - binds iron in milk
  - antimicrobial effect (protects newborns from gastrointestinal infections)
- **Haptoglobin**
  - binds hemoglobin in the plasma

Iron storage:

- **Ferritin** (Fe^{3+})
  - storage of iron (hepatocytes, RES, muscles)
  - in the blood → sensitive indicator of the amount of iron in the body
- **Hemosiderin**
  - when iron is in excess (amorphous iron deposition)

Iron-containing proteins:

1. Heme proteins

Hemoglobin

Myoglobin

Enzymes that contain heme as their prosthetic group (catalase, peroxidase, NO synthase)

2. Nonheme proteins

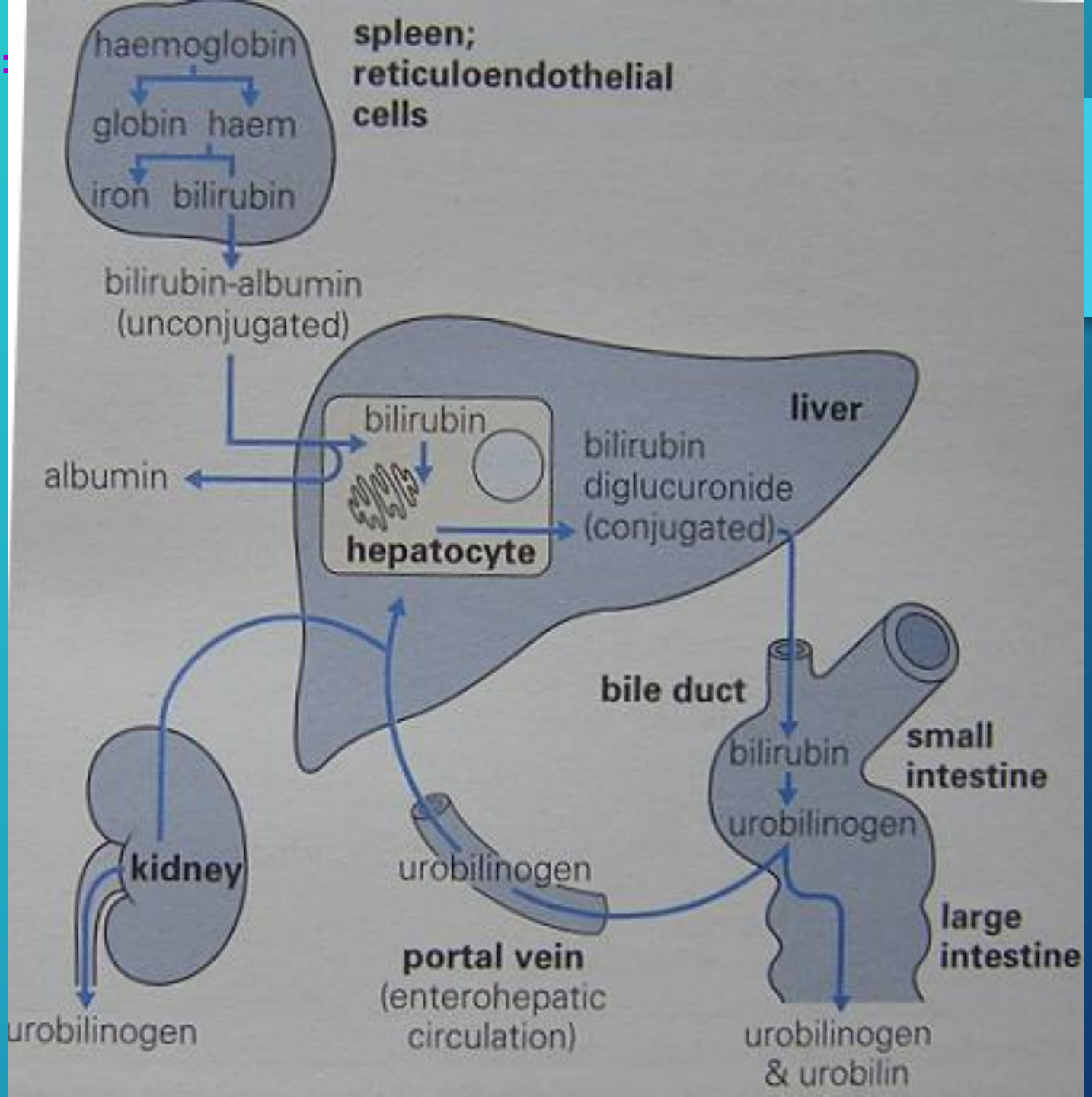
Transferrin

Ferritin

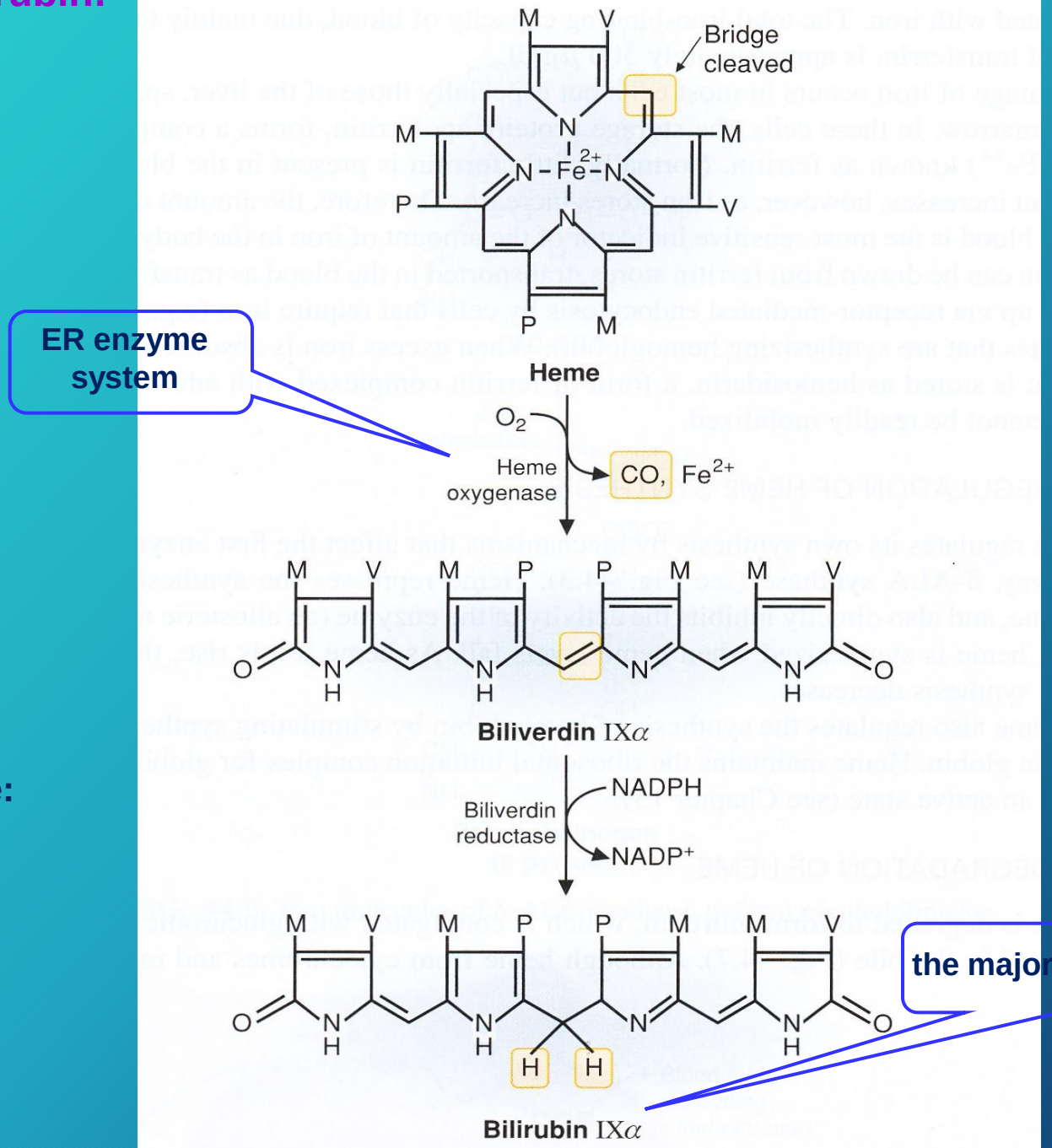
Enzymes that contain iron at the active site

Iron-sulphur proteins

Degradation of heme:



Conversion of heme to bilirubin:



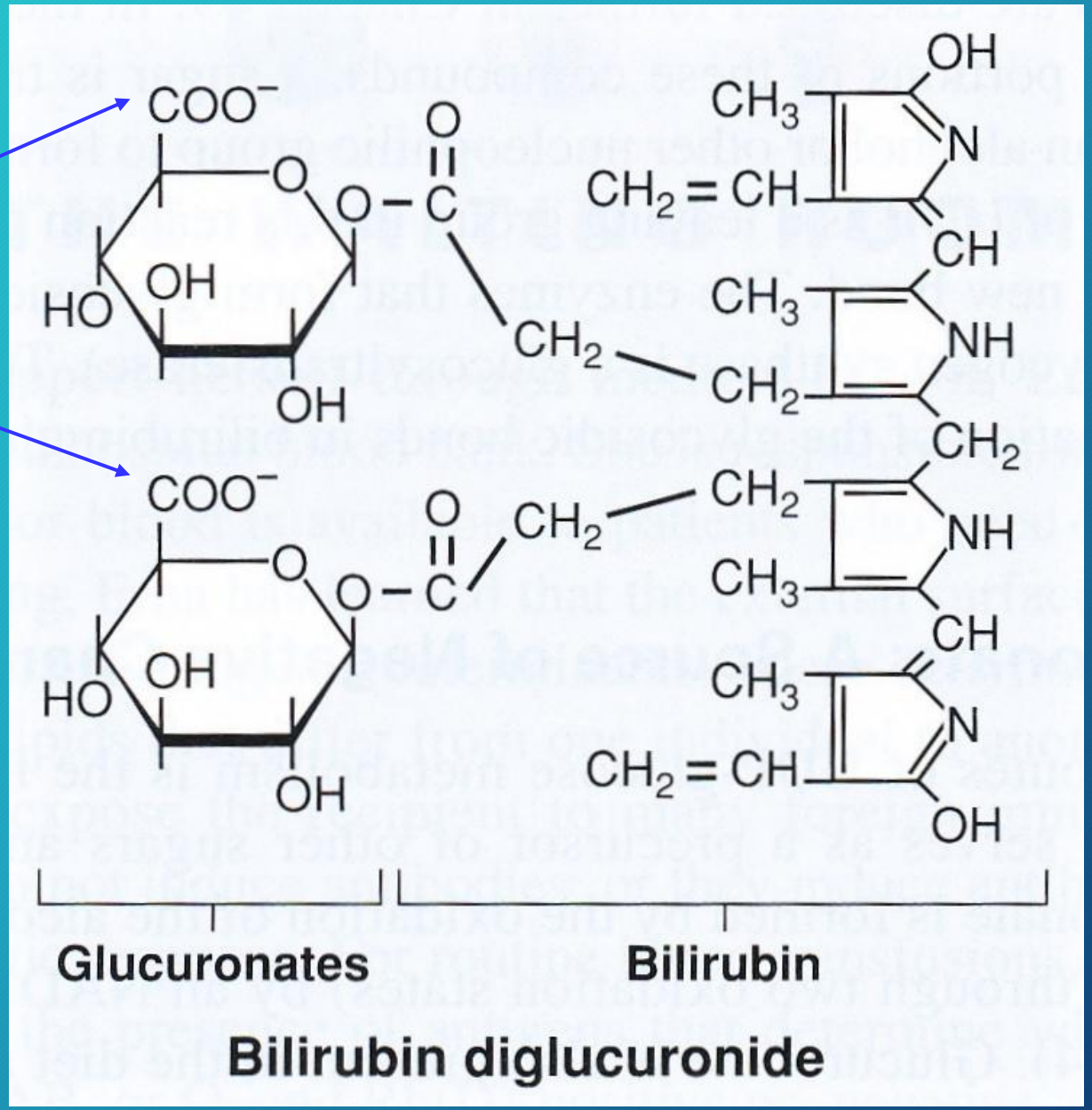
Cytoprotective role:

- CO
- biliverdin

the major source is Hg

Formation of bilirubin diglucuronide:

increase the water solubility of bilirubin



Bilirubin diglucuronide

Hyperbilirubinemia

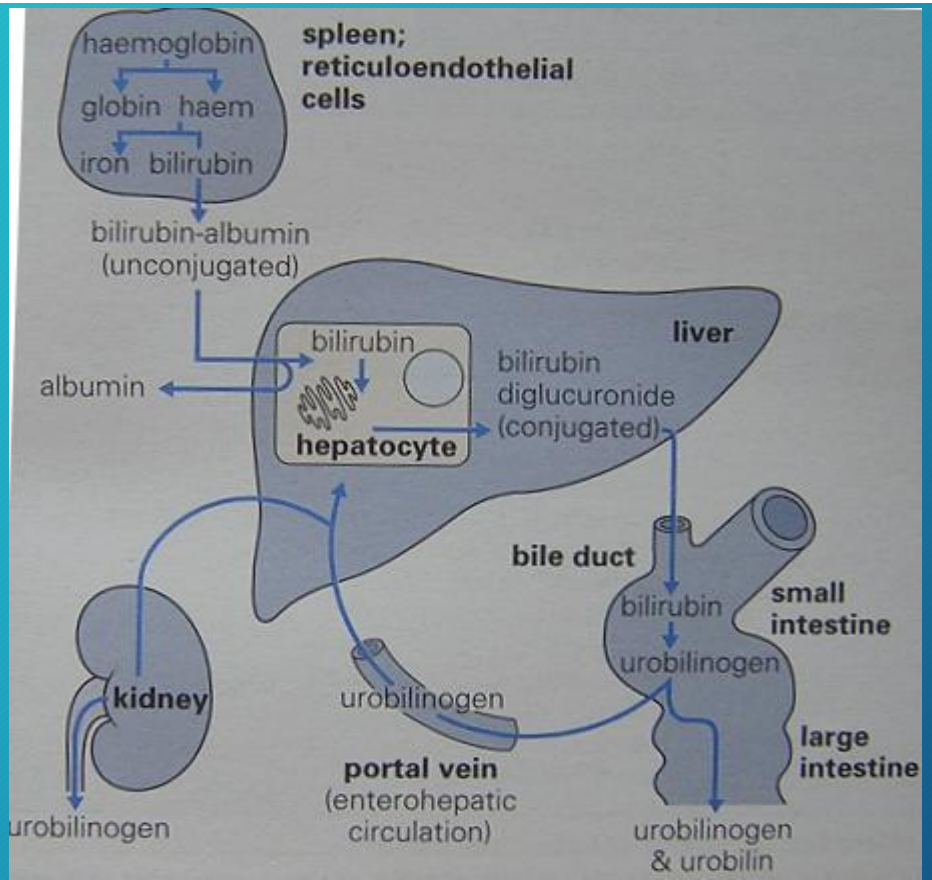
- Elevated bilirubin levels in the blood (>10 mg/l); bilirubin may diffuse into peripheral tissues, giving them a yellow color (jaundice)
- Cause:

  1. **Pre-hepatic**: excessive formation of bilirubin by increased degradation of erythrocytes (icterus neonatus, hemolytic anemia)
  2. **Hepatic:** insufficient processing of bilirubin as a result of liver defects (hepatitis, liver toxic damage, cirrhosis, hepatic failure)
  3. **Post-hepatic:** by impaired excretion of gall (obstructive jaundice due to gallstones, inflammation of biliary tract)

- Unconjugated bilirubin can cross the blood-brain barrier, leading to brain damage
- Jaundice in neonates (increased bilirubin degradation+immaturity of the conjugation enzymes): phototerapy – isomerization of bilirubin to more soluble pigments

Type	Cause	Example	Frequence
Prehepatic	Hemolysis	Autoimmune Haemoglobinopathy	Rare According to the region
Hepatic	Infection Damage Genetics Autoimmune Newborn	Hepatitis A,B,C Alcohol, drugs Gilbert´s syndrome Wilson´s disease α_1-Antitrypsin deficiency Chronic hepatitis Physiologic	Very common Common 1 in 20 1 in 200 000 1 in 1000 Rare Very common
Posthepatic	Intrahepatic bile ducts Extrahepatic bile ducts	Drugs Primary biliary cirrhosis Cholangitis Gallstones Pancreatic cancer	Common Rare Common Very common Rare

	Bilirubin			Urobilinogen	
	blood	urine	deriv. in feces	blood	urine
Prehepatic	↑↑(UC)	**N**	↑	↑	↑
Intrahepatic	↑↑(both)	↑	**N**	↑↑	↑↑
Posthepatic	↑↑(C)	↑	↓	↓	↓



METABOLISM OF BILE PIGMENTS IN HEPATIC JAUNDICE