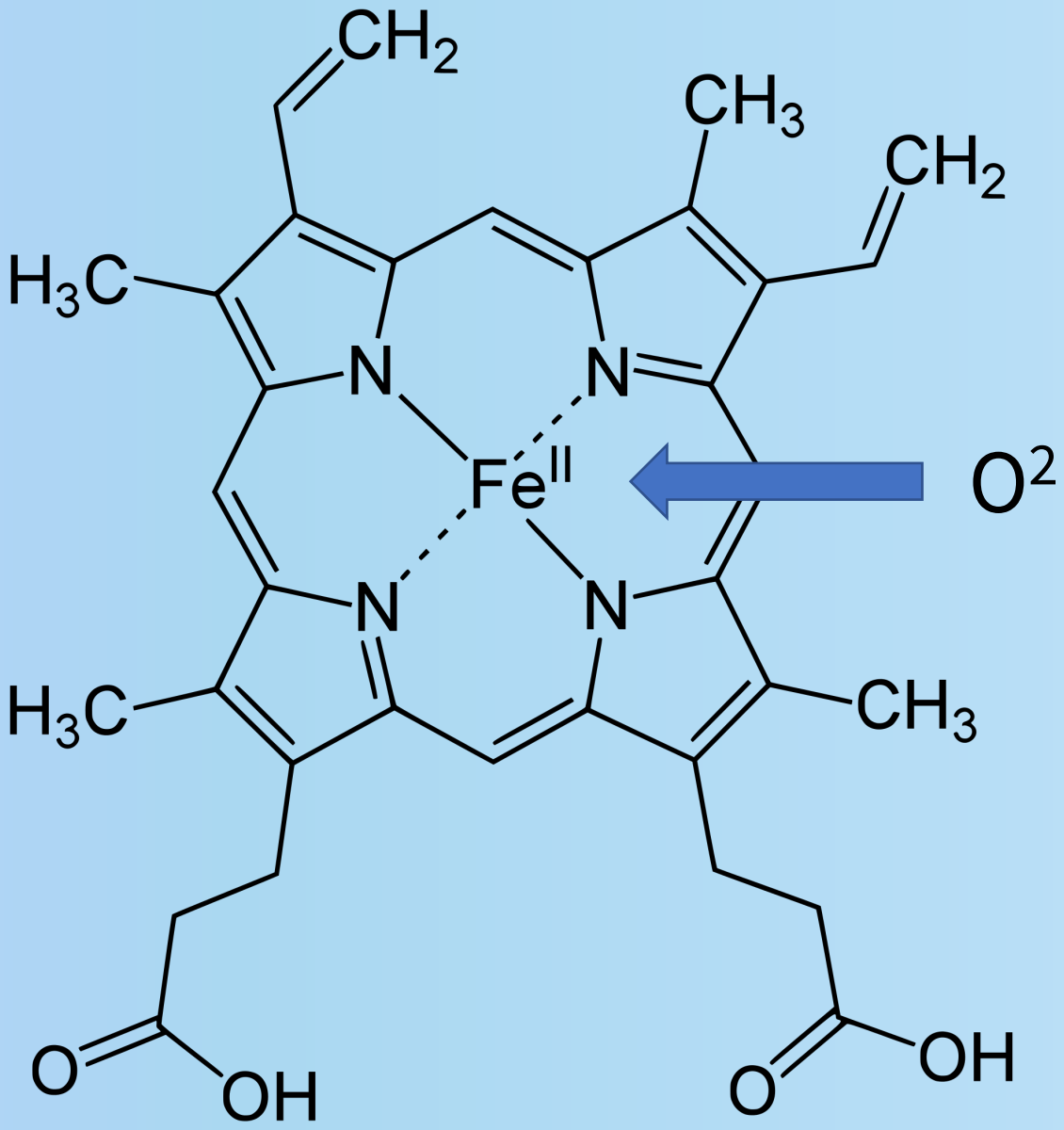
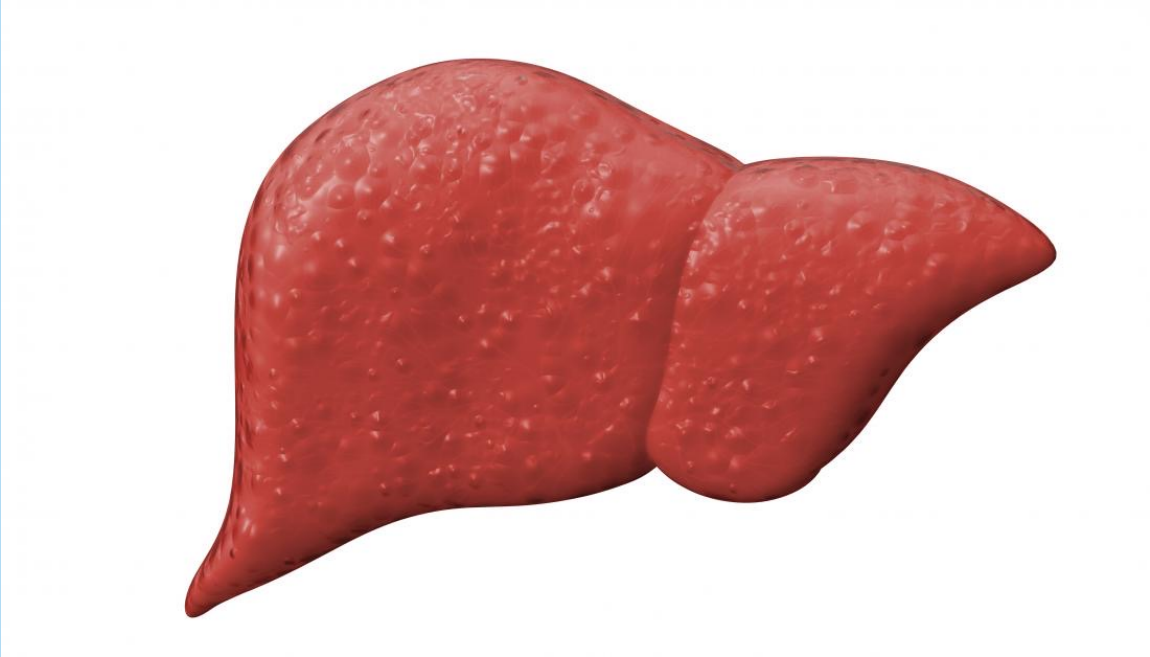
Heme Synthesis & Degradation

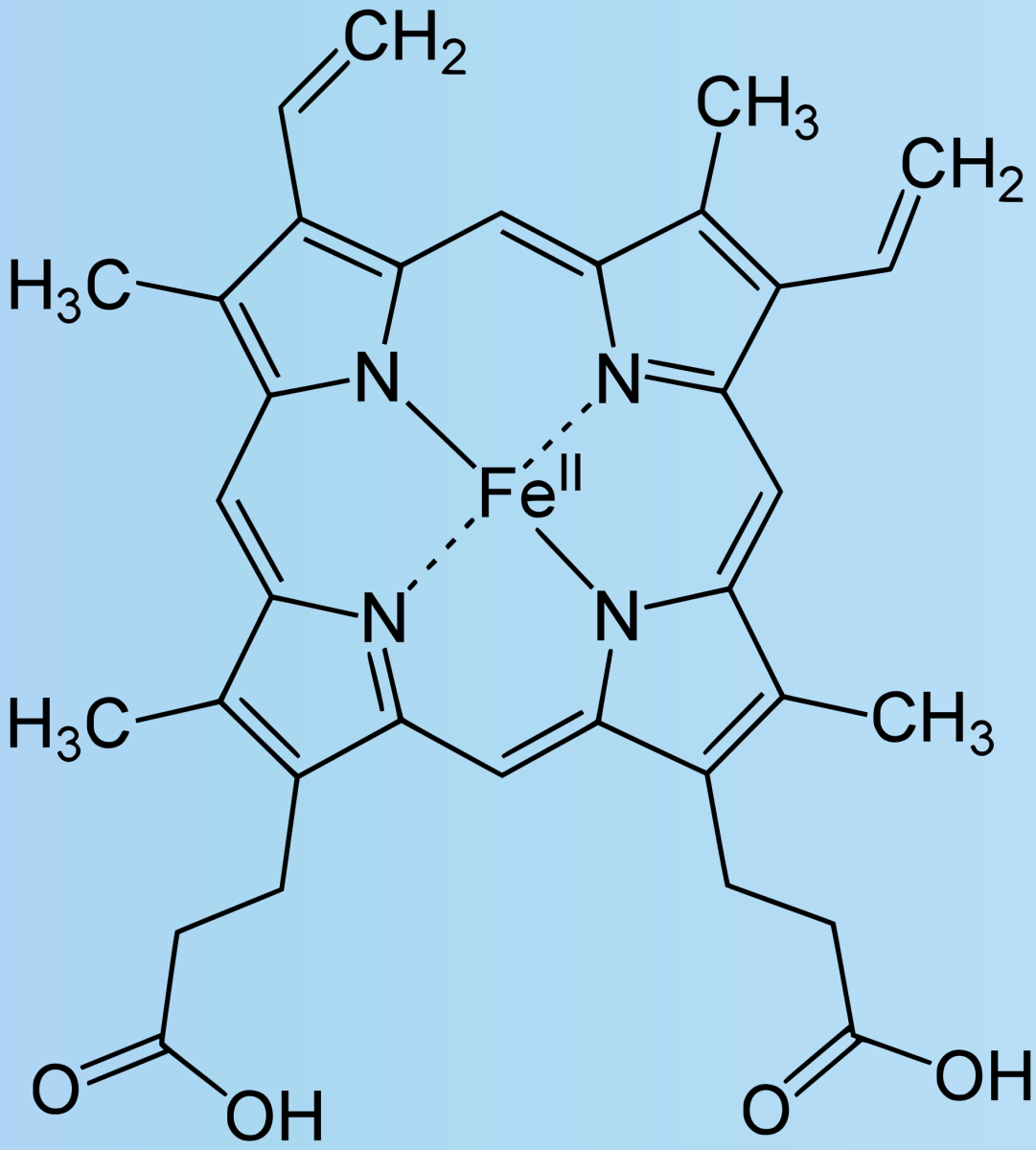
By Marte Rydland

HEME?



HEME SYNTHESIS





Synthesis of heme

Succinyl CoA + Glycine → (CoASH, ALA synthase — RATE LIMITING) → δ- Aminolevulinate

HEMATIN
GLUCOSE

δ- Aminolevulinate → 2 δ- Aminolevulinate

2 δ- Aminolevulinate → (4H₂O, ALA dehydrogenase; Zn²⁺; LEAD) → Porphobilinogen

Porphobilinogen → 4-Porphobilinogen

4-Porphobilinogen → (4NH₃, Uroporphyrinogen I Synthase & Hydroxymethylbilane Synthase OR) → Uroporphyrinogen I / Hydroxymethybilane

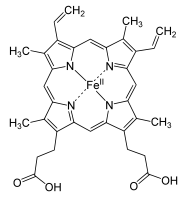
Uroporphyrinogen I / Hydroxymethybilane → (RING CLOSURE; Uroporphyrinogen III Cosynthase) → Uroporphyrinogen III

Uroporphyrinogen III → (4CO₂, Uroporphyrinogen decarboxylase) → Coproporphyrinogen III

Coproporphyrinogen III → (4CO₂, Coprophyrinogen oxidase) → Protoporphyrinogen III

Protoporphyrinogen III → (4H⁺, Protophyrinogen oxidase) → Protoporphyrin IX

Protoporphyrin IX → (Fe²⁺, Ferrochelatase; LEAD) → Heme



Diseases related to poor synthesis of heme:

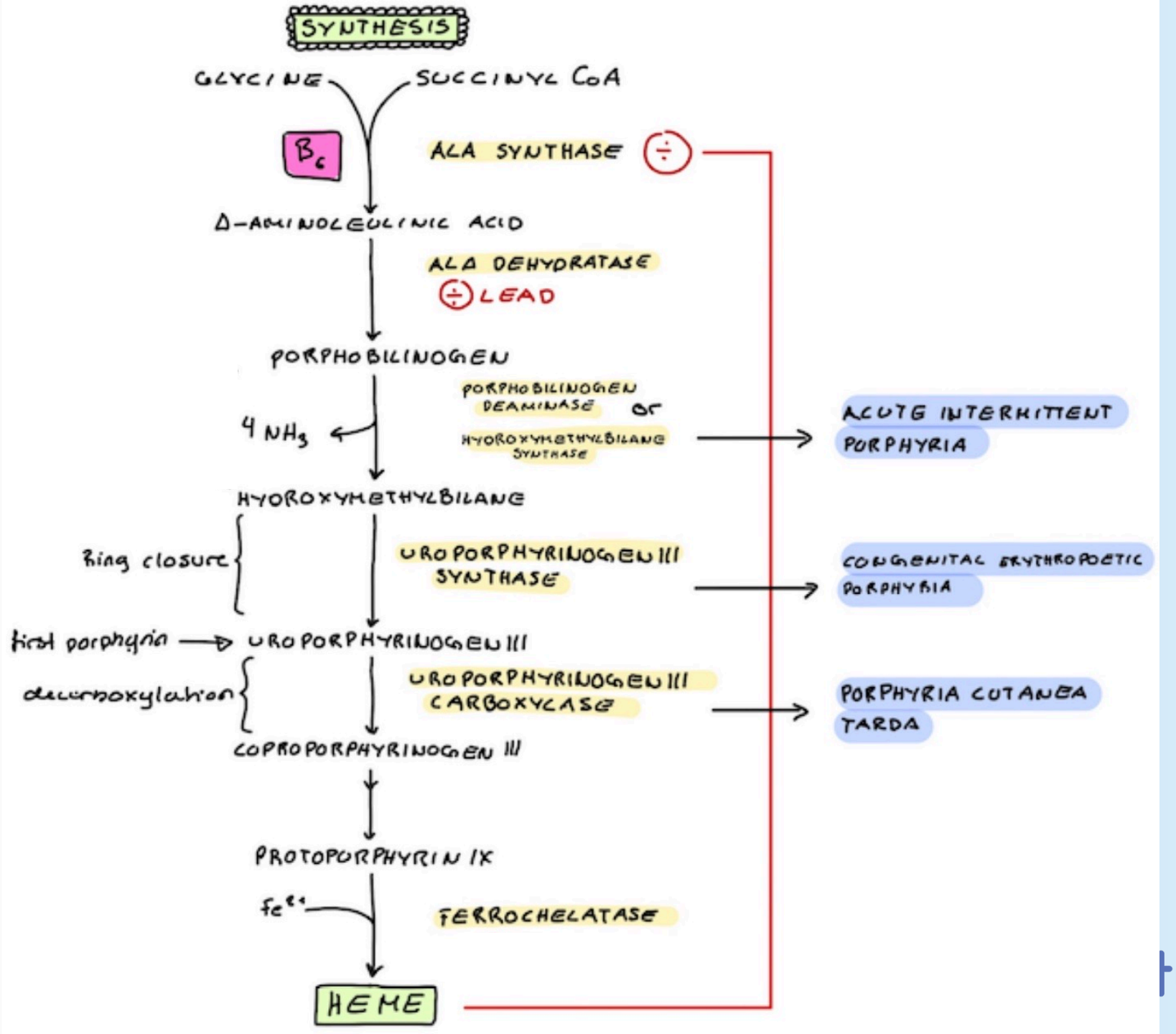
Anemias

- Lead poisoning
  - ALA dehydrogenase
  - Ferrochelatase
- Iron deficiency
  - Ferrochelatase
  - Oxygen cannot bind heme

Porphyrias

1) Hepatic
   - Drugs, alcohol, hormones, diet, inf
   - Abd. pain + CNS
2) Erythropoietic
   - Enzyme deficiency
   - Cutaneous + photosensitivity

1. **Acute intermittent porphyra**
2. **Congenital erythropietic porphyria**
3. **Porphyria cutanea tarda**


SYNTHESIS
GLYCINE
SUCCINYL CoA
B_6
ALA SYNTHASE
÷
Δ-AMINOLEVULINIC ACID
ALA DEHYDRATASE
÷ LEAD
PORPHOBILINOGEN
PORPHOBILINOGEN DEAMINASE or HYDROXYMETHYLBILANE SYNTHASE
$4\ NH_3$
ACUTE INTERMITTENT PORPHYRIA
HYDROXYMETHYLBILANE
Ring closure
UROPORPHYRINOGEN III SYNTHASE
CONGENITAL ERYTHROPOETIC PORPHYRIA
first porphyria
UROPORPHYRINOGEN III
decarboxylation
UROPORPHYRINOGEN III CARBOXYLASE
PORPHYRIA CUTANEA TARDA
COPROPORPHYRINOGEN III
PROTOPORPHYRIN IX
Fe^{++}
FERROCHELATASE
HEME

Acute intermittent porphyria (AIP)

- Deficiency of hydroxymethylbilane synthase (HMBS)
- Hepatic
- Triggers Diet, alcohol, drugs, infections, stress and hormonal changes
- Women in puberty
- Symptoms:
  - Abdominal symptoms
  - CNS; seizures, hallucinations, confusion
  - Muscle pain and weakness
  - Heart palpitations
- Tx: IV glucose – inhibits ALA synthase

Congenital erythropietic porphyria (CEP)

- Deficiency of uroporphyrinogen lll cosynthase (UROS)
- Photosensitivity of the skin
- Blisters, lesions and scarring of the skin
- Hands, feet and face
- Infancy
- Tx: Avoid sunlight

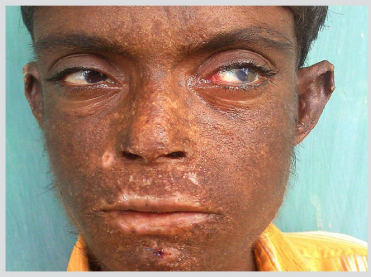


Figure 1. Vesicles, scarring, pigmentation, hypertrichosis on the face and scleromalacia of the left eye

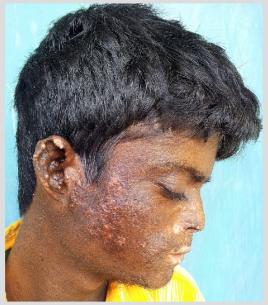


Figure 2. Vesicles, scarring, pigmentation, hypertrichosis of the face and mutilation of the ear lobule

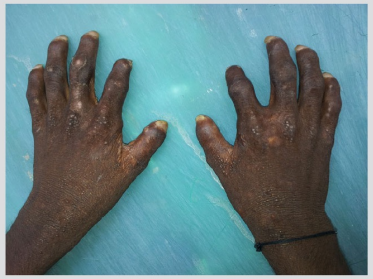
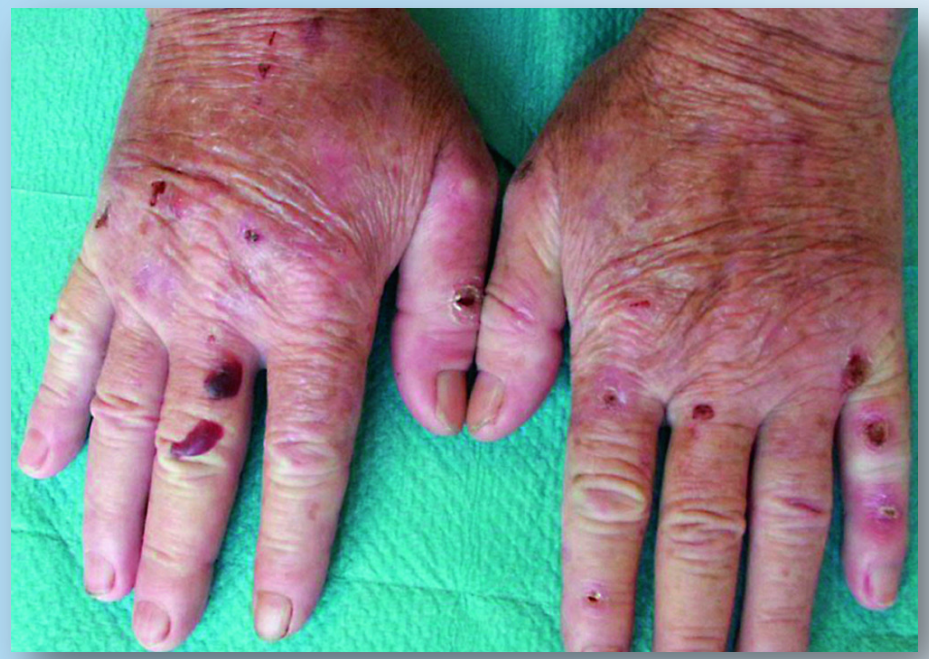


Figure 3. Vesicles, scarring of the hands, mutilating deformities of the fingers and dystrophic nails.

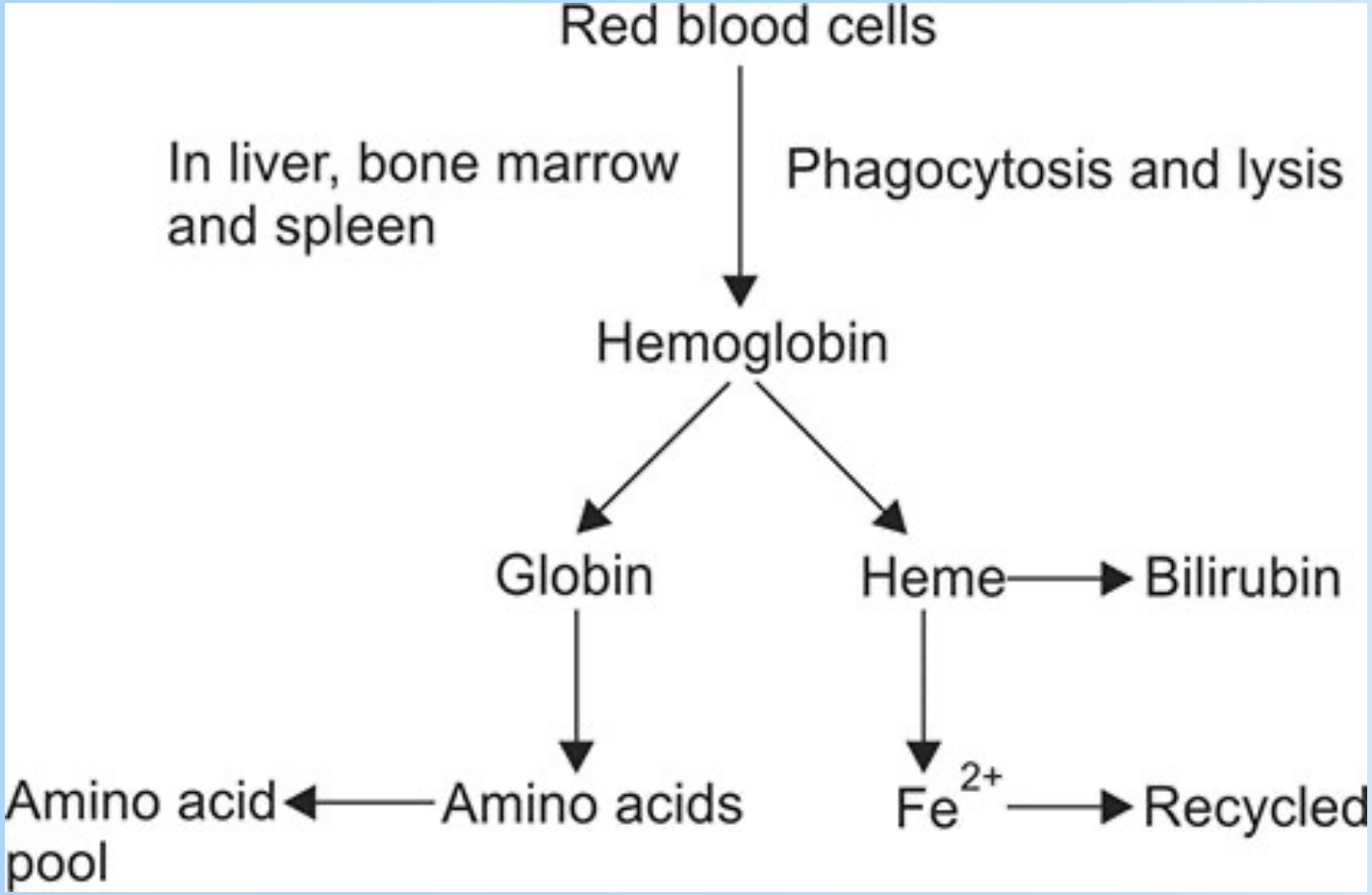
Figure 4. Urine turning reddish pink on standing

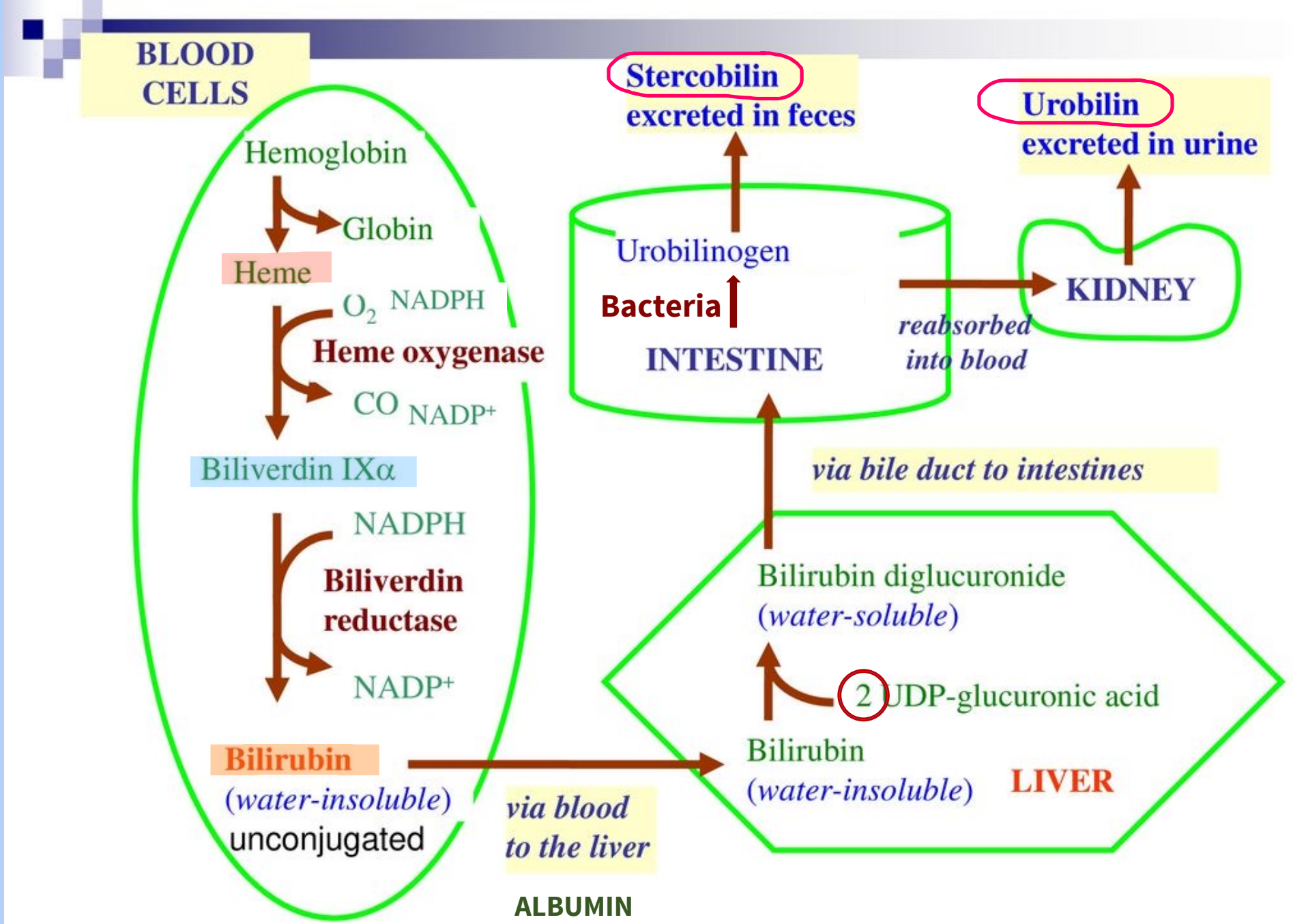
Porphyria Cutanea Tardea (PCT)

- Deficiency of uroporphyrinogen decarboxylase (UROD)
- Severe photosensitivity of the skin
- 1/3 – hereditary: early onset
- 2/3 – liver disease: late onset
- Women > 30 yo
- Tx: avoid sunlight



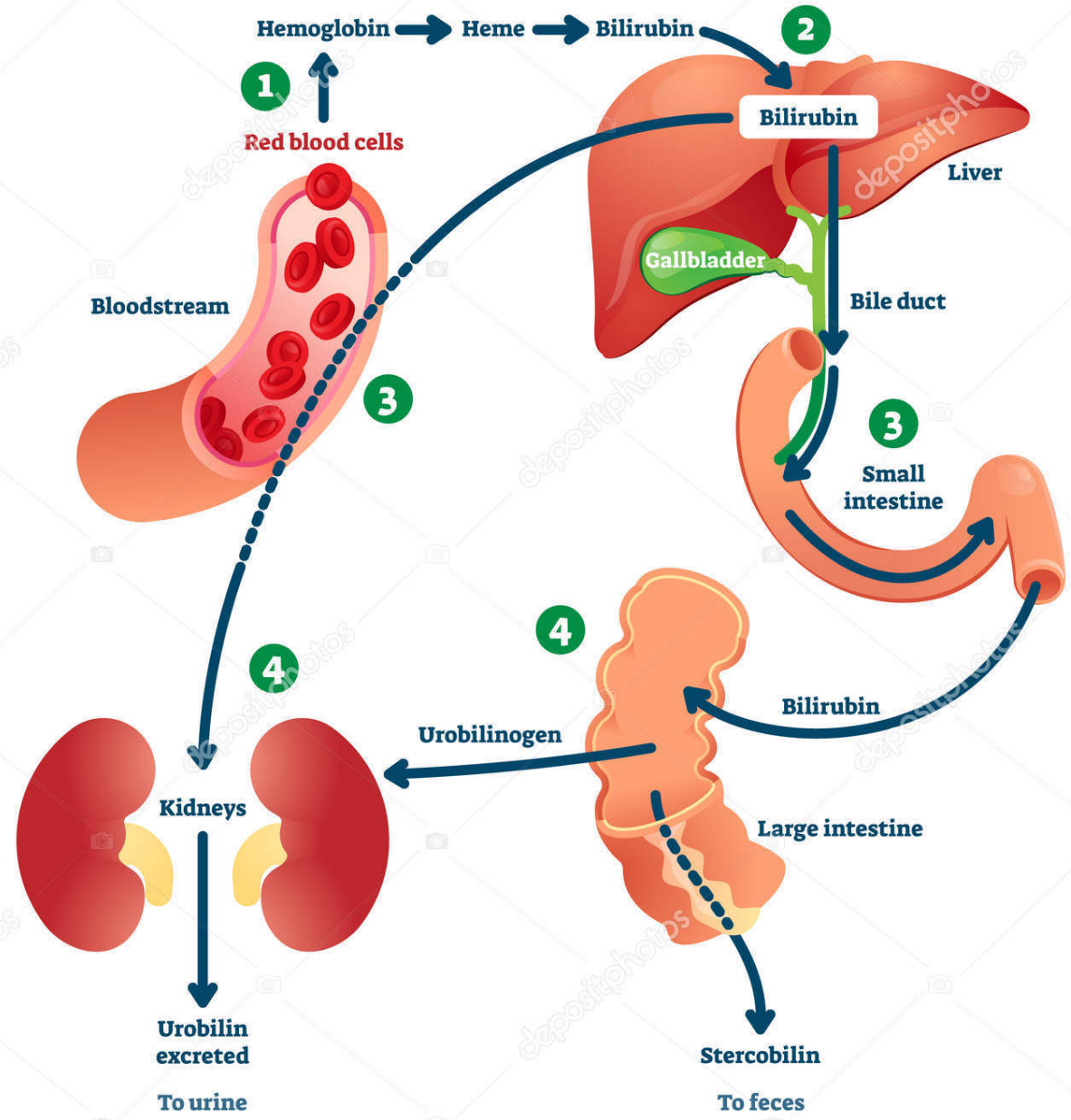
Degradation of heme





Catabolism of hemoglobin

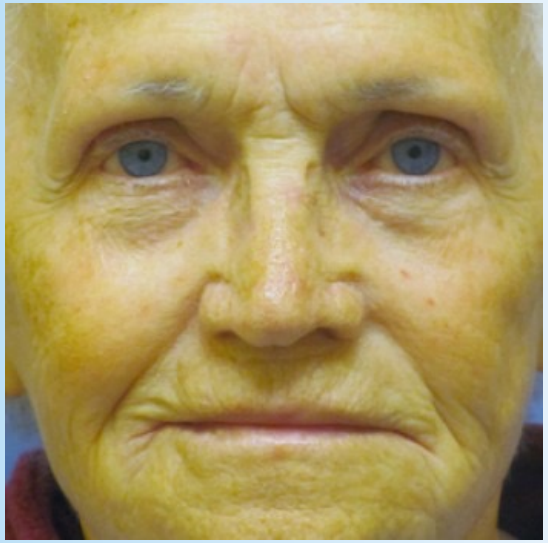
HEME CATABOLISM



Jaundice = Icterus

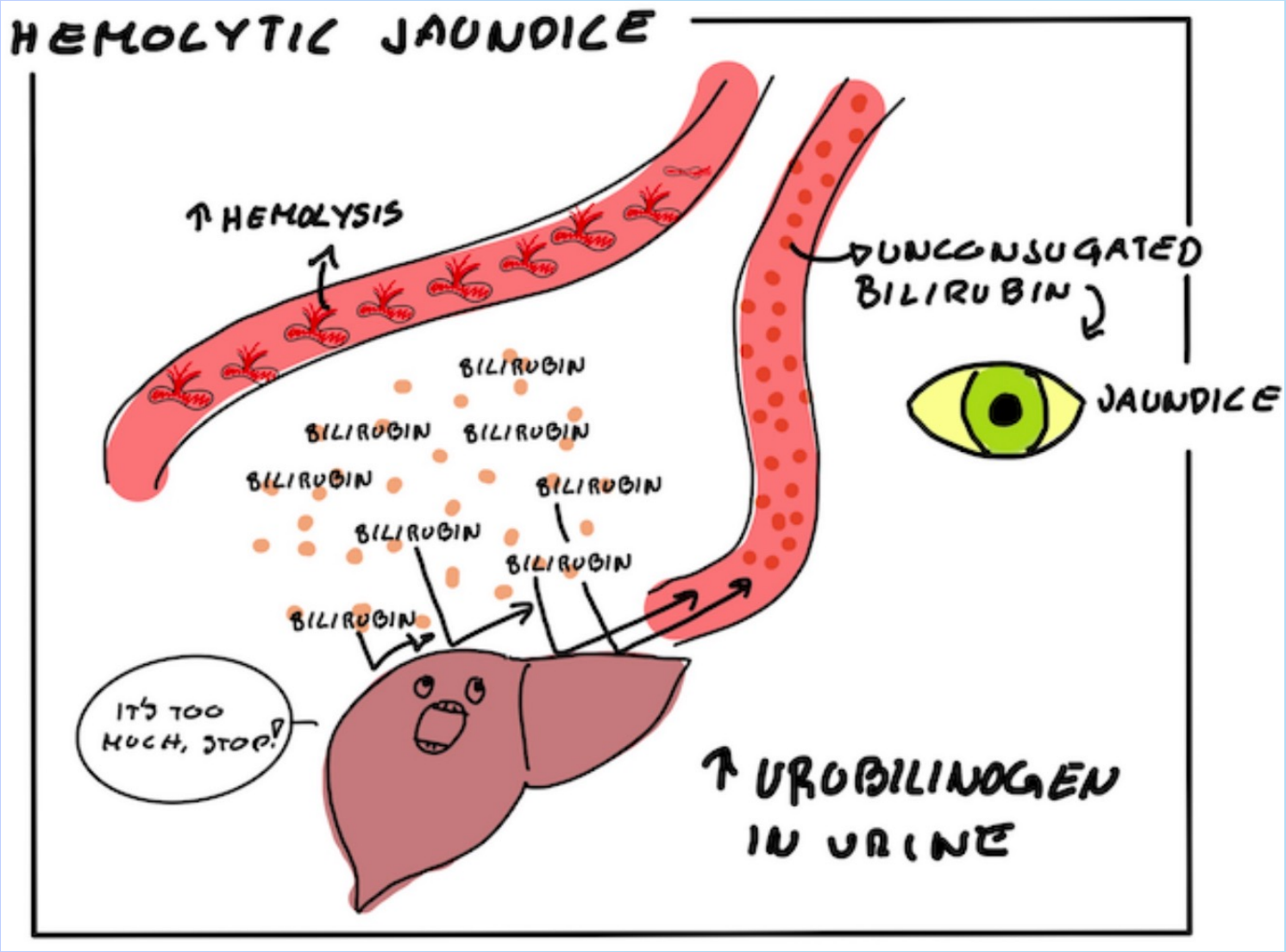
- Symptoms:
  - Yellow discoloration
  - Light colored stools
  - Dark colored urine
  - Itching of the skin
- Bilirubin > 3 mg/dL (normal < 1.3 mg/dL)
  - Hyperbilirubinemia
- Neonatal jaundice

1. **PRE-HEPATIC**
2. **HEPATIC**
3. **POST-HEPATIC**



Scleral icterus

PRE-HEPATIC



↑ **Unconjugated bilirubin in serum**

↑ **Stercobilin in stool**

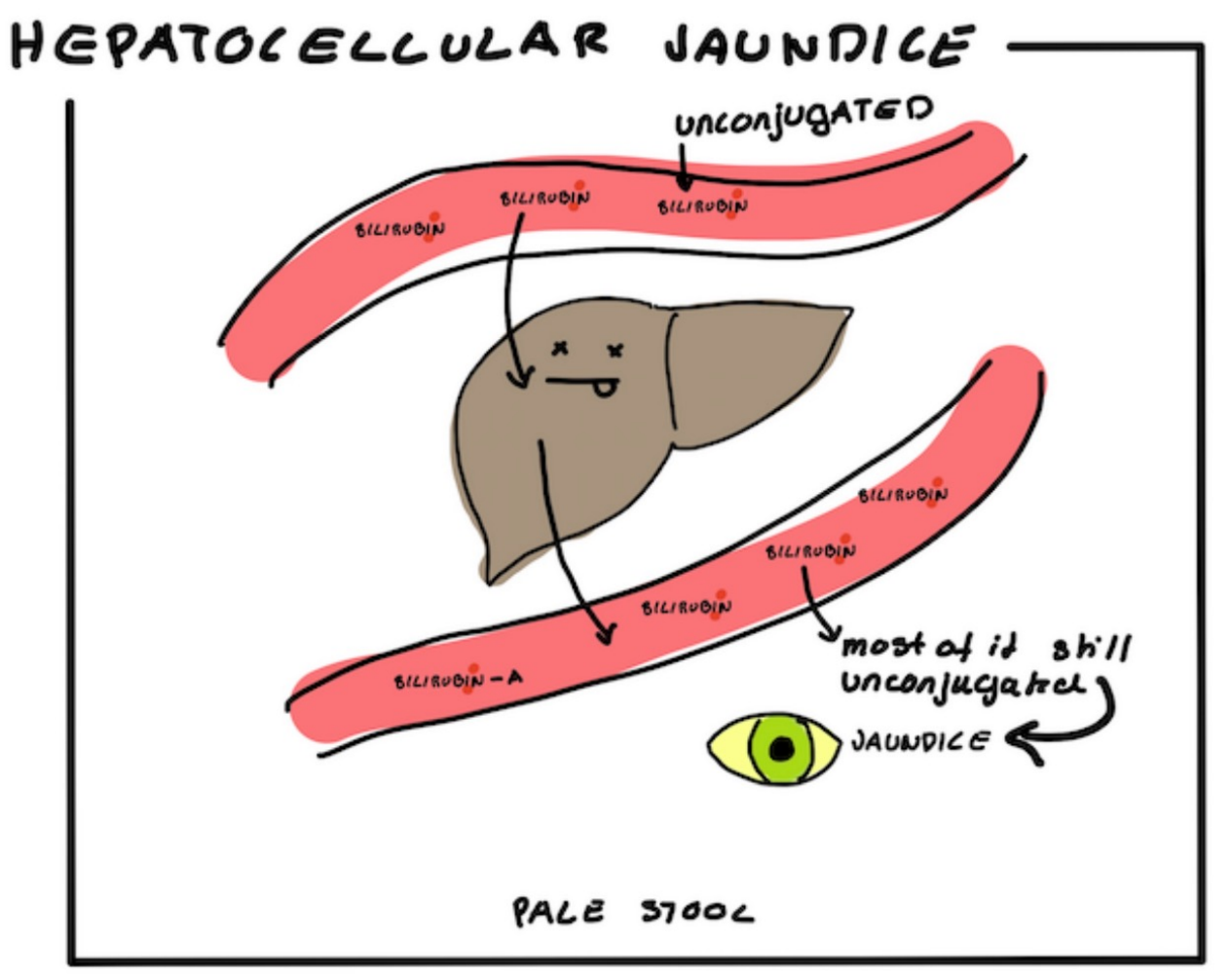
↑ **Urobilinogen in urine**

Normal color of urine and stool

Causes:

- Hemolytic anemia – Malaria
- Blood transfusion
- Hemolytic drugs
- Ineffective hematopoiesis

HEPATIC JAUNDICE



↑ **Unconjugated and conjugated bilirubin in the serum**

↓ **Urobilinogen in the urine**
Stercobilin in stool

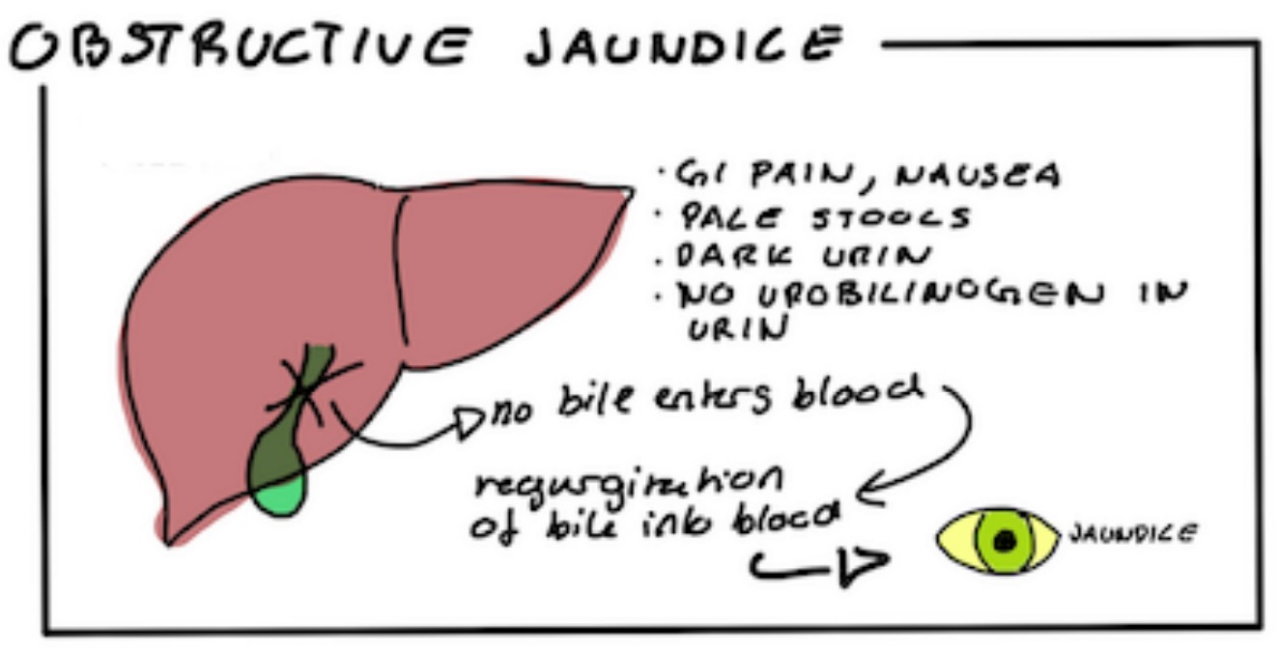
Dark urine due to conjugated bilirubin in the urine

Pale stool due to decreased stercobilin in stool

Causes:

- Liver damage
- Crigler-Najjar syndrome
- Dubin-Johnson syndrome
- Gilbert syndrome

POST-HEPATIC / OBSTRUCTIVE JAUNDICE



↑ **Conjugated bilirubin in serum**

↑ **Bilirubin in the urine**

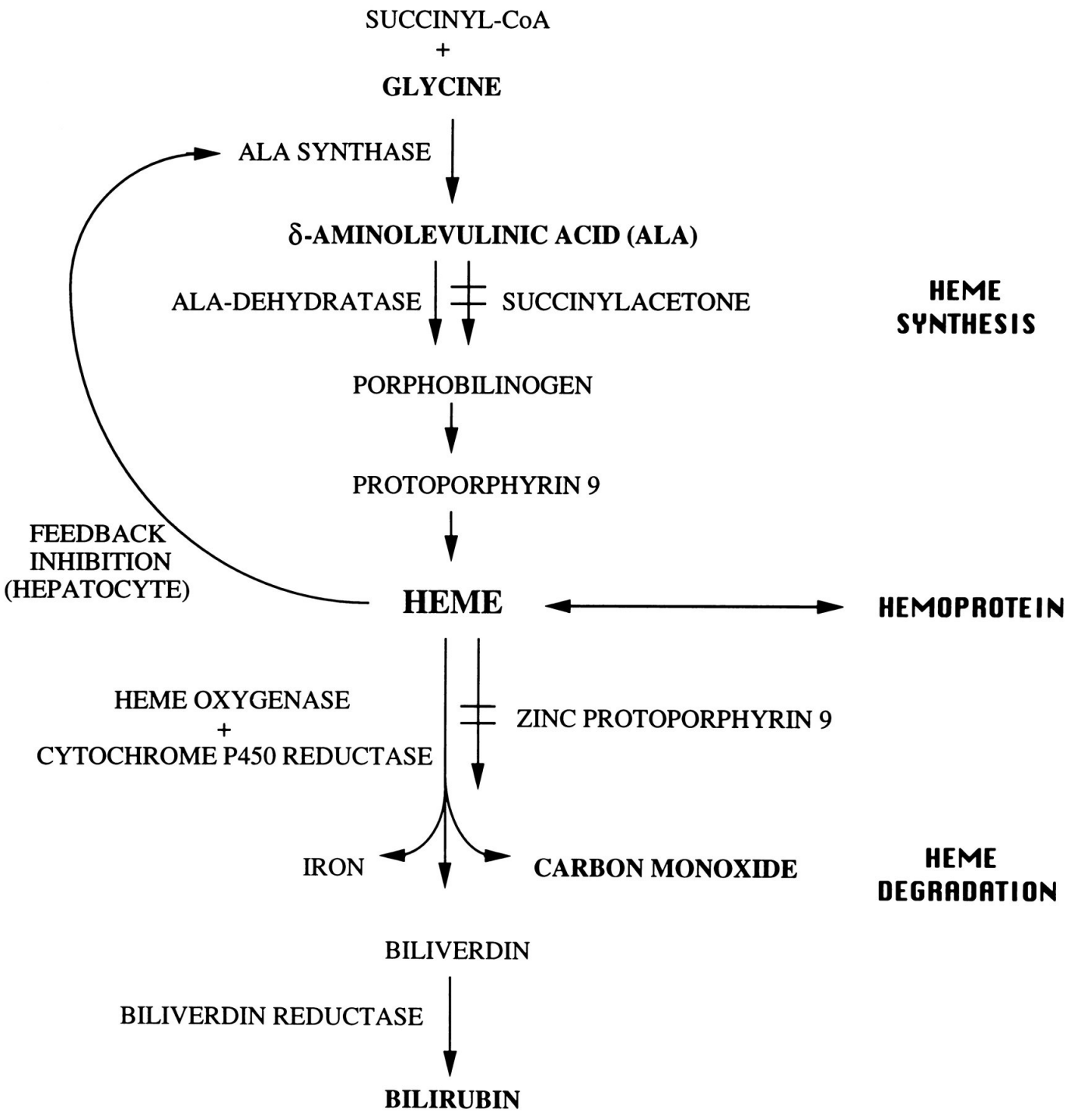
↓ **Stercobilin in stool**

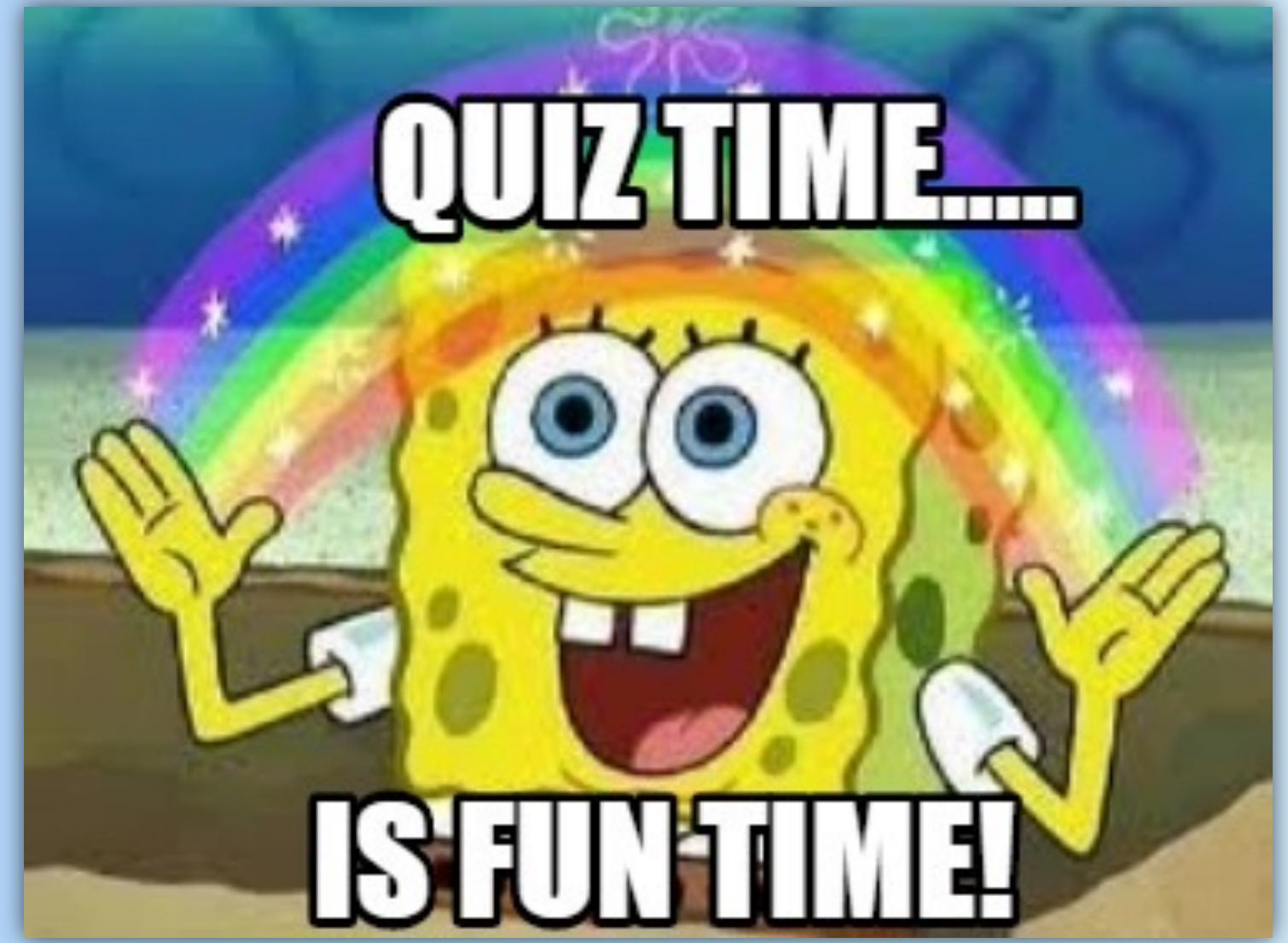
↓ **Urobilinogen in urine**

Dark urine due to increased conjugated bilirubin in the urine
Pale stool due to lack of stercobilin

Causes:

- Calculus Cholecystitis
- Acalculus Cholecystits
- Carcinoma of head of Pancreas
- Pancreatic edema
- Hepatic swelling/fibrosis


SUCCINYL-CoA
+
GLYCINE
ALA SYNTHASE
δ-AMINOLEVULINIC ACID (ALA)
ALA-DEHYDRATASE
SUCCINYLACETONE
HEME SYNTHESIS
PORPHOBILINOGEN
PROTOPORPHYRIN 9
FEEDBACK INHIBITION (HEPATOCYTE)
HEME
HEMOPROTEIN
HEME OXYGENASE
+
CYTOCHROME P450 REDUCTASE
ZINC PROTOPORPHYRIN 9
IRON
CARBON MONOXIDE
HEME DEGRADATION
BILIVERDIN
BILIVERDIN REDUCTASE
BILIRUBIN



FEEDBACK <3