بسم الله الرحمن الرحيم

Physiology

﴿ وَقُل رَّبِّ أَدْخِلْنِي مُدْخَلَ صِدْقٍ وَأَخْرِجْنِي مُخْرَجَ صِدْقٍ وَاجْعَل لِّي مِن لَّدُنكَ سُلْطَانًا نَّصِيرًا ﴾

ربنا آتنا من لدنك رحمة وهيئ لنا من أمرنا رشدًا

MID | Lecture 4

Erythropoiesis requirements (Pt.2) & Anemia, Polycythemia and Lab Tests

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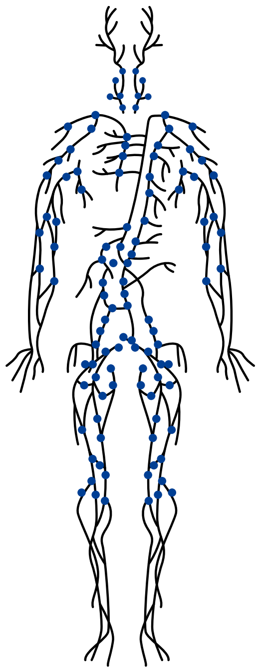

Erythropoiesis requirements Part II Pathophysiology of Anemia 2nd week Lab tests Theory

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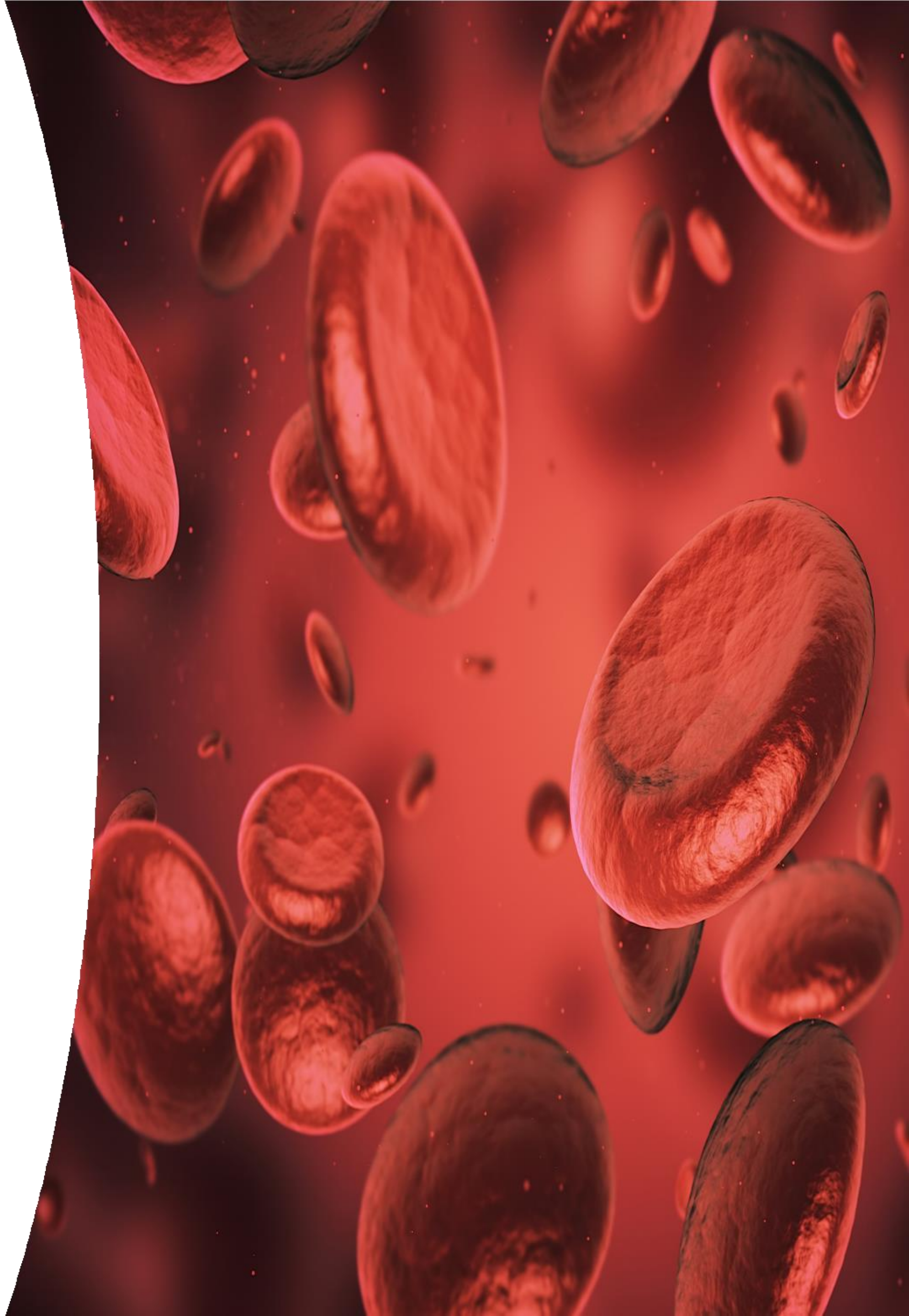

Clinical Perspective

Anemias

(clinical application on erythropoiesis)

By definition: Deficiency of Hemoglobin (it can be due to: less number of RBCs **or** less hemoglobin in RBCs)

- Anemia can be due to **Blood loss (acute, chronic).**

- **After hemorrhage**, there are feedback mechanisms to restore blood volume as well as RBCs number:

- Fluid volume restored in 1 – 3 days, to restore blood volume; water is added to ECF with the arterial BP regulatory mechanisms

- RBC concentration restored in 3-6 weeks, erythropoietin is released 24h after hemorrhage, thus the first increase in new RBC production will be after 5 days, however restoring to normal RBCs concentration will take 3-6 weeks -in average 4 weeks- .

Anemias

- **Chronic blood loss can lead to iron deficiency with hypochromic, microcytic anemia** due to continuous increase in RBCs production that needs iron for hemoglobin (the absorption of iron from the GIT will not be enough), as a result we will have RBCs with less hemoglobin leading to hypochromic, microcytic anemia (both are characteristics of iron deficiency).

Clinical Perspective

Aplastic Anemia

(another type of anemia)

- Bone marrow aplasia means that bone marrow fails to produce blood cells
- **Bone marrow failure caused by…**
  - **Radiation** high dose of radiation sometimes in cancer therapy
  - **Chemotherapy** might lead to destruction of hematopoietic stem cells which may cause anemia in few weeks.
  - **Chemical toxins** or drugs such as high doses of toxins or insecticides
  - **Auto-immune:** production of Ig antibodies for the bone marrow stem cells or RBCs; e.g., lupus erythromatosis.
  - ***Idiopathic*** (unknown cause)

- Patients of aplastic anemia are **Supported by transfusions or treated by bone marrow transplantation** (transplantation of new stem cells)

if not treated it might cause death

Clinical Perspective

Megaloblastic Anemia

- Results from **Deficiency of Vitamin B_{12} and / or Folic Acid**, these deficiencies can result from:
  - **Pernicious anemia**
  - **Dietary deficiency**
  - **Malabsorption**

- **Impairs DNA replication** in proliferating hematopoietic cells, **causing maturation failure** due to the deficiency of Vitamin B12 and / or Folic Acid

- **Formation of large, fragile cells with bizarre shapes** (abnormal & odd shapes), **which rupture easily, potentially causing profound anemia**

Vitamin B_{12} and Folic Acid

- Rapid, large-scale cellular proliferation of hematopoietic stem cells in erythropoiesis requires optimal nutrition (B12, folic acid & iron)

- Cell proliferation requires DNA replication

- Vitamin B_{12} and folate both are needed to make thymidine triphosphate necessary for DNA (thus, DNA)

- Abnormal DNA replication due to these deficiencies causes failure of nuclear maturation and cell division…

$\longrightarrow$ maturation failure $\longrightarrow$ large, irregular, fragile "macrocytes"

Clinical Perspective

Pernicious Anemia

(may cause megaloblastic anemia)

- **It is due to Failure to absorb vitamin B_{12}**

- Because of **Atrophic gastric mucosa…** leads to
  - **Failure to produce *intrinsic factor*** which is important for absorbing vit B12

- **Intrinsic factor binds to vitamin B_{12}**
  - **Protects it from digestion** by digestive enzymes
  - **Binds to receptors in the ileum**, after vit B12 binds to intrinsic factor they both bind to receptors in the ileum which enhances vit B12 absorption
  - **Mediates transport by pinocytosis** which is how B12 is absorbed

- **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**, so pernicious anemia may not appear until 3 or 4 yrs.

Clinical Perspective

استغفر الله العظيم

Folic Acid Deficiency

(the 2nd cause of megaloblastic anemia)

- **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**
- Folic acid deficiency leads to **Maturation failure** of RBCs **may reflect combined B_{12} and folate deficiency** if there is abnormal intestinal absorption, eg: tropical sprue.

Clinical Perspective

Hemolytic Anemia

(another type of anemia)

- **Hereditary conditions causing fragility of RBCs, such as:**
  - **Hereditary spherocytosis**
  - **Sickle cell anemia**

- **Immune-mediated destruction, such as:**
  - **Erythroblastosis fetalis**: when there is incompatibility between the fetus who has (Rh+) blood type & the mother who has (Rh-) blood type and she has antibodies against Rh factor, fetus RBCs will be attacked which leads to hemolytic anemia

Clinical Perspective

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Circulatory Effects of Anemia

- **Anemia**
  - **Decreased viscosity**
  - **Decreased O_2 - carrying capacity**
  - As a result body tissues need more oxygen

➡ **Increased cardiac output** to provide more O2 (more load on heart, capillaries &local circulation. Precapillary sphincters will also dilate inducing more blood flow in the microcirculation which increases venous return thus increased cardiac output)

- **Markedly decreased exercise capacity**

normal daily physiological activities already increase cardiac output, if anemic patients increase physical activity (heavy exercise)--> O2 insufficiency--> higher load on the heart --> serious complications due to hypoxia (the heart is unable to work harder)

Clinical Perspective

Polycythemia

higher number of RBCs, there are 2 types:

It is a genetic form of the disease resulting in continuous proliferation in all blood cell types even when there is enough number of RBCs

Secondary to hypoxia in tissues (RBC↑~30%; 6-7 million/mm^3)

- Chronic hypoxemia due to (heart or lung disease)
- *Physiologic polycythemia*

- Living at 14 - 17,000 feet (high altitudes)

- Markedly enhanced exercise capacity at altitude

Hypoxia in tissue --> more erythropoietin stimulation, higher rate of RBC production --> higher number of RBCs (6-7 million/mm3) 30% more than normal

Polycythemia Vera

- Clonal abnormality causing excessive proliferation
- Usually all lineages (RBCs, WBCs, platelets)
- 7- 8 million RBCs / mm^3; Hematocrit 60-70%, instead of 45-50%
- Blood volume increased almost two-fold
- Hyperviscosity, up to 3-fold than normal which is (10 x water)

-Hyperviscosity increases the resistance and impedes blood flow especially in the capillaries.

Clinical Perspective

Polycythemia & Circulation

- Increased viscosity decreases venous return
- Increased blood volume increases venous return

They accompany each other and cardiac output will be found to be nearly normal.

- 2/3 normotensive, 1/3 hypertensive

maybe due to failures in arterial blood pressure regulatory mechanisms to correct the increase in the resistance.

- 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

سبحان الله وبحمده عدد خلقه ورضا
نفسه وزنة عرشه ومداد كلماته

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%)

-How to measure PCV?
Withdraw blood, place it in a tube, centrifuge it, then measure the volume of the red **bottom layer** and compare it to the total blood volume.

- It decreases in cases of anemia and increases in polycythemia and dehydration.
- PCV is also called hematocrit

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 is **non-specific** as it indicates the presence of inflammation without indicating its reason or the site.

- 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,

  More inflammation = faster sedimentation

- Changes in red cell shape or numbers may also affect the ESR, e.g. in anemia.

Note: In this test, since the blood must sediment on its own and separate from the plasma, we do not centrifuge it. Also, an anticoagulant is added to prevent coagulation.

RBCs sedimentation

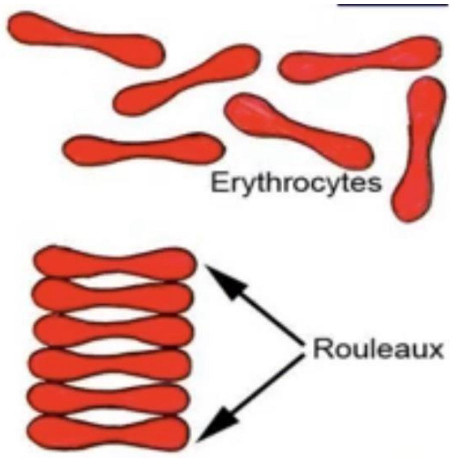
- The RBCs sediment even without centrifuging because their density is greater than that of plasma. The sedimentation increases if stacking of RBCs (rouleaux formation) happens.

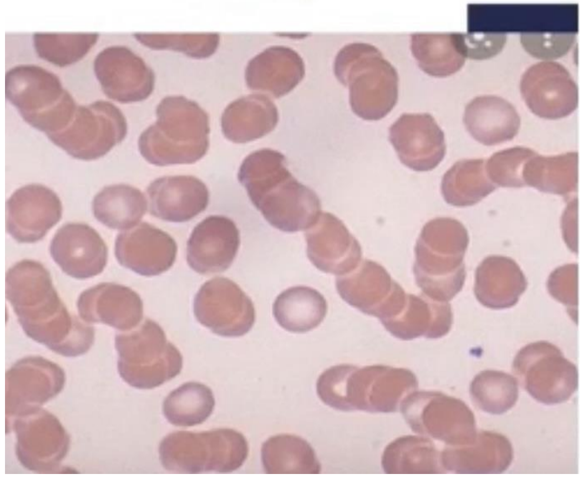
disk-like
- Rouleaux formation is possible because of the discoid shape of RBCs

- 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





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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.

High room temperature increases ESR because it **reduces plasma viscosity** and **enhances red cell kinetics**, allowing RBCs to settle faster. Low temperature has the opposite effect.

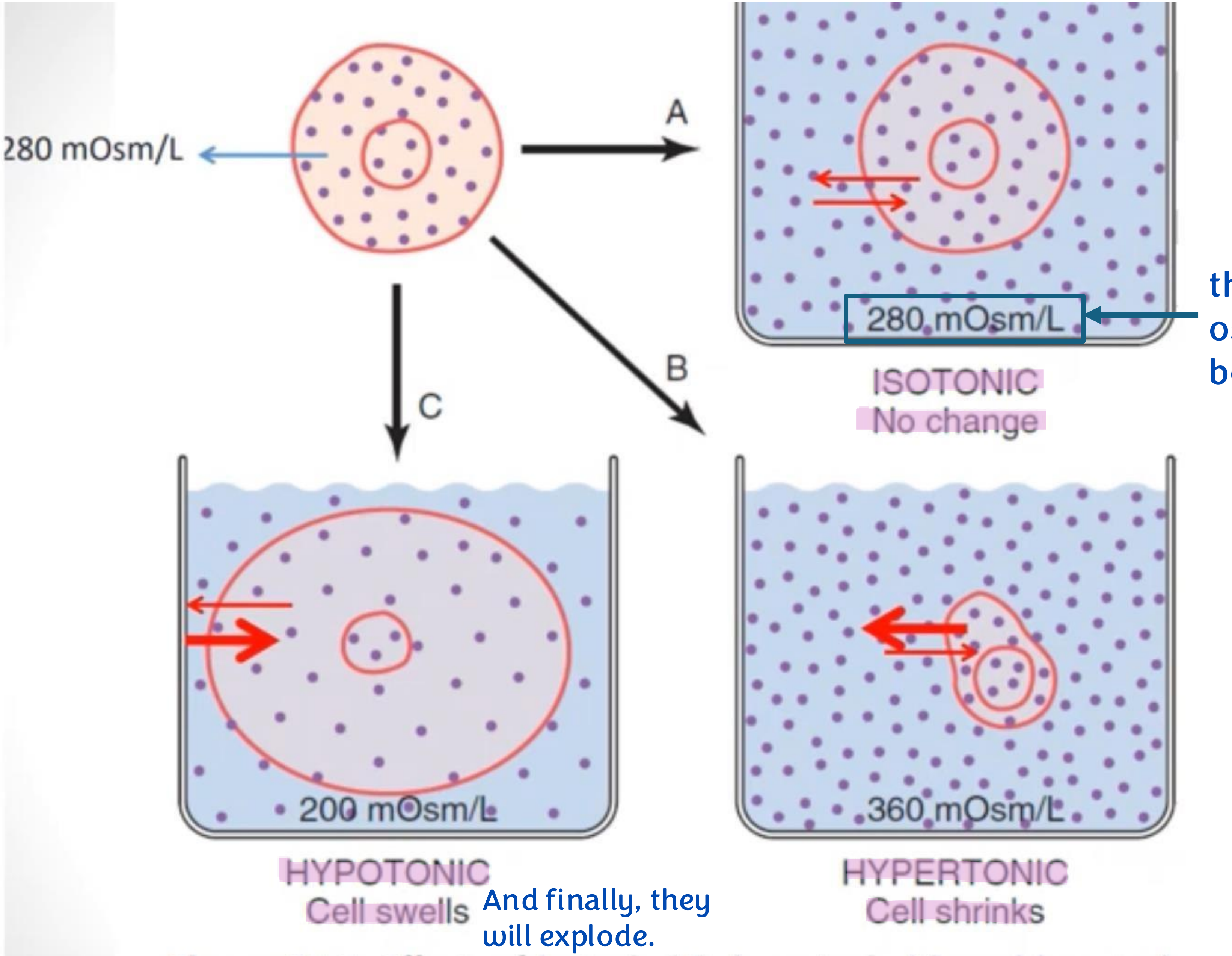
- **Some interferences which decrease ESR:**
- Abnormally shaped RBC (sickle cells and spherocytosis)
- Polycythemia
- Technical factors: low room temperature, delay in test performance (>2 hours), clotted blood sample

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 and they will shrink

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



the normal osmolarity of body fluids

And finally, they will explode.

Figure 25-5. Effects of isotonic (*A*), hypertonic (*B*), and hypotonic (*C*) solutio[redacted]

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:

Divided by

- **Surface area to volume ratio.**
- Cell membrane composition and integrity

- This test is mainly used to diagnose hereditary spherocytosis.

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Osmotic fragility test

Note: numbers indicates saline concentrations

- **Normally:**

➢ Form 0.7% to 0.5% there is no hemolysis

➢ At the concentration of 0.48% hemolysis starts, and the solution becomes red in color (Due to the explosion of **some** cells), but there are some settled RBCs in the tube.

➢ The concentration of 0.36% the solution is bright red and there are no settled RBCs (complete hemolysis)

- When does spherocytosis hemolysis at the concentration of 0.68% which means RBCs can't resist hemolysis as they normally do (They are more fragile)

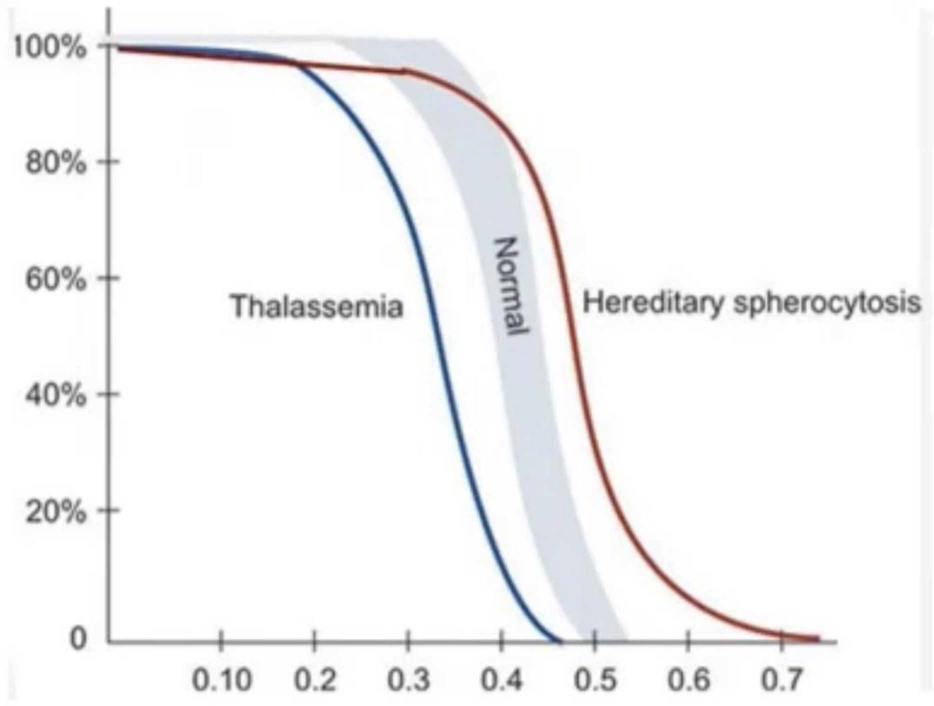
RBC Osmotic fragility

- 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 <u>low (surface area: volume) ratio</u>

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

✓ These cells have a <u>high (surface area: volume) ratio</u>



- In hereditary spherocytosis, the hemolysis starts in a less diluted solution (a solution with higher concentration).
- While in thalassemia, the hemolysis starts in a more diluted solution (a solution with less concentration).

-note the X axis-

Physiology Quiz 4

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For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			rearrangement
V1 → V2			