Slide 1

Slide 2

LECTURE OUTLINE

- An overview of the structure of hemoglobin.
- Different types of hemoglobin.
- Definition of hemoglobinopathies
- Sickle Cell Disease and Hemoglobin C

Slide 3

HEMOGLOBIN

- It belongs to the class of proteins referred to as Globular Heme Proteins.
- Heme is made of protoporphyrin and iron.

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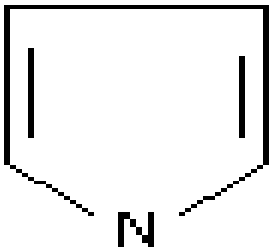
PYROLE RING



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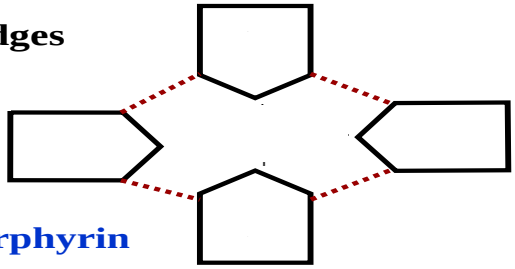
PORPHYRIN IS COMPLEX OF FOUR PYRROLE RINGS CONNECTED BY METHENYL BRIDGES

Methenyl bridges (=HC-) are indicated by dotted lines



A porphyrin (Tetrapyrrole)

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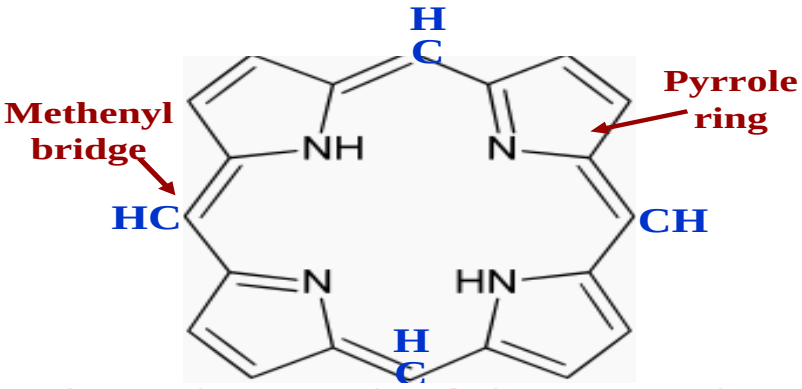

STRUCTURE OF A SIMPLE PORPHYI

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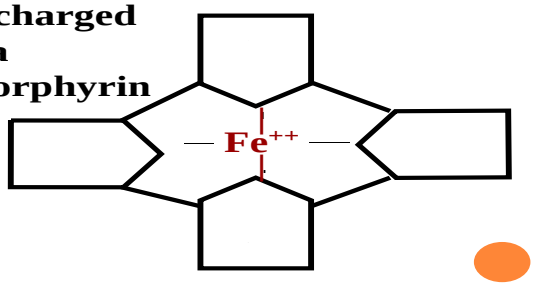
HEME IS A TETRA PYRROLE

- Composed of:
  - Protoporphyrin
  - Iron (Fe) ion (charged atom) held in a heterocyclic Porphyrin ring



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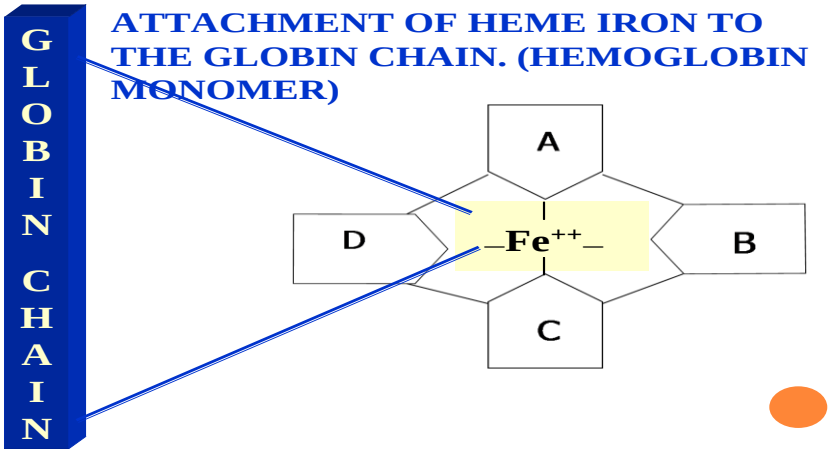

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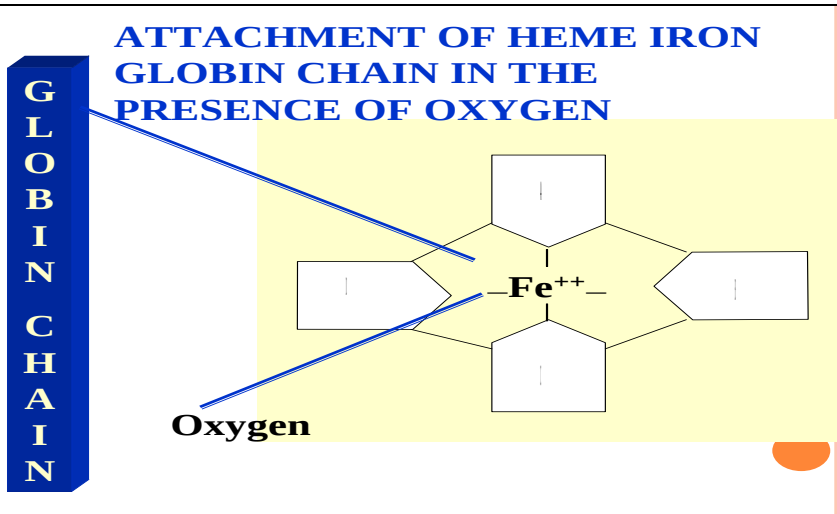

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- **HEME is synthesized in the mitochondria.**
- **Globin synthesis occurs via transcription and translation.**
- **Heme and globin are joined together in the cytosol.**

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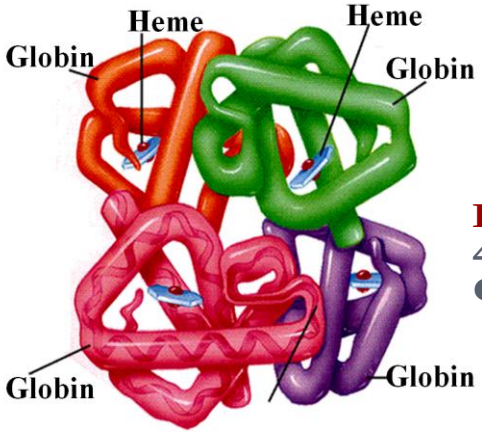

HEMOGLOBIN
4 HEME + 4 GLOBIN CHAINS

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BIOLOGICAL FUNCTIONS OF HEMOGLOBIN

- **Hemoglobin performs two vital and major transport functions:**
  - **Transport, and maintenance of Oxygen supply to peripheral tissues.**
  - **Transport of CO_2 & Protons (H^+) from peripheral tissues to respiratory organ for subsequent disposal.**
- **Hb acts as an important blood pH buffer.**

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GLOBIN CHAINS

- The genes for the synthesis of globin are present on chromosome 11 and chromosome 16.
- This determines the different variants of haemoglobin present at different ages.

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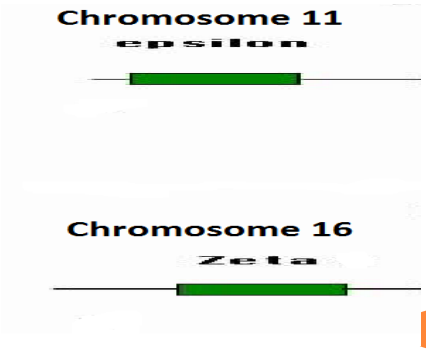
EMBRYONIC LIFE

- Embryonic Haemoglobin is referred to as Gower's Haemoglobin.
- Embryonic Haemoglobin (2 Epsilon and 2 Zeta chains)



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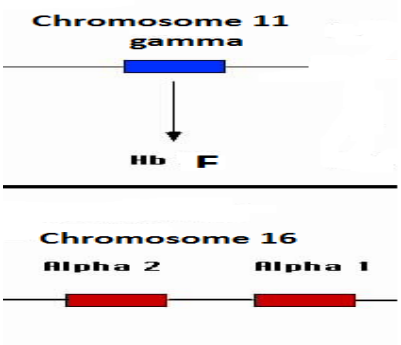
FETAL HEMOGLOBIN

- HbF
- Fetal Haemoglobin (2 Alpha and 2 Gamma chains)
- Hemoglobin F (α2γ2)



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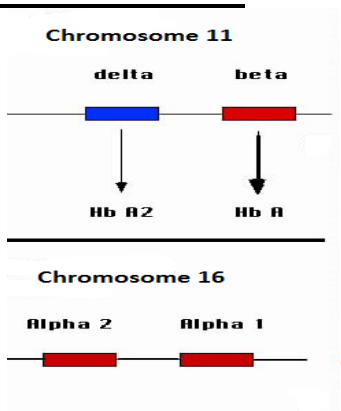
ADULT HEMOGLOBIN

- Hemoglobin A and Hemoglobin A2
- Hemoglobin A (2 Alpha and 2 beta chains) and Hemoglobin A2 (2 alpha and 2 delta chains)



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ADULT HEMOGLOBIN

- In adults(Adult Hb):
  - Hemoglobin A ($\alpha 2\beta 2$) - normal amount over 95%
  - Hemoglobin A2 ($\alpha 2\delta 2$) - normal range of 1.5-3.5%
  - Hemoglobin F ($\alpha 2\gamma 2$) – normal range < 1%

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HEMOGLOBINOPATHIES

- An inherited mutation of the globin genes leading to a qualitative or quantitative abnormality of globin synthesis

- Classified as

→Quantitative

→Qualitative

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- **Structural abnormalities (Qualitative abnormalities)**

→Sickle cell haemoglobin.

→HbC disease.

- **Insufficient synthesis (Quantitative abnormalities)**

→Thalassemia

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SICKLE CELL DISEASE

- **Basic abnormality is in beta chain.**
- **Due to a point mutation in the β-globin gene there is a variation in the β-chain gene (Chromosome 11).**
- **The form of hemoglobin in persons with sickle cell anemia is referred to as HbS.**

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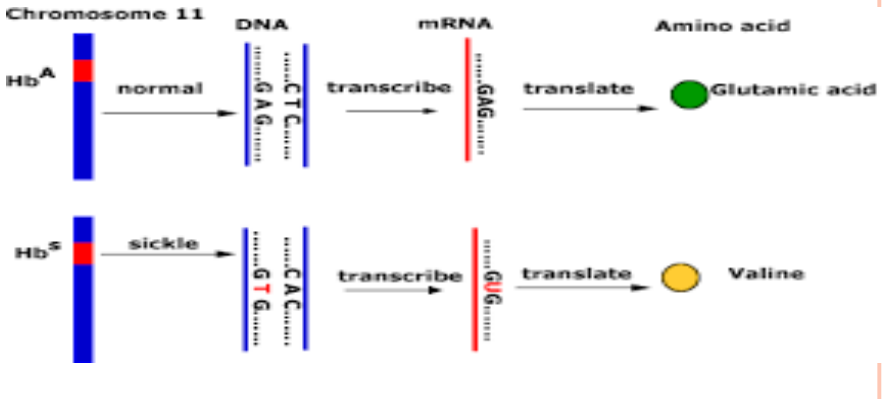
SICKLE CELL DISEASE



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SICKLE CELL DISEASE AND SICKLE CELL TRAIT

- Sickle Cell Trait- Heterozygous (HbAS)
- Sickle Cell Disease- Homozygous (HBSS)

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THE UNDERLYING PROBLEM IN SICKLE CELL ANEMIA IS THAT THE CHANGE RESULTS IN HB TETRAMERS THAT AGGREGATE INTO ARRAYS UPON DEOXYGENATION IN THE TISSUES

This aggregation leads to deformation of the red blood cell making it relatively inflexible and unable to traverse the capillary beds.

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FACTORS THAT FAVOR DEOXY HEMOGLOBIN

- Decreased partial pressure of Oxygen (High Altitude)
- Decreased pH (when H+ ions bind with Hb, it results in release of oxygen)
- Increased partial pressure of carbon dioxide (exercise)
- Increased 2,3 Bisphosphoglycerate

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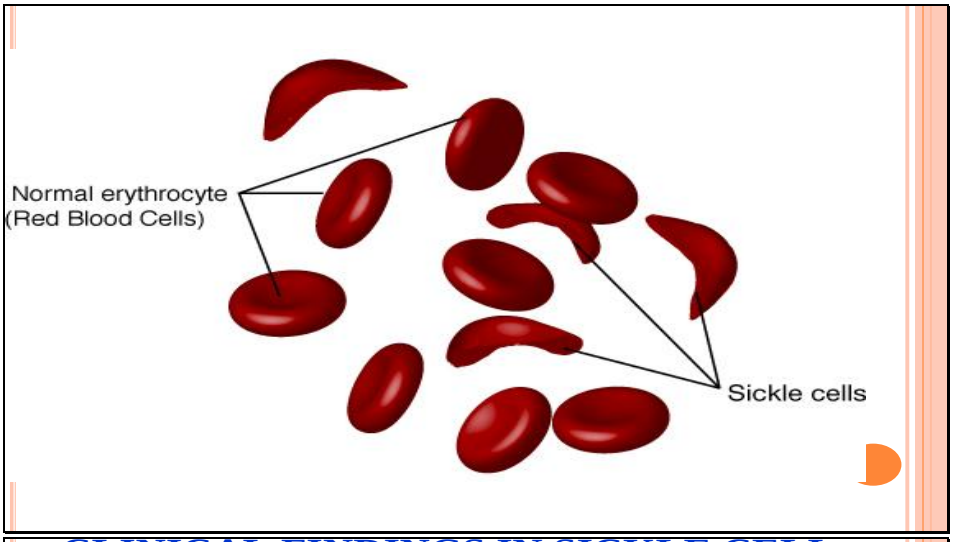

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CLINICAL FINDINGS IN SICKLE CELL DISEASE

CHRONIC ANEMIA AND HYPERBILIRUBINEMIA

- **The continual destruction of the sickled red blood cells leads to:**
  - **Chronic anemia (Sickle Cell Anemia) 20 days**
  - **Episodes of hyperbilirubinemia.**

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CLINICAL FINDINGS IN SICKLE CELL DISEASE

SEVERE BONE PAIN

- **Because bones are particularly affected by the reduced blood flow, frequent and severe bone pain results.**
- **This is the typical symptom during a sickle cell "crisis".**

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CLINICAL FINDINGS IN SICKLE CELL DISEASE

DAMAGE TO THE INTERNAL ORGANS (PAIN ATTACKS)

Long term the recurrent clogging of the capillary beds leads to damage to the internal organs, in particular the kidneys, heart and lungs

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DIAGNOSIS

- **Hemoglobin Electrophoresis**

LIFE SAVING TREATMENT

- **Exchange Transfusion**

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TREATMENT

- **Hydration**
- **Analgesics**
- **Antibiotics**
- **Blood transfusions**
- **Hydroxyurea (leads to increased production of gamma globin chain leading to less sickling)**

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HEMOGLOBIN C

- In hemoglobin C, mutation at the same point results in replacement of glutamic acid by lysine.
- It is not symptomatic mostly.