

# Hemoglobin (Structure, Oxygen and Carbon Dioxide, Transport, Abnormal Hemoglobins)

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## ? HEMOGLOBIN

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*(Structure, Oxygen & CO<sub>2</sub> Transport, Oxygen Dissociation Curve)*

This is written in clean MedMentor MBBS/PG style — crisp, conceptual, and ready for use in your platform.

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## ? STRUCTURE OF HEMOGLOBIN

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### ? Basic Composition

- Hemoglobin (Hb) is a **tetrameric protein**.
- Consists of **4 globin chains + 4 heme groups**.
- Each heme contains **protoporphyrin IX + Fe<sup>2+</sup>**.
- One molecule of Hb binds **4 O<sub>2</sub> molecules**.

### ? Adult Hemoglobins

- **HbA<sub>1</sub>** (α<sub>2</sub>β<sub>2</sub>) — main adult Hb (~97%).
- **HbA<sub>2</sub>** (α<sub>2</sub>β<sub>2</sub>) — ~2%.
- **HbF** (α<sub>2</sub>β<sub>2</sub>) — <1% in adults; predominant in fetus.

### ? Globin Chains

- Globin is a **protein** with helical regions.
- Each chain surrounds one **heme pocket**.
- Fe<sup>2+</sup> is held by:
  - Proximal histidine (F8)
  - Distal histidine (E7) helps binding O<sub>2</sub>.

## ? Quaternary Structure

- Hb has **two ?? dimers**.
- Exists in two states:
  - **T-state (Tense)**: low O<sub>2</sub> affinity
  - **R-state (Relaxed)**: high O<sub>2</sub> affinity
- Binding of O<sub>2</sub> shifts Hb ? **T ? R transition** (cooperative binding).

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## ? TRANSPORT OF OXYGEN

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### ? How much O<sub>2</sub> is carried?

- Each Hb carries **4 O<sub>2</sub> molecules** (one per heme iron).
- Hb carries **98% of total oxygen**; plasma carries 2%.

### ? Mechanism of O<sub>2</sub> Binding

- O<sub>2</sub> binds reversibly to **Fe<sup>2+</sup>** without oxidation.
- Fe<sup>2+</sup> remains in reduced state (oxyhemoglobin is NOT Fe<sup>3+</sup>).

### ? Factors Affecting O<sub>2</sub> Binding (Bohr Effect)

- ? pH (acidic)
- ? CO<sub>2</sub>
- ? Temperature
- ? 2,3-BPG
- ? **Shift O<sub>2</sub> curve to the right** (? affinity, ? release).

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## ? TRANSPORT OF CARBON DIOXIDE

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CO<sub>2</sub> is transported in three forms:

### ? 1. As Bicarbonate (HCO<sub>3</sub><sup>-</sup>) — 70%

- CO<sub>2</sub> + H<sub>2</sub>O ⇌ H<sub>2</sub>CO<sub>3</sub> ⇌ H<sup>+</sup> + HCO<sub>3</sub><sup>-</sup>
- Enzyme: **Carbonic anhydrase** (RBC cytosol).

### ? 2. As Carbaminohemoglobin — 20%

- CO<sub>2</sub> binds to **terminal amino groups** of globin chains (not heme).
- Deoxygenated Hb carries more CO<sub>2</sub> (**Haldane effect**).

### ? 3. Dissolved CO<sub>2</sub> — 10%

- Directly dissolved in plasma.

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## ? OXYGEN DISSOCIATION CURVE (ODC)

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The ODC is **sigmoid** due to **cooperative binding** of oxygen.

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### ? Right Shift (? O<sub>2</sub> affinity — easier release)

Memory: **CADET** ? right shift

**CO** ? ?

**Acid** ? (? pH)

**DPG** ? (2,3-BPG)

**Exercise** ?

**Temperature** ?

Seen in:

- Exercise
- Anemia
- High altitude
- Fever
- Acidosis (DKA, sepsis)

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### ? Left Shift (? O<sub>2</sub> affinity — harder release)

- ? 2,3-BPG
- ? Temperature
- ? CO?

- ? pH (alkalosis)
- **HbF (fetal hemoglobin)**
- CO poisoning
- Methemoglobinemia

Left shift means **less O<sub>2</sub> delivered to tissues.**

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### ? P50 Value (Very Important)

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- **P50 = PO<sub>2</sub> at which Hb is 50% saturated.**
- Normal P50 ? **26 mmHg.**

**Interpretation:**

- **Right shift:** ? P50
- **Left shift:** ? P50

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### ? Fetal Hemoglobin (HbF)

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- Structure: ?????
- Higher O<sub>2</sub> affinity due to **low 2,3-BPG binding.**
- Facilitates transfer of O<sub>2</sub> from mother to fetus.
- Curve is shifted **left.**

## ? Myoglobin vs Hemoglobin

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- Myoglobin = **monomer**, hyperbolic curve, no cooperativity.
- Has **higher O<sub>2</sub> affinity** than Hb.
- Acts as O<sub>2</sub> reservoir in muscle.

## ? HEMOGLOBIN INTERACTION (ALLOSTERIC BEHAVIOR)

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Hemoglobin is an **allosteric protein**, meaning its activity changes when molecules bind at sites other than the oxygen-binding site.

### ? 1. Cooperative Binding (O<sub>2</sub>-O<sub>2</sub> Interaction)

- Binding of the **first O<sub>2</sub>** **increases the affinity** for the next O<sub>2</sub>.
- Called **positive cooperativity**.
- Responsible for the **sigmoid shape** of the O<sub>2</sub> dissociation curve.

### ? 2. T-state ? R-state Transition

- Deoxygenated Hb = **T-state (tense)** ? low O<sub>2</sub> affinity.
- Oxygenated Hb = **R-state (relaxed)** ? high O<sub>2</sub> affinity.
- O<sub>2</sub> binding causes **conformational change** that breaks salt bridges ? R-form.

### ? 3. Interaction with Hydrogen Ions (H<sup>+</sup>)

- ? H<sup>+</sup> (acidosis) stabilizes T-form ? Hb releases more O<sub>2</sub>.

- This is the **Bohr effect**.

#### ? 4. Interaction with CO?

- CO? binds to **terminal amino groups** ? carbaminohemoglobin.
- Stabilizes T-form ? promotes O? release (Haldane effect).

#### ? 5. Interaction with 2,3-BPG

- 2,3-BPG binds between ?-chains ? stabilizes T-form ? ? O? affinity.
- Helps unloading of O? in tissues.

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### ? EFFECT OF 2,3-BPG (KEY REGULATOR OF OXYGEN AFFINITY)

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2,3-BPG is produced in RBCs via the **Rapoport–Luebering shunt**.

#### ? Role

- Binds to the **central cavity** of deoxygenated Hb.
- Binds only to **?-chains** ? therefore:
  - HbA (????) ? strongly affected
  - HbF (????) ? weakly affected ? **higher O? affinity**

#### ? Effects on Hemoglobin

- **Decreases hemoglobin's affinity for oxygen.**

- Shifts the **O<sub>2</sub> dissociation curve to the right.**
- Increases **P50** (more O<sub>2</sub> needed for 50% saturation).
- Improves O<sub>2</sub> delivery to tissues.

### ? Conditions with ? 2,3-BPG

- High altitude
- Anemia
- Hypoxia
- Chronic lung disease
- Exercise
- Hyperthyroidism

### ? Conditions with ? 2,3-BPG

- Stored blood (banked blood)
- Hypothermia
- HbF presence (poor binding of 2,3-BPG)
- Alkalosis

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## ? ISOHYDRIC TRANSPORT OF CARBON DIOXIDE

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Isohydric transport refers to **CO<sub>2</sub> being carried in blood without altering the pH dramatically**, thanks to buffering by hemoglobin.

### ? Mechanism

1. CO<sub>2</sub> enters RBC.
2. Combined with water ? H<sub>2</sub>CO<sub>3</sub> ? H<sup>+</sup> + HCO<sub>3</sub><sup>-</sup>
  - Catalyzed by **carbonic anhydrase**.
3. **H<sup>+</sup> is buffered by deoxygenated hemoglobin.**
  - Hb acts as a **buffer** ? prevents drastic change in pH.
4. HCO<sub>3</sub><sup>-</sup> leaves RBC and is carried in plasma.

### ? Importance

- Allows **70% of CO<sub>2</sub>** to be transported as bicarbonate without making the blood acidic.
- Hemoglobin binding of H<sup>+</sup> is key.

### ? Relationship With O<sub>2</sub>

- Deoxygenated Hb (in tissues) binds H<sup>+</sup> better ? favors CO<sub>2</sub> transport.
- This is part of the **Haldane effect**.

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### ? CHLORIDE SHIFT (HAMBURGER PHENOMENON)

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This is the **exchange of bicarbonate and chloride ions** between RBCs and plasma to maintain electrical neutrality.

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### ? At Tissues (High CO<sub>2</sub>) – “Forward Chloride Shift”

1. CO<sub>2</sub> diffuses into RBC.
2. Converts to HCO<sub>3</sub><sup>-</sup> + H<sup>+</sup> (carbonic anhydrase).
3. HCO<sub>3</sub><sup>-</sup> leaves RBC into plasma.
4. **Cl<sup>-</sup> enters RBC** to maintain charge balance.

? RBC becomes **chloride-rich** in tissues.

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### ? At Lungs (Low CO<sub>2</sub>) – “Reverse Chloride Shift”

1. CO<sub>2</sub> is expelled from blood.
2. HCO<sub>3</sub><sup>-</sup> enters RBC from plasma.
3. **Cl<sup>-</sup> moves out** of RBC to maintain neutrality.
4. HCO<sub>3</sub><sup>-</sup> + H<sup>+</sup> → H<sub>2</sub>CO<sub>3</sub> → CO<sub>2</sub> (exhaled).

? RBC loses chloride in lungs.

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### ? Significance of Chloride Shift

- Maintains **electrical neutrality**.

- Enables **maximum transport of CO<sub>2</sub> as bicarbonate**.
- Essential for acid-base homeostasis.
- Occurs in **all RBCs during CO<sub>2</sub> transport**.

## ? FETAL HEMOGLOBIN (HbF)

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### ? Structure

- HbF = **α<sub>2</sub>γ<sub>2</sub>**
- γ-chains replace β-chains of adult Hb.
- Predominant Hb in fetus and newborn.

### ? Key Properties

- **Higher affinity for oxygen** than HbA.
- Curve shifted **left**.
- Because 2,3-BPG binds poorly to γ-chains.
- Facilitates O<sub>2</sub> uptake from maternal blood.

### ? Physiological Importance

- Allows fetal RBCs to extract oxygen across the placenta.
- Protects fetus from low oxygen tension in utero.

## ? When does HbF disappear?

- HbF declines rapidly after birth.
- Major switch from  $\alpha\gamma$  chains completed by 6 months.
- Adult pattern (HbA) predominates thereafter.

## ? Conditions with Increased HbF

- $\alpha$ -thalassemia major
- Hereditary persistence of fetal Hb (HPFH)
- Sickle cell disease (after hydroxyurea therapy)

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## ? HEMOGLOBIN DERIVATIVES

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(Abnormal chemical forms of hemoglobin)

### ? 1. Oxyhemoglobin

- Hb + O<sub>2</sub>
- Normal physiologic oxygenated form.

### ? 2. Deoxyhemoglobin

- Hb without oxygen.
- Found in venous blood.

### ? 3. Methemoglobin (MetHb)

- Hb where iron is **Fe<sup>3+</sup>** (ferric).
- Cannot bind oxygen.

#### ? 4. Carboxyhemoglobin (CO-Hb)

- Hb bound to **carbon monoxide (CO)**.

#### ? 5. Carbaminohemoglobin

- CO bound to terminal NH<sub>2</sub> groups of globin chains.

#### ? 6. Sulfhemoglobin

- Hb with sulfur atom incorporated.
- Irreversible.
- Seen with sulfur-containing drugs.

#### ? 7. Cyanmethemoglobin

- MetHb + cyanide ion.
- Used in laboratory estimation of Hb.

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### ? CARBOXYHEMOGLOBIN (CO-Hb)

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(A highly important exam topic)

#### ? Definition

Hemoglobin bound to **carbon monoxide**.

## ? Affinity

- Hb has **200–250 times higher affinity** for CO than for O<sub>2</sub>.
- CO shifts the O<sub>2</sub> dissociation curve **left** ? reduced O<sub>2</sub> unloading.

## ? Features

- Causes **tissue hypoxia** without anemia.
- CO poisoning symptoms:
  - Headache
  - Cherry-red skin
  - Confusion
  - Seizures
  - Coma
- Pulse oximetry is **normal** (false reading).
- CO-Hb gives blood a **bright red** color.

## ? Sources

- Car exhaust
- Fire/smoke inhalation
- Tobacco smoke

- Generators used in closed rooms

## ? Treatment

- 100% oxygen
- Hyperbaric oxygen (severe cases)
- Remove exposure

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## ? METHEMOGLOBIN (Met-Hb)

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### ? Definition

Hemoglobin with **iron oxidized to Fe<sup>3+</sup>** instead of Fe<sup>2+</sup>.  
Fe<sup>3+</sup> **cannot bind O<sub>2</sub>** ? functional anemia.

### ? Causes

- Drugs/chemicals:
  - Nitrites
  - Dapsone
  - Nitrates
  - Aniline dyes
  - Local anesthetics (benzocaine)
- Congenital:

- Cytochrome b<sub>5</sub> reductase deficiency

### ? Clinical Features

- Cyanosis with **normal PaO<sub>2</sub>**.
- Chocolate-brown colored blood.
- Low pulse oximetry readings (85% “methemoglobin saturation plateau”).
- Shortness of breath, headache, fatigue.

### ? Diagnosis

- Co-oximetry (gold standard).
- Methemoglobin level measurement.

### ? Treatment

- **Methylene blue** (reduces Fe<sup>3+</sup> → Fe<sup>2+</sup>).
- Vitamin C (adjunct).
- Avoid causative drugs.

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### ? KEY DIFFERENTIATION (Very High Yield)

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CONDITION	IRON STATE	O <sub>2</sub> BINDING	BLOOD COLOR	O <sub>2</sub> CURVE
Oxy-Hb	Fe <sup>2+</sup>	Yes	Bright red	Normal



CONDITION	IRON STATE	O <sub>2</sub> BINDING	BLOOD COLOR	O <sub>2</sub> CURVE
Deoxy-Hb	Fe <sup>2+</sup>	No O <sub>2</sub> bound	Dark red	Normal
<b>Met-Hb</b>	<b>Fe<sup>3+</sup></b>	<b>Cannot bind O<sub>2</sub></b>	Chocolate brown	Left shift
<b>CO-Hb</b>	Fe <sup>2+</sup> + CO	O <sub>2</sub> blocked	Bright red	Left shift

## ? HEMOGLOBIN VARIANTS

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Hemoglobin variants are **structural abnormalities** of globin chains due to **single amino acid substitutions** or deletions.

### ? Examples of important variants:

- **HbS** (sickle cell hemoglobin) – ?6 Glu ? Val
- **HbC** – ?6 Glu ? Lys
- **HbE** – ?26 Glu ? Lys (common in NE India)
- **HbD-Punjab** – another ?-chain variant
- **Hb M** – oxidation of Fe<sup>2+</sup> ? Fe<sup>3+</sup> (methemoglobinemia)
- **HbF persistence** – Hereditary persistence of fetal Hb (HPFH)

### ? Why variants cause disease:

- Affect **solubility**, **stability**, or **oxygen affinity** of Hb.

- Some variants cause **hemolysis, polymerization, or decreased oxygen delivery.**

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## ? SICKLE CELL HEMOGLOBIN (HbS)

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(Most important hemoglobinopathy)

### ? Genetic Defect

- Point mutation in  $\beta$ -globin gene: **Valine replaces Glutamic acid at position 6** (Glu  $\rightarrow$  Val).
- Produces abnormal HbS.

### ? Mechanism of Sickling

- In low O<sub>2</sub>  $\beta$  HbS polymerizes  $\rightarrow$  forms **rigid, sickle-shaped RBCs.**
- Sickled cells cause:
  - Hemolysis
  - Vaso-occlusion
  - Microinfarcts

### ? Clinical Features

- Painful crises
- Avascular necrosis
- Acute chest syndrome

- Anemia
- Dactylitis in children
- Autosplenectomy ? Howell–Jolly bodies

### ? Lab Findings

- Sickle cells on smear
- ? Reticulocytes
- ? Indirect bilirubin
- ? LDH
- Positive sickling test

### ? Treatment

- **Hydroxyurea** ? ? HbF (reduces sickling)
- Blood transfusion
- Pain control
- Bone marrow transplant (curative)

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## ? THALASSEMIAS

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Genetic disorders causing **reduced synthesis** of  $\alpha$ - or  $\beta$ -globin chains.

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## 1. $\alpha$ -Thalassemia

### Cause

- Gene deletion of  $\alpha$ -globin genes (4 total).

### Severity

- 1 gene deleted  $\alpha$  Silent carrier
  - 2 deleted  $\alpha$   $\alpha$ -thalassemia trait
  - 3 deleted  $\alpha$  HbH disease ( $\alpha\alpha$  tetramers)
  - 4 deleted  $\alpha$  Hydrops fetalis (Hb Bart's;  $\alpha\alpha$ )  $\alpha$  fatal
- 

## 2. $\beta$ -Thalassemia

### Cause

- Mutations causing decreased  $\beta$ -chain production.

### Types

- $\beta^+$  (partial reduction)
- $\beta^0$  (complete absence)

### $\beta^+$ -Thalassemia Minor

- Mild anemia

- Very high HbA? (>3.5%)

### ? ?-Thalassemia Major (Cooley's anemia)

- Severe microcytic anemia
- Extramedullary hematopoiesis ? chipmunk facies
- Splenomegaly
- High HbF levels
- Iron overload from transfusions

### ? Treatment

- Regular transfusions
- Iron chelation (deferoxamine)
- Bone marrow transplant (curative)

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## ? MYOGLOBIN

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### ? Structure

- **Monomer** (single polypeptide).
- Contains **one heme group** ? binds **one O?**.

### ? Oxygen Binding

- **Very high O<sub>2</sub> affinity.**
- No cooperativity (hyperbolic curve).
- Acts as an **oxygen reservoir** in muscle.

## ? Clinical Importance

- **Myoglobinuria** seen in:
  - Rhabdomyolysis
  - Crush injuries
  - Severe muscle damage
- Causes **dark red/brown urine.**
- Can precipitate in kidneys ? acute renal failure.

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## ? ANEMIAS

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(From the hemoglobin perspective)

### ? Definition

Reduced **oxygen-carrying capacity** of blood.

### ? Classification Based on Hb Issues

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## ? 1. Hemolytic Anemia

- Premature RBC destruction.
  - Causes: HbS, HbC, G6PD deficiency, thalassemia, autoimmune.
  - Features:
    - ? unconjugated bilirubin
    - ? LDH
    - ? haptoglobin
    - Reticulocytosis
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## ? 2. Hypochromic Microcytic Anemia

- Reduced Hb synthesis ? small, pale RBCs.
  - Causes:
    - Iron deficiency
    - Thalassemias
    - Sideroblastic anemia
    - Chronic disease
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### ? 3. Normocytic Normochromic Anemia

- Acute blood loss
- Hemolysis
- Chronic kidney disease (? EPO)

### ? 4. Macrocytic Anemia

- Vitamin B12 or folate deficiency
- Alcoholism
- Liver disease
- Reticulocytosis

### ? KEY DIFFERENCES — HbS vs Thalassemia vs Myoglobin

FEATURE	HBS	THALASSEMIA	MYOGLOBIN
Defect	Structural mutation	Reduced synthesis	Structural monomer
O <sub>2</sub> Affinity	Low	Normal/high	Very high
Curve	Right-shift & polymerization	Affected by chain imbalance	Hyperbolic



FEATURE	HBS	THALASSEMIA	MYOGLOBIN
Clinical	Pain crises, hemolysis	Microcytosis, marrow expansion	Muscle oxygen store

## ? IMPORTANT POINTS TO REMEMBER (Whole Hemoglobin Chapter)

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### ? Structure of Hemoglobin

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- Hb is a **tetramer**: ???? in adults.
- Each chain contains a **heme group with Fe<sup>2+</sup>**.
- **Fe<sup>2+</sup>** binds O<sub>2</sub>; **Fe<sup>3+</sup>** cannot.
- Exists in two states:
  - **T-state** (tense, low O<sub>2</sub> affinity)
  - **R-state** (relaxed, high O<sub>2</sub> affinity)

### ? Oxygen Transport

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- Hb carries **98% of oxygen** in blood.
- O<sub>2</sub> binding is **cooperative** ? sigmoid O<sub>2</sub> dissociation curve.

- Exchange of one O<sub>2</sub> changes affinity of other subunits.

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## ? Oxygen Dissociation Curve (ODC)

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- Sigmoid shape due to **cooperative binding**.
- **Right shift (? affinity, ? O<sub>2</sub> release):**
  - ? CO<sub>2</sub>, ? H<sup>+</sup> (? pH), ? Temperature, ? 2,3-BPG, Exercise.
- **Left shift (? affinity):**
  - HbF, CO-Hb, Met-Hb, ? CO<sub>2</sub>, ? Temperature, ? 2,3-BPG.
- **P50 = 26 mmHg**; increased by right shift.

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## ? Bohr Effect

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- ? CO<sub>2</sub> or ? pH ? Hb releases O<sub>2</sub> (right shift).
- Helps oxygen delivery to tissues.

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## ? Haldane Effect

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- Deoxygenated Hb binds **more CO<sub>2</sub> and H<sup>+</sup>**.
  - Oxygenated Hb releases CO<sub>2</sub>.
  - Important for CO<sub>2</sub> unloading in lungs.
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## ? 2,3-BPG (Key Modulator)

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- Produced in RBCs via **Rapoport–Luebering shunt**.
- Binds to **?-chains** ? stabilizes T-state ? ? O? affinity.
- ? in high altitude, hypoxia, anemia, exercise.
- ? in stored blood, alkalosis, HbF presence (?-chains do not bind it).

## ? Isohydric Transport of CO?

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- $\text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H}^+\text{CO}_2 \rightleftharpoons \text{H}^+ + \text{HCO}_3^-$  (carbonic anhydrase).
- **H? buffered by deoxygenated Hb** ? prevents acidosis.
- Allows 70% of CO? transport as bicarbonate.

## ? Chloride Shift

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- At tissues:  $\text{HCO}_3^-$  leaves RBC ? **Cl? enters** (forward shift).
- At lungs:  $\text{HCO}_3^-$  enters RBC ? **Cl? exits** (reverse shift).
- Maintains electrical neutrality.

## ? Fetal Hemoglobin (HbF)

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- Structure: ?????.

- Binds O<sub>2</sub> more strongly (left shift).
- Poor interaction with 2,3-BPG.
- High levels in fetus ? facilitates placental oxygen transfer.
- ? in HPFH,  $\alpha$ -thalassemia, hydroxyurea therapy.

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## ? Hemoglobin Derivatives

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- **Oxyhemoglobin:** normal oxygenated form.
- **Deoxyhemoglobin:** venous blood.
- **Carboxyhemoglobin:** Hb + CO (bright red).
- **Methemoglobin:** Fe<sup>3+</sup> form, cannot bind O<sub>2</sub>.
- **Carbaminohemoglobin:** Hb + CO<sub>2</sub> (globin binding).
- **Sulfhemoglobin:** irreversible sulfur binding.

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## ? Carboxyhemoglobin (CO-Hb)

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- CO binds Hb **200–250 times** more strongly than O<sub>2</sub>.
- Causes tissue hypoxia despite normal PaO<sub>2</sub>.
- Pulse oximeter is falsely normal.
- Treat with **100% oxygen** or hyperbaric O<sub>2</sub>.

- Seen in smoke inhalation, exhaust exposure, smoking.

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## ? Methemoglobin (Met-Hb)

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- Iron is oxidized to **Fe<sup>3+</sup>** ? cannot bind O<sub>2</sub>.
- Blood becomes **chocolate brown**.
- Causes: nitrates, nitrites, dapsone, benzocaine.
- Treated with **methylene blue**.

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## ? Hemoglobin Variants

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- Structural changes in globin chains.
- Examples: HbS, HbC, HbE, HbD-Punjab, HbM.
- May affect solubility, stability, or O<sub>2</sub> affinity.

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## ? Sickle Cell Hemoglobin (HbS)

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- Mutation: **6 Glu → Val**.
- Polymerizes in low O<sub>2</sub> ? sickling.
- Causes hemolysis, vaso-occlusion, pain crises.
- HbF reduces sickling ? hydroxyurea benefits.

- Spleen becomes auto-infarcted ? Howell–Jolly bodies.

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## ? Thalassemias

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- ? Synthesis of ?- or ?-globin chains.

### ? ?-Thalassemia

- One gene deletion ? silent carrier.
- Four deletions ? Hb Bart's ? hydrops fetalis (fatal).

### ? ?-Thalassemia

- ? ?-chain synthesis.
- Major: severe anemia, crew-cut skull, hepatosplenomegaly, ? HbF.
- Minor: mild anemia, ? HbA? (>3.5%).

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## ? Myoglobin

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- Monomeric, one heme group.
- **Very high O? affinity** (hyperbolic curve).
- O? storage protein in muscle.

- Elevated in rhabdomyolysis ? myoglobinuria ? renal damage.

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## ? Anemias Related to Hemoglobin Issues

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- **Hemolytic anemia:** HbS, G6PD deficiency, thalassemia.
- **Microcytic anemia:** iron deficiency, ?-thalassemia, chronic disease.
- **Normocytic anemia:** acute blood loss, CKD.
- **Macrocytic anemia:** B12/folate deficiency.

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## ? Ultra-Short Rapid Revision

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- HbA = ????; HbF = ???? (left shift).
- P50 = 26 mmHg.
- CO binds Hb 200–250x stronger than O<sub>2</sub>.
- Met-Hb = Fe<sup>3+</sup>; treat with methylene blue.
- Right shift = CADET ? (CO<sub>2</sub>, Acid, DPG, Exercise, Temp).
- HbS = Glu ? Val (?6).
- ?-thalassemia major ? ? HbF, skeletal deformities.
- Chloride shift = HCO<sub>3</sub><sup>-</sup> ? Cl<sup>-</sup> exchange.
- Myoglobin = monomer, hyperbolic curve, high affinity.

## ? MCQs — Hemoglobin (Whole Chapter)

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1. The quaternary structure of adult hemoglobin (HbA) is:

- A. ?????
- B. ?????
- C. ?????
- D. ??

**Answer: C**

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2. Iron in heme that binds oxygen must be in the:

- A. Ferric state
- B. **Ferrous state**
- C. Elemental state
- D. Ferritin-bound state

**Answer: B**

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3. The sigmoid shape of the oxygen dissociation curve is due to:

- A. Bohr effect
- B. Haldane effect
- C. **Cooperative binding of oxygen**
- D. Binding of CO?

**Answer: C**

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4. A right shift in the O<sub>2</sub> dissociation curve indicates:

- A. Increased affinity for oxygen
- B. Left shift of curve
- C. Reduced tissue oxygenation
- D. **Reduced affinity ? increased O<sub>2</sub> delivery to tissues**



**Answer: D**

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**5. Which of the following causes a right shift of the O<sub>2</sub> curve?**

- A. Low temperature
- B. High pH
- C. Low 2,3-BPG
- D. **High CO<sub>2</sub>**

**Answer: D**

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**6. P<sub>50</sub> is increased when:**

- A. Affinity for O<sub>2</sub> is increased
- B. **Affinity for O<sub>2</sub> is decreased**
- C. HbF is dominant
- D. CO is bound

**Answer: B**

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**7. 2,3-BPG binds to which part of hemoglobin?**

- A. Heme iron
- B.  $\alpha$ -chains
- C.  **$\beta$ -chains in the central cavity**
- D.  $\gamma$ -chains

**Answer: C**

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**8. 2,3-BPG has the weakest binding with:**

- A. HbA
- B. HbA<sub>2</sub>
- C. **HbF**
- D. Methemoglobin

**Answer: C**

---

**9. Isohydric transport refers to:**

- A. CO bound to hemoglobin
- B. Shifting of chloride across RBC membrane
- C. CO<sub>2</sub> dissolved in plasma
- D. **CO<sub>2</sub> transport as HCO<sub>3</sub><sup>-</sup> while H<sup>+</sup> is buffered by hemoglobin**

**Answer: D**

---

**10. Chloride shift at the tissues results in:**

- A. Chloride leaving RBC
- B. **Chloride entering RBC**
- C. Potassium entering RBC
- D. CO<sub>2</sub> entering plasma

**Answer: B**

---

**11. HbF has higher oxygen affinity because:**

- A. It has more  $\alpha$ -chains
- B. It has more iron
- C. **It binds poorly to 2,3-BPG**
- D. It contains ferric iron

**Answer: C**

---

**12. Which form of hemoglobin cannot bind oxygen?**

- A. Oxyhemoglobin
- B. Deoxyhemoglobin
- C. Carboxyhemoglobin
- D. **Methemoglobin (Fe<sup>3+</sup>)**

**Answer: D**

---

**13. Carboxyhemoglobin forms due to:**

- A. Nitrite exposure
- B. Iron deficiency
- C. **Carbon monoxide exposure**
- D. ATP depletion in RBCs

**Answer: C**

---

**14. Carboxyhemoglobin shifts O<sub>2</sub> curve to:**

- A. Right
- B. **Left**
- C. Flat
- D. Hyperbolic

**Answer: B**

---

**15. The mutation in sickle cell disease is:**

- A. ?26 Glu ? Lys
- B. **?6 Glu ? Val**
- C. ?6 Glu ? Asp
- D. ?1 deletion

**Answer: B**

---

**16. Sickling occurs most readily during:**

- A. High oxygen tension
- B. Cold exposure only
- C. **Low oxygen tension**
- D. High HbF

**Answer: C**

---

**17. Thalassemias are disorders of:**

- A. Heme synthesis
- B. Iron absorption
- C. **Globin chain synthesis**
- D. Chloride transport

**Answer: C**

---

**18.  $\beta$ -thalassemia major typically shows:**

- A. High HbA<sub>1c</sub>
- B. Normal HbF
- C. **Markedly increased HbF**
- D. High 2,3-BPG deficiency

**Answer: C**

---

**19.  $\alpha$ -thalassemia with all four  $\alpha$ -genes deleted produces:**

- A. HbH disease
- B. HbC disease
- C. **Hydrops fetalis (Hb Bart's)**
- D. Mild anemia

**Answer: C**

---

**20. Myoglobin differs from hemoglobin because:**

- A. It has 4 heme groups
- B. It is a tetramer
- C. **It has a hyperbolic O<sub>2</sub> curve**
- D. It has lower affinity for oxygen

**Answer: C**

---

**21. Myoglobinuria is most commonly seen in:**

- A. Malaria
- B. Iron deficiency
- C. **Rhabdomyolysis**
- D. Pneumonia

**Answer: C**

---

**22. A patient shows chocolate brown blood and normal PaO<sub>2</sub>. Diagnosis?**

- A. Carboxyhemoglobin
- B. Anemia
- C. **Methemoglobinemia**
- D. HbE disease

**Answer: C**

---

**23. Treatment of methemoglobinemia is:**

- A. Hydroxyurea
- B. Blood transfusion
- C. Iron therapy
- D. **Methylene blue**

**Answer: D**

---

**24. In CO poisoning, pulse oximetry:**

- A. Falls to zero
- B. Shows high CO<sub>2</sub>
- C. **May remain falsely normal**
- D. Shows low pH

**Answer: C**

---

**25. Which hemoglobinopathy gives a "crew-cut skull" on X-ray?**

- A. HbS
- B. HbC
- C.  $\beta$ -Thalassemia major
- D. HbE trait

**Answer: C**

## **? CLINICAL CASE–BASED QUESTIONS (Whole Hemoglobin Chapter)**

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**1. A 22-year-old man presents with severe chest pain, bone pain, and fatigue. Smear shows sickled RBCs. Hemoglobin electrophoresis shows increased HbS and elevated HbF.**

**Diagnosis:** Sickle cell disease

**Mechanism:**  $\beta^6$  Glu  $\rightarrow$  Val mutation  $\rightarrow$  polymerization of HbS in low O $_2$

**Why high HbF helps:** HbF inhibits sickling

---

**2. A 6-month-old infant has severe anemia, frontal bossing, hepatosplenomegaly, and “crew-cut” skull X-ray. Hb electrophoresis shows very high HbF.**

**Diagnosis:**  $\beta$ -Thalassemia major

**Mechanism:** Absent  $\beta$ -chains  $\rightarrow$  excess  $\alpha$ -chains  $\rightarrow$  ineffective erythropoiesis

---

**3. A newborn presents with hydrops fetalis and dies hours after birth. Hemoglobin electrophoresis shows Hb Bart’s (??).**

**Diagnosis:**  $\alpha$ -Thalassemia — deletion of all four  $\alpha$ -genes

**Mechanism:** No  $\alpha$ -chains  $\rightarrow$  Hb Bart’s has extremely high O $_2$  affinity  $\rightarrow$  no O $_2$  delivery

---

**4. A mountain climber at 14,000 ft experiences tachycardia and dyspnea. Labs show increased 2,3-BPG.**

**Diagnosis:** Physiological adaptation to high altitude

**Mechanism:** 2,3-BPG ? ? right shift ? enhanced O<sub>2</sub> release

---

**5. A patient trapped in a house fire has headache, dizziness, and bright red skin. Pulse oximeter shows 100% saturation.**

**Diagnosis:** CO poisoning (Carboxyhemoglobin)

**Mechanism:** CO binds Hb 250x stronger than O<sub>2</sub> ? ? tissue hypoxia

**Treatment:** 100% O<sub>2</sub> or hyperbaric O<sub>2</sub>

---

**6. A child eats nitrate-contaminated well water. Blood sample appears chocolate-brown. Pulse ox ~85% regardless of O<sub>2</sub>.**

**Diagnosis:** Methemoglobinemia (Fe<sup>3+</sup> state)

**Mechanism:** Oxidation of Fe<sup>2+</sup> ? ? Fe<sup>3+</sup>

**Treatment:** Methylene blue

---

**7. A neonate has persistent cyanosis since birth but normal PaO<sub>2</sub>. Family history positive.**

**Diagnosis:** Congenital methemoglobinemia

**Mechanism:** Cytochrome b<sub>5</sub> reductase deficiency

---

**8. A patient with pneumonia shows right shift of O<sub>2</sub> dissociation curve. Which factor explains this?**

**Diagnosis:** Tissue hypoxia due to infection

**Mechanism:** Fever + acidosis ? ? O<sub>2</sub> affinity ? better tissue delivery

---

**9. A patient with COPD has elevated carbaminohemoglobin.**

**Diagnosis:** Chronic CO<sub>2</sub> retention

**Mechanism:** CO<sub>2</sub> binding to amino terminals of globin chains

**Relevance:** Haldane effect ? deoxygenated Hb binds more CO<sub>2</sub>

---

**10. A man collapses after using benzocaine throat spray. Cyanosis does not improve with oxygen.**

**Diagnosis:** Benzocaine-induced methemoglobinemia

**Reason:** Fe<sup>3+</sup> cannot bind oxygen

**Treatment:** Methylene blue

---

**11. A child has pallor, fatigue, and microcytic hypochromic RBCs. Iron therapy shows no improvement. HbA<sub>2</sub> is elevated.**

**Diagnosis:**  $\alpha$ -Thalassemia minor

**Mechanism:** Reduced  $\alpha$ -chain synthesis  $\rightarrow$  compensatory  $\uparrow$  HbA<sub>2</sub>

---

**12. An adult presents with dark urine after a crush injury. Serum CK is high.**

**Diagnosis:** Myoglobinuria due to rhabdomyolysis

**Mechanism:** Myoglobin released from muscle  $\rightarrow$  renal toxicity

---

**13. A 25-year-old athlete has high myoglobin in muscle but normal hemoglobin.**

**Diagnosis:** Physiological adaptation

**Mechanism:** Myoglobin acts as muscle O<sub>2</sub> reservoir

---

**14. A smoker has chronically elevated carboxyhemoglobin.**

**Diagnosis:** CO exposure from cigarettes

**Result:** Tissue hypoxia despite normal Hb

**Long-term risk:** Polycythemia (compensatory)

---

**15. A patient with severe anemia has normal MCV and normal RDW. Hemoglobin is low but RBC count normal.**

**Diagnosis:** Dilutional/acute blood loss anemia

**Mechanism:** RBCs normal size; loss due to hemorrhage

---



**16. A baby born to a diabetic mother shows oxygen saturation drop despite normal PaO<sub>2</sub>. Hb electrophoresis shows high HbF.**

**Diagnosis:** High fetal hemoglobin level

**Mechanism:** HbF has high O<sub>2</sub> affinity ? less O<sub>2</sub> released to tissues

---

**17. A patient has dyspnea and confusion after taking dapsone. Blood is chocolate-brown.**

**Diagnosis:** Methemoglobinemia

**Mechanism:** Oxidation of Fe<sup>2+</sup> ? Fe<sup>3+</sup>

**Best test:** Co-oximetry

---

**18. A young man with G6PD deficiency develops severe jaundice after malaria treatment.**

**Diagnosis:** Hemolytic anemia

**Mechanism:** Hb breakdown ? ? unconjugated bilirubin

---

**19. A child from NE India presents with mild anemia and target cells on smear. Hb electrophoresis shows HbE.**

**Diagnosis:** HbE disease

**Mechanism:** ?26 Glu ? Lys mutation

**Prevalent in:** Assam, Bengal, Thailand

---

**20. A patient has cyanosis, but PaO<sub>2</sub> is normal and pulse oximetry shows 85–88% plateau.**

**Diagnosis:** Methemoglobinemia

**Clue:** Saturation plateau at 85% is diagnostic

**? VIVA VOCE — Hemoglobin (Whole Chapter)**

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**1. What is the basic structure of hemoglobin?**

A tetramer of **two  $\alpha$  and two  $\beta$  chains**, each containing a heme group with  $\text{Fe}^{2+}$ .

---

**2. Why must iron be in the  $\text{Fe}^{2+}$  state?**

Only  $\text{Fe}^{2+}$  can bind oxygen;  $\text{Fe}^{3+}$  cannot.

---

**3. What bonds hold  $\text{O}_2$  in hemoglobin?**

Reversible coordination bond between  **$\text{O}_2$  and  $\text{Fe}^{2+}$**  in heme.

---

**4. What is the T-state of hemoglobin?**

Tense state ? **low oxygen affinity**.

---

**5. What is the R-state?**

Relaxed state ? **high oxygen affinity**.

---

**6. What causes the sigmoid shape of the  $\text{O}_2$  dissociation curve?**

**Cooperative binding** of oxygen.

---

**7. What is  $P_{50}$ ?**

$P_{\text{O}_2}$  at which Hb is **50% saturated**; normal ~26 mmHg.

---

**8. What does an increased  $P_{50}$  indicate?**

Decreased oxygen affinity (right shift).

---

**9. What shifts the  $\text{O}_2$  curve to the right?**

?  $\text{CO}$ ?, ?  $\text{H}^+$ ?, ? Temperature, ? 2,3-BPG.

---

### 10. What is the Bohr effect?

H<sup>+</sup> and CO<sub>2</sub> decrease Hb's O<sub>2</sub> affinity ? O<sub>2</sub> release in tissues.

---

### 11. What is the Haldane effect?

Oxygenated blood carries less CO<sub>2</sub>; deoxygenated blood carries more.

---

### 12. What is the role of 2,3-BPG?

Binds  $\beta$ -chains ? stabilizes T-state ? **reduces O<sub>2</sub> affinity**.

---

### 13. Why does HbF have higher O<sub>2</sub> affinity than HbA?

HbF (???) binds 2,3-BPG weakly ? O<sub>2</sub> affinity rises ? left shift.

---

### 14. What is the Rapoport–Luebering shunt?

Pathway in RBCs producing **2,3-BPG**.

---

### 15. What is carbaminohemoglobin?

CO<sub>2</sub> bound to terminal **amino groups** of globin chains.

---

### 16. What is isohydric transport?

Transport of CO<sub>2</sub> as **HCO<sub>3</sub><sup>-</sup>** while H<sup>+</sup> is buffered by Hb.

---

### 17. What is the chloride shift?

Exchange of **HCO<sub>3</sub><sup>-</sup>** and **Cl<sup>-</sup>** across RBC membrane for neutrality.

---

### 18. What is HbF useful for clinically?

Protects against sickling ? increased by **hydroxyurea** in sickle cell disease.

---

**19. Name hemoglobin derivatives.**

Oxy-Hb, Deoxy-Hb, **Carboxy-Hb**, **Met-Hb**, Sulf-Hb, Carbamino-Hb.

---

**20. What is carboxyhemoglobin?**

Hb combined with **carbon monoxide**.

---

**21. Why is CO dangerous?**

CO binds Hb **200–250x** stronger than O<sub>2</sub>? ? severe tissue hypoxia.

---

**22. What is the treatment of CO poisoning?**

**100% oxygen** or hyperbaric oxygen.

---

**23. What is methemoglobin?**

Hemoglobin with iron in **Fe<sup>3+</sup>** state ? cannot bind oxygen.

---

**24. What causes methemoglobinemia?**

Nitrates, nitrites, benzocaine, dapsone, aniline dyes.

---

**25. What color is blood in methemoglobinemia?**

**Chocolate-brown**.

---

**26. Treatment of methemoglobinemia?**

**Methylene blue**.

---

**27. What is the mutation in sickle cell disease?**

?6 Glutamic acid ? **Valine**.

---

**28. Why do RBCs sickle in HbS disease?**

HbS polymerizes in **low O<sub>2</sub>**, forming rigid fibers.

---

**29. What protects infants with sickle cell disease early in life?**

High levels of **HbF**.

---

**30. What is Howell–Jolly body?**

Nuclear remnants seen after **autosplenectomy** in sickle cell.

---

**31. What is the defect in thalassemias?**

Reduced **synthesis** of  $\alpha$ - or  $\beta$ -globin chains.

---

**32. What is elevated in  $\alpha$ -thalassemia minor?**

**HbA<sub>2</sub>** (>3.5%).

---

**33. What is HbH?**

$\beta\delta$  tetramers seen in  **$\alpha$ -thalassemia (3 gene deletion)**.

---

**34. What forms in complete  $\alpha$ -gene deletion (4 genes)?**

Hb Bart's ( $\gamma\delta$ ) causes **hydrops fetalis**.

---

**35. Why is HbF increased in  $\alpha$ -thalassemia major?**

Compensation due to absent  $\alpha$ -chains.

---

**36. What differentiates myoglobin from hemoglobin?**

Myoglobin is **monomeric**, binds one O<sub>2</sub>, and has hyperbolic curve.

---

**37. What is myoglobinuria?**

Myoglobin in urine after muscle damage (rhabdomyolysis).

---

**38. What type of anemia is caused by thalassemia?**

**Microcytic hypochromic anemia.**

---

**39. Why is stored blood poor at O<sub>2</sub> delivery?**

Stored RBCs have **low 2,3-BPG** ? left shift.

---

**40. Which form of Hb cannot bind oxygen?**

**Methemoglobin (Fe<sup>3+</sup>).**