HLS

MODIFIED NO. 1

PHYSIOLOGY

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Introduction: Red Blood Cells, Anemia and Polycythemia

Color code

- Slides
- Doctor
- Additional info
- Important

Clinical Perspective

Anemias (Reduced Hgb in Blood)

By definition: Deficiency of Hemoglobin

Either less number of RBCs due to blood loss or less number of Hgb in RBCs

- **Blood loss (acute, chronic)**

- **After hemorrhage…**
  - **Fluid volume restored in 1 – 3 days**
  - **RBC concentration restored in 3-6 weeks**

Let's explain them in the next slide

- **Chronic blood loss can lead to iron deficiency, with hypochromic, microcytic anemia.**

the continuous increased RBC production, requires iron to build new hemoglobin, and the absorption of iron from the digestive tract will not be enough to meet the demand in cases of chronic blood loss. Leading to hypochromic microplasticity, which is the characteristic of iron deficiency.

Notes about previous slide:

feedback mechanisms to restore blood volume as well as the RBCs number.

- First, the arterial blood pressure regulation mechanism works to correct blood volume by adding more water to the extracellular fluid volume. This process restores the volume in 1-3 days
- After erythropoietin is released within 24 hours of the bleeding, new red blood cells begin to appear five days later however, it will take 3-6 weeks (4 in average) for the RBC concentration or number to return to normal.

Clinical Perspective

Aplastic Anemia

- **Bone marrow failure** ➡ **(Bone marrow aplasia means that bone marrow has failed in RBCs production)**
- **caused by…**
  - **Radiation**
  - **Chemotherapy.**
  - **Chemical toxins**
  - **Auto-immune**
  - ***Idiopathic***

Let's explain them in the next slide

- **Supported by transfusions or treated by bone marrow transplantation** transplanted stem cells

If not treated it could lead to death

Notes about previous slide:

Radiation: High dose of radiation sometimes in radiotherapy in cancer treatment
Chemotherapy: It can lead to hematopoietic stem cells (HSCs) destruction which leads to Anemia within few weeks. We know that HSCs divide very rapidly and this is the target of chemotherapy.
Chemical toxins: chemical toxins or drugs can lead to apalsia of bone marrow; like high dose of toxins or insecticides.
Auto-immune: production of immunoglobulins (antibodies against bone marrow stem cells or RBCs). For example : lupus erythematosus which is a disease in which body attacks its own healthy tissues including bone marrow leading to reduce its ability to produce blood cells it can leads to aplastic anemia
Idiopathic: It was found that half of the cases of aplastic anemia are due to unknown cause.

Clinical Perspective

Megaloblastic Anemia

Caused by

Deficiency of Vitamin B_{12} and / or Folic Acid:

Deficiency in these vitamins might result from:

- Pernicious anemia
- Dietary deficiency
- Malabsorption

What happens is that the DNA replication in the reproducing and proliferating hematopoietic cells will be abnormal because of the lack of these vitamins causing maturation failure resulting in abnormal and odd shapes.

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)**

Thyamidine triphosphate is necessary for DNA replication

- **Abnormal DNA replication** Due to deficiency in any of these vitamins **causes failure of nuclear maturation and cell division…**

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

With short lifespan

Clinical Perspective

Pernicious Anemia

Remember..! This condition causes megaloblastic 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**

Protect it from digestive enzymes

Vit.B_{12} bound to intrinsic factor bind to their receptor enhancing vit.B_{12} reabsorption

Pinocytosis results in vitamin B_{12} absorption

- **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**

Notes about previous slide:

*** pernicious anemia occur due to the failure of absorption of vitamin B12**, and that's because of atrophy in the gastric mucosa, which leads to a deficiency in the production of intrinsic factor, which is important for absorbing vitamin B12.

*** lack of intrinsic factor will lead to deficiency in vitamin B12, as well as megaloblastic anemia.**

*** Vitamin B12 is usually stored in the liver and released on demand.**

***The daily need is only 1-3 micrograms**, so if there is nutritional deficiency of vitamin B_{12} or malabsorption of vitamin B12, the stores, three milligrams, can be adequate for three to four years, so the pernicious anemia will not appear until maybe the stores are diminished after three or four years.

Clinical Perspective

Folic Acid Deficiency

Remember..! This condition causes megaloblastic anemia

- **Folic acid is present in green vegetables, some fruits, and meats**
- **Destroyed during cooking**
- **Subject to dietary deficiencies**

Since it is easily destroyed during cooking

- **May also be deficient in cases of intestinal malabsorption**

Like in sprue disease (celiac disease), which leads to folate and vitamin B_{12} deficiency

- **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**

This is another type of anemia !!
caused by
1- hereditary conditions
Like

2- Or it might result from immune mediated destruction

** **erythroblastosis fetalis** occur when there's incompatibility between fetus (with **Rh+** blood type) and his mother (with **Rh-** blood type) who has **antibodies against Rh factor** resulting in attacking fetus RBCs causing this hemolytic anemia !!

Clinical
Perspective

Circulatory Effects of Anemia

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

➡ Increased cardiac output

- **Markedly decreased exercise capacity**

Let's explain them in the next slide

Notes about previous slide:

- In anemia, the viscosity of blood is decreased which will increase the cardiac output and the cardiac flow.
- Also, the decreased oxygen-carrying capacity due to the dilution of blood, **[RBCs]** is very low, and the body tissues need more oxygen, so this will make the body increase its cardiac output to provide more oxygen.
- Further more, the capillaries and the local circulation, the pre-capillary sphincters will also dilate, inducing more blood flow in the microcirculation, which will increase venous return. All of that increase cardiac output.
- **Increase in cardiac output means more load on the heart !!**
- Based on the previous notes, anemic patients have their cardiac output high in order to do the normal and regular physiological activities So, If they increase the physical activity by doing heavy exercise, this will increase the load over the heart since more cardiac output is needed **And since the heart is already working harder from the beginning**, that will lead to insufficient oxygen. Oxygen will not be supplied to tissues, and that may cause serious complications due to hypoxia because the heart is not able to work harder.

Clinical Perspective

Polycythemia

This clinical condition results from higher number of RBCs

Secondary – (RBC ↑ ~30%; 6-7 million/mm3)

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

Results in hypoxia in tissues resulting in more erythropoietin and high RBC production rate

Living in high altitude

Polycythemia Vera

- **Clonal abnormality causing excessive proliferation**
- **Usually all lineages**
- **7- 8 million RBCs / mm³; Hematocrit 60-70%**
- **Blood volume increased almost two-fold**
- **Hyperviscosity, up to 3-fold normal (10 x water)**

- 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
- **It is actually associated with all lineage including WBCs and platelets**

- Hematocrit will become 60-70% instead of 45-50%
- Hyperviscosity (x3 than normal,x10 than water viscosity) increases the resistance as well as it impedes blood flow (in capillaries specifically)

Clinical Perspective

The effects of polycythemia on circulation

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**

They accompany each other

maybe due to failures in arterial blood pressure correction mechanisms, for correcting the increase of resistance

LAB TEST

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

Packed Cell Volume (PCV)

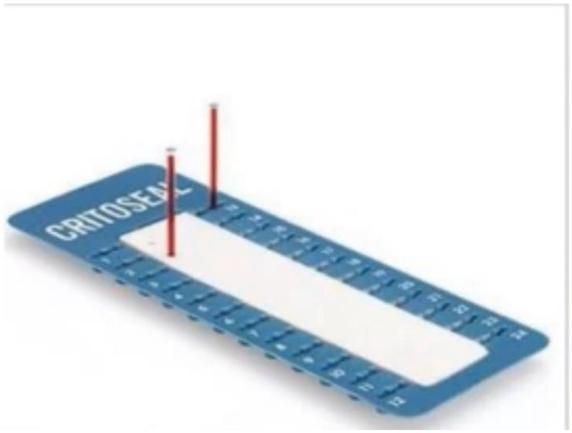
Its other name is Hematocrit

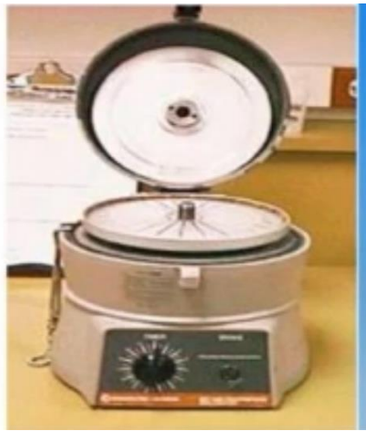
- PCV is the ratio of the volume of packed red cells to the total blood volume.
- Adult males: 40-54% (avg = 47%).
- Adult females: 38-46% (avg = 42%)

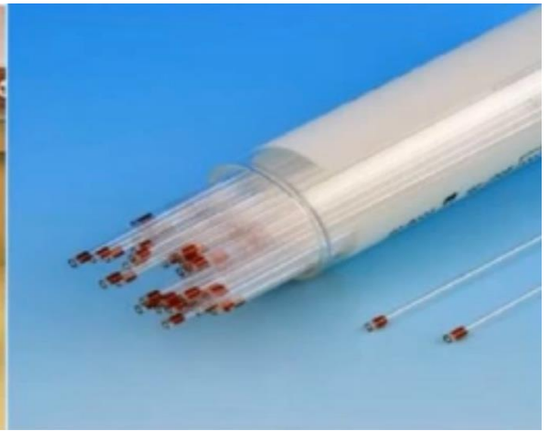
How to get it in short, we will need to draw the blood then centrifuge it, then measure the volume of the bottom layer (the red layer) and compare it, to the total blood volume.

- It decreases in cases of anemia and increases in polycythemia and dehydration.

CRITOSEN







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.

More inflammation = faster sedementaion

•Changes in red cell shape or numbers may also affect the ESR.

Like in anemia

Notes about the previous slide:

In this test due the fact that we will need the blood to sediment on its own and separate from the plasma, we WONT centrifuge the blood, and we will use anticoagulants to prevent the blood from coagulation.

And because it's just a non-specific screening test, it will just show us that there is an issue, but not the site or reason for it.

- You may say why fibrinogen increases and how it affects ESR? In inflammation, IL-6 will be released (remember immunology last year),which stimulate the liver to produce more fibrinogen. **But what its role?** as you will read in the next slide RBCs have negative charge, so there will be repulsion **And here comes the role of fibrinogen,** as many plasma proteins, fibrinogen has positive charge which will neutralize the negative charge **allowing rouleaux formation** , And in inflammation as we said fibrinogen will increase which means more neutralization and faster sedimentation **(higher ESR).**
- Extra notes about last point, **"Changes in red cell shape or numbers may also affect the ESR"** :

Doctor mentioned an example about the number: Anemia, in anemia there will be smaller number of RBCs which means less repulsion forces ,which means higher 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.

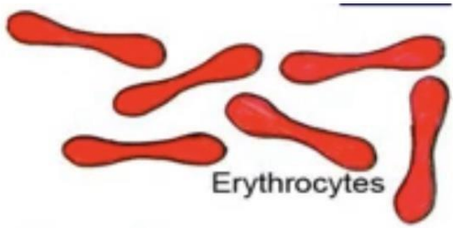
•Rouleaux formation is possible because of the discoid shape of RBCs

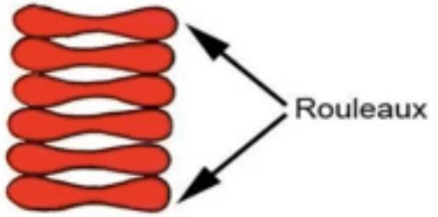
•Normally, RBCs have negative charges on the outside of the cells, which cause them to repel each other and decreases or prevents rouleaux formation.

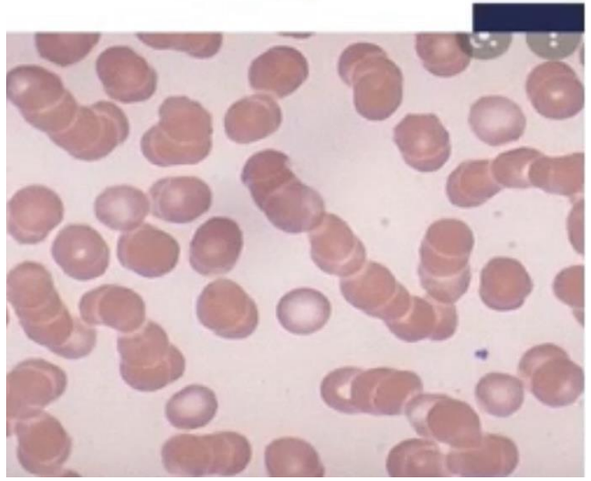
•Many plasma proteins have positive charges and can neutralize the negative charges of the RBCs, which allows for the formation of the rouleaux.

More proteins = more rouleaux formation

•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

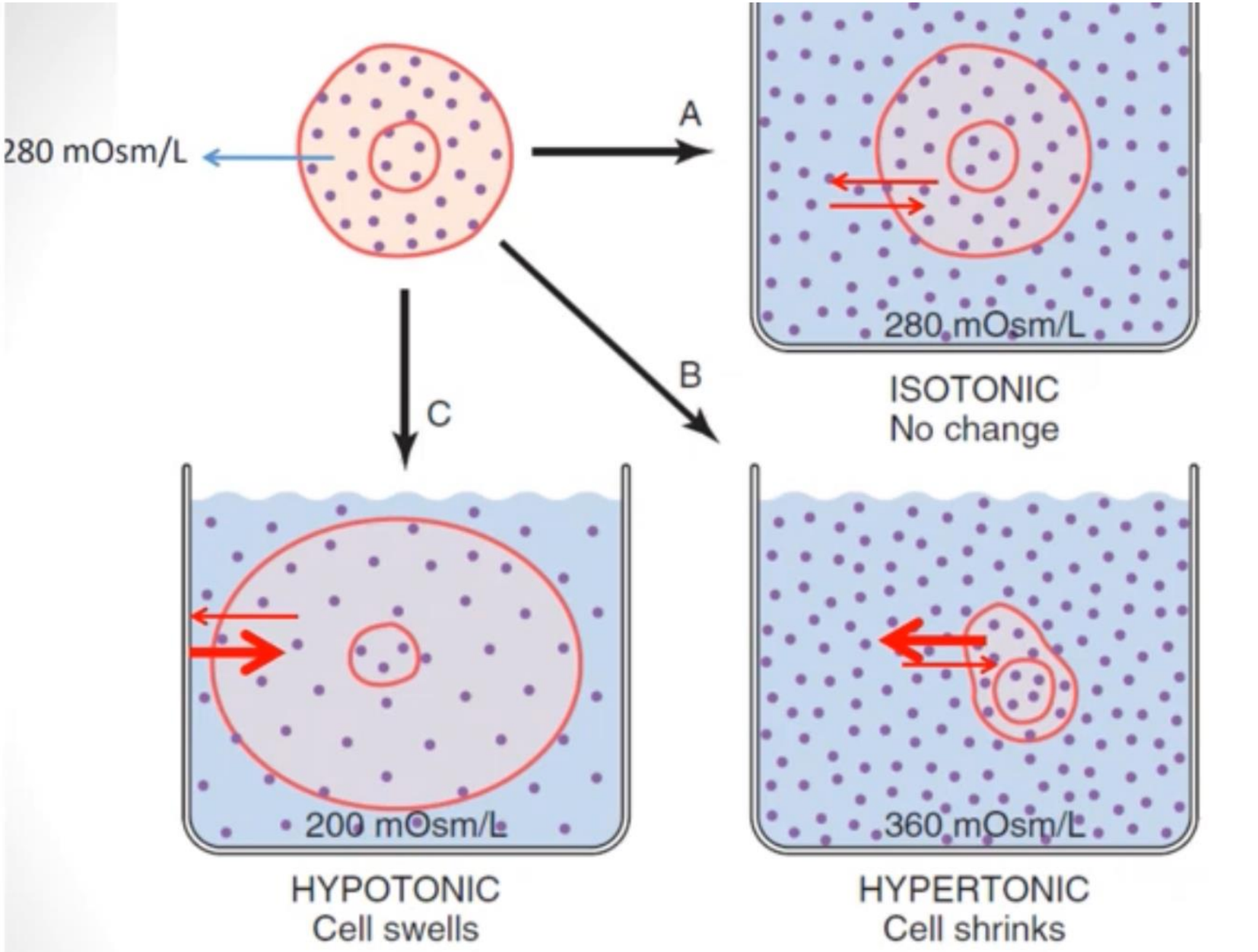


Figure 25-5. Effects of isotonic (*A*), hypertonic (*B*), and hypotonic (*C*) solutions on cell volume.

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

- 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, but there are some settled RBCs in the tube.

- The concentration of 0.38% 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>

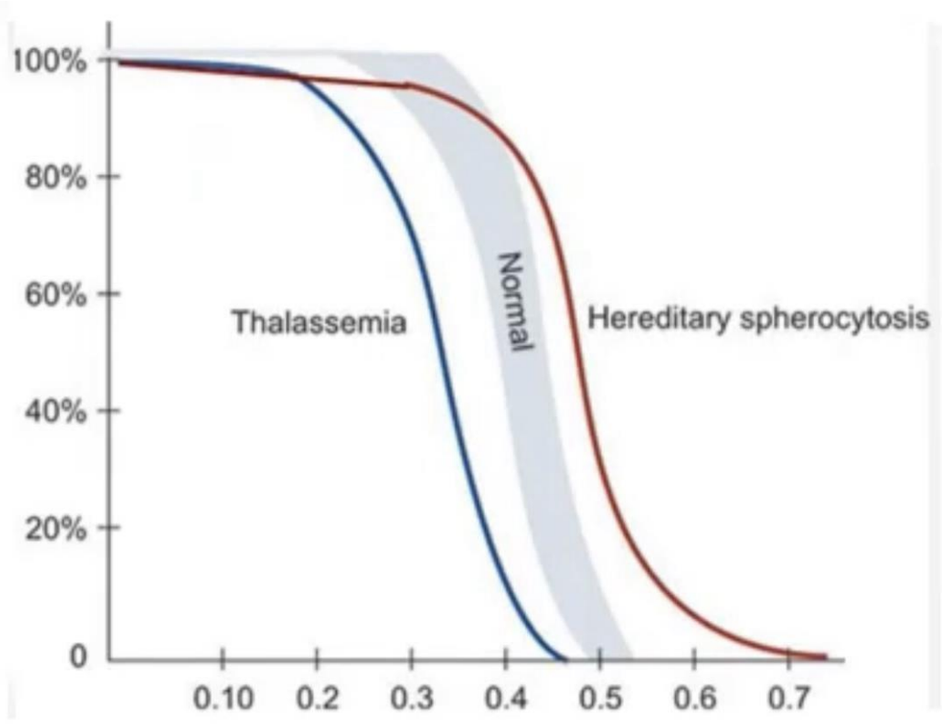
- Decreased red cell fragility (increased resistance to hemolysis) is seen with the following conditions:

➢ Thalassemia.
➢ Iron deficiency anemia.

High surface area: volume ratio

✓ These cells have a high surface area: volume ratio

In hereditary spherocytosis, the hemolysis starts in a less diluted solution (a solution with higher concentration – note the X axis)



While in thalassemia, the hemolysis starts in a more diluted solution (a solution with less concentration – note the X axis)

يقول الشافعي :

شَكَوتُ إلى وَكِيعٍ سوءَ حِفظي
فَأرشَدَني إلى تَركِ المَعاصي
وأخبرني بِأنَّ العلمَ نورٌ
ونورُ اللهِ لا يُهدى لِعاصي

Additional sources:

VERSIONS	SLIDE #	BEFORE CORRECTION		AFTER CORRECTION
V1→ V2	16 18 20 27	-		16--> for correcting the increase of resistance 18&20-->Extra notes were added 27-->High surface area: volume ratio
V2→V3				

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!