PORPHYRINS AND BILE PIGMENTS

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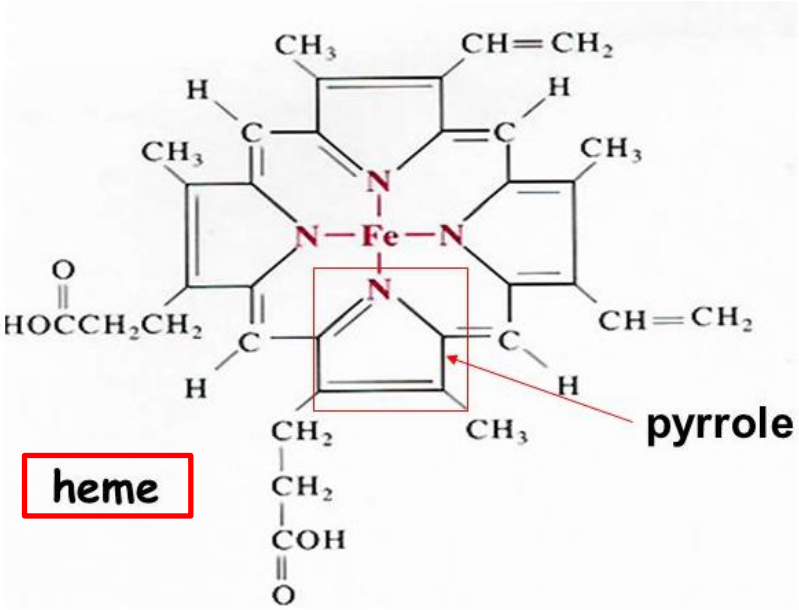
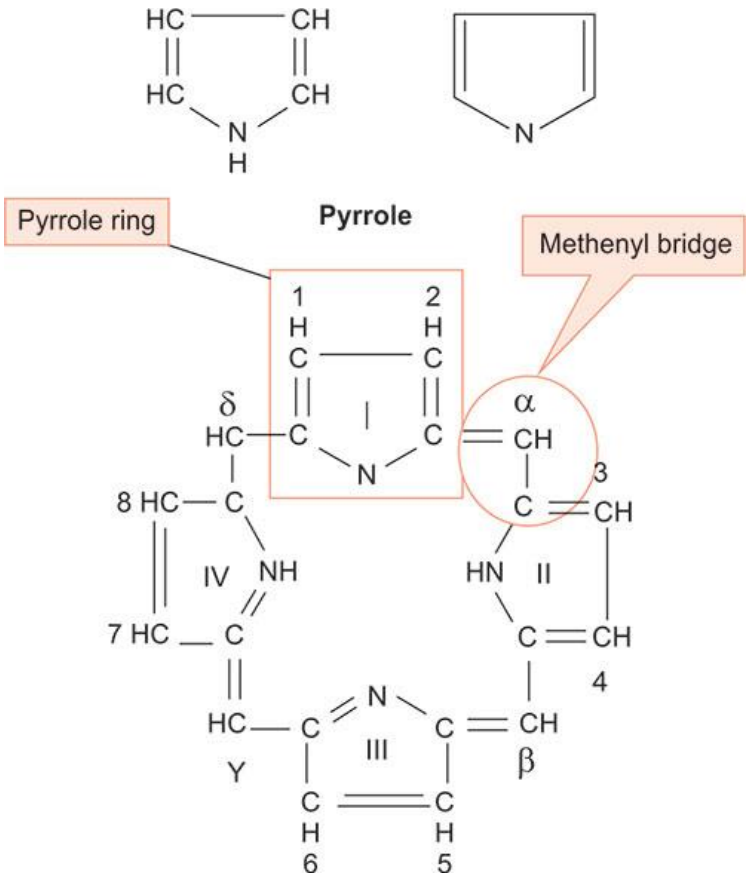
Porphyrins

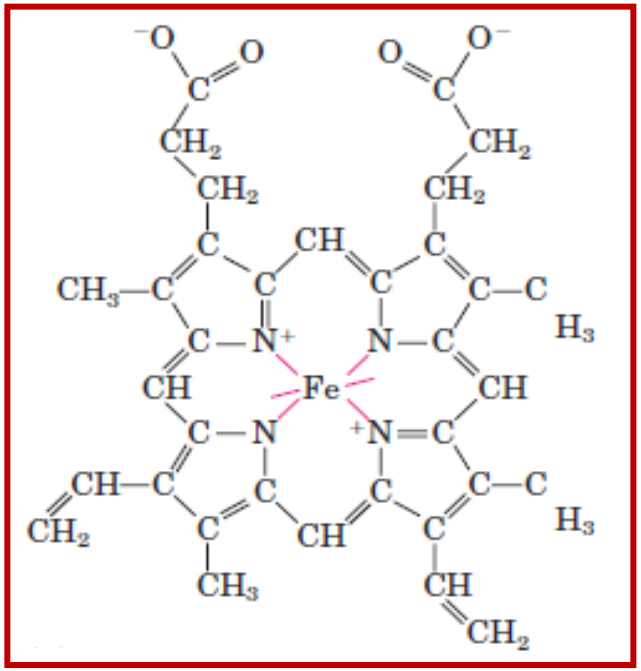
- cyclic compounds; conjugated (aromatic) system → **colored compounds**
- exhibit pink-red fluorescence when viewed by **UV light** (at 405 nm)
- **4 pyrrole rings (I-IV)** linked by methenyl bridges (=CH-) (α-δ)
- porphyrin types: I-IV

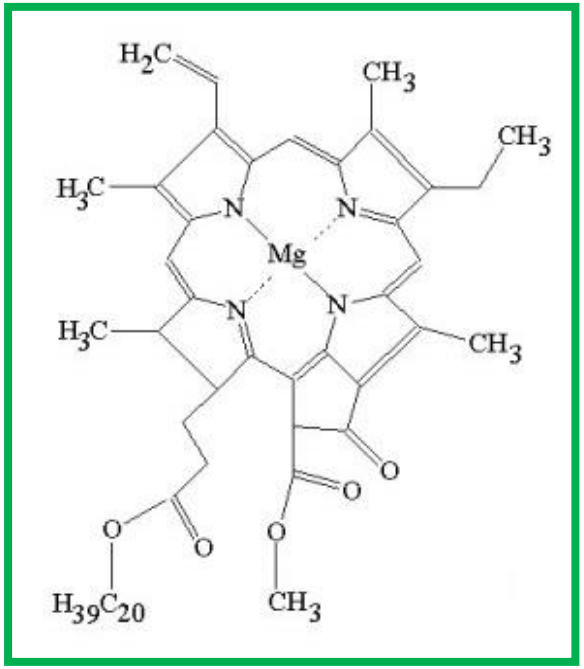




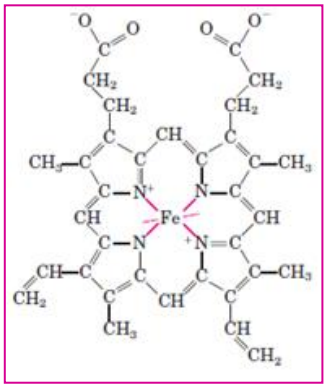
Porphyrins

- form complexes with metal ions bound to the nitrogen atom of the pyrolle ring:
  - **iron (heme) → protoporphyrin IX + Fe^{2+}**
  - **magnesium** (chlorophyll)



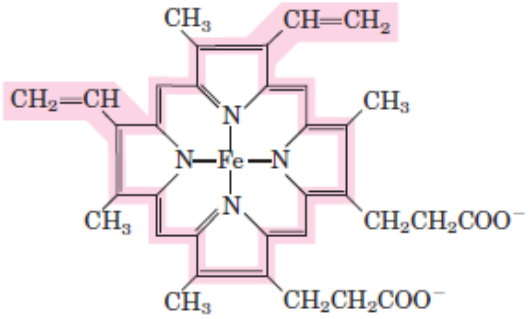


Hemoproteins

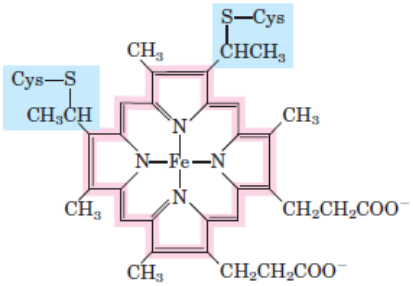


- **heme containing proteins**
  - prostetic group: **porphyrin ring + iron**
  - proteins linked to a nonprotein, iron-bearing component
    → the iron (heme) group attached to the protein that can undergo reversible oxidation and reduction reactions (electron carriers within the mitochondria)

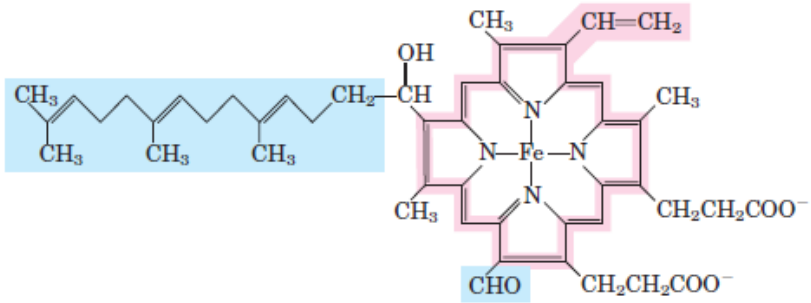
- <u>necessary for life</u>:
  - **oxigen transport** (Hb) and **storage** (myoglobine)
  - mitochondrial **respiration** (cytochrome b i c, c1, a i a3…)
  - **drugs/xenobiotics metabolism** (cytochrome P450 monooxigenases)



Iron protoporphyrin IX
(in *b*-type cytochromes)



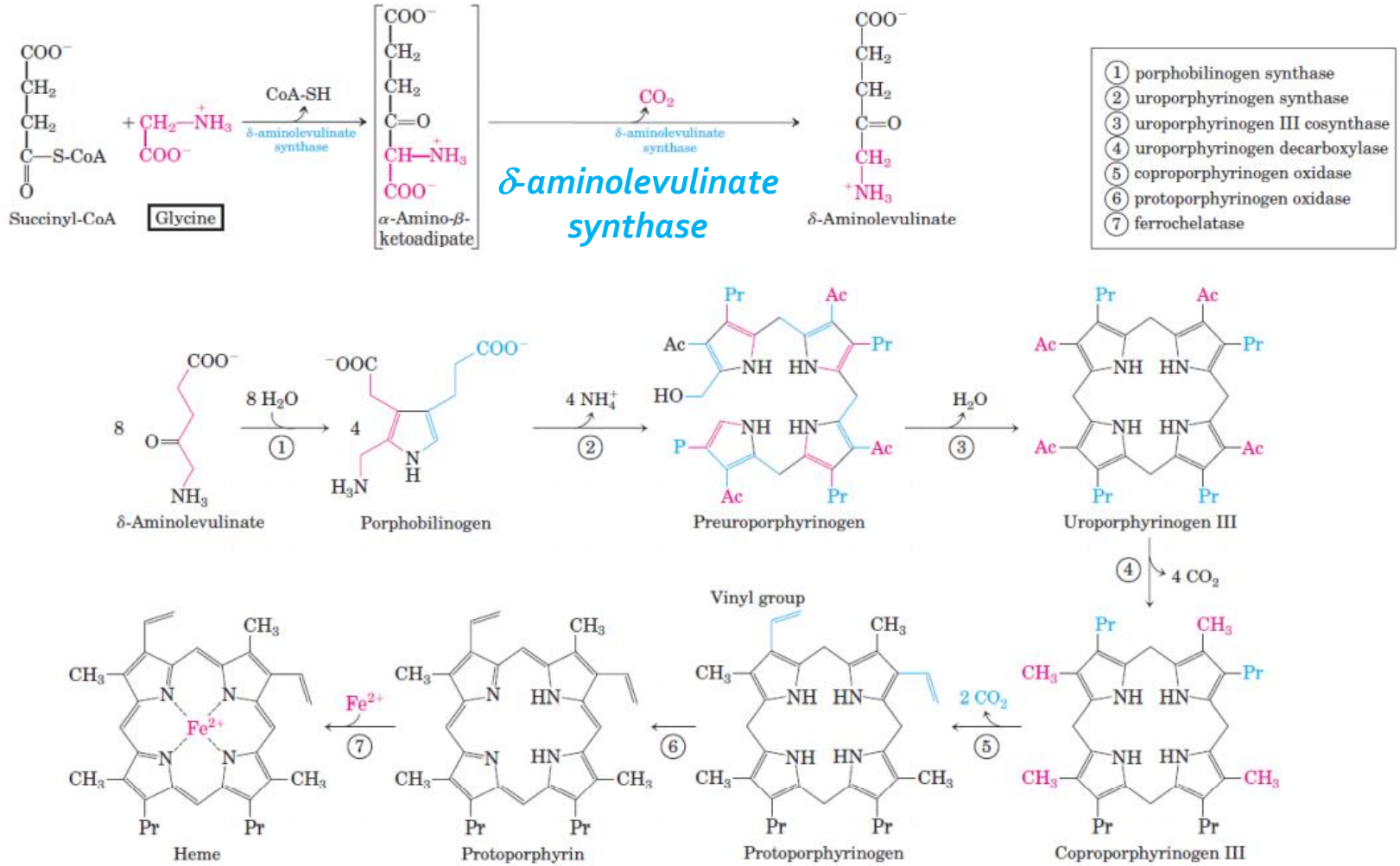
Heme C
(in *c*-type cytochromes)



Heme A
(in *a*-type cytochromes)

Heme Biosynthesis

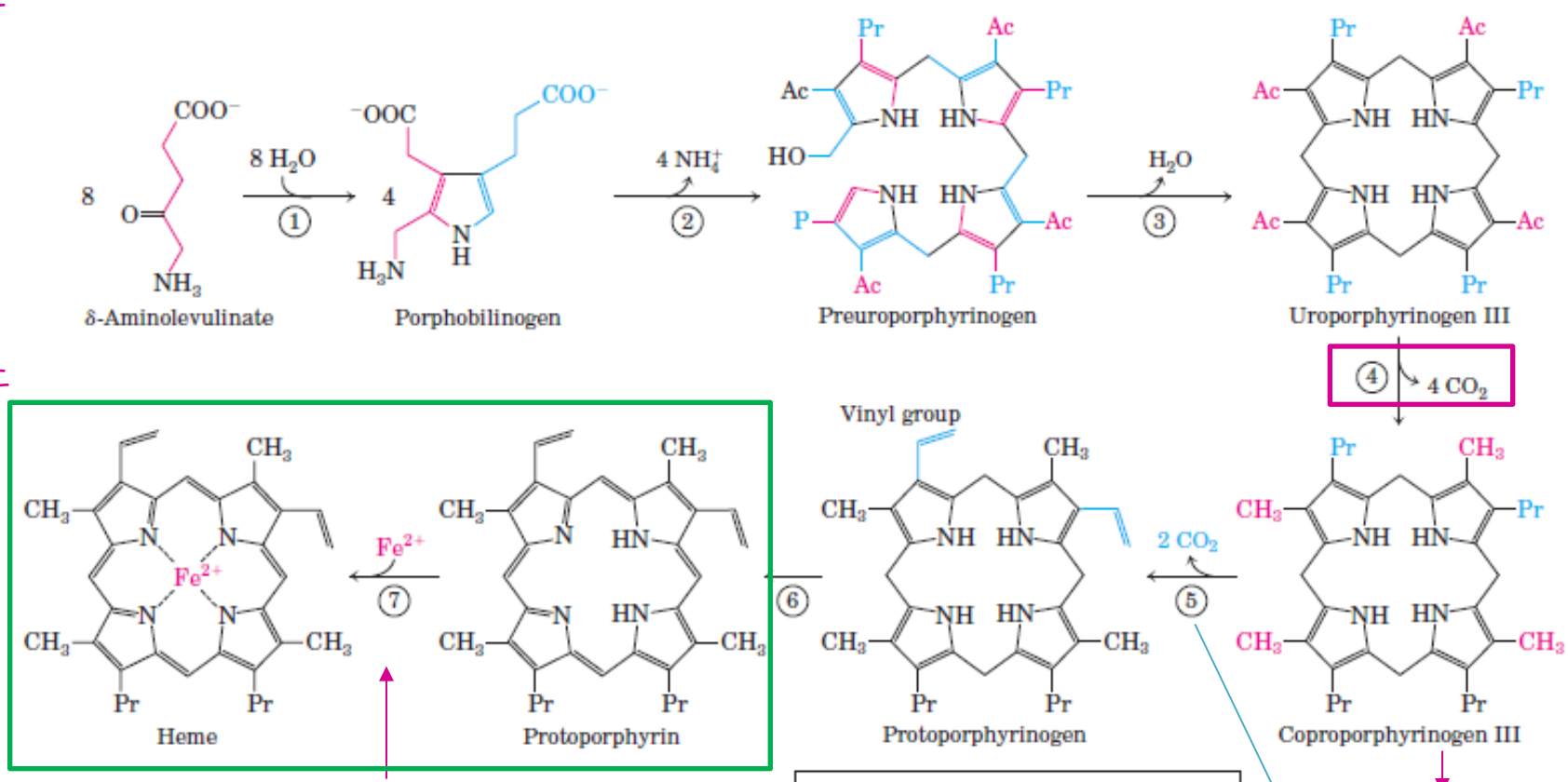
- 85% → **bone marrow**
- the rest: mostly **liver,** but also in other tissues
  - **except in mature erythrocytes (RBC)!**



Heme Biosynthesis - Cyclization

cytosol

mitochondria



1. porphobilinogen synthase
2. uroporphyrinogen synthase
3. uroporphyrinogen III cosynthase
4. uroporphyrinogen decarboxylase
5. coproporphyrinogen oxidase
6. protoporphyrinogen oxidase
7. ferrochelatase

- *last 3 reactions + ALA synthase*

ferrochelatase (heme synthase)

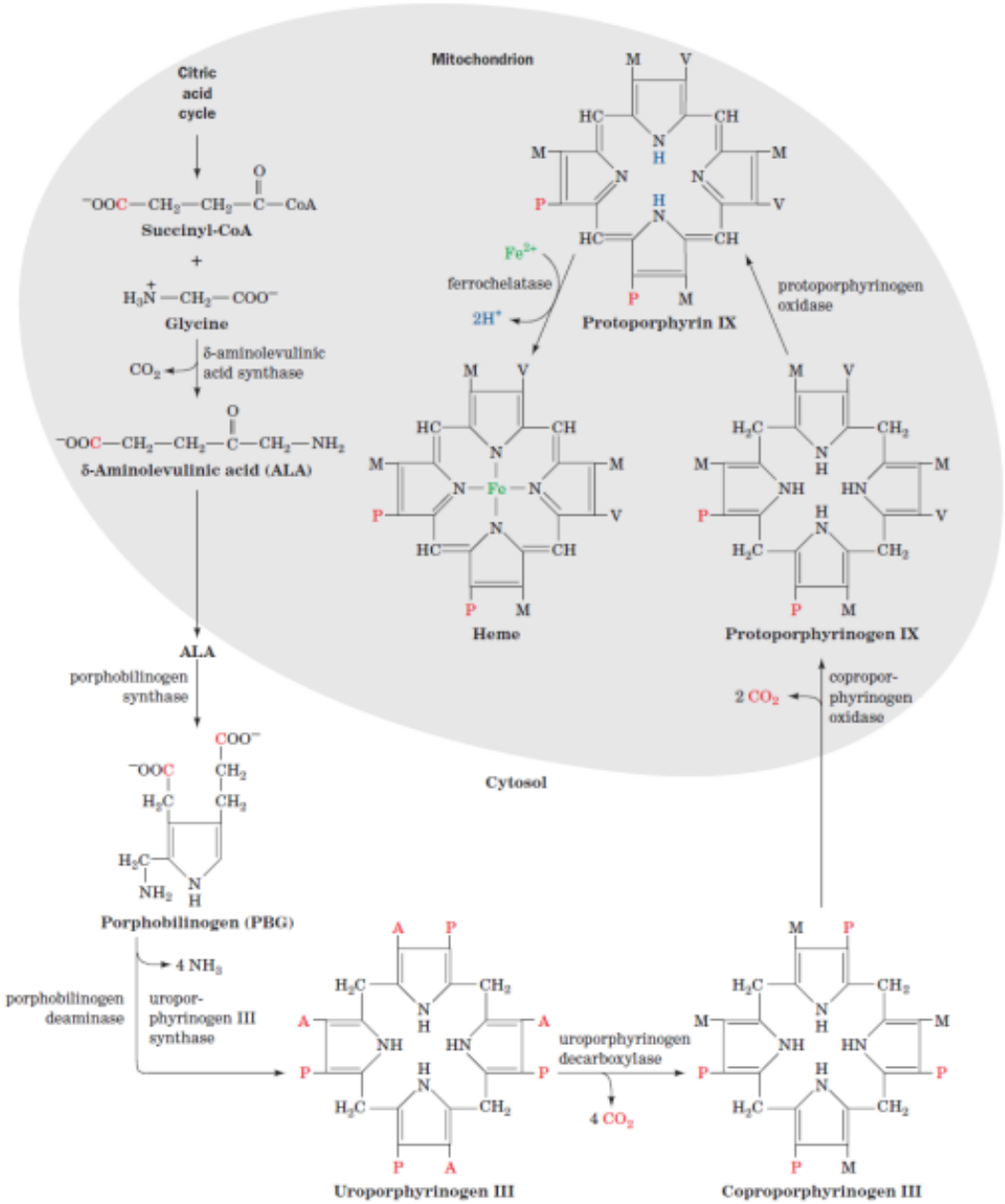
- Fe^{2+} ion incorporation

u mitohondrij

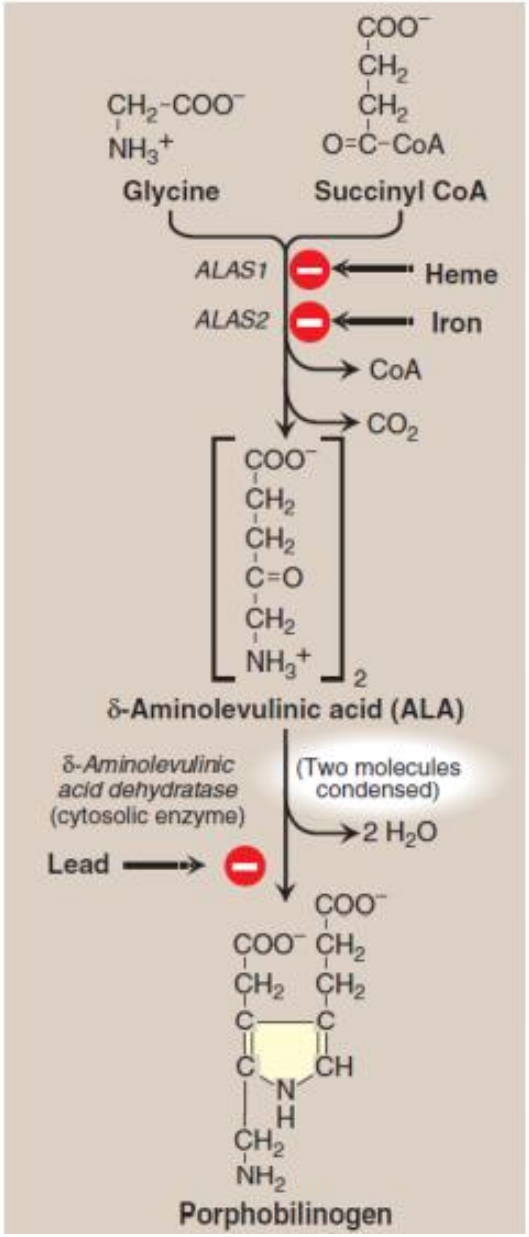
- **liver:** necessary O_2

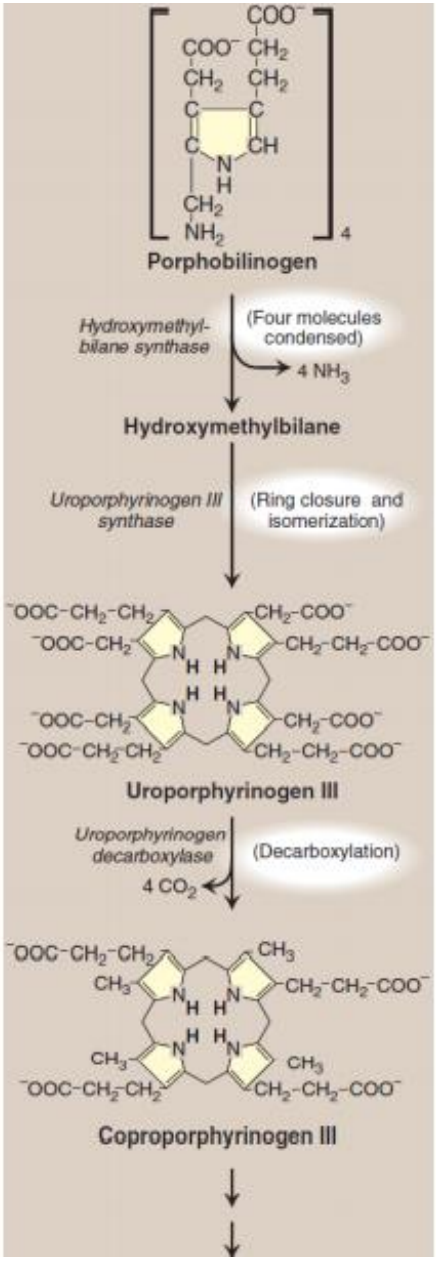
FIGURE 22-24 **Biosynthesis of heme from δ-aminolevulinate.** Ac represents acetyl (—CH_2COO^-); Pr, propionyl (—$CH_2CH_2COO^-$).

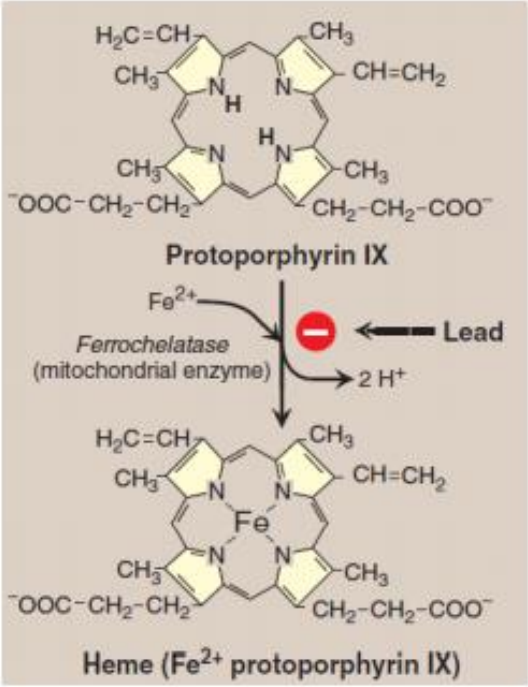
Heme Biosynthesis

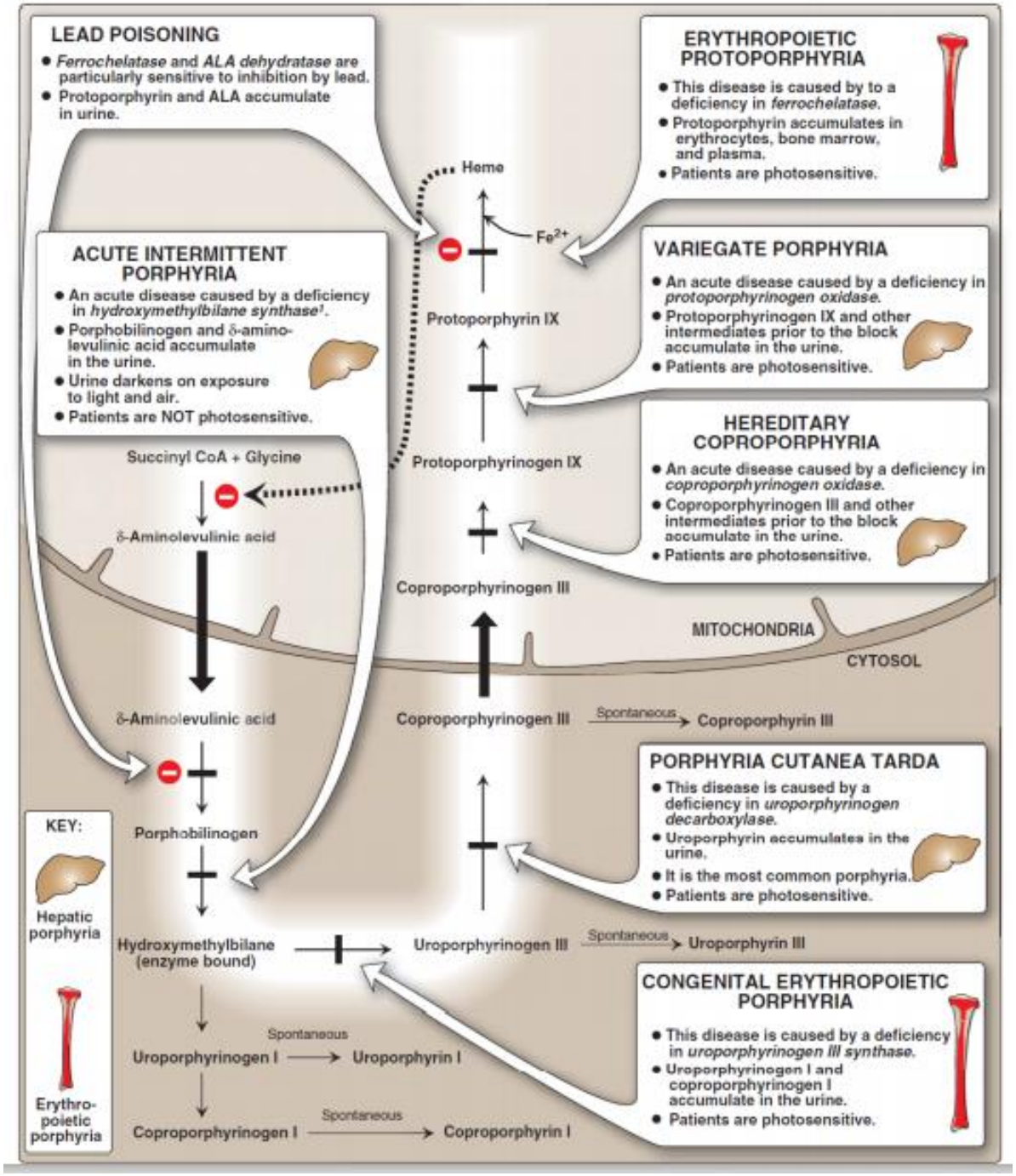


Heme Biosynthesis - Regulation



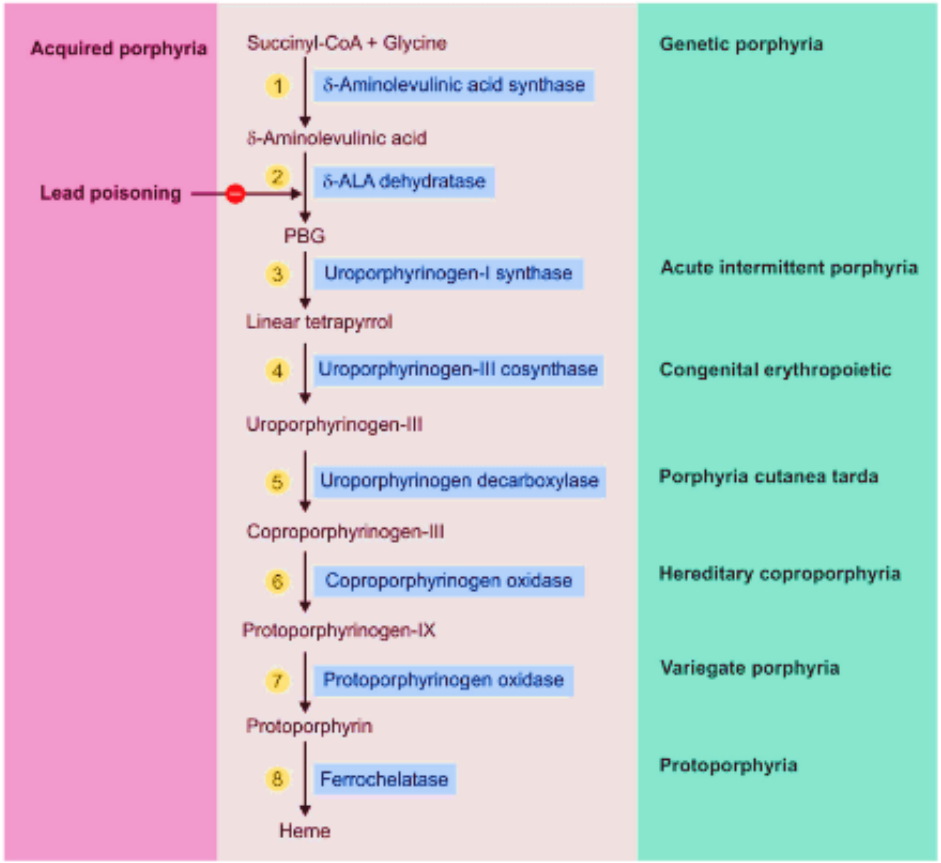





LEAD POISONING
• Ferrochelatase and ALA dehydratase are particularly sensitive to inhibition by lead.
• Protoporphyrin and ALA accumulate in urine.
ERYTHROPOIETIC PROTOPORPHYRIA
• This disease is caused by to a deficiency in ferrochelatase.
• Protoporphyrin accumulates in erythrocytes, bone marrow, and plasma.
• Patients are photosensitive.
Heme
Fe2+
ACUTE INTERMITTENT PORPHYRIA
• An acute disease caused by a deficiency in hydroxymethylbilane synthase1.
• Porphobilinogen and δ-aminolevulinic acid accumulate in the urine.
• Urine darkens on exposure to light and air.
• Patients are NOT photosensitive.
Protoporphyrin IX
VARIEGATE 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
• This disease is 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

Porphyrias

- rare disorders caused by genetic or acquired deficiencies of enzymes of the heme biosynthetic pathway
- heme precursors accumulate, causing toxicity
- defined by the specific enzyme deficiency
- two major clinical manifestations:
  - **neurovisceral abnormalities** (the acute porphyrias)
  - **cutaneous photosensitivity** (the cutaneous porphyrias)



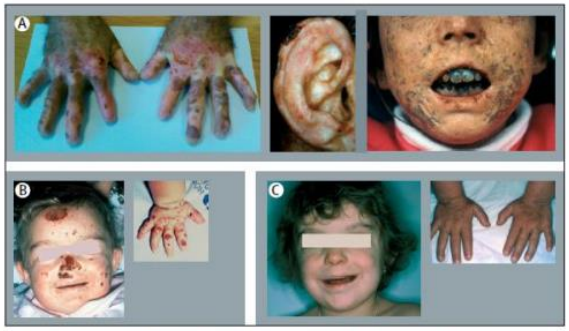
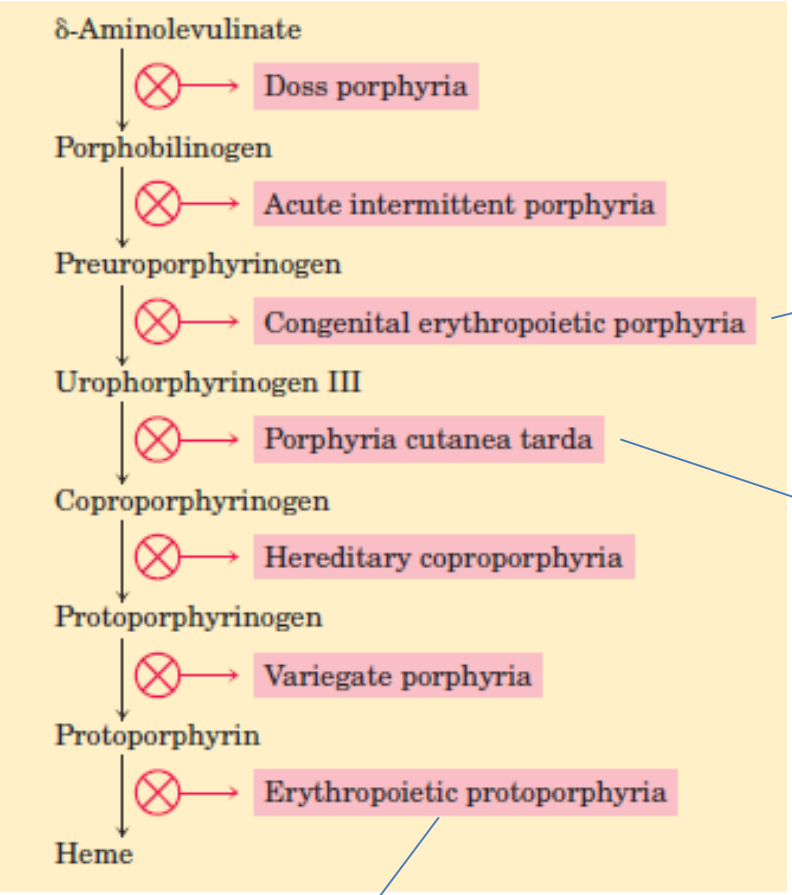
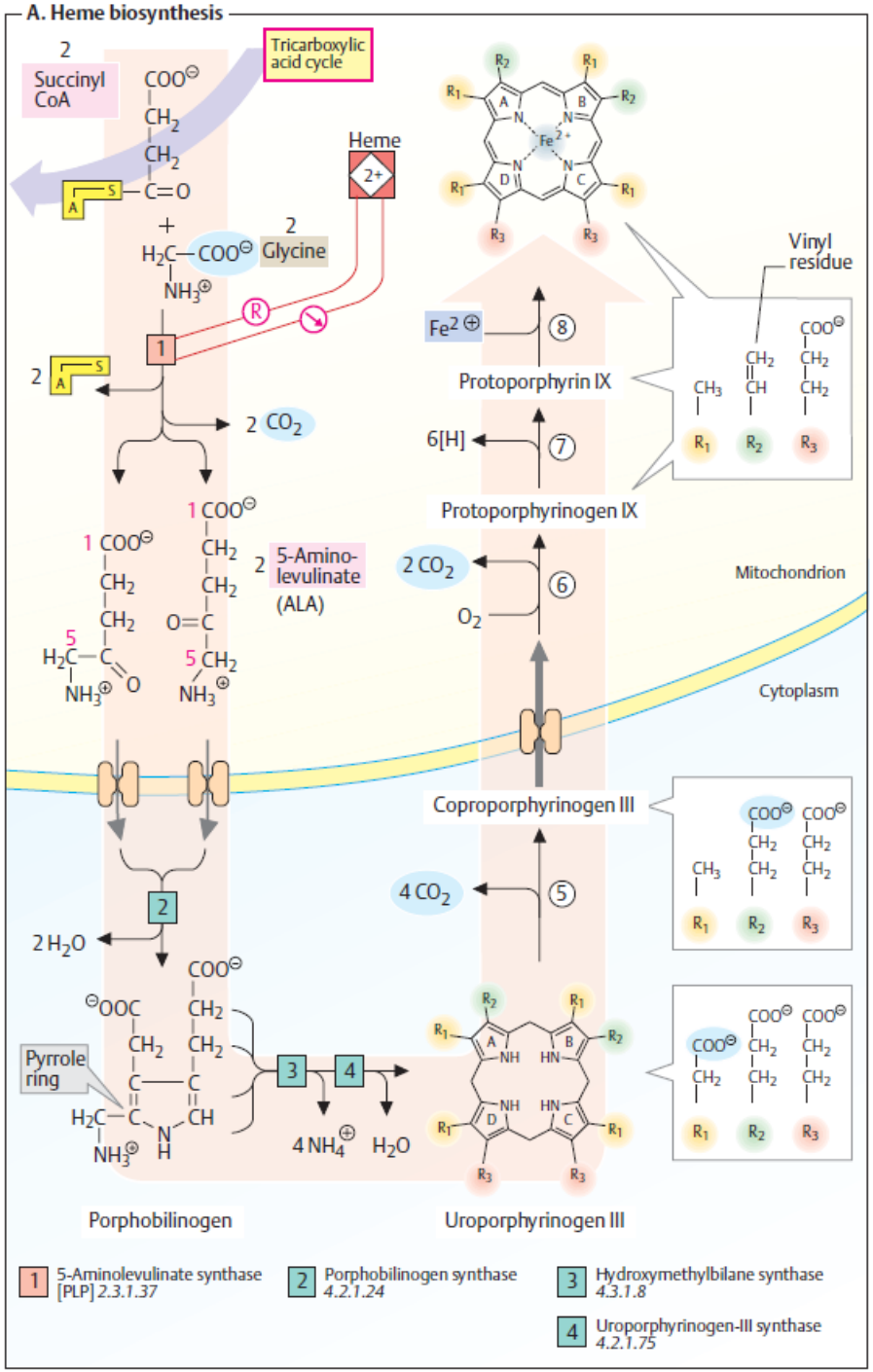


Figure 7: **Clinical presentation of congenital erythropoietic porphyria (Günther's disease).**
Severe presentation in adults (A); severe presentation in a newborn before (B) and 2 years after (C) bone marrow transplantation with persistence of erythrodontia.

Porphyrias



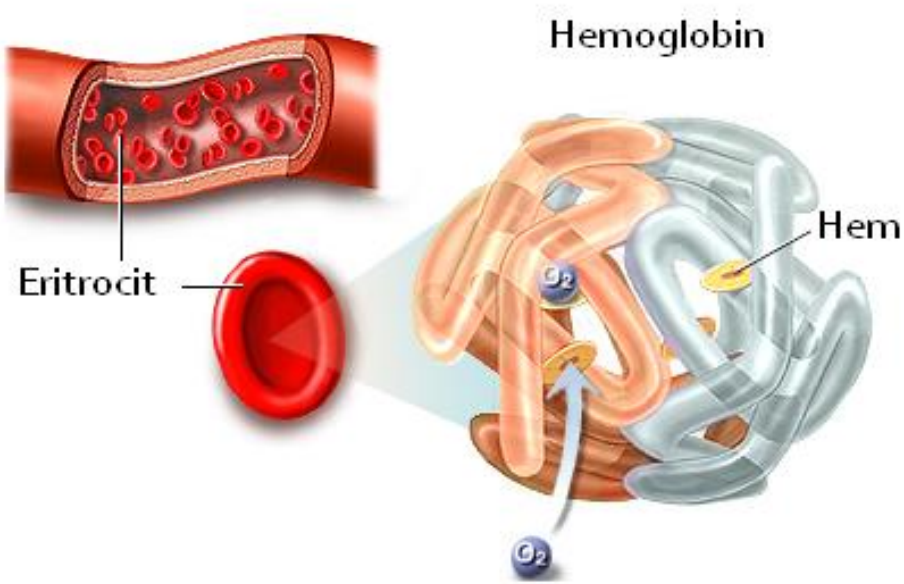
- "Draculas disease"
- King George III (1738.- 1820.) – madness episodes; posibly caused by porphyria



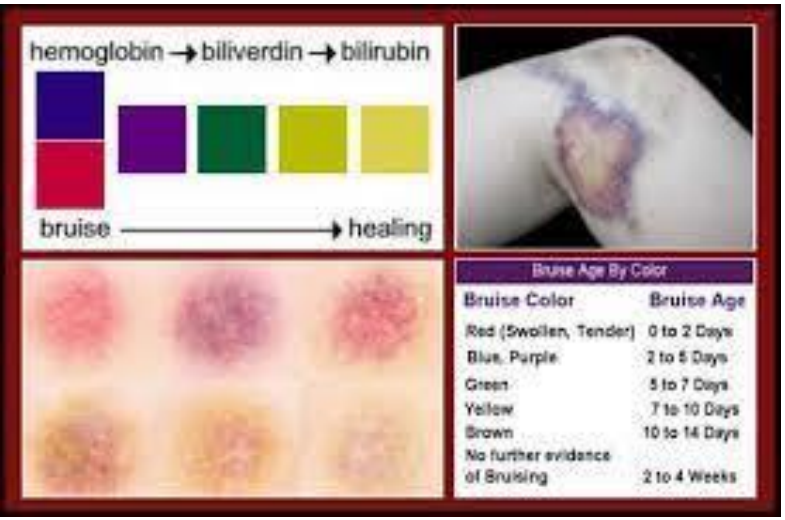
J. Koolman, K.H. Roehm: ***Color Atlas of Biochemistry****, Thieme, 2nd Ed. (2005)*

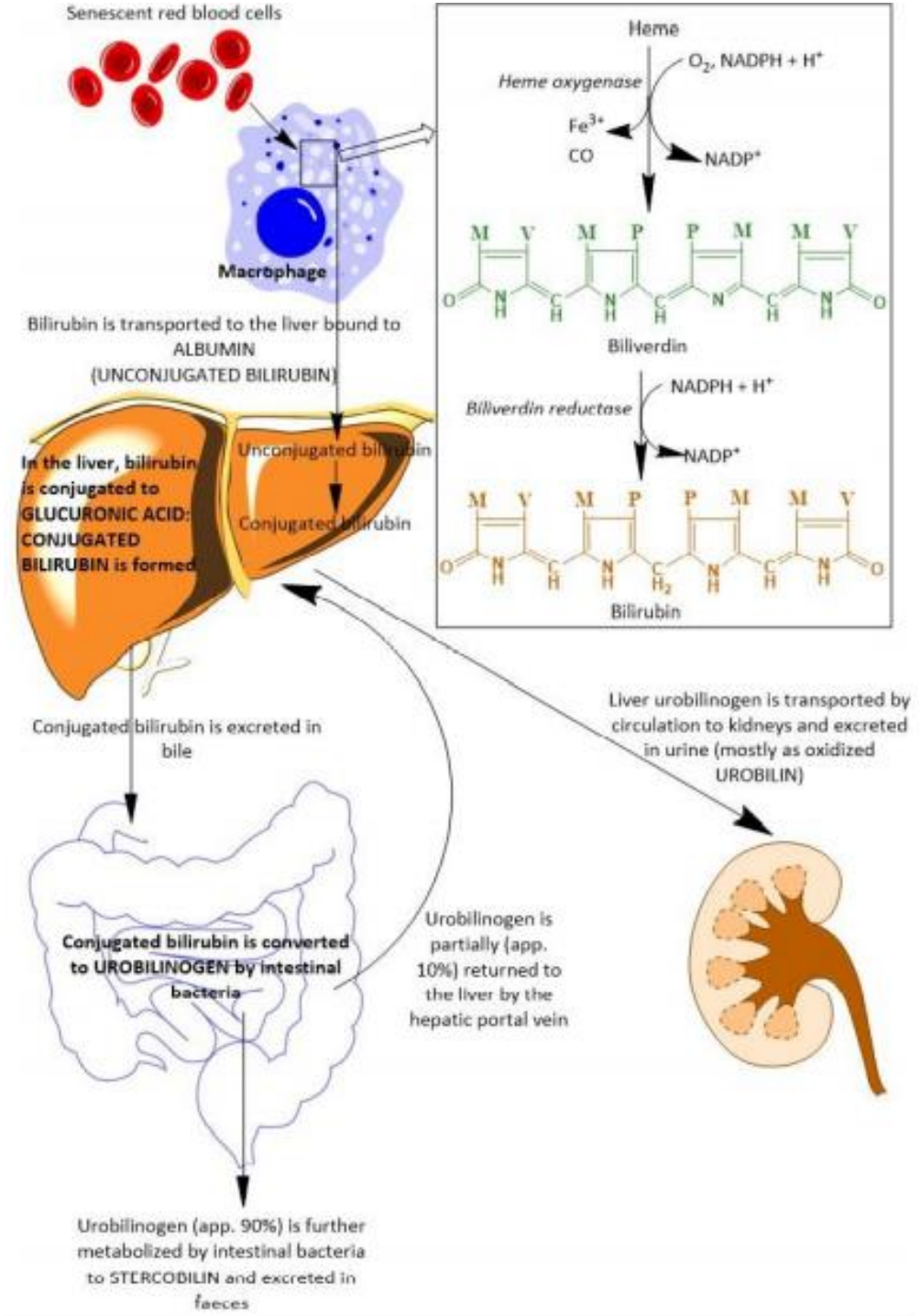
Hemoglobin Degradation

- **erytrocytes** life span: 100-120 days
  - adult human degradation: **2** x **10^8 RBC** per hour!
- **RES** – reticuloendothelial system (macrophage-monocyte system)
  - **spleen, liver, bone marrow**
- globine – degradation to amino acids
- iron - recycling
- heme – degradation products → **bile pigments**

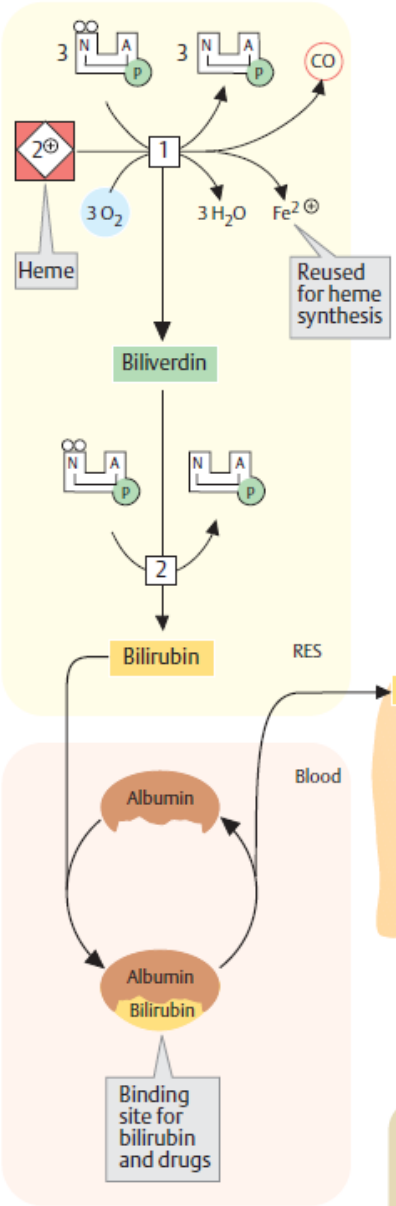


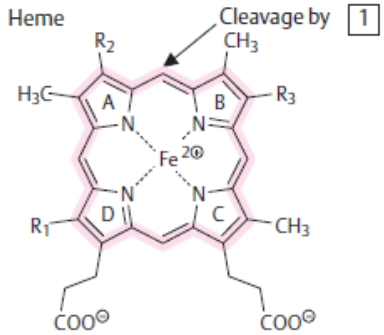
Hemoglobin Degradation

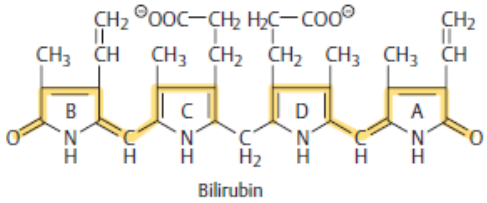


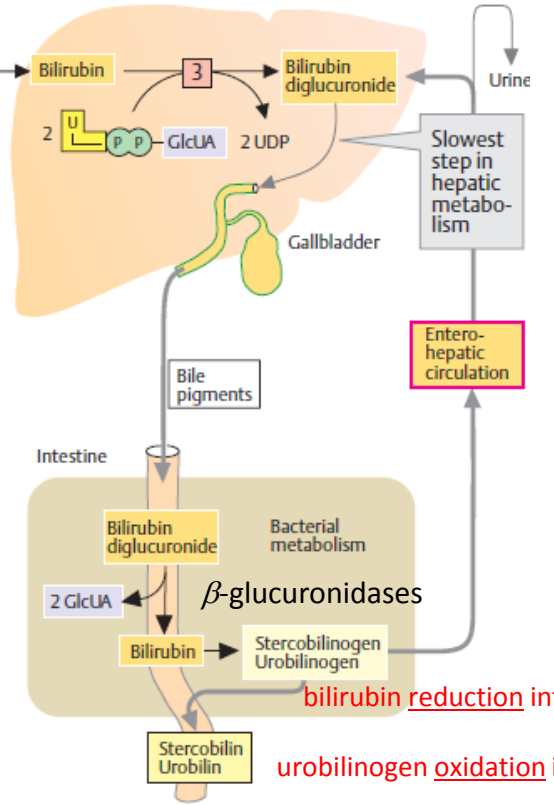


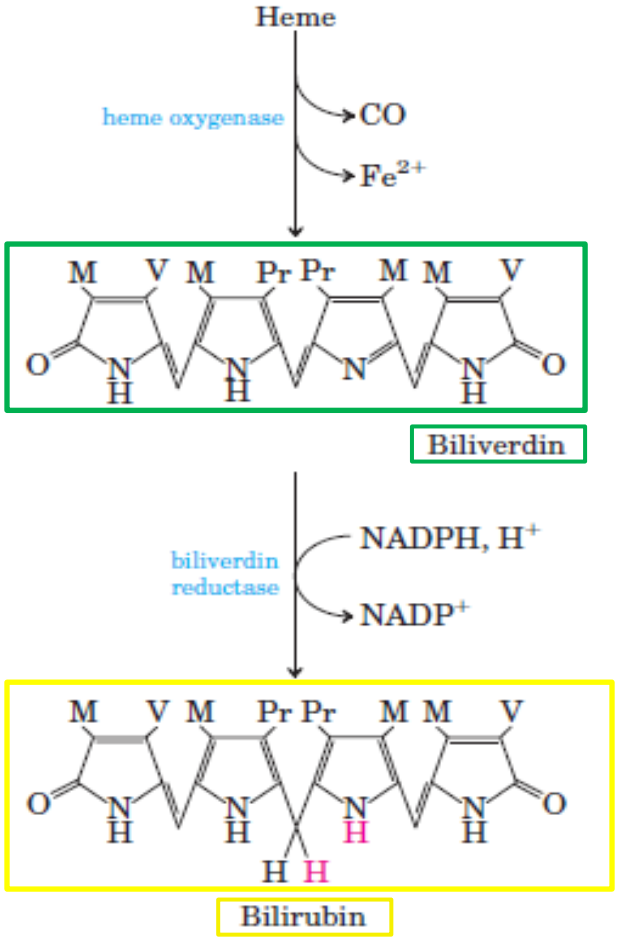
Hemoglobin Degradation











1 Heme oxygenase (decyclizing) *1.14.99.3*

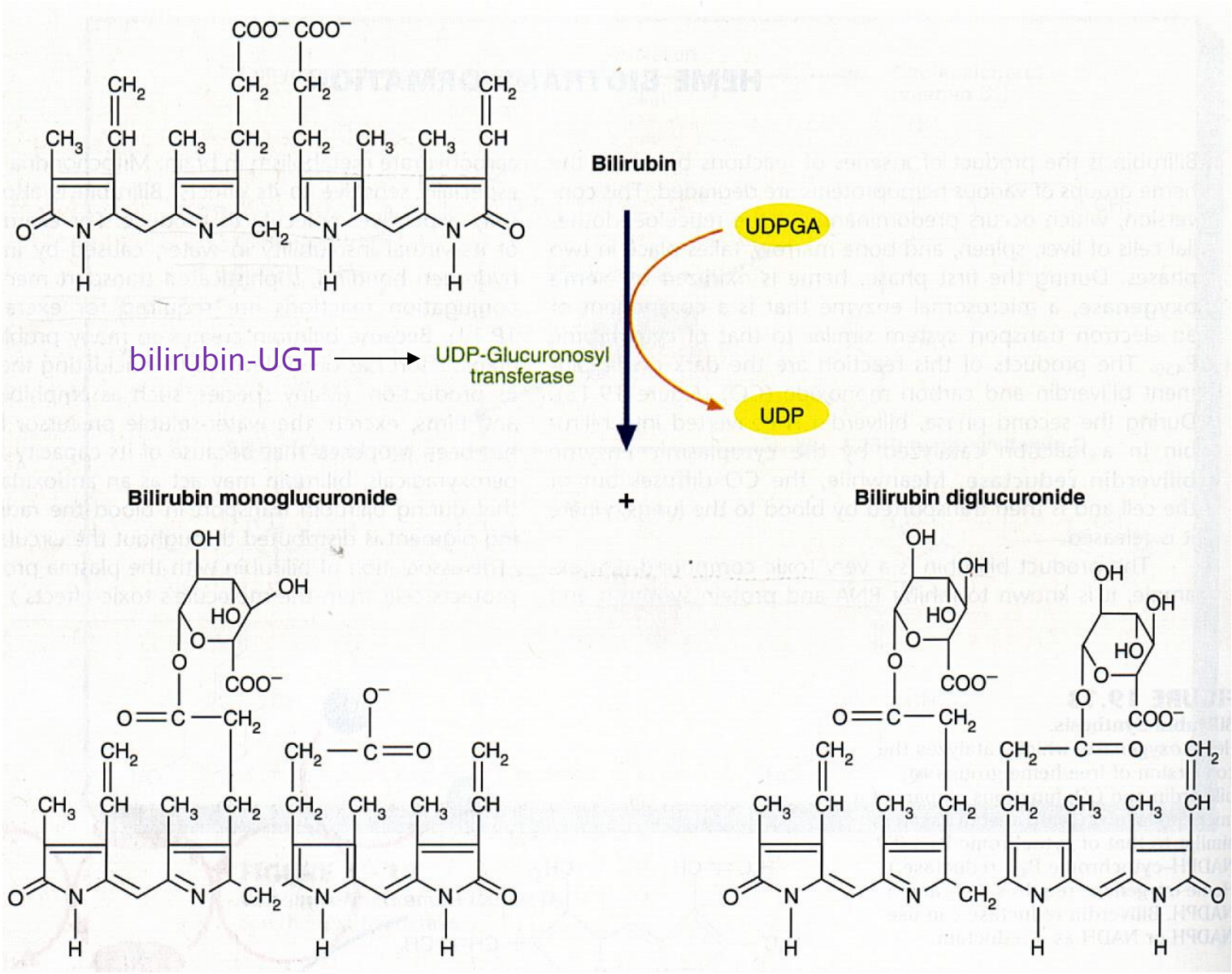
2 Biliverdin reductase *1.3.1.24*

3 Glucuronosyl transferase *2.4.1.17*

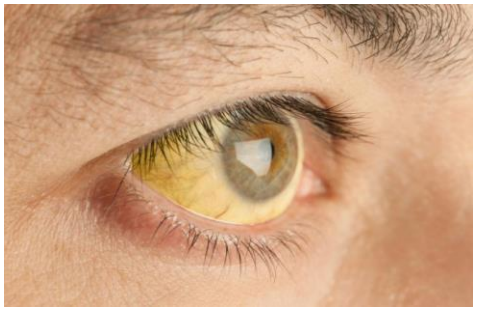
bilirubin reduction into (colorless) **urobilinogen**

urobilinogen oxidation into (colored) **urobilin**

Bilirubin Conjugation in the Liver

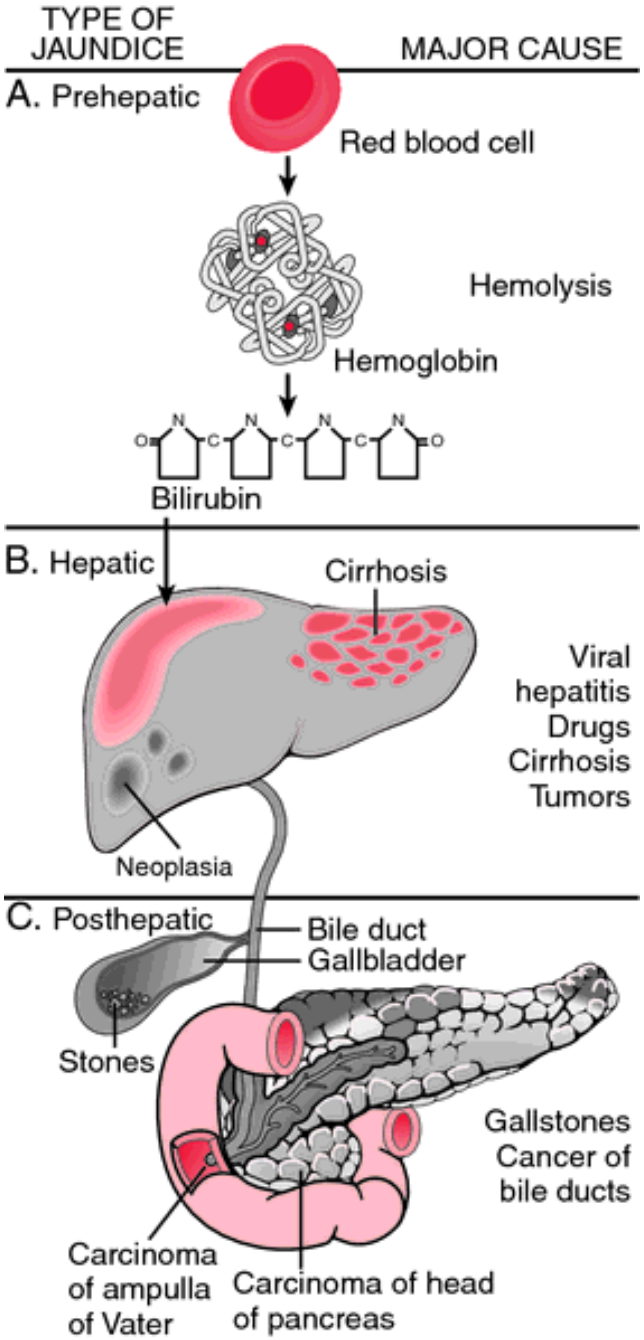


Hyperbilirubinemia



- **elevated bilirubin level in the blood (< 10 mg/L)**
- causes:
  - intense bilirubin formation
  - disabled bilirubin degradation
- bilirubin elevation (< 25 mg/L) - bilirubin exit into tissues → **jaundice** (icterus)
- **types of jaundice:**

PRE HEPATIC	HEPATIC	POST HEPATIC
Hemolytic Anemia	Hepatitis, cirrhosis, Crigler-Najjar Syndrome, Dubin-Johnson Syndrome, Rotor's Syndrome	Gallstone, malignancy, inflammation

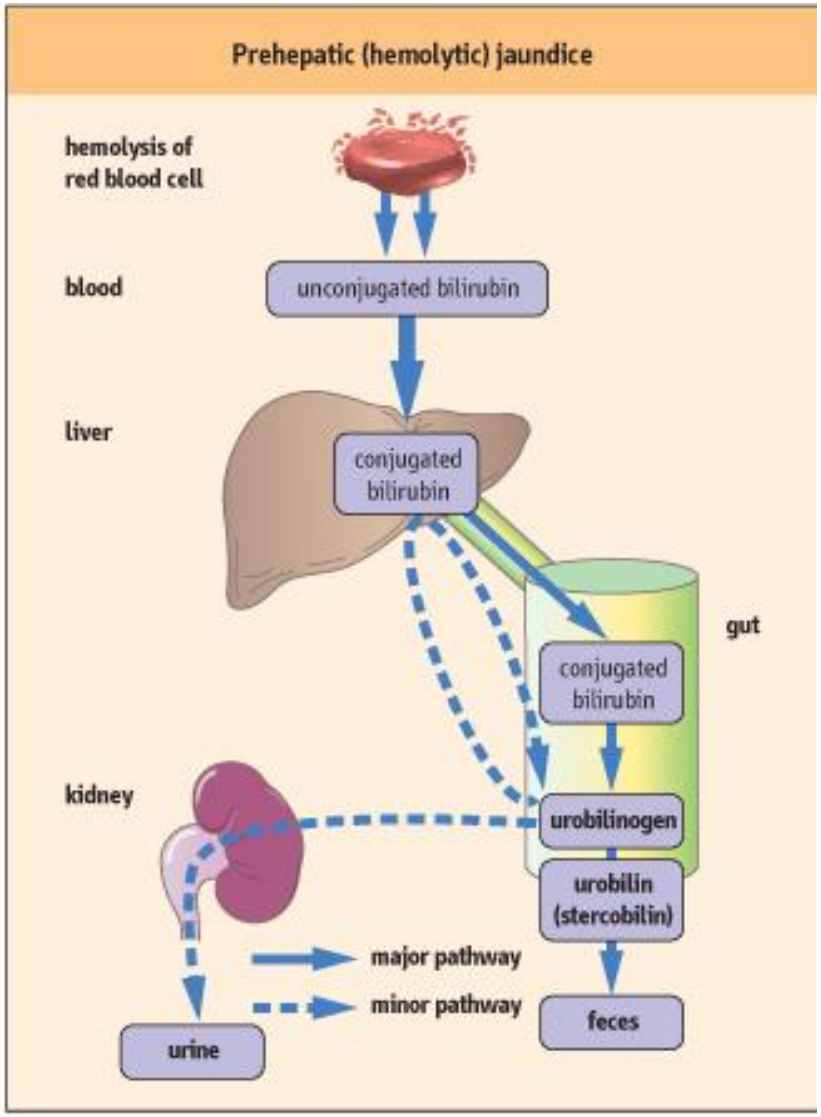

TYPE OF JAUNDICE
MAJOR CAUSE
A. Prehepatic
Red blood cell
Hemolysis
Hemoglobin
Bilirubin
B. Hepatic
Cirrhosis
Viral hepatitis
Drugs
Cirrhosis
Tumors
Neoplasia
C. Posthepatic
Bile duct
Gallbladder
Stones
Gallstones
Cancer of bile ducts
Carcinoma of ampulla of Vater
Carcinoma of head of pancreas

Prehepatic jaundice

- caused by hemolysis – hemolytic anemia

-prehepatic – the disorder takes place „before" the liver (in bilirubin metabolism)

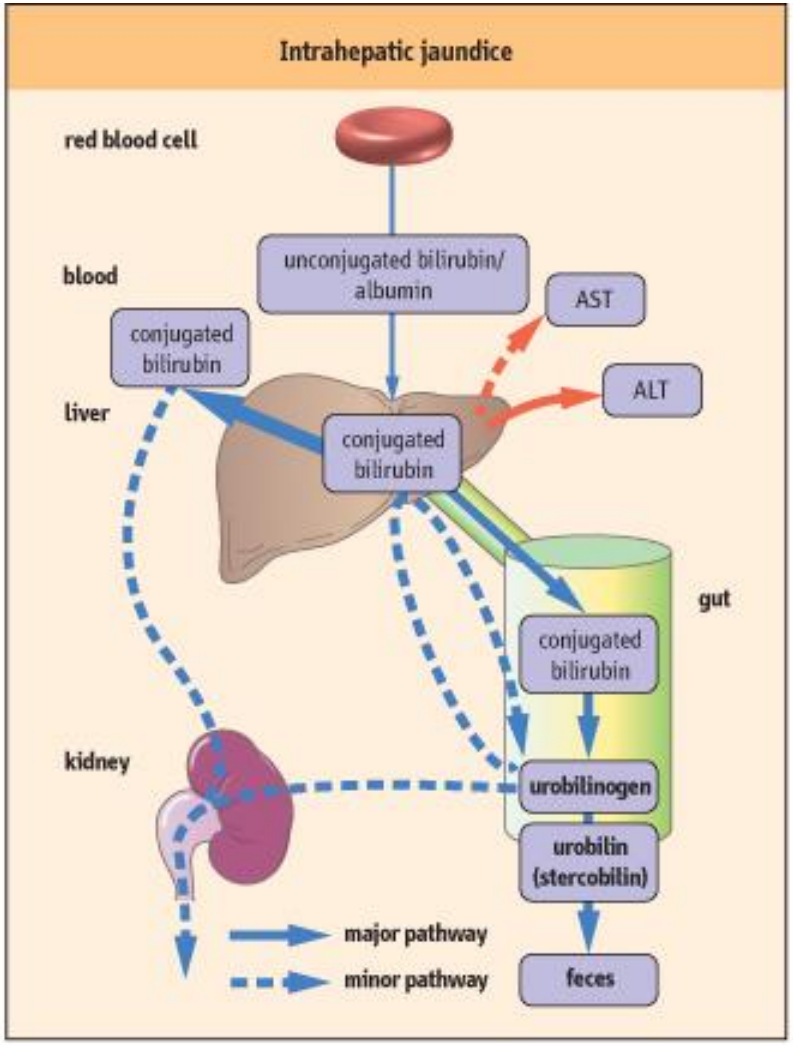
- **unconjugated hyperbilirubinemia**



Serum bilirubin			Urine	
Total bilirubin	**Conjugated bilirubin**	**Feces color**	Urobilinogen (colorless)	Bilirubin
↑	normal	dark	↑	-

Hepatic (hepatocelular) jaundice

- **liver cell** (hepatocytes) damage:
- hepatitis
- chyrosis
- tumor...

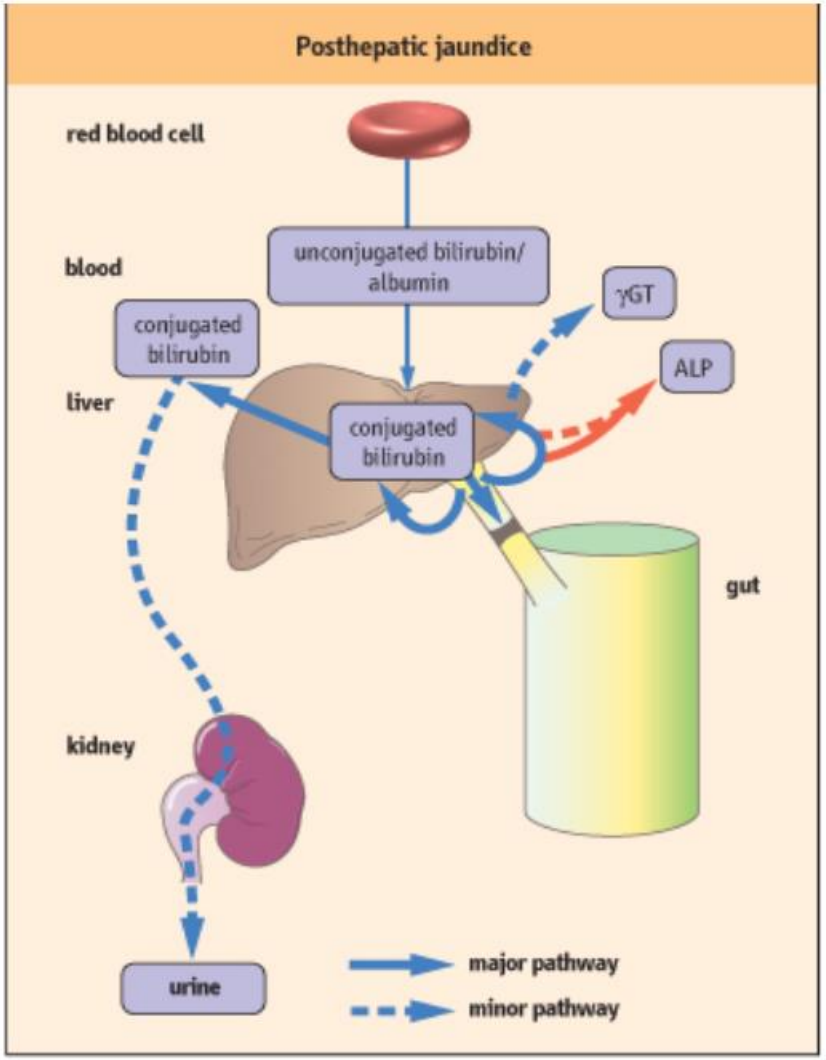


Serum bilirubin			Urine	
Total bilirubin	**Conjugated bilirubin**	**Feces color**	Urobilinogen (colorless)	Bilirubin
↑	↑	pale	↑	+

Posthepatic (obstructive) jaundice

- obstructive or cholestatic jaundice → gallstones, tumor… causing blockage in the bile flow
- no bilirubin entering the gut → no formation of urobilinogen by bacterial metabolism → no pigment in the stool → acholic stool

- very high bilirubin concentrations in the blood



Serum bilirubin			Urine	
Total bilirubin	**Conjugated bilirubin**	**Feces color**	Urobilinogen	Bilirubin
↑↑↑	↑	pale (acholic)	-	+

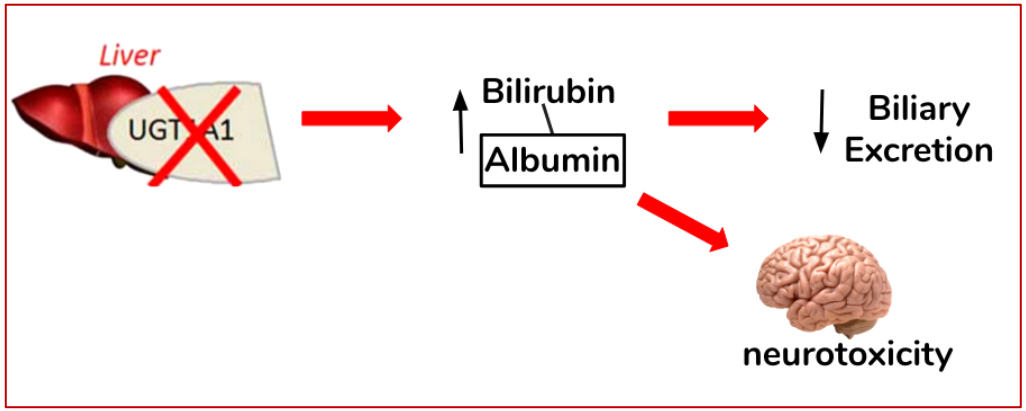
Neonatal (newborn) jaundice

- 50% newborns have visible jaundice in first 5 days of life
- **unconjugated hyperbilirubinemia**
- efficient therapy - **phototherapy**

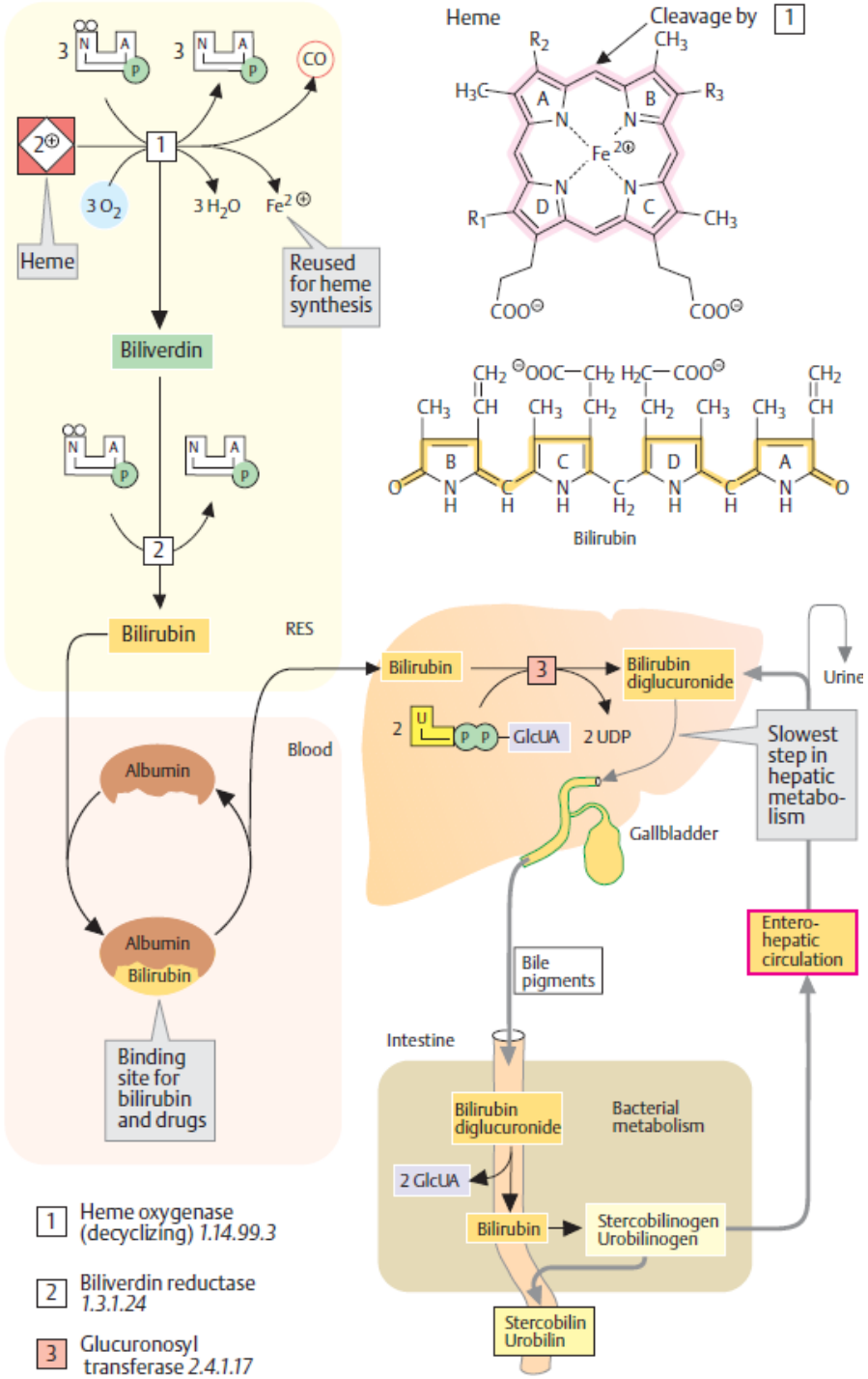
- unconjugated bilirubin is <u>not</u> water soluble (therefore needs albumin for transport, similar to fatty acids) → it is lipophylic and it can damage all cells, especially brain cells
- **<u>KERNICTERUS</u>** (hyperbilirubinemic toxic encephalopathy)
  - rare type of neuronal degeneration and necrosis
  - the term *kernicterus* literally means "yellow kern," with kern indicating the most commonly afflicted region of the brain (ie, the nuclear region)

Other Disorders

- **Crigler-Najjar syndrome**
  - congenital jaundice (serum bilirubin > 342 µmol/L; norm. up to 17)
  - mutation/deficient UDP glucuronosyl transferase gene ((UGT1A1)
  - often fatal



- **Gilbert syndrome**
  - mutation in UDP glucuronosyl transferase (bilirubin-UGT); 30% enzyme activity
  - hiperbilirubinemia (sligh
  - common and harmless condition


Heme
Cleavage by 1
Bilirubin
Biliverdin
Heme
Reused for heme synthesis
CO
3 O2
3 H2O
Fe2⊕
RES
Blood
Albumin
Albumin
Bilirubin
Binding site for bilirubin and drugs
Bilirubin
Bilirubin diglucuronide
GlcUA
2 UDP
Slowest step in hepatic metabolism
Urine
Gallbladder
Entero-hepatic circulation
Bile pigments
Intestine
Bilirubin diglucuronide
Bacterial metabolism
2 GlcUA
Bilirubin
Stercobilinogen Urobilinogen
Stercobilin Urobilin
1 Heme oxygenase (decyclizing) 1.14.99.3
2 Biliverdin reductase 1.3.1.24
3 Glucuronosyl transferase 2.4.1.17

Literature:

- *J. Koolman, K.H. Roehm:* ***Color Atlas of Biochemistry****, Thieme, 2nd Ed. (2005)*

- *Robert K. Murray, David A Bender, Kathleen M. Botham, Peter J. Kennelly, Victor W. Rodwell, P. Anthony Weil:* ***Harper's Illustrated Biochemistry****, Lange Medical Books/McGraw-Hill, Medical Publishing Division, 26th Ed. (2003)*

- *David L. Nelson, Michael M. Cox :* ***Lehninger Principles of Biochemistry****, Worth Publishers, 4rd Ed. (2005)*

- STUDENT CONSULT (ver. 2.3) (gusc.lv)

- Jaundice in newborn infant | Download Scientific Diagram (researchgate.net)