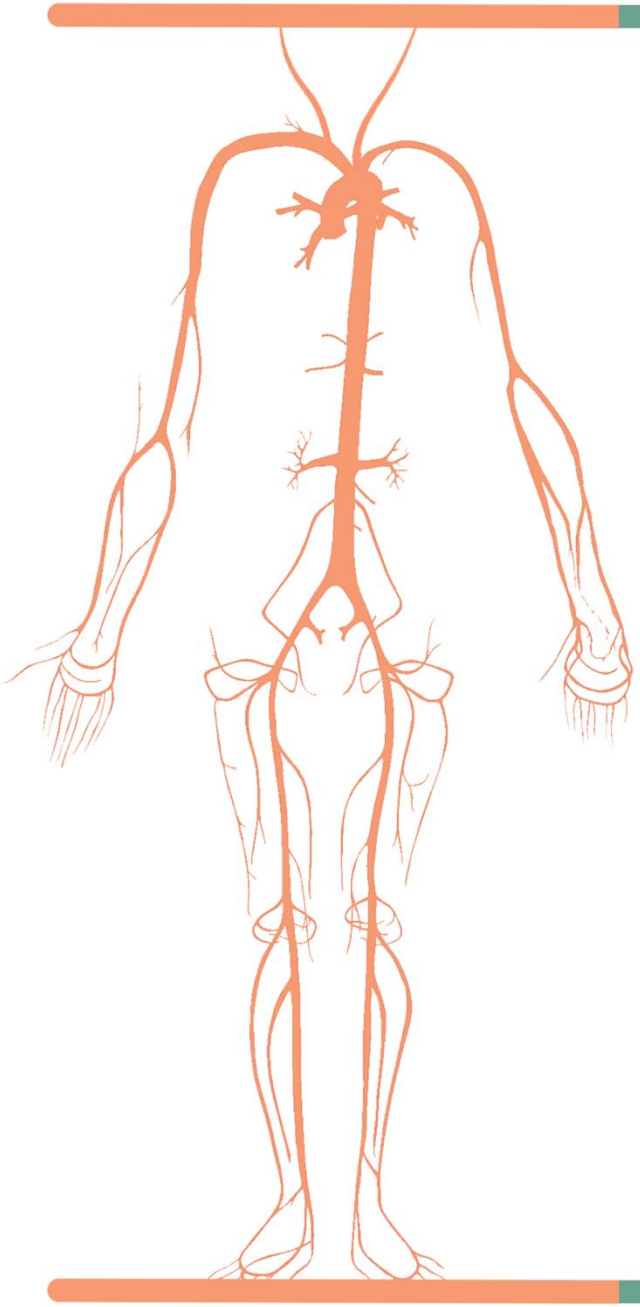
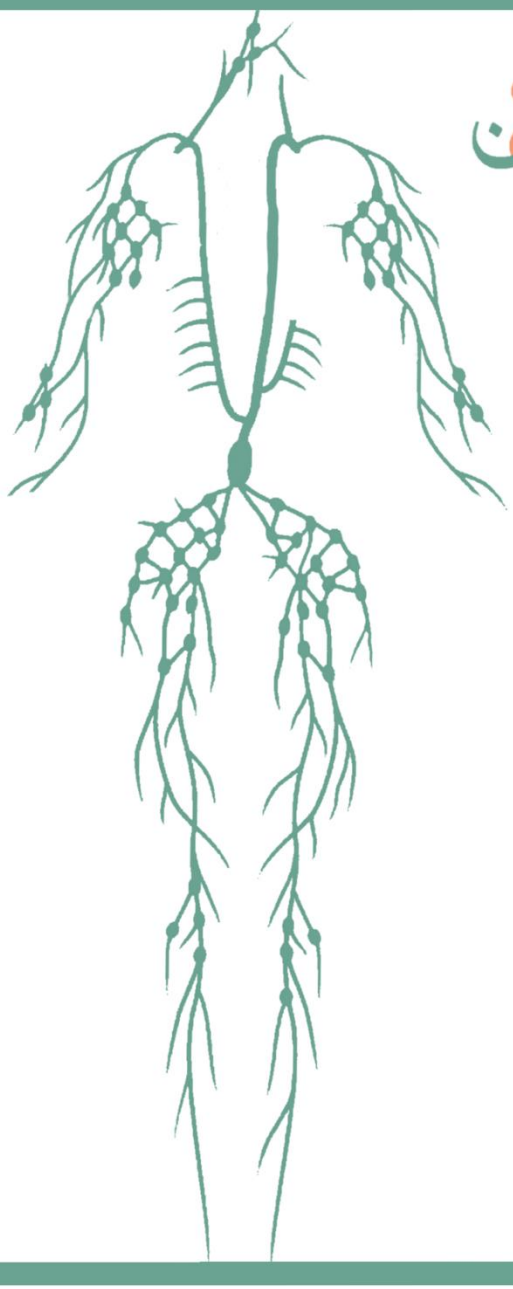
Pathology

HematoLymphatic





Title: Sheet 1 – Introduction to Anemia

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Let's first talk about RBC disorders in general...

We can classify RBCs disorders into two main types:

1- **Anemia:** the reduction in the function of RBCs and their mass
2- **Polycythemia:** the excess production of RBCs and the increase in their mass

Anemia is much more common than polycythemia. Most of us have certain degrees of anemia in her/his life.

In contrast, WBC disorders are mostly due to increase in the number of WBCs.

Definition of anemia:

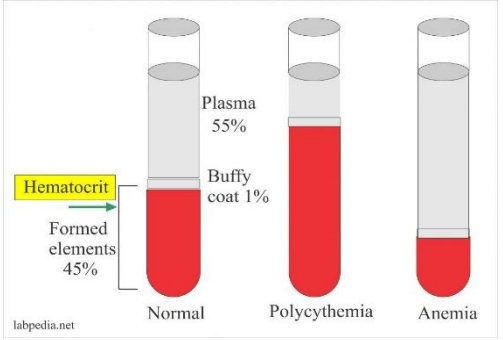
→ Reduction of oxygen carrying capacity of blood due to decrease in red blood cell **mass**. Notice that we said red blood cell mass and not red blood cell number **[why? Most of the time the number correlates with the mass that is when the number is decreased, the mass is decreased too, and when the number is increased, the mass is increased too. But that's NOT always true, sometimes the number of RBCs is normal, but the RBCs are empty, so the mass is much less, and the cells are not functioning well, and that's also is considered anemia!!]**

→ **anemia Leads to tissue hypoxia**. **[remember that ischemia also leads to tissue hypoxia, and it is different than anemia of course. In ischemia there is no delivery of blood to tissue leading to tissue hypoxia and infarction, so in ischemia the cause isn't related to the RBCs themselves.]**

→ now, how to diagnose anemia?

There are two ways to diagnose anemia: (numeric diagnosis) (the two ways are almost identical and it depends on what the clinicians prefer to use)

A) By measuring **Hemoglobin concentration (g/L):** these days, this measurement is automated, we just put the blood sample inside the device and wait for the results. If the Hemoglobin concentration is less than a certain number, it is considered anemia.
B) By calculating **Hematocrit (%):** it is the percentage of RBCs to the entire blood. it correlates with Hemoglobin concentration.
We calculate hematocrit by counting the RBCs multiplying them by their size (mean cell volume). If it less than a certain number, it is considered anemia.
→ It was called Packed Cell Volume (PCV), and it was a measured (not calculated) test, in which we put the blood into a tube and leave it for a certain period of time to let the RBCs precipitate and the plasma floats, then we measure the length of the RBCs in the tube and divide it on the total length of the blood in the tube multiplied by 100%.



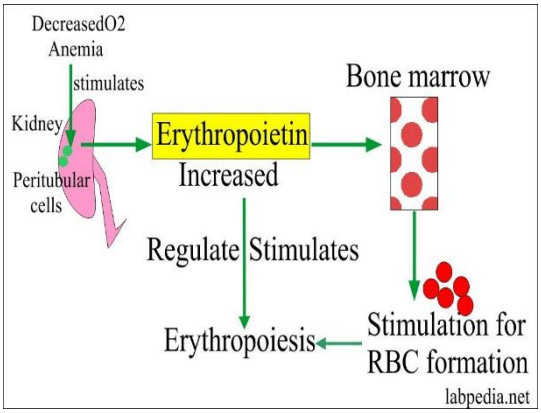
Anemia and erythropoietin:

Erythropoietin is a hormone secreted mainly from the kidneys (lesser amount from the liver) that activates the bone marrow to produce RBCs.

→ **Anemia triggers production of erythropoietin.**

when there is anemia and the mass of RBCs is decreased, erythropoietin should increase.

The increase in erythropoietin **causes compensatory erythroid hyperplasia in bone marrow (BM).** [erythroid cells will increase in number in the bone marrow in order to compensate for the reduction]



→ **In acute anemia, production** of RBCs **can increase by 5x or more in healthy people** due to the release of erythropoietin**.**

→ **while in severe cases,** erythropoietin **causes extramedullary hematopoiesis in secondary hematopoietic organs (spleen, liver and lymph nodes).** [in chronic / long standing anemia, there is persistent production of erythropoietin from the kidneys, this will activate other organs to produce RBCs. ***Extramedullary hematopoiesis means hematopoiesis from places other than bone marrow***]

➔ **Additional note: in fetal life, the production of RBCs is mainly from these organs then it shifts to bone marrow after birth.**

→ Exceptions: [there is anemia, but no erythropoietin is produced]

A) **Anemia of renal failure:** in renal failure, kidneys are no longer functional meaning that they don't produce erythropoietin.
B) **Anemia of chronic inflammation**

Classification of anemia according to etiology (cause)

- **Blood loss**
- **Diminished RBC production** — most common cause
  - Iron deficiency anemia (most common type of anemia), Pure red cell aplasia, Anemia of chronic inflammation, Myelophthisic anemia, Megaloblastic anemia, Myelodysplastic syndrome (neoplastic disease of the bone marrow results in anemia), Aplastic anemia, Anemia of renal failure, Anemia of hypothyroidism

  (**the common problem >> there is no enough production of RBCs in bone marrow.**
- **Increased destruction (hemolytic anemia)** normal production of RBCs, but they die early
  - The bone marrow is functioning normally, but the problem is in the RBCs

  A-Extrinsic factors (infection, antibody, mechanical) extrinsic =the problem is outside the RBCs)

  B- **Intrinsic RBC abnormalities**:
  1) Hereditary (membrane, enzyme, Hg abnormalities) **more common than acquired**
  2) Acquired (Paroxysmal nocturnal hematuria)

Classification of anemia according to morphology blood film

(this classification is used in clinical diagnosis , the previous one for education)

Size

Normocytic

Microcytic

Macrocytic

According to mean cell volume (MCV) which is expressed in **femtoliters**

Normal MCV is 80-100 femtoliters

If MCV is 65 femtoliters → microcytic anemia

Color

Normochromic: Normally there is a central pale area (30%) because of the biconcave shape

Hypochromic: If the pale area is larger that means, there isn't enough Hemoglobin

According to mean cell Hemoglobin.

If there is anemia but the RBCs have normal color that's called normochromic anemia

****Hyperchromic is equal to macrocytic but we don't use the word hyperchromic.**

Shape

Anisopoikelocytosis = variable shapes and sizes (spherocytes, sickle, schistocytes)

According to RBC distribution width ➔ if the RBCs have different sizes and shapes, the value will be large. If the RBCs are the same, the value will be smaller.

→ size and color go together. EXAMPLES:

1- **Hypochromic microcytic anemia** usually reflects impaired Hg synthesis. (due to impaired heme synthesis or globin synthesis like in thalassemia)

2- **Macrocytic anemia** reflects stem cell disease and maturation.

(26:00)

RBCs Indices: 

- ✓ Indices mean indications, and based on that "RBCs Indices" are blood tests that provide information about the hemoglobin content, size, mass and number of red blood cells.
- ✓ Can be directly measured or automatically calculated by specialized instruments in clinical laboratories. Previously, we used special slides which are divided into squares then by adding the patient's blood, the number of RBCs and WBCs in each square can be counted through some mathematics, but nowadays we use automated measures.
- ✓ There might be a slight variation between labs and geographic areas. The table below is taken from a certain lab. If we look at the measurements from different labs, we

	Units	Men	Women
Hemoglobin (Hb)	g/dL	13.2–16.7	11.9–15.0
Hematocrit (Hct)	%	38–48	35–44
Red cell count	$\times 10^6/\mu L$	4.2–5.6	3.8–5.0
Reticulocyte count	%	0.5–1.5	0.5–1.5
Mean cell volume (MCV)	fL	81–97	81–97
Mean cell Hb (MCH)	pg	28–34	28–34
Mean cell Hb concentration (MCHC)	g/dL	33–35	33–35
Red cell distribution width (RDW)		11.5–14.8	

*Reference ranges vary among laboratories. The reference ranges for the laboratory providing the result should always be used in interpreting a laboratory test.

might find different ranges. Also, people living at higher altitudes might have higher level of RBCs than other areas in the world [the PO2 Inside the lungs > than the environment so it's difficult for the lungs to get O2 efficiently >> So lower O2 in the blood >> stimulates the production of erythropoietin >> more blood cells.]

- ✓ The indices differ according to:

Sex: there is a physiological variation between men and women. Men usually have a higher reading of the Hg conc. than women due to menstruation and the difference in androgen levels between both sexes, which is important to activate the BM to produce RBCs.

Age: in newborns, the Hg conc is high (the highest value during life) since in utero there is some kind of hypoxia (the baby takes the O2 from the mother) so requires high conc of Hg to obtain more O2. after birth, the baby starts to breath by their own. The Hg conc initially within the first 2 days remains high, then starts to decrease. After few weeks, it reaches the lowest values. Then, it increases gradually until it reaches the usual adult level. While in older ages, there might be a slight decrease in Hg conc since with aging most organs become less functional and one of them is Bone Marrow.

Race: African usually have lower level of Hg than non-African populations.

Mobility state: Athletes who have more demand for oxygen than non-active individuals, usually have higher conc. of Hg.

An example of indices is: Reticulocyte count; reticulocytes **immature RBCs (fresh RBCs that are produced from the BM, have remnant amounts of nuclear material, appear more bluish in color than RBCs, normally appear in BM and peripheral blood vessels in low amounts (0.5-1.5%) of the entire RBCs.**

This measure plays an important role **in identifying and distinguishing the hemolytic anemia** (in which there is destruction of RBCs so the BM start to compensate by producing large amounts of RBCs including reticulocytes so will appear **higher** than normal situations) **from aregenerative anemia** (anemia due to a decrease in the production from BM so the level of reticulocytes will be **low**).

- ✓ It can be calculated by a device or can be seen in Blood smear (large and more bluish). The blood film will be described as polychromasia- poly: multiple, chrom: color; so, there will be more than one color of cells indicating different types of blood cells (reticulocytes more bluish and the usual RBCs etc.…).

Clinical features of anemia:

- ❖ We can classify them into general symptoms and specific symptoms related to each type of anemia:

The general symptoms (shared and common in all types):

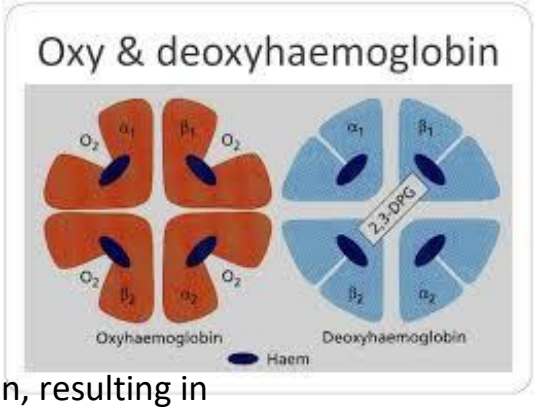
Dizziness , **headache** , **pallor** (decreased vascularization in the superficial part of the skin, thus will appear brighter in color like in lips, tongue and conjunctiva) (they appear pale in anemic patients) , and **fatigue** (MSS won't function optimally so the patient will be tired most of the time)

❖ According to the definition of Anemia, which is defined as decreased mass of RBCs, the entire blood will have a lower weight than normal, thus decreasing the pressure; the pressure of the blood against the wall of BVs resulting in **hypotension** (low BP), now as compensatory mechanisms, the deficit is partially compensated by adaptive changes such as:

Tachycardia: the cardiovascular system will increase the cardiac output and heart rate (beating faster at higher speed).

Tachypnea: increasing respiratory rate to gain more oxygen from the outer environment.

At the level of the cell: increased red blood cell 2,3 diphosphoglycerate (sugar formed by glycolytic pathway when the cell breaks down Sugar for energy), which is a molecule that binds to Hemoglobin and plays a role in liberating oxygen to the tissue. This substance does not bind to hemoglobin at the oxygen-binding sites rather it acts to stabilize the low oxygen affinity state (T state: tense) of the oxygen carrier Hg (deoxyhemoglobin), enhancing the release of O2 to be delivered more to the tissue.



✓ Notice that these symptoms don't affect the patient's life significantly, but if they have heart or lung diseases, the symptoms will be worse and major, because the adaptive changes won't be enough to compensate.

Clinical symptoms in special types of Anemia:

✓ **Chronic hemolytic anemia**:

- **Jaundice**: The Hg is metabolized into bilirubin, resulting in hyperbilirubinemia (build up of bilirubin in the blood) , thus **jaundice.** This can be diagnosed by examining the patient's skin of the hands and the sclera of the eye.
- **Pigmented gallbladder stones**: also, with time the increased excretion of bilirubin into the biliary tract, results in deposition, condensation and formation of stones within the gallbladder which is different from the regular common cholesterol stones.

	Pigmented anemic stones	Cholesterol stones
Color	Dark in color	translucent
Number	Multiple	Usually solitary

- **Red urine** due to destruction of RBCs that will release the Hb into the urine giving it the red color

➔**All 3 result from increased hemoglobin turnover.**

✓ **Extramedullary hematopoiesis**:

- more prominent in **thalassemia** and **sickle cell anemia**. Chronic course of the disease >> elevated erythropoietin >> activation of blood cells production from extramedullary places like spleen and liver >> increasing the demand >> results in increasing the size of these organs producing splenomegaly, hepatomegaly or both in a condition known as **hepatosplenomegaly**

  -inherited disease:

  Inherited so>>it appears in early childhood, kids with hepatosplenomegaly have huge abdomen.

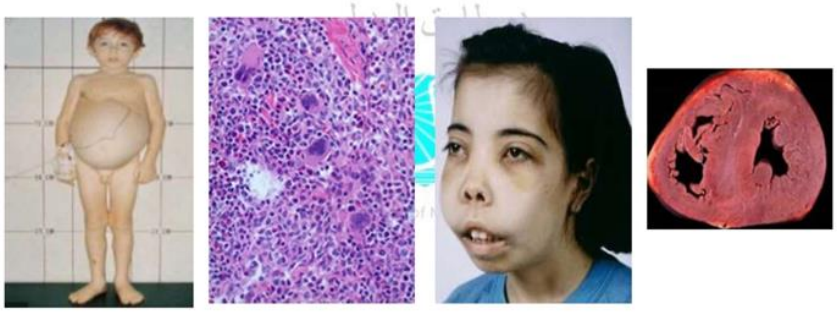
  -tissue examination of spleen or liver under the microscope, shows the elements of hematopoiesis similar to the one in BM (but here it's rather called extramedullary hematopoiesis)

  So in addition to the general symptoms of anemia, there will be :

  1)**splenomegaly, 2)hepatomegaly ,3) growth retardation** (the skeleton doesn't grow normally secondary to hypoxia (anemia >> leads to hypoxia >> increase the erythropoietin production >> erythroid cells hyperplasia (increase demand) >> impaired bone growth>> skeletal deformities)

  4)bone deformities particularly in face (called sickle faces)

  5)secondary hemochromatosis (damage to heart, damage to endocrine glands with more other symptoms) due to the deposition of the iron in the organs, like in the heart (appeared thick and blue leading to dysfunction in the heart)



Anemia of acute blood loss:

✓ Symptoms are related to decreased intravascular volume, more severely and significantly as (**shock**: which happens when the organ stops functioning due to the sudden decrease in the blood perfusion, specifically occurs in vital organs like kidney and brain).

✓ If the loss is >20% of blood volume, the vital organ can't handle the situation and the patient might have **hypovolemic shock** (decreased the volume of the blood) and death.

✓ If the loss is <20%, Body responds by shifting fluid from interstitial to

intravascular space, causing **dilutional anemia** (the shifted fluid + the original blood loss) and **worse hypoxia** (stays 2-3 days; if the patient passes after this time interval, they survive)

- ✓ Erythropoietin secretion is stimulated, activating BM erythropoiesis (needs 5-7 days)
- ✓ In internal hemorrhage (inside the body; skin, lungs), iron is restored from extravasated RBCs and used again in erythropoiesis.
- ✓ In external and GIT hemorrhage, iron is lost, which may be complicated later by iron deficiency anemia.
- ✓ The anemia in the blood smear is **normochromic normocytic** (no problem in the structure), with **reticulocytosis** (due to increase in the production from the Bone Marrow).

Anemia of chronic blood loss:

- ✓ Occurs when the rate of RBC loss exceeds the ability to regenerate the blood cells.
- ✓ Mostly occurs in **gastrointestinal diseases** like peptic ulcer, hemorrhoids (rectal or anal), early stage of colon cancer, also in **excessive menstruation**
- ✓ Results in iron deficiency. Anemia appears **hypochromic and microcytic** (pale and small) with **low reticulocytes** (due to a decrease in the production of blood cells from the BM).