Erythropoiesis requirements Part II
Pathophysiology of Anemia
2nd week Lab tests Theory

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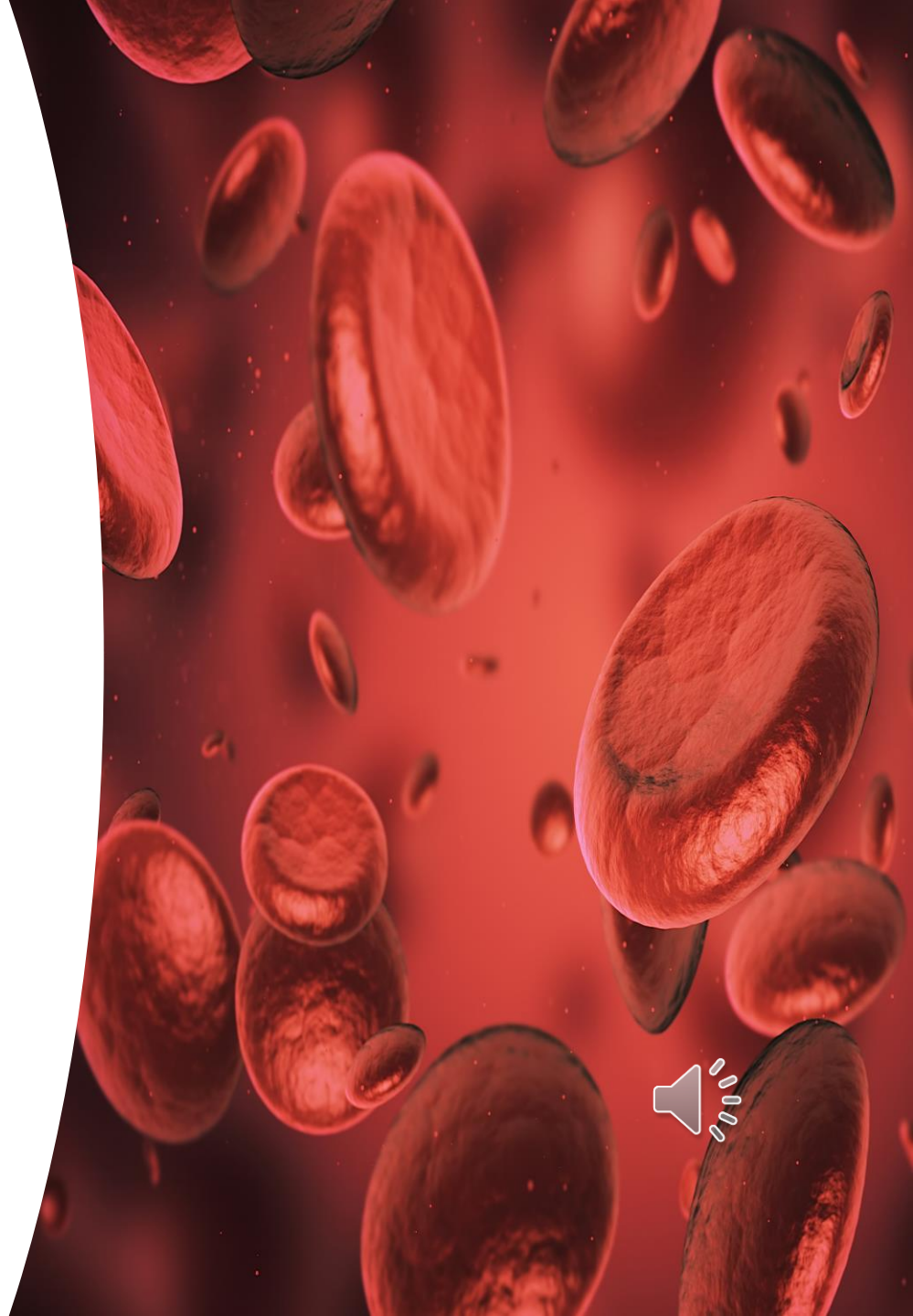


Clinical Perspective

Anemias

By definition: Deficiency of Hemoglobin

- **Blood loss (acute, chronic)**
- **After hemorrhage…**
  - **Fluid volume restored in 1 – 3 days**
  - **RBC concentration restored in 3-6 weeks**
- **Chronic blood loss can lead to iron deficiency, with hypochromic, microcytic anemia.**

Clinical Perspective

Aplastic Anemia

- **Bone marrow failure caused by…**
  - **Radiation**
  - **Chemotherapy**
  - **Chemical toxins**
  - **Auto-immune**
  - ***Idiopathic***

- **Supported by transfusions or treated by bone marrow transplantation**

Clinical Perspective

Megaloblastic Anemia

- **Deficiency of Vitamin B_{12} and / or Folic Acid**
  - **Pernicious anemia**
  - **Dietary deficiency**
  - **Malabsorption**
- **Impairs DNA replication, causing maturation failure**
- **Formation of large, fragile cells with bizarre shapes, which rupture easily, potentially causing profound anemia**

Vitamin B_{12} and Folic Acid

- **Rapid, large-scale cellular proliferation requires optimal nutrition**
- **Cell proliferation requires DNA replication**
- **Vitamin B_{12} and folate both are needed to make thymidine triphosphate (thus, DNA)**
- **Abnormal DNA replication causes failure of nuclear maturation and cell division…**

➡ ***maturation failure*** ➡ ***large, irregular, fragile "macrocytes"***

Clinical Perspective

Pernicious Anemia

- Failure to absorb vitamin B_{12}
- Atrophic gastric mucosa…
  - Failure to produce *intrinsic factor*
- Intrinsic factor binds to vitamin B_{12}
  - Protects it from digestion
  - Binds to receptors in the ileum
  - Mediates transport by pinocytosis
- Vitamin B_{12} - stored in liver, released as needed
- Usual stores: 1 – 3 mg Daily needs: 1 – 3 µg
- Thus normal stores are adequate for 3 – 4 years

Clinical Perspective

Folic Acid Deficiency

- **Folic acid is present in green vegetables, some fruits, and meats**
- **Destroyed during cooking**
- **Subject to dietary deficiencies**
- **May also be deficient in cases of intestinal malabsorption**
- **Maturation failure may reflect combined B_{12} and folate deficiency**

Clinical Perspective

Hemolytic Anemia

- **Hereditary conditions causing fragility**
  - **Hereditary spherocytosis**
  - **Sickle cell anemia**

- **Immune-mediated destruction**
  - **Erythroblastosis fetalis**

Clinical Perspective

Circulatory Effects of Anemia

- **Anemia**
  - **Decreased viscosity**
  - **Decreased O_2 - carrying capacity**

➡ **Increased cardiac output**

- **Markedly decreased exercise capacity**

Clinical Perspective

Polycythemia

Secondary (RBC ⬆ ~30%; 6-7 million/mm^3)

- - Chronic hypoxemia (heart or lung disease)
- - *Physiologic polycythemia*
  - - Living at 14 - 17,000 feet
  - - Markedly enhanced exercise capacity at altitude

Polycythemia Vera

- Clonal abnormality causing excessive proliferation
- Usually all lineages
- 7- 8 million RBCs / mm^3; Hematocrit 60-70%
- Blood volume increased almost two-fold
- Hyperviscosity, up to 3-fold normal (10 x water)

Clinical Perspective

Polycythemia & Circulation

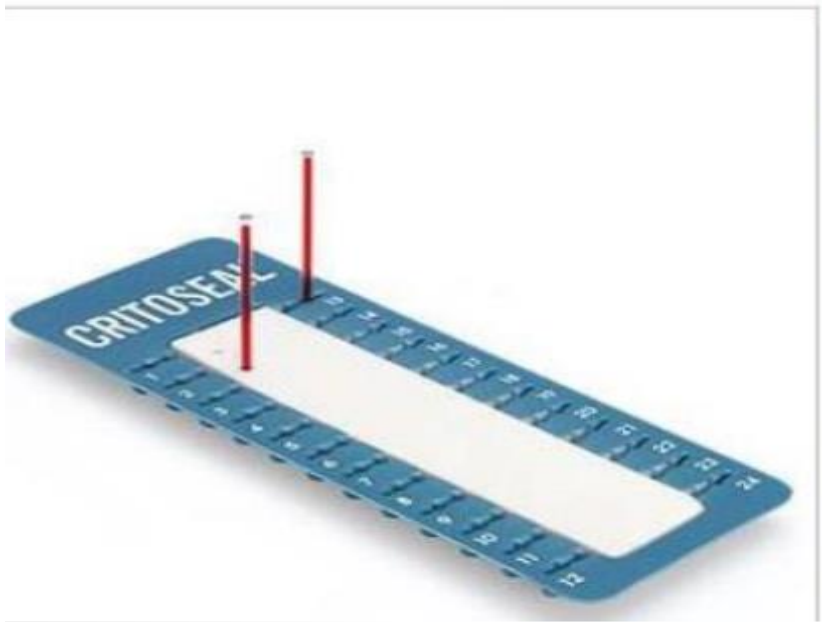
- Increased viscosity decreases venous return
- Increased blood volume increases venous return
- 2/3 normotensive, 1/3 hypertensive
- The subpapillary venous plexus under the skin becomes engorged with slow-moving, de-saturated blood, producing a ruddy complexion with a bluish tint to the skin

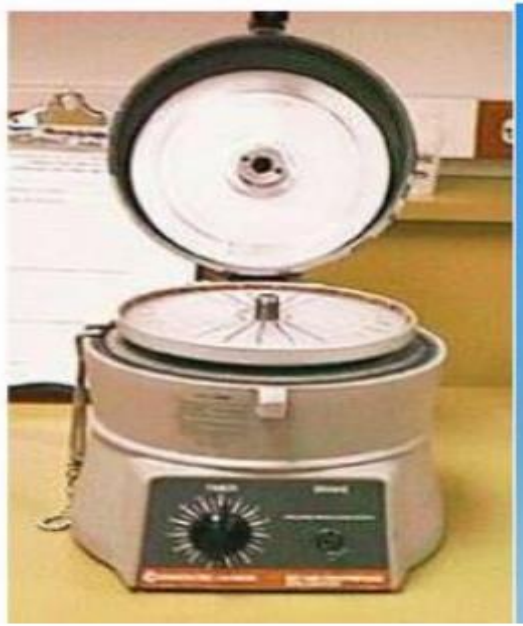
LAB TESTS

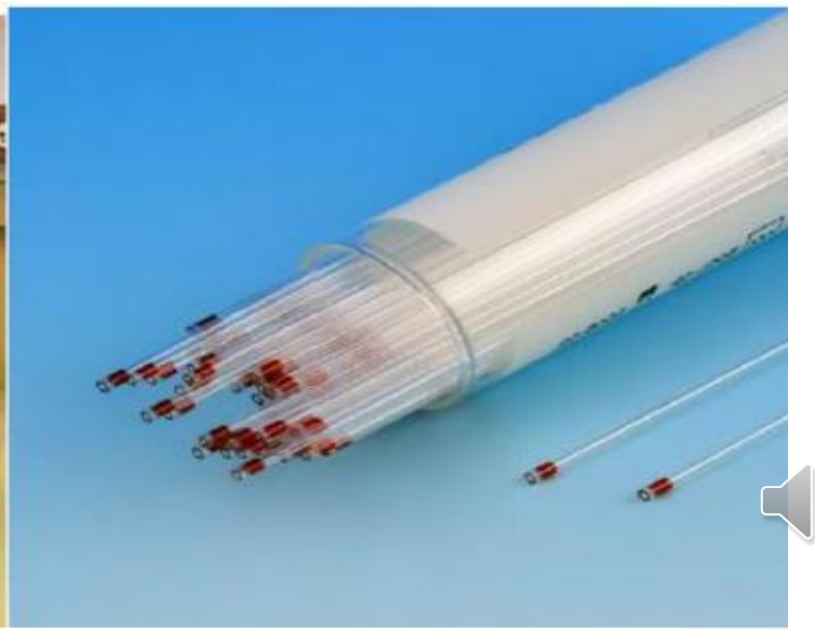
- Packed Red Blood Cell Volume PCV
- Erythrocytes Sedimentation Rate ESR
- Red Blood Cell Osmotic Fragility Test

Packed Cell Volume (PCV)

- PCV is the ratio of the volume of packed red cells to the total blood volume.
  - Adult males: 40–54% (avg = 47%).
  - Adult females: 38–46% (avg = 42%)
- It decreases in cases of anemia and increases in polycythemia and dehydration.







Erythrocyte Sedimentation Rate (ESR)

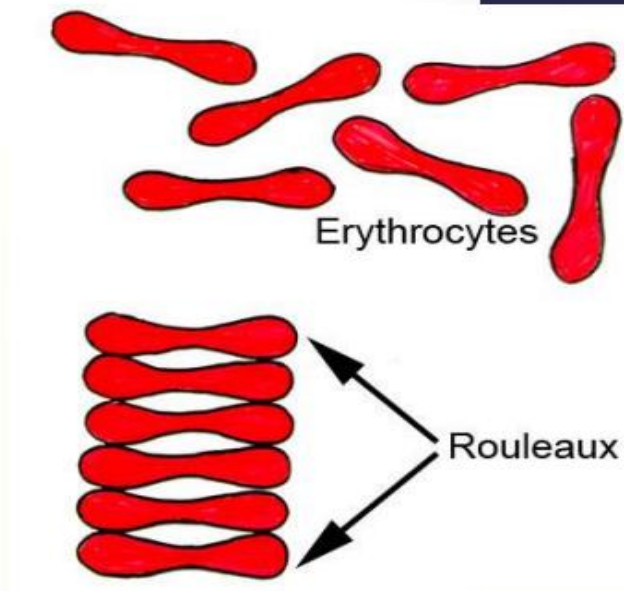
- The rate at which red blood cells settle out when anticoagulated whole blood is allowed to stand for a period of one hour.

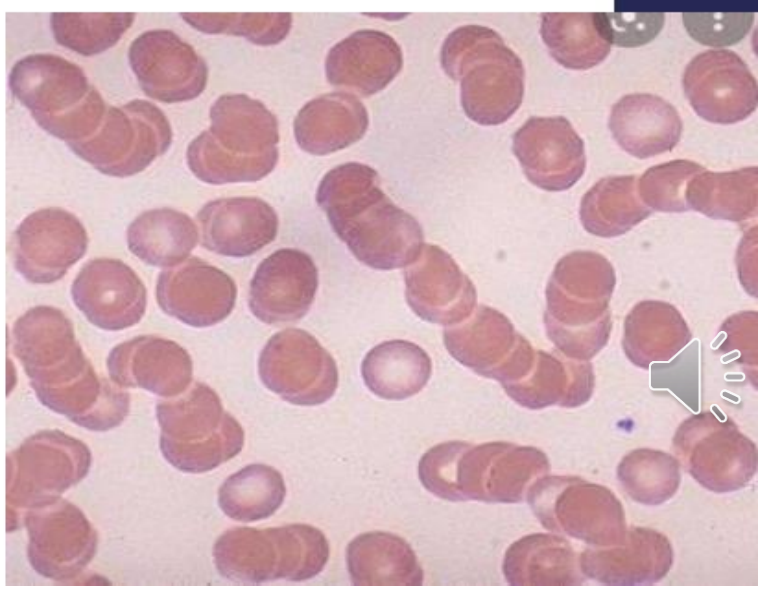
- The ESR is a simple, sensitive but **non-specific** screening test that indirectly measures the presence of inflammation in the body.

- It's increase reflects the tendency of red blood cells to settle more rapidly in the presence of inflammatory conditions, usually because of increases in plasma fibrinogen, immunoglobulins, and other acute-phase reaction proteins.
- Changes in red cell shape or numbers may also affect the ESR.

RBCs sedimentation

- The RBCs sediment because their density is greater than that of plasma. The sedimentation increases if stacking of RBCs (rouleaux formation) happens.
  - Rouleaux formation is possible because of the discoid shape of RBCs
- Normally, RBCs have negative charges on the outside of the cells, which cause them to repel each other and decreases or prevents rouleaux formation.
- Many plasma proteins have positive charges and can neutralize the negative charges of the RBCs, which allows for the formation of the rouleaux.
- Therefore, an increase in plasma proteins (present in inflammatory conditions) will increase the rouleaux formations, which settle more readily than single red blood cells leading to increased ESR during inflammation





- # Normal ESR values
  - Adult males < 15mm/hr
  - Adult females < 20mm/hr

- High ESR
  - Inflammation
  - Anemia
  - Old age
  - Pregnancy
  - Technical factors: tilted ESR tube, high room temperature.

- **Some interferences which decrease ESR:**
- Abnormally shaped RBC (sickle cells and spherocytosis)
- Polycythemia
- Technical factors: low room temperature, delay in test performance (>2 hours), clotted blood sample

Osmotic fragility

- When RBCs reside in an isotonic medium, the intracellular and extracellular fluids are in osmotic equilibrium across the cell membrane, and there is no net influx or efflux of water.

- When RBCs reside in a hypertonic media , a net efflux of water occurs so the cells lose their normal biconcave shape, undergoing collapse.

- When RBCs reside in a hypotonic medium, a net influx of water occurs so the cells swell and the integrity of their membranes is disrupted resulting in **hemolysis**

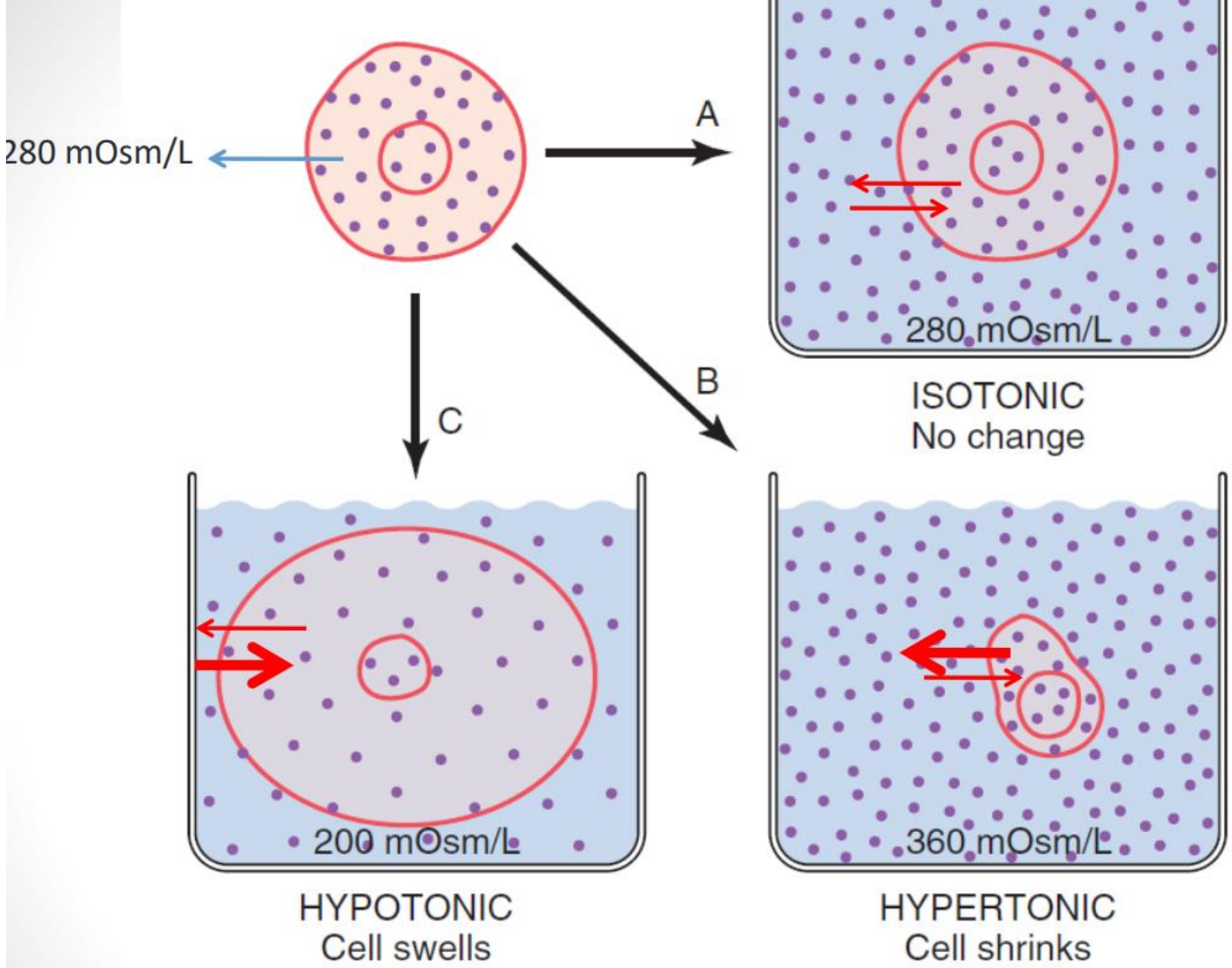


Figure 25-5. Effects of isotonic (*A*), hypertonic (*B*), and hypotonic (*C*) solutions on cell volume.

Osmotic fragility test

- A test designed to measures red blood cell's resistance to hemolysis when exposed to a series of increasingly dilute saline solutions.

- The susceptibility of RBCs to hemolysis is determined by:
  - **Surface area to volume ratio.**
  - Cell membrane composition and integrity

- This test is mainly used to diagnose hereditary spherocytosis.

Osmotic Fragility Test

- From 0.7% to 0.5% there is no hemolysis.
- At the concentration of 0.48% hemolysis starts and the solution becomes red in color, but there are some settled RBCs in the tube.
- At the concentration of 0.36%, the solution is bright red and there are no settled RBCs (complete hemolysis).
- With spherocytosis hemolysis starts at the concentration of 0.68% which means RBCs can't resist hemolysis as they normally do (they are more fragile)

RBC Osmotic Fragility

- Increased red cell fragility (increased susceptibility to hemolysis) is seen in the following conditions:
  - Hereditary spherocytosis
  - Autoimmune hemolytic anemia
  - Toxic chemicals, poisons, infections, and some drugs.
  - Severe burns.

✓ These cells have a low surface area: volume ratio

- Decreased red cell fragility (increased resistance to hemolysis) is seen with the following conditions:
  - Thalassemia.
  - Iron deficiency anemia.

✓ These cells have a high surface area: volume ratio