Sickle cell anemia

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Introduction

Mutations in the globin genes can cause a quantitative ***reduction in output*** from that gene or ***alter the amino acid sequence*** of the protein produced or a ***combination*** of the two.

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-**Quantitative defects cause thalassaemia syndromes,**

-Qualitative changes, referred to as haemoglobin variants, cause wide range of problems, including sickle cell disease , unstable haemoglobins, decreased oxygen affinity, increased oxygen affinity, and methaemoglobinaemia.

- the majority of qualitative mutations cause no significant change in haemoglobin properties or clinical problems.

Collectively**, the clinical syndromes resulting from disorders of haemoglobin synthesis are referred to as 'Haemoglobinopathies'.**

They can be grouped into three main categories:

1. Those resulting from a genetically determined structural variant of haemoglobin , such as haemoglobin S.

2. Those owing to failure to synthesise one or more of the globin chains of haemoglobin at a normal rate, as in the thalassaemias.

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3. Those owing to failure to complete the normal neonatal switch from fetal haemoglobin (haemoglobin F) to adult haemoglobin (haemoglobin A) .

This category comprises a group of disorders referred to as hereditary persistence of fetal haemoglobin (HPFH)

An individual can also have a combination of two or more of these abnormalities (e.g. a variant haemoglobin can be synthesised at a reduced rate).

Sickle cell disease

The term ‘sickle cell disease’ is used to denote all entities associated with sickling of haemoglobin within red cells .

Sickle cell disease is a group of haemoglobin disorders resulting from the inheritance of the sickle β-globin gene .

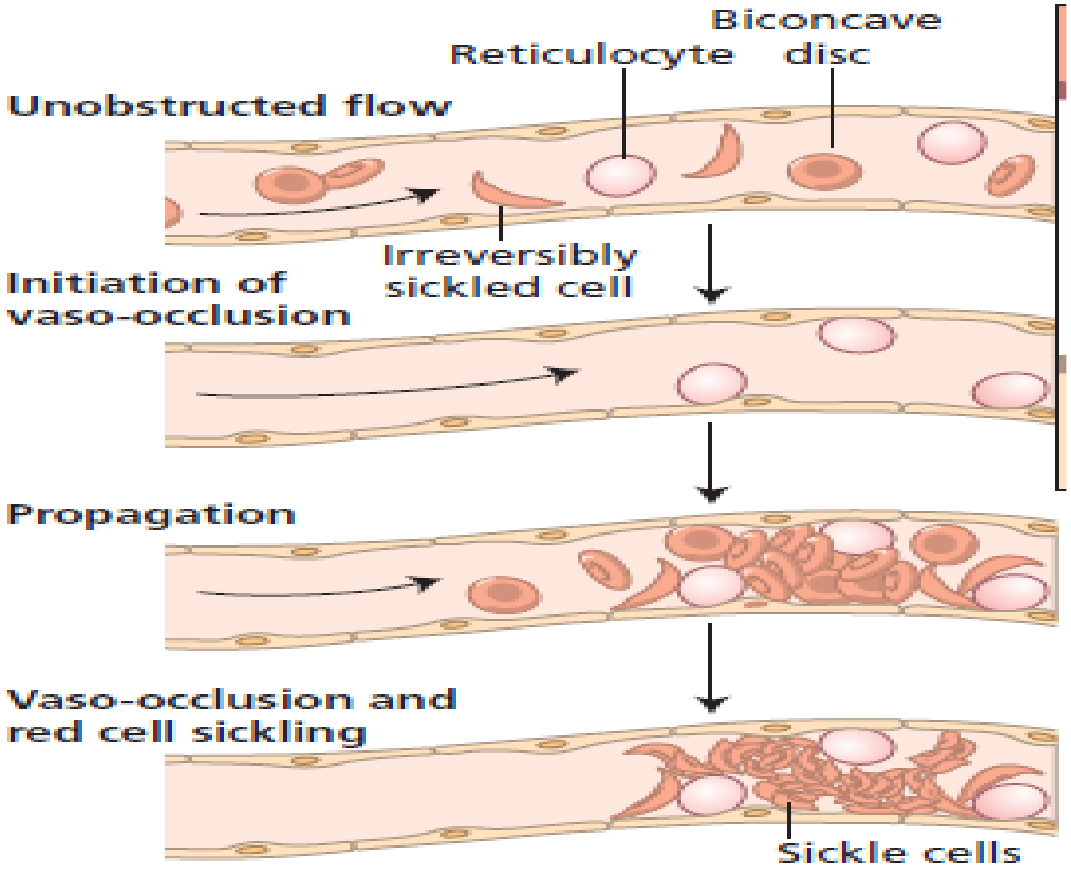
The sickle β-globin abnormality is caused by substitution of valine for glutamic acid in position 6 in the β chain

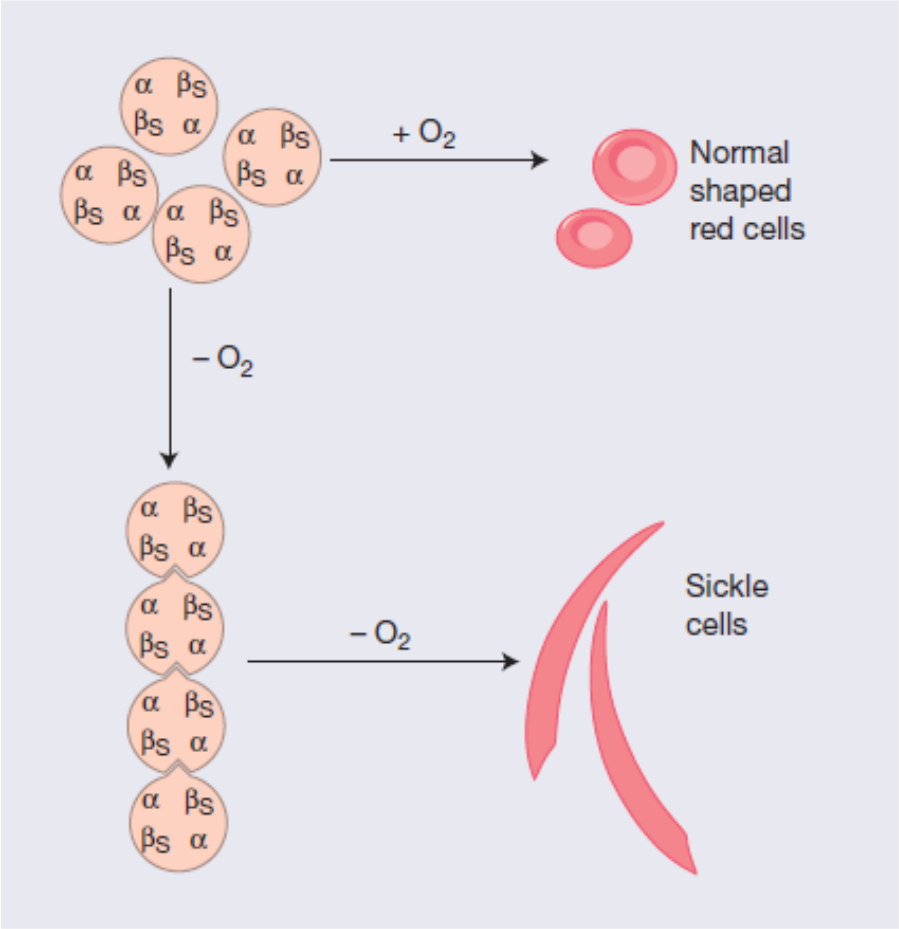
Normal β-chain	Amino acid	pro	glu	glu
	Base composition	CCT	GAG	GAG
Sickle β-chain	Base composition	CCT	GTG	GAG
	Amino acid	pro	val	glu

Homozygous sickle cell anaemia (Hb SS) is the most common severe syndrome while the **doubly heterozygote conditions of Hb S/C and Hb S/β thal also cause sickling disease.**

Hb S(Hb $\alpha_2\beta_2^s$) is insoluble and forms crystals when exposed to low oxygen tension. Deoxygenated sickle haemoglobin polymerizes into long fibres , each consisting of seven intertwined double strands with cross-linking . The red cells sickle and may block different areas of the microcirculation or large vessels causing infarcts of various organs

The polymerization of HbS in the circulating red cells is influenced by the oxygenation status, the intracellular haemoglobin concentration and the presence of non-sickle haemoglobins.


Biconcave
disc
Reticulocyte
Unobstructed flow
Irreversibly
sickled cell
Initiation of
vaso-occlusion
Propagation
Vaso-occlusion and
red cell sickling
Sickle cells


α βS
βS α
+ O2
Normal shaped red cells
– O2
– O2
Sickle cells

Acidosis and elevated levels of 2,3 diphosphoglycerate (2,3- DPG) promote polymer formation by reducing the oxygen affinity of haemoglobin. The presence of HbA within the red cells, as in sickle trait, inhibits polymerization by diluting HbS.

The HbF has an inhibitory effect on polymerization of HbS

SCD is characterized by ***chronic intravascular and extravascular haemolysis.***

Sickling-induced membrane fragmentation and *complement-mediated lysis* cause **intravascular** destruction of red cells.

Membrane damage also leads to **extravascular haemolysis** through entrapment of poorly deformable cells or uptake by macrophages.

Individuals with concomitant deletion of one or two α-globin genes, or the Senegal or Arab–Indian haplotypes, have higher baseline haemoglobin levels.

The carrier state is widespread and is found in up to 30% of West African people ,the sickle trait bestows survival benefit in areas endemic for *falciparum* malaria, and the distribution of SCD historically paralleled this disease. The sickle haemoglobin containing red cells inhibit proliferation of *Plasmodium falciparum*, and are more likely to become deformed and removed from the circulation.

In recent times, the dissemination of the sickle mutation in different areas of the world took place from The movement of populations via trade routes and the slave trade

Homozygous disease

Clinical features

Clinical features are of a severe haemolytic anaemia punctuated by crises.

The symptoms of anaemia are often mild in relation to the severity of the anaemia because Hb S gives up oxygen (O_2) to tissues relatively easily compared with Hb A (low affinity to oxygen).

The clinical expression of Hb SS is very variable, some patients having an almost normal life, free of crises, but others develop severe crises even as infants and may die in .

This is partly due to the effects of inherited modifying factors, such as interaction with α thalassaemia or increased synthesis of haemoglobin F, and partly to socioeconomic conditions and other factors that

influence general healthearly childhood or as young adults..

Crises may be :

1)vaso-occlusive (painful or visceral),
2)aplastic

3) haemolytic.

There may be serious damage to many organs

Vaso-occlusive crises

- **Painful:**

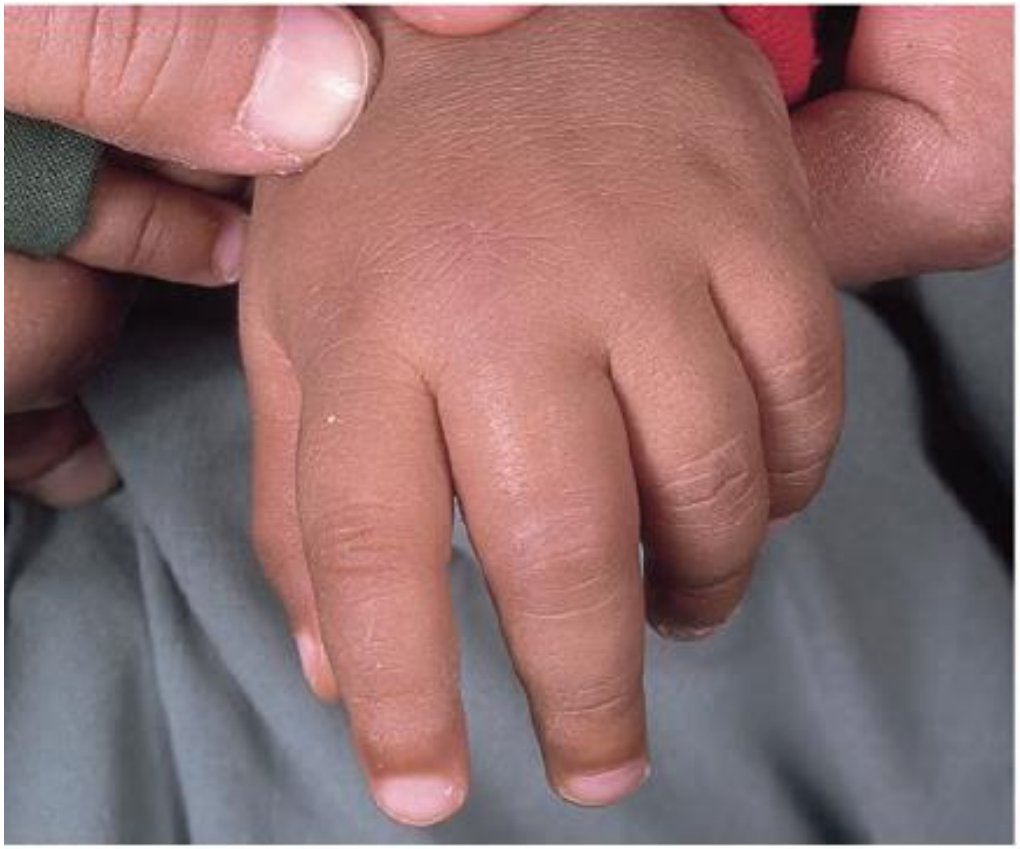
-These are the most frequent.

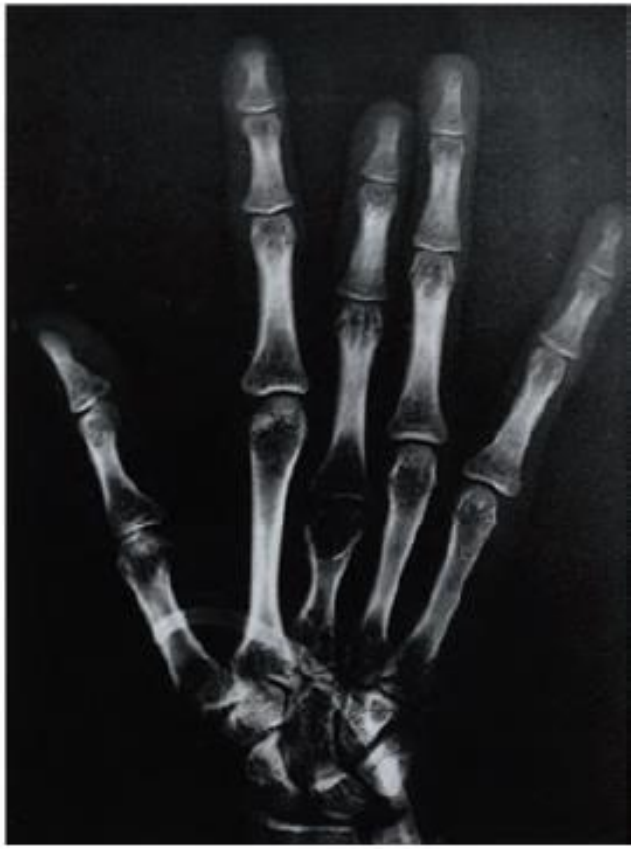
-They may be sporadic and unpredictable or precipitated by infection, acidosis, dehydration or deoxygenation (e.g. altitude, operations, obstetric delivery, stasis of the circulation, exposure to cold, violent exercise).

-Infarcts causing **severe pain occur in the bones** (hips, shoulders and vertebrae are commonly affected) .

-**The ‘hand– foot’ syndrome** (painful dactylitis caused by infarcts of the small bones) is frequently the first presentation of the disease and may lead to digits of varying lengths

'hand–foot' syndrome.





- **Visceral**

These are caused by sickling within organs causing infarction and pooling of blood, often with a severe exacerbation of anaemia.

The **acute sickle chest syndrome** is the most common cause of death both in children and adults. It presents with dyspnoea , falling arterial PO_2, chest pain and pulmonary infiltrates on chest X-ray .

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The pathogenesis of acute chest syndrome involves vaso-occlusion, infection or embolization of bone marrow fat.

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Hypoxia due to acute chest syndrome can result in widespread sickling and vaso-occlusion, with risk of multiorgan failure.

--Hepatic and girdle sequestration crises may lead to severe illness requiring exchange transfusions.

-Splenic sequestration is typically seen in infants and presents with an enlarging spleen, falling haemoglobin and abdominal pain

Attacks tend to be recurrent and splenectomy is often needed..

-Priapism and liver and kidney damage due to repeated small infarcts .

Aplastic crises

- These occur as a result of infection with **parvovirus** or from **folate deficiency** .
- They are characterized by a sudden fall in haemoglobin and reticulocytes, usually requiring transfusion.

Haemolytic crises

- These are characterized by an increased rate of haemolysis and fall in haemoglobin but rise in reticulocytes and usually accompany a painful crisis.

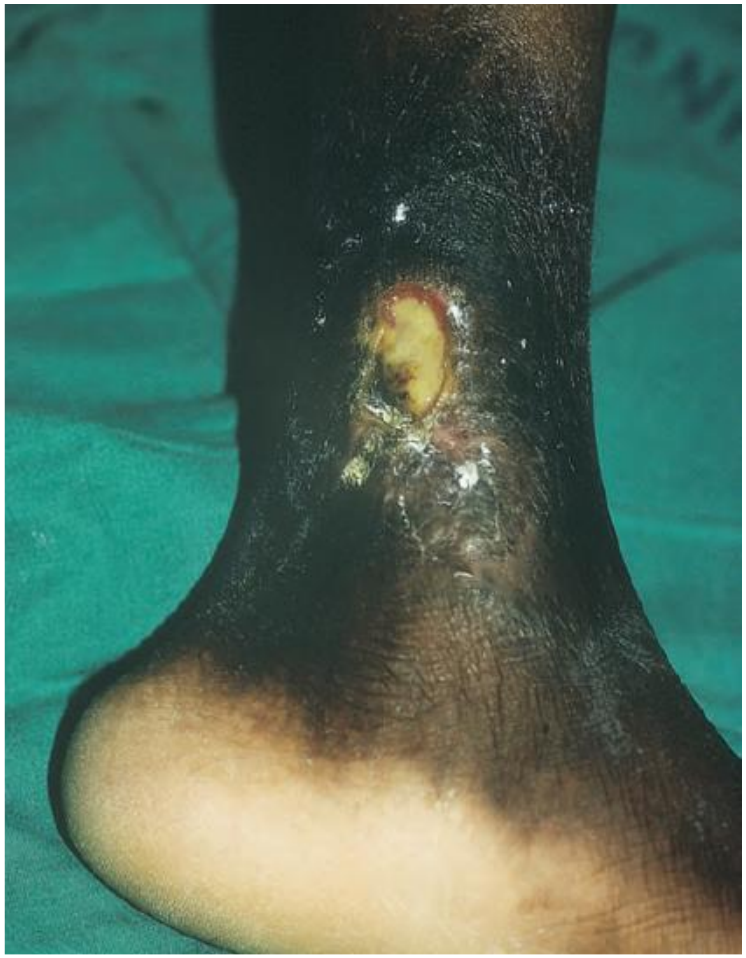
Other organ damage

-The most serious is of the brain or spinal cord.

- Stroke , cognitive impairment in children •

- **Ulcers of the lower legs** are common. Ulcers arise near the medial or lateral malleolus and may be single or multiple. Occlusion of skin microvasculature from sickle red cells predisposes to ulcers, which are made worse by trauma , infection or warm climate .

Leg Ulcer



The spleen is enlarged in infancy and early childhood but later is often reduced in size as a result of infarcts **(autosplenectomy)**.

-Infections are frequent partly due to hyposplenism .

-Pneumonia, urinary tract infections and Gram-negative septicaemia are common.

-Osteomyelitis may also occur, usually from *Salmonella* spp

-Vaso-occlusion of retinal and other vascular beds in the eye can lead to grave complications.

Growth and development

- Children with SCD are born with normal weight , but fall behind other children by the end of the first year .

The pubertal growth spurt is delayed by 1–2 years , but the final adult height is normal. Delays also occur in skeletal maturation and onset of puberty, and female patients achieve menarche 1–2 years later than their peers.

Pregnancy

-The steady-state haemoglobin level falls in SCD during pregnancy, similar to the decline in haemoglobin observed in normal pregnant women.

-Folate deficiency can exacerbate the anaemia and supplements should be
-provided throughout pregnancy.

-Painful episodes become more common in the last trimester.

-The incidence of pre-eclampsia is higher than normal in SCD patients and there is a slight increase in maternal mortality.

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Risk to the fetus from abortion, stillbirth, low birth weight and neonatal death is also increased.

Laboratory findings

1 -The haemoglobin is usually 60–90 g/L – low in comparison to mild or no symptoms of anaemia.

2 -Sickle cells and target cells occur in the blood film.

Features of splenic atrophy (e.g. Howell–Jolly bodies) may also be present.

3- Screening tests for sickling are positive when the blood is deoxygenated .

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-Sickling of red cells can be induced by sealing a drop of blood under a coverslip to exclude oxygen or by adding 2% sodium metabisulfite

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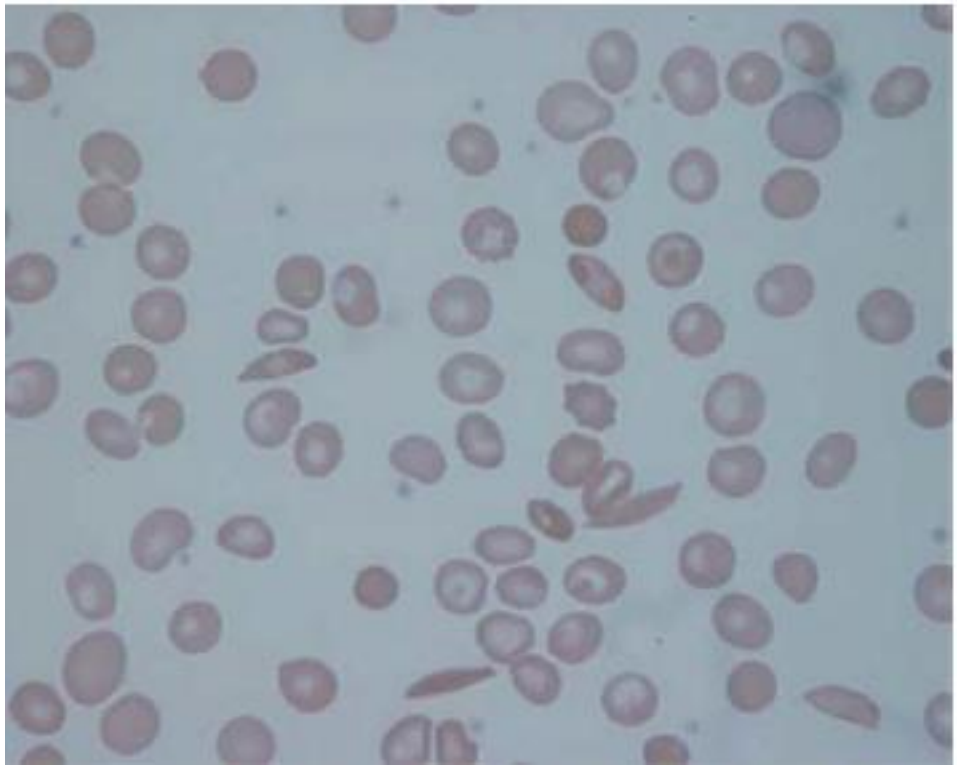
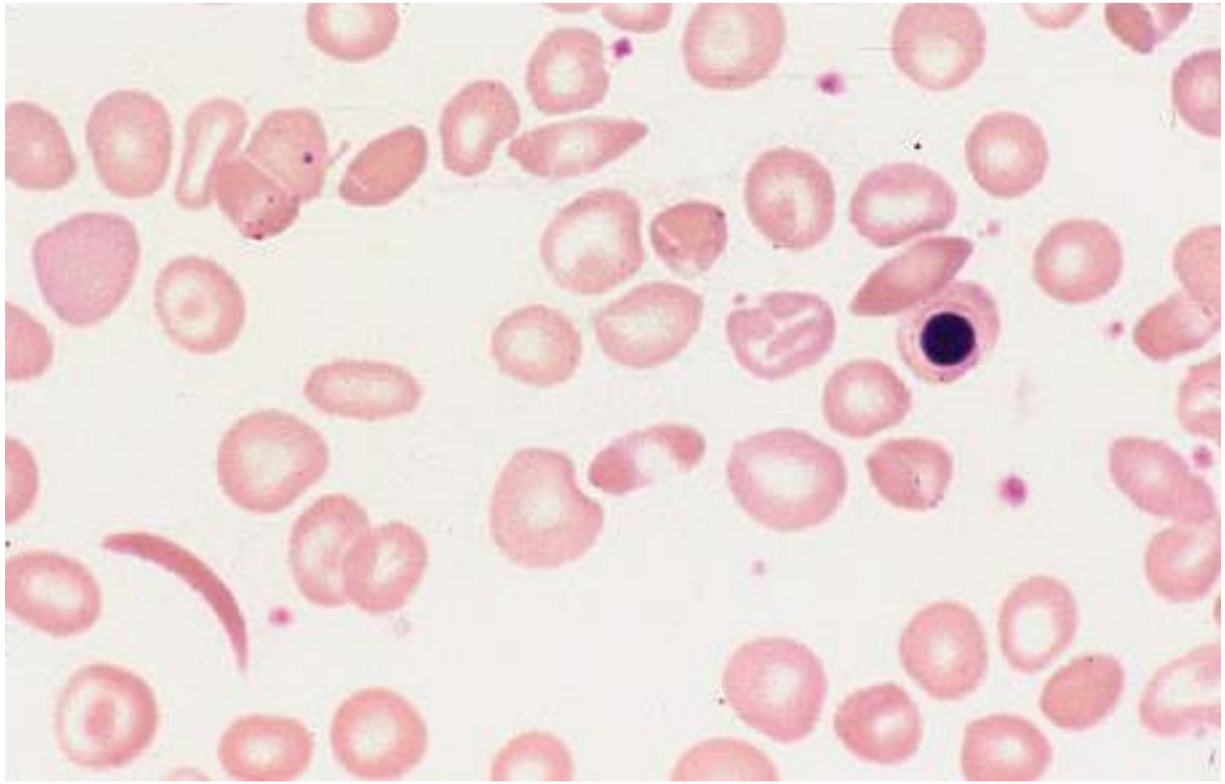
-**The solubility test for HbS utilizes a reducing agent such as sodium dithionite, which is added to the haemolysate**.

Deoxy-HbS is insoluble and renders the solution turbid .

Both these tests are unable to distinguish

sickle cell trait from sickle cell anaemia and cannot be used for primary diagnosis. They are useful aids in the identification of an abnormal electrophoretic band as HbS and for identifying sickle cell trait in units of red cells prior to transfusion.





Sickle cell solubility test. In this test, whole blood is added to a high phosphate buffer with saponin and sodium dithionite, which causes the hemoglobin to become deoxyhemoglobin. Deoxyhemoglobin S is insoluble. The turbidity of the sample on the left indicates the

presence of HbS. The clear sample on the right contains no HbS.

4.HbS can be identified by cellulose acetate electrophoresis at pH 8.4 .HbD and HbG have the same electrophoretic mobility with this method, but can be distinguished using citrate agar electrophoresis at pH 6.2 or thin-layer isoelectric focusing.

HPLC or haemoglobin electrophoresis in Hb SS, no Hb A is detected. The amount of Hb F is variable and is usually 5–15%, larger amounts are usually associated with a milder disorder