The Leukemia

Types of Leukemia:

The different types of leukemia are categorized as either acute or chronic. In acute leukemia, the abnormal blood cells are blasts that remain very immature and cannot carry out their normal functions. With acute leukemia the number of blasts increases rapidly, and the disease gets worse quickly In chronic leukemia cases, some blast cells are present, but in general, these cells are more mature and can carry out some of their normal function Also, the number of blasts increases less rapidly than in acute leukemia

as a result, chronic leukemia gets worse gradually Leukemia can arise in either of the two main types of white blood cells-lymphoid cells or myeloid cells. When leukemia affects lymphoid cells. it is called lymphocytic leukemia. When myeloid cells are affected, the disease is called myeloid or myelogenous leukemia

These are the most common types of leukemia:

Acute lymphocytic leukemia : (Lymphoblastic) (ALL): Is the most common type of leukemia in young children Acute lymphocytic leukemia also affects adults, especially those age 65 and older .

Acute myeloid leukemia: (Myelogenous) (AML) :Occurs in both adults and children (common in adults). This type of leukemia is sometimes called Acute Non Lymphocytic Leukemia (ANLL)

In blood seen decreased in red blood cells, and increase in abnormal and immature white blood cells like (myelocyte, mycloblast, and lymphocyte)

Clinical Features:

1) Anemia, fever, Septicemia
2) Purpura, bleeding because thrombocytopenia
3) Moderate. Splenomegaly, hepatomegaly in ALI

Lab. Diagnosis :

1) Normochromic. Normocytic, Anemia
2) WBCS count may be decreased, normal, or increased
3) Thrombocytopenia.
4) Blood Film: shows variable number of blast cells in AML. the blasts may contain Auer Rods, and other abnormal cell may be present. Promyelocyte , meylocytes, pseudo - pelger cell.

Chronic Lymphocytic Leukemia: (lymphoid) (CLL)

Most often affects adults over the age of 55, and rare before age 20 years, and uncommon before age 50 years, the median age of onset is 68 years, but it almost never affects children

Symptoms:

1) Low- grade fever, night sweats

2) Weakness, fatigue, Anorexia, Weight loss.
3) Hepatosplenomegaly

Lab. Diagnosis:

1) Leukocytosis.
2) Absolute lymphocytosis
3) Peripheral blood smear : 80-90 % small lymphocyte , large lymphoblast may be noted, granulocytes normal, platelet normal, Basket cell

Chronic Myeloid Leukemia : (myelogenous) (CML) Occurs mainly in young and middle age adults, 30- 50 years old. A very small number of children also develop chronic myeloid leukemia. Male are affected more than female 5-10 % of patient history of excessive exposure of radiation .

Clinical Signs and Symptoms :

1) Fever, Fatigue, weight loss, anorexia
2) Bone pain, night sweats, and fever.
3) Splenic enlargement
4) Excessive bleeding and fever occur in later stage

Lab Diagnosis:

1) Anemia, leukocytosis

2) Peripheral blood smear: shows increased number of granulocytic forms such as Neutrophil segmented and band decreased number of immature form, myoblast rarely exceed 5 % of nucleated cell , Eosinophil Basophil may also increased
3) Thrombocytosis

Chronic Monocytic Leukemia: This form of leukemia is less common than other chronic forms The incidence of this variety is rare in young persons, it is seen after middle age

Symptoms:

1) Anaemia.
2) Enlarged lymph node and spleen
3) Leukopenia.

Lab. Diagnosis :

1) Leukopenia
2) Peripheral blood smear: Shows increase in large mature monocyte with irregular nuclei
3) Moderately decreased platelets.

Chronic Myelomonocytic Leukemia :

Lab. Diagnosis :

1) Peripheral blood smear : shows monocytosis, neutrophilia, blast cell are usually seen
2) Bone marrow film : increased promonocyies

The Hypoproliferative Anemias

The hallmark of hypoproliferation is *lower than expected* marrow erythroid cellularity and red cell production for the degree of anemia. Although production parameters (absolute reticulocyte count and G:E ratio) may be normal or even increased relative to levels seen in normal subjects, they are, nevertheless, *lower than expected* for the degree of anemia. In the case of anemia of sudden onset, the assessment of erythroid production must be made after anemia has been present for seven to ten days, in order to give the marrow time to respond.

The hypoproliferative anemias are due to three basic mechanisms:

- An insufficient supply of iron for hemoglobin synthesis (iron deficiency or sequestration).
- Low erythropoietin levels for the degree of anemia.
- Marrow damage.

Iron Deficiency Anemia

Iron deficiency is one of the hypoproliferative anemias: reticulocyte production does not increase and the marrow has fewer red cells precursors than expected for the degree of anemia.

The mechanism of iron deficiency

The mechanism of iron deficiency in adults is usually blood loss, exceptions to this rule are (**babies** whose rapid growth exceeds dietary iron availability and the **patient who absorbs iron poorly** because of a small bowel disorder called celiac disease or because the stomach or duodenum has been altered by surgery. In contrast to **younger women,** where iron deficiency is usually a consequence of menstrual losses or pregnancy) .

Iron deficiency **in adult men** and in **post-menopausal women** is nearly always due to **gastrointestinal blood loss**:

- **lesions** that commonly lead to blood loss include esophagitis, ulcers of the stomach and duodenum, inflammatory bowel disease, carcinoma of the colon and stomach, and even hemorrhoids.
- **Aspirin** may also cause blood loss and iron deficiency by increasing normal gastrointestinal blood loss (0.5 ml per day) to 5 ml/day.
- **Gastrointestinal parasites** are a major cause of blood loss in many parts of the world. The serious nature of many of these disorders makes it critical to determine the cause of each patient's iron deficiency.

Iron deficiency begins with negative iron balance (Table 2.3). The typical laboratory signs of iron deficiency only appear after the stores of ferritin and hemosiderin have been completely exhausted.

TABLE 2.3. STAGES IN DEVELOPMENT OF IRON DEFICIENCY OR INFLAMMATION

State	Iron stores	Hgb g/dl	Fe µg/dl	TIBC µg/dl	Fe saturation, %	Ferritin µg/l	RBC morphology	EPO level	Shift cells
Normal	N	15	100	300	33	100	N	N	A
Iron depletion	D	15	100	300	33	25	N	N	A
Borderline deficiency	A	15	50	300	17	20	N	N	A
Mild iron deficiency	A	13	30	350	8	10	N	I	P
Severe iron deficiency	A	7	20	450	4	4	Microcytosis Hypochromia poikilocytosis	I	P
Acute inflammation	N	15	50	280	15	300	N	N or D	A
Chronic inflammation	I	9	20	220	15	300	Microcytosis hypochromia	N or D	A

reviations: N, normal; D, decreased; I, increased; P, present; A, absent

Iron deficiency affects body organ function in many ways: "some overt, some subtle"

1-Iron is present in many enzymes (cytochromes, cytochrome oxidase, xanthine oxidase, catalase, succinate dehydrogenase, peroxidases, etc.). It is not surprising that **iron deficiency affects tissues other than erythrocytes**. Nearly half of the enzymes of the Krebs cycle contain iron or require it as a cofactor.

2- Severe iron deficiency is associated with cheilosis (fissures at the angles of the mouth), atrophy of lingual epithelium, and brittle fingernails and toenails, which are flat or concave (spoon nails).

3-Iron deficiency also produces abnormalities in brain metabolism. There is now an important body of evidence showing delayed sensory development, motor function, and language skills in young children with iron deficiency.

4- Iron deficiency sometimes creates a desire to eat odd substances such as ice, clay, or starch, **a disorder called "pica."** This may result in young children chewing on painted surfaces, causing lead poisoning.

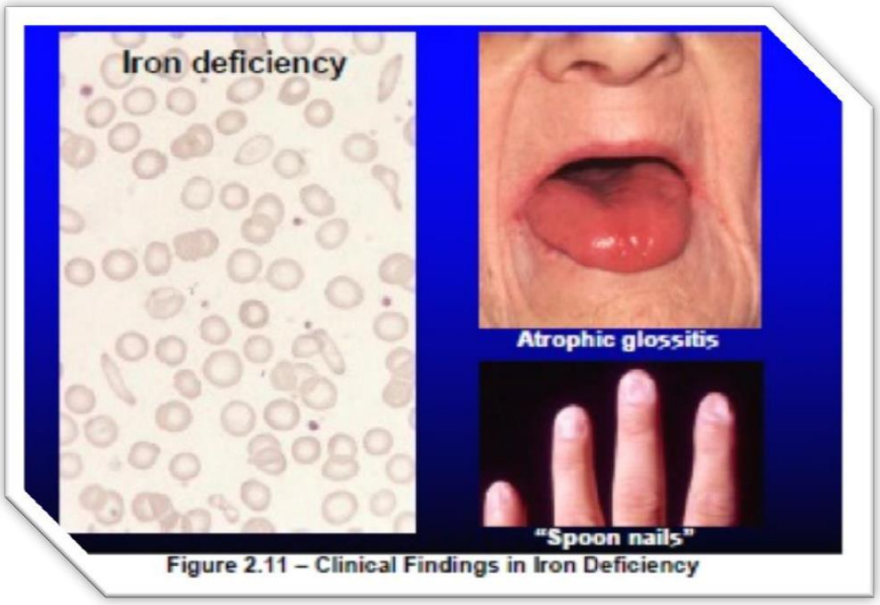


Figure 2.11 – Clinical Findings in Iron Deficiency

Treatment of Iron Deficiency

The treatment of iron deficiency consists of administration of oral or parenteral iron preparations when iron intake in the diet is inadequate to meet body needs. Oral iron usually corrects the deficiency just as rapidly and completely as parenteral iron if GI absorption is normal. Improvement in hemoglobin concentration typically begins within two weeks.

- Several therapeutic iron salts are available as supplements. Usual dosing is 600-1200 mg of an iron salt PO QD.
-Most common adverse effects are GI: constipation, abdominal pain, dyspepsia stool discoloration, and nausea and vomiting.
Adverse effects can diminish with use and may be reduced by taking iron immediately after meals for a few days.
Liquid preparations of iron salts can produce tooth discoloration, a superficial and temporary staining of tooth enamel.

Anemia of Inflammation

Inflammation that lasts for weeks regularly leads to anemia. Usually the hematocrit is in the 25-32% range. While iron deficiency is the most common cause of anemia worldwide, anemia of inflammation is the second most common cause and the most common type of anemia in hospitalized persons. Inflammation may be due to infection, such as pneumonia, to an inflammatory disease like rheumatoid arthritis, or to a malignant

tumor, even when symptoms of inflammation are not apparent. The anemia of inflammation (aka, the anemia of chronic disease) has three pathophysiologic mechanisms.

1- Sequestration of iron in macrophages, resulting in low plasma iron levels.
2- Lower levels of erythropoietin than expected for the degree of anemia.
3- Decreased marrow response to erythropoietin.

*All of these effects are due to the release of various cytokines in inflammatory states.

-The most important of these mechanisms is the reduction in plasma iron, making less available for red cell production. Bacterial polysaccharides and the cytokine interleukin 6 generated during inflammation are powerful stimulators of hepcidin production by hepatocytes. Hepcidin in turn suppresses ferroportin and iron remains in macrophages (Fig. 2.8).

-The optimal treatment of the anemia of inflammation is the elimination of the cause of the inflammation. It does not respond to iron therapy. It may improve with administration of erythropoietin.

-To distinguish iron deficiency from the anemia of inflammation, both of which may be microcytic, the transferrin level (TIBC) and the ferritin are the most helpful tests. Elevated markers of inflammation such as the sedimentation rate (ESR) or C-reactiveprotein (CRP) help confirm the presence of an inflammatory state.

Low Erythropoietin Anemias

In addition to inflammation, a variety of chronic medical conditions can cause decreased erythropoietin production, which in turn causes a hypoproliferative anemia. The most important of these is chronic kidney disease, which is discussed below. Other examples of conditions that cause low-erythropoietin anemia include endocrine deficiency states and severe malnutrition.

Chronic Kidney Disease

Anemia usually appears when the creatinine clearance falls from the normal adult level of about ml/min to about 25 ml/min, indicating a 75% loss of renal function .Injections of recombinant erythropoietin dramatically improve anemia in patients with chronic renal failure.

Hematopoiesis (Hemopoiesis) is normal healthy person there is a constant break down and new formation of cell, and the procedure of blood cell formation called Haematopoiesis

Hematopoietic (Hemopoietic) System: It consists of all organs and tissues involved in hematopoiesis, and these are divided into **myeloid tissue and lymphoid tissue.**

Hematopoietic stem cell (HSC) is the progenitor of all the cells in blood and gives rise to cells of both myeloid and lymphoid system.

1. **The myeloid tissue** consists of bone marrow (medullary cavity) and the cells derived from
it, which include
• **Red blood cells** (RBCs/ erythrocytes)

• **White blood cells** (WBCs/leukocytes, except lymphocytes): WBCs consist of:
- Granulocytes: Neutrophils, eosinophils and basophils are collectively called
granulocytes because of their different types of cytoplasmic granules. However, the
term granulocyte is often referred to only neutrophils.
- Monocytes
- Lymphocytes (even though included under WBCs; they are lymphoid derived).

• **Platelets** (thrombocytes)

Normal sites of blood formation :
1-fetus :less than 2 months in yolk sac.
*2-7 months in the liver and a few in the spleen.
*2-9 months in the bone marrow for RBCs,PLTs,and granulocytes , but lymph nodes and lymphoid tissues (liver and bone marrow with less numbers)

2-After birth: Mainly from bone marrow even monocytes,except lymphocytes
Still from spleen and lymph tissues

3- in adult :main sites of hematopoiesis are the verterbrae ,ribs, sternum,skull bones ,pelvis, sacrum , and proximal end of femunr

Hematopoietic Stem Cells (HSC)

These are small, undifferentiated mononuclear cells that can generate all the blood cell lineages .HSCs possess two fundamental properties:

• **Self -renewal:** HSCs are capable of cell division to give rise to more stem cells.

• **Differentiation:** HSCs can differentiate and give rise to two kinds of lineage-specific multipotent **progenitor** cells, the **common myeloid** and the **common lymphoid progenitors.**

Note: Apart from blood cells, the stem cells may be able to differentiate into diverse tissue types (e.g. neuronal, muscle, liver, vascular cells). This change in the differentiation of a cell

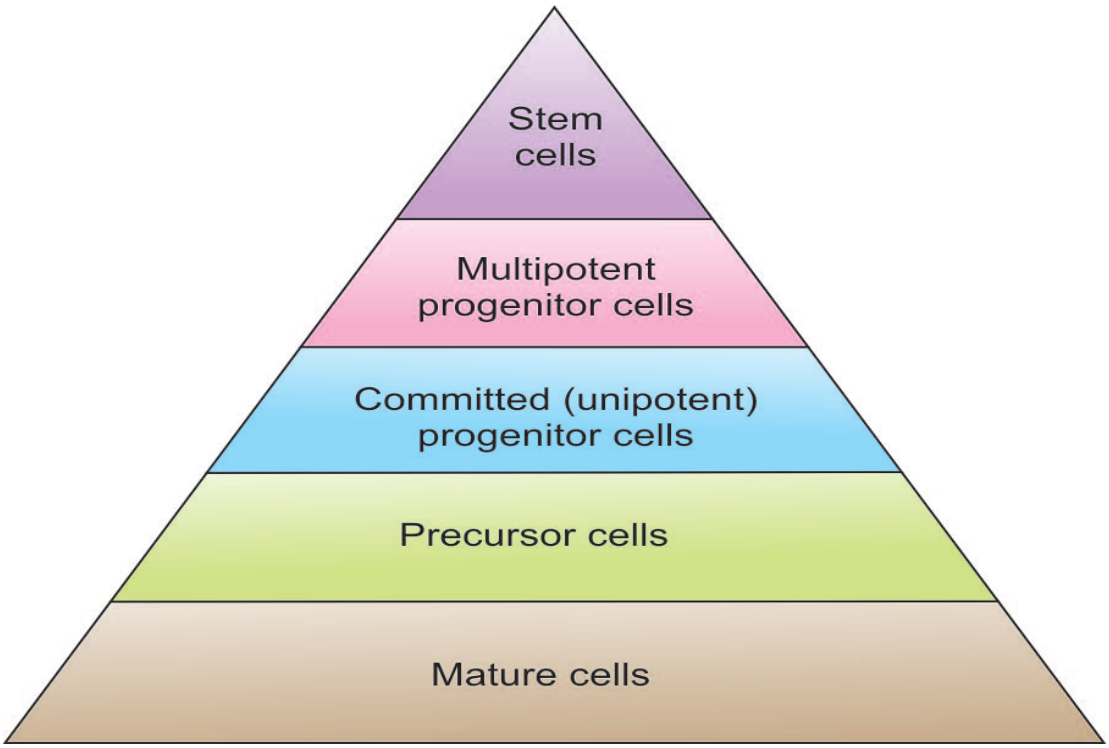


Fig. 1.1: Cell hierarchy in hematopoiesis

Abnormal sites of Hematopoiesis

In certain disorder the fetal hematopoietic organs revert to their old function supported by the reticulum cells, this occurs when bone marrow can not fulfill the requirements or demand for new cell, this **called (Extra-Medallary)** hematopoietic **(myeloid metaplasia)** .
In some rare cases adrenal gland ,cartilages, adipose tissue , intra thoracic areas,kindeys , and –sternum can produce blood cell

Erythropoiesis

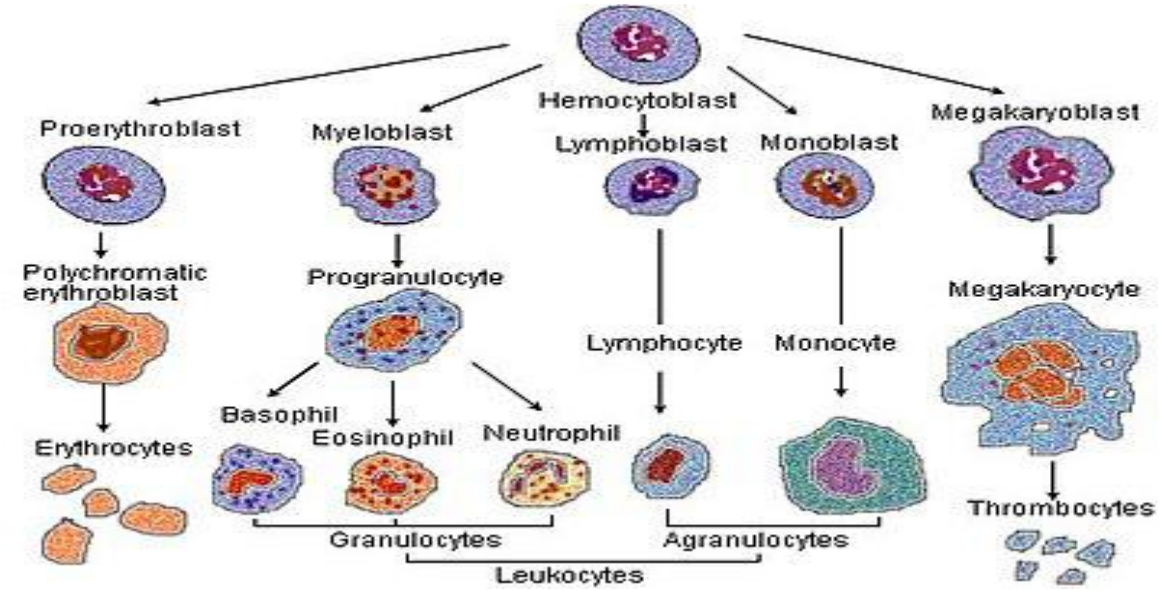
Is the process by which red blood cell (erythrocytes) are produced .it is stimulated O_2 in circulation, which is detected by the kidneys, which then hormone erythropoietin

The hormone stimulates proliferation and differentiation of red cell precusors, which activates increased erythropoiesis in the hemopoietic tissues, ultimately producing red blood cell.

Erythropoiesis differentiation

In the process of red blood cell maturation ,a cell undergrose of differentiation .the following stages 1-7 of development all occur within the bone marrow :
1-hemocytoblaste a pluripotent hematopoietic stem cell
2-common myeloid progenitor multipotent stem cell
3- unipotent stem cell.
4-pronormoblast, also commonly called an proerythroblast or a rubriblast.
5 -basophilic or early normoblast, also commonly called an erythroblast.
6- polychromatophilic or intermediate normoblast.
7- orthochromatic or late normoblast. At this stage the nucleus is expelled before the cell becomes
8-reticulocyte.

The cell is released from the bone marrow after Stage 7, and so in newly circulating red blood cells there are about 1% reticulocytes. After one to two days, these ultimately become "erythrocytes" or mature red blood cells



Characteristics seen in erythrocytes during erythropoiesis

The following characteristics can be seen changing in the erythrocytes when they are maturing

1-they show a reduction in the cell size.

2-the cytoplasmic matrix increases in amount.

3-staining reaction of the cytoplasm changes from blue to pinkish red (this is because of the decrease in the amount of RNA and DNA).

4- Initially, the nucleus was large in size and contains open chromatin. But, as red blood cells mature, the size of the nucleus decreases, until it finally disappears with the condensation of the chromatin material.

Regulation of erythropoiesis

erythropoietin helps regulate the process of erythropoiesis so that, in non-disease states, the production of red blood cells is equal to the destruction of red blood cells and the red blood cell number is sufficient to sustain adequate tissue oxygen levels but not so high as to cause sludging, thrombosis, or stroke. Erythropoietin is produced in the kidney and liver in response to low oxygen levels. In addition, erythropoietin is bound by circulating red blood cells; low circulating numbers lead to a relatively high level of unbound erythropoietin, which stimulates production in the bone marrow.

Recent studies have also shown that the peptide hormone hepcidin may play a role in the regulation of hemoglobin production, and thus affect

erythropoiesis. The liver produces hepcidin. Hepcidin controls iron absorption in the gastrointestinal tract and iron release from reticuloendothelial tissue. Iron must be released from macrophages in the bone marrow to be incorporated into the heme group of hemoglobin in erythrocytes. There are colony forming units that the cells follow during their formation. These cells are referred to as the committed cells including the granulocyte monocyte colony forming units.

IRON DEFICIENCY ANEMIA (IDA)

(IDA):- Iron-deficiency anemia is the most common type of anemia, a condition that happens when your body does not make enough healthy red blood cells or the blood cells do not work correctly. Iron-deficiency anemia happens when you don't have enough iron in your body. Your body needs iron to make hemoglobin, the part of the red blood cell that carries oxygen through your blood to all parts of your body.

♦ Iron deficiency anemia is the most important cause of a microcytic hypochromic anemia , in which the two red cell indices MCV (mean cell volume) and MCH (mean cell hemoglobin) are reduced and the blood film shows microcytic and hypochromic cells. This appearance of cells is caused by a defect in hemoglobin synthesis.

Iron absorption and metabolism

Iron is one of the commonest elements in the earth's crust, yet iron deficiencies the commonest cause of anemia. This is because

- the body has a limited ability to absorb iron.

- and excess loss of iron due to hemorrhage is frequent. Iron is absorbed in small intestine (duodenum & upper jejunum). it is favored by factors such as acid and reducing agents keeping the iron **soluble**, particularly maintaining it in the ferrous(Fe2+) rather than ferric state (Fe3+).

REGULATION OF IRON ABSORPTION

Only ferrous iron can reversibly bind and release O2 molecules in an efficient fashion. When ferrous iron within the Hb molecule becomes oxidized to the ferric state , the result is an unstable Hb derivative called methemoglobin. If the ferric iron in methemoglobin is not quickly reduced to ferrous iron , methemoglobin molecules become denatured and precipitate within the red blood cell , giving rise to hemolytic anemia.

♦ Iron is found in two forms :

- Haem form which forms (90%) is present in red meat and liver and is absorbed rapidly , -

Non-haem iron which forms (10%) is present in vegetables, cereals eggs or dairy foods and needs to be converted into ferrous state. ♦ Iron is absorbed 2-3 times more efficiently from human milk than from modified cow's milk. During the first years of life , because relatively small quantities of iron-rich foods are taken , it is often difficult to attain sufficiently iron. The diet should include foods such as infant cereals or formulate that have been fortified with iron. Breast-fed infants should receive iron supplements from 4 months of age.

Causes of iron deficiency anemia

1. Nutritional deficiency: in which insufficient amount of iron is consumed to meet the normal and daily demand (e.g poor diet and imbalanced vegetarian diet) , therefore it occurs among low social class people.

2. Faulty or incomplete iron absorption: e.g achlorhydria in certain disorders or following gastric resection , chronic diarrhea associated with celiac disese , sprue , Crohn disease , resection of small bowel and gastrectomy.

3. Increased demand of iron: e.g pregnancy , growth years of children and in prematurity.

4. Excessive blood loss: e.g acute and chronic hemorrhages (peptic ulcers , carcinoma of stomach , colon or rectum , heavy menstruation in females , hematuria , bleeding hemorrhoids and worm infestation by the hook worm Ancylostoma duodenale.

Symptoms

Iron-deficiency anemia often develops slowly. In the beginning, you may not have any symptoms, or they may be mild. As it gets worse, you may notice one or more of these symptoms:

- Fatigue (very common)
- Weakness (very common)
- Dizziness
- Headaches

- Low body temperature
- Pale or yellow "sallow" skin
- Rapid or irregular heartbeat
- Shortness of breath or chest pain, especially with physical activity
- Brittle nails
- Pica (unusual cravings for ice, very cold drinks, or non-food items like dirt or paper)4 If you think you may have iron-deficiency anemia, talk to your doctor or nurse

Exams and Tests

To diagnose anemia, the doctor may order theses blood tests:

I. Hematocrit and hemoglobin

2. RBC indices

3. Blood smear examination

Tests to check iron levels in blood include

1 Bone mnrrow exam (rare).

2. Iron hinding capacity (TIBC) in the blood

A measurement called iron saturation (serum iron/TIBC) often can show whether you have enough iron in your body

3. Serum ferritin

4 Serum iron level

Tests that may he done to look for the cause of iron deficiency

1. Colonoscopy

2. Fecal occult blood test

3. Upper endoscopy.

Treatment:

Taking iron supplements and eating iron-rich foods are important parts of treating iron deficiency anemia. Iron supplements (most often ferrous sulfate) are needed to build up the iron stores in the body. Most of the time, the doctor or nurse will measure your iron levels before starting supplements

Pregnant and breastfeeding women will need to take extra iron because their normal diet usually will not provide the amount they need.The hematocrit should return to normal after 2 months of iron therapy However, keep taking iron for another 6-12 months to replace the body's iron stores in the bone marrow

Iron-rich foods include:

1-Chicken and furkey

2. Dried lentils, peas, and beans

3. Eggs (yolk)

4. Fish

5. Meats (liver is the highest source)

6. Peanut butter

7. Soybeans

8. Whole- grain bread

Other sourees include:

Oatmeal .

Raisins, prunes, and apricots

Spinach, kale, and other greens

What is anemia?

Anemia is a medical condition in which the red blood cell count or hemoglobin is less than normal. The normal level of hemoglobin is generally different in males and females. For men, anemia is typically defined as hemoglobin level of less than 13.5 gram/100 ml and in women as hemoglobin of less than 12.0 gram/100 ml. These definitions may vary slightly depending source and the laboratory reference used

Symptoms of Anemia

Some patients with anemia have no symptoms others with anemia may feel

1- Tired

2-Fatigue easily

3-Appear pale

4-Develop palpitations (feeling heart racing)

5-Become short of breath

Additional symptoms may include

1. Hair Loss.

2. Heart failure

If anemia is longstanding (chronic anemia), the body may adjust to low oxygen levels and the individual may not feel different unless the anemia becomes sever. and If the anemia occurs rapidly (acute anemia), the patient may undergo significant symptoms relatively quickly.

There may specific causes of anemia

I-Koilonychias (spoon nails) associated with Iron deficiency anemia.

2-Jaundice (associated with Haemolytic or Megaloblastic anemia

3-Bone deformities » associated with Thalassemia major, and Sever congenital haemolytic anaemias.

4-Leg ulcers »» seen in sickle-cell disease.

Classification of Anemia:-

A-Based on the causes

I- failure of blood production

2 -Increase blood loss

3- Increase of red cell destruction

4- The age of the patient

B- Based on red cell indices

l-Microcytic, hypochromic: -MCV, MCH reduced (80 fl,<27 pg.) eg. Iron deficiency anemia , thalassemia, lead poisoning ,Sideroblastic anemia

2- Normocytic, Normochromic :- MCV, MCH. Normal

(MCV. 80-95 MCH 27-34 pg.) e.g (after acute blood loss, many hemolytic anemia ,bone marrow failure, Renal disease

3- Macrocytic : MCV. Is raised. MCV-95fl

eg, Megaloblastic anemia (Vit.B12 or folate deficieney, alcohol, liver disease, Aplastic anemia

Type Of Anemia:-

1 - Iron Deficiency Anemia

2- Megaloblastic Anemia

3- Sickle Cell Anaemia

4-Aplastic Anaemia

5 -Haemolytic Anaemia

6- Pemicious Anaemia

7- Acquired And Autoimmune Hemolytic Anemia

8- Thalassemia

Diagnosis:-

Diagnosing anemia usually starts with a medical history review and exam by doctor. Next, your doctor may apply for one or more of the tests below to determine the type of anemia. Specialized analyses that are not presented at all medical centers

Blood Tests :-

The first test you will receive is a complete blood count, which measures the number of white blood cells, red blood cells and platelets in blood sample. If test results show you have anemia, other blood tests may be done to identify the type and cause, including

l. Hemoglobin electrophoresis: This test helps diagnose anemia by checking different proteins called hemoglobin in blood.

2. Reticulocyte count: A reticulocyte count shows the number of young red blood cells in blood to determine if your bone marrow is making them at the right rate

3. Serum iron and serum ferritin: These tests check the amount of iron in blood and body.

5. Peripheral blood smear: A peripheral smear assesses whether the shape of red blood cells have changed due to anemia

6. Osmotic fragility: This test determines if red blood cells have become more fragile than usual.

Tests related to underlying conditions

If doctor thought that an underlying chronic disease or iron deficiency is causing anemia, one or more of the following tests may be optional to diagnose your condition

1. Stool sampling: If doctor thinks bleeding internally, may need to provide a stool sample for testing.

2. Urine analysis : Urine analysis can reveal the presence or absence anemia-related condition provide a stool sample for testing, of specific substances that help identify which anemia-related condition.

3. Endoscopy: Endoscopy is a procedure used to visually examine camera on the end of a long, flexible tube. If necessary upper digestive system for signs of bleeding, using a tiny cell samples can be taken for examination under a microscope (biopsy) by a pathologist

4. Colonoscopy: This test involves passing a lighted tube through the return to search for tumors or other problems in the large intestine and surrounding areas

5. Bone marrow biopsy : A bone marrow sample may be taken for examination by u pathologist to determine if your bone marrow, the body's blood factory, is working correctly or has abnormality

6. Genetic tests and counseling: If doctor suspects that your anemia is related to a genetic condition, a consultation with a genetic counselor may be recommended.

Laboratory Evaluation

Table 2-1 lists the tests used in the initial workup of anemia. A routine complete blood count (CBC) is required as part of the evaluation and includes the hemoglobin, hematocrit, and red cell indices: the mean cell volume (MCV) in femtoliters, mean cell hemoglobin (MCH) in pictograms per cell, and mean concentration of hemoglobin per volume of red cells (MCHC) in grams per liter (non-SI: grams per deciliter). The red cell indices are calculated as shown in **Table 2-2**, and the normal variations in the hemoglobin and hematocrit with age are shown in **Table 2-3**.A number of physiologic factors affect the CBC, including age, sex, pregnancy, smoking, and altitude. High-normal hemoglobin values may be seen in men and women who live at altitude or smoke heavily. Hemoglobin elevations due to smoking reflect normal compensation due to the displacement of O2 by CO in hemoglobin binding.Other important information is provided by the reticulocyte count and measurements of iron supply including *serum iron*, *total iron-binding capacity* (TIBC; an indirect measure of the transferrin level), and *serum ferritin*. Marked alterations in the red cell indices usually reflect disorders of maturation or

iron deficiency. A careful evaluation of the peripheral blood smear is important, and clinical laboratories often provide a description of both the red and white cells, a white cell differential count, and the platelet count. In patients with severe anemia and abnormalities in red blood cell morphology and/or low reticulocyte counts, a bone marrow aspirate or biopsy may be important to assist in the diagnosis. Other tests of value in the diagnosis of specific anemias are discussed in chapters on specific disease states. The components of the CBC also help in the classification of anemia. *Microcytosis* is reflected by a lower than normal MCV (<80), whereas high values (>100) reflect *macrocytosis*. The MCH and MCHC reflect defects in hemoglobin synthesis (*hypochromia*). Automated cell counters describe the red cell volume distribution width (RDW).The MCV (representing the peak of the distribution curve) is insensitive to the appearance of small populations of macrocytes or microcytes. An experienced laboratory technician will be able to identify minor populations of large or small cells or hypochromic cells before the red cell indices change

.

ANEMIA

II. Iron supply studies
A. Serum iron
B. Total iron-binding capacity
C. Serum ferritin
III. Marrow examination
A. Aspirate
1. M/E ratio[a]
2. Cell morphology
3. Iron stain
B. Biopsy
1. Cellularity
2. Morphology

TABLE 2-2

RED BLOOD CELL INDICES

INDEX	NORMAL VALUE
Mean cell volume (MCV) = (hematocrit ± 10)/ (red cell count × 10^6)	90 ± 8 fL
Mean cell hemoglobin (MCH) = (hemoglobin × 10)/ (red cell count × 10^6)	30 ± 3 pg
Mean cell hemoglobin concentration = (hemoglobin × 10)/ hematocrit, or MCH/MCV	33 ± 2%

TABLE 2-3

CHANGES IN NORMAL HEMOGLOBIN/HEMATOCRIT VALUES WITH AGE AND PREGNANCY

AGE/SEX	HEMOGLOBIN g/dL	HEMATOCRIT %
At birth	17	52
Childhood	12	36
Adolescence	13	40
Adult man	16 (±2)	47 (±6)
Adult woman (menstruating)	13 (±2)	40 (±6)
Adult woman (postmenopausal)	14 (±2)	42 (±6)
During pregnancy	12 (±2)	37 (±6)

Aplastic anemia

A plastic anemia is a blood disorder that occurs when the bone marrow produces too few of all types of blood cell: red cells, white and platelets (Pancytopenia)

- A low number of red blood cells reduces the blood's ability carry oxygen
- A reduced number of white blood cells makes the child susceptible to infection s
- A low number of platelets redluces the blood's ability to clot.

Causes

A\Primary:

1 Idiopathic occurring with no known reason. The disorde can be the rather of previous illness or presented problrm.

2 Inherited genetic disorder

1. Specific infectious diseases, such as hepatitis, Epstein-Barr auses

2 be the result of a previous illness or presented problen

B/ Secondary: (Acquired causes)

1.**Specific infection disease** ,such as hepatitis.

2. taking certain medications including some antibiotics and an drugs

3. exposure to certain toxins, such as benzene.

4. exposure to radiation or chemotherapy.

Symptoms:

1. lack of energy .

2. pale skin, lips, and hands, or paleness under the eyelids

3. shortness of breath

4. fevers or infections

5. bleeding, such as bruising, bleeding gums, nosebleeds .

6. irregular heartbeat

7. headache

Laboratory Tests

The initial test for anemia, the complete blood count (CBC).

1. Hemoglobin and/or hematocrit may be low.

2. RBC and WBC counts are low

3. Platelet count is low

4. Red blood cell indices are usually normal

5. The differential white blood count shows a decrease in most types of cells but not lymphocytes

Some additional tests that may be performed to help determine the type and cause of anemia include:

1. Reticulocyte count- result is usually low.

2. Bleeding time is increased

3. Erythropoietin -usually increased in aplastic anemia.

4. A bone marrow aspiration will show a decrcase in the number of all types of mature cells

5. Tests for infections such as hepatitis, EBV, CMV help to determine the cause

6. Test for arsenic (a heavy metal) and other toxins

7. exposure to toxins or certain drugs (for example, chloramphenicol) or prior treatment for cancer.

Hematology:-is the science that study the blood, and its structure, function , disease ,and the convenience between and the function .

Blood:-is highly specialized (sterile) connective tissues, which circulate in a closed system of vessels as a liquid with red color

But in out this system a solid phase will perform, which we called plug or blood clot.

Blood Component

Mainly we can divide blood into two parts:-

1- Cellular elements, including **leukocytes, platelets,** and **erythrocytes.**

2- Liquid called **plasma.**

** The normal adult has about 6 liters of this vital fluid, which composes from 7% to 8% of the total body weight.

Plasma:- plasma is a pale yellow fluid in which blood cells are suspended in.

*Plasma forms about 55% of blood volume composed 95% or more water , and many solutes including proteins ,minerals ,ions, organic materials ,hormones ,enzymes , products of digestion ,and waste products .

* Whereas about 45% of the volume is composed of erythrocytes and 1% of the volume is composed of leukocytes and platelets (**thrombocytes**).

Blood cell

1-Red blood cell

2-White Blood Cell

3-Platetes

Function of blood

1-oxygen transportation by hemoglobin from lungs to the tissues

2-blood also can transports the nutrients absorbed by the digestive system to the tissuse for use or storage

3-hormones are carried from endocrine glands to the organ.

4-wastes are transported from tissues for excretion e.g:(carbon dioxide ,urea, createnine……

Regulatory:-

1-Plasma maintain the PH. of blood (7.35-7.45), and in the tissues

2-Osmotic pressure in plasma is regulate by proteins and salts

(sodium, chloride) to prevent excessive loss of fluid from the blood into tissues.

3-Regulation of the blood temperature.

Protective

1-platelets and coagulation factors control the blood loss by thrombus formation

2-leukocytes defend and produce antibodies and toxin against

HEMOSTASIS

Hemostasis is the process of forming clots in the walls of damaged blood vessels and preventing blood loss while maintaining blood in a fluid state within the vascular system. A collection of complex interrelated systemic mechanisms operates to maintain this balance between coagulation and anticoagulation. Whenever a vessel is severed or ruptured, hemostasis is achieved by several mechanisms

(1) Vascular constriction.

(2) Formation of a platelet plug.

(3) Formation of a blood clot as a result of blood coagulation.

(4) Eventual growth of fibrous tissue into the blood clot to close the hole in the vessel permanently.

Blood Coagulation:-

The mechanisms of coagulation are set into play by (1): trauma to the vascular wall and adjacent tissues, (2): trauma to the blood, or (3): contact of the blood with damaged endothelial cells or with collagen and other tissue elements outside the blood vessel. In each instance, this leads to the formation of Prothrombin activator, which then causes prothrombin conversion to thrombin and all the subsequent clotting steps . Prothrombin activator is generally considered to be formed in two ways, (1):- The extrinsic pathway that begins with trauma to the vascular wall and surrounding tissues and (2):- The intrinsic pathway that begins in the blood itself.

Extrinsic Pathway for Initiating Clotting:-

As shown in the figure 2.1, the following steps occur in the extrinsic pathway:-

(1):- Release of tissue factor:- Traumatized tissue releases tissue factor or tissue thromboplastin.

(2):- Activation of factor X-role of factor VII and tissue factor in the presence of calcium ions.

(3):- Effect of activated factor X (Xa)to form prothrombin activator-role of factor V. The activated factor X combines immediately with tissue phospholipids that are part of tissue factor or with additional phospholipids released from platelets as well as with factor V to form the

complex called prothrombin activator. Within a few seconds, in the presence of calcium ions, this splits prothrombin to form thrombin

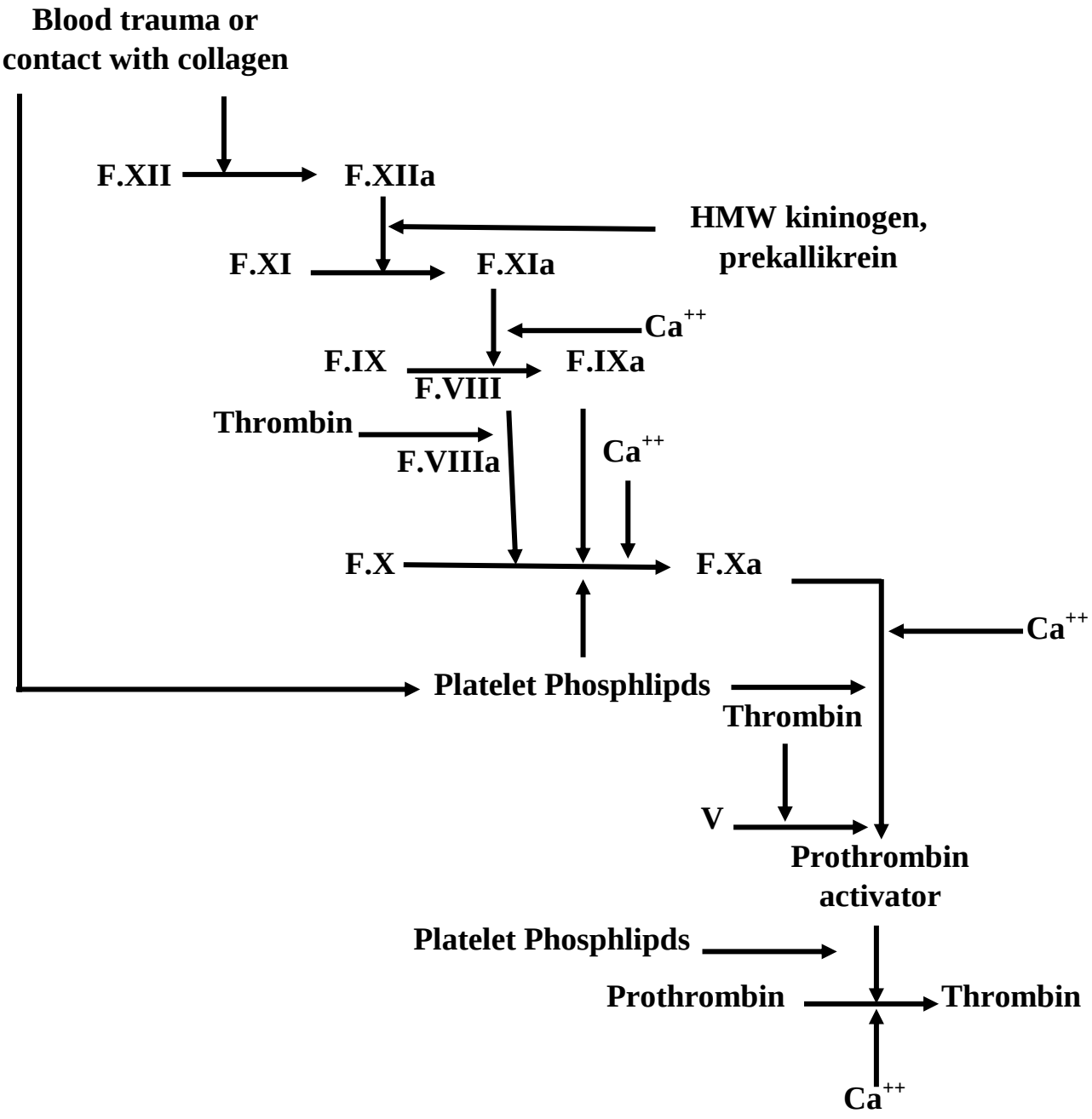


Figure (1) Extrinsic Pathway

Intrinsic Pathway for Initiating Clotting:-

The following steps occur in the intrinsic pathway (figure 2.1) :-

(1):- Blood trauma causes activation of factor XII.

(2):- Activation of factor XI:- The activated factor XII acts enzymatically on factor XI to activate.

(3):- Activation of factor IX by activated factor XI:- The activated factor XI then acts enzymatically on factor IX to activate this factor also.

(4):- Activation of factor X—role of factor VIII:- The activated factor IX, acting in concert with activated factor VIII and with the platelet phospholipids, activates factor X. It is clear that when either factor VIII or platelets are in short supply, this step is deficient. Factor VIII is the factor that is missing in a person who has classic hemophilia, for which reason it is called antihemophilic factor.

(5):- Action of activated factor X to form prothrombin activator—role of factor V:- This step in the intrinsic pathway is the same as the last step in the above extrinsic pathway.

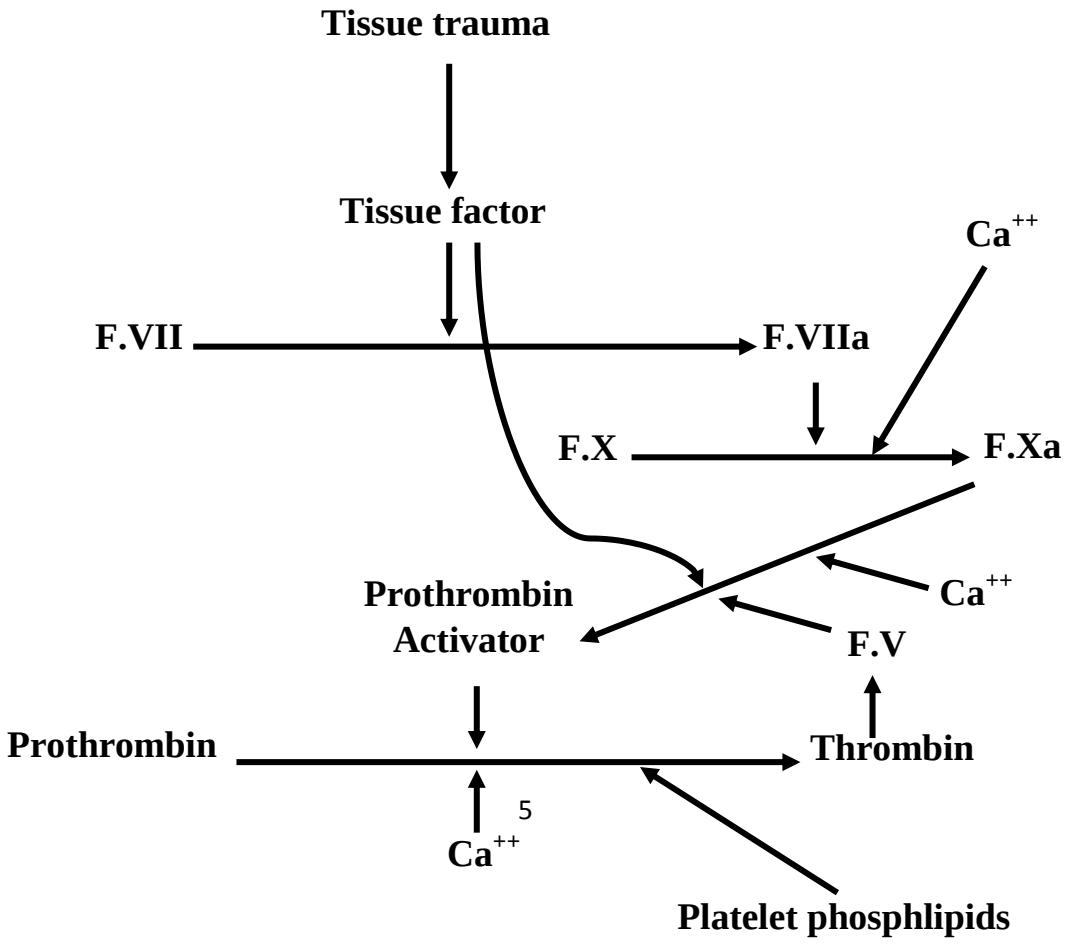


Figure (2) Intrinsic Pathway

HEMOLYTIC ANEMIAS

Anemia is an abnormally low level of red blood cells. Hemolytic anemia occurs when red blood cells are destroyed too quickly In people with hemolytic anemia, red blood cells have an abnormally short life span. There can be something wrong with the red blood cells Or the red blood cells are normal but are destroyed by an external process

Classification of hemolytic anemia

Classification of hemolytic anemia depends on the causes behind them, which can be either genetic or acquired:

1. Genetic (hereditary) hemolytic anemia:

- Genetic conditions of RBC membrane e.g hereditary spherocytosis , hereditary elliptocytosis , and hereditary stomatocytosis
- Genetic conditions of RBC metabolism (enzyme defects) e.g Glucose - 6- phosphate dehydrogenase deficiency (G6PD) and Pyruvate kinase deficiency anemia
- Genetic conditions of hemoglobin e.g sickle cell anemia and thalassemia.

Many different problems can cause hemolytic anemia. These include

1. Inherited abnormalities in red blood cell membranes:

A red blood cell is like a little balloon tilled with fluid. Defects in the membrane can cause the cells to change shape. Abnormally shaped red blood cells are identified by the spleen as abnormal, and destroyed

e.g.: **1**-Hereditary Spherocytosis

2- Hereditary Fliptocytosis

3- Hereditary Stomatocytosis

2. Inherited enzyme deficiencies inside red blood cells:

Enzymes are proteins. Certain abnormal enzyme levels cause red blood cells to become fragile

3.Hemoglobin disorders:

Some people inherit a gene that makes an abnormal kind of hemoglobin Hemoglobin disorders include:

1- Sickle cell anemia (defective hemoglobin)

2- Thalassemia (defective synthesis): Hemoglobin disorders can cause red blood cells to be destroyed easily

2.Acquired hemolytic anemia

Acquired hemolytic anemia can be further divided into immune and non-immune mediated:

A- Immune-mediated acquired hemolytic anemia , and these include:

- Autoimmune acquired hemolytic anemia e.g warm and cold antibody types
- Alloimmune hemolytic anemia e.g hemolytic disease of the newborn (HDN) , Rh disease , blood transfusion reactions , and other blood group and Rh incompatibility diseases.
- Drug induced immune mediated hemolytic anemias e.g Penicillin and methyl dopa

B- Non-immune mediated hemolytic anemia

- Drugs : some drugs and other ingested substances lead to hemolysis by direct action on RBCs e.g ribavirin.
- Toxins: e.g snake venom and plant poisons such as aesculin.
- Trauma: Mechanical such as heart valves , and extensive vascular surgery

- Microangiopathic hemolytic anemia : a specific type with causes such as thrombotic thrombocytopenic purpura (TTP) , hemolytic uremic syndrome (HUS) , disseminated idiopathic coagulation (DIC) , and hemolysis , elevated liver enzymes , and low platelet count (HELLP) syndrome.

- Infections : e.g malaria , Babesiosis and septicemia.

Signs and symptoms of hemolytic anemia's:-

All signs and symptoms of anemia are generally present with pallor of mucous membranes ,

- mild jaundice .

- splenomegaly .

- and later heart failure.

- There is increased bilirubin in blood.

- and therefore jaundice with increased urobilinogen in urine.

- Pigmented gall stones may be found.

- In chronic hemolytic anemia , erythroid hyperplasia may be so extensive that the medullary spaces may expand at the expense of cortical bones (particularly skull and long bones).

(1)Hereditary Hemolytic Anemia

A -Defects of membrane

1 - Hereditary Spherocytosis

The commonest hereditary hemolytic anemia in north European , due to defect in a structural protein of the red cell membrane . The cell becomes more spherical and unable to pass through the splenic microcirculation , where the spherocyte die prematurely the reason for loss of the normal biconcave shape of the red cells

Laboratory Diagnosis of Hereditary Spherocytosis : Blood picture:

1- Hb. 9-12 g/dl

2 - Osmotic Fragility up to 0.7-0.8

3 - Reticulocyte count are raised to 5-7 % .

4 - Coombs test negative

5- Auto-hemolysis is increased

6-Platelets count decreased

7- Blood smear spherocyte

8-MCV normal Or reduced

9- MCH normal

10 MCHC often increased (34-40 %) . 2

Biochemistry:

1- Bilirubin slightly raised

2-Urine bilinogen raised

3- Haptoglobin decreased

B- Defect of Haemoglobin

1 Abnormal of Haemoglobin

These are divided into main groups

a - Synthesis of an Abnormal Hemoglobin

These contain an amino acid substitution in either alpha or Bata globin chairn The most important of these diseases in Sickle cell anemia

b- Reduced Synthesis Of Abnormal Globin Chains:

This includes the alpha and Beta-thalassemia In which synthesis of one or other globin chain is reduced

Sickle Cell Anemia This disease is due to the synthesis of an abnormal Haemoglobin , which only differ from the normal adult Hb In that the amino acid in the sixth position from the amino end of one of the two peptide chain types is Valine instead of the glutamic acid in beta chain This abnormality represents a different only one amino acid in zoo

Laboratory Diagnosis:-

1- Hb. Is usually 6-9 gm. /dl

2- Sickle cell and target cell occur in the blood

3- Features of splenic atrophy (eg. Howelly-Jolly bodies may also be present).

-Thalassaemia s There are 2 types :

1-Alpha , affecting mainly Alpha chain

2 - Beta, affecting mainly Beta chain. There is reduced Beta chain production hence reduced Hb. A Leading to microcytic, hypochromic anaemia, Increase in Hb. A2 and Hb. F, because the lack of Bate chain alpha chains accumulate in cells forming aggregates in

Laboratory findings of hemolytic anemia's

Laboratory findings depend largely on the cause and type of the hemolytic anemia , but in general we can say that patients will show

≈ increased serum unconjugated bilirubin ,

≈ increased urine urobilinogen and fecal stercobilinogen.

≈ There will be reticulocytosis ,

≈ decreased serum haptoglobin ,

≈ increased LDH and ≈ bone marrow erythroid hyperplasia.

≈ Blood film may show microspherocytes , fragmented red cells , helmet cells or nucleated red cells … etc.

≈ Direct Coomb's test (Antihuman globulin test) is always almost positive in immune mediated hemolytic anemia.

≈ The peripheral blood smear often but not invariably shows morphologic changes in the red blood cells compatible with hemolysis. For example, many spherocytes suggest hereditary spherocytosis or immunohemolytic anemia and sickle cells suggest one of the sick cell syndromes

Megaloblastic Anemia

Megaloblastic anemia is the commonest cause of macrocytosis , in which the red cells are larger because they can not produce DNA quickly enough to divide at the right time as they grow , and thus grow too large before division.

The erythroblast in the bone marrow shows a characteristic **abnormality** and therefore the maturation of the nucleus being delayed relative to that of the cytoplasm , And thus the megaloblastic bone marrow **produces macrocytic, oval red cells.** This is often due to the deficiency of vitamin B12 and / or folic acid , which are needed to produce DNA. The basic underlying defect in megaloblastic anemia is defective DNA synthesis and cell division. This result in **ineffective erythropoiesis**, that is, death of immature erythyroid cells before release from the bone marrow, associated with some early destruction of circulating erythrocytes as well.

CLINICAL FEATURES OF MEGALOBLASTIC ANEMIA

The onset is usually insidious with a gradually progressive symptoms and signs of anemia. The patient may be

- mildly jaundiced

- glossitis ,

- angular stomatitis ,

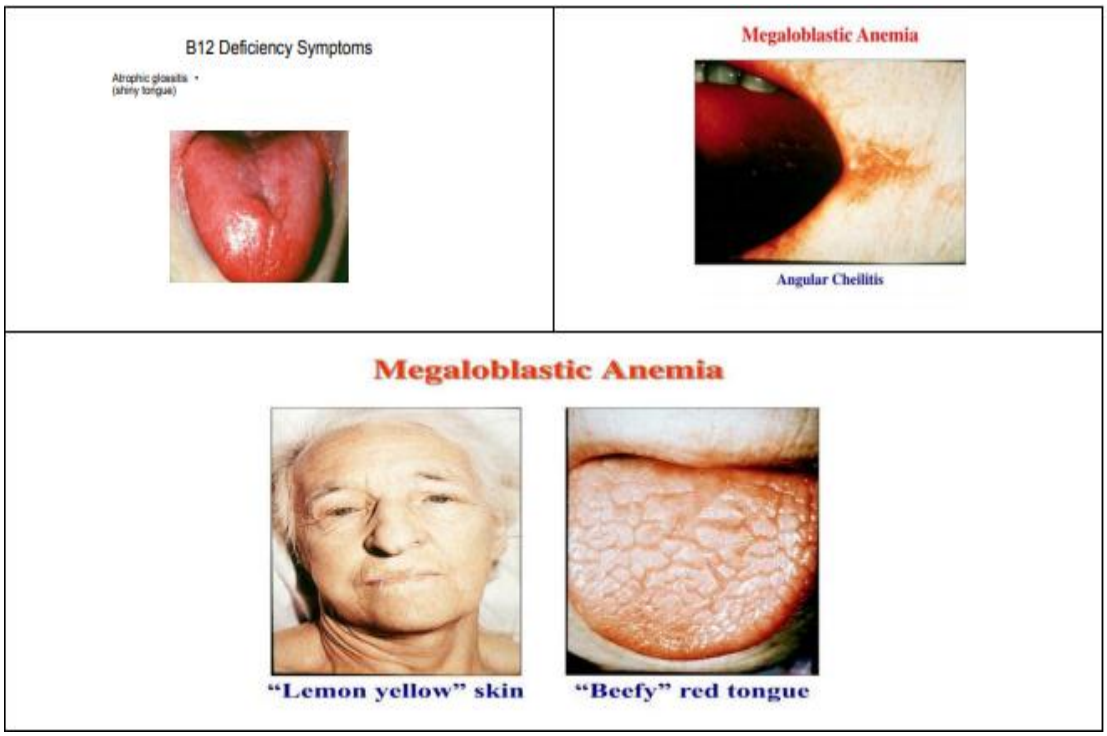
- purpura ,

- wide spread melanin pigmentation and

- loss of weight may also present.

Ξ Severe megaloblastic anemia may cause a progressive neuropathy affecting the peripheral sensory nerves and the spinal cord. The neuropathy is symmetrical and affects the lower limbs more than the upper. The patient suffers from tingling and numbness in the feet with difficulty in walking. This condition is called subacute combined degeneration of the spinal cord (SCDSC).

Ξ Folate or vitamin B12 deficiency in the mother predisposes to neural tube defect (NTD) or spina bifida in the fetus.



CAUSES OF MEGALOBLASTIC ANEMIA

1. Nutritional :

- dietary Vit. B12 or folate deficiency , or
- vegans (vegetarians) in case of Vit. B12 deficiency.
- Megaloblastic anemia develops in infants fed on goat milk.

2. Malabsorption

- disease celiac,
- gastrectomy total or partial
- and gastric carcinoma

3. Increased demand : as in pregnancy , infants and growth requirements.

4. Abnormal metabolism of Vit. B12 or folate.

5. Defects in DNA synthesis: and this defect may be due to :

a-Congenital causes

b-Acute severe pancreatitis and fish tape worm infestation (Diphyllobotherium latum).

c- Therapy with cytochemical drugs (hydroxyurea or methotextrate) or with certain antiviral and antibacterial drugs.

Vitamin B12 (Cobalamin) metabolism

Vitamin B12 is an essential vitamin. This means that the body requires vitamin B12 to work properly. .

- Vitamin B12 is synthesized in nature by microorganisms and by internal production from intestinal bacteria.

- It is found in foods of animal origin , such as meat, liver , fish , and dairy products.

- It can also be made in a laboratory - It is often taken in combination with other B vitamins

- Daily requirement of vitamin B12 is 1-2 mg/day.

- The total stores in the liver and in all body is 1-2 gm , which is enough for 2-3 years.

Folic acid (Pterol glutamic acid) metabolism/ vitamin B9

- Folic acid is found in green vegetables , milk and wheat.

- So deficiency due to decreased uptake is rare , but tissue stores can be depleted in few weeks.

- Folate is absorbed in the duodenum and jejunum and conjugated in the presence of vitamin B12 , which is very important in the DNA synthesis.
- The daily requirement of folate is 100µg , while the tissue stores is about 200 mg , which is enough for few weeks.

Laboratory diagnosis of megaloblastic anemia

1-Hb concentration and RBC counts are below normal , while MCV is high > 100FL

2- Reticulocytes are normal or slightly decreased

3- Leukocytes and platelets are moderately reduced

4- Blood film shows macrocytes with ovalocytes. Anisocytosis and poikilocytosis are also seen.

5- Presence of hypersegmented neutrophils in the blood films of megaloblastic anemia. Blood biochemistry may show increased unconjugated bilirubin and LDH enzyme

6- Decreased serum B12 concentration in case of vitamin B12 deficiency , and decreased serum folate in case of folic acid deficiency

7- Bone marrow reveals megaloblastic hyperplasia (hypercellular megaloblasts).

Hemoglobin

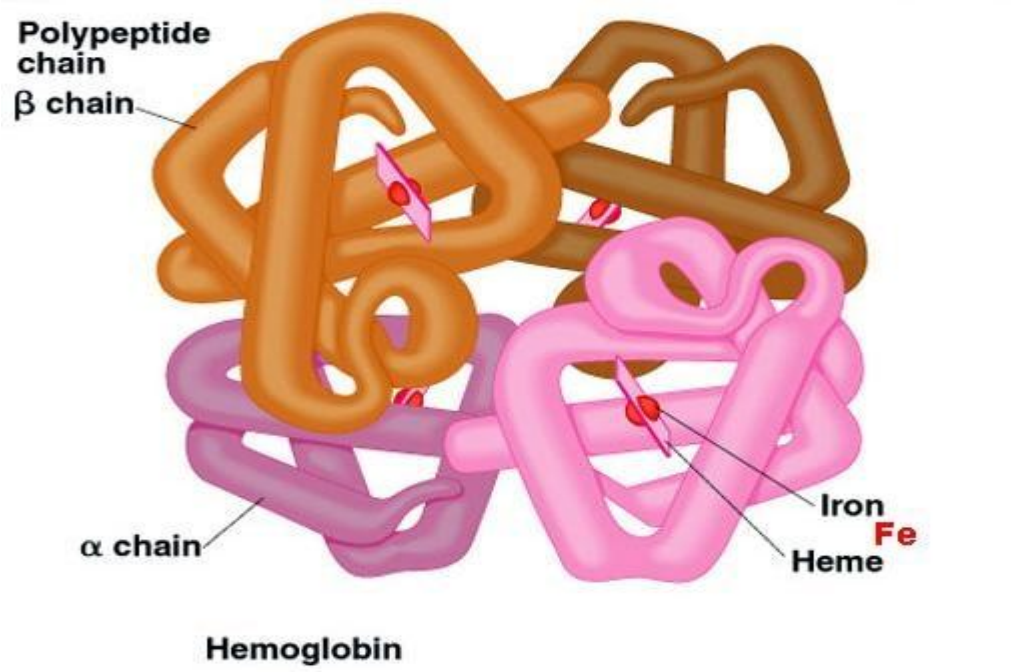
Hemoglobin Structure And Synthesis

Hemoglobin is the specialized protein molecule in red blood cells that carriers oxgeny from the lung to the body tissues and returns carbon dioxide from the tissuse back to the lungs .

Hemoglobin is made up of four protein molecules (globin chains) that are connected together .the normal adult hemoglobin (Hb) molecule contains two alpha-globulin chains and two beta –globulin chains .in fetus and infants ,beta chains are not common and the hemoglobin molecule is made up of two alpha chains and two gamma beta chains .As the infant grows ,the gamma chains are gramma chains are gradually replaced by beta chains forming the adult hemoglobin structure.

Each globulin chain contains an important central structure called the heme molecule. Embedded within the heme molecule is molecule is iron that is vital in transporting oxgen and carbon dioxide in our blood .the iron contained in hemoglobin is also responsible for the red color of blood

Hemoglobin also plays an important an important role in maintaining the shape of the red blood cell. In their natural shape ,red blood cell are round with narrow centers similar to a donut without a hole in the middle.
Abnormal hemoglobin structure can ,for that reason ,disorder the shape of red blood cells and hold back their function and flow through blood vessels



Hemoglobin

Normal Hemoglobin values :

The Hemoglobin level is expressed as the amont of Hemoglobin in grams (gm) per deciliter (dL) of whole blood ,a deciliter being 100 millititers
The normal ranges for Hemoglobin depend on the age beginning in adolescence ,the gender of the person

The normal ranges are
1-newborns :17-22 gm/dl
2-one(1)week of age :15-20 gm/dl
3-children:11-13 gm/dl
4-children:11-13 gm/dl
5-Adult male:14-18 gm/dl
6-men after middle age :12.4-14.9 gm/dl
7-women after middle age :11.7-13.8 gm/dl

Normal Hemoglobin types:

Normal Hemoglobin types found in our body include Hb.A, Hb.A2.and Hb.F.

- Hemoglobin A (Hb A): makes up about 95%-98% of hemoglobin found in adults; it contains two alpha (α) chains and two beta (β) protein chains.

- Hemoglobin A2 (Hb A_2): makes up about (1.5-3.2)% of hemoglobin found in adults; it has two alpha (α) and two delta (δ) protein chains.
- Hemoglobin F: makes up about (0.5-0.8)% of the Hb.found in your body it has two alpha and two gamma protein chains.
  *65% of hemoglobin is synthesized in the erythroblasts
  *35% of hemoglobin is synthesized at reticulocyte stage .
  *haem synthesis occurs largely in the mitochondria by series of biochemical reaction

Hemoglobin variants

Several hundred abnormal forms of hemoglobin (variants) have been identified, but only a few are common and clinically significant.
Common hemoglobin variants

- ***Hemoglobin S:*** this is the primary hemoglobin in people with sickle cell disease (also known as sickle cell anemia). Approximately 1 in 375 African American babies are born with sickle cell disease, and about 100,000 Americans live with the disorder, according to the Centers for Disease Control and Prevention. Those with Hb S disease have two abnormal beta chains and two normal alpha chains. The presence of hemoglobin S causes the red blood cell to deform and assume a sickle shape when exposed to decreased amounts of oxygen (such as might happen when someone exercises or has infection in the lungs). Sickled red blood cells are rigid and can block small blood vessels, causing pain, impaired circulation, and decreased oxygen delivery, as well as shortened red cell survival. A single beta (β^S) copy (known as sickle cell trait, which is present in approximately 8% of African Americans) typically does not cause significant symptoms unless it is combined with another hemoglobin mutation, such as that causing Hb C or beta thalassemia.
- ***Hemoglobin C:*** about 2-3% of African Americans in the United States are heterozygotes for hemoglobin C (have one copy, known as hemoglobin C trait) and are often asymptomatic. Hemoglobin C disease (seen in homozygotes, those with two copies) is rare (0.02% of African Americans) and relatively mild. It usually causes a minor amount of hemolytic anemia and a mild to moderate enlargement of the spleen.
- ***Hemoglobin E:*** Hemoglobin E is one of the most common beta chain hemoglobin variants in the world. It is very prevalent in Southeast Asia, especially in Cambodia, Laos, and Thailand, and in

individuals of Southeast Asian descent. People who are homozygous for Hb E (have two copies of β^E) generally have a mild hemolytic anemia, microcytic red blood cells, and a mild enlargement of the spleen. A single copy of the hemoglobin E gene does not cause symptoms unless it is combined with another mutation, such as the one for beta thalassemia trait.

Less common hemoglobin variants

There are many other variants. Some are silent – causing no signs or symptoms – while others affect the functionality and/or stability of the hemoglobin molecule. Examples of other variants include: Hemoglobin D, Hemoglobin G, Hemoglobin J, Hemoglobin M, and Hemoglobin Constant Spring caused by a mutation in the alpha globin gene that results in an abnormally long alpha (α) chain and an unstable hemoglobin molecule. Additional examples include:

- ***Hemoglobin F:*** Hb F is the primary hemoglobin produced by the fetus, and its role is to transport oxygen efficiently in a low oxygen environment. Production of Hb F decreases sharply after birth and reaches adult levels by 1-2 years of age. Hb F may be elevated in several congenital disorders. Levels can be normal to significantly increased in beta thalassemia and are frequently increased in individuals with sickle cell anemia and in sickle cell-beta thalassemia. Individuals with sickle cell disease and increased Hb F often have a milder disease, as the F hemoglobin inhibits sickling of the red cells. Hb F levels are also increased in a rare condition called hereditary persistence of fetal hemoglobin (HPFH). This is a group of inherited disorders in which Hb F levels are increased without the signs or clinical features of thalassemia. Different ethnic groups have different mutations causing HPFH. Hb F can also be increased in some acquired conditions involving impaired red blood cell production. Some leukemias and other myeloproliferative neoplasms are also associated with mild elevation in Hb F.
- ***Hemoglobin H:*** Hb H is an abnormal hemoglobin that occurs in some cases of alpha thalassemia. It is composed of four beta (β) globin chains and is produced due to a severe shortage of alpha (α) chains. Although each of the beta (β) globin chains is normal, the tetramer of 4 beta chains does not function normally. It has an increased affinity for oxygen, holding onto it instead of releasing it

to the tissues and cells. Hemoglobin H is also associated with significant breakdown of red blood cells (hemolysis) as it is unstable and tends to form solid structures within red blood cells. Serious medical problems are not common in people with hemoglobin H disease, though they often have anemia.

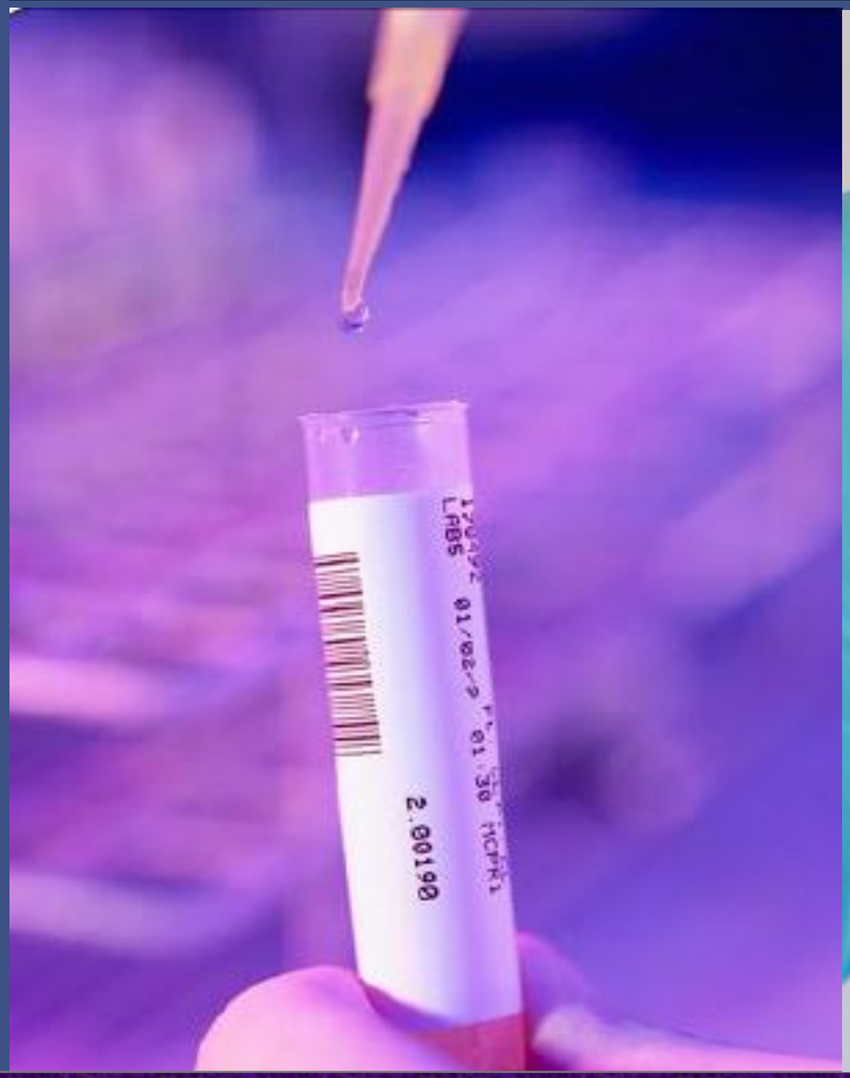
- ***Hemoglobin Barts:*** Hb Barts develops in fetuses with alpha thalassemia. It is formed of four gamma (γ) protein chains when there is a shortage of alpha chains, in a manner similar to the formation of Hemoglobin H. If a small amount of Hb Barts is detected, it usually disappears shortly after birth due to dwindling gamma chain production. These children have one or two alpha gene deletions and are silent carriers or have the alpha thalassemia trait. If a child has a large amount of Hb Barts, he or she usually has hemoglobin H disease and a three-gene deletion. Fetuses with four-gene deletions have hydrops fetalis and usually do not survive without blood transfusions and bone marrow transplants.

A person can also inherit two different abnormal genes, one from each parent. This is known as being compound heterozygous or doubly heterozygous. Several different clinically significant combinations are listed below.

- ***Hemoglobin SC disease***: inheritance of one beta S gene and one beta C gene results in Hemoglobin SC disease. These individuals have a mild hemolytic anemia and moderate enlargement of the spleen. Persons with Hb SC disease may develop the same vaso-occulsive (blood vessel-blocking) complications as seen in sickle cell anemia, but most cases are less severe.
- ***Sickle Cell – Hemoglobin D disease:*** individuals with sickle cell – Hb D disease have inherited one copy of hemoglobin S and one of hemoglobin D-Los Angeles (or D-Punjab) genes. These people may have occasional sickle crises and moderate hemolytic anemia.
- ***Hemoglobin E – beta thalassemia***: individuals who are doubly heterozygous for hemoglobin E and beta thalassemia have an anemia that can vary in severity, from mild (or asymptomatic) to severe, dependent on the beta thalassemia mutation(s) present.
- ***Hemoglobin S – beta thalassemia:*** sickle cell – beta thalassemia varies in severity, depending on the beta thalassemia mutation inherited. Some mutations result in decreased beta globin production ($beta^+$) while others completely eliminate it ($beta^0$). Sickle cell – $beta^+$ thalassemia tends to be less severe than sickle cell – $beta^0$ thalassemia. People with sickle cell – $beta^0$ thalassemia tend to have more irreversibly sickled cells, more frequent vaso-

occlusive problems, and more severe anemia than those with sickle cell – beta^{+}thalassemia. It is often difficult to distinguish between sickle cell disease and sickle cell – beta^{0} thalassemia.

β-thalassemia Syndromes



Developed by-Dr.Abdulrazzaq Othman Alagbare
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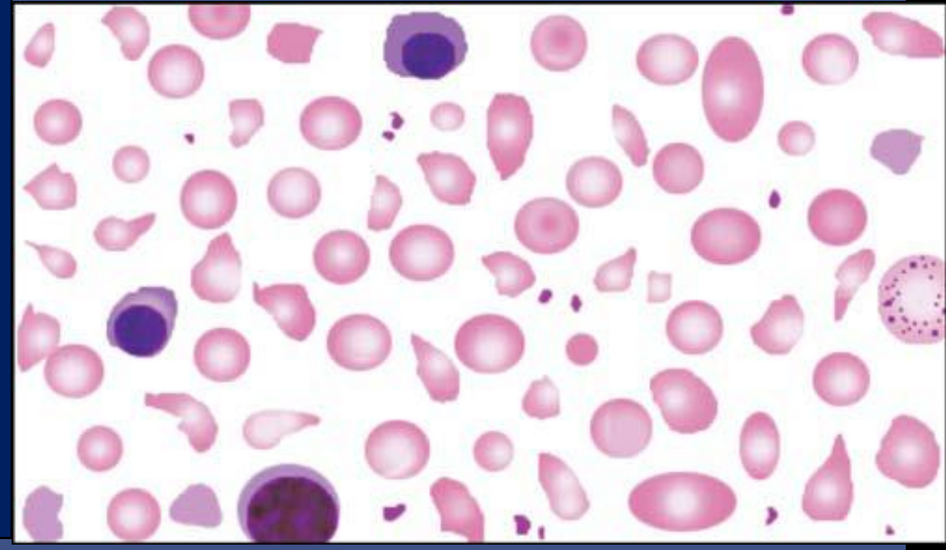
β Thalassaemia major
(homozygous β thalassaemia), (Mediterranean or Cooley's anaemia

- Sever anemia
- Defect in **both beta chains** (the tow beta chains are absent).. Homozygous (β0/β0).
- Presents with severe anemia **at 6 months**
- **HbF not developed** to **HbA** in the first year of the life
- The main Hb is the **HbF remain all life** with sever hemolysis
- Most patients need **regular transfusion.**
- The main problem of those patients is **iron over load.**
- Onset at 6–9 months; severe anaemia, jaundice, failure to thrive, hepatosplenomegaly, bony abnormalities, gallstones,leg ulcers, intercurrent infections

β-thalassaemia Major	Homozygous forms 1. β^0/β^0 2. β^0/β^+ 3. β^0/HbE, 4. β^+/HbE,

- Usually sever symptoms,
- sever microcytic hypochromic anemia (Hb 2 and 6 g/dl),
- Target cells, basophilic stippling, NRBC
- Increase of reticulocytes 5-15%
- HbF >90% , HbA :Absent

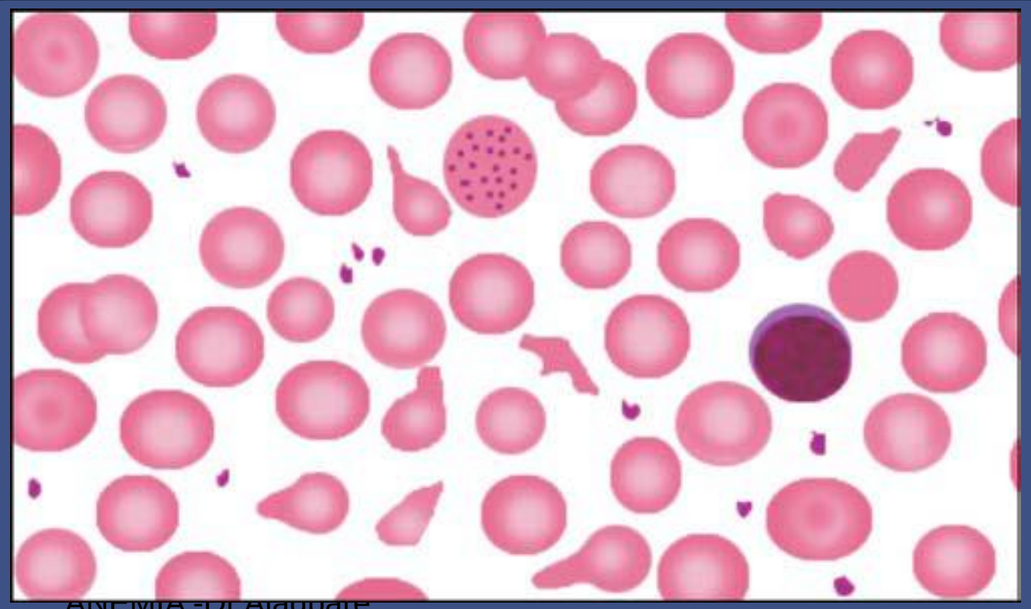


β Thalassaemia trait (heterozygous carrier)

- Mild hypochromic microcytic anaemia
- Heterozygous for β^{+} or β°
- RBC is elevated over ***5.5 million per cum***
- Not needs blood transfusion,
- No hemolysis signs
- Patient is asymptomatic phenotype
- **Raised Hb A2 level**

β-thalassaemia Trait	Heterozygous forms 1. β0/β 2. β/β+

- **Usually asymptomatic;**
- **mild microcytic hypochromic anaemia (Hb 10–11 g/dL)**
- **Raised HbA2 (4–8% of total Hb, normally 2%)**



- **Target cells**
- **Basophilic stippling**
- **Microcytosis**
- **Hypochromia**

Typical clinical and laboratory features in β thalassaemias

Type	Genotype	Anaemia	Red cell morphology	Hb electrophoresis	Clinical features
β thalassaemia minor	β/β^+, β/β^0	Absent or mild (Hb > 10 g/dl)	Microcytic hypochromic; target cells, basophilic stippling	HbA2 > 3.5%; HbF<10%	Asymptomatic
β thalassaemia major	β^0/β^0, β^0/β^+, β^+/β^+, β^0/HbE, β^+/HbE	Severe (Hb <7 g/dl)	Severe aniso-poikilocytosis, microcytosis, hypochromia, many target cells, basophilic stippling, many nucleated red cells	HbF (10–95%); Absent or little HbA; HbA2 normal or raised	Onset in infancy; splenomegaly +++; marked skeletal changes; transfusion-dependent

Thalassaemia Diagnostic tests results

Clinical syndrome	Electrophoresis Result			
	HbA	HbA2	HbF	Pathological Hb
❖β-thalassaemia major	Zero	Normal	90%	
❖β-thalassaemia minor (trait)	50-70%	7%	20%	

Clinical syndrome	DNA analysis Result	
	β - chains	**α - chains**
❖β-thalassaemia major	**Absence**	Normal
❖β-thalassaemia minor (trait)	One β chains absent	Normal


الحمد لله رب
العالمين
هذاعمل ابتغي به
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