Hemoglobin

- **ILOs**
- **1. Describe the biochemical structure of hemoglobin, List the different types and derivatives of hemoglobin.**
- **2. List the steps of heme synthesis, determine the sites where they occur, describe the regulation of heme synthesis and disorders of heme synthesis.**
- **3. Define HMP shunt, describe its regulation, List the products and hemolytic anemia due to glucose-6-phosphate dehydrogenase deficiency (Favism).**

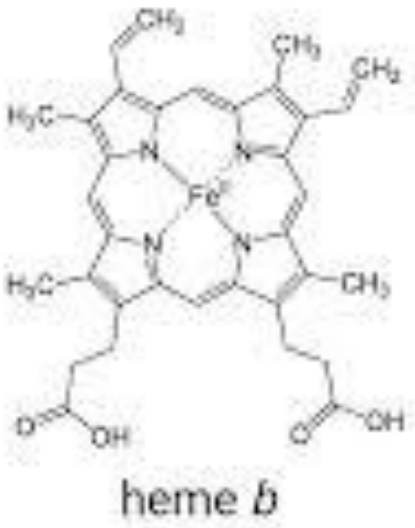
- **Hemoglobin is an oxygen/CO2 carrier protein present in the red blood corpuscles of blood. Hemoglobin is a conjugated chromo-protein having heme as its prosthetic group. Heme is the prosthetic group, not only of hemoglobin but also of myoglobin, cytochromes etc.**

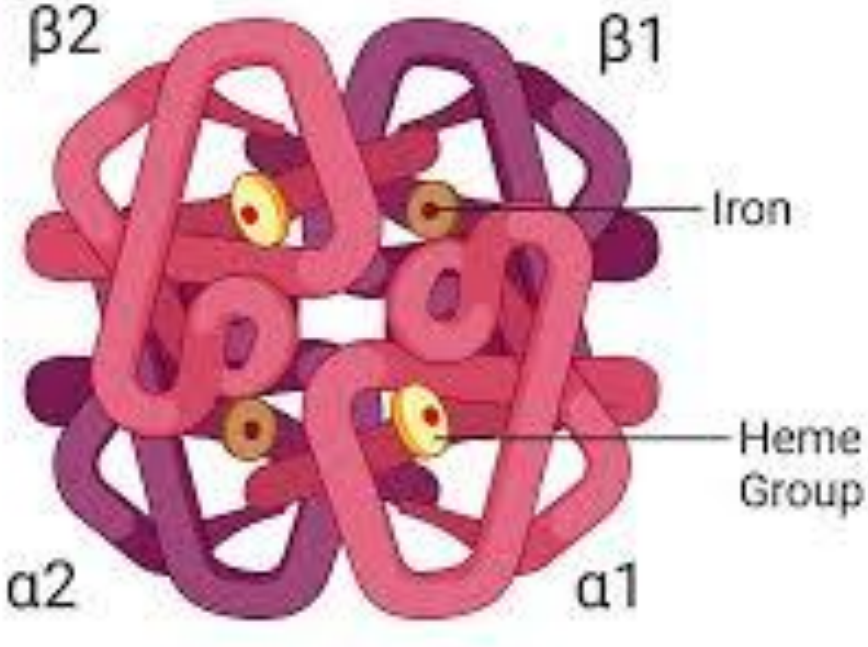
Structure

- **Hemoglobin is formed by the combination of heme with globin (protein). Globin is made up of four polypeptide chains (an oligomeric protein). Two of these polypeptides are known as alpha (α) and the other two are known as beta (β). Each alpha chain has 141 amino acids and each beta chain has 146 amino acids.**

- **Each polypeptide forms a cup like structure with a pocket like area where the prosthetic group, heme is buried. Heme has iron, which is linked to the imidazole nitrogen of the histidine in positions 58 and 87 of the alpha chains. In the beta chain the heme iron is linked with histidine in positions 92 and 63. There are four heme groups in one hemoglobin molecule.**

Hemoglobin





Different types and derivatives of hemoglobin

Normal Hemoglobin Types

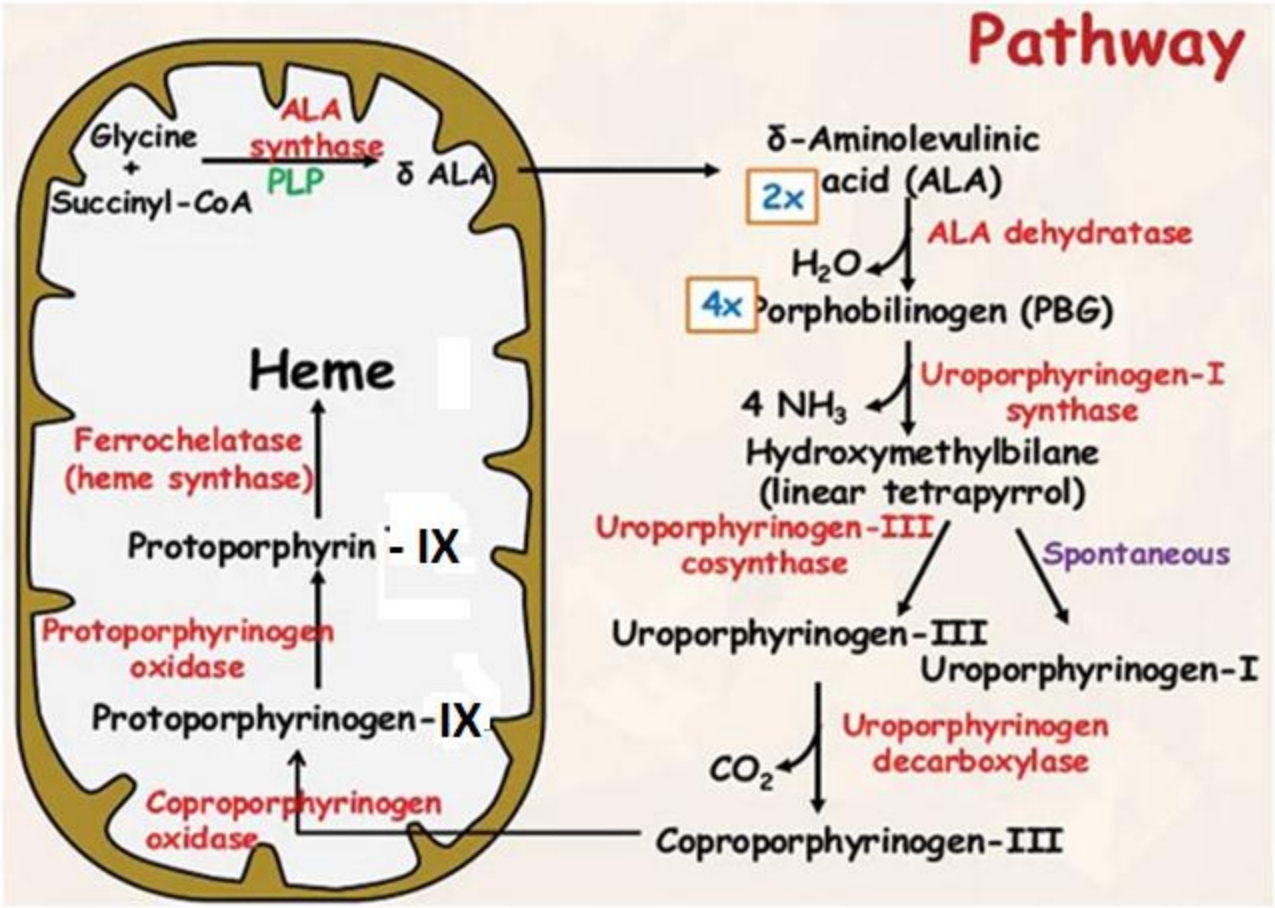
- Hemoglobin A (HbA) ($\alpha_2\beta_2$): The primary adult hemoglobin, making up most of your blood.
- Hemoglobin A2 (HbA2) ($\alpha_2\delta_2$): A minor component in adults, with two delta chains replacing beta chains.
- Fetal Hemoglobin (HbF) ($\alpha_2\gamma_2$): Dominant in fetuses, with gamma chains; switches to HbA after birth

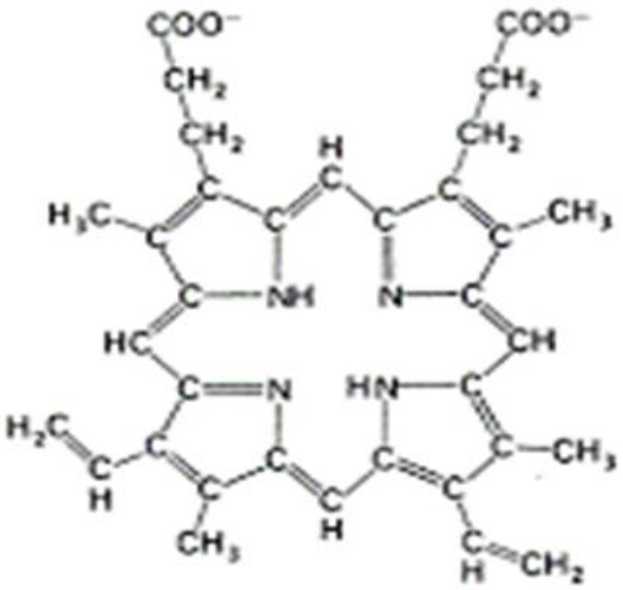
Abormal Hemoglobin Types

Name of Hb	Abnormality present at position	Actual amino acid present in normal Hb	Replaced amino acids in abnormal Hb
Hemoglobin (Hb) with abnormal α chain			
HbI	16	Lysine	Glutamic acid
HbG	23	Glutamic acid	Valine
HbM_B	58	Histidine	Tyrosine
Hemoglobin (Hb) with abnormal β chain			
HbS	6	Glutamic acid	Valine
HbC	6	Glutamic acid	Lysine
HbM_S	63	Histidine	Tyrosine

Biosynthesis of heme

Heme synthesis starts in mitochondria with the condensation of succinyl-CoA with the amino acid glycine, activated by pyridoxal phosphate. ALA synthase catalyzes this irreversible reaction forming an intermediate amino-ketoadipic acid. ALA synthase is the rate limiting enzyme of heme synthesis. Two forms of ALA synthase are found: erythroid (ALAS2) and hepatic (ALAS1).


Pathway
Glycine
+
Succinyl-CoA
ALA synthase
PLP
δ ALA
δ-Aminolevulinic acid (ALA)
2x
ALA dehydratase
H_2O
4x
Porphobilinogen (PBG)
Uroporphyrinogen-I synthase
4 NH_3
Hydroxymethylbilane (linear tetrapyrrol)
Uroporphyrinogen-III cosynthase
Spontaneous
Uroporphyrinogen-III
Uroporphyrinogen-I
Uroporphyrinogen decarboxylase
CO_2
Coproporphyrinogen-III
Coproporphyrinogen oxidase
Protoporphyrinogen-IX
Protoporphyrinogen oxidase
Protoporphyrin - IX
Ferrochelatase (heme synthase)
Heme



Protoporphyrin IX

Regulation of Heme Synthesis

- **Rate-Limiting Step catalyzed by ALA synthase (ALAS), is the primary control point.**
- **1. Cell-Specific ALAS:**
- **1. ALAS1 (Liver): Inhibited by heme (negative feedback). Drugs increasing heme demand (like for P450 enzymes) upregulate ALAS1 activity.**
- **2. ALAS2 (Erythroid): Regulated by iron availability. Iron deficiency increases ALAS2 synthesis, promoting heme production for hemoglobin.**

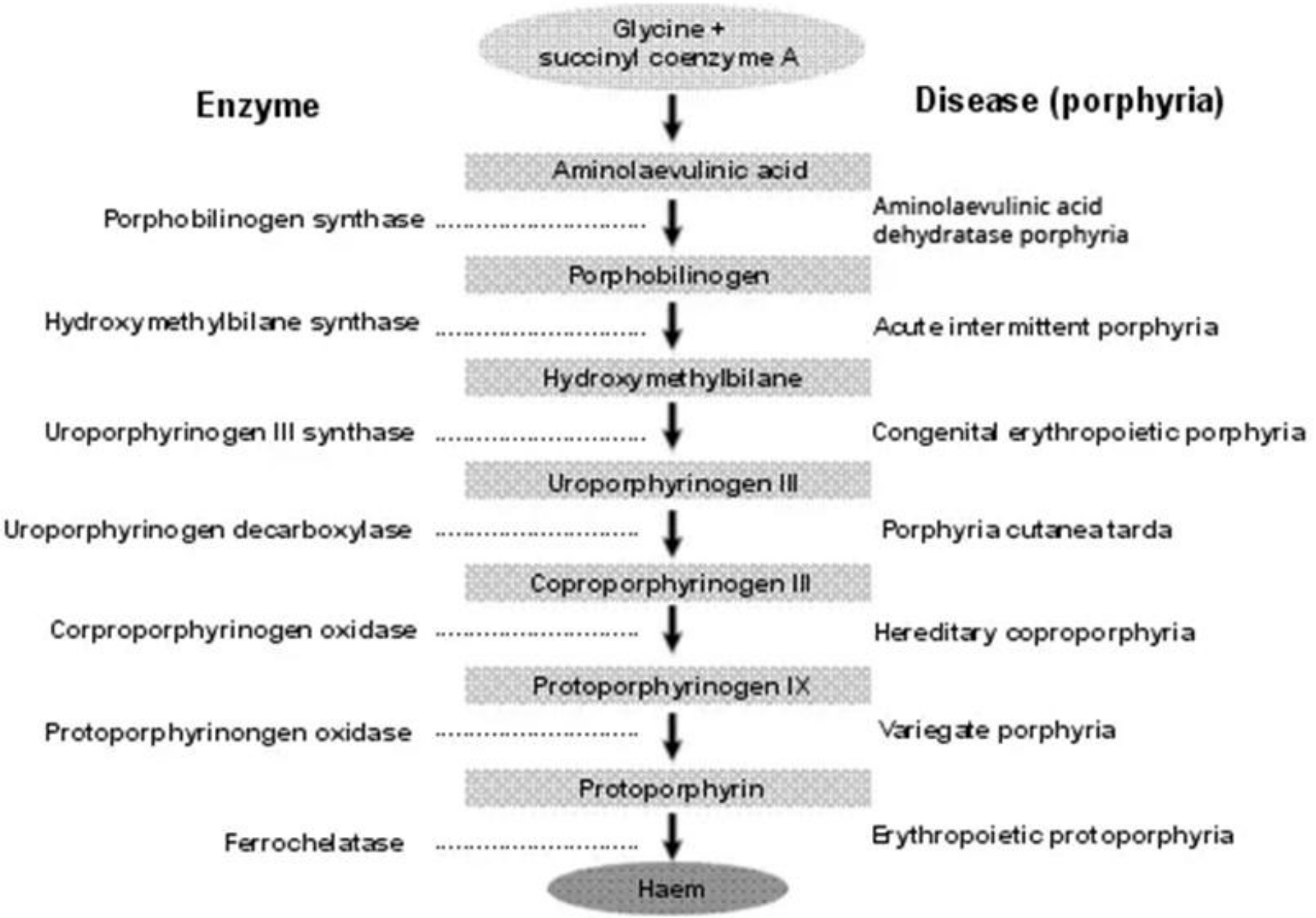
- **2. Iron Availability:** Essential for the final step (ferrochelatase), iron levels influence overall pathway activity, especially in red blood cells.
- **3. Oxygen Levels:** Low oxygen stimulates erythropoietin (EPO) release, boosting red blood cell production and heme synthesis.
- **4. Heme as a Regulator:** High heme levels inhibit ALAS1 and signal cessation of synthesis, preventing toxic accumulation

Porphyrias (Heme Synthesis Disorders)

- **These disorders involve deficiencies in one of the enzymes in heme pathway, leading to precursor accumulation.**
- **Porphyrias are classified based on the primary site of accumulation of heme precursors:**
- **1- The liver (hepatic)**
- **2-The bone marrow/red blood cells (erythropoietic).**

Porphyria symptoms

- Porphyria symptoms often include severe abdominal pain, nausea, vomiting, and constipation (acute attacks)
- Skin symptoms:like blistering, redness, and sun sensitivity. skin symptoms in often appear after sun exposure. Urine may also turn red or brown
- Neurological symptoms in acute porphyrias can involve muscle weakness, paralysis, confusion, hallucinations, seizures, and rapid heart rate.


Glycine +
succinyl coenzyme A
Enzyme
Disease (porphyria)
Aminolaevulinic acid
Porphobilinogen synthase
Aminolaevulinic acid dehydratase porphyria
Porphobilinogen
Hydroxymethylbilane synthase
Acute intermittent porphyria
Hydroxymethylbilane
Uroporphyrinogen III synthase
Congenital erythropoietic porphyria
Uroporphyrinogen III
Uroporphyrinogen decarboxylase
Porphyria cutanea tarda
Coproporphyrinogen III
Corproporphyrinogen oxidase
Hereditary coproporphyria
Protoporphyrinogen IX
Protoporphyrinongen oxidase
Variegate porphyria
Protoporphyrin
Ferrochelatase
Erythropoietic protoporphyria
Haem

- **Acute Hepatic Porphyrias:** Defects in early enzymes (like PBG deaminase) cause accumulation of neurotoxic ALA and PBG, leading to attacks with abdominal pain, neurological, and psychiatric symptoms.
- **Erythropoietic Protoporphyria:** Deficiency in Ferrochelatase (FECH) leads to protoporphyrin accumulation, causing severe skin photosensitivity.
- **Porphyria Cutanea Tarda:** Porphyria Cutanea Tarda is the most common of the Porphyrias and results from a deficiency of the enzyme uroporphyrinogen decarboxylase. Symptoms often triggered by alcohol or iron, causes skin fragility and blisters.

Sideroblastic Anemia (ALAS Deficiency)

A problem with the first enzyme, 5-aminolevulinic acid synthase (ALAS), specifically ALAS2 in red blood cells.

Cause: X-linked genetic mutation or acquired, often from Vitamin B6 deficiency (due to alcohol, isoniazid), causing iron to accumulate in mitochondria (ring sideroblasts).

Symptoms: Anemia, fatigue, iron overload in organs.

Other Related Conditions

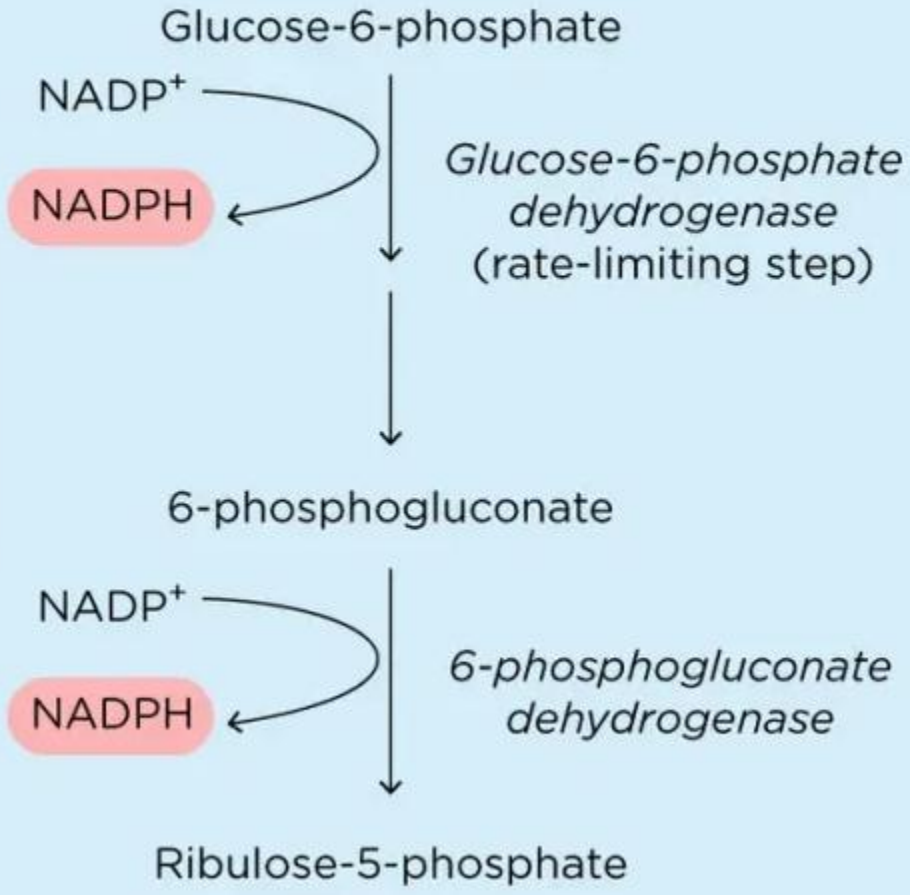
- **Lead Poisoning: Lead inhibits ALA dehydratase and Ferrochelatase, mimicking porphyria**

The Pentose Phosphate Pathway in red blood cells (RBCs)

- **The Pentose Phosphate Pathway in red blood cells (RBCs) is crucial for producing NADPH, their sole source, which protects them from oxidative damage by regenerating reduced glutathione, neutralizing harmful free radicals, and preventing hemolytic anemia, also generating ribose-5-phosphate for nucleotide synthesis. The rate-limiting enzyme, Glucose-6-Phosphate Dehydrogenase (G6PD), starts the oxidative phase, generating NADPH, making RBCs highly dependent on this pathway for survival against oxidative stress.**

Pentose Phosphate Pathway

Oxidative (irreversible)



Functions of NADPH:

1. Cholesterol synthesis
2. Fatty acid synthesis
3. Reduction of **Glutathione** (protects the cell from ROS)

Glucose-6-phosphate dehydrogenase (G6PD) deficiency

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a common genetic disorder where red blood cells lack enough G6PD enzyme, making them vulnerable to breakdown (hemolysis) when exposed to triggers like certain drugs, infections, or fava beans, leading to jaundice, fatigue, and dark urine, especially in newborns. While most people are asymptomatic, the condition can cause hemolytic anemia, and management focuses on avoiding triggers, with treatment for severe jaundice in infant.

Causes & Inheritance

Genetic: An X-linked recessive disorder, meaning it's more common in males.

Enzyme Role: G6PD produces NADPH, which protects red blood cells from oxidative damage; deficiency reduces this protection.

Symptoms (During a Hemolytic Episode)

1. Jaundice (yellow skin/eyes) and dark urine.
2. Fatigue, weakness, pallor (pale skin).
3. Shortness of breath, rapid heartbeat, dizziness.
4. Abdominal pain, enlarged spleen (splenomegaly).

Common Triggers

1. Medications: Certain antibiotics (sulfa drugs), antimalarials, aspirin.
2. Foods: Fava beans (favism).
3. Infections: Viral or bacterial infection

Quiz

- **What is the rate limiting step of Heme Biosynthesis pathway?**

A. ALA Dehydratase
B. ALA Synthase
C. Uroporphyrinogen Decarboxylase
D. Coproporphyrinogen Oxidase

- **What is the cofactor for the first step of Heme synthesis (the production of ALA)?**

A. Vitamin B5

B. Vitamin B12

C. Vitamin B6

D. Vitamin B1

- **Which type of porphyria cause photosensitivity in the patient?**

A. ALA synthase deficiency
B. ALA Dehydratase deficiency
C. Acute intermittent porphyria
D. Porphyria cutanea tarda