<u>Sickle cell Anemia:</u>

Sickle cell disease is the *most common structural hemoglobin variant*. It is an *inherited chronic hemolytic anemia* whose clinical manifestations arise from the tendency of the hemoglobin (HbS or sickle haemoglobin) to polymerize and deform red blood cells into the characteristic sickle shape.

This property is due to a *single nucleotide change in the β-globin gene* (due to GAG→GTG mutation) leading to *substitution of valine for glutamic acid at codon position 6 of the β-globin chain* (**β6glu→val**).

Sickle cell anemia occurs when an individual is homozygous for the sickle cell gene. Sickle trait occurs with heterozygote mutation and is entirely benign. Sickle cell disease term is reserved for patients with combined heterozygote hemoglobinopathy.

Hemoglobin S occurs with greatest prevalence in tropical Africa. The high prevalence of the gene for sickle hemoglobin in areas where malaria has been common is due to that persons with sickle cell trait have a selective advantage over normal individuals when they contract this disease.

Hemoglobin S becomes polymerized and poorly soluble when the oxygen tension is lowered and red cells that contain this hemoglobin become distorted and rigid.

Deoxygenation of HbS leads to a conformational change that exposes a hydrophobic patch on the surface of the βs-globin chain at the site of β6 valine. Binding of this site to a complementary hydrophobic site on a βsubunit of another hemoglobin tetramer triggers the formation of large polymers.

The hemoglobin level is normal in the newborn period, but anemia develops and sickle cells can be observed in the peripheral blood by 3–4 months of age as HbF declines.

Peripheral blood findings: In HbSS disease, the red cells are normocytic and normochromic, and it may show the characteristic shape change, so-called sickle cells.

Reticulocyte % is increased.

The white cell count is elevated as a result of an increase in mature neutrophils. The platelet count is also elevated as a result of decreased splenic function.

Diagnosis: depends upon demonstrating the presence of the abnormal hemoglobin using hemoglobin electrophoresis.

HbS solubility test and Sickling test are useful but they don't differentiate between sickle cell anemia (HbSS) and trait (HbAS).

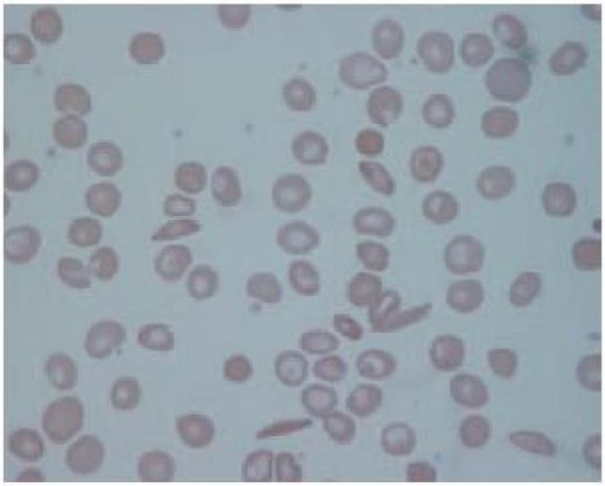
Neonatal screening may be indicated.

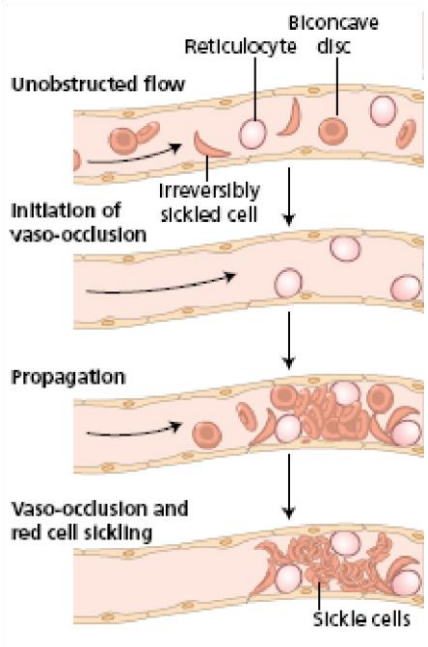
Complications: include splenic infarction and autosplenectomy, stroke, bone infarcts and aseptic necrosis of the femoral head, leg ulcers, priapism, pulmonary hypertension, and renal failure.

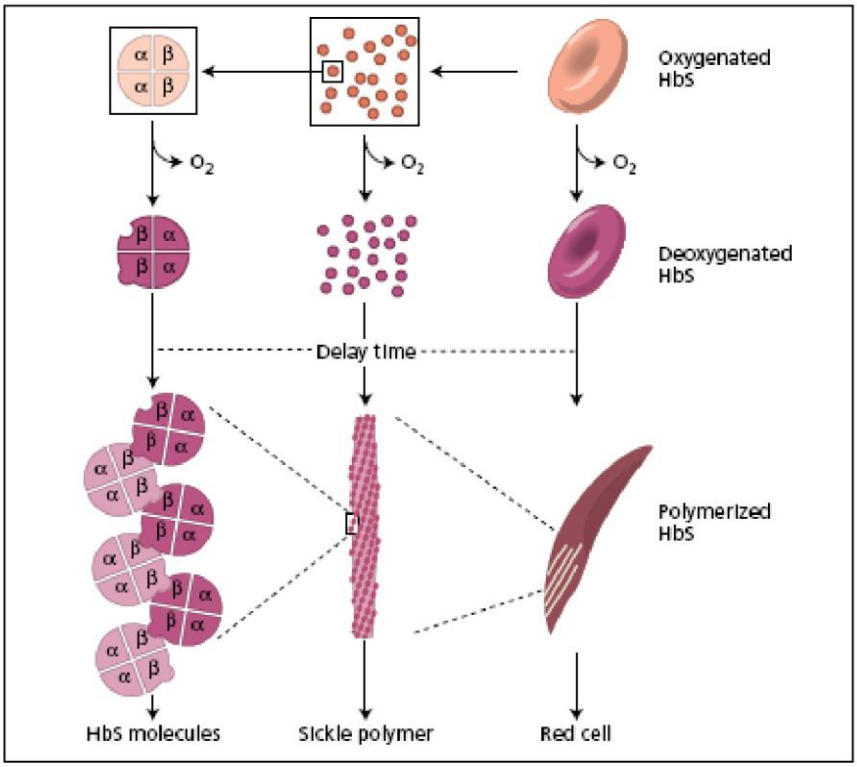
The disease is characterized by *hemolytic anemia* and by three types of *crises*: painful (vaso-occlusive), sequestration, and aplastic.

The severity of clinical manifestations varies greatly from patient to patient, and the aggressiveness of treatment needs to be modified accordingly.

Early diagnosis, immunization against pneumococcal infection, and treatment of infections contributed to improved survival of those born with these disorders. Treatment with hydroxyurea results in amelioration of crises. The rationale for administration of hydroxyurea is its effect of increasing hemoglobin F levels.







Both partially and fully deoxygenated hemoglobin S can be incorporated into a polymer. Long polymers distort the red cell into a crescent or sickle shape that *hinders blood flow through capillaries*, because of both 1st

reduced deformability and 2nd increased adhesion to endothelial cells resulting from *secondary changes in the red cell membrane*.

When fully oxygenated, hemoglobin S is as soluble as hemoglobin A.

The presence of hemoglobin A in a red cell slows polymerization.

Hemoglobin F and hemoglobin A_2 are even more effective at retarding sickling. Hemoglobin F and hemoglobin A_2 cannot copolymerize with hemoglobin S.

Sickling is facilitated by the presence of hemoglobin C, hemoglobin D-Punjab or hemoglobin O-Arab.

Because acidosis and a rise in temperature shift the oxygen dissociation curve to the right, they favor sickling.

However, in clinical practice, exposure to cold can also provoke sickling because of slowed circulation through capillaries.