

Heme Metabolism

By Iyobosa Iyare
MD 2



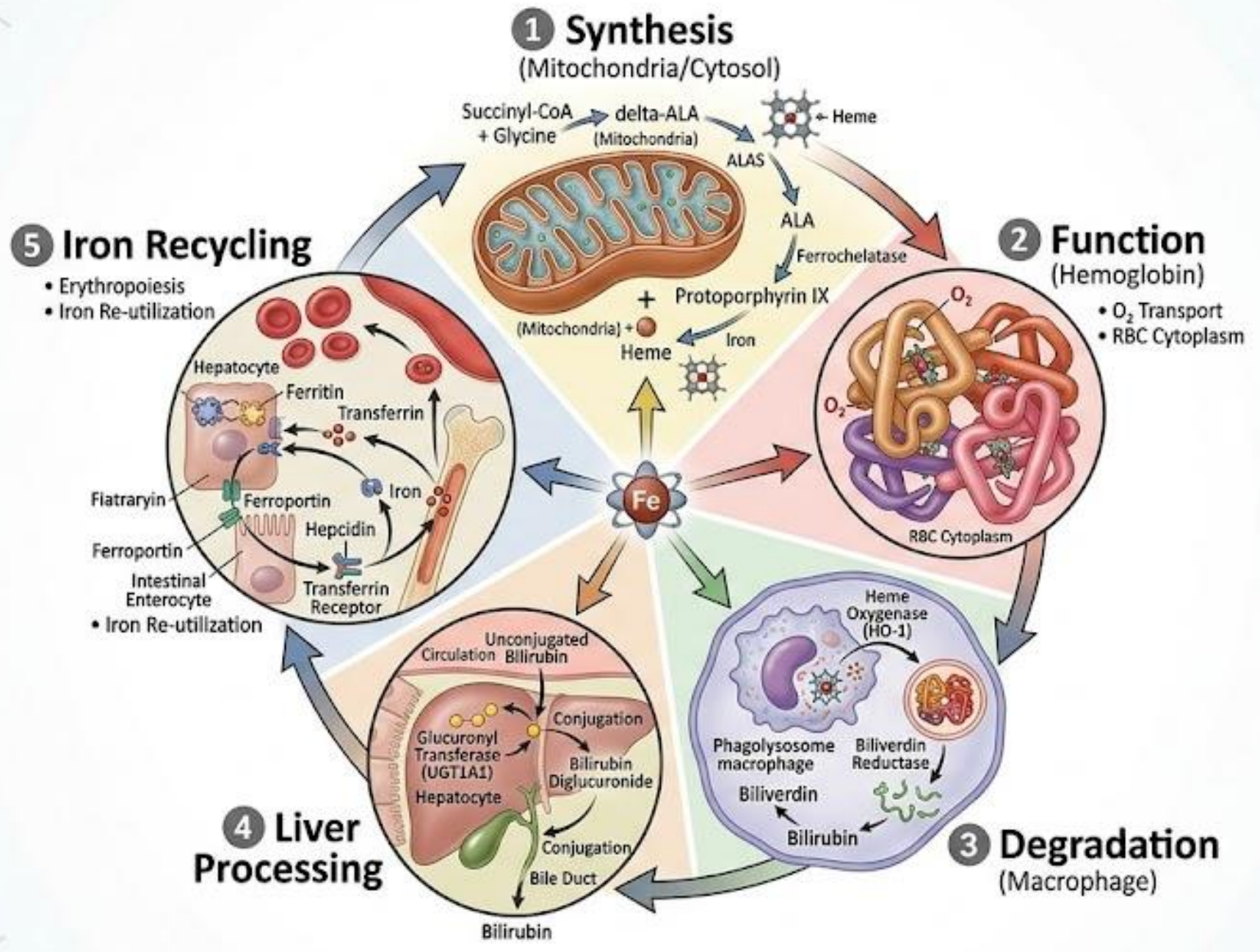
Question

A 25-year-old man presents with severe abdominal pain, anxiety, and dark-colored urine. He recently started a new medication for seizures. There is no photosensitivity. Laboratory tests show increased levels of ALA and porphobilinogen.

Which of the following enzymes is most likely deficient?

- A. ALA synthase
- B. ALA dehydratase
- C. Porphobilinogen deaminase
- D. Uroporphyrinogen decarboxylase
- E. Ferrochelatase





THE INTEGRATED HEME & IRON METABOLIC CYCLE



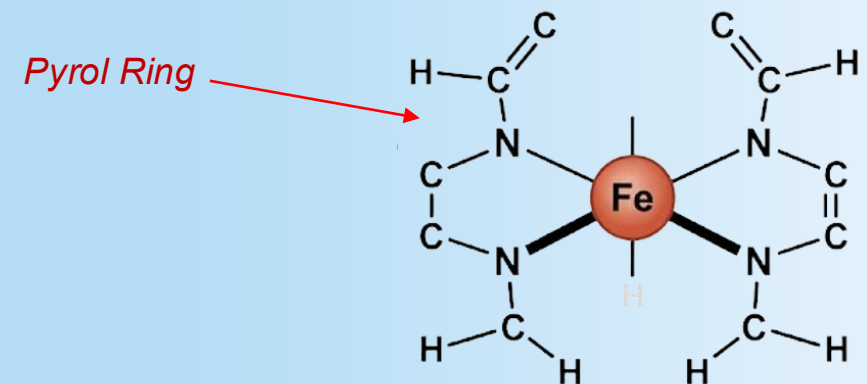
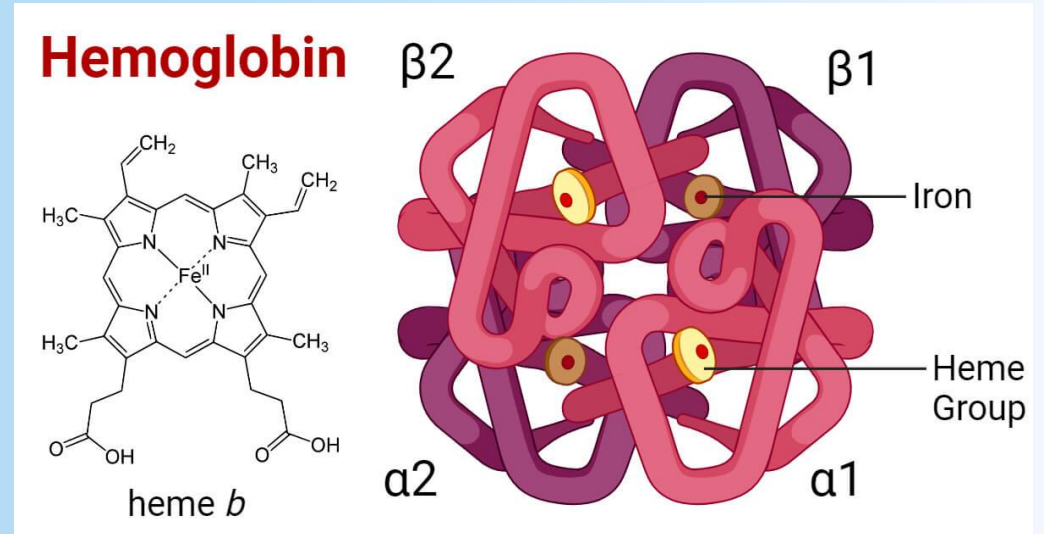
WHAT IS HEME?

❖ Heme is a prosthetic group composed of:

- **Protoporphyrin IX (tetrapyrrole ring)**
- **Central ferrous iron (Fe^{2+})**

❖ The iron binds oxygen reversibly, allowing transport and electron transfer

No heme = no oxygen = no you



Planar structure allows interaction with proteins (hemoglobin, cytochromes)

Functions of Heme

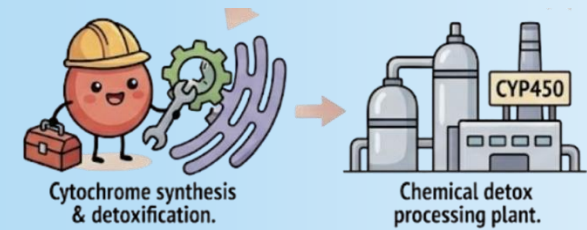
- Hemoglobin → oxygen transport
 - Myoglobin → oxygen storage
- Cytochromes → electron transport chain
 - Cytochrome P450 → drug metabolism
- Catalase/peroxidase → oxidative defense



The Birth Of Heme

Heme synthesis occurs primarily in:

- Erythroid cells of bone marrow
(hemoglobin production)
- Hepatocytes (cytochrome synthesis)



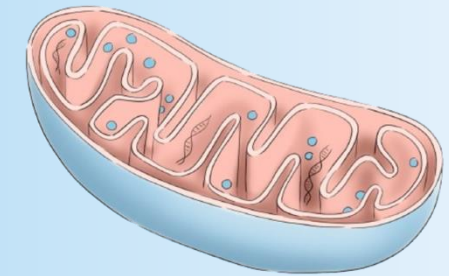
Heme is incorporated into cytochrome P450 enzymes, which are responsible for drug metabolism and detoxification. These enzymes require heme as their active center for electron transfer reactions.

INTRACELLULAR LOCALIZATION

Mito → Cytosol → Mito

❖ Steps of heme synthesis are compartmentalized:

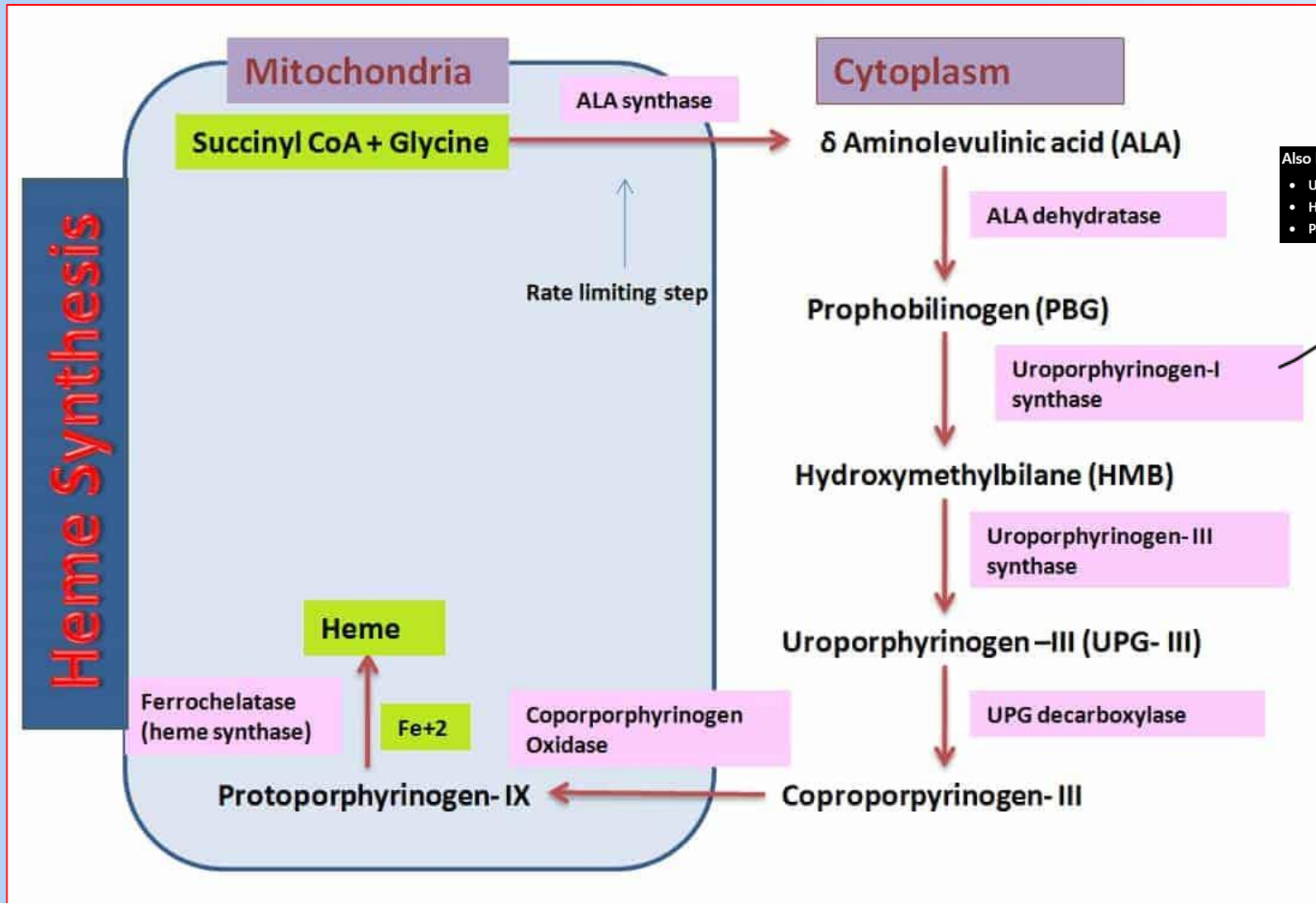
- Step 1: Mitochondria
- Steps 2-6: Cytosol
- Final steps: Mitochondria



NOTE

This compartmentalization is essential for regulation and efficiency

GENERAL PATHWAY OF HEME SYNTHESIS

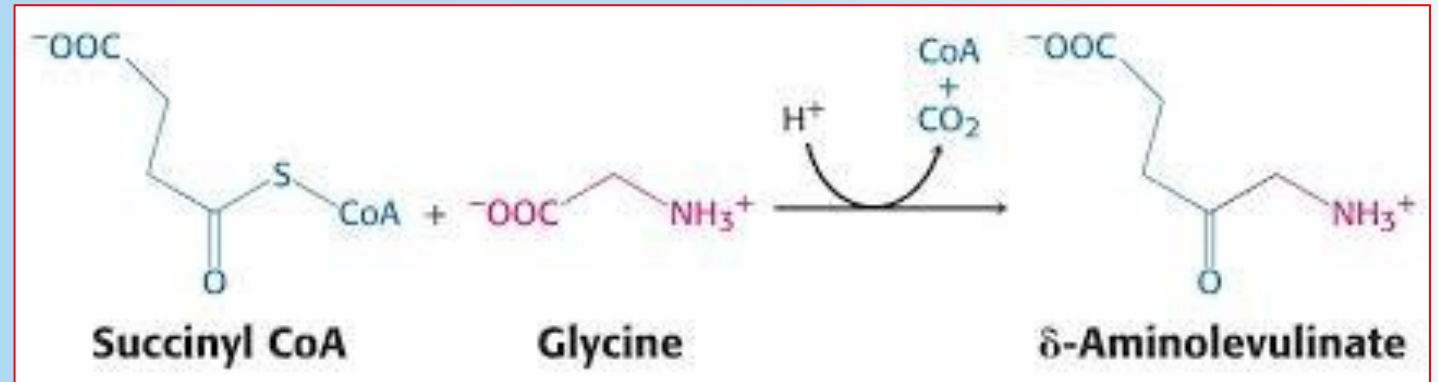


Also known as:

- Uroporphyrinogen I synthase (older name)
- Hydroxymethylbilane synthase (most accurate biochemical name)
- Porphobilinogen deaminase (common clinical name)

FIRST REACTION (Most Important!!!)

- **First and rate-limiting step:**
- **Glycine + Succinyl-CoA → δ -Aminolevulinic acid (ALA)**
- **Enzyme: ALA synthase (ALAS)**



Cofactor: Pyridoxal phosphate (Vitamin B6)

Location: Mitochondrial matrix



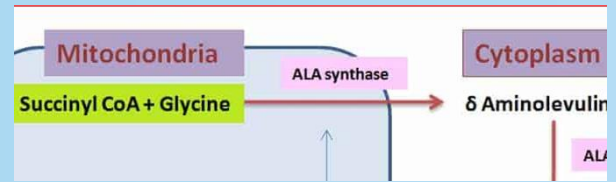
ALAS 1 = Liver Form
ALAS 2 = Erythroid Form

REGULATION OF ALA SYNTHASE (ALAS1) IN LIVER

Heme  inhibits ALAS

Heme acts as a **negative feedback inhibitor**:

- Decreases ALAS transcription
- Inhibits mitochondrial import



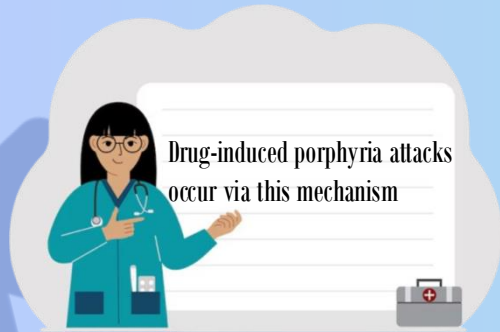
Induction:

- Drugs metabolized by cytochrome P450 increase demand
- Leads to increased ALA synthesis”

When more drugs are present:

More CYP450 enzymes are induced
Existing heme gets “used up” in enzyme turnover and synthesis demand increases
So the cell senses:

“We need more heme to build more CYP450.”



REGULATION OF ALA SYNTHASE IN BONE MARROW

NOT regulated by heme feedback

- **Regulated by iron availability**

Mechanism:

- **When iron is LOW:**

→ ↓ ALAS2 → ↓ heme → ↓ hemoglobin

- **When iron is HIGH:**

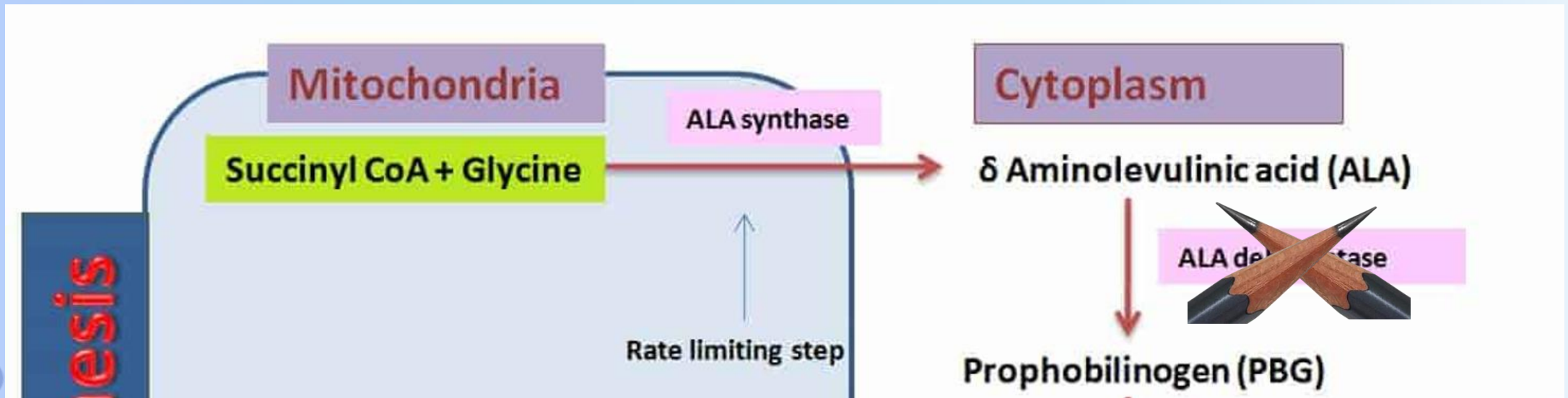
→ ↑ ALAS2 → ↑ heme → ↑ hemoglobin

FORMATION OF PORPHOBILINOGEN

Two molecules of ALA condense to form porphobilinogen (PBG)

Enzyme: ~~ALA dehydratase~~
Location: **Cytosol**

ALA buildup → neurotoxicity (abdominal pain, neuropathy)



Lead inhibits ALA dehydratase

Other Reactions

- 4 Porphobilinogen (PBG) → Hydroxymethylbilane → Uroporphyrinogen III
- Enzyme: PBG deaminase
- Then: Uroporphyrinogen III cosynthase

- Uroporphyrinogen III → Coproporphyrinogen III (Decarboxylation Reaction)
- Enzyme: Uroporphyrinogen decarboxylase

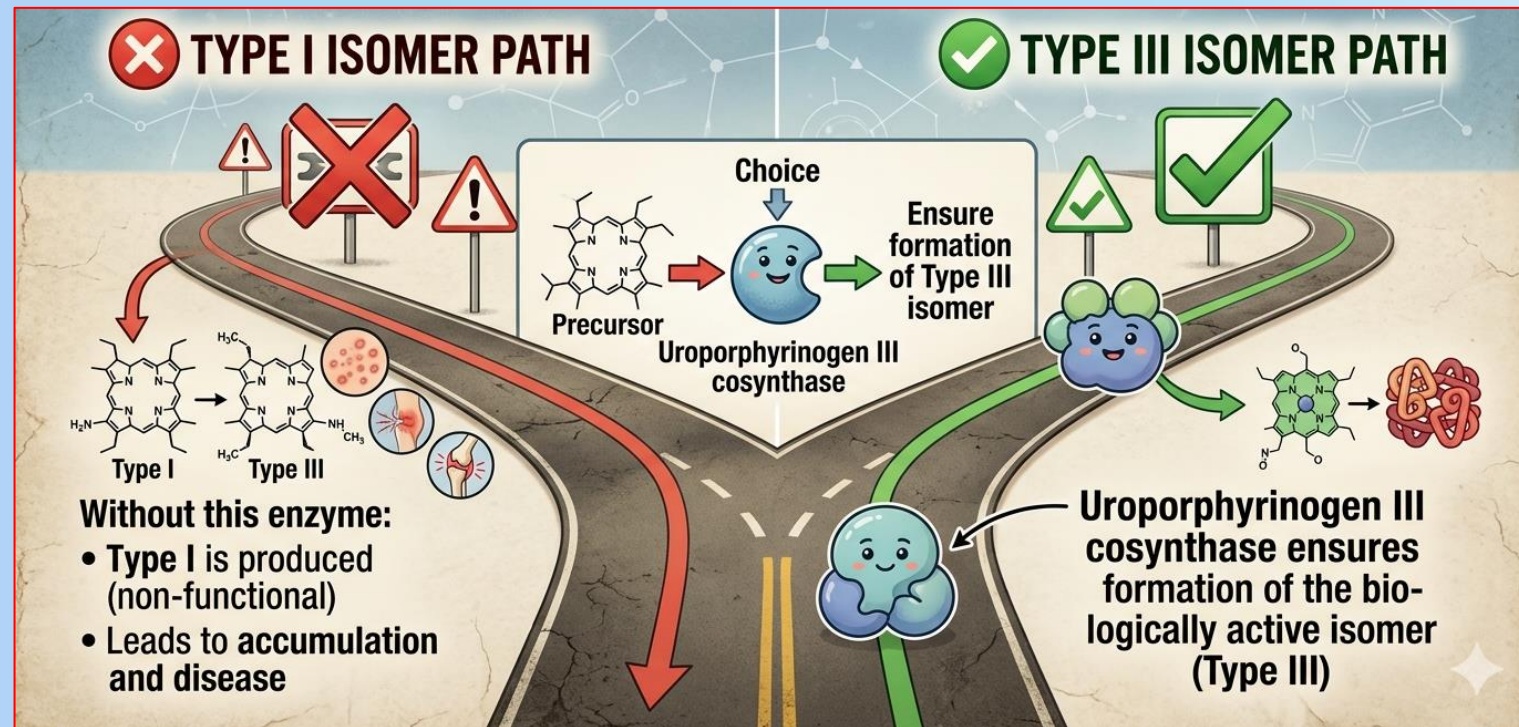
- Coproporphyrinogen III enters mitochondria → Protoporphyrinogen IX (Colourless) → *Protoporphyrin IX (Red coloured compound)*
Enzyme: Oxidation steps (mitochondria)



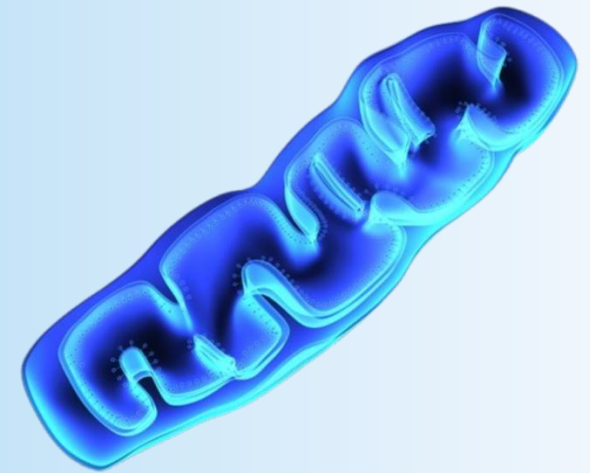
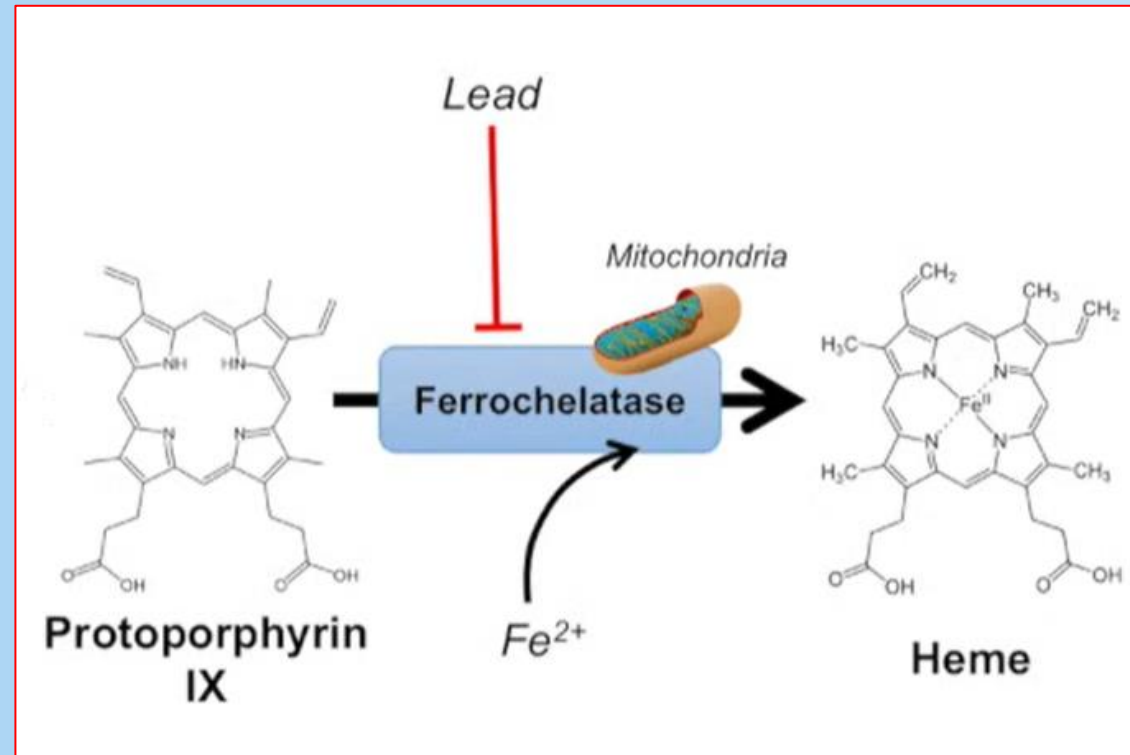
Hydroxymethylbilane → Uroporphyrinogen III

Enzyme: Uroporphyrinogen III cosynthase

Hydroxymethylbilane can either form Type 1 or Type III

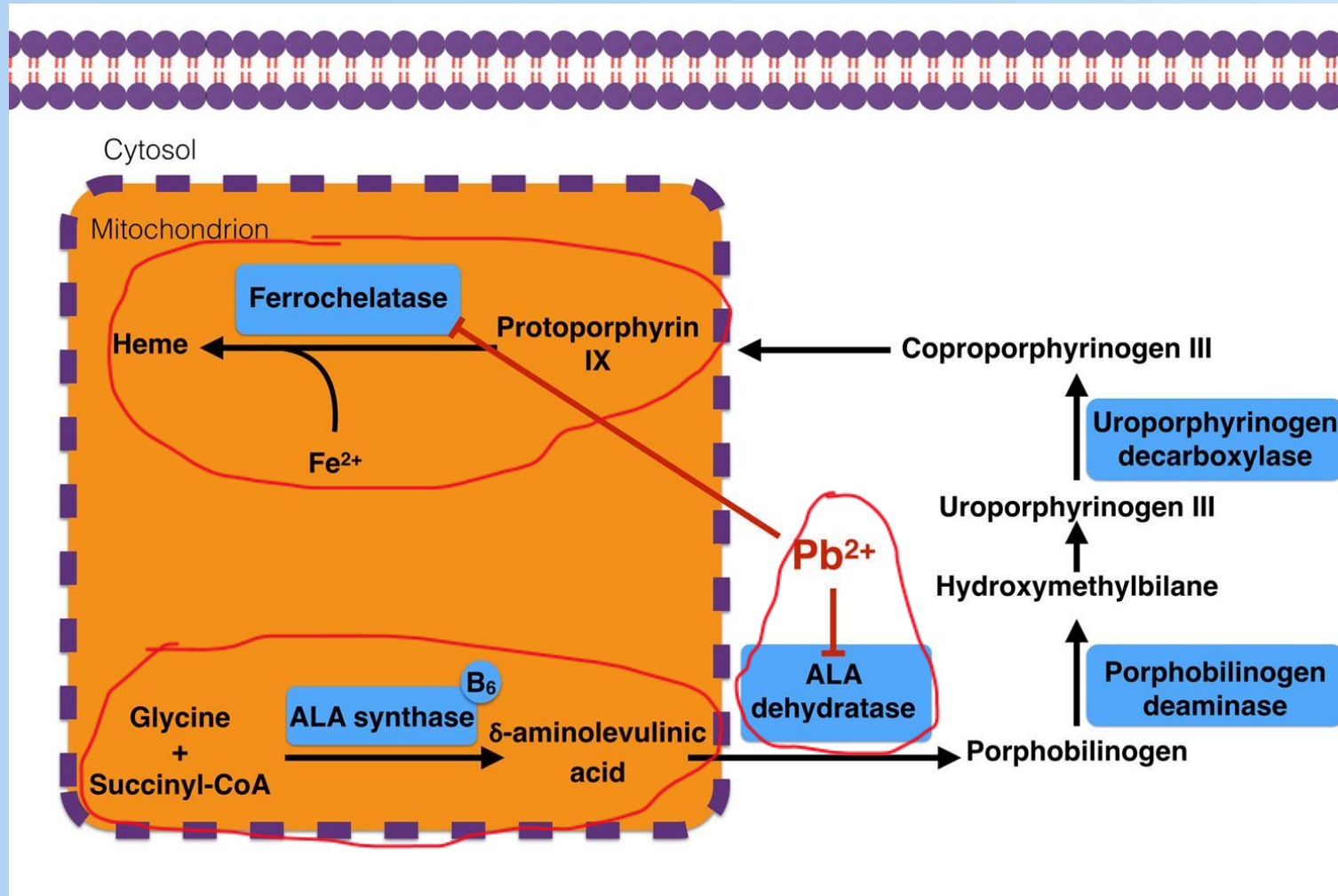


FINAL STEP OF HEME SYNTHESIS



Summary/ Most Important To Remember

Lead De**FER**s heme



Effects Of Lead

- Accumulation of ALA
- Decreased heme synthesis
- Microcytic anemia

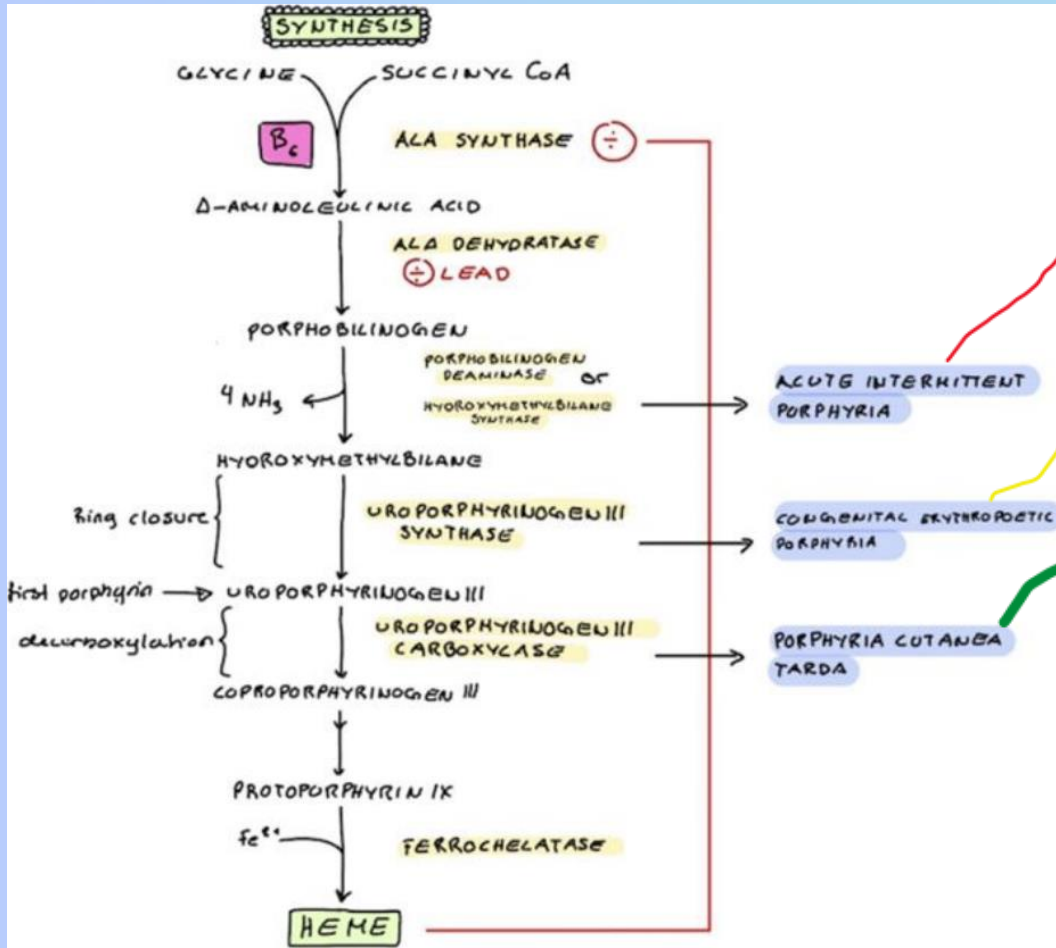
PORPHYRIAS

- **Porphyrias** are disorders caused by defects in enzymes of heme synthesis
- Result:
 - Accumulation of intermediates
 - Toxic effects depending on location

Three Main Types for Exam Purposes:

- Acute intermittent porphyria (Hepatic)
- Congenital erythropoietic porphyria (Marrow)
- Porphyria cutanea tarda (Hepatic)





Disease	Defect	Main Feature
AIP	PBG deaminase	Neuro
CEP	Uroporphyrinogen III synthase	Severe photosensitivity
PCT	Uroporphyrinogen decarboxylase	Blistering skin

“A cute **Con-Cop** Pretends to **Cut** People with Sunlight”



Porphyrinogens in Heme Synthesis

- Uroporphyrinogen III (first cyclic intermediate)
- **Uroporphyrinogen I???**
- Coproporphyrinogen III
- Protoporphyrinogen IX

Porphyrinogens are reduced, cyclic intermediates that can oxidize into photoactive porphyrins.

Uro → Copro → Proto (U-C-P progression)



Uro → Copro → Proto (U-C-P progression)

PHOTOSENSITIVITY

- Accumulated porphyrinogens are oxidized to porphyrins, which are photoactive
- Porphyrins absorb light → generate reactive oxygen species (ROS)

This causes:

1. Skin Damage
2. Blistering
3. Pain





Acute intermittent porphyria

Features:

- Abdominal pain
- Neurological symptoms
- **No photosensitivity**

Porphobilinogen deaminase
Blocked reaction:



What accumulates?

1. Porphobilinogen (PBG)
2. Aminolevulinic acid (ALA)

What triggers attacks?

- Drugs
- Alcohol
- Fasting

No porphyrins = no light absorption

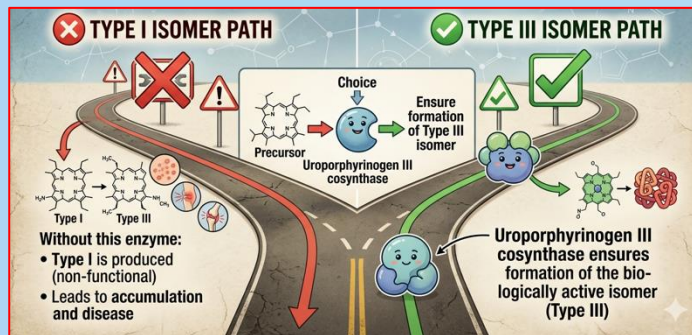
↓ heme → loss of ALAS1 inhibition → ↑ ALA production → accumulation in AIP.



Congenital erythropoietic porphyria (CEP)

Problem:

- **Defective Enzyme:** Uroporphyrinogen III synthase (cosynthase)
- Hydroxymethylbilane cannot properly form uroporphyrinogen III
- Abnormal type I porphyrinogens form and accumulate in RBC precursors
- **Photosensitivity (Severe)**
- *Causes Blisters, lesions and scarring of the skin*



Treatment for CEP is avoiding sunlight



Porphyria Cutanea Tardea (PCT)

Problem:

- **Defective Enzyme:** Uroporphyrinogen decarboxylase
- **Blocked reaction:** Uroporphyrinogen III cannot become coproporphyrinogen III
- **What accumulates?** Uroporphyrinogen III → oxidizes to uroporphyrin
- **Photosensitivity**

Accumulated porphyrins in skin absorb light:

- ROS formation blistering, and fragile skin



Treatment for CEP is avoiding sunlight

Question

A patient presents with: **blistering skin lesion, severe photosensitivity**
dark urine. Symptoms worsen with **sun exposure**.

Which porphyria is most likely?

- A) Acute intermittent porphyria
- B) Porphyria cutanea tarda
- C) Congenital erythropoietic porphyria
- D) Lead poisoning
- E) Hereditary spherocytosis

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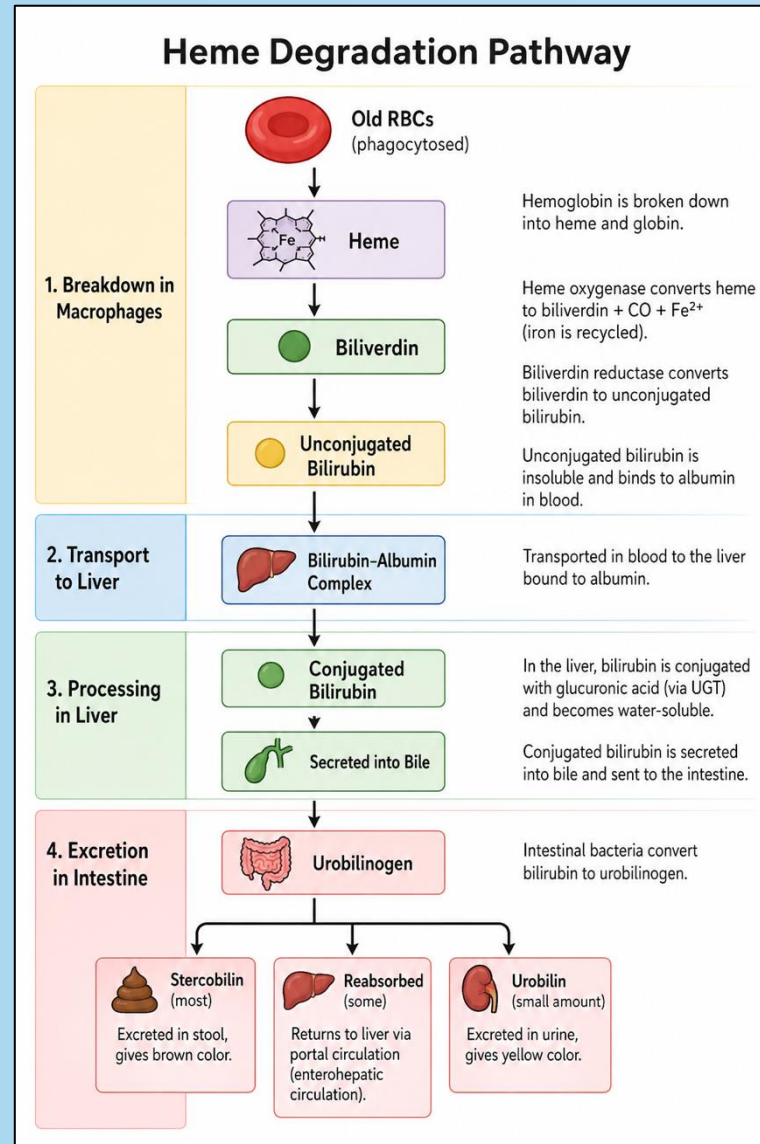
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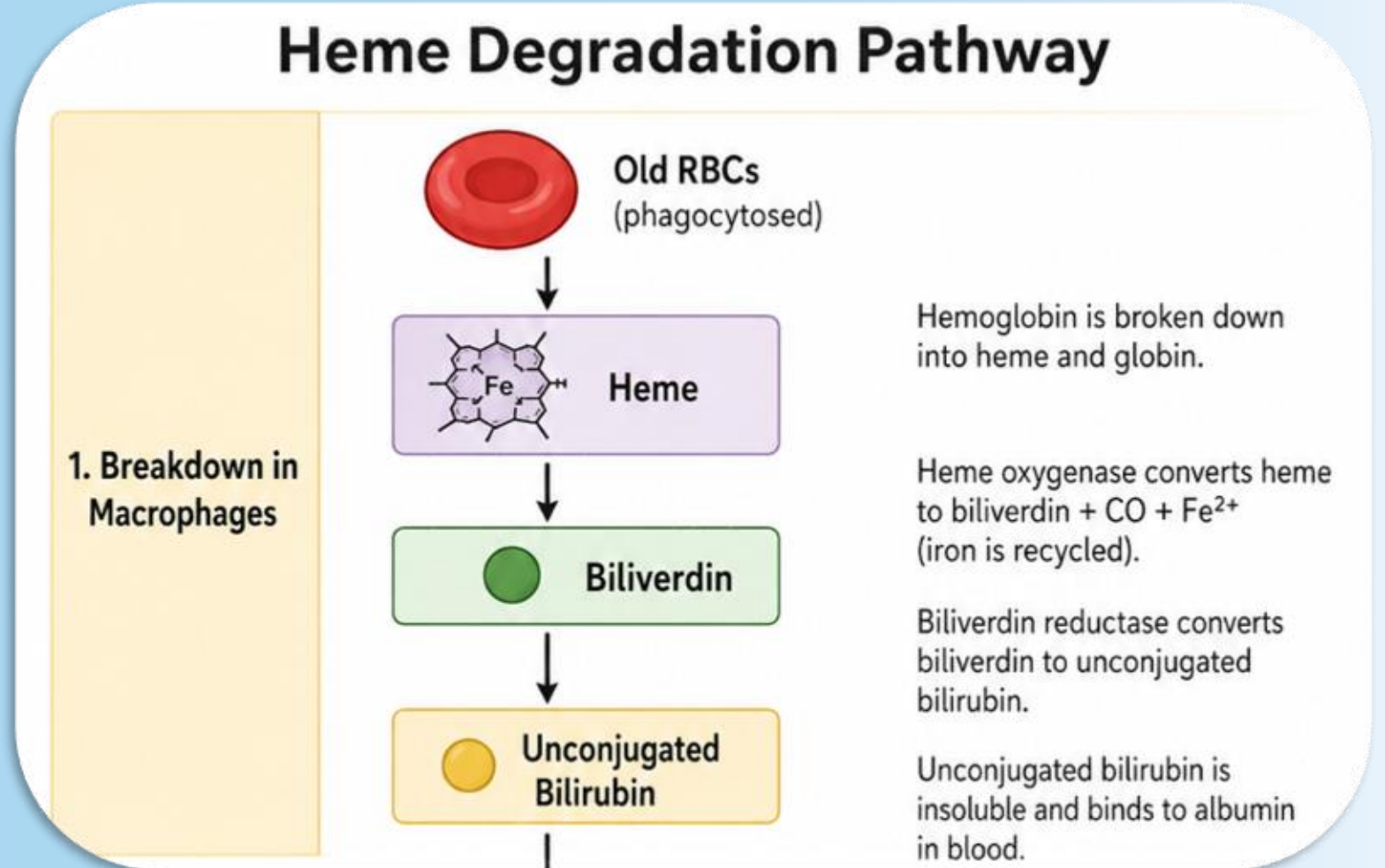
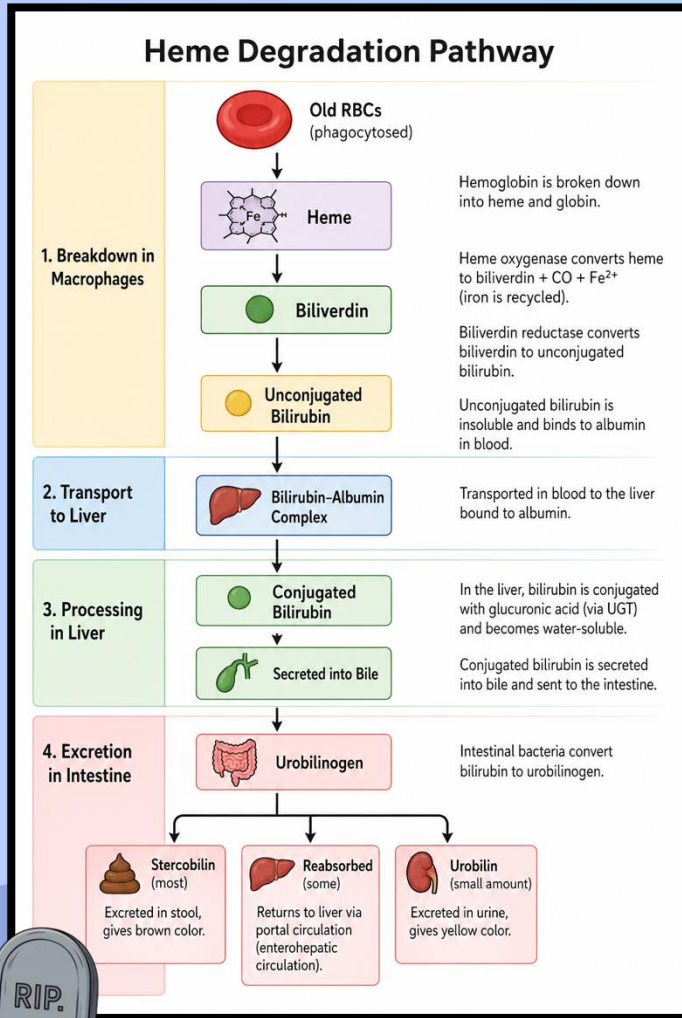
Summary Of Porphyrrias

Disease	Accumulates	Main symptom	Photosensitivity?
AIP	ALA + PBG	Neuro	✗
CEP	Porphyrins	Severe skin disease	✓
PCT	Porphyrins	Blistering skin	✓

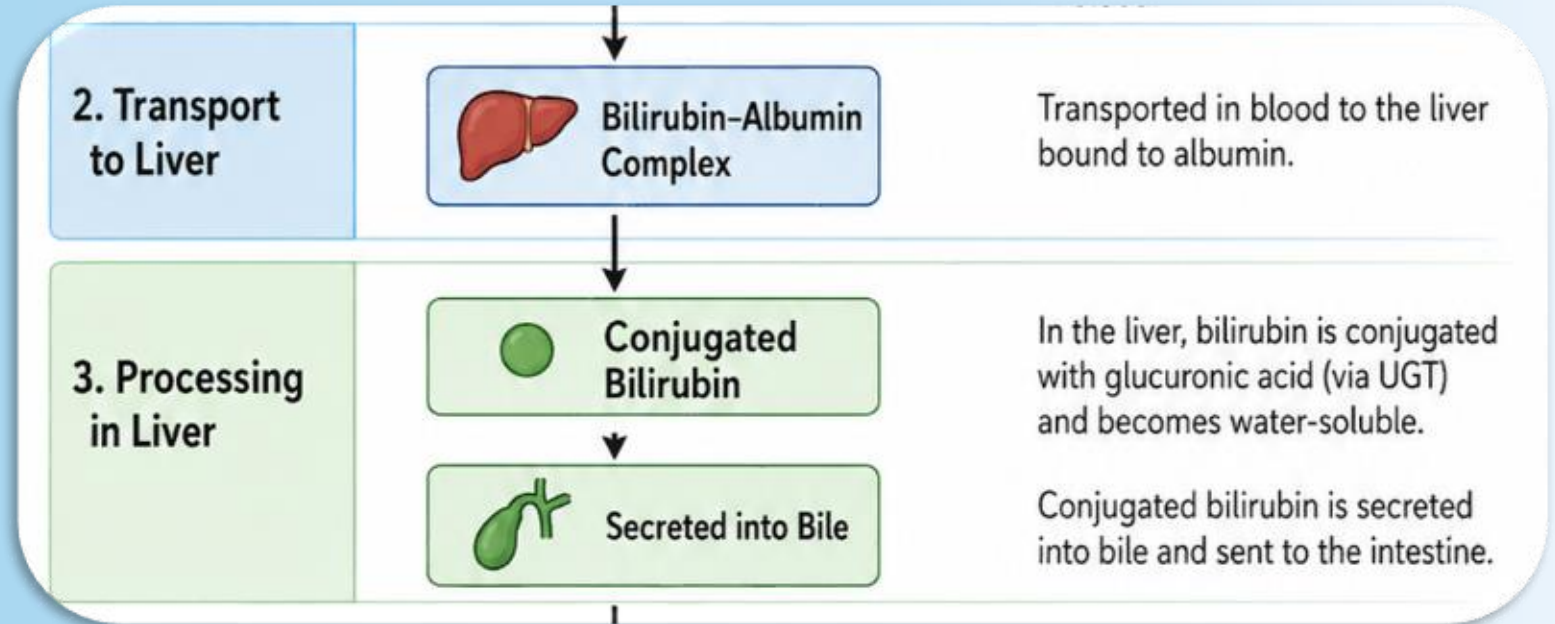
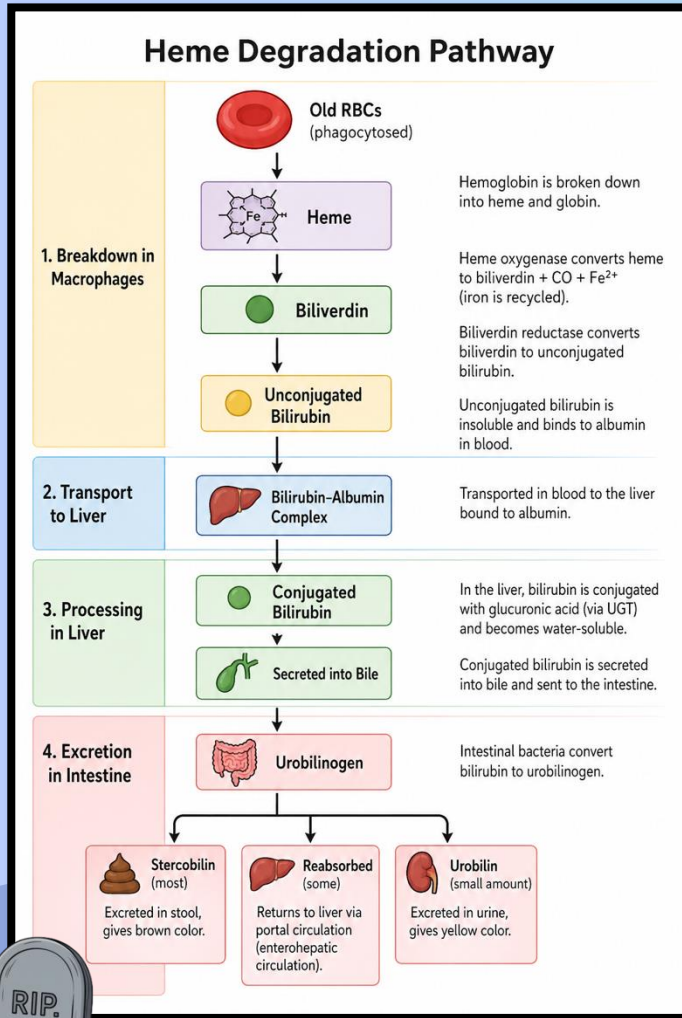
Degradation Of Heme



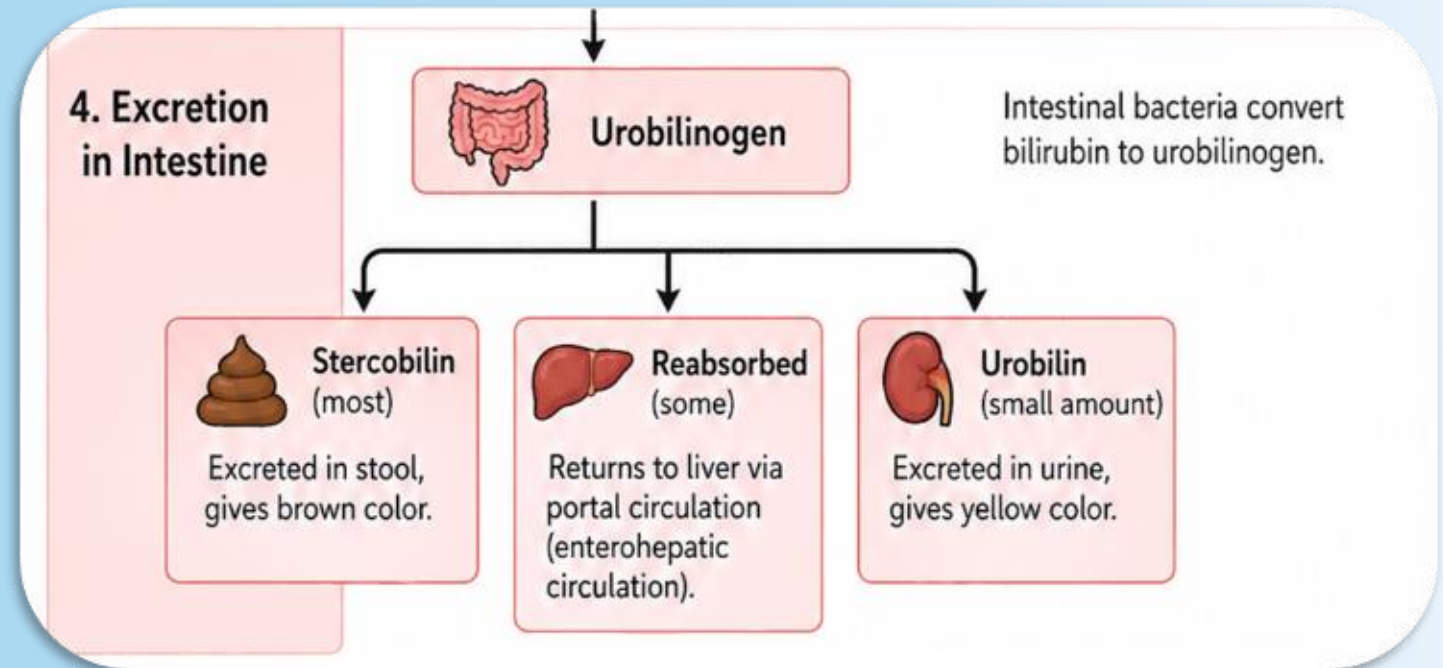
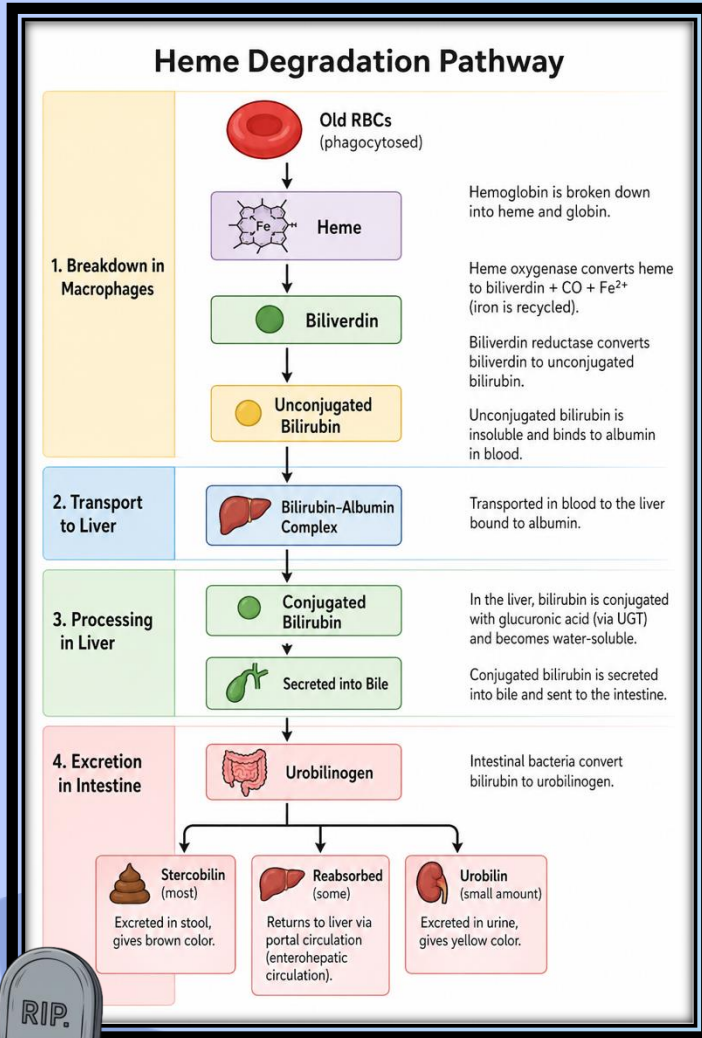
Degradation Of Heme



Degradation Of Heme



Degradation Of Heme



Problems with Heme Degradation

Jaundice = Icterus

- Bilirubin > 3 mg/dL (normal < 1.3 mg/dL)
- Hyper-bilirubin-**emia**
- Neonatal jaundice

Symptoms:

- Yellow discoloration
- Light colored stools
- Dark colored urine
- Itching of the skin








JAUNDICE

TYPES OF JAUNDICE

3 MAIN TYPES

	PRE-HEPATIC (HEMOLYTIC)	HEPATIC (HEPATOCELLULAR)	POST-HEPATIC (OBSTRUCTIVE)
WHAT'S HAPPENING?	Increased breakdown of red blood cells causes excess unconjugated bilirubin.	Liver cells are damaged and cannot properly take up, conjugate or excrete bilirubin.	Bile flow is blocked after it leaves the liver, causing conjugated bilirubin to back up.
BILIRUBIN TYPE ELEVATED	Unconjugated (Indirect)	Mixed (Direct + Indirect)	Conjugated (Direct)
KEY FEATURES	<ul style="list-style-type: none"> No bilirubin in urine Dark stools May have anemia, splenomegaly 	<ul style="list-style-type: none"> Dark urine Mild – moderate jaundice Elevated liver enzymes (AST, ALT) 	<ul style="list-style-type: none"> Dark urine Pale/clay-colored stools Itching (pruritus) Fat malabsorption 
COMMON CAUSES	<ul style="list-style-type: none"> Hemolytic anemia Malaria Transfusion reaction 	<ul style="list-style-type: none"> Viral hepatitis Cirrhosis Drug-induced liver injury 	<ul style="list-style-type: none"> Gallstones Pancreatic cancer Biliary strictures



QUICK TIP:

Before liver (Pre-hepatic) = too much bilirubin made
 Inside liver (Hepatic) = liver cell problem
 After liver (Post-hepatic) = bile flow is blocked



Before



Inside



After

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Quick Recap

1. Rate-limiting step of heme synthesis occurs in which cellular compartment?

- A. Mitochondrial matrix via ALA synthase
- B. Cytosol via porphobilinogen deaminase
- C. Mitochondrial intermembrane space via ferrochelatase
- D. Cytosol via ALA dehydratase
- E. Mitochondrial matrix via coproporphyrinogen oxidase

Quick Recap

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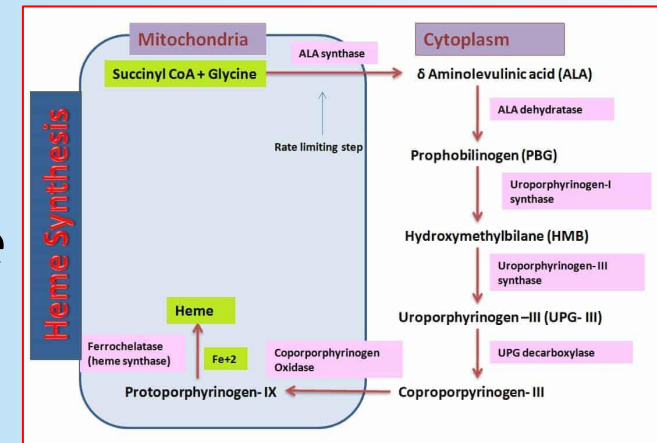
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B. Cytosol via porphobilinogen deaminase

C. Mitochondrial intermembrane space via ferrochelatase

D. Cytosol via ALA dehydratase

E. Mitochondrial matrix via coproporphyrinogen oxidase



Quick Recap

2. Which pairing of enzyme and cofactor is **CORRECT** in heme synthesis?

- A. Porphobilinogen deaminase – requires iron
- B. Ferrochelatase – requires NADPH
- C. ALA dehydratase – requires pyridoxal phosphate
- D. Coproporphyrinogen oxidase – requires biotin
- E. Uroporphyrinogen III synthase – requires vitamin B12

Quick Recap

3. Which pairing of enzyme and cofactor is CORRECT in heme synthesis?

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- C. ALA dehydratase — requires pyridoxal phosphate
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- E. Uroporphyrinogen III synthase — requires vitamin B12

Correct Answer: ALA synthase — pyridoxal phosphate

Quick Recap

3. Which statement best distinguishes direct vs indirect bilirubin?

- A. Direct bilirubin is albumin-bound and lipid soluble
- B. Indirect bilirubin is water soluble after glucuronidation
- C. Direct bilirubin is conjugated and water soluble
- D. Indirect bilirubin is excreted unchanged in urine
- E. Direct bilirubin cannot enter hepatocytes

Quick Recap

3. Which statement best distinguishes direct vs indirect bilirubin?

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- C. Direct bilirubin is conjugated and water soluble**
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- E. Direct bilirubin cannot enter hepatocytes

Quick Recap

4. Lead poisoning inhibits multiple enzymes. Which combination is most directly affected?

- A. Coproporphyrinogen oxidase and heme oxygenase
- B. ALA synthase and porphobilinogen deaminase
- C. Ferrochelatase and uroporphyrinogen synthase
- D. ALA dehydratase and ferrochelatase
- E. Biliverdin reductase and ALA dehydratase

Quick Recap

4. Lead poisoning inhibits multiple enzymes. Which combination is most directly affected?

- A. Coproporphyrinogen oxidase and heme oxygenase
- B. ALA synthase and porphobilinogen deaminase
- C. Ferrochelatase and uroporphyrinogen synthase
- D. ALA dehydratase and ferrochelatase**
- E. Biliverdin reductase and ALA dehydratase

Lead **DeFERs** heme

That's All For Now. Study Hard!

~~Party Hard!~~

Do your best!

THE END

