Hematology

- Histology
- Biochemistry
- Pathology ☆
- Pharmacology
- Physiology
- Microbiology

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- lecture number : **1**
- Done BY : **Ali Khreisat**

- Handout
- Sheet
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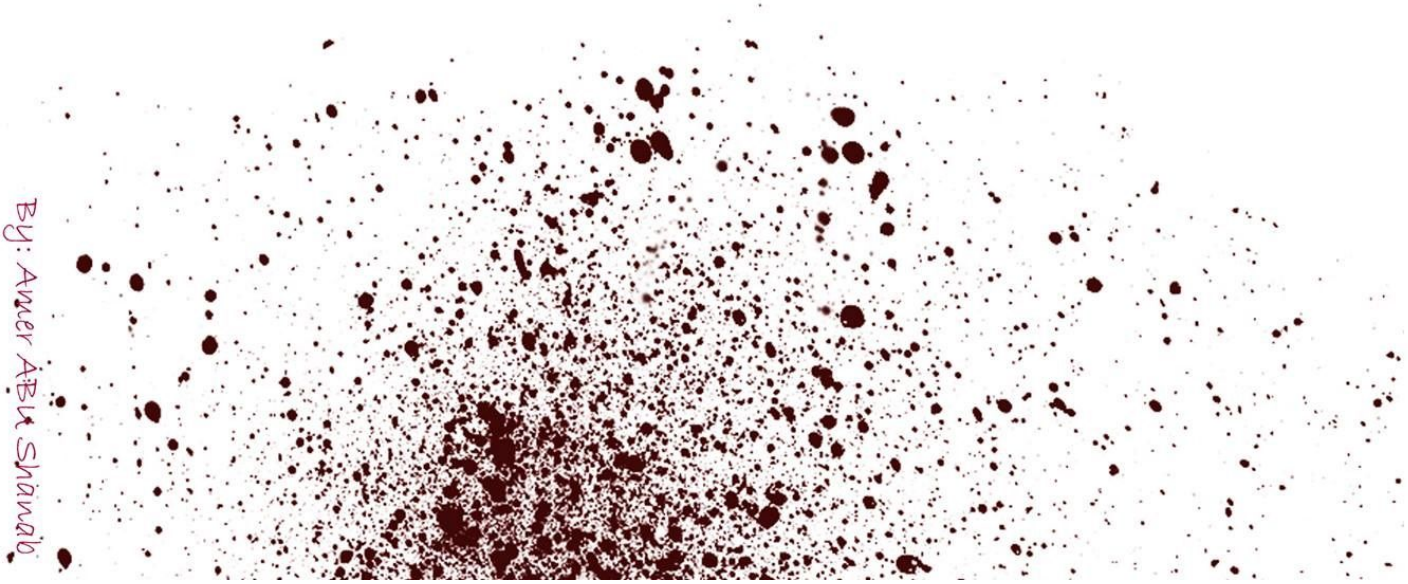


By: Amer Abu Shanab

Introduction to hematopathology And Anemia

Overview

Disease in this system are divided into :

1- Diseases related to RBC : mostly anemia and more rarely polycythemia .

2- Diseases related to WBC : most commonly associated with excessive proliferation as a result of malignant transformation .

In this lecture we are going to discuss diseases related to RBC

Red blood cell Anemia

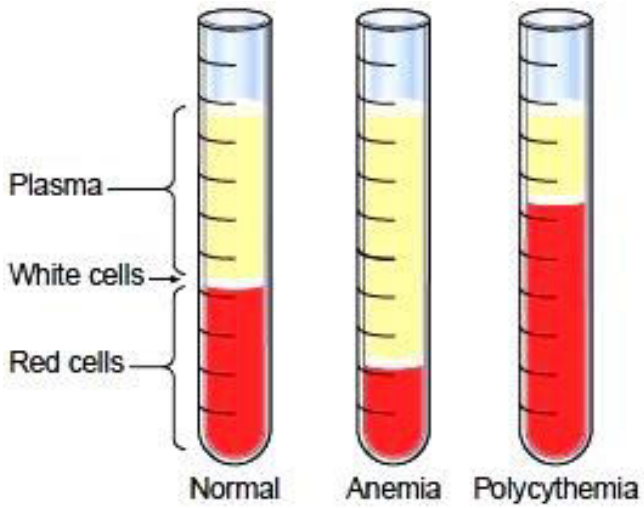
The most accurate definition of anemia is a reduction of the total mass of RBC below the average normal level which causes reduction in the oxygen carrying capacity of the RBC which consequently leads to **tissue hypoxia**.

How we can measure the total mass of the RBC? by two ways :

1- By measuring Hemoglobin concentration in **gram/dl**

2- By measuring **Hematocrit** which is defined as the volume **percentage** of RBC to the whole blood

The normal percentage of hematocrit is 46% in men and 42% in women . If it is lower than this level it indicates **anemia**, if its higher it indicates **polycythemia.**



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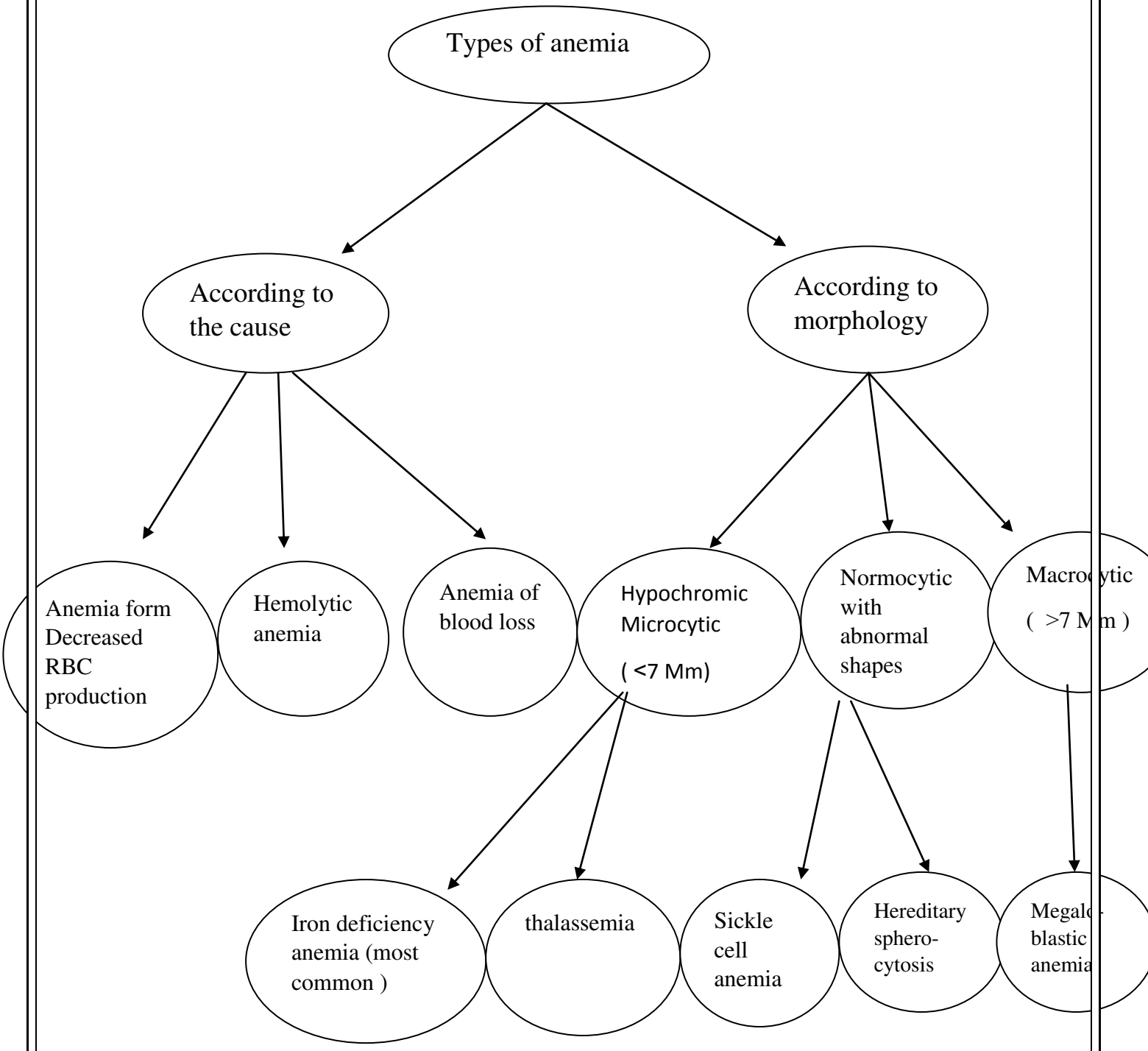
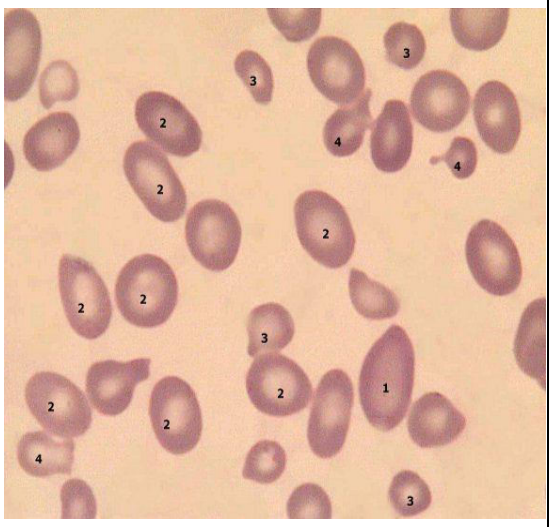
Classification of anemia

There are numerous types of anemia that are classified according to **cause** and **morphology**



In anemia caused from decreased RBC production, the bone marrow is not producing enough RBC for the body . The underlying cause for this phenomenon is either **nutritional** like iron deficiency or megaloplastic anemia from vitamin B12 deficiency or **non-nutritional** like aplastic anemia caused from idiopathic bone marrow failure.

There is an important concept called **Anisopoikilocytosis** (An :different , iso : size , poikilo : shape) which describes a blood film with red blood cells varying in size and shape . Most commonly seen in **iron deficiency anemia.**

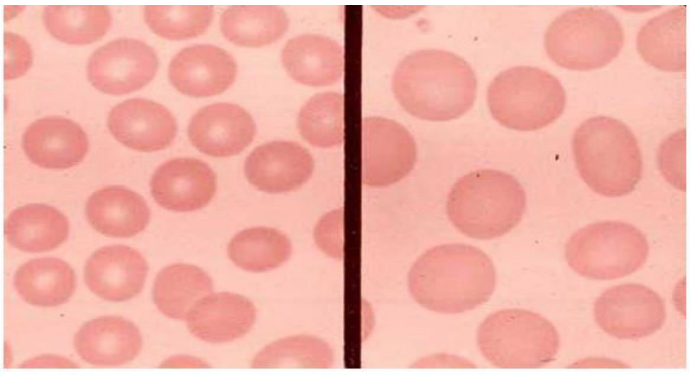


(this picture show RBC'S with different shapes and sizes marked by different numbers)

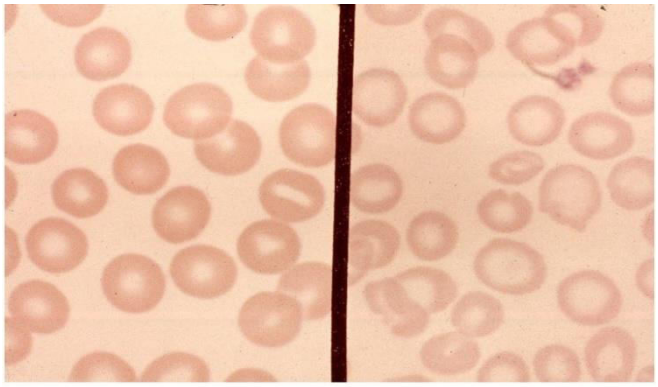
There is a blood measurement test that can diagnosis Ansiopoikilocytosis called **RBC distribution width (RBW)**, it indicates how variable in shape the RBC's are. If it is high that indicates the presence of anisopoikilocytosis .

What is the main difference between hypochromic microcytic anemia and macrocytic anemia ?

In hypochromic microcytic (they're small and pale) anemia the abnormality is in hemoglobin , either from defected synthesis (thalassemia) or iron deficiency (most common cause) .On the other hand in macrocytic anemia the abnormality is in the stem cell that's found in the bone marrow, the



normal red cells macrocytic red cells



Normal red blood cells Microcytic anemia

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RBC's are large but their number is low. This is usually seen in megaloplastic anemia, myelodesplastic syndrome and hypothyroidism.

Statistical Red blood cell measurements

Ranges of red blood cells measurements is variable according to the geographical region so it is not unified all over the world .You can refer to the one that are used in Jordan .

The most important statistical notes that you should memorize from CBC (complete blood count) references in Jordan hospitals

1.Hemoglobin concentration is 14-18 g/dl in men and 12-16 g/dl in women .Why it is lower in women compared to men? for two reasons : because of the presence of higher levels of androgenic hormones that stimulate the cells of the bone marrow in men and because of the regular menstrual cycle that happens in women which caused constant loss of blood each month. Anemia is when the hemoglobin concentration is below 14g/dl in men and below 12g/dl in women.

2.Hemoglobin concentration in infants is higher than adults because they lived in hypoxic conditions in the intrauterine life> The level of hemoglobin comes back to normal level in infants at the 6^{th} month of their life .

3.Hematocrit which is the volume percentage of RBC compared to the whole blood . It is 46% in men and 42 % in women (+-5).

4.Red blood cell count which represent the total number of RBC . This is not an accurate diagnostic measure to diagnose anemia .Why ? because you might have normal number of RBC but their oxygen carrying capacity is low .

5.Mean cell volume (MCV): it represent the size of a single RBC which ranges from 80-100 **femtoliter(10^{-15})** , if MCV is lower than 80 -> **microcytic** anemia , within range -> **normocytic** anemia , larger than 100 -> **macrocytic** anemia .

6.Mean cell hemoglobin (MCH) which represent the mass of hemoglobin inside the RBC ,it is between 26-34 **picogram**. If it is lower than 26 pg -> **hypochromic** anemia , if it is higher than 34 -> **hyperchromic** anemia (the term hyperchromic is not used to refer to RBC , usually it accompanies macrocytic anemia)

7.Mean cell hemoglobin concentration (MCHC) : It represent the ratio MCH /MCV expressed in gram /dl . this measurement not useful because if someone has hypochromic microcytic anemia then both MCH and MCV will be low but the ratio between them is normal .The only case in which MCHC is high and used as a diagnostic tool is in case of anemia caused from **hereditary spherocytosis** because in this disease the RBC's are small, round and filled with hemoglobin so MCH is higher than MCV consequently MCHC will be high as well .

8.Reticulocyte count (important) : reticulocyte is a premature anucleated RBC , it is produced in the bone marrow after removal of the nucleus and it stays there for a period of time then goes to the blood and develops within 48 hours to a mature RBC .How does it mature ? by producing the remaining hemoglobin ,degradation of the residual organelles and by removal of part of the RBC membrane to create biconcavity and get smaller. it measures 0.5-1.5 % of the total RBC count

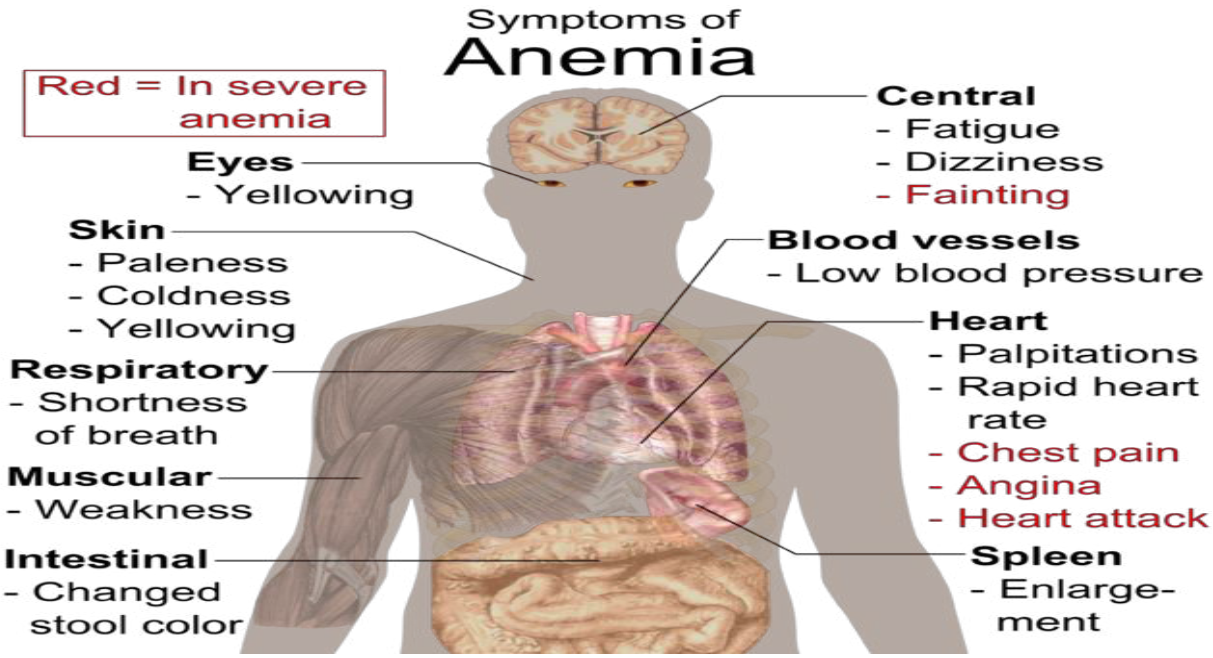
Why reticulocyte count is considered an important diagnostic tool ?

It is used to differentiate between anemia caused from increased RBC destruction (hemolytic anemia) and anemia caused from decreased RBC production from the bone marrow . How ? if you diagnose a patient with anemia and you measure reticulocyte count and found it above 1.5 % this indicates that the bone marrow is functioning normally to compensate the low level of RBC and the cause is hemolytic anemia . But if reticulocyte count was lower than 0.5 % this indicates that the anemia is caused from bone marrow failure.

Clinical Manifestations of anemia

We said that anemia cause tissue hypoxia because of the decrease O2 carrying capacity, which leads to the following manifestation :

1- Hypoxia in the brain which leads to dizziness and headache
2- Hypoxia in the skeletal muscles leads to fatigue
3- Pallor : because RBC's are pale, the superficial barriers like the skin and the lips become pale
4- Hypotension : because the mass of the blood is lower than normal
5- **Tachycardia** : because when tissues become hypoxic there will be an increased demand on the heart to pump more blood
6- **Tachypnea** (increased respiration)
7- **Jaunice and spleenomegaly** happen in hemolytic anemia
8- **Joint and bone pain** happen because of hypoxia.
9- **Growth retardation in children.**



Anemia of acute Blood loss

in case of acute blood loss ,the body is not only losing RBC it is losing the entire blood components .When acute blood loss exceeds 20% of the blood volume ,hypovolemic shock will happen which leads to

organs failure especially the vital ones (brain and kidneys) and death , so the main cause of death is actually the shock not the anemia .

causes of acute blood loss :

1- Trauma : which is the most common cause
2- Hemophilia : it is a disease characterized by increased bleeding tendency either because of inherited factors or drugs .
3- Surgery

How does the body responds to hypovolemic shock in acute bleeding?

We know that 1/3 of the body's fluids is found in the blood and the remaining 2/3 is found inside the cells and between the cells. So when blood is lost, the fluids from outside the circulation will shift to the circulation in order for blood volume to return to normal . This process is called **Hemodilution** and it takes 2-3 days to achieve its full effect if the person didn't die from the initial shock.

the disadvantage of Hemodilution is that it worsens the anemia , because we already had RBC's lost from the body and when there is dilution, the concentration of RBC's will decrease furthermore.

How does the body recover from anemia caused from acute blood loss ?

By a compensatory rise in the hormone **erythropoietin** which is secreted from the kidneys , it will stimulate RBC production from the bone marrow precursor cells and reticulocytosis which will take around **5 days** and that can be measured to know the patient is recovering.

Sings of anemia from acute blood loss (what you find using tests) :

1- **RBC'S have a normal morphology (normochromic normocytic anemia)**
2- **Reticulocytosis**
3- **Increase in the number leukocyte count due to stress from blood loss. (from doctor faraj handout he wrote that in stress glucocorticoids are secreted and they stimulate neutrophils to divide which cause neutrophilia)**

Anemia of chronic blood loss

In this type of blood loss, blood is not lost from the body suddenly like in acute blood loss , it is lost in separated periods of time , so the body has a chance compensate for the decreased blood volume without hypovolemic shock .

Causes : there are many causes but the most common are bleedings in the gastrointestinal tract (peptic ulcer , hemorrhoids , colonic cancer) , bleeding from the female genital tract (menorrhaiga , cancers)

The manifestation of anemia of chronic blood loss is iron deficiency anemia because in this type of bleedings iron is lost from the body . Due of the limited sources of iron (only in red meat), any loss of iron from the body is hard to be compensated for so the patient will end up with iron deficiency anemia .

Clinical signs of anemia from chronic blood loss : initially the anemia is normochromic normocytic anemia , but when iron becomes lost in large amounts it become hypochromic microcytic anemia

	Anemia of acute blood loss	Anemia of chronic blood loss
Morphology of anemia	Normochromic ,Normocytic	Initially Normo but with Constant iron loss it becomes Hypochromic ,hypocytic
Causes	Trauma , hemophilia ,surgery	Chronic bleeding from peptic ulcer Or heavy menstrual cycle
Outcome	Hypovolemic shock which causes Death , hemodilution and further Worsening of anemia	Iron deficiency anemia
Recovery	Within 5-7 days by the production of erythropoietin	

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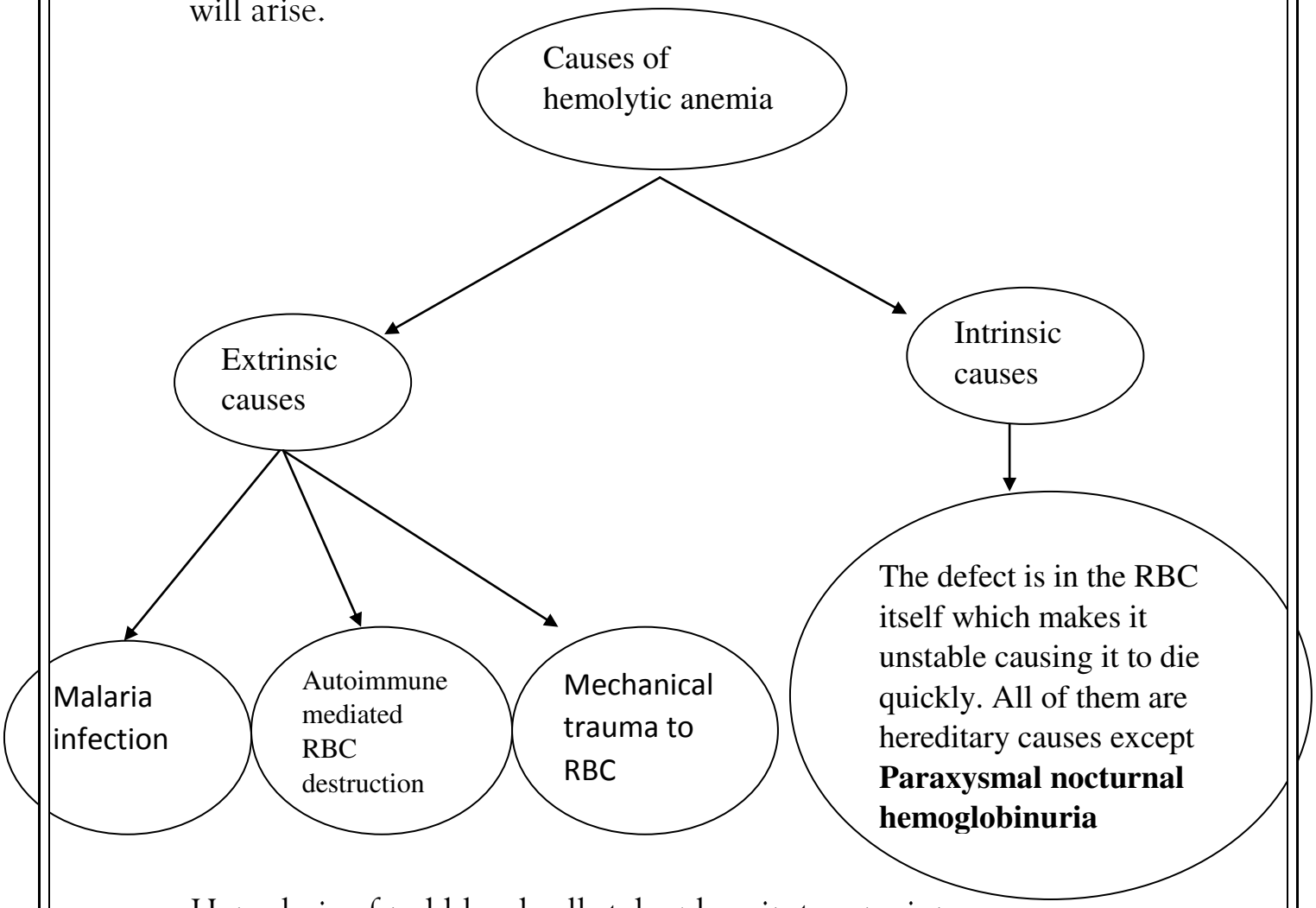
Hemolytic anemia

It is a group of diseases caused by accelerated premature destruction of red blood cells. Normal life span of RBC is about 120 days, if they die prematurely either from **intrinsic** or **extrinsic** factors hemolytic anemia will arise.



Hemolysis of red blood cells take place in two major compartments :

1- Intravascular hemolysis inside blood vessels
2- Extravascular hemolysis in the spleen

Since hemolytic anemia is a group of diseases ,some diseases have intravascular hemolysis while others have extravascular hemolysis .

Symptoms of hemolytic anemia depend on the site of hemolysis

General features of all types of hemolytic anemia

1- Since there is pre-mature destruction of red blood cells , compensatory increase in **erythropoietin** will happen which stimulates erythropoiesis .

2- Increased number of reticulocytes in the blood (reticulocytosis)

3- **Hemolysis of RBC causes elevation of serum levels of lactate dehydrogenase (LDH) which is an enzyme found inside the RBC ,this is useful for diagnostic purposes .**

4- **Hemolytic anemia is associated with increased number of erythroid cells in the bone marrow (Erythroid hyperplasia) ,these erythroid cells are the precursors of reticulocytes .This can be noticed by taking a bone marrow biopsy to diagnose hemolytic anemia**

Hemolytic anemia with extravascular hemolysis

It is more common than intravascular hemolysis and it takes place outside the circulation in the spleen.

The spleen is an organ made of sinusoidal meshwork of small capillaries. Biconcaved RBCs can pass through those capillaries easily because they have the ability to deform . But when the RBC becomes old or have an abnormal shape it can't pass through this meshwork so it becomes sequestered in the spleen and then gets phagocytosed by **histocytes** (splenic macrophages) .

Patients with extravascular hemolysis usually have anemia caused from abnormal shaped RBC like sickle cell anemia .

Hemoglobin that is found in RBC is toxic if it was alone in the blood so Histocytes will convert hemoglobin from the phagocytosed RBC into bilirubin which increases in the body and

causes jaundice, if hemoglobin leak out from the histocyte to the circulation it will be neutralized by a circulating protein called **Haptoglobin** .

Features of hemolytic anemia of the extravascular type :

1- Since the function of the histocytes in the spleen is increased, the patient will have hyperplasia in the mononuclear phagocytes presented by **Spleenomegaly**.

2- Increased levels of bilirubin that is produced from hemoglobin causes **jaundice**

3- **Decreased** levels of haptoglobin because it was consumed to neutralize free hemoglobin

Note : Iron in this type of hemolytic anemia is efficiently recycled from the histocytes to the bone marrow so it is not associated with any problem .

Hemolytic anemia with intravascular hemolysis

It is less common than extravascular hemolysis ,but it is more serious because components of the lysed RBC are spelled directly to the blood and not preserved in the spleen like extravascular hemolysis

Causes: (here there is no abnormalities in the shape of RBCs)

1- Malarial infection
2- Mechanical damage to the RBC
3- Drugs and toxins
4- Complement fixation

Features of hemolytic anemia of the intravascular type

1- **Complete depletion of haptoglobin which leads to the persistence of toxic hemoglobin in the blood which will cause hemoglobinuria (presence of hemoglobin in urine)**

2- Worsening of tissue hypoxia : because Free hemoglobin is metabolized by O2 in the blood to met-hemoglobin (oxidized formed of hemoglobin and it isn't present normally in blood) , this met-hemoglobin doesn't release bound O2 easily so it will worsen tissue hypoxia . Haptoglobin and met-hemoglobin are both excreted in the urine causing red urine.

3- Iron is spelled into the circulation from the lysed RBC which is also toxic when it is free so it will accumulate in the kidneys causing renal hemosidorsis (iron masses in kidneys)

	Intra vascular hemolysis	Extra vascular hemolysis
Shape of the RBC	Normal	Abnormal
LDH level	Increased	Increased
Haptoglobin level	Depleted	Decreased
Met-hemoglobin formation	Yes	No
Jaundic	No	Yes
Spleenomegaly	No	Yes
Hemoglobinuria	Yes	No
Most common cause	Malarial infection	Sickle cell anemia
Reticulocytosis	Presented	Presented

I apologize for any mistake in the sheet

Dedicated to : Moazz Al-Qasem