HEMOGLOBIN METABOLISM
RBC

Are biconcave discs, with a diameter of about 7 microns.

- RBCs live for about 120 days in peripheral circulation, during which time they traverse about 160 km.
- In a 70 kg person, there will be about $25 \times 10^{12}$ RBCs & 750 g Hb.
Mature RBC is non-nucleated, have no mitochondria and no TCA cycle enzymes.

The glycolytic pathway is active which provides energy and 2,3-bisphosphoglycerate (2,3-BPG). The HMP shunt pathway provides the NADPH
RBC formation in the bone marrow requires: amino acids, iron, copper, folic acid, vit B$_{12}$, vit C, pyridoxal phosphate, & pantothenic acid.
Heme is a derivative of the porphyrin. Porphyrines are cyclic compounds formed by fusion of 4 pyrrol rings linked by methylene bridges (==CH—)
Hemoglobin is a conjugated protein having heme as the prosthetic group and the protein, the globin. It is a tetrameric protein with 4 subunits, each subunit having a prosthetic heme group and the globin polypeptide.
The polypeptide chains are usually 2 alpha & 2 beta chains.
Hb has a MWt of about 67,000 D.
Each gram of Hb contains 3.4 mg of Iron.
Heme present in:
Hemoglobin, myoglobin, cytochromes, peroxidase, catalase, nitric oxide synthase.
Heme is produced by the combination of iron with a porphyrin ring.
Structure of Hemoglobin

Beta chains

Heme units with iron atom

Alpha chains

Hemoglobin
Hemoglobin

* Normal level of Hb in blood in males 14—16 g/dl & in females 13—15 g/dl.
* Hb is globular in shape.
* The adult Hb (HbA) has 2 alpha & 2 beta chains.
* The fetal Hb (HbF) is made up of 2 alpha & 2 gamma chains.
* HbA2 is made of 2 alpha & 2 delta chains..
* Normal adult blood contains 97% HbA, 2% HbA2 & about 1% HbF.
* Alpha chain is on chromosome 16 while the beta, gamma and delta chains are on chromosome 11.
* Each alpha chain has 141 amino acids.
* The beta, gamma & delta have 146 amino acids.
HEME SYNTHESIS

Step one:
The formation of $\alpha$-aminolevulinate (ALA):
From: SUCCINYL-COA + GLYCINE
succinyl-CoA, is derived from citric acid cycle.
This step occurs in the mitochondria.

Step two:
two molecules of ALA are condensed to form: PORPHO-BILINOGEN (PBG).
This step occurs in the cytosol.
HEME SYNTHESIS

Step three: THE FORMATION OF: the tetrapyrrole:  uro-porphyrinogen
By condensation of four molecules of PBG
This step occurs in the In the cytosol.
Step four: The formation of: protoporphyrin.

The last Step in heme synthesis:

The Incorporation of Iron Into Protoporphyrin
Enzymes of the synthesis

1– ALA synthase (mitochondrial & rate limiting)
2– ALA dehydratase (cytoplasmic, contain Zn & inhibited by lead)
3– PBG–deaminase & UPG–III co–synthase
4– Uroporphyrinogen decarboxylase
5– Copro porphyrinogen (Mitochondrial) oxidase
6– Protoporphyrinogen (mitochondrial) oxidase
7– Heme synthase or Ferrochelatase
Glycine + Succinyl-CoA → ALA-SYNTHASE → 5-Aminolevulinic acid → ALA-DEHYDRATASE → Porphobilinogen → PBG-DEAMINASE → Hydroxy methylbilane

Porphyria cutanea tarda
- Most common
- Autosomal dominant
- Photosens. (blisters, hyperpig.)
- Red-brown urine
- Exacerbatd by alcohol

Acute intermittent porphyria
- Autosomal dominant
- Paraesthesia
- Abdominal pain
- Port-wine urine
PORPHYRIAS

Definition:
Are a group of **GENETIC DISORDERS OF**
**HEME METABOLISM** due to abnormalities in the pathway of biosynthesis of heme.

Cause: Enzymic Deficiency Or Blockage which could be genetic or acquired.
PORPHYRIAS

Types:

HEPATIC PORPHYRIAS
The defect is primarily in the liver

ERYTHROPOIETIC PORPHYRIAS
The defect is primarily in the bone marrow.
Signs and symptoms

1- Anemia

2- Recurrent abdominal pain.

3- Skin abnormalities and photosensitivity.

4- Inflammation of the nerve (neuritis).

5- Neuropsychiatric signs.
Biochemical findings:

1- low Hb levels.

2- increased Porphyrin products in the blood.

3- excretion of porphyrines in urine as (Uroporphyrins) or in the feces as (coproporphyrines) which may change color on standing.

4- Enzymic studies.
Catabolism of Heme

Formation of Bilirubin

1 – The end product of heme catabolism are bile pigments. Bilirubin has no function in the body and is excreted through bile.

2 – From hemoglobin, the globin chains are separated, they are hydrolyzed and the amino acids are channelled into the body amino acid pool. The iron liberated from the heme is reutilized.

3 – The porphyrin ring is broken down in reticuloendothelial (RE) cells of liver, spleen & bone marrow to bile pigments, mainly bilirubin
4– Heme is degraded primarily by microsomal enzyme; heme oxygenase.
5– The ferrous (Fe+2) liberated is oxidized to Ferric (Fe+3) and taken up by transferrin.
6– The linear tetrapyrrolo formed is bilivedrin, which is green in color. In mammals it is further reduced to bilirubin, a red–yellow pigment.
Formation of Bilirubin

- Heme
  - Heme Oxygenase
    - Oxygen ($O_2$)
  - Cytochrome P450 Reductase
    - NADPH
- Carbon monoxide
- Biliverdin
  - Biliverdin Reductase
    - NADPH
  - Bilirubin
- Ferritin
  - Iron ($Fe^{2+}$)