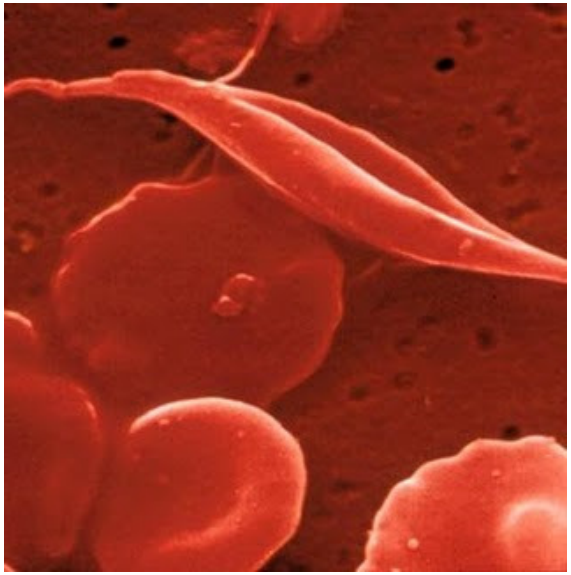
Haemoglobinopathies

sickle cell anaemia



Dr. Abdullah Aljedai

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Haemoglobin synthesis

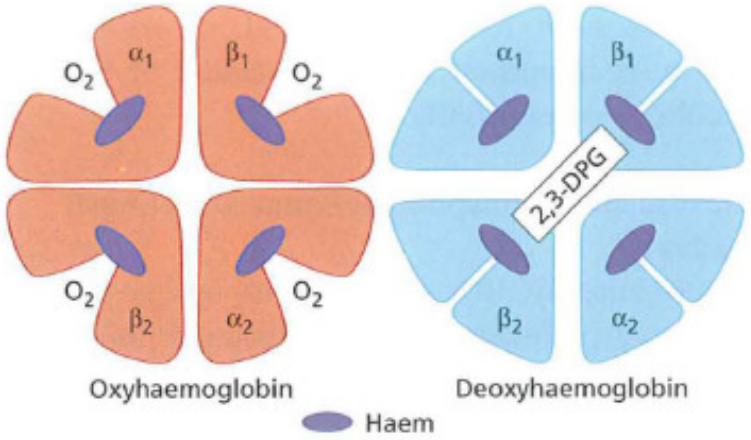
- In the embryo and fetus, Gower 1, Portland, Gower 2 and fetal Hb are the dominant forms of Hb.
- The major switch from fetal to adult haemoglobin occurs 3-6 months after birth.
- Each molecule of normal adult haemoglobin Hb A (the dominant

haemoglobin in blood after the age of 3 6 months) consists of four polypeptide chains, α2β2 each with its own haem group.

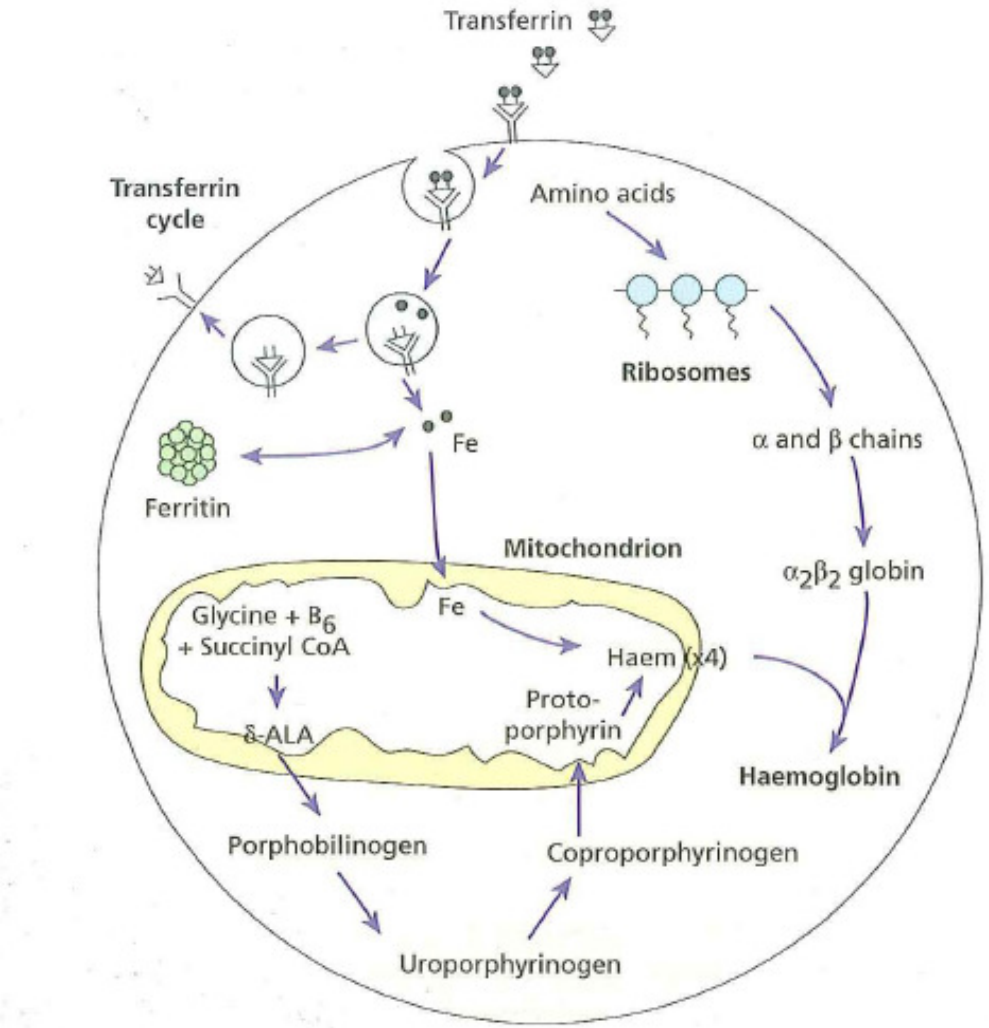
- Normal adult blood also contains small quantities of two other haemoglobins: Hb F and Hb A2.
- Haem synthesis occurs largely in the mitochondria.
- Globin chains snthesis occurs in the ribosomes.

Table 2.2 Normal haemoglobins in adult blood.

	Hb A	Hb F	Hb A_2
Structure	$\alpha_2\beta_2$	$\alpha_2\gamma_2$	$\alpha_2\delta_2$
Normal (%)	96–98	0.5–0.8	1.5–3.2



Haemoglobin synthesis



Haemoglobinopathies

- Disorders of abnormal haemoglobin synthesis are called haemoglobinopathies.
- Haemoglobinopathies can be due to structural or quantitative defects .
- These abnormal Hb defects may result in red cell haemolysis because of changes in Hb solubility or because of instabilities in the Hb molecule.
- ***Structural abnormalities*** are due to alterations in the polypeptide sequence changing the molecular structure and, often, the function of the globin chains. (eg., Hb SS (Sickle cell disease); Hb SA (Sickle cell trait);Hb C disease; Hb SC disease; Hb E disease).
- ***Quantitative abnormalities*** are secondary to decreased rates of globin chain synthesis (beta-thalassemia; alpha-thalassemia).
- The most common haemoglobinopathies are thalassemia and sickle cell disease/trait.

Hemoglobinopathies

Sickle cell disease
Sickle cell trait
Hemoglobin C disease
Hemoglobin C trait
Hemoglobin D disease
Hemoglobin E disease
Hemoglobin S- **β** thalassemia
Hemoglobin C- **β** thalassemia
Hemoglobin E- **β** thalassemia
Hemoglobin S- **α** thalassemia

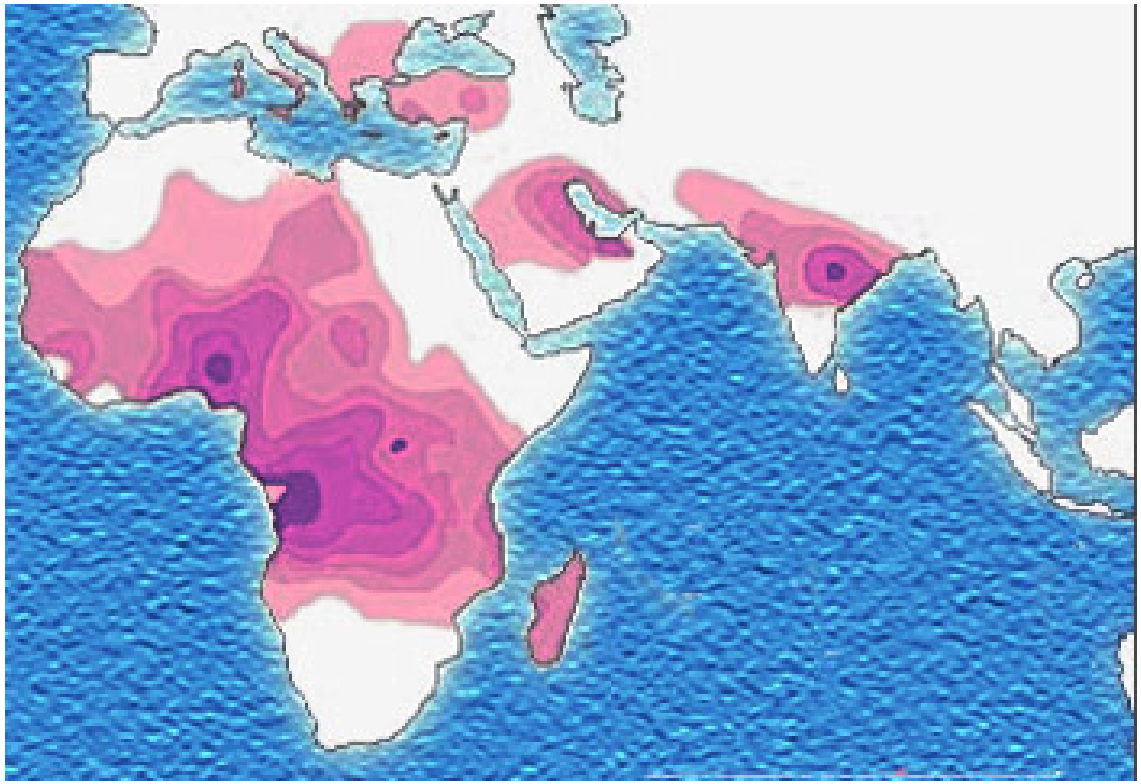
α thalassemia

β thalassemia

Sickle cell disease

- Sickle cell disease and sickle cell anaemia are serious, inherited conditions affecting the blood and various organs in the body.
- Sickle cell anaemia is a genetic (inherited) disease which affects the red blood cells.
- The abnormal haemoglobin S can be **Homozygous sickle cell anaemia (Hb SS)** or **Hb AS (carrier or sickle cell trait).**
- Carriers have symptoms only if they are deprived of oxygen (for example, while climbing a mountain) or while severely dehydrated.
- Homozygous sickle cell anaemia (Hb SS) is the most common type.
- Hb S is poorly soluble in low oxygen tension situations
- This distorts the red cells causing them to become rigid and sickled.

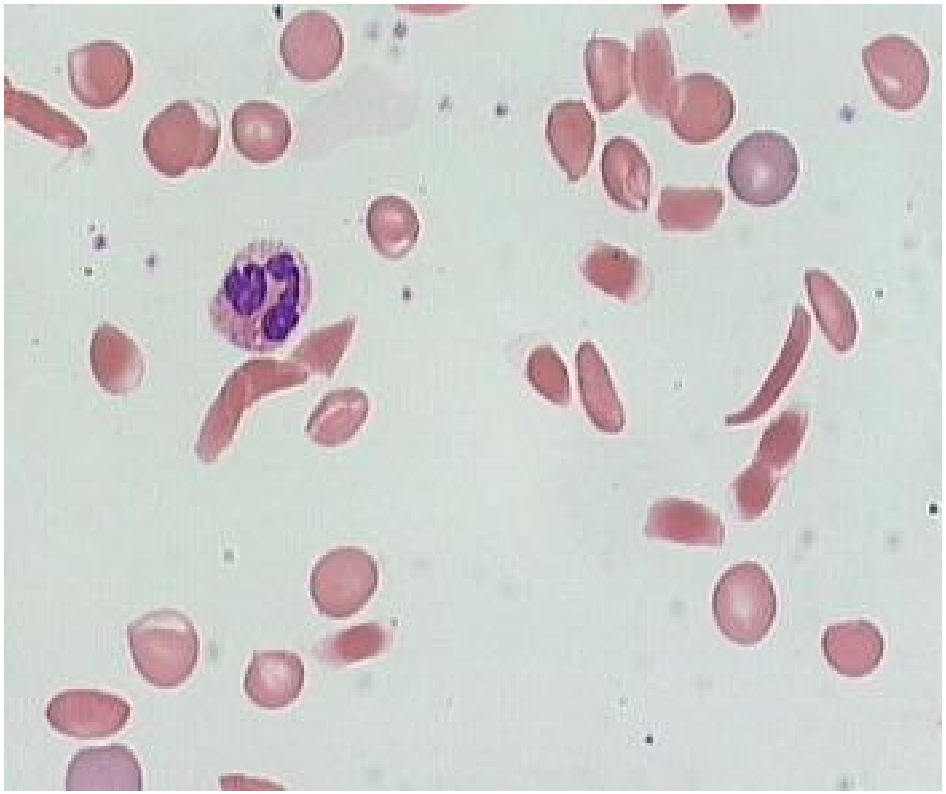
Sickle cell distribution



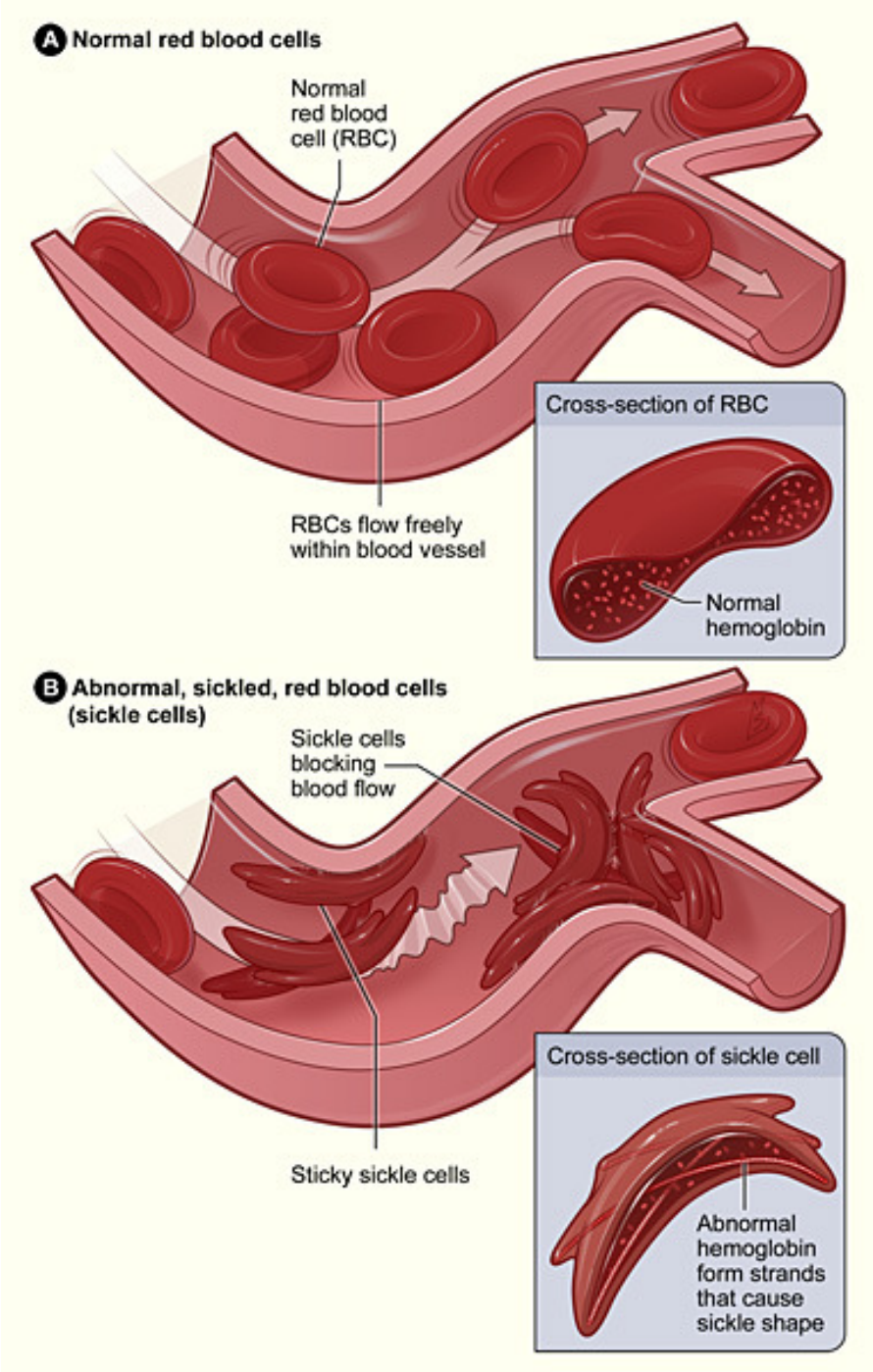
Morphology of sickle cells

Normal red
blood cell
(which is shaped
a bit like a doughnut)

A sickle shaped
red blood cell of
sickle cell anaemia

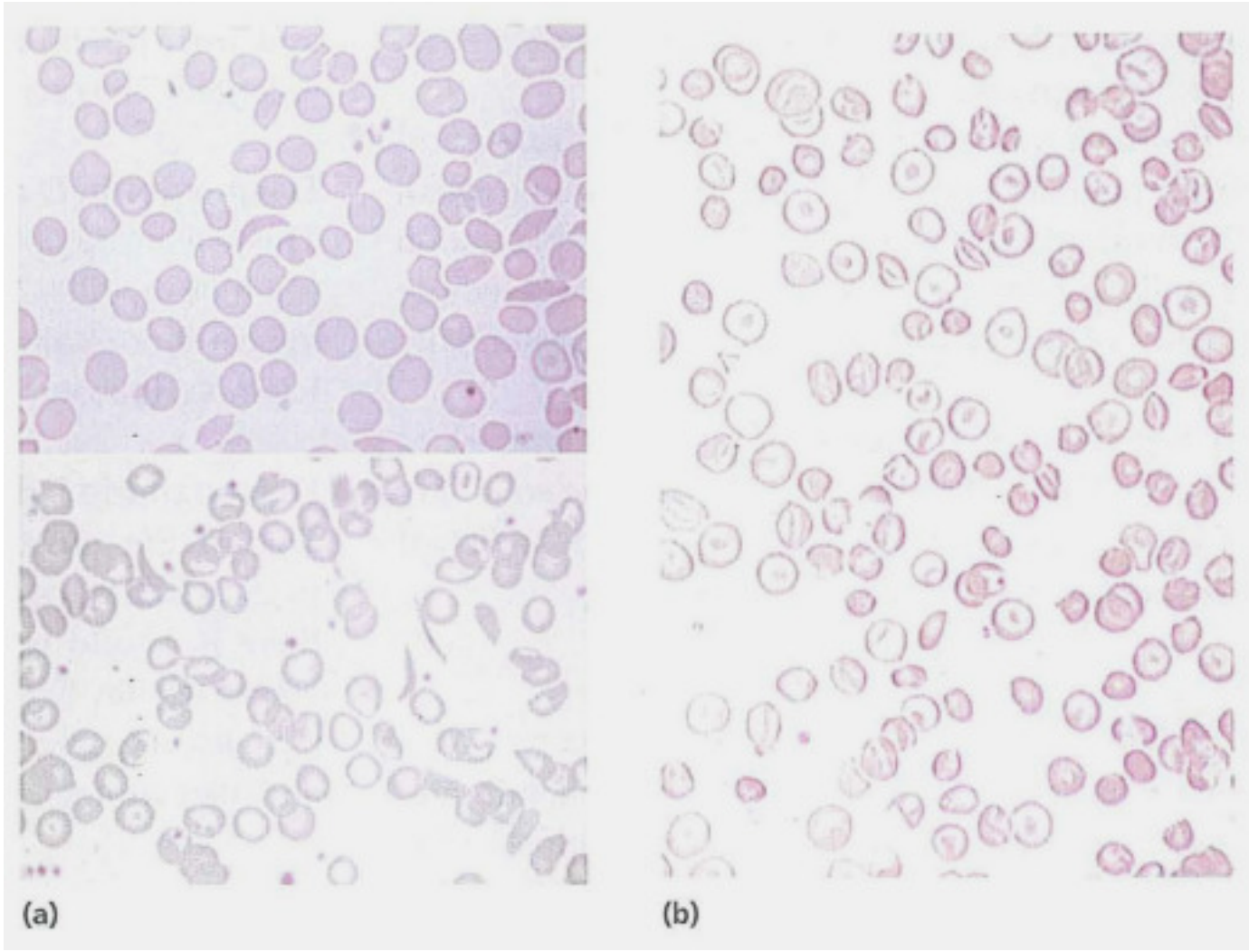


Red blood cells have a tendency to go out of shape and become sickle-shaped (like a crescent moon) - instead of their normal biconcave disc shape.



sickle cells are harder and less flexible than normal red blood cells.

sickle cells are destroyed more easily than normal red blood cells



(a) **Sickle cell anaemia:** peripheral blood film showing deeply staining sickle cells, target cells and polychromasia.

(b) **Homozygous Hb C disease:** peripheral blood film showing many target cells and spherocytic cells.

What causes sickle cell disease?

- A point mutation (**GAG Æ GTG**) in the ß-chain at position 6 of the β chain which results in encoding of a valine instead of the normal glutamine.

Normal β- chain	Amino acid	pro	glu	glu
	Base composition	CCT	G A G	GAG
Sickle β- chain	Base composition	CCT	G T G	GAG
	Amino acid	pro	val	glu

- The resulting abnormal ßs chains combine with normal a-chains to form the abnormal hemoglobin 'S'.
- Hb S (Hb α2 β2) is insoluble and forms crystals when exposed to low oxygen tension.
- The red cells sickle and may block different areas of the microcirculation or large vessels causing infarcts of various organs.

Clinical picture

- Although some patients live a near normal life, most develop "sickle crises". Three types of "crises" are described:
- Hemolytic
- Aplastic
- vaso-occlusive (painful)

Sickling crisis

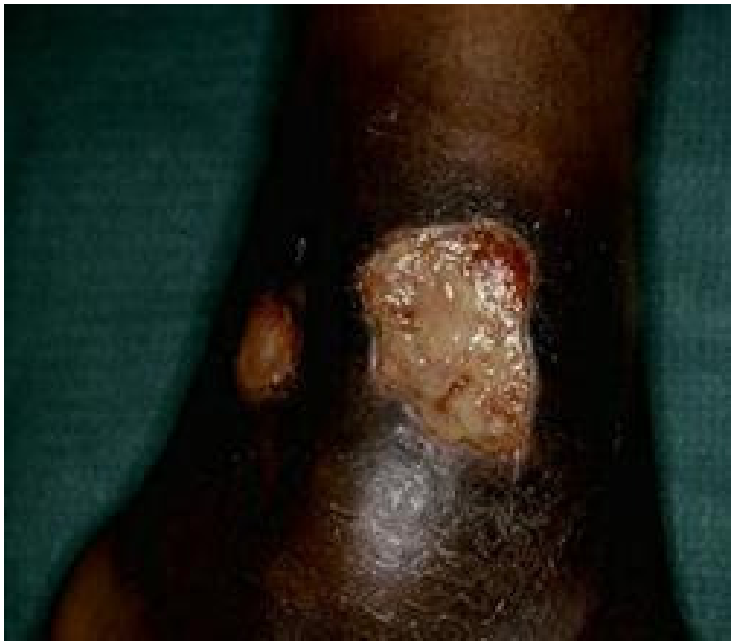
- **Hemolytic crises** are characterized by increased hemolysis resulting in an acute drop of the Hct and Hgb. This is accompanied by extraordinary reticulocytosis.

- **Aplastic crises** in which an acute drop in Hct and Hgb is accompanied by a fall in reticulocytes. Aplastic crises are most often associated with infections (>90% due to parvovirus B19).

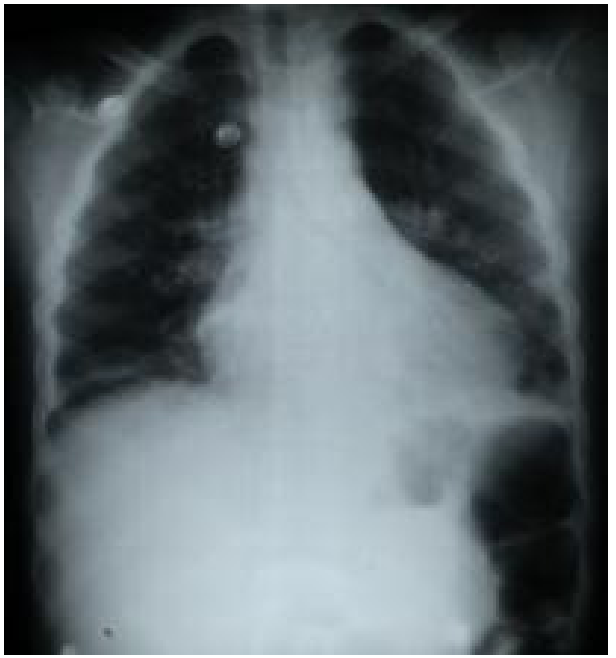
- **Vascular-occlusive crises** are the "classic" sickle cell crises. These may be caused by infection, acidosis, dehydration or hypoxia (altitude, anesthesia, circulatory stasis, pregnancy, strenuous exercise, etc). Sickled RBCs block small vessels causing infarcts, splenic sequestration (RBC trapping).

- **Infarcts** may occur in any organ, but are most notable in bones (childhood dactylitis of small bones may cause variable length digits), lungs, kidney, skin (leg ulcers), spleen, eye, and CNS.

- Factors which can trigger sickling include: cold, lack of oxygen, dehydration, hard exercise, fever and infection



Bone infarction



Respiratory distress

Sickle cell trait

- In sickle cell trait (carriers) (Hgb SA):

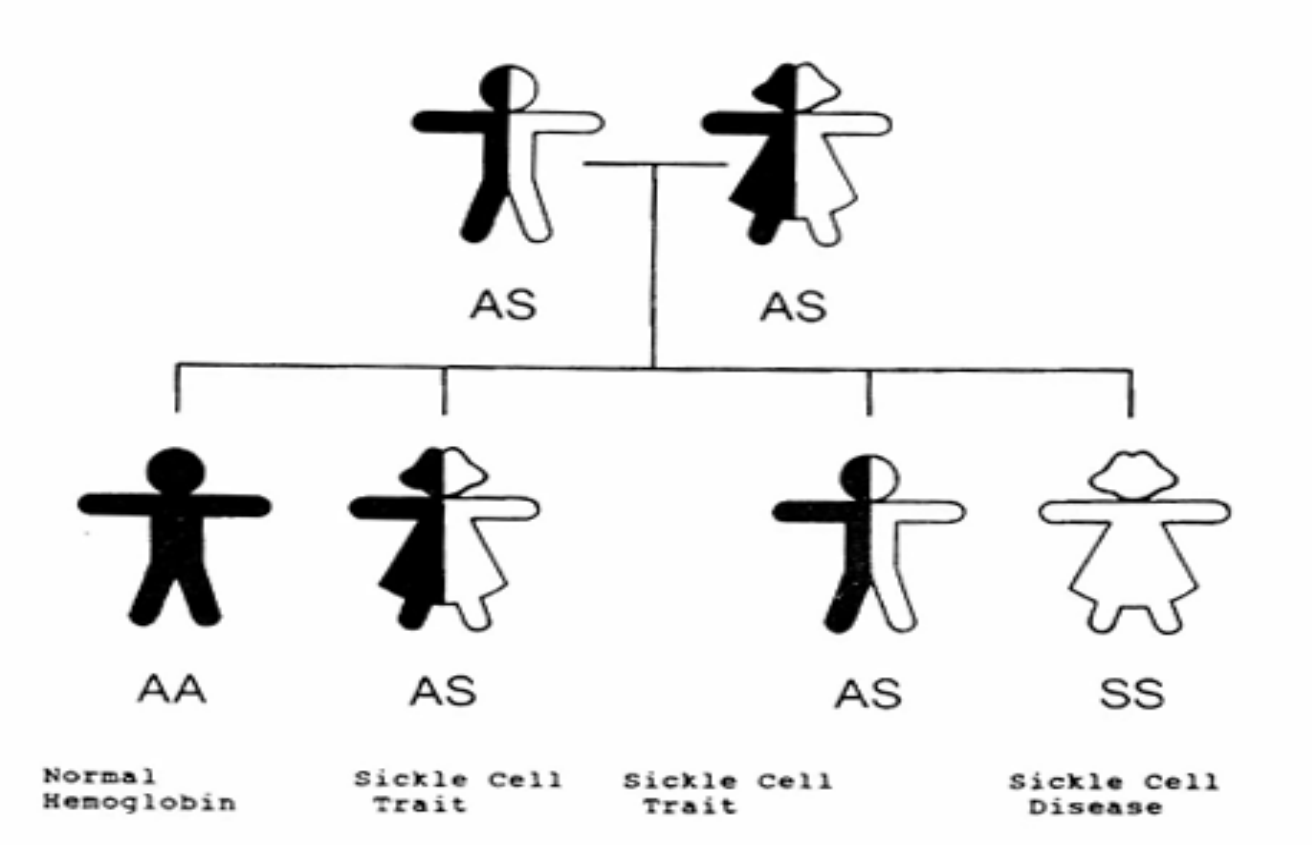
25 - 45% of the hemoglobin is Hgb S; the remainder being Hgb A and as well as Hgb F and Hgb A2.

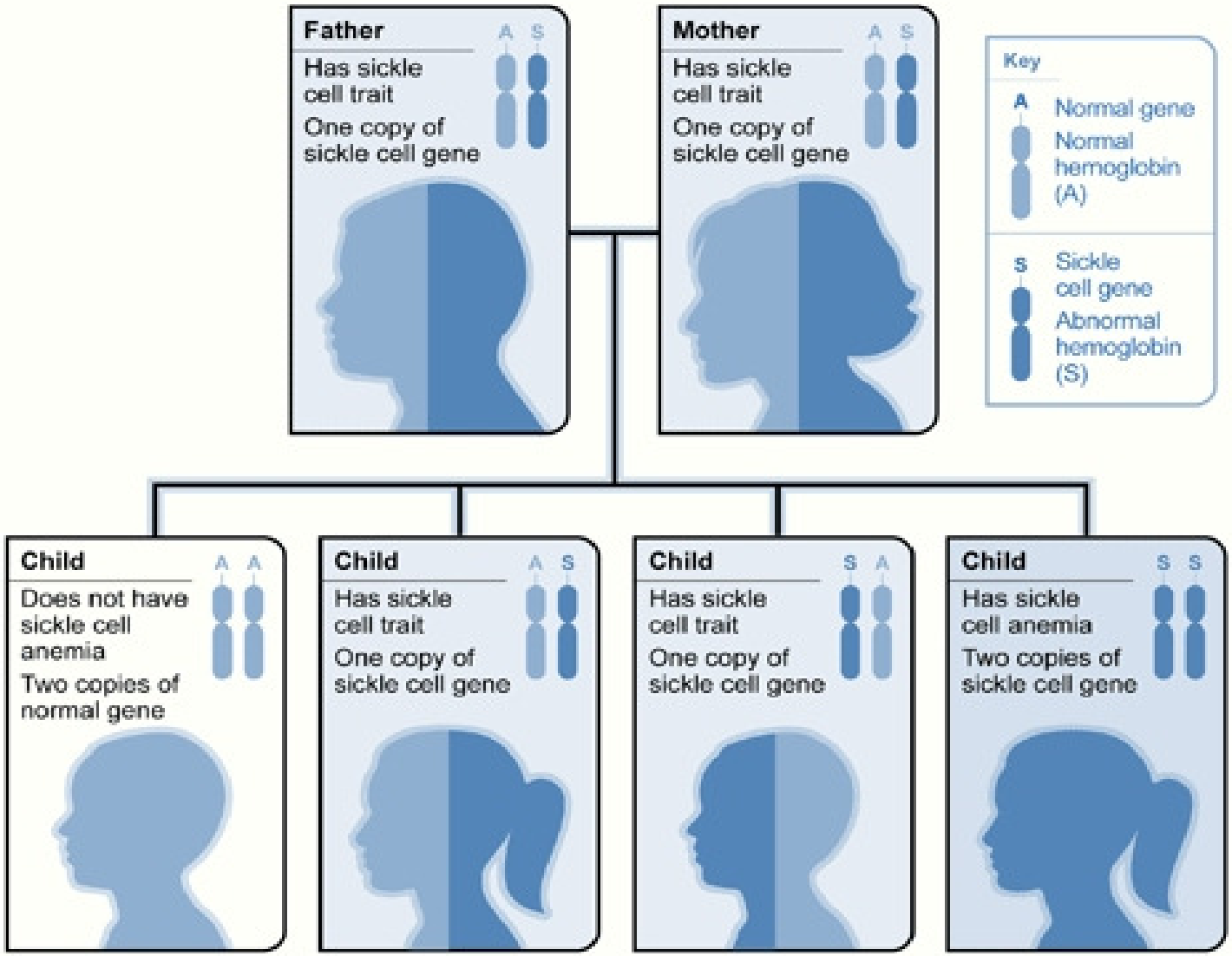
- No anemia and normal RBC morphology.
- Rare complications: haematuria and splenic infarction are associated with sickle trait.
- Individuals with sickle cell trait have normal growth and development, normal life spans and should not be considered ill

Inheritance

- To get Sickle Cell Disease, you need to have **two** altered haemoglobin genes, one from each parent. If you only have one of these genes, you will have 'sickle cell trait'
- If one parent has sickle-cell anaemia (SS) and the other has sickle-cell trait (AS), there is a 50% chance of a child's having sickle-cell disease (SS) and a 50% chance of a child's having sickle-cell trait (AS).
- When both parents have sickle-cell trait (AS), a child has a 25% chance (1 of 4) of sickle-cell disease (SS

Inheritance of sickle cell anaemia

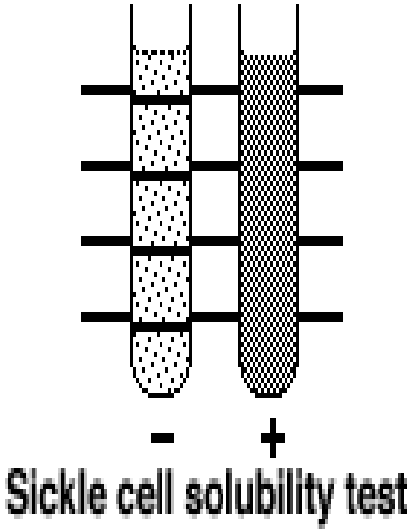



Father
Has sickle cell trait
One copy of sickle cell gene
A S
Mother
Has sickle cell trait
One copy of sickle cell gene
A S
Key
A
Normal gene
Normal hemoglobin (A)
S
Sickle cell gene
Abnormal hemoglobin (S)
Child
Does not have sickle cell anemia
Two copies of normal gene
A A
Child
Has sickle cell trait
One copy of sickle cell gene
A S
Child
Has sickle cell trait
One copy of sickle cell gene
S A
Child
Has sickle cell anemia
Two copies of sickle cell gene
S S

Laboratory findings

- 1 The haemoglobin is usually 6-9 g/dL.
- 2 blood film: Sickle cells, Polychromasia, spherocytes, target cells, and Howell-Jolly bodies may also be seen. NRBCs may be present in sickle cell crisis.
- 3- Reticulocytosis
- 4 Screening tests for sickling are positive when theblood is deoxygenated (e.g. with dithionate and Na_2HPO_4).
- 5 Confirmatory test: Haemoglobin electrophoresis in HbSS, no Hb A is detected

SICKLING TEST



- The sickle cell solubility test is a widely used screening method for sickle cell anemia.

-HbS in concentrated phosphate buffers compared to Hgb A and other Hgb variants precipitates causing a cloudy solution.

Haemoglobin electrophoresis

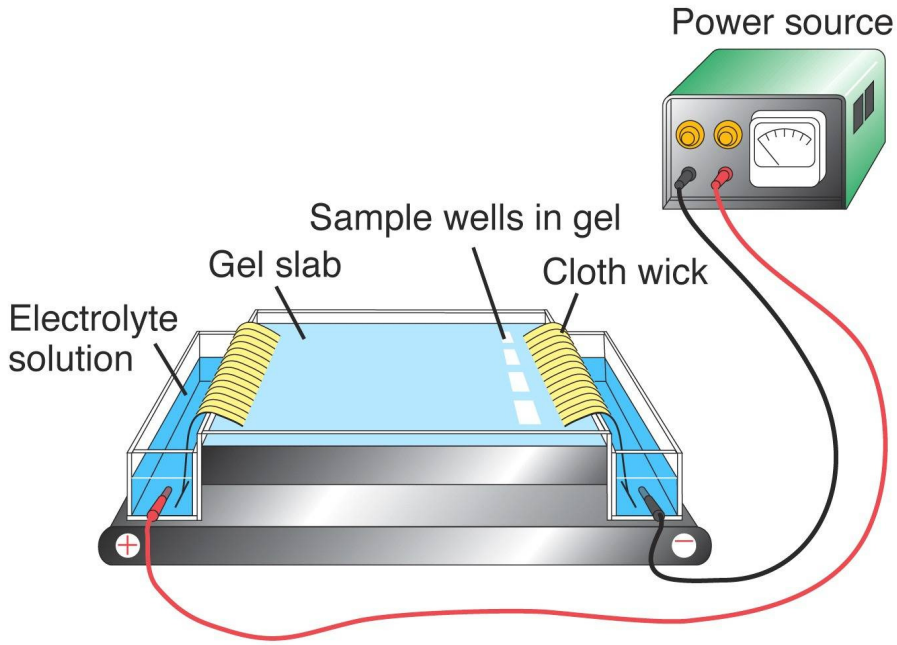
1- Different haemoglobins have different charges, and according to those charges and the amount, haemoglobins move at different speeds in the gel.

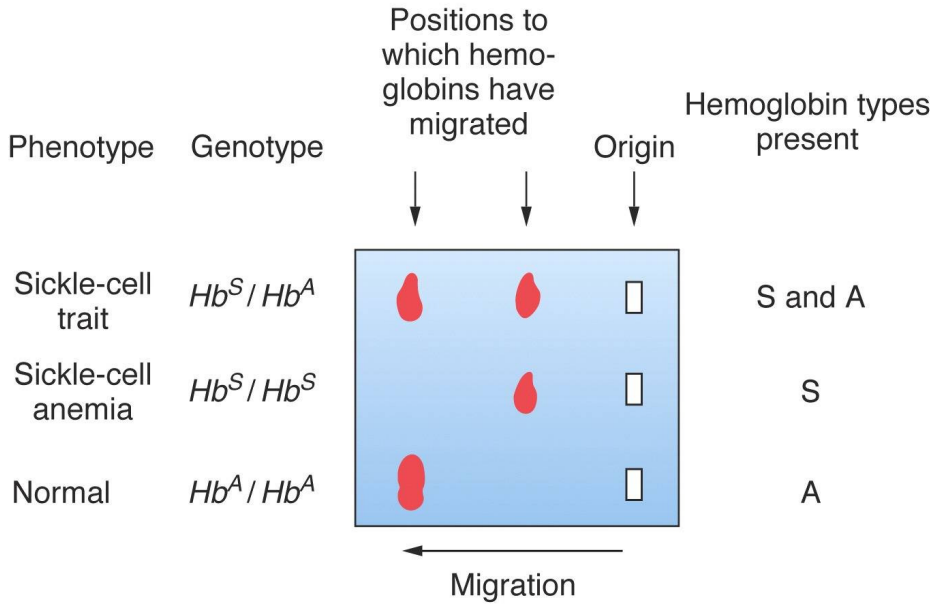
(Hb will migrate from the Negative to the positive end of the electrical field)

2- RBCs are lysed and electrophoresed on cellulose acetate at pH 8.4 separating the haemoglobin proteins into bands by charge.

3- After staining, haemoglobins can be identified by their position and quantitated.

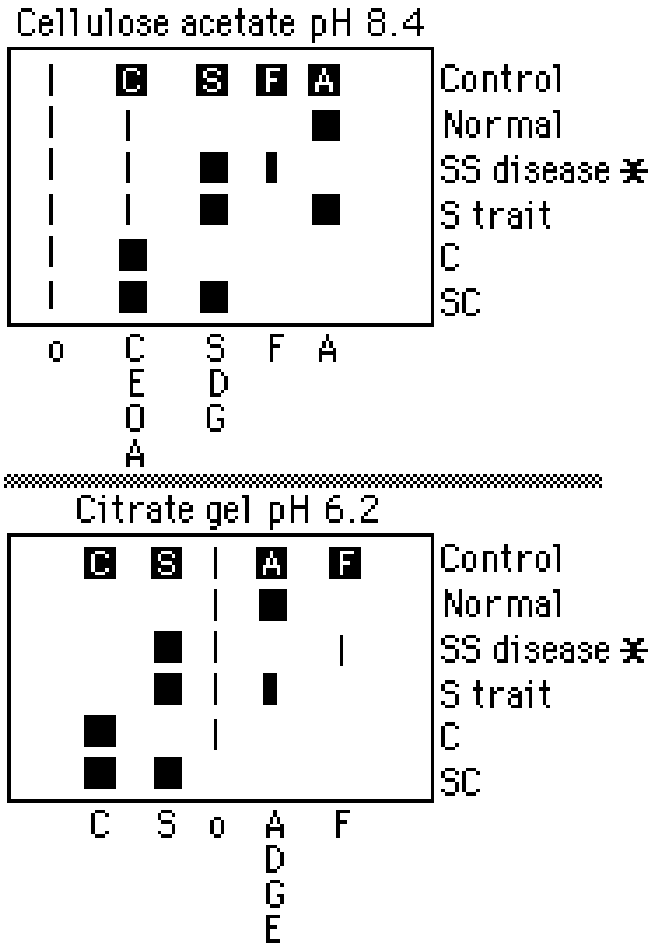
4- Hb SS migrate slowly because it has a slightly reduced negative charge.

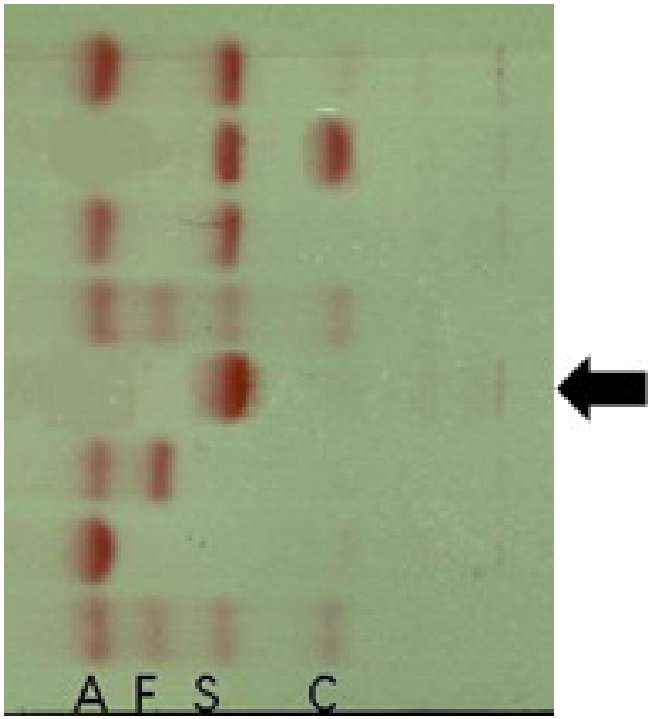




http://www.mun.ca/biology/scarr/Hemoglobin_Electrophoresis.html

Hemoglobin electrophoresis





Treatment

- Hydroxyurea
- Cyanate (in food)
- Painkillers for Painful (vaso-occlusive) crisis
- Folic acid and penicillin
- Bone marrow transplantation

References

- Essential haematology.

- http://www.patient.co.uk/health/Sickle-Cell-Disease-and-Sickle-Cell-Anaemia.htm

- http://www.meded.virginia.edu/courses/path/innes/rcd/hgbsyn.cfm