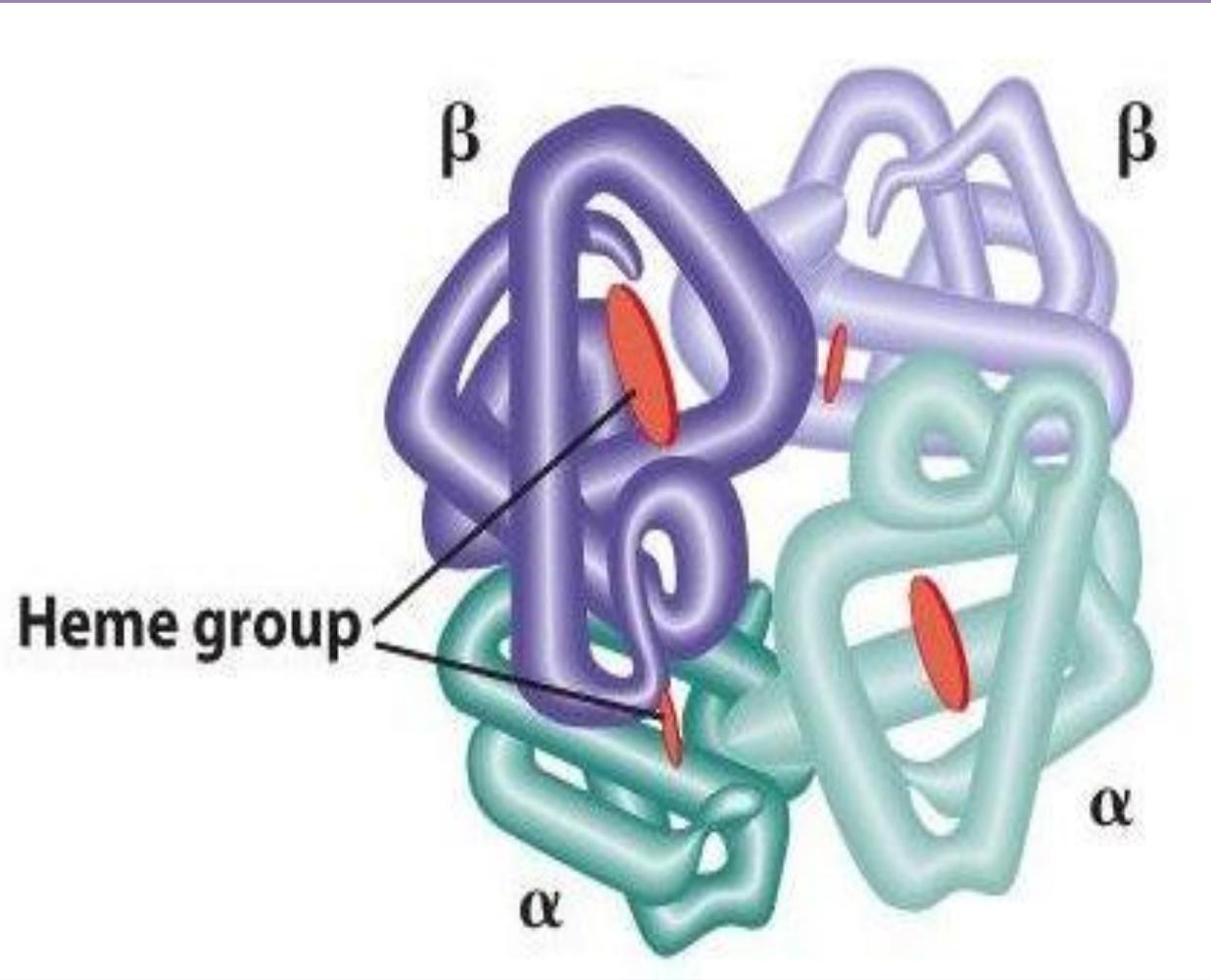


Disorders of Red Blood Cells

The function of RBC, facilitated by hemoglobin molecule, is to transport oxygen to the tissue.

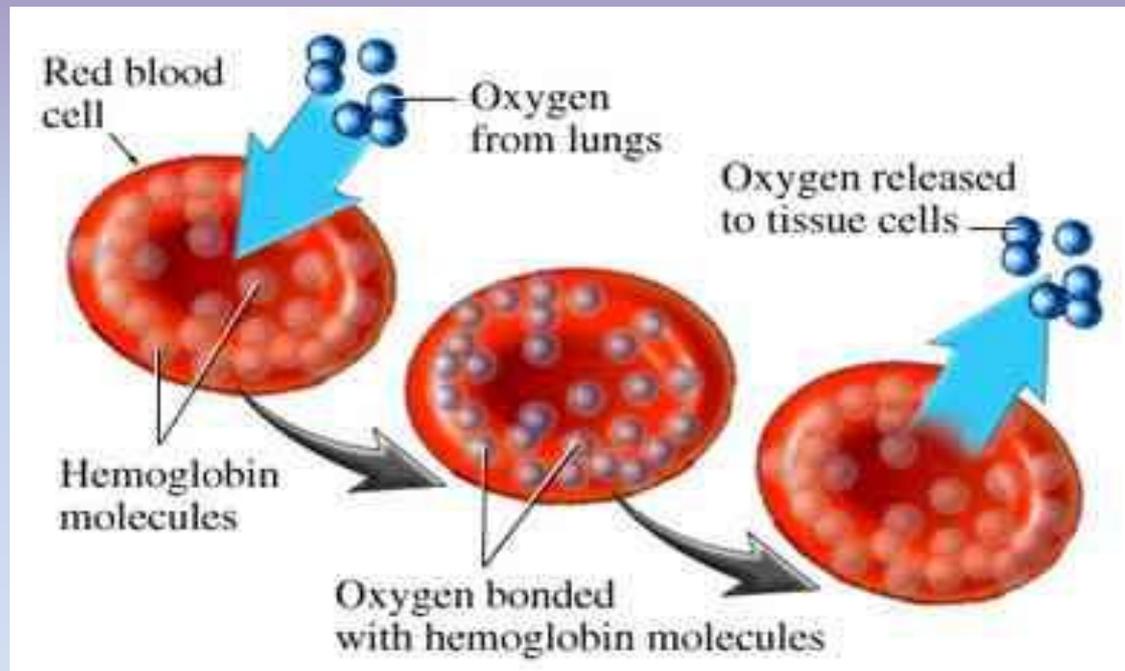
Oxygen is poorly soluble in plasma, So about 95%-98% is carried bound to hemoglobin.

The Hb molecule is composed of two pairs of structurally different α and β chains. Each of four polypeptide chains consists of globin (protein) and a haeme unit which surrounds an atom of iron that binds oxygen. Thus Hb can carry four molecules of Oxygen.



- The production of each type of globin chain is controlled by individual structural genes with five different gene loci.
- Mutations which occurs in anywhere in these five loci resulted over 550 types of abnormal Hb molecules.

Red cell Metabolism



- The RBC lacks mitochondria; it depends on glucose and glycolytic pathway for its metabolic needs.
- The enzyme mediated anaerobic metabolism of glucose generates the ATP need for normal membrane function and ion transport.
- The depletion of glucose or the functional deficiency of one the glycolytic enzymes leads to the premature death of RBC.

An offshoot of the glycolytic pathway is the production of **2,3-diphosphoglycerate (2,3-DPG)**, which binds to the Hb molecule and reduces the affinity of Hb for Oxygen.

This facilitates the release of Oxygen at the tissue level.

- An increase in the concentration of 2,3- DPG occurs in conditions:

Chronic hypoxia like in case anemia, chronic lung disease, and residence at high attitudes.

Hemoglobin Oxidation

- The combination of Hb with oxygen can be interrupted by certain chemicals (e.g. nitrates and sulfates) and drugs that oxidize Hb to the inactive form.
- The nitrite ion reacts with Hb to produce methemoglobin, which has a low affinity for Oxygen.
- Large doses of nitrites can result in high levels of methemoglobin, causing pseudocyanosis and tissue hypoxia. For example, sodium nitrate, which is used in curing meat, can produce methemoglobin when taken in large amounts.

Anemia

- Abnormally low number of circulating RBC or level of Hb or both, resulting in diminished oxygen-carrying capacity.
- Causing:
 - 1). Excessive loss of RBC:
 - Hemorrhage
 - Hemolysis
 - 2). Impaired RBC production result from:
 - Depression in bone marrow
 - Inhered
 - Nutritional
 - Bone marrow cancer

Hemolytic Anemia

- It is characterized by the premature destruction of RBC , the retention in the body of iron and the other products of Hb destruction and an increase in erythropoiesis.
- All most all types of hemolytic anemia are distinguished by normocytic normochromic RBC

- Because of the red blood cells shortened life span, the bone marrow usually is hyperactive, resulting an increased number of reticulocytes in the circulating blood.
- There is hemoglobinuria and hemoglobinemia and jaundice when the hemolysis occurs intravascular.
- The person is easy fatigable, dyspnea, tachycardia

Classification of Hemolytic anemia

1). According the occurrence of RBC breakdown (outside or inside of blood vessel):

a) Intravascular breakdown e.g. toxin, drug, parasite.

b) Outside the vascular compartments like in spleen occurs when there is deformity in RBC.

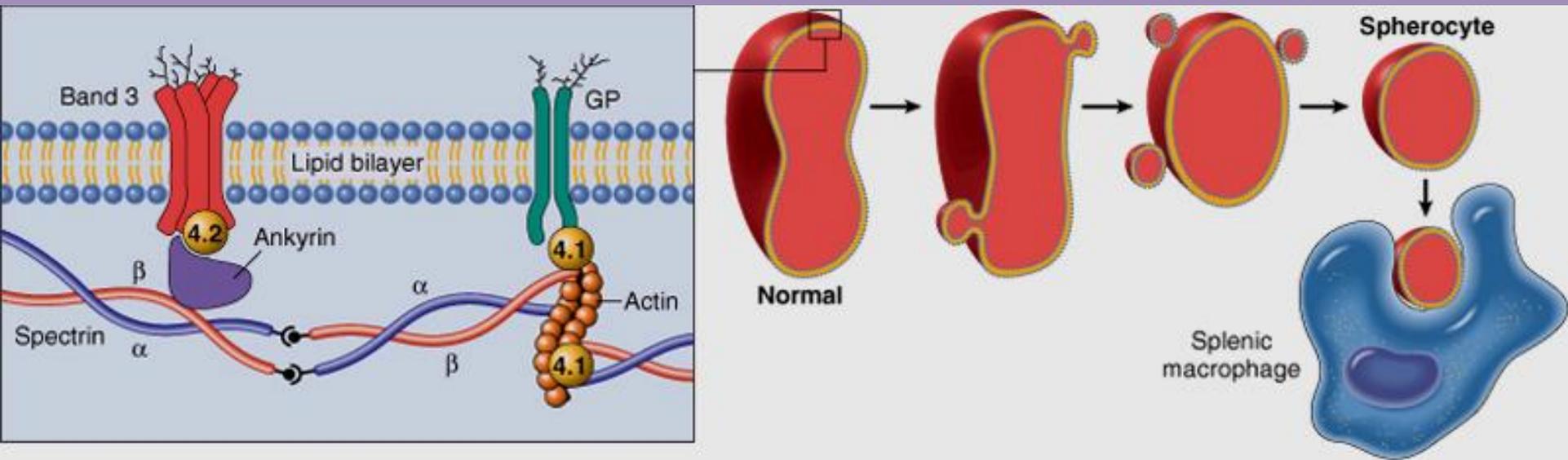
2). According to the cause, either intrinsic or extrinsic

- Intrinsic causes include defects of the red blood cell membrane, the various hemoglobinopathies, and inherited enzyme defect.
- Extrinsic causes occur due to toxin, malaria, antibodies....ect.

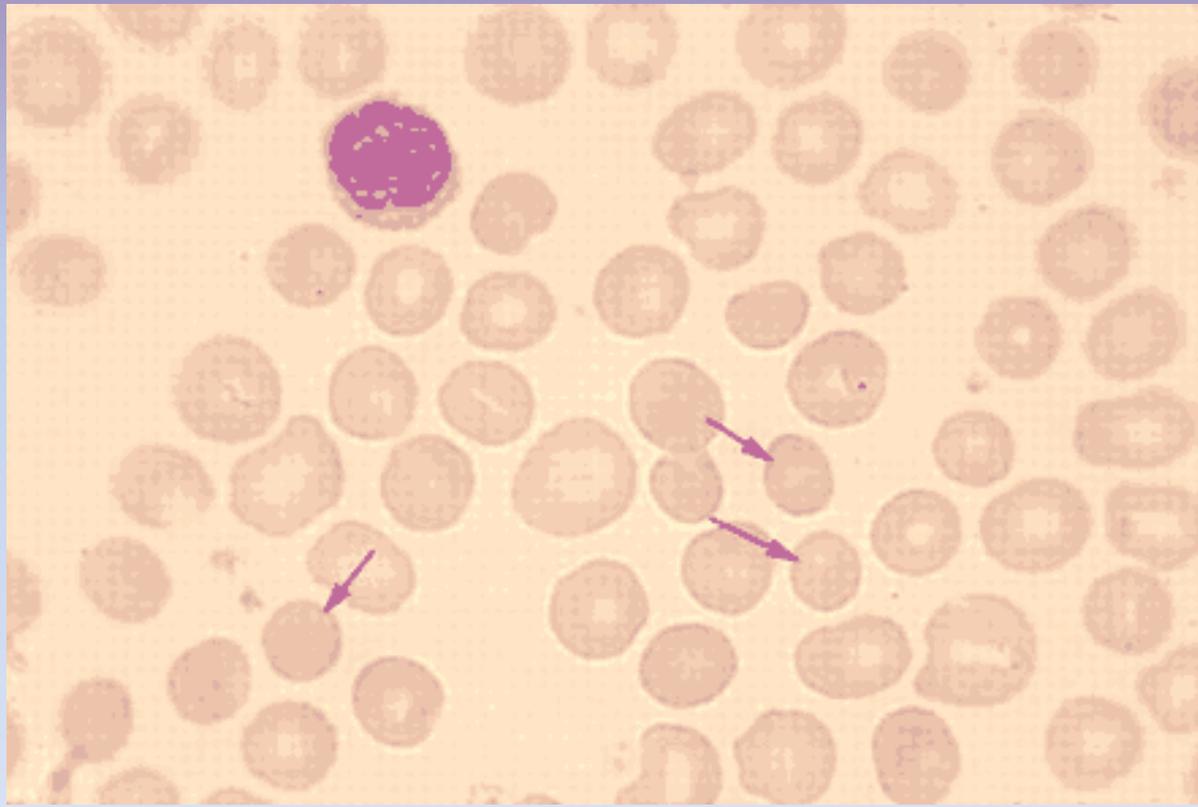
Intrinsic Causes

- **Inherited disorders of RBC membrane**
- Hereditary Spherocytosis:
 - The most common inherited disease of the red blood cell membrane.
 - The disorder is caused by *abnormalities of the two types of membrane proteins*, that lead to a gradual loss of the membrane surface.
 - These changes lead the cell to become a *tight sphere instead of a concave disk*.

Pathogenesis of hereditary spherocytosis



The red cell membrane cytoskeleton and the effect of alterations in the cytoskeleton proteins on red cell shape. With mutations that affect the integrity of the membrane cytoskeleton, the normal biconcave erythrocyte loses membrane fragments. To accommodate the loss of surface area, the cell adopts a spherical shape. Such spherocytic cells are less deformable than normal and are therefore trapped in the splenic cords, where they are phagocytosed by macrophages. GP, glycophorin.



In this case the cell has ability to carry Oxygen but membrane deformity makes the cell susceptible to destruction as it pass through the spleen

- Clinical signs
- Mild hemolytic anemia, jaundice, Splenomegaly, and gall stone.
- Treatment
Splenectomy to reduce RBC destruction.
blood transfusion

2). Acanthosis

- Acanthosis refers to a group of anemias in which the erythrocyte membrane shows multiple irregular projections by defect in the lipid bilayer.
- Occurs in liver diseases and inherited defect in absorption and transport of lipid by intestine.

Abnormality in the HB

The Thalassemias

- The Thalassemias are the group of inherited disorders of Hb synthesis characterized by lack of or decreased synthesis of either α or β globin chains.
- In α -thalassemia, α globin chain synthesis is reduced.
- In β -thalassemia, β chain synthesis is either absent or markedly deficient.

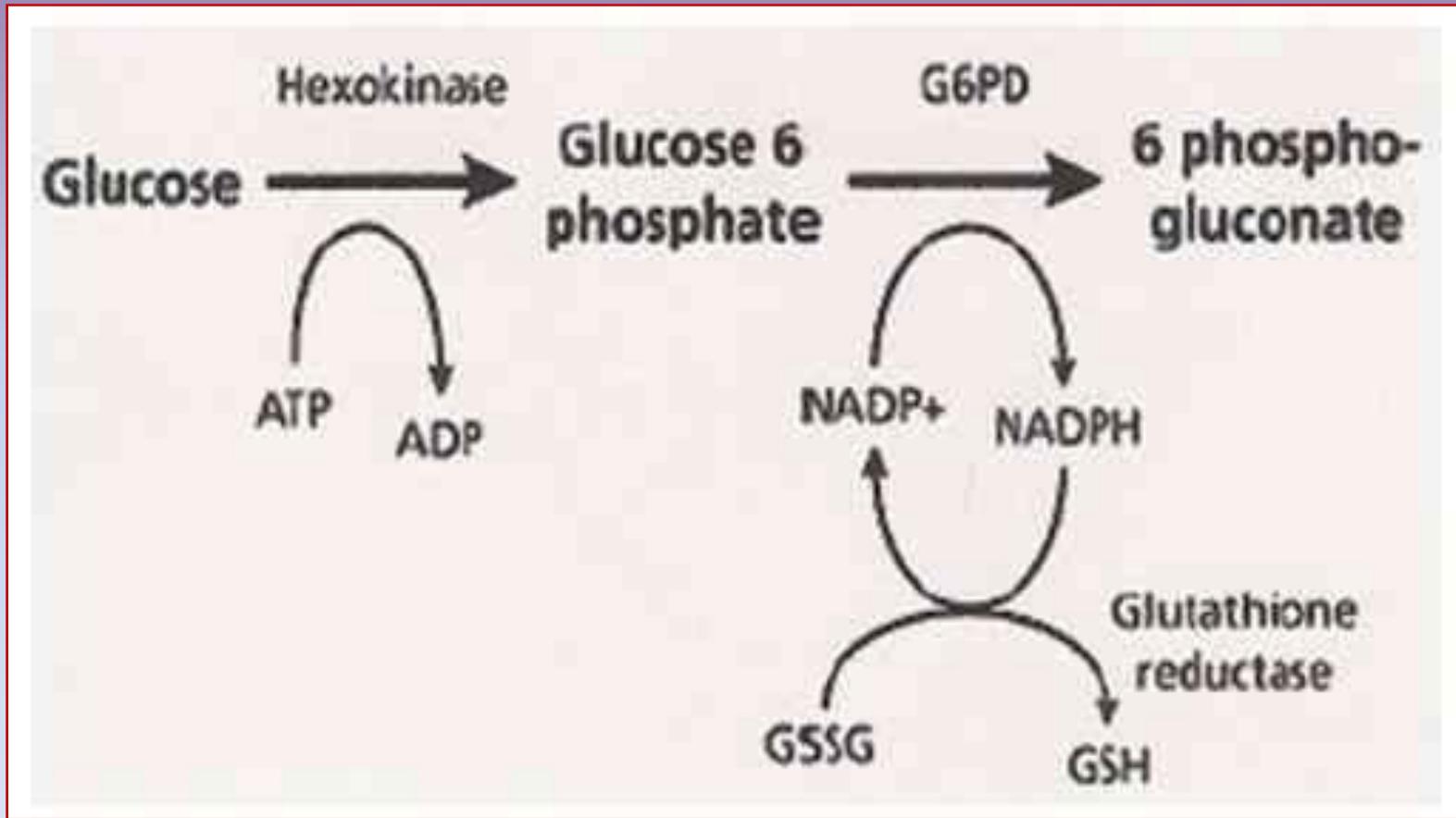
Two factors contribute to the anemia that occurs in Thalassemias:

- 1). Low intracellular HB (hypochromic) is due to the decrease synthesis of the affected chain.
- Continued production and accumulation of the unaffected globin chain.

- The reduce Hb synthesis result in hypochromic, microcytic anemia
- The accumulation of the unaffected chain refers with normal red cell maturation and contributes to membrane changes that lead to hemolysis and anemia.
- *α chain is insoluble* so when accumulated in the RBC form precipitate (Heinz bodies).
- The Heinz bodies impair DNA synthesis and cause damage to the RBC.

- Accumulation of α chain leads to breakdown RBC precursor in the bone marrow, and few of those abnormal red cells leave bone marrow will be destruct in spleen.
- β chain is soluble, so accumulation of β chain produce less severity of thalasseмииas.
- The clinical manifestations of β thalasseμία are based on the severity of anemia.
- Person who carries one normal gene (heterozygous) has minor thalasseμία.
- Homozygous undergoes major thalasseμία.

Glucose-6-phosphate Dehydrogenase Deficiency (G-6-PD)



Glucose-6-phosphate Dehydrogenase Deficiency (G-6-PD)

- Glucose-6-phosphate dehydrogenase is an X-linked recessive hereditary disease.
- characterized by abnormally low levels of glucose-6-phosphate dehydrogenase, a metabolic enzyme especially important in red blood cell metabolism.
- and the individuals with the disease may exhibit hemolytic anemia in response to infection and chemicals

The defect expressed only in the male and homozygous females.

- The inclusion bodies makes red cells more vulnerable to oxidants and causes direct oxidation of Hb to methmoglobin.
- Methmoglobin cannot transport oxygen and denaturing of the hemoglobin molecule to form Heinz bodies.

Heinz Bodies

- These are inclusion bodies appeared in the red blood cells due to damaging in Hb molecules.
- Many substances are potentially harmful into people with G6PD deficiency such as:
- Antimalaria (primaquine, Pamaquine, and chloroquine)

Other types of Anemias

- Decrease production of RBC:
- Occurs due to: Deficiency of nutrient for Hb synthesis like iron deficiency.
- Deficiency of nutrient for DNA synthesis like B12 (cobalamin) deficiency and folic acid deficiency.
- Vitamin B12 is essential for DNA synthesis and nuclear maturation.
- Vitamin B12 involved in reaction that prevents abnormal fatty acid from being incorporate into neuronal lipid.

- Vitamin B12 needs intrinsic factor for absorption from intestine.
- When Vit. B12 is deficient the red cells that produced are abnormally large because excess cytoplasmic anemia. The cells have immature nuclei and show evidence of cellular destruction.
- The loss of red cells is a moderate to severe anemia and mild jaundice.

Polycythemia

- Polycythemia or erythrocytosis is an increased concentration of red blood cells.
- Such increase may be relative or absolute.

- Relative Polycythemia:

The red blood cell mass increase because of loss of plasma.

This occurs due to water deprivation, dehydration, vomiting, and excess use of diuretics.

- Absolute Polycythemia is a rise in red blood cells due to an increase in total red blood cell mass and is classified as primary or secondary.

Primary Polycythemia (*Polycythemia Vera*)

- Is a neoplastic disease of the pluripotential cells of bone marrow characterized by an absolute increase in total red blood cell mass accompanied by elevated white cell and platelet counts. It is seen in men with median age of 62 years but may occurs in many age.

MANIFESTATION OF *POLYCYTHEMIA VERA*

- Increase in red blood cells, Hb and blood viscosity.
- Splenomegaly and depletion of iron store.
- Increase blood viscosity interferes with cardiac output and blood flow.
- Hypertension is common and associated with headache, dizziness, inability to concentrate and some difficulty with hearing and vision because of decrease cerebral blood flow

- Venous stasis, thromboembolism, and hemorrhage due to defect in function of platelet.

- **Treatment:**

1. Phlebotomy
2. Chemotherapy

Secondary Polycythemia

- Increase erythropoietin due to hypoxic conditions like chronic heart and lung diseases.
- Erythropoietin is secreted by kidney and on bone marrow to increase production of blood cells.