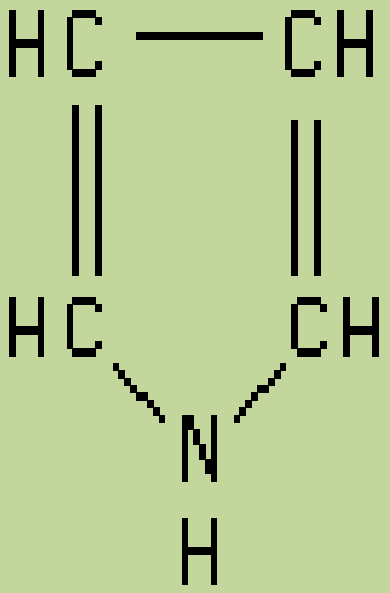
Porphyria
Hemoltytic anemias

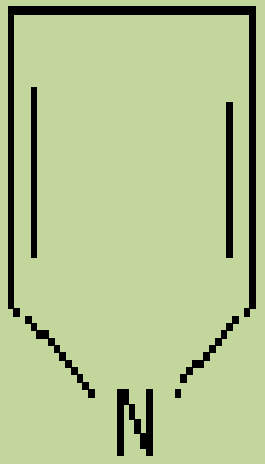
By

Dr. Walaa Bayoumie El Gazzar

Hem is a ferrous protoporphyrin III



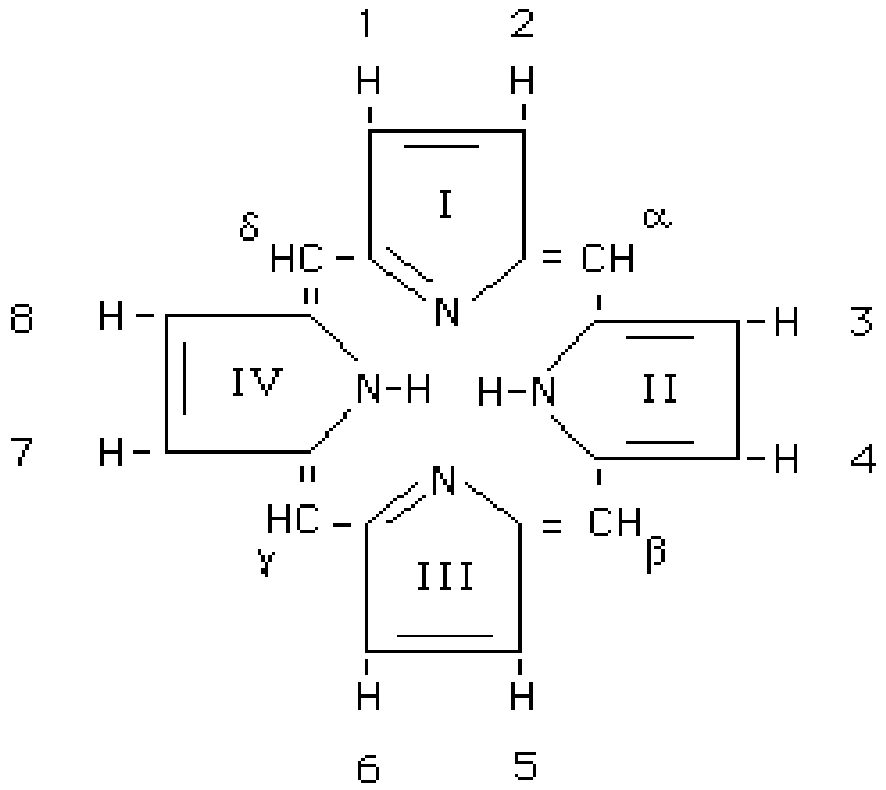
Pyrrole



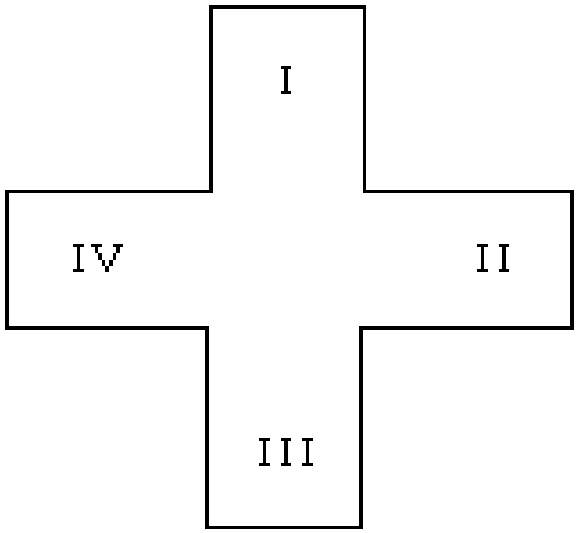
Abbreviated version of pyrrole

- **Pyrrole ring**
- **Porphin ring = cyclic tetrapyrrole united by 4 methene (=CH-) bridges.**
- **Porphyrins = derivatives of Porphin**

(Porphyrins found in nature differ in the substituents replacing the hydrogen atoms at C 1,2,3,……..8)

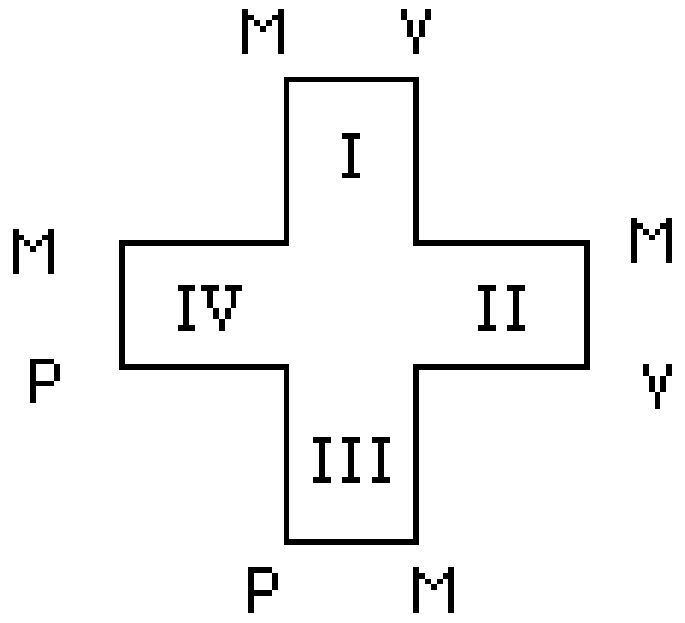


Porphin, showing the four pyrrole rings and the Roman numerals which designate them. Arabic numbers indicate positions at which substituents may be attached. Greek letters denote the methene bridges.

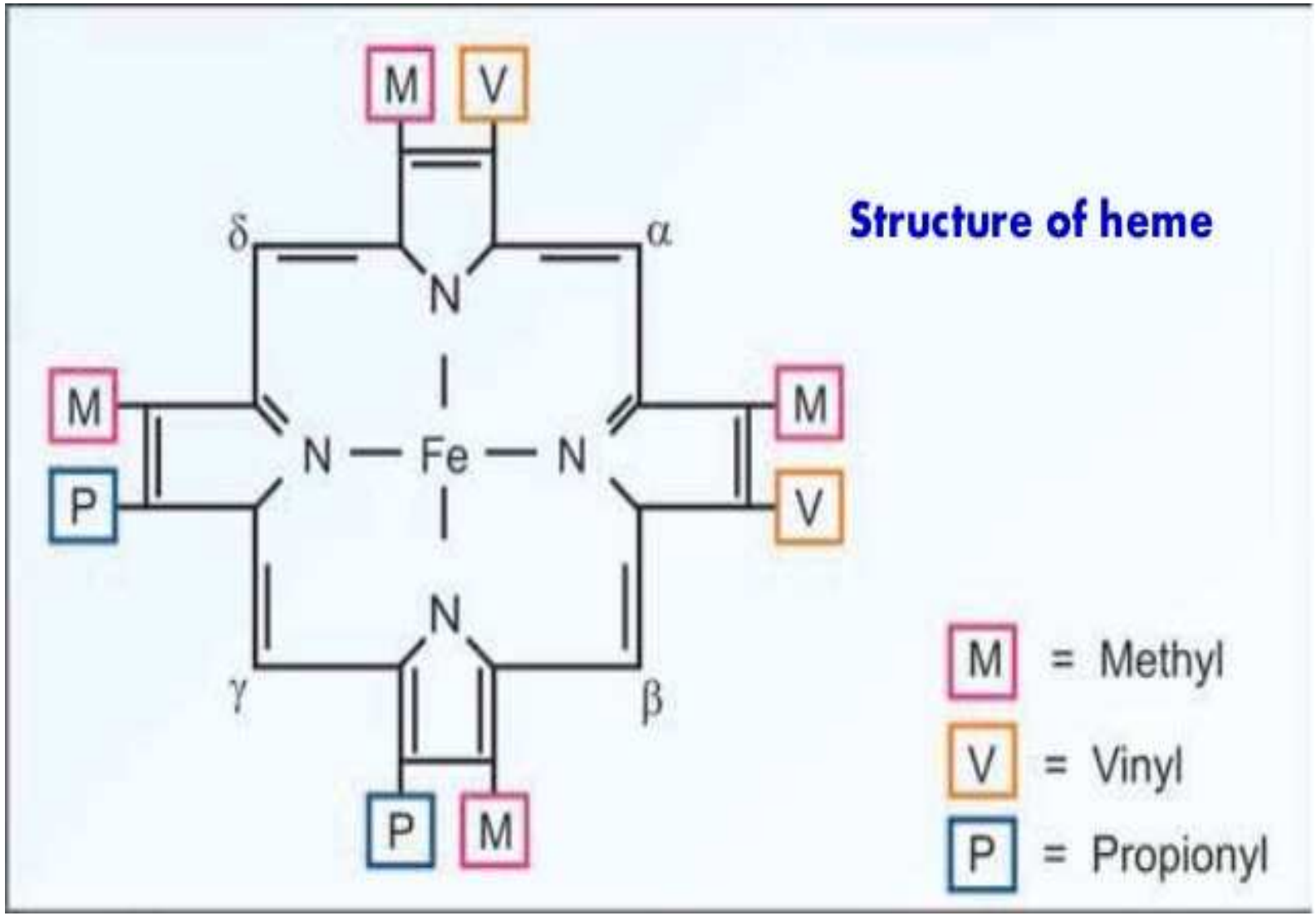


Schematic representation of porphin.

PROTOPORPHYRIN III (IX)



This diagram represents a protoporphyrin because the substituents are M ($-CH_3$), P ($-CH_2CH_2COOH$) and V ($-CH=CH_2$)

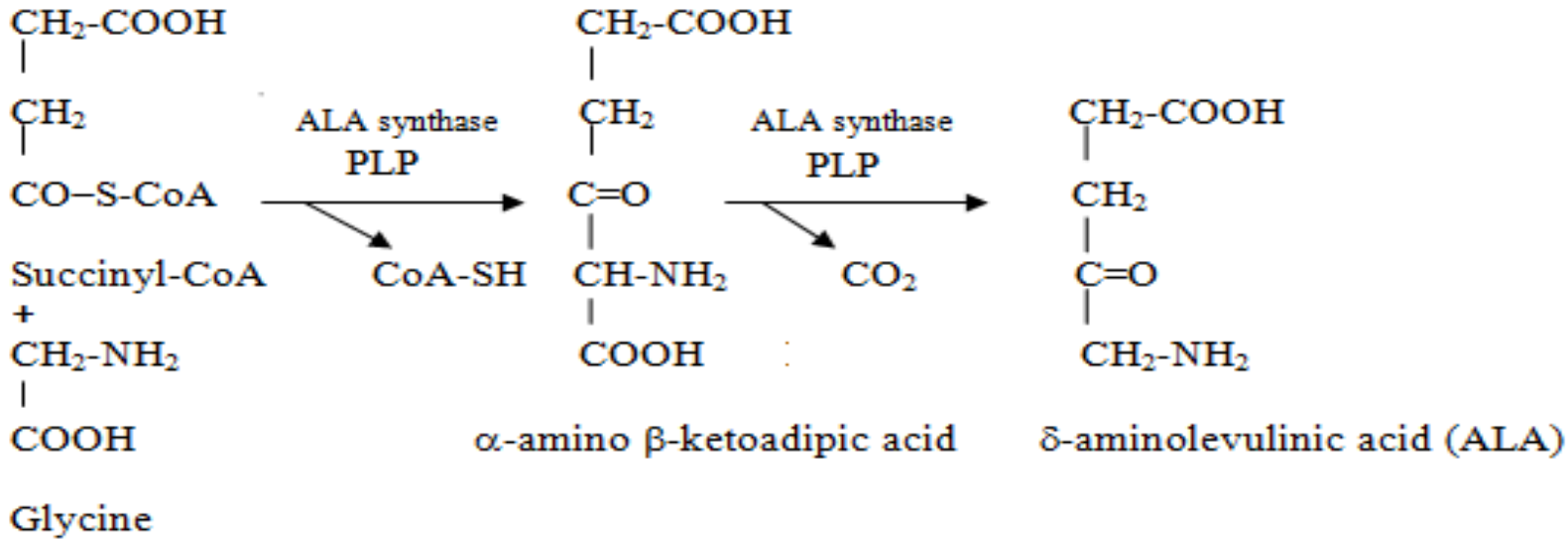

Structure of heme
M
V
δ
α
N
M
M
N — Fe — N
P
V
N
γ
β
P
M
M = Methyl
V = Vinyl
P = Propionyl

Biosynthesis of heme

- **Site:** mainly in the liver and bone marrow (both in mitochondria and cytoplasm).
- **Steps:**

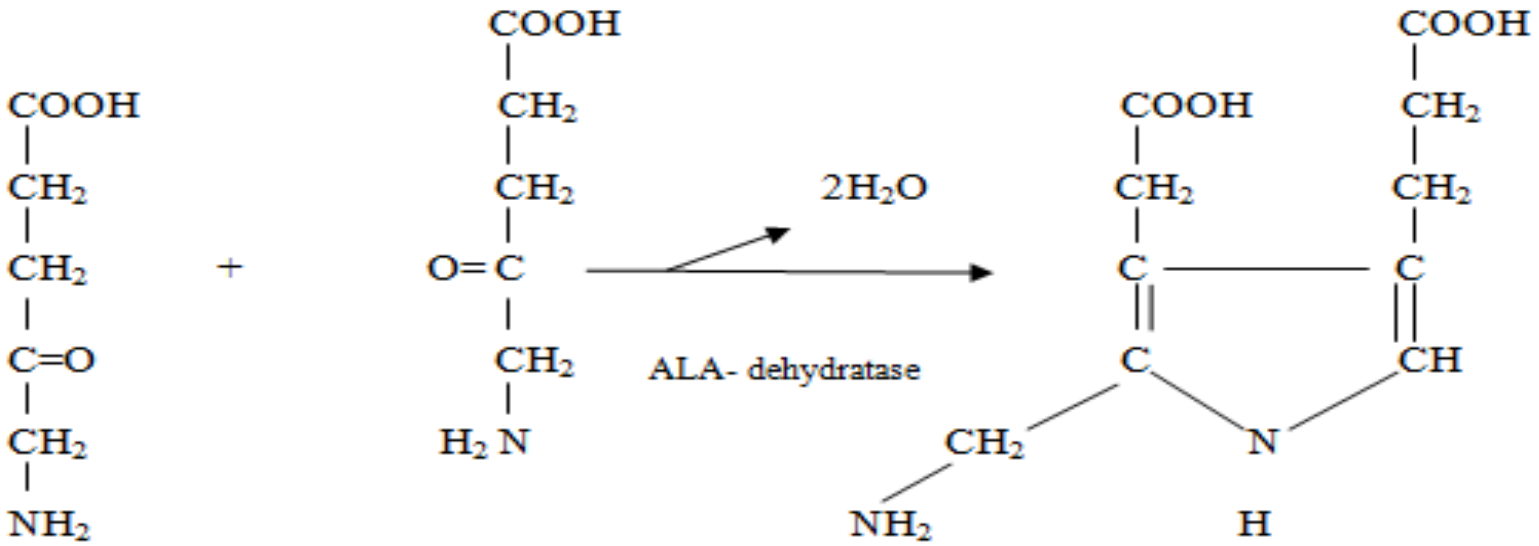
1-Formation of δ-aminolevulinic acid (ALA):

It occurs in *the mitochondria.*



- **<u>2-Formation of porphobilinogen (PBG):</u>**

It occurs in *the cytosol*



2 δ aminolevulinic acid

porphobilinogen

- **3-Formation of uroporphyrinogen III:**

It occurs in *the cytosol*

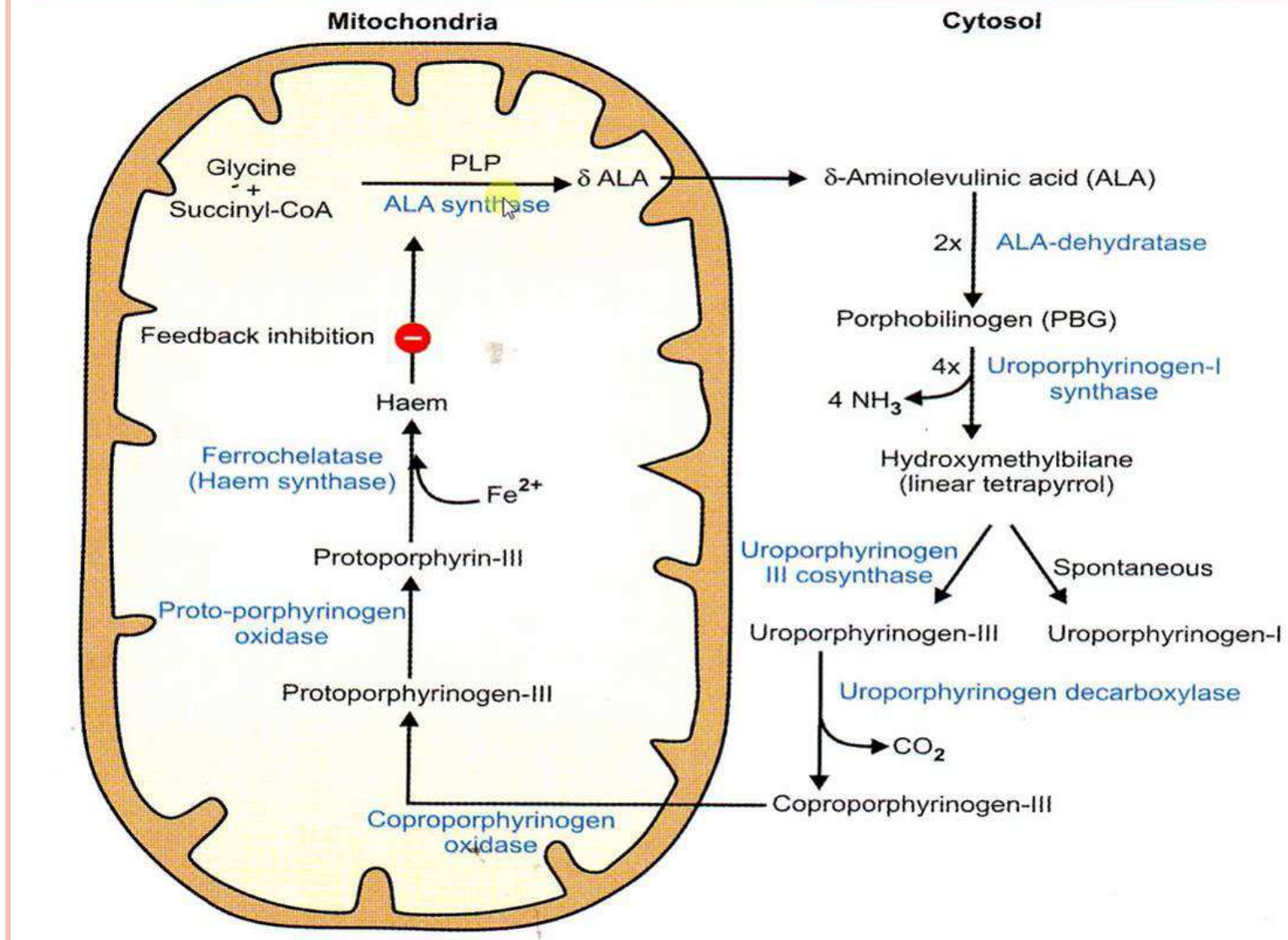
four molecules of porphobilinogen condense in the presence ***uroporphyrinogen I synthase*** ***(PBG deaminase)*** to give a linear hydroxymethylbilane which is converted to uroporphyrinogen III by the action of ***uroporphyrinogen III synthase*****.**

The four acetyl groups of uroporphyrinogen III undergo decarboxylation into methyl groups by **uroporphyrinogen decarboxylase** forming **coproporphyrinogen III.**

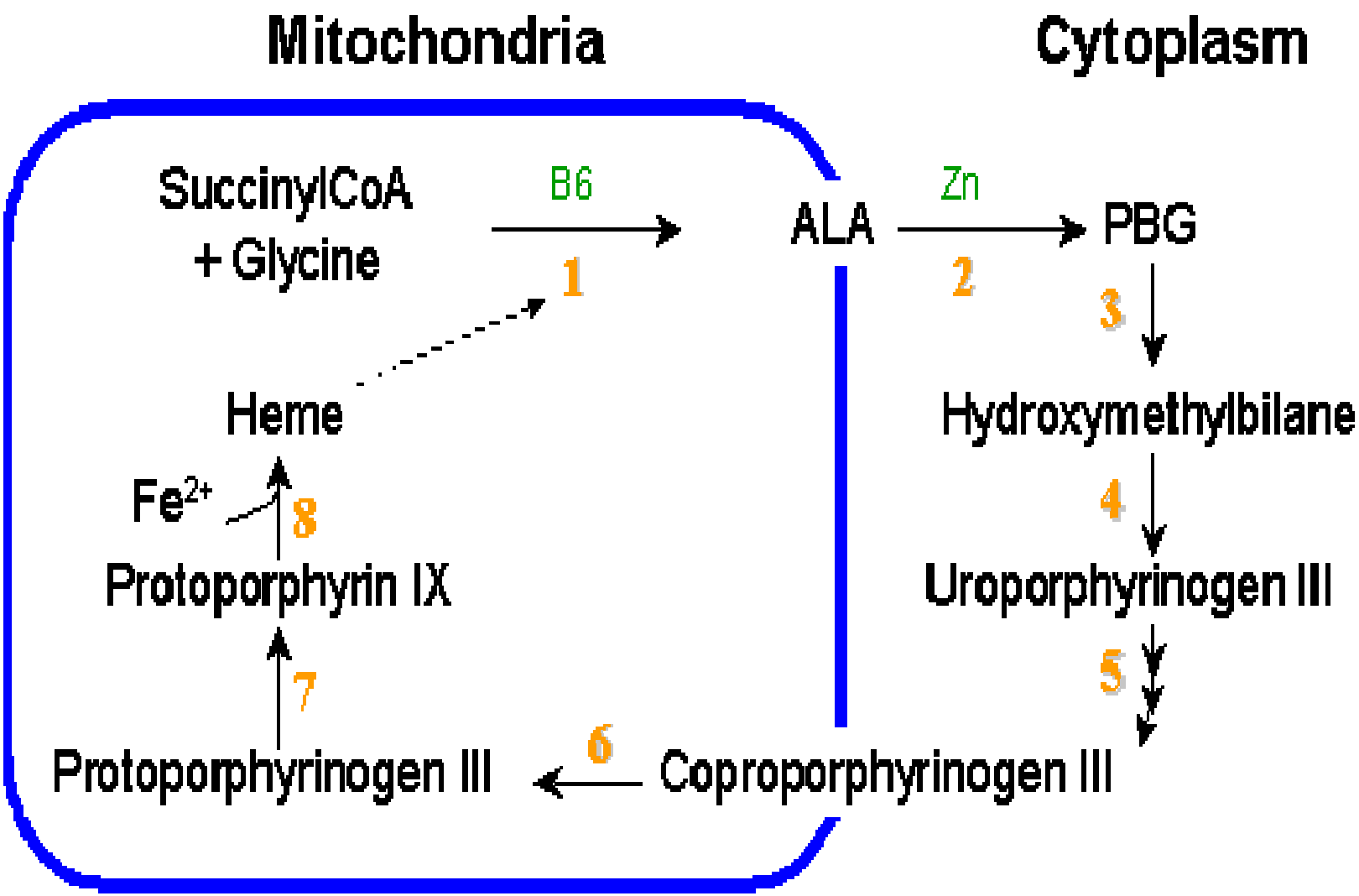
- **4-Formation of protoporphyrinogen III:** In *the mitochondria*, two propionate side chains are converted into vinyl groups by ***coproporphyrinogen oxidase*** forming protoporphyrinogen III. This enzyme acts only on type III coproporphyrinogen.

- **5-Formation of protoporphyrin IX:** In *the mitochondria*, oxidation of protoporphyrinogen to protoporphyrin IX is catalyzed by mitochondrial enzyme ***protoporphyrinogen oxidase.***

- **6- Formation of heme:** Iron (ferrous form) is inserted into the centre of the protoporphyrin ring which is catalyzed by **ferrochelatase** (**heme synthase**) to form heme.
- ***Ferrochelatase enzyme*** is inhibited by lead in lead poisoning.



: Biosynthetic pathway of haem


Mitochondria
Cytoplasm
Succinyl CoA
+ Glycine
B6
1
ALA
Zn
2
PBG
3
Hydroxymethylbilane
4
Uroporphyrinogen III
5
Coproporphyrinogen III
6
Protoporphyrinogen III
7
Protoporphyrin IX
8
Fe2+
Heme

Porphyria

- **Definition:**

  Porphyria is a metabolic disease caused by **congenital deficiency of one of the enzymes needed for heme synthesis.** This leads to accumulation of the metabolic products before the site of the deficient enzyme.

-The symptoms depend on the site of the defect as following:

- **Enzyme defect before the formation of porphyrinogens**:

- It leads to accumulation of δ-aminolevulinic acid and porphobilinogen. Both have neurotoxic effect on sympathetic and somatic nerves and central nervous system leading to abdominal pain, peripheral neuritis and neuropsychiatric symptoms.
- This occurs in **acute intermittent porphyria** due to deficiency of **uroporphyrinogen I synthase.**

- **Enzyme defect after the formation of porphyrinogens:**

➢ Porphyrinogens will accumulate and undergo oxidation into corresponding porphyrin. On exposure to light, porphyrins become excited and react with oxygen forming reactive oxygen species that destroy lysosomal membrane and release its degradative enzymes producing **photosensitivity** and **skin damage and scaring**.

➢ As in **porphyria cutanea tarda** which is caused by deficiency of **uroporphyrinogen decarboxylase** and in **hereditary coproporphyria** which is caused by deficiency of **coproporphyrinogen oxidase.**

Hemoltytic anemias

- They may be classified according to the means of hemolysis into:

Intrinsic : in cases where the cause is related to the red blood cell (RBC) itself

Extrinsic : in cases where factors external to the RBC dominate

Intrinsic causes:

- Defects of red blood cell membrane include abnormalities of membrane proteins (as in **hereditary spherocytosis** and **hereditary elliptocytosis**). Principally caused by abnormalities in the amount or structure of spectrin (the major protein of the cytoskeleton).

- Causes inside the RBC include **hemoglobinopathies** (as in sickle cell anemia, thalassemias)and **enzymopathies** (abnormalities of enzymes in the pentose phosphate pathway and in glycolysis)

Extrinsic causes:

- Any of the causes of hypersplenism (increased activity of the spleen), such as portal hypertension.
- Immunologic abnormalities as in autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis.
- Low-grade hemolytic anemia occurs in 70% of prosthetic heart valve recipients, and severe hemolytic anemia occurs in 3%

Laboratory investigations that aid in the diagnosis of hemolytic anemia:

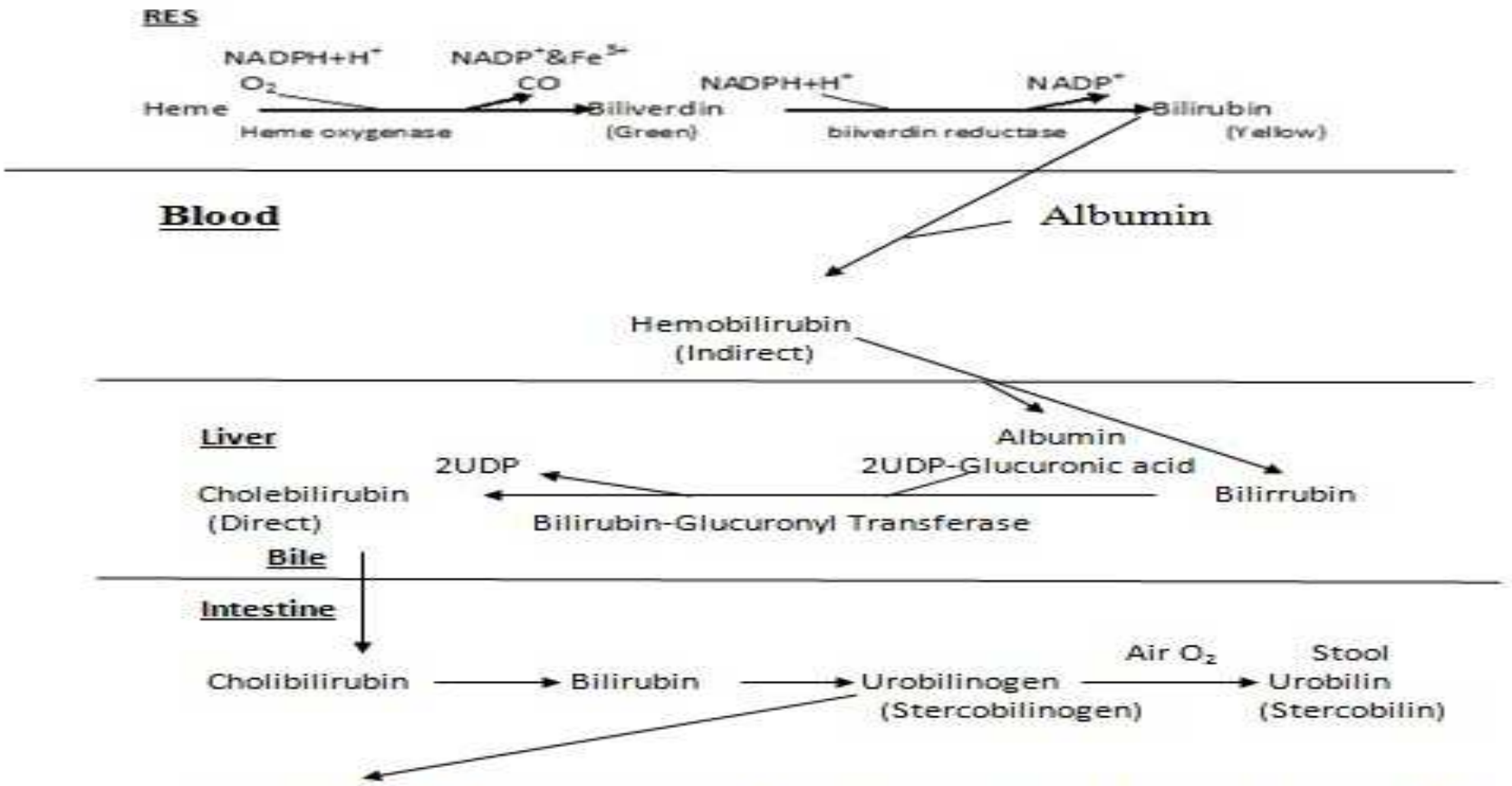
- **General tests and findings:**

1- increased nonconjugated (indirect) bilirubin
2- reticulocytosis
3- hemoglobinemia
4- low level of plasma haptoglobin

- **Specific tests and findings:**

1- Hb electrophoresis (eg,HbS)
2- red cell enzymes (eg,G6PD or PK deficiency)
3- osmotic fragility (eg, hereditary spherocytosis)
4- coombs test

The end products of heme catabolism are bile pigments (blirubin & biliverdin)



Urobilinogen by enterohepatic circulation to blood to kidney and excreted in urine as Urobilin.

Reticulocyte count:

- Reticulocytes are newly produced, relatively immature red blood cells (RBCs). A reticulocyte test determines the number and/or percentage of reticulocytes in the blood and **is a reflection of recent bone marrow function or activity.**

- When hemolysis occur,the body compensates by increasing the rate of RBC production and by releasing RBCs sooner into the blood, before they become more mature.

- This test provides information **on the number of relatively immature red blood cells** in a person's blood sample.

- When someone has anemia (low RBC count, hemoglobin, and hematocrit), the results of this test can help determine the cause and/or help classify the type of anemia. **For example**, for a person with anemia, an inappropriately low reticulocyte count often indicates decrease in red blood cell production in the bone marrow.

Haptoglobin

- Haptoglobin is a protein produced by the liver that the body uses to clear free hemoglobin (found outside of red blood cells) from circulation.

- Haptoglobin binds to free hemoglobin in the blood. This forms a haptoglobin-hemoglobin complex that is rapidly cleared out of circulation for degradation and iron recycling.

- When large numbers of RBCs are destroyed, haptoglobin concentrations in the blood **will temporarily decrease as the haptoglobin is used up faster than the liver can produce it**.

- A decrease in the amount of haptoglobin may be a sign that a person has a condition that is causing red blood cells to be destroyed or break apart. **When the binding capacity of haptoglobin is exceeded, free hemoglobin level in circulation goes up and may cause tissue damage and organ dysfunction.**

Osmotic fragility test:

- In this test, the RBCs are exposed in vitro to decreasing concentrations of NaCL. The physiologic concentration of NaCL is 0.85 g/dl. When exposed to a concentration of NaCL of 0.5 g/dl, very few normal RBCs are hemolyzed, whereas approximately 50% of spherocytes would lyse under these conditions.

- The explanation is that the **spherocyte, being almost circular, has little potential extra volume to accommodate additional water and thus lyses readily** when exposed to a slightly lower osmotic pressure than is normal.

coombs test:

- The direct coombs test detects the presence of antibodies on red cells, whereas the indirect test detects the presence of circulating Abs to Ags present on red cells.