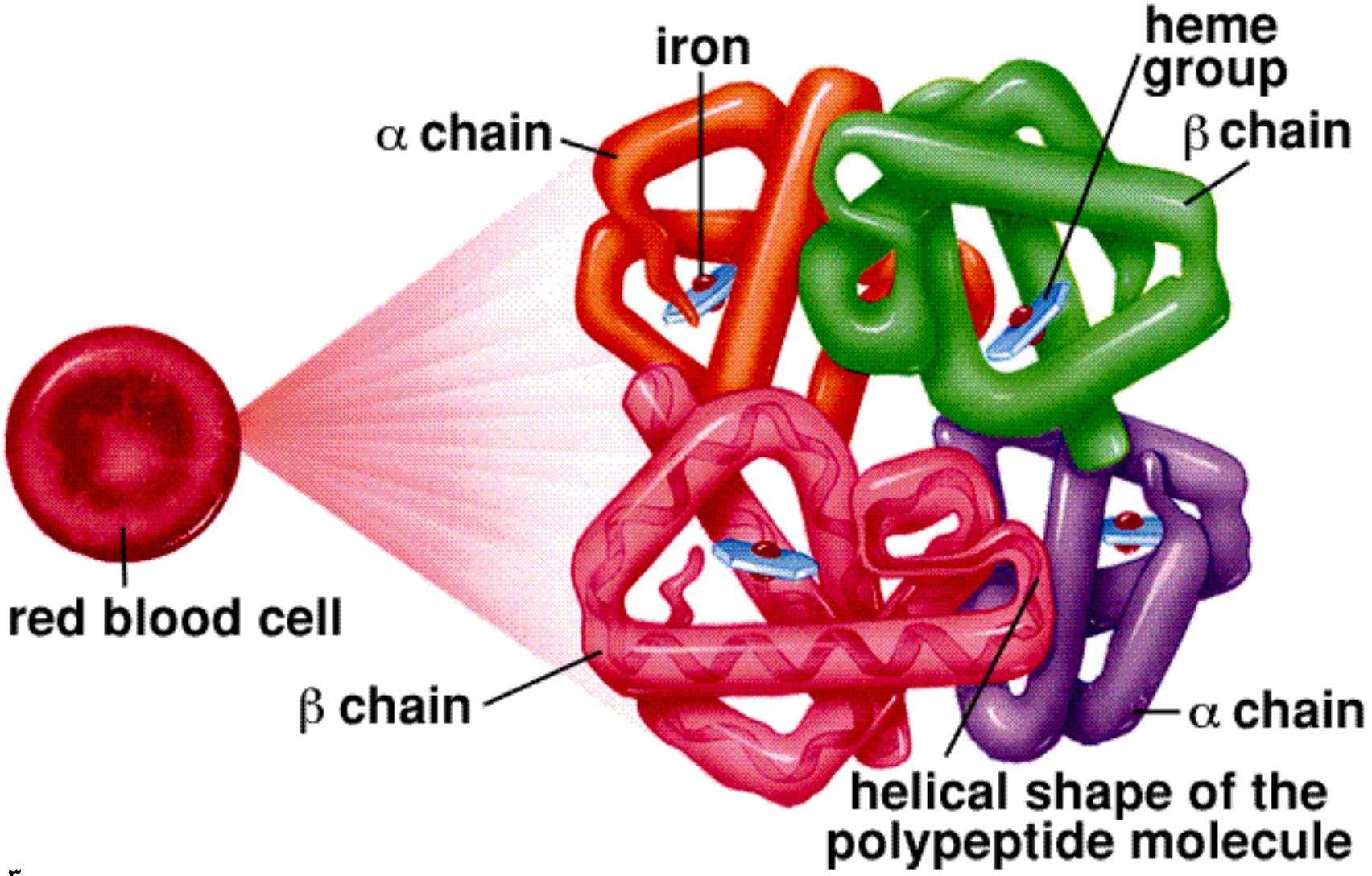
Inherited Hemoglobin Disorders

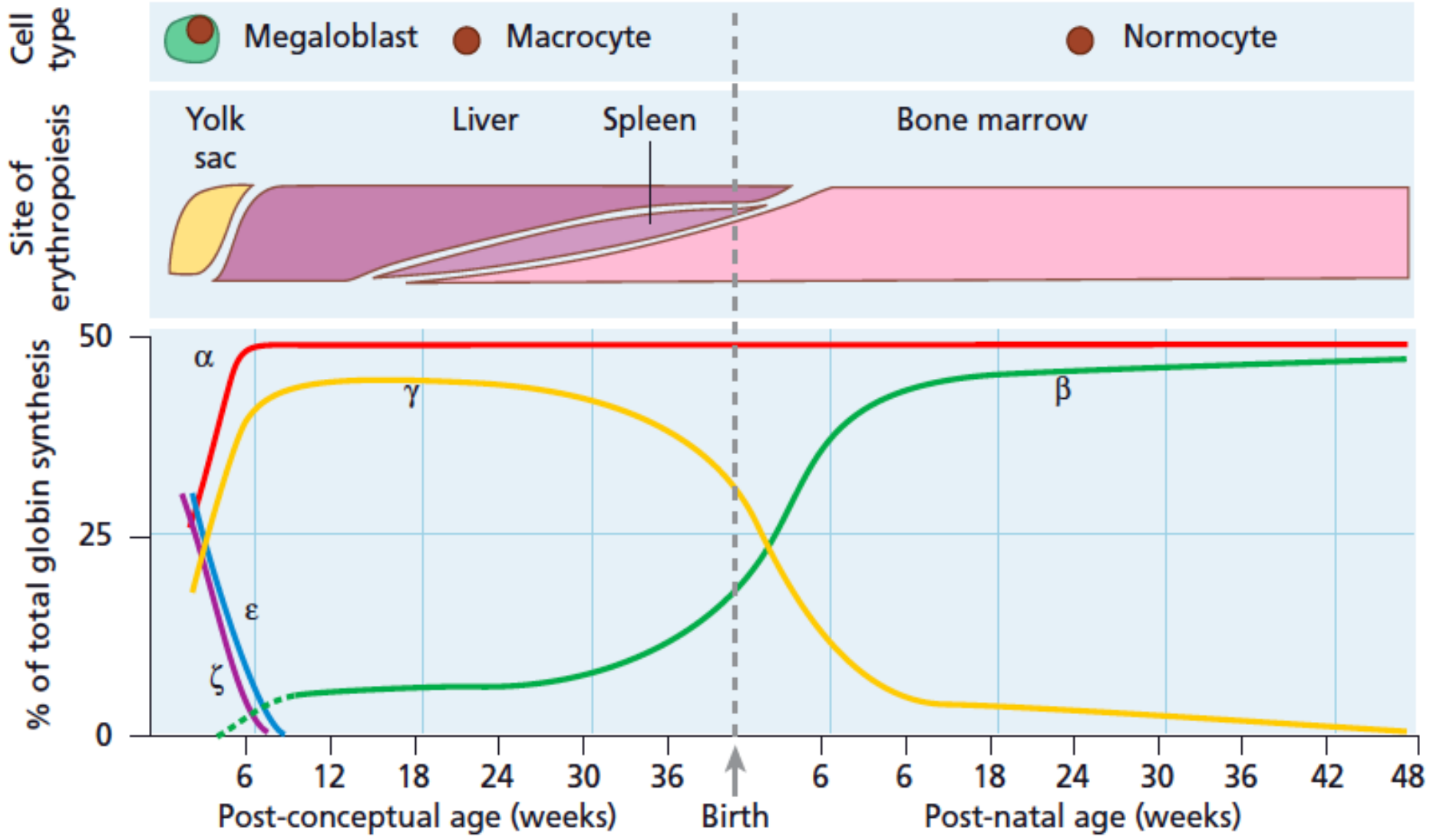
THE HEMOGLOBINOPATHIES

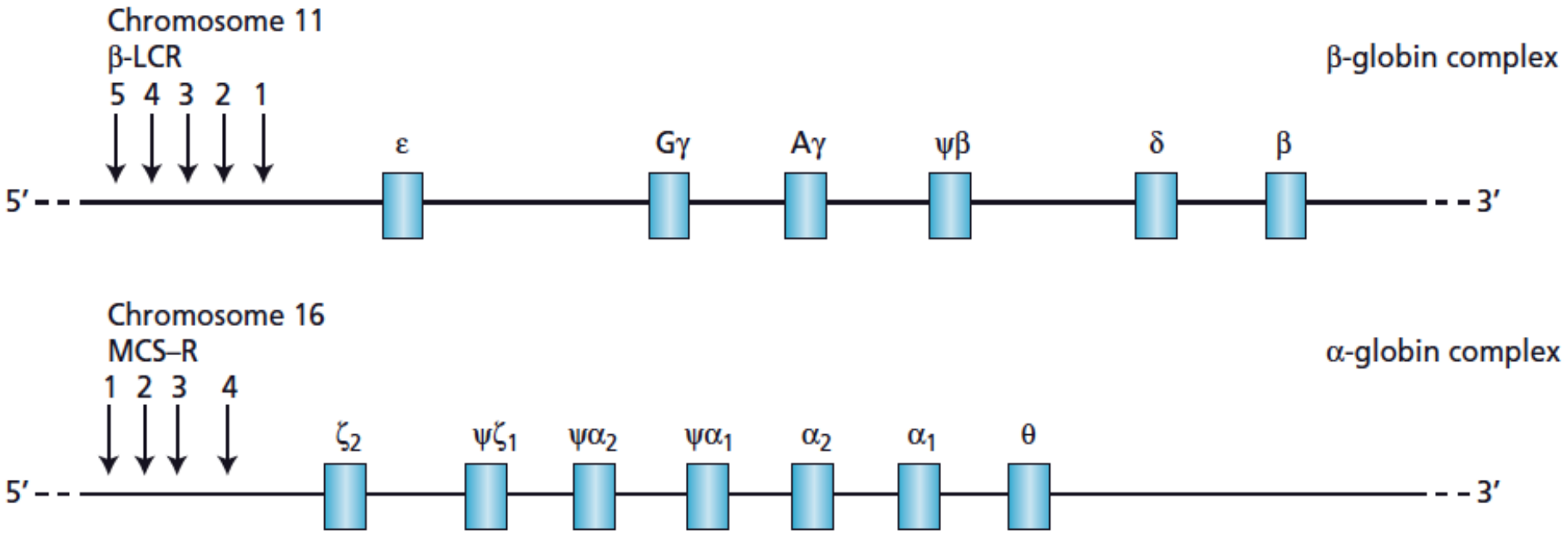
The inherited disorders of hemoglobin are common among many parts of the world. Different hemoglobins are synthesized in the embryo, fetus & adult. Each adapted to particular oxygen requirements. All hemoglobins are tetramers made up of two different pairs of globin chains. Single hem group is attached to chain.

The main hemoglobin in the postnatal life is Hb A (α2β2). The β like globin genes form a linked cluster on chromosome 11. The α like globin genes form a linked cluster on chromosome 16.

Hemoglobin Molecule




Cell type
Megaloblast
Macrocyte
Normocyte
Site of erythropoiesis
Yolk sac
Liver
Spleen
Bone marrow
% of total globin synthesis
50
25
0
α
γ
β
ε
ζ
6
12
18
24
30
36
Birth
6
6
18
24
30
36
42
48
Post-conceptual age (weeks)
Post-natal age (weeks)



Embryonic	Fetal	Adult
Hb Gower 1 ($\zeta_2\varepsilon_2$)	HbF ($\alpha_2\gamma_2$)	HbA ($\alpha_2\beta_2$)
Hb Gower 2 ($\alpha_2\varepsilon_2$)		HbA2 ($\alpha_2\delta_2$)
Hb Portland ($\zeta_2\gamma_2$)		

Classification of genetic disorders of Hb:

1. The thalassemias: inherited disorders of hemoglobin in which synthesis of one or more globin chains is reduced or absent.
2. The structural variants: inherited disorders of hemoglobin in which there is a change of hemoglobin structure leading to instability of the hemoglobin molecule or abnormal oxygen transport. They usually result from point mutation.

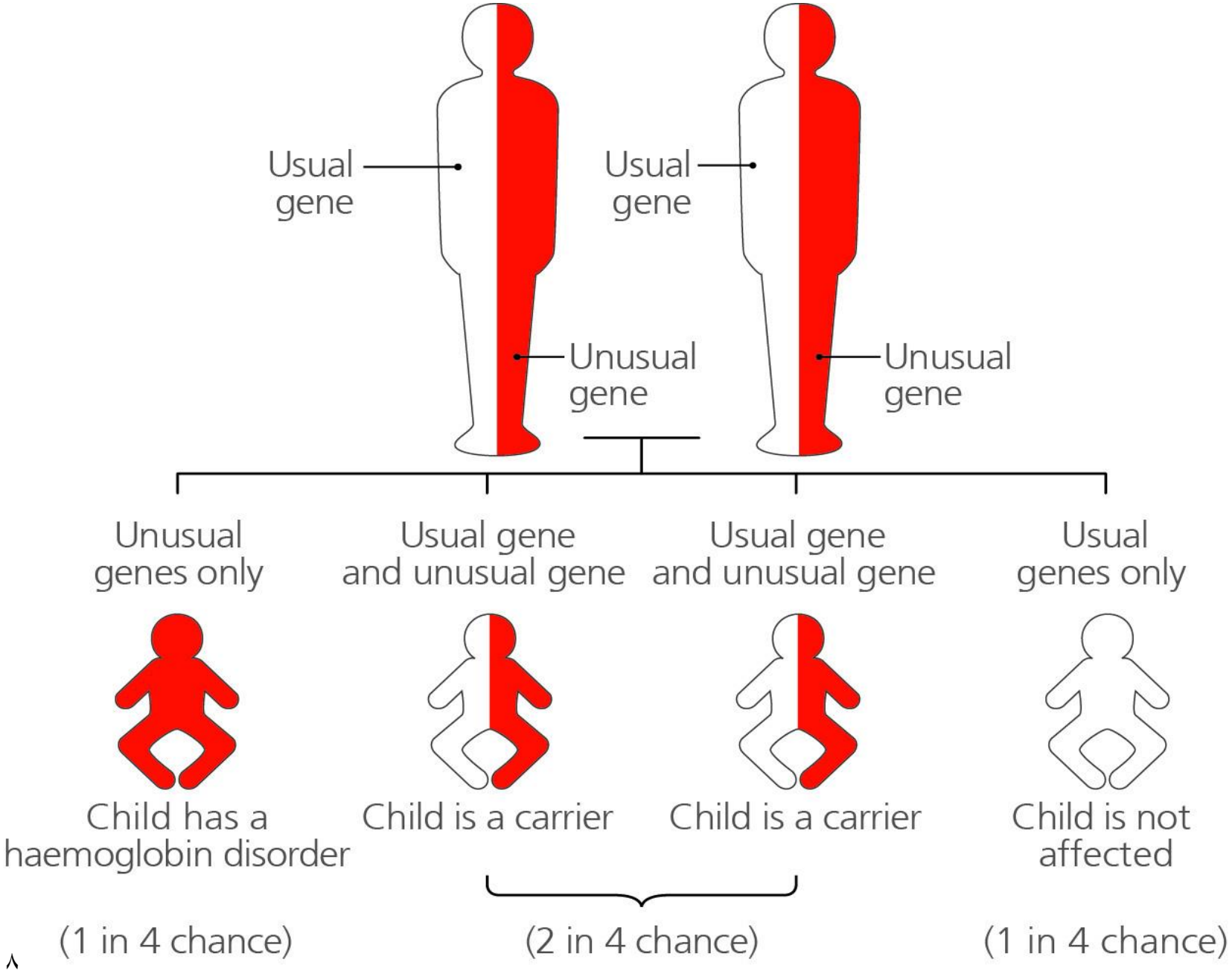
The Thalassemias

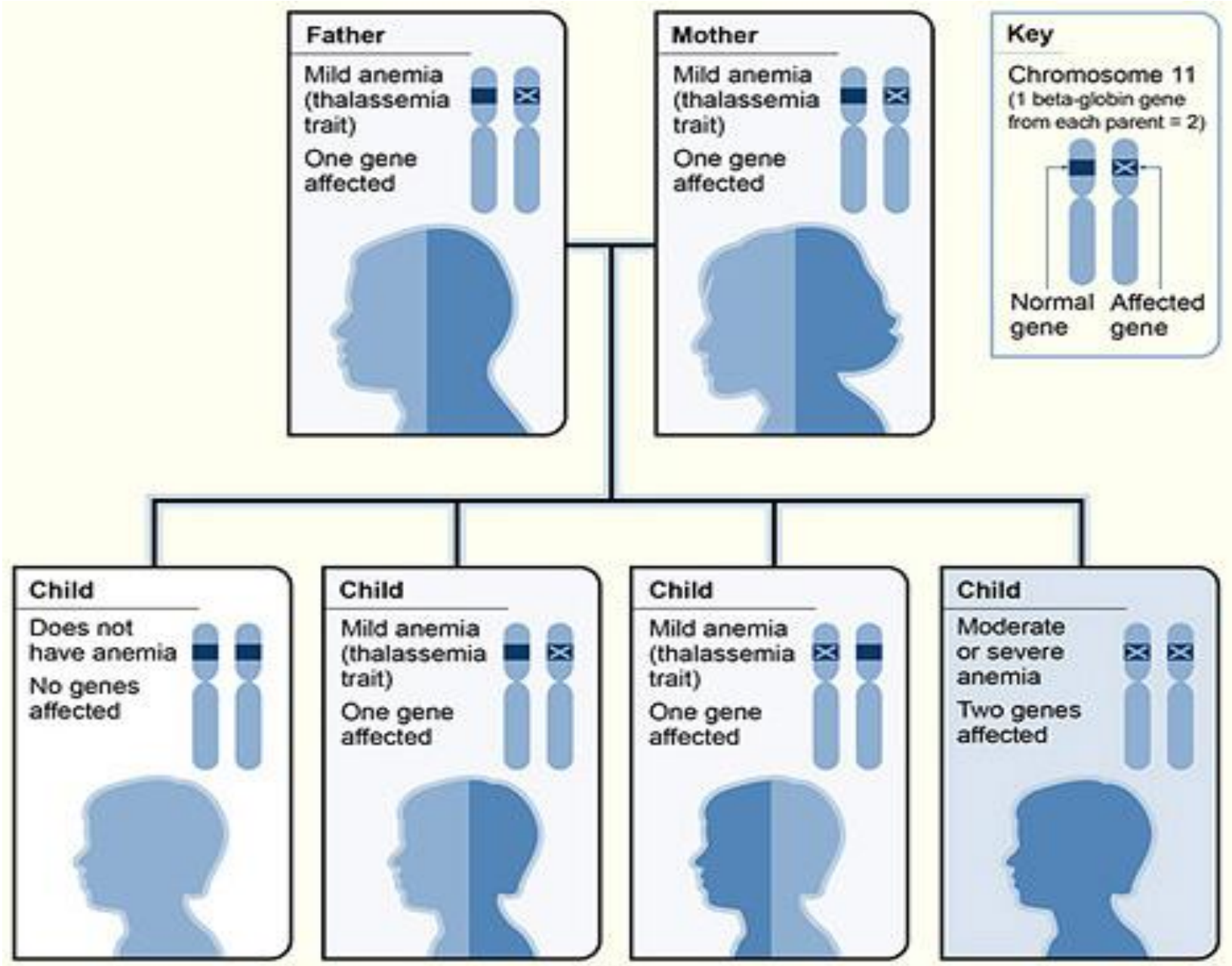
They are a heterogeneous group of genetic disorders of hemoglobin synthesis, all of which result from reduced production of one or more of the globin chains of hemoglobin. Most thalassemias are inherited in a Mendelian recessive way. Heterozygotes are usually asymptomatic; while severe forms result from homozygosity for α or β thalassemia or compound heterozygosity for different molecular forms of α or β thalassemia.

Thalassemias are classified according to the defective globin into:

α thalassemia

β thalassemia

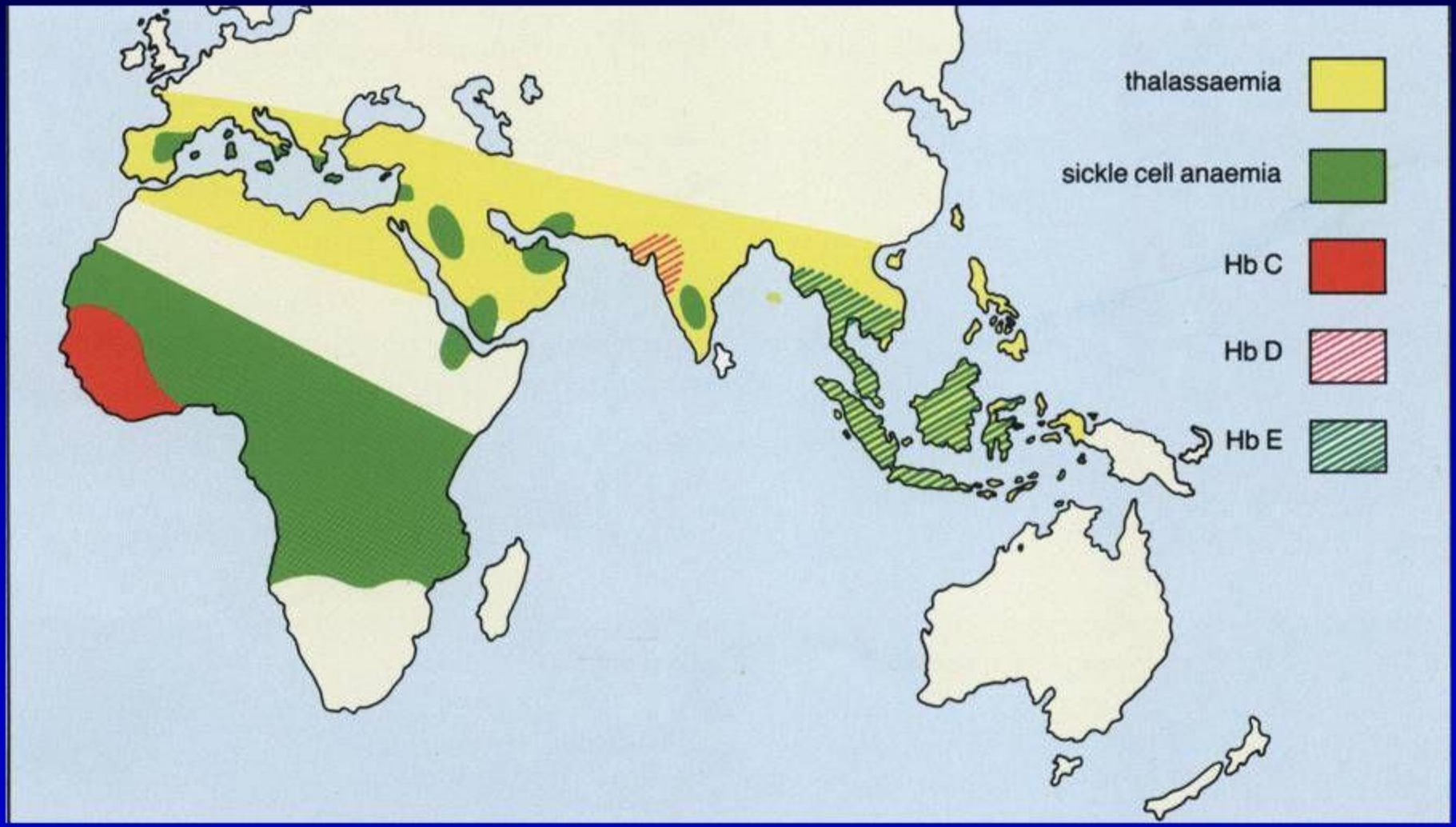

Usual gene
Usual gene
Unusual gene
Unusual gene
Unusual genes only
Usual gene and unusual gene
Usual gene and unusual gene
Usual genes only
Child has a haemoglobin disorder
Child is a carrier
Child is a carrier
Child is not affected
(1 in 4 chance)
(2 in 4 chance)
(1 in 4 chance)

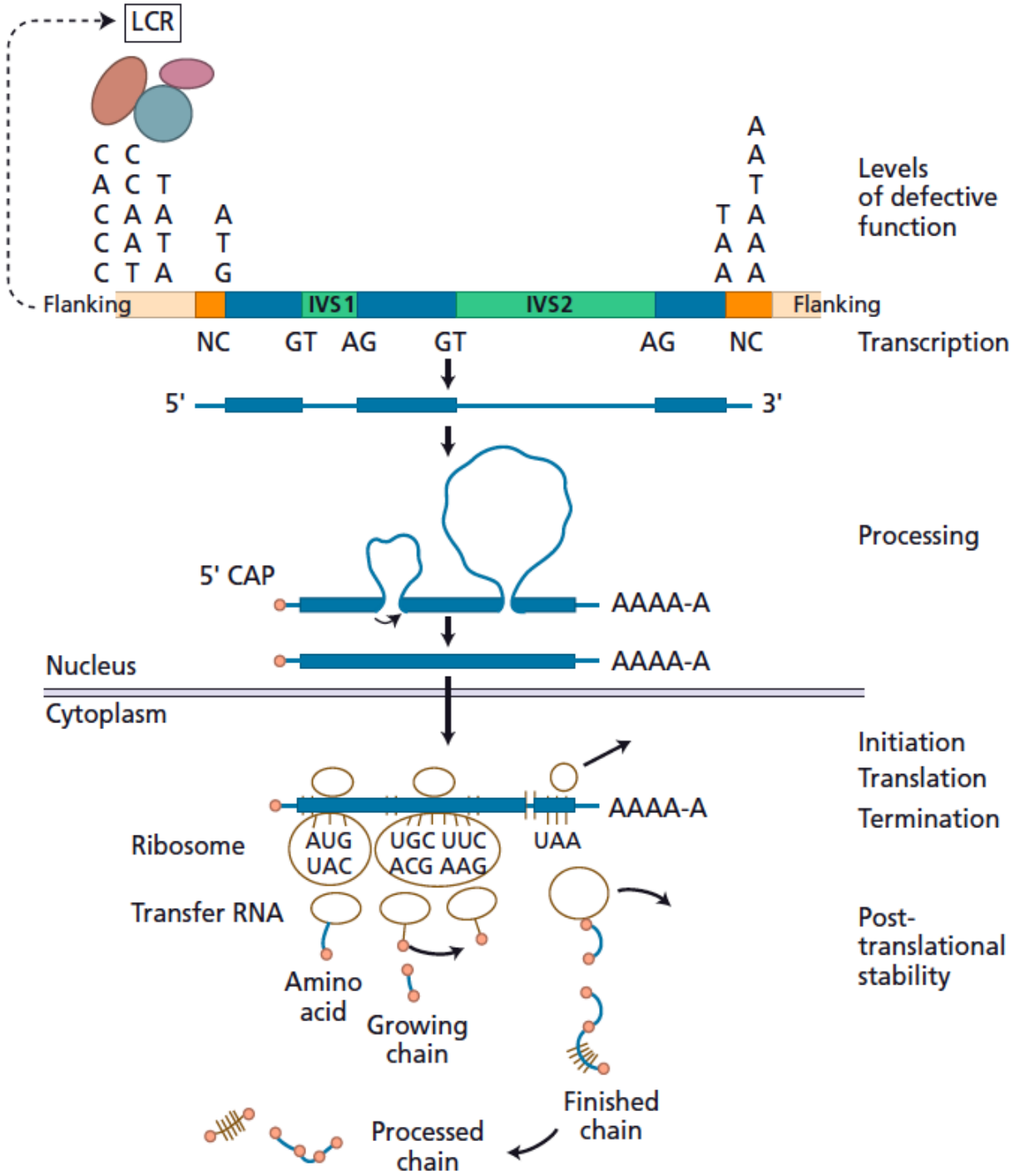

Father
Mild anemia (thalassemia trait)
One gene affected
Mother
Mild anemia (thalassemia trait)
One gene affected
Key
Chromosome 11
(1 beta-globin gene from each parent = 2)
Normal gene
Affected gene
Child
Does not have anemia
No genes affected
Child
Mild anemia (thalassemia trait)
One gene affected
Child
Mild anemia (thalassemia trait)
One gene affected
Child
Moderate or severe anemia
Two genes affected

β Thalassemia

The β thalassemia is the commonest thalassemia & it produces the most severe form of the disease. It is prevalent in the Mediterranean parts of Africa, Middle East, India & South East Asia. Most of β thalassemia mutations are point mutations affecting the transcription or translation of β chains. Complete absence of β chain is called β^0 & partial reduction is called β+. The homozygous state is β thalassemia major while the heterozygous is β thalassemia minor.

Geographical Distribution of Thalassemia and Hemoglobin Disorders

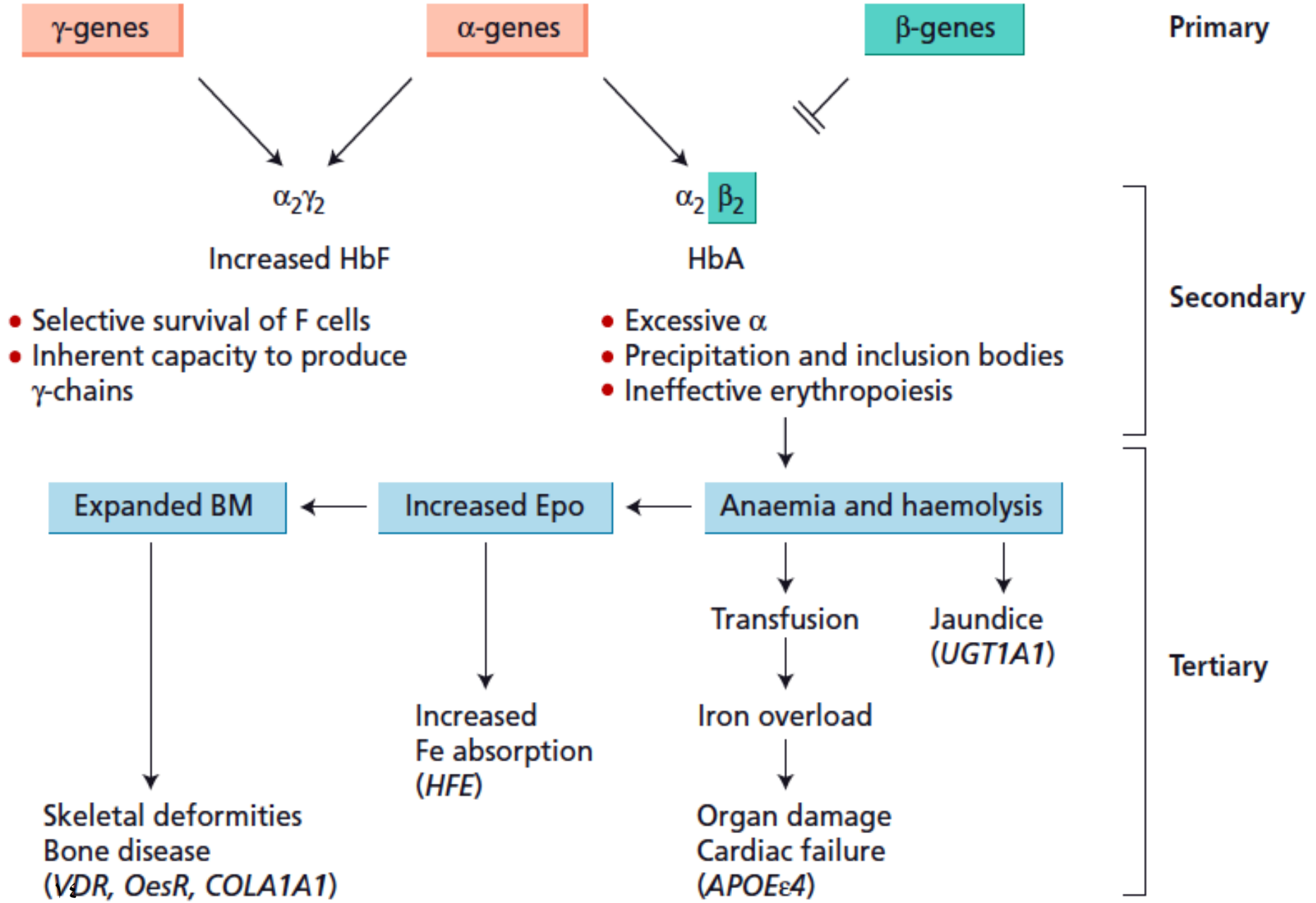



LCR
C C
A C T
C A A
C A T
C T A
A
T
G
A
A
T
T A
A A
A A
Levels of defective function
Flanking
IVS1
IVS2
Flanking
NC
GT
AG
GT
AG
NC
Transcription
5'
3'
Processing
5' CAP
AAAA-A
AAAA-A
Nucleus
Cytoplasm
Initiation
Translation
Termination
AAAA-A
Ribosome
AUG
UAC
UGC UUC
ACG AAG
UAA
Transfer RNA
Amino acid
Growing chain
Post-translational stability
Finished chain
Processed chain

B thalassemia major (homozygote or double heterozygote)

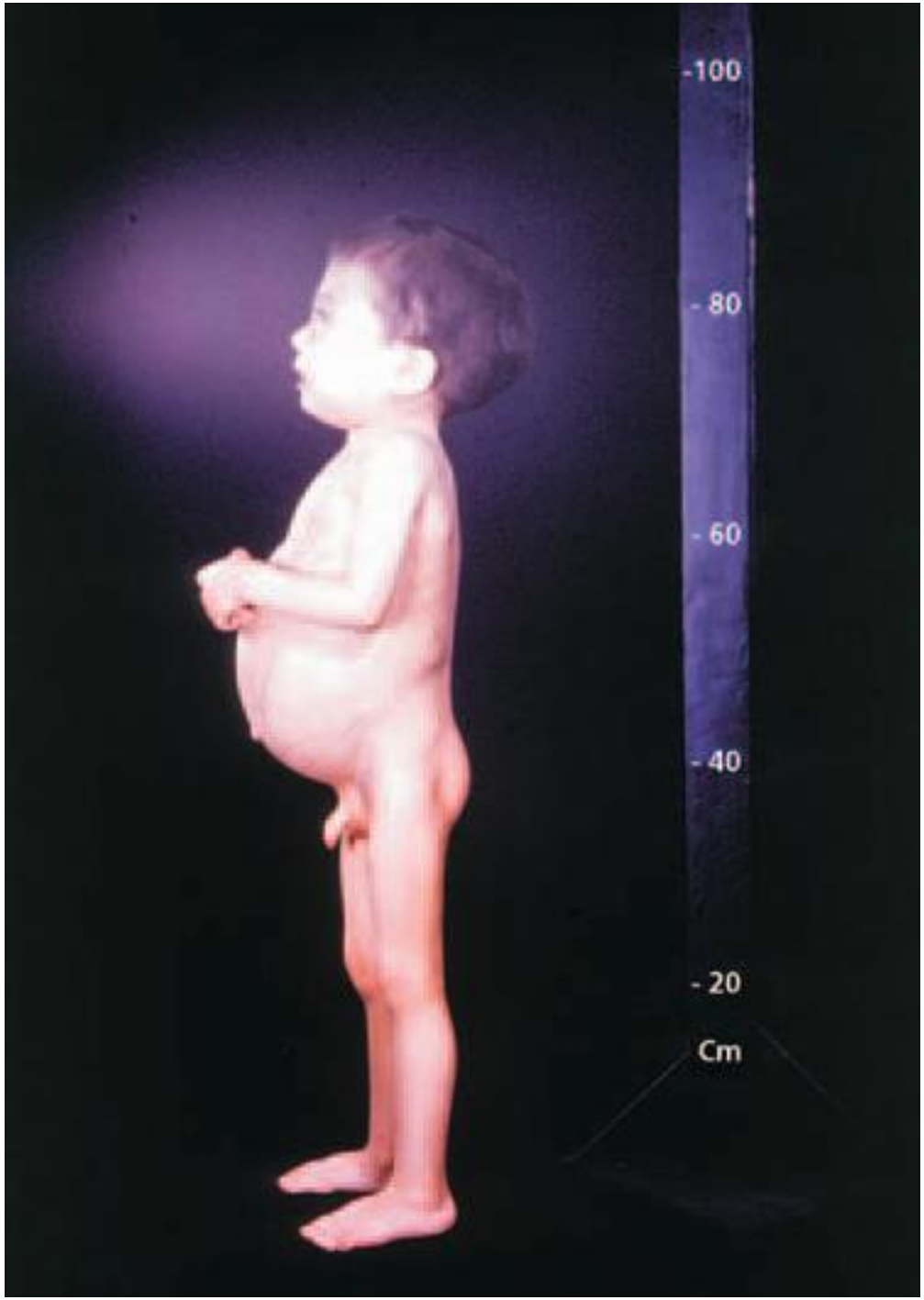
β chain synthesis is reduced or absent while α chain is synthesized in normal amounts leading to imbalance. The excess α chain will precipitate in the red cell precursors leading to their intramedullary destruction (ineffective erythropoiesis) as well as destruction of the mature red cells in the spleen leading to splenomegaly.

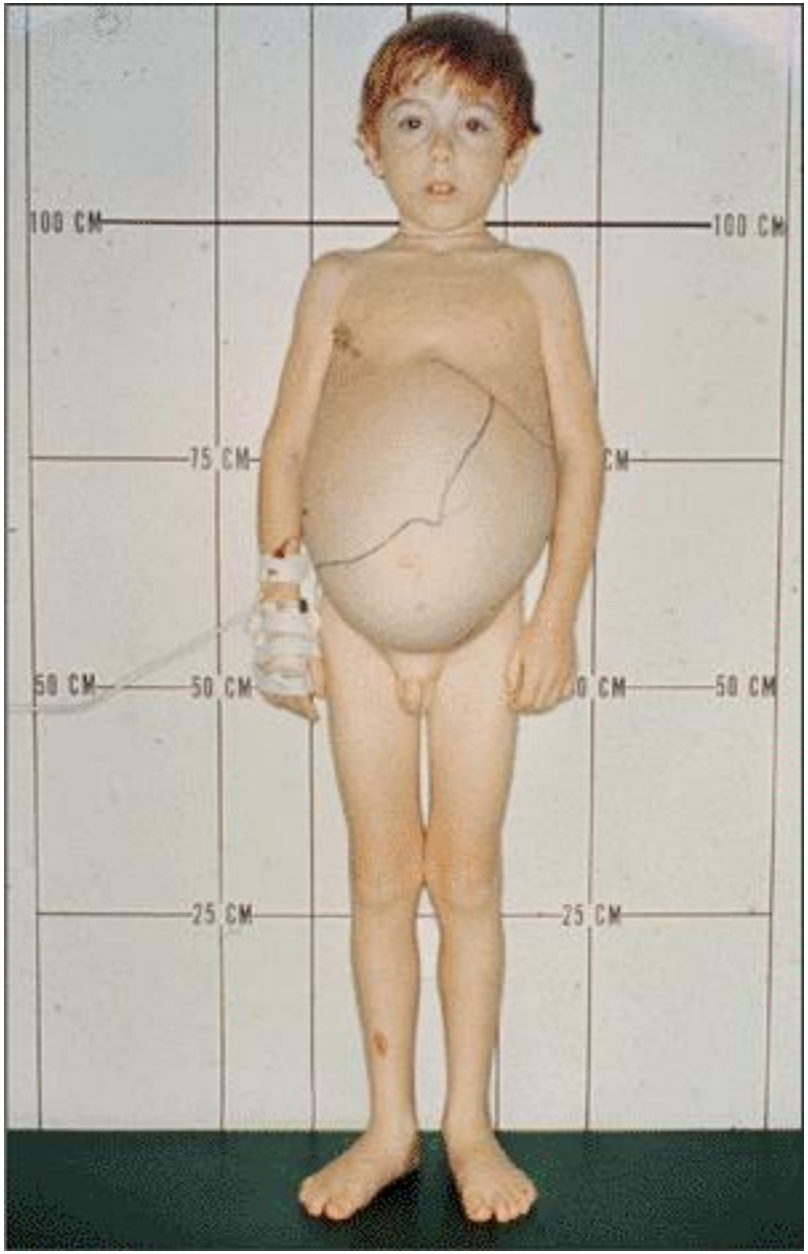
The anemia will stimulate the bone marrow expansion leading to serious deformities of the skull & long bones.


γ-genes
α-genes
β-genes
Primary
$\alpha_2\gamma_2$
$\alpha_2\beta_2$
Increased HbF
HbA
• Selective survival of F cells
• Inherent capacity to produce γ-chains
• Excessive α
• Precipitation and inclusion bodies
• Ineffective erythropoiesis
Secondary
Expanded BM
Increased Epo
Anaemia and haemolysis
Transfusion
Jaundice (*UGT1A1*)
Increased Fe absorption (*HFE*)
Iron overload
Skeletal deformities
Bone disease
(*VDR, OesR, COLA1A1*)
Organ damage
Cardiac failure
(*APOEε4*)
Tertiary

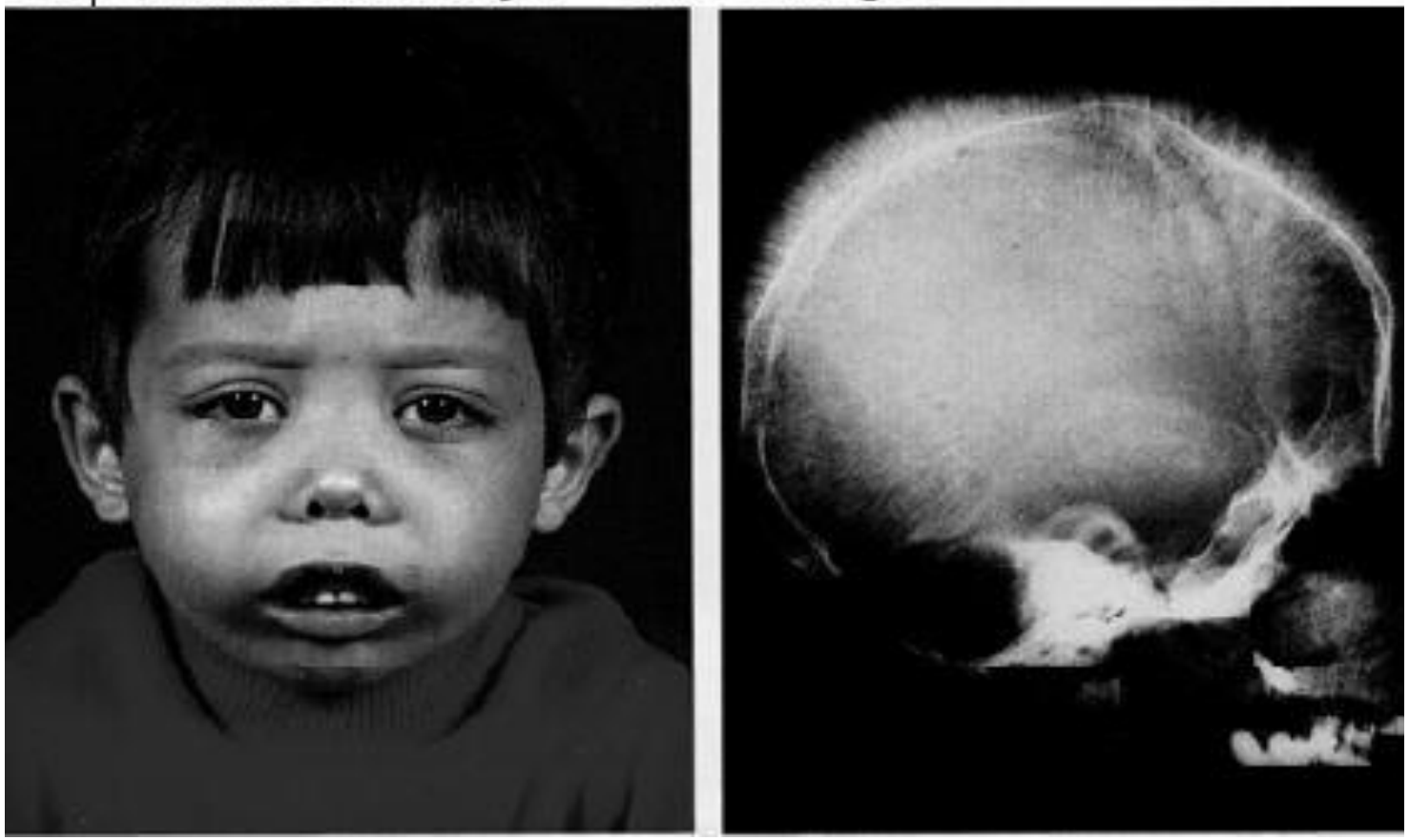
Clinical features:

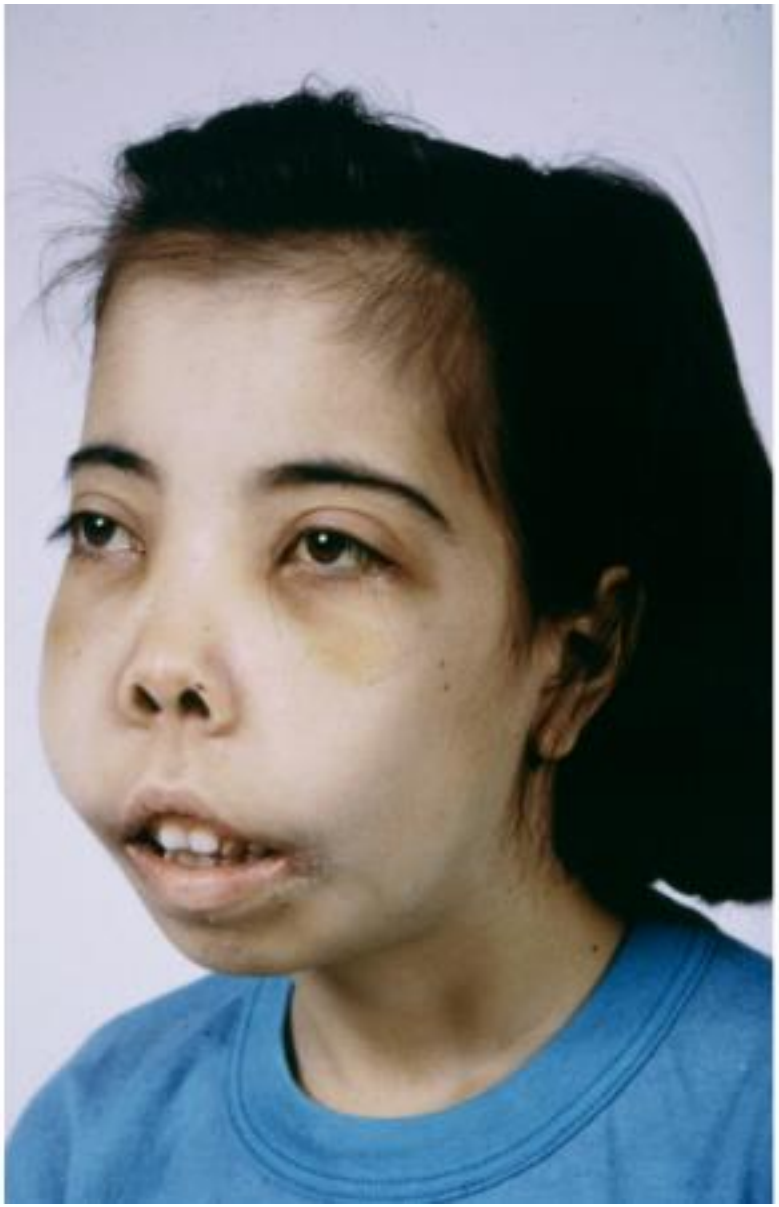
Patients present in the first year of life with failure to thrive, poor feeding, repeated infections, pallor & splenomegaly. They suffer from ill health & severe anemia that can lead to cardiac failure. Without regular transfusion, growth & development are retarded. Bone marrow expansion will lead to skull bossing & overgrowth of zygoma giving rise to mongoloid facies & malocclusion of teeth. Radiologically, there is widening of the medulla with thinning of the trabeculae & cortex.

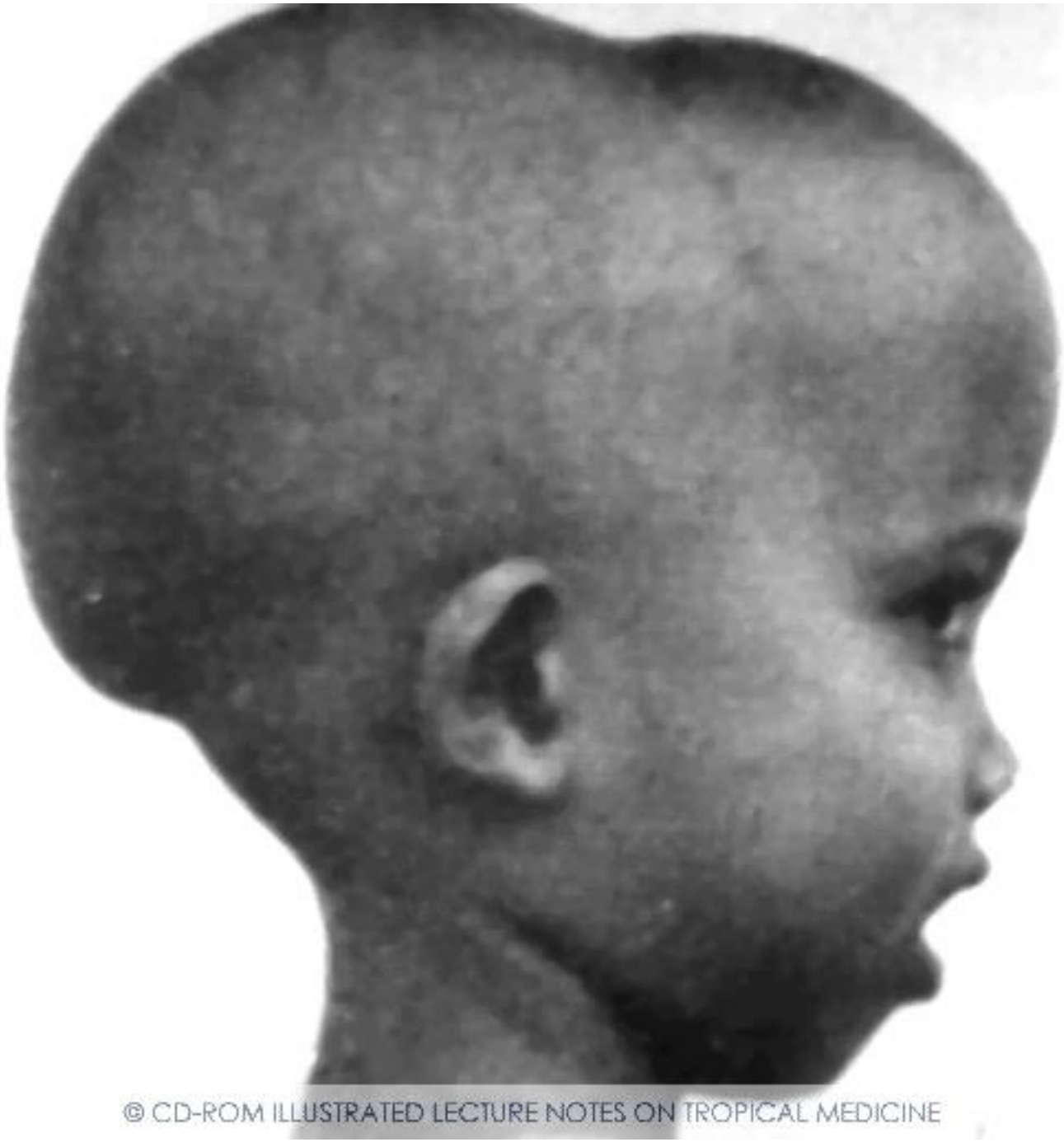

-100
- 80
- 60
- 40
- 20
Cm

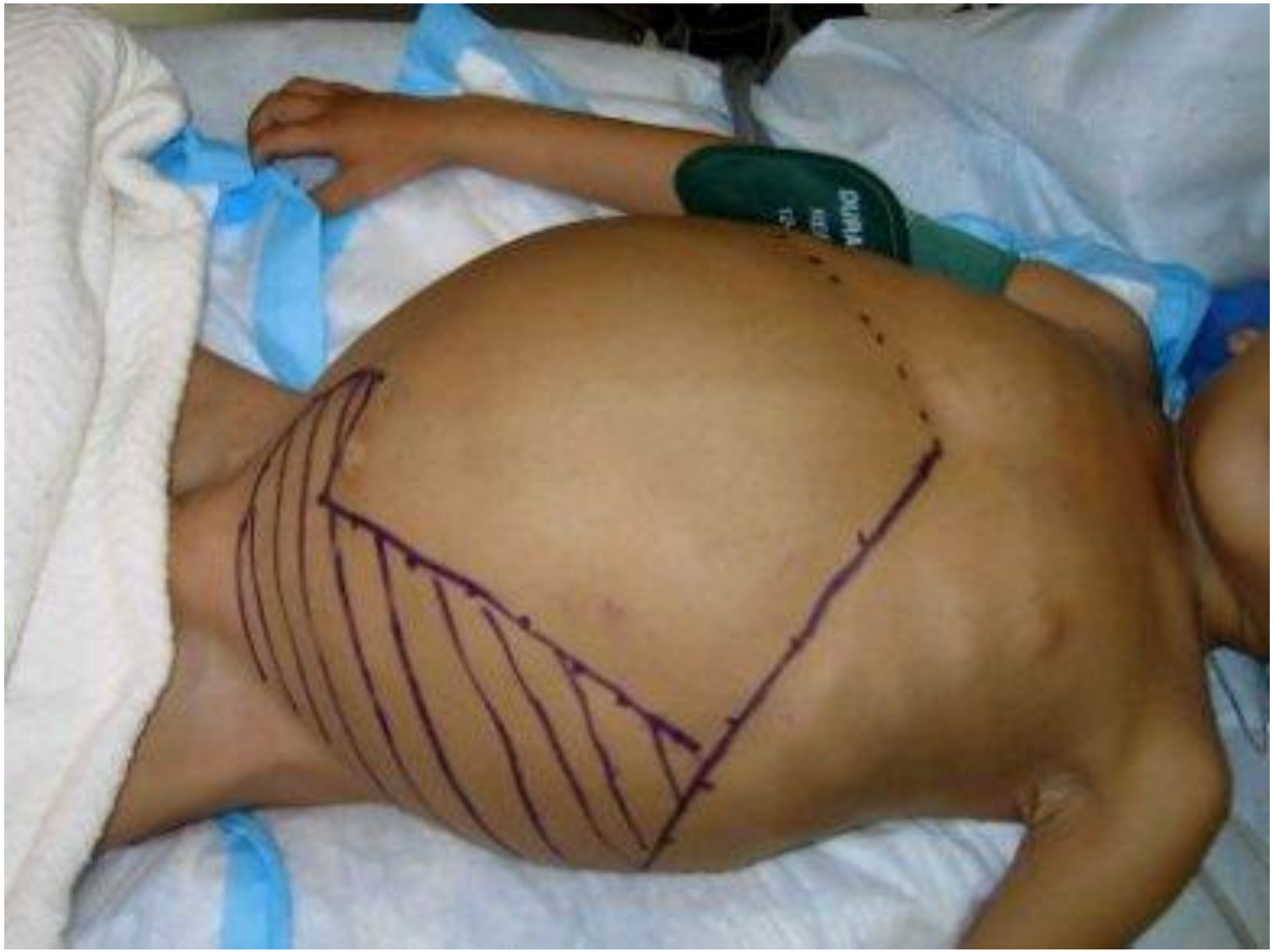

100 CM
100 CM
75 CM
50 CM
50 CM
50 CM
25 CM
25 CM

Beta Thalassemia Major – bone changes







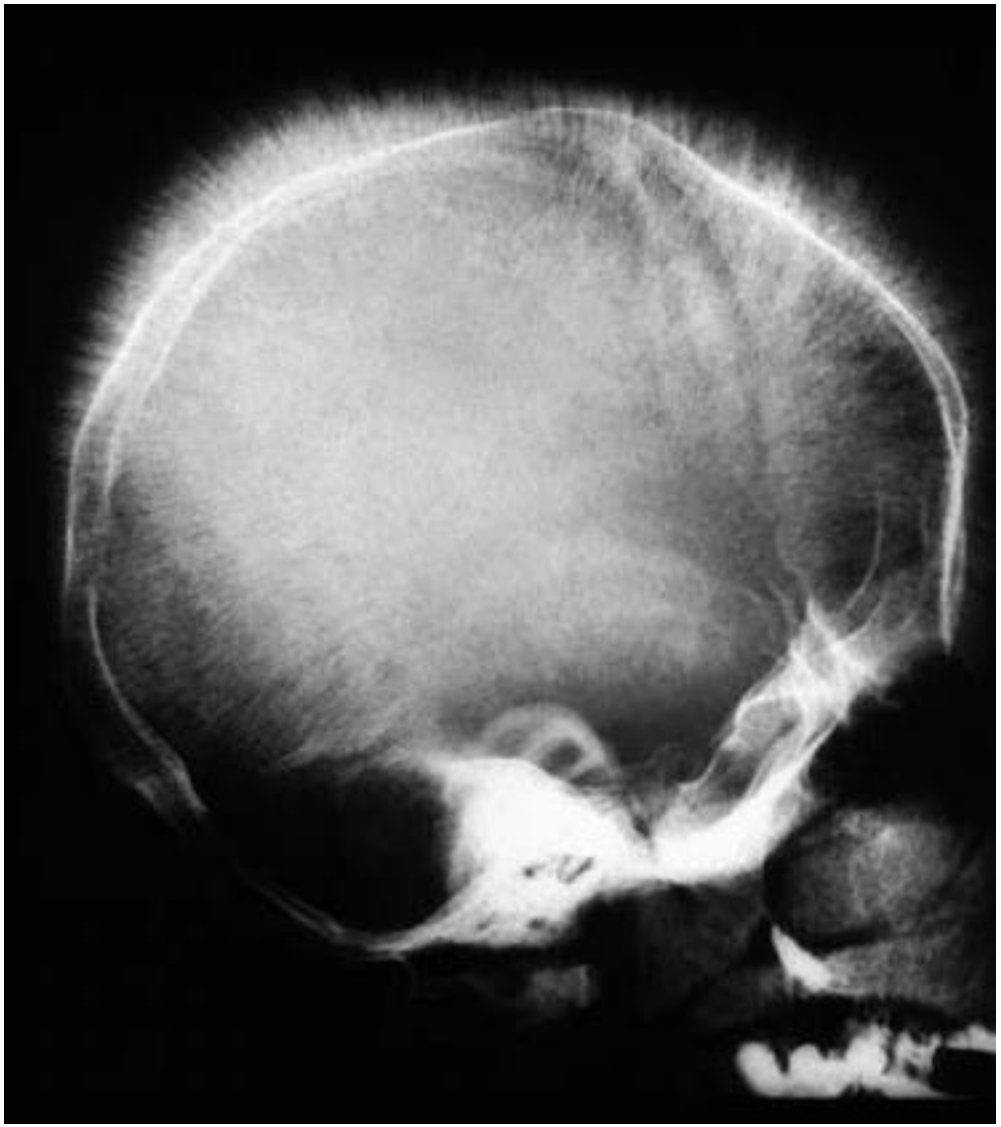


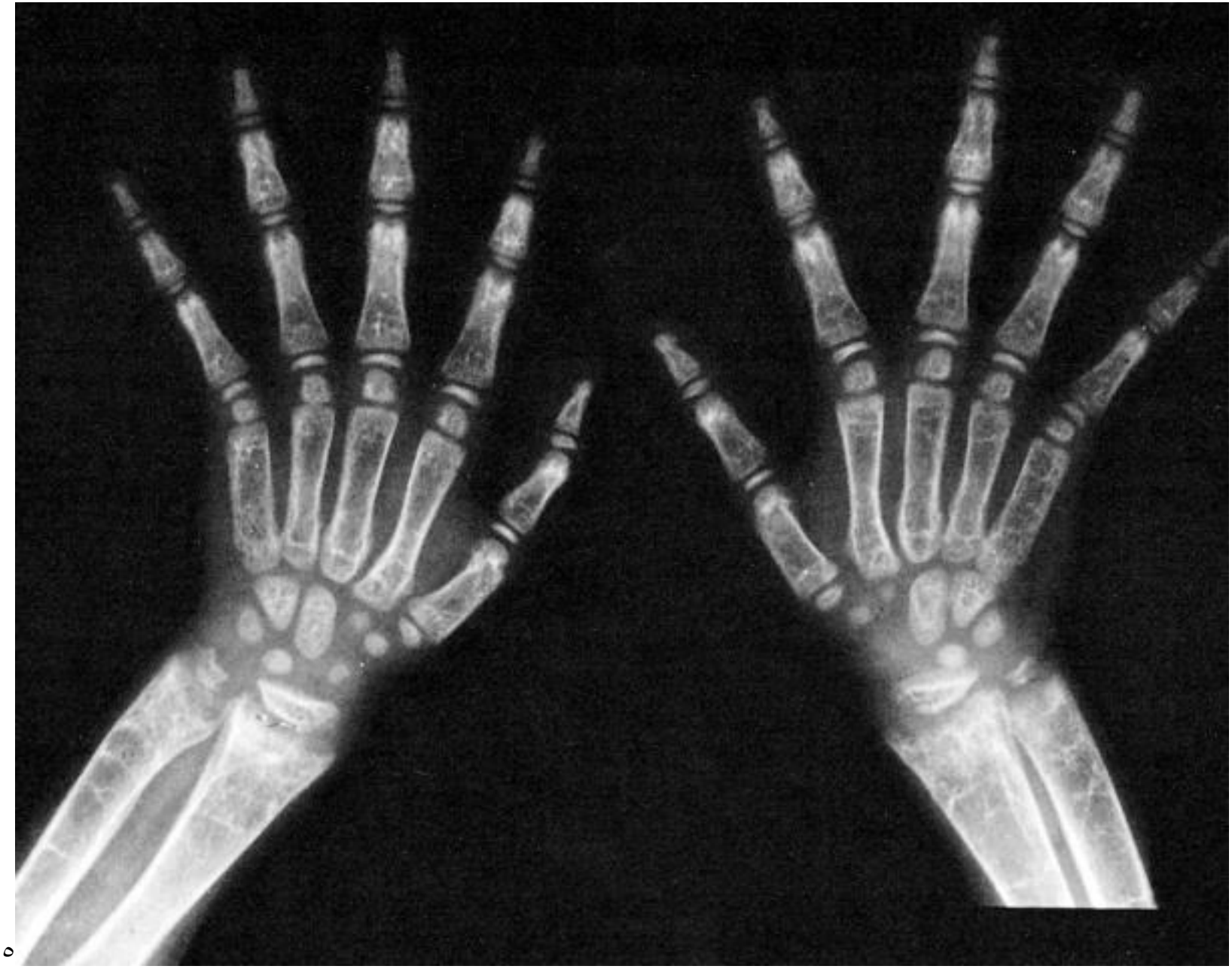
This appearance is called hair on end appearance of the skull xray & in other bones. The bones become vulnerable to pathological fractures.

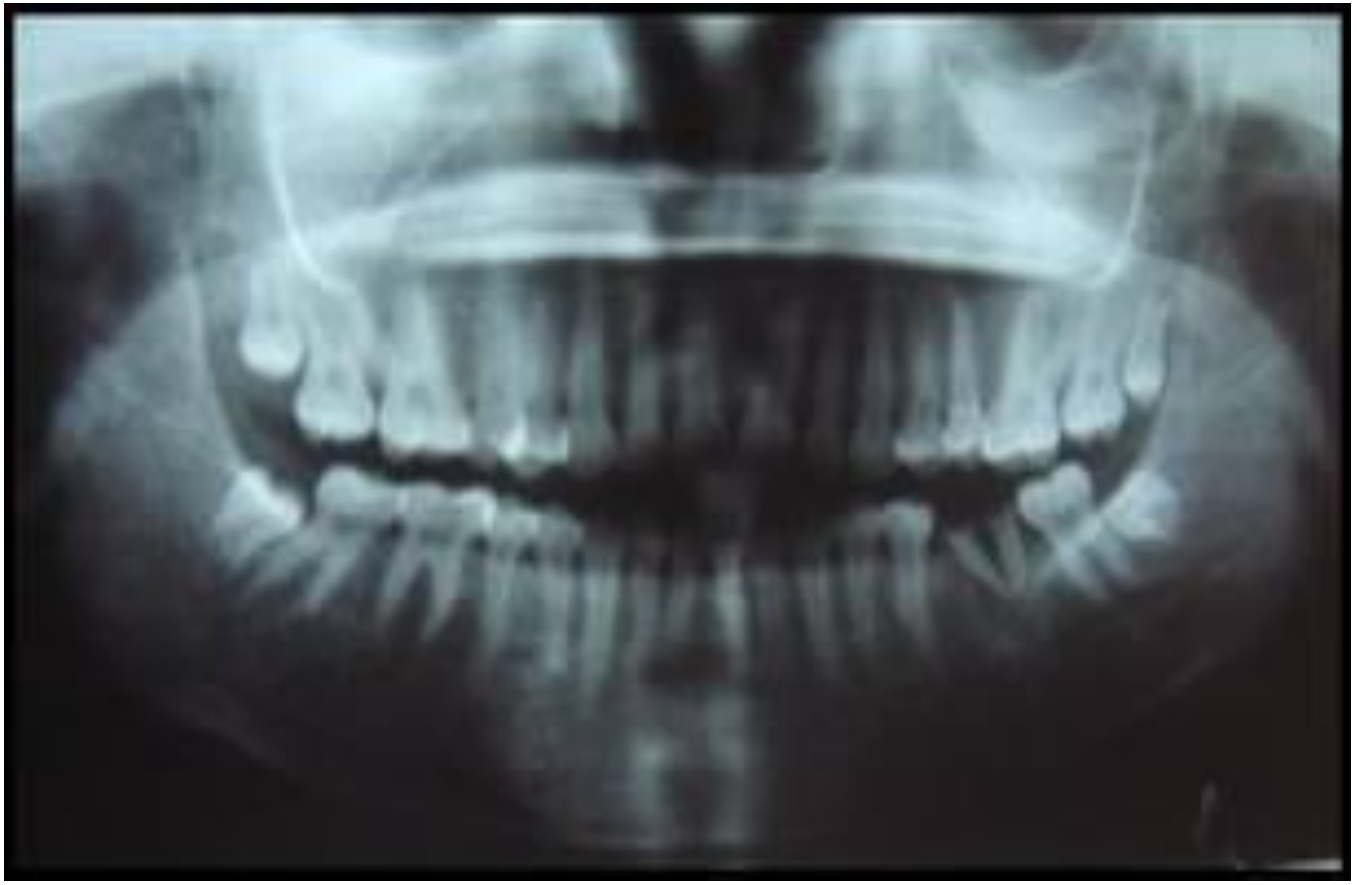
Without transfusion these patients die early in life.

The well transfused child will develop normally until the effects of iron overload will lead to hepatic, endocrine & cardiac damage by the end of the first decade.


AMTF
HUSAIN

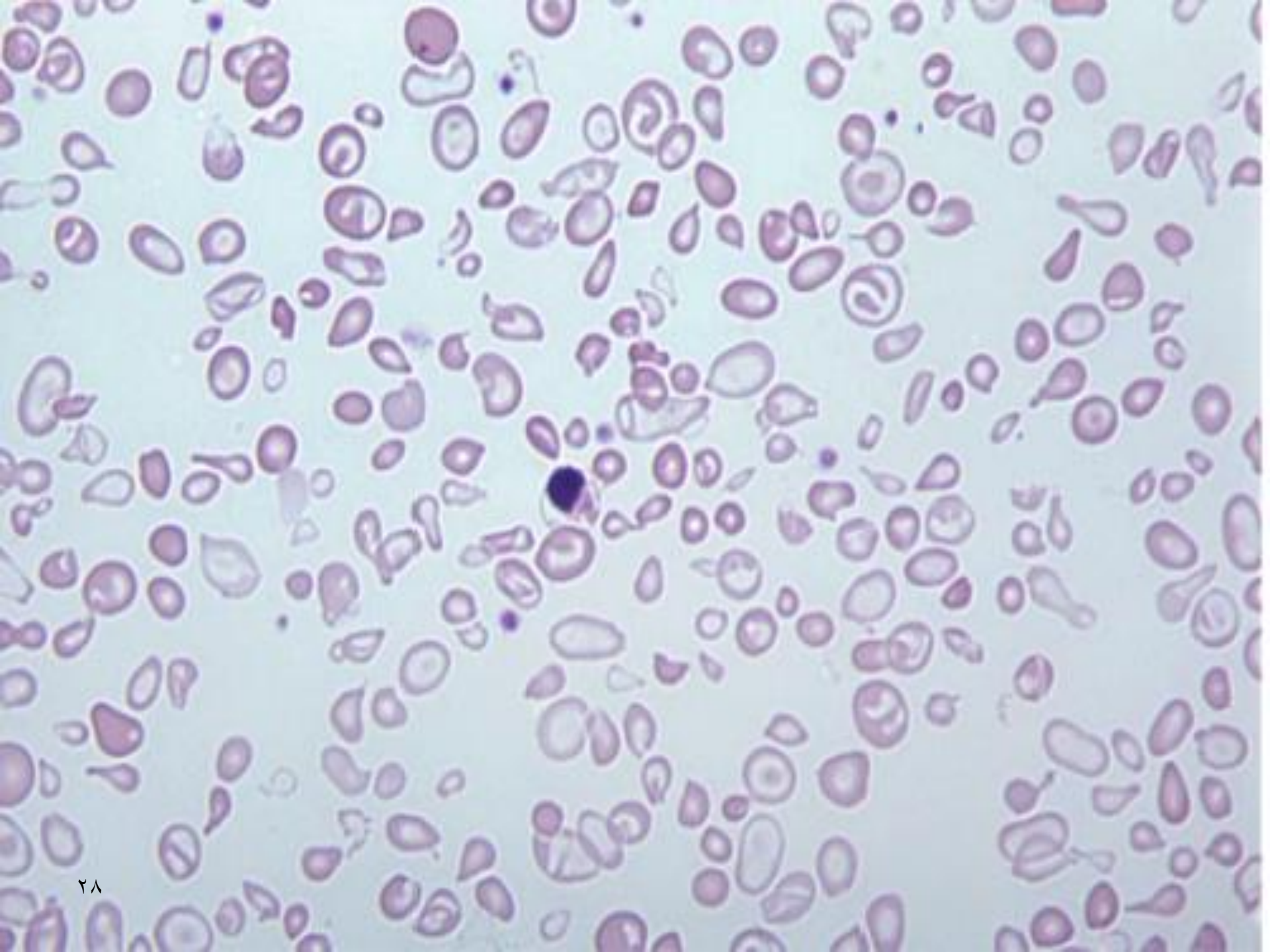


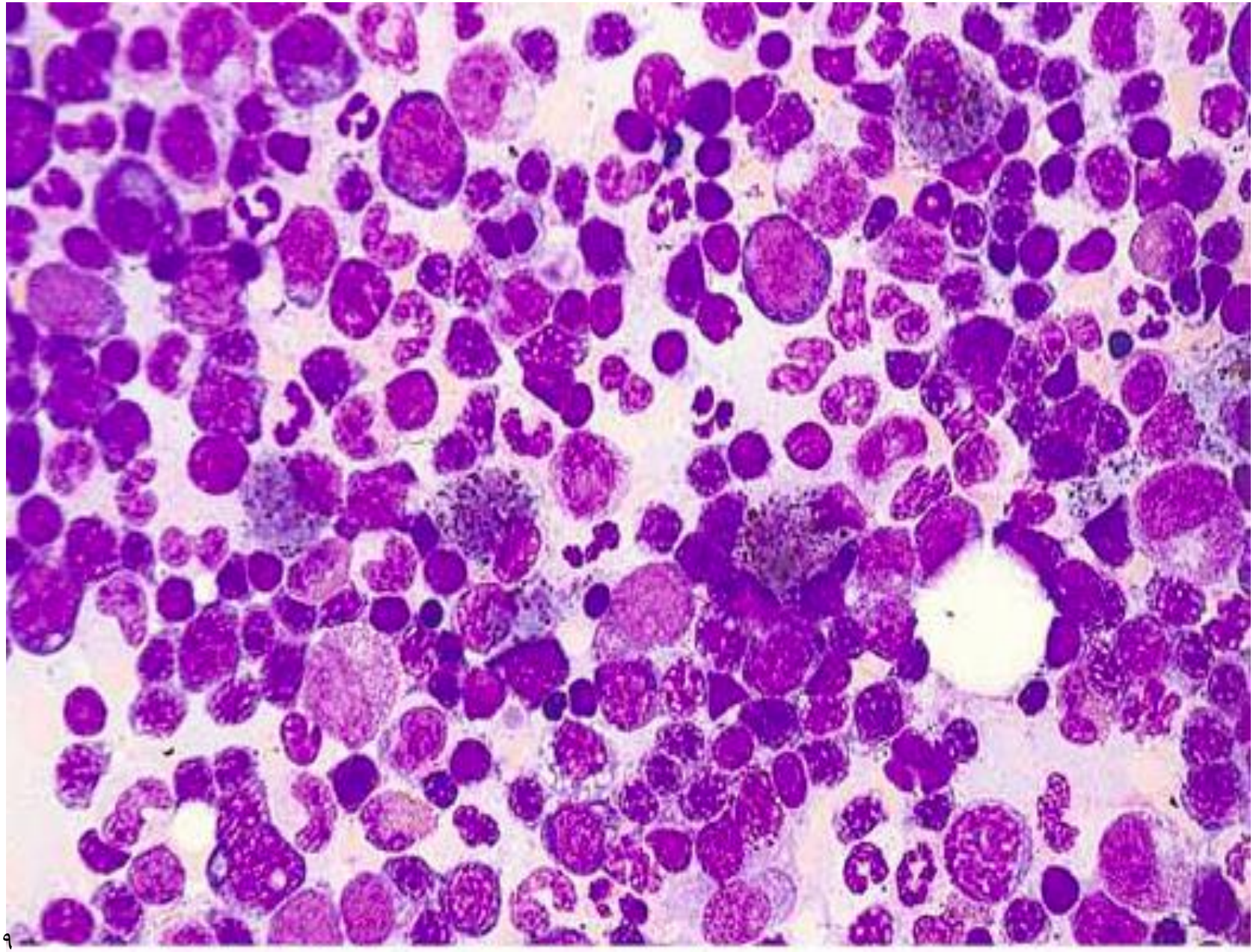




Laboratory findings:

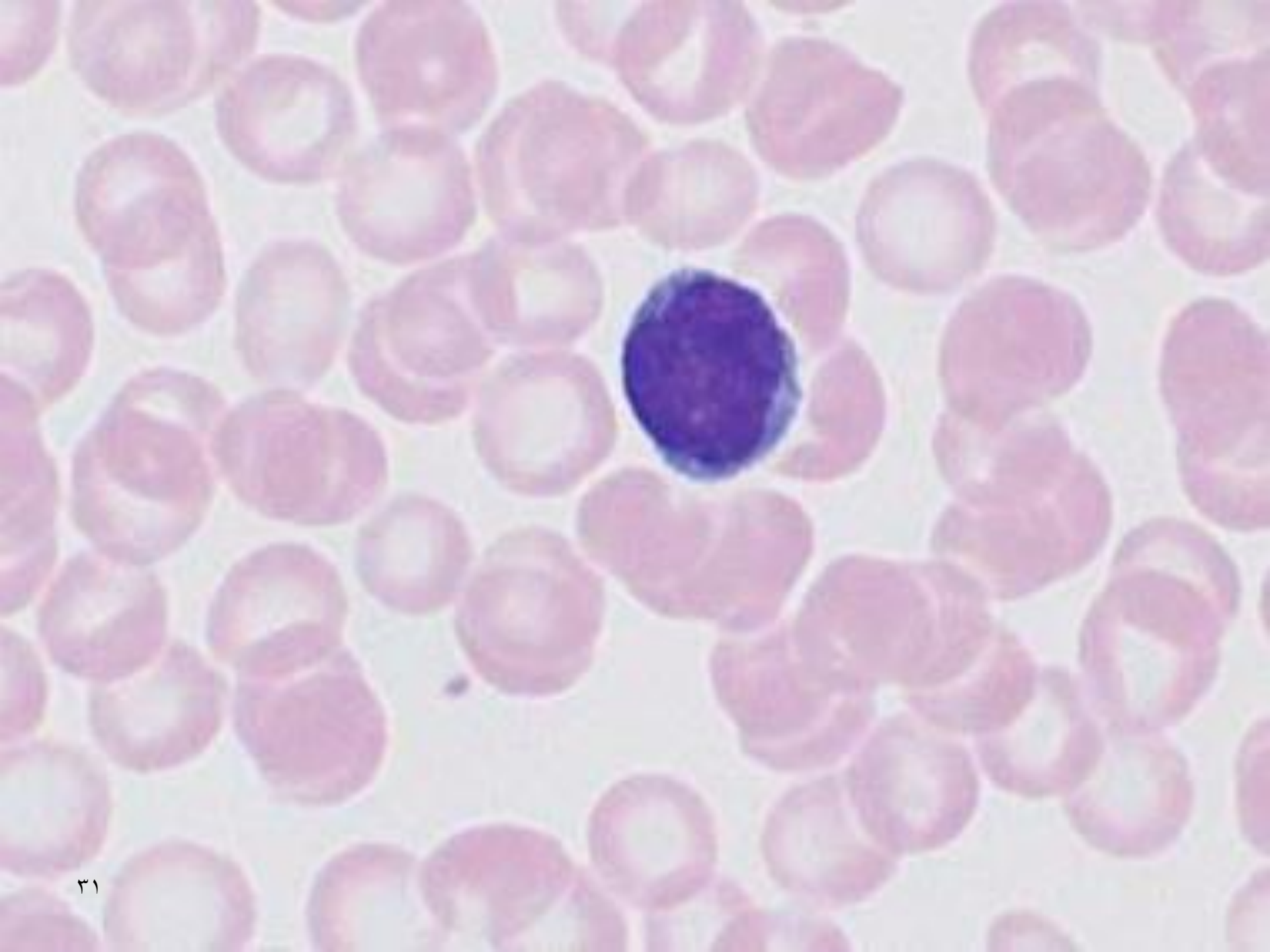
1. **The complete blood picture shows low hemoglobin, low MCV, low MCH.**
2. **The blood film shows hypochromic microcytic red cells with prominent anisocytosis, poikilocytosis, red cell fragments & nucleated cells.**
3. **Mild reticulocytosis(because of ineffective erythropoiesis: most of the red cells are destroyed inside the marrow not in the circulation)**
4. **Hemoglobin electrophoresis: characteristically in β^0 the major hemoglobin is HbF> 90% with HbA2 being a minor component & no HbA. In case of β+ , HbA is present in reduced amount & HbF is the major hemoglobin (30-90%) with HbA2.**

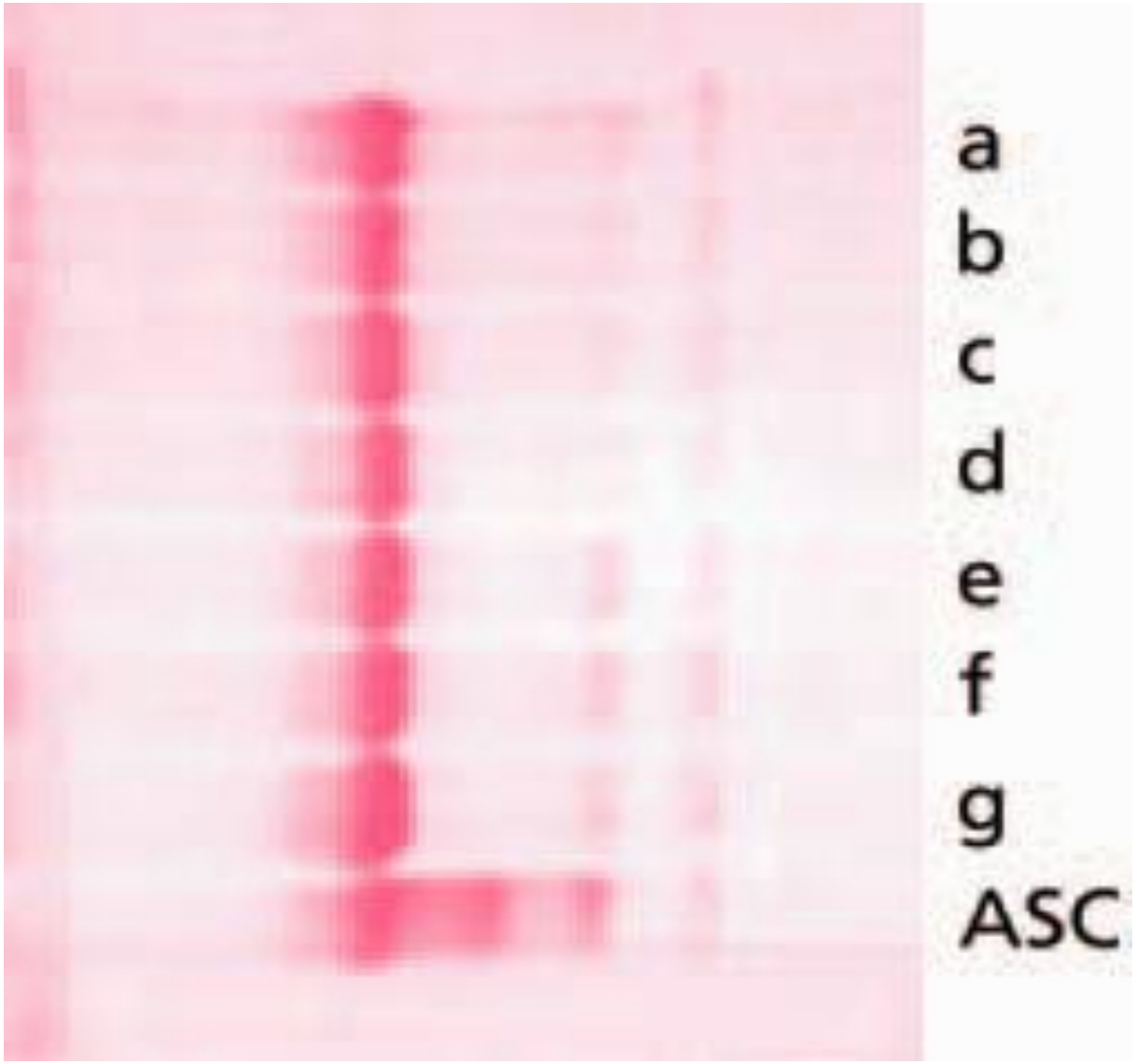




β thalassemia minor or trait (heterozygote)

Carriers of β thalassemia are usually asymptomatic except in periods of stress such as pregnancy. There is mild anemia (Hb 9-11 g/dL), low MCV, low MCH & the blood film shows hypochromic microcytic red cells. The characteristic finding is elevated HbA2 (>3.5%) on Hb electrophoresis



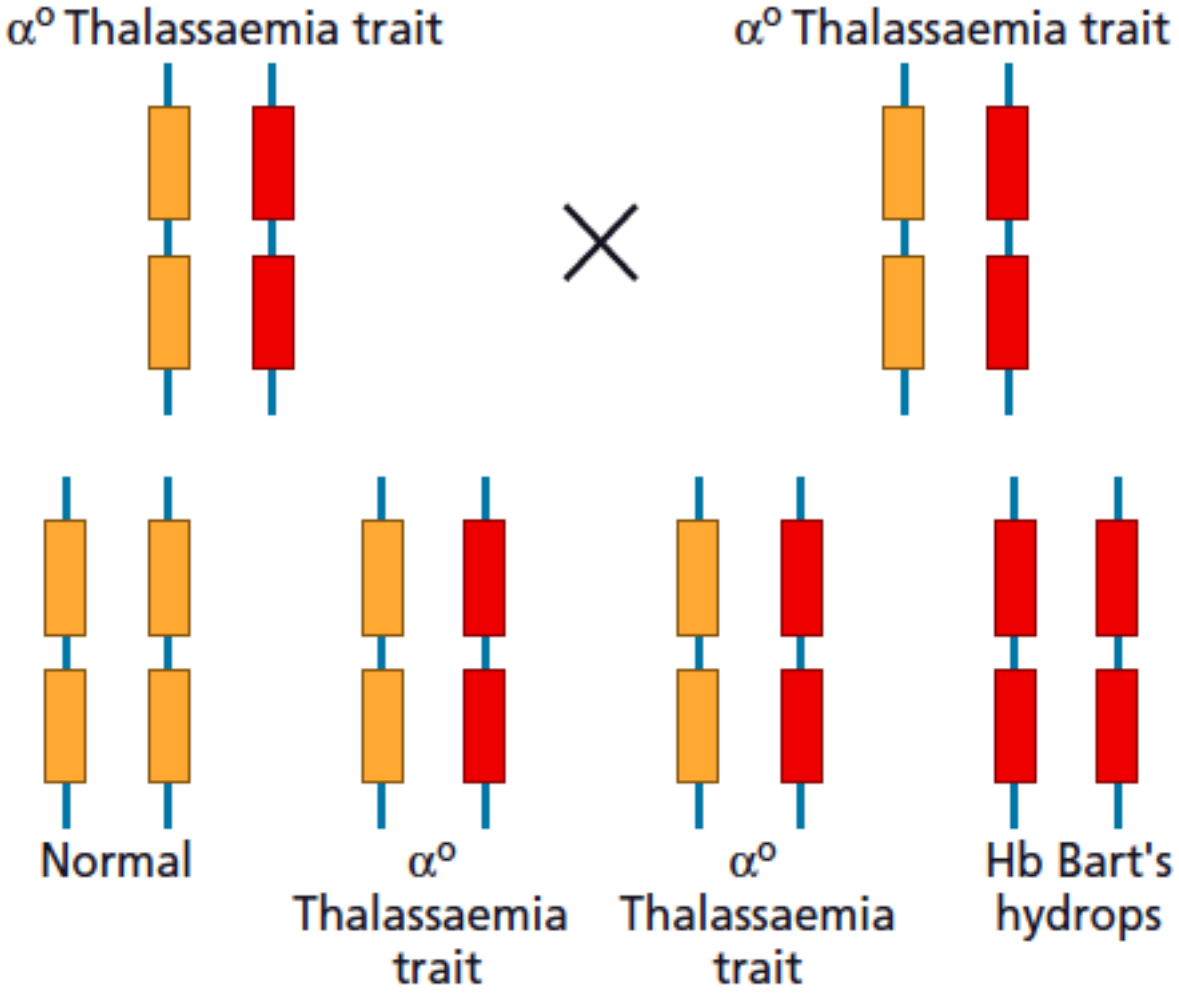

a
b
c
d
e
f
g
ASC

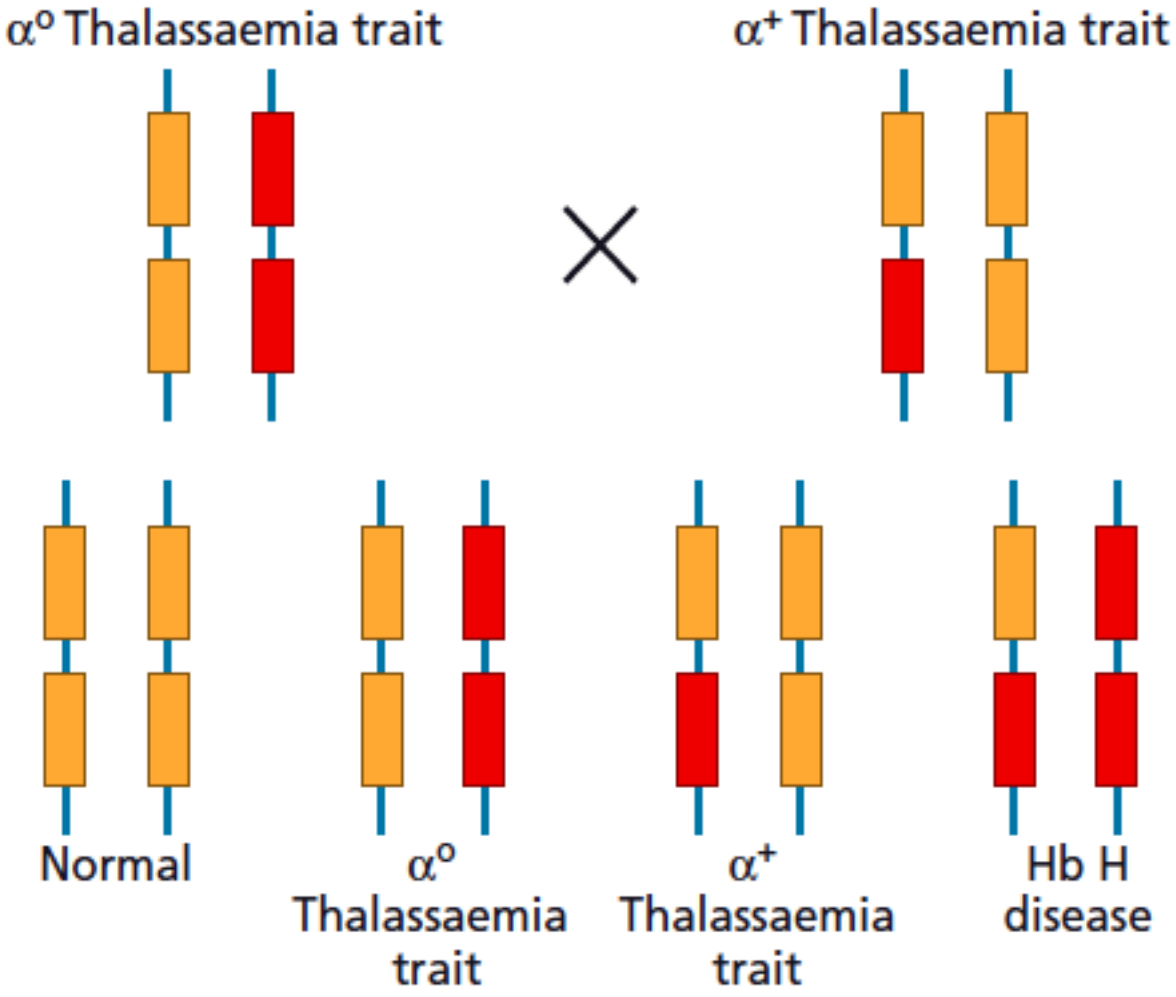
α Thalassemia

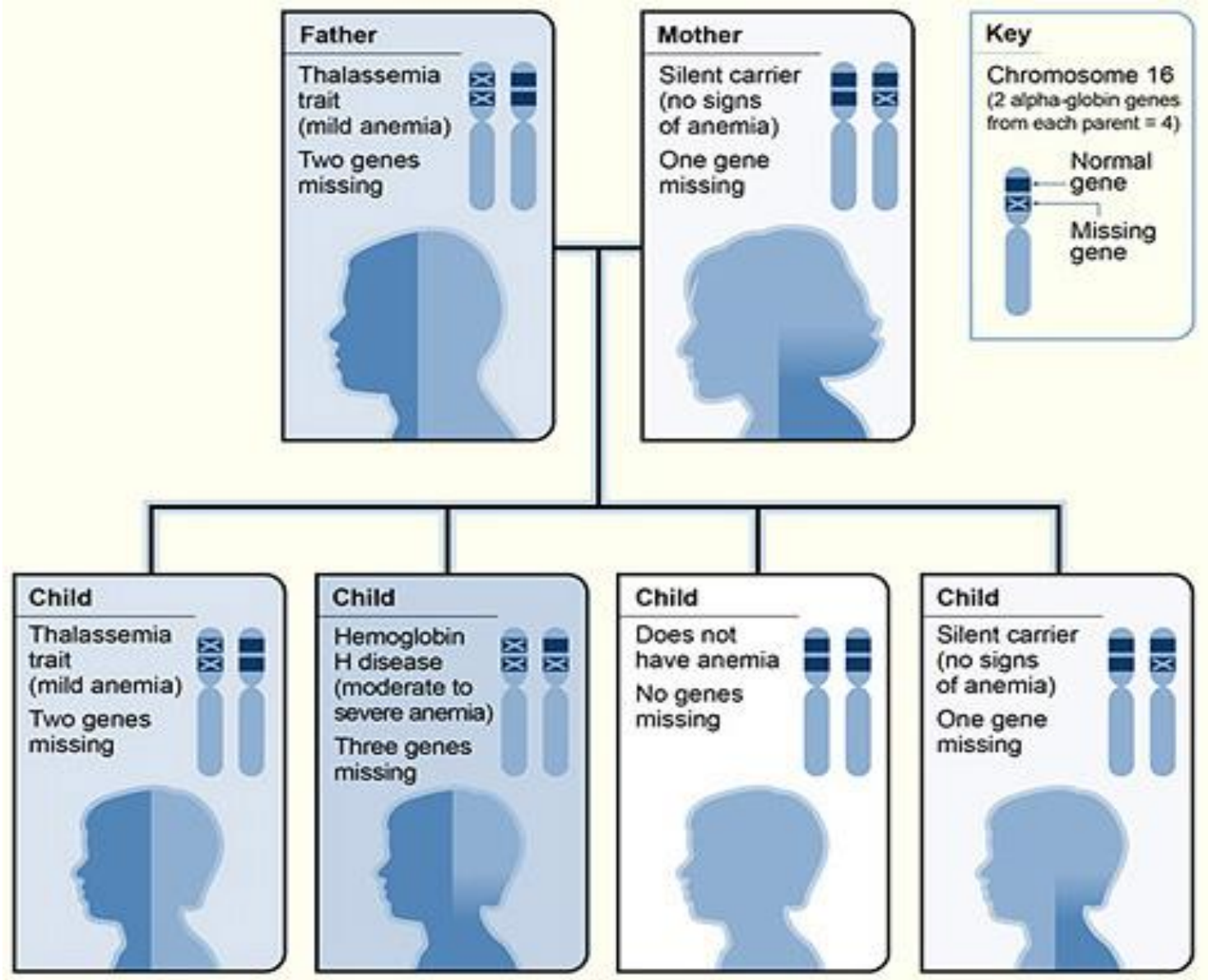
The α thalassemias occur widely throughout the world especially in south east Asia but it is uncommon in Iraq.

Normally, there are two α globin genes on chromosome 16. So every individual inherit 2 α genes from each parent & the normal genotype is (αα/αα). That is to say four α genes are necessary for normal α chain synthesis.

Most α thalassemias result from gene deletion. Deletion of one gene is called α+(– α) & deletion of 2 genes is called α0(– –).


αº Thalassaemia trait
αº Thalassaemia trait
Normal
αº Thalassaemia trait
αº Thalassaemia trait
Hb Bart's hydrops


αº Thalassaemia trait
α+ Thalassaemia trait
Normal
αº Thalassaemia trait
α+ Thalassaemia trait
Hb H disease


Father
Thalassemia trait (mild anemia)
Two genes missing
Mother
Silent carrier (no signs of anemia)
One gene missing
Key
Chromosome 16
(2 alpha-globin genes from each parent = 4)
Normal gene
Missing gene
Child
Thalassemia trait (mild anemia)
Two genes missing
Child
Hemoglobin H disease (moderate to severe anemia)
Three genes missing
Child
Does not have anemia
No genes missing
Child
Silent carrier (no signs of anemia)
One gene missing

types of α thalassemia:

1. Single gene deletion (– α/αα).
2. Two gene deletion in the same haploid (– –/αα) or one from each haploid (– α/– α).

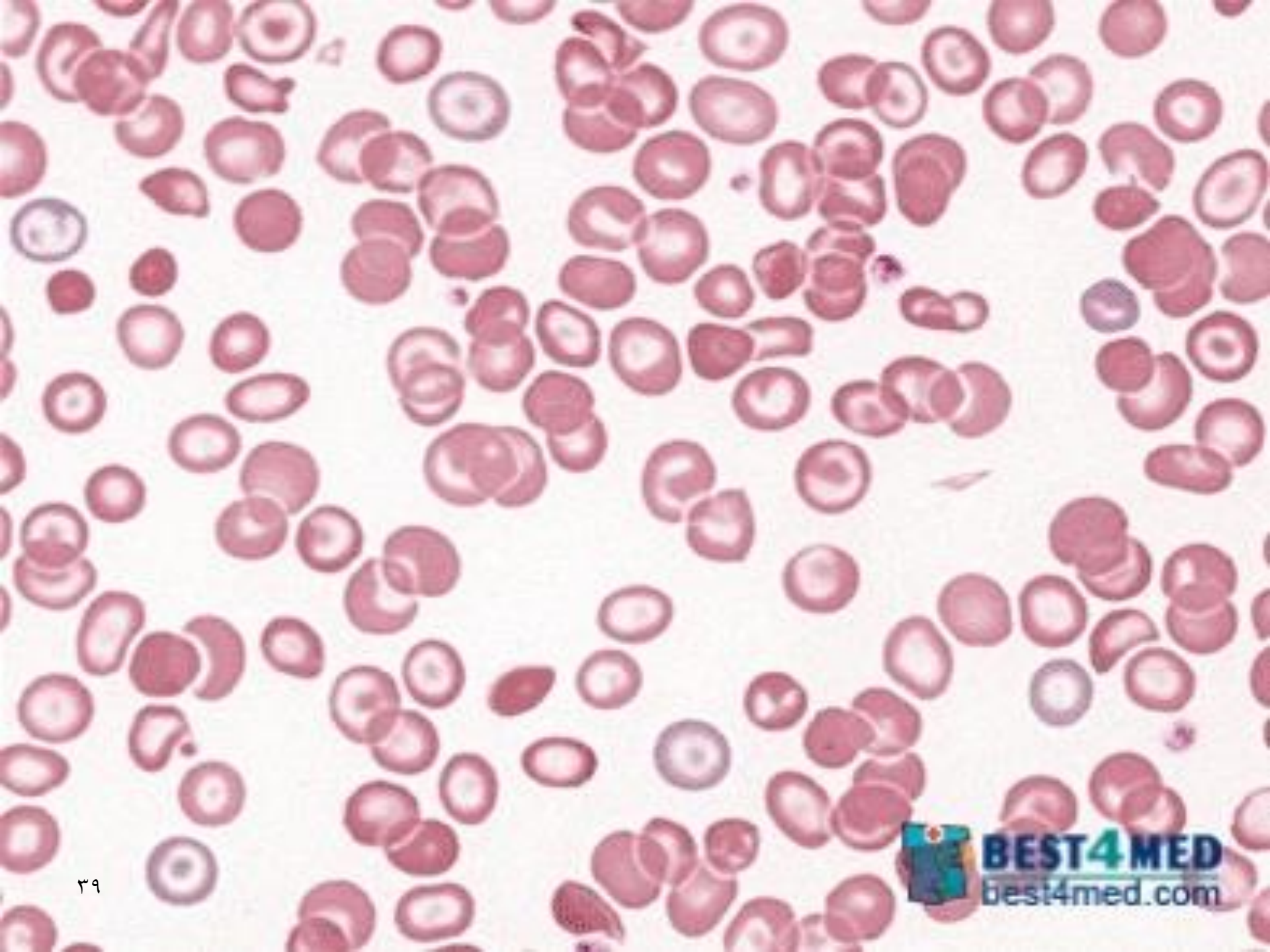
Both a & b produce no clinical disease & can not be diagnosed by conventional methods.

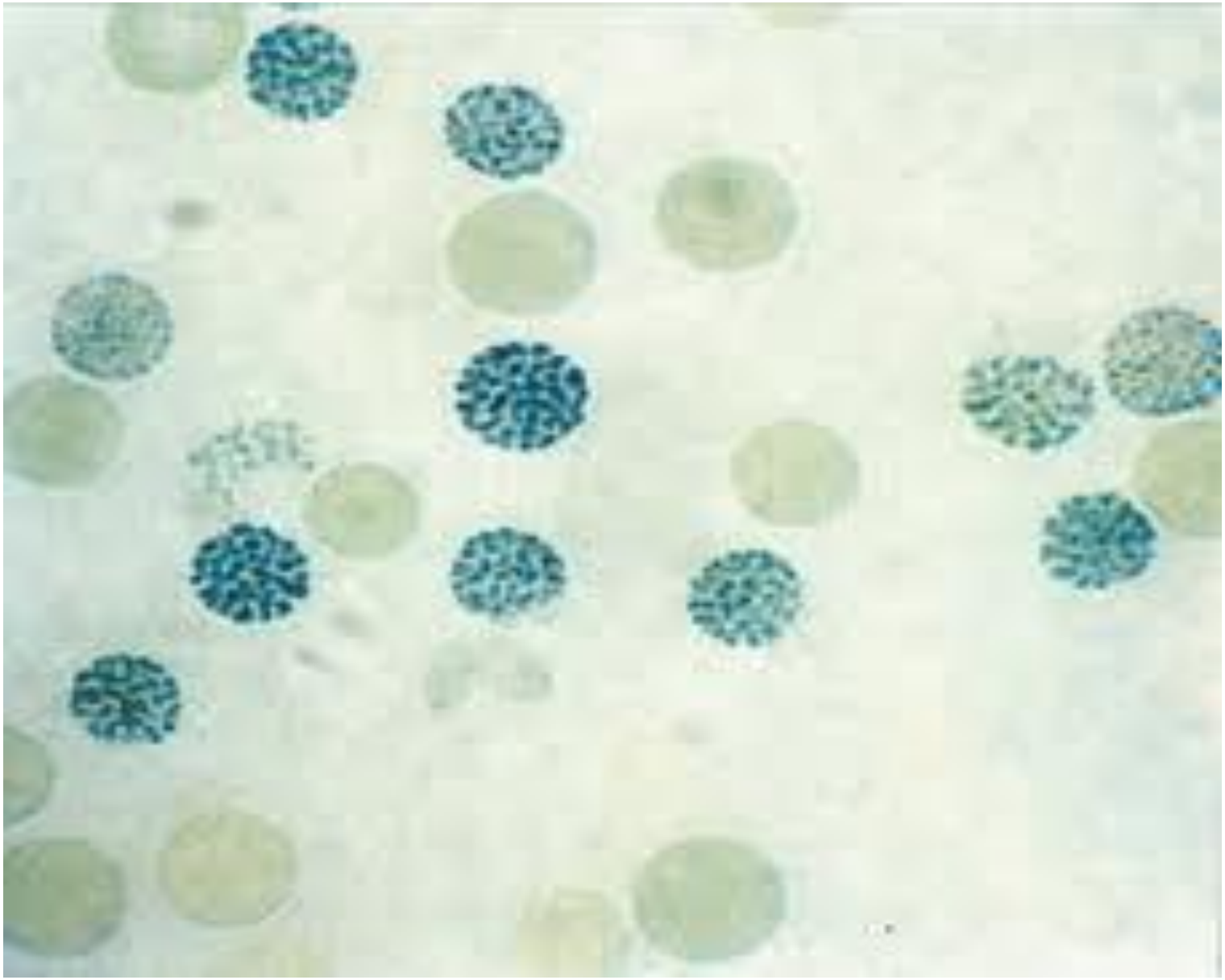
3. Three gene deletion: Hb H disease (– – /– α)

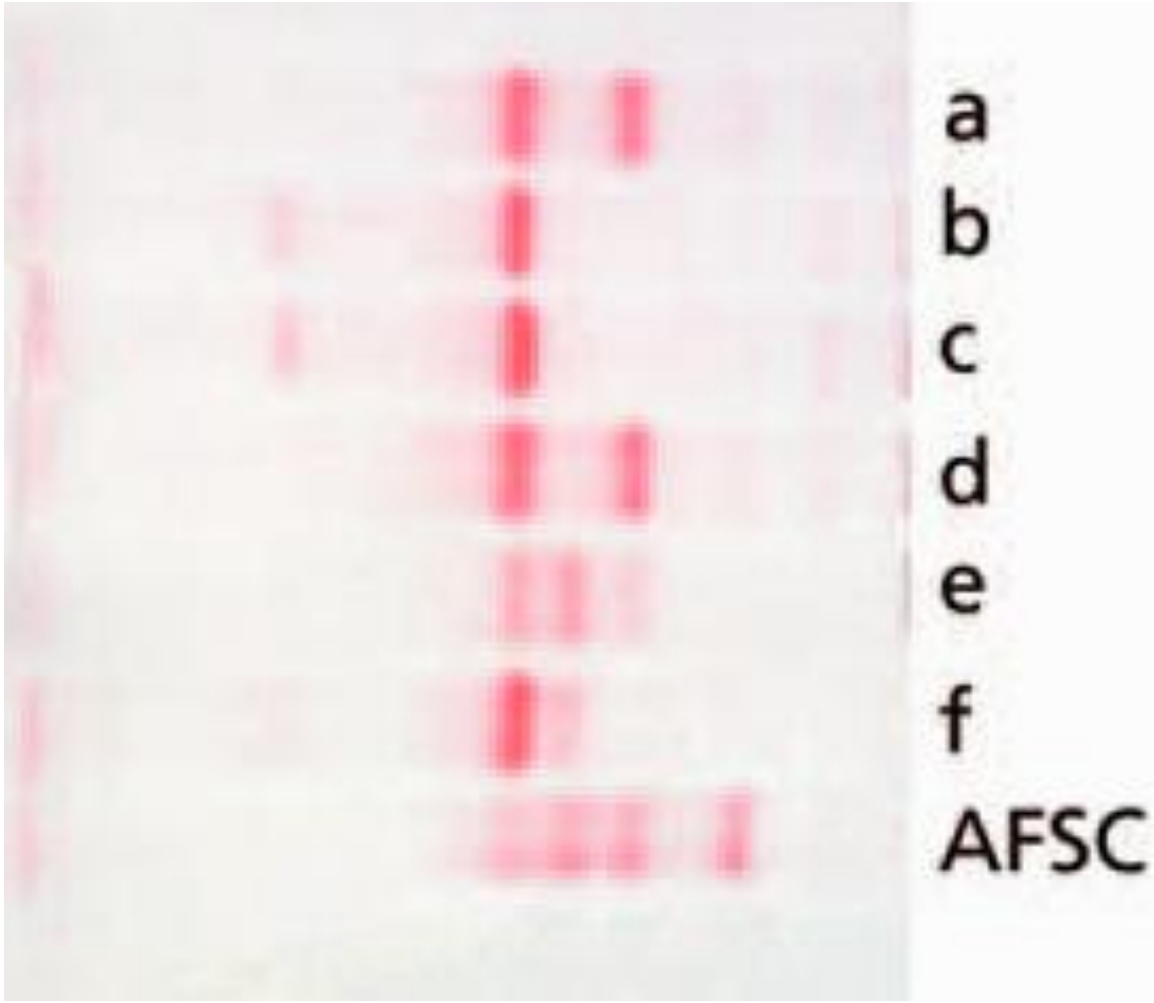
Hb H is a tetramer of normal β chains (β4).

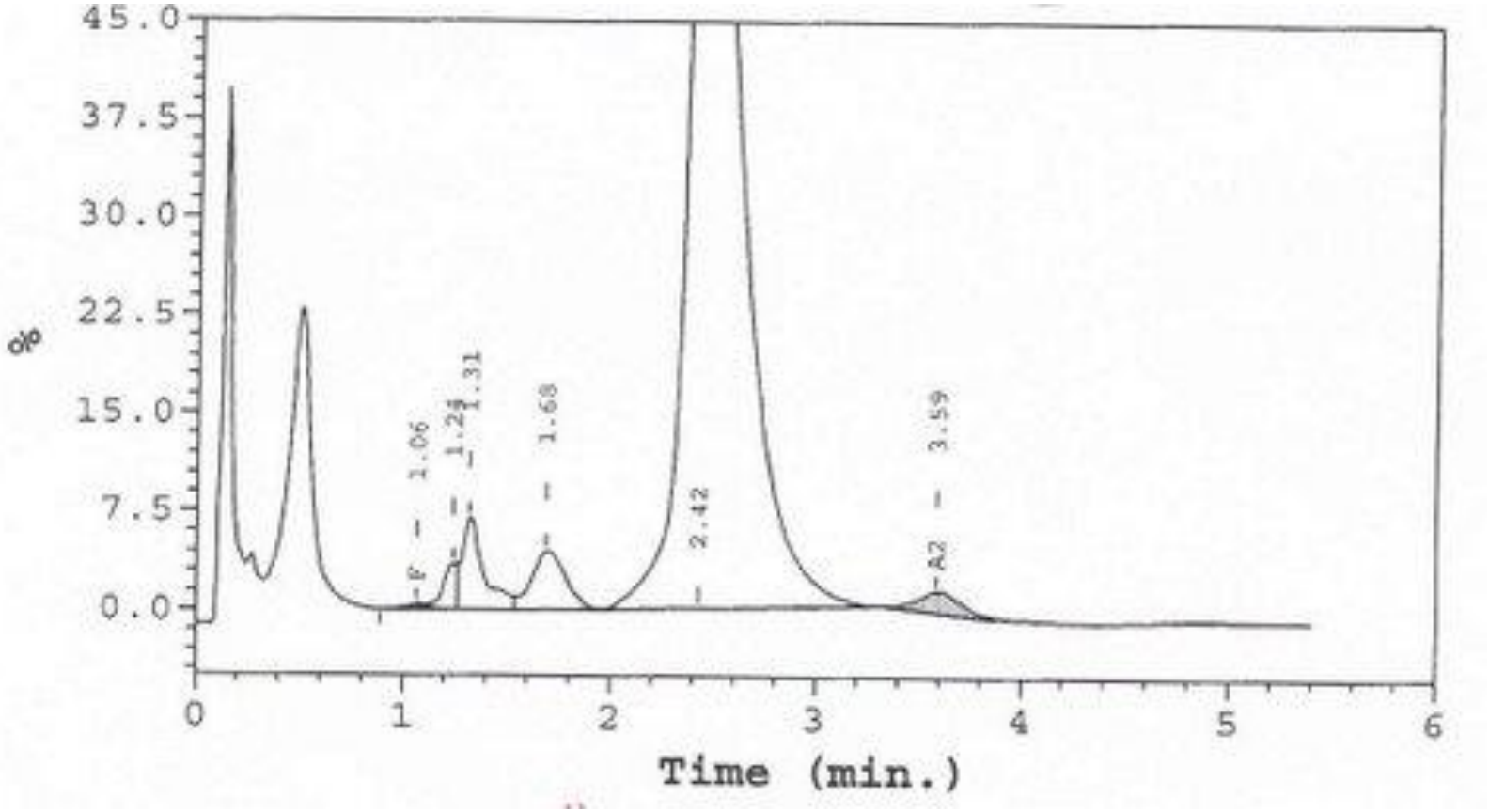
There is a variable degree of anemia & splenomegaly but it is unusual to see bone changes.

Blood film shows thalassemic changes. Hb H preparation shows golf ball appearance. Hb electrophoresis reveals 5-40 % HbH plus HbA & normal HbA2.





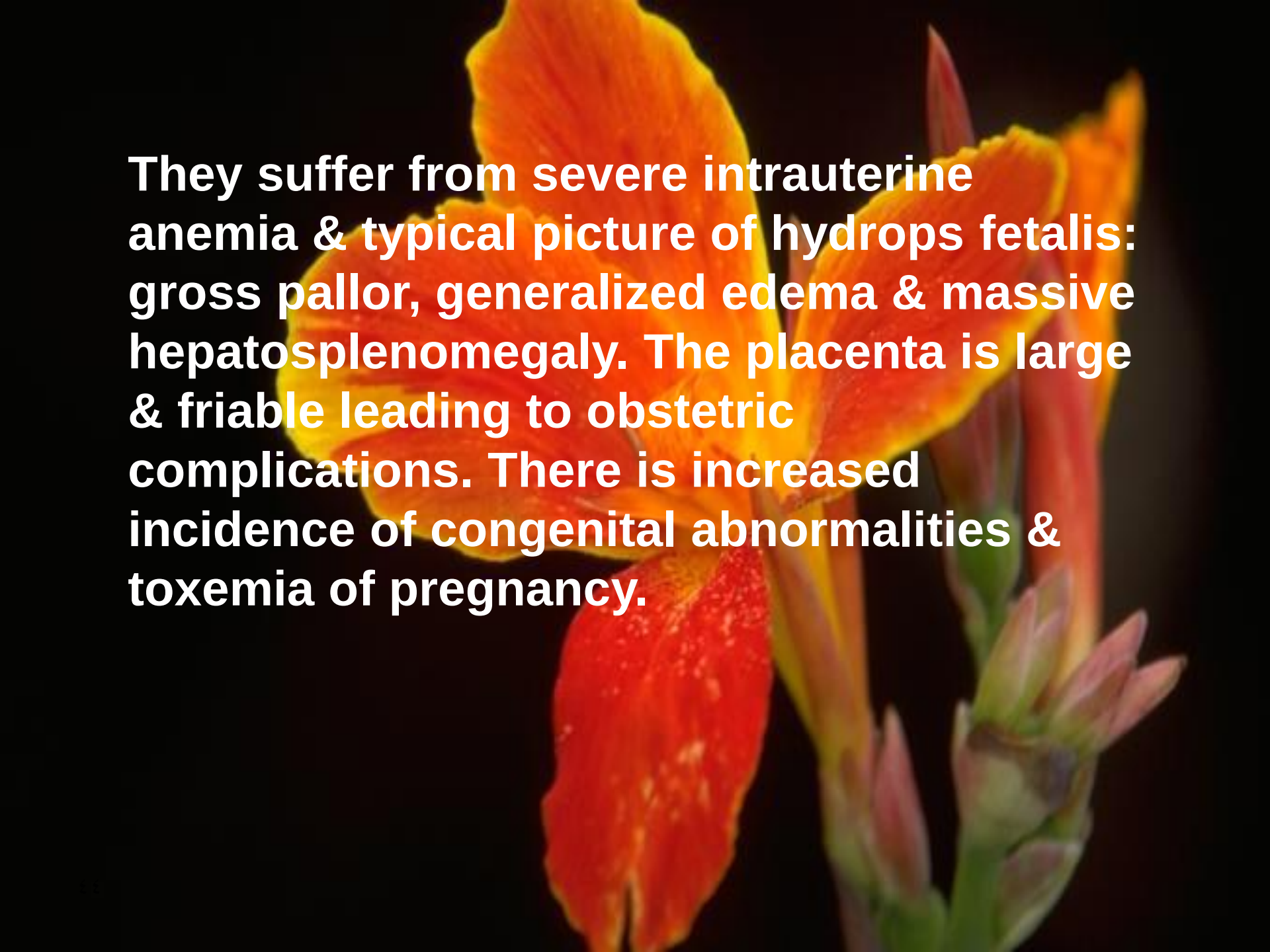

a
b
c
d
e
f
AFSC


45.0
37.5
30.0
22.5
15.0
7.5
0.0
%
0
1
2
3
4
5
6
Time (min.)
F - 1.06
1.25
1.31
1.68
2.42
A2 - 3.59

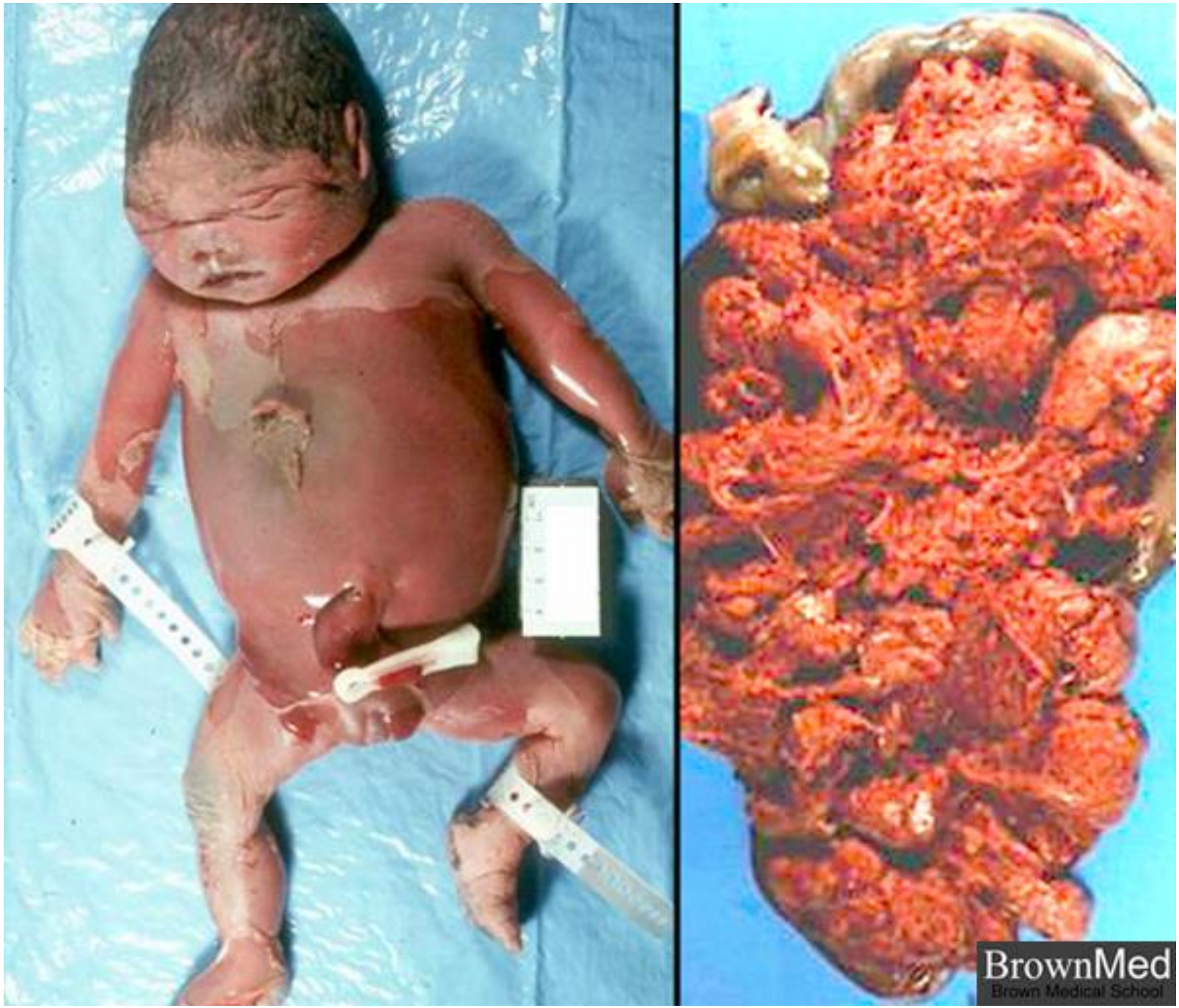
4. Four gene deletion (– –/– –): Hb Bart's hydrops fetalis.

This is a common cause of fetal loss in south east Asia. The affected infants produce no α chains.

This leads to the formation of Hb Bart's (γ_4) with a very high oxygen affinity. They are still born or die shortly after birth.

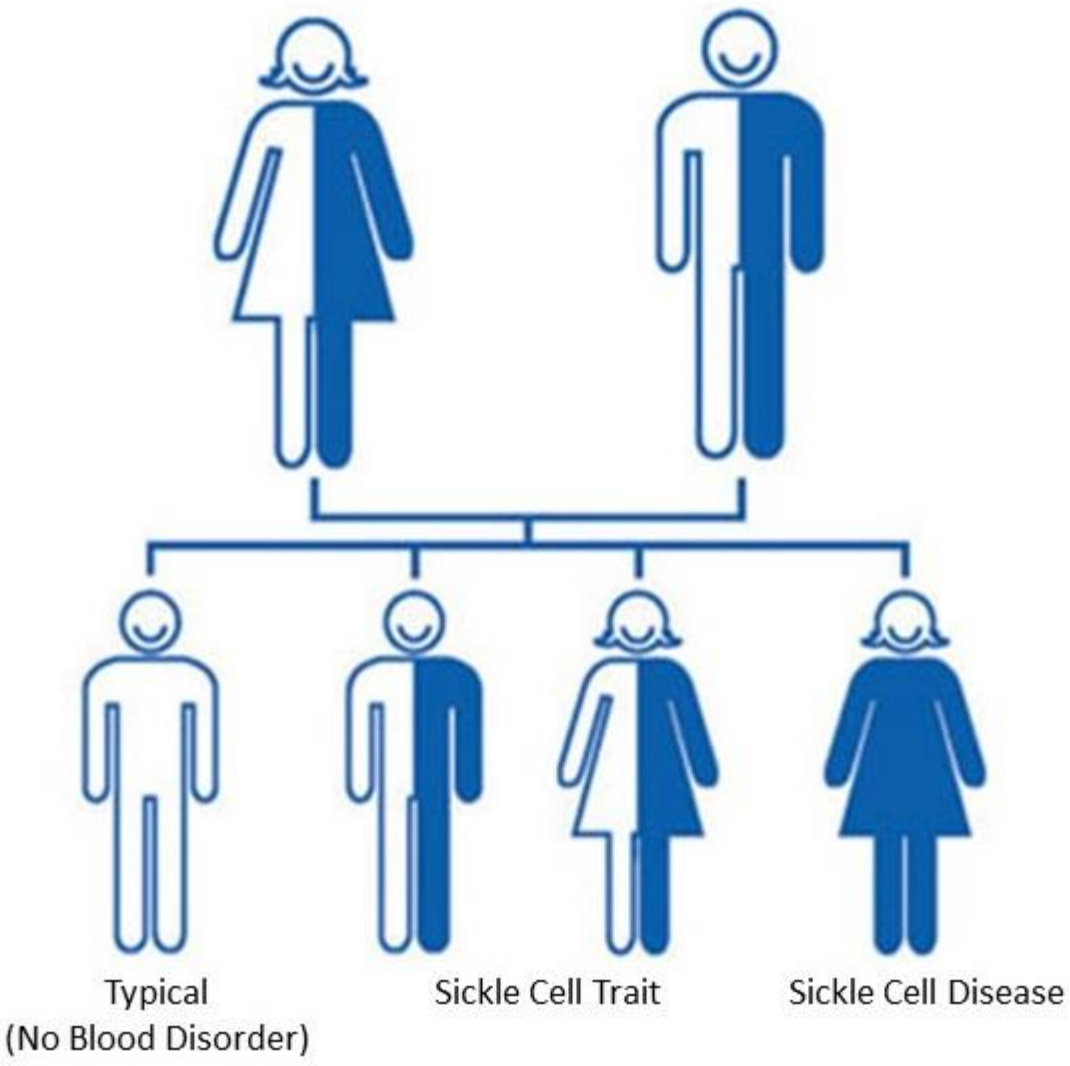


They suffer from severe intrauterine anemia & typical picture of hydrops fetalis: gross pallor, generalized edema & massive hepatosplenomegaly. The placenta is large & friable leading to obstetric complications. There is increased incidence of congenital abnormalities & toxemia of pregnancy.


BrownMed
Brown Medical School

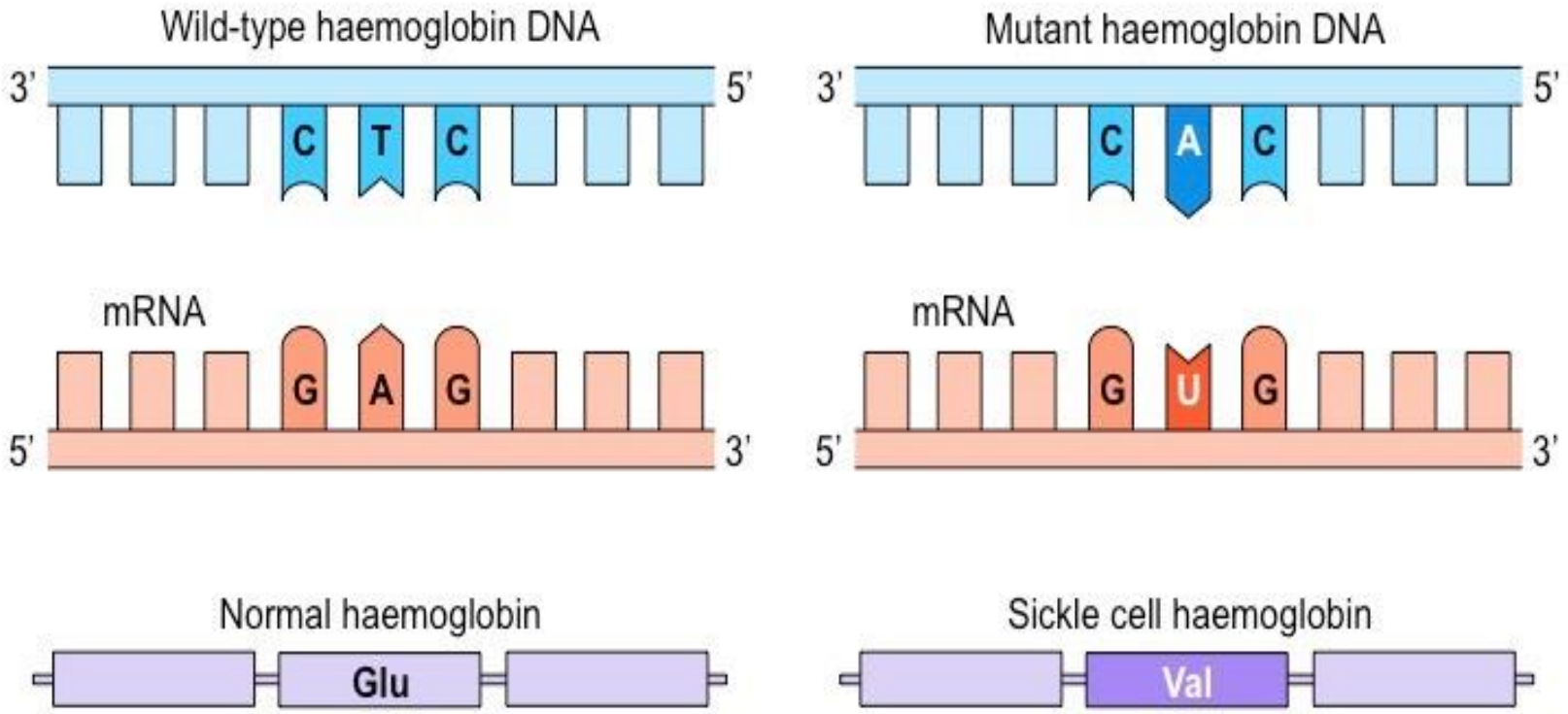
Sickling disorders

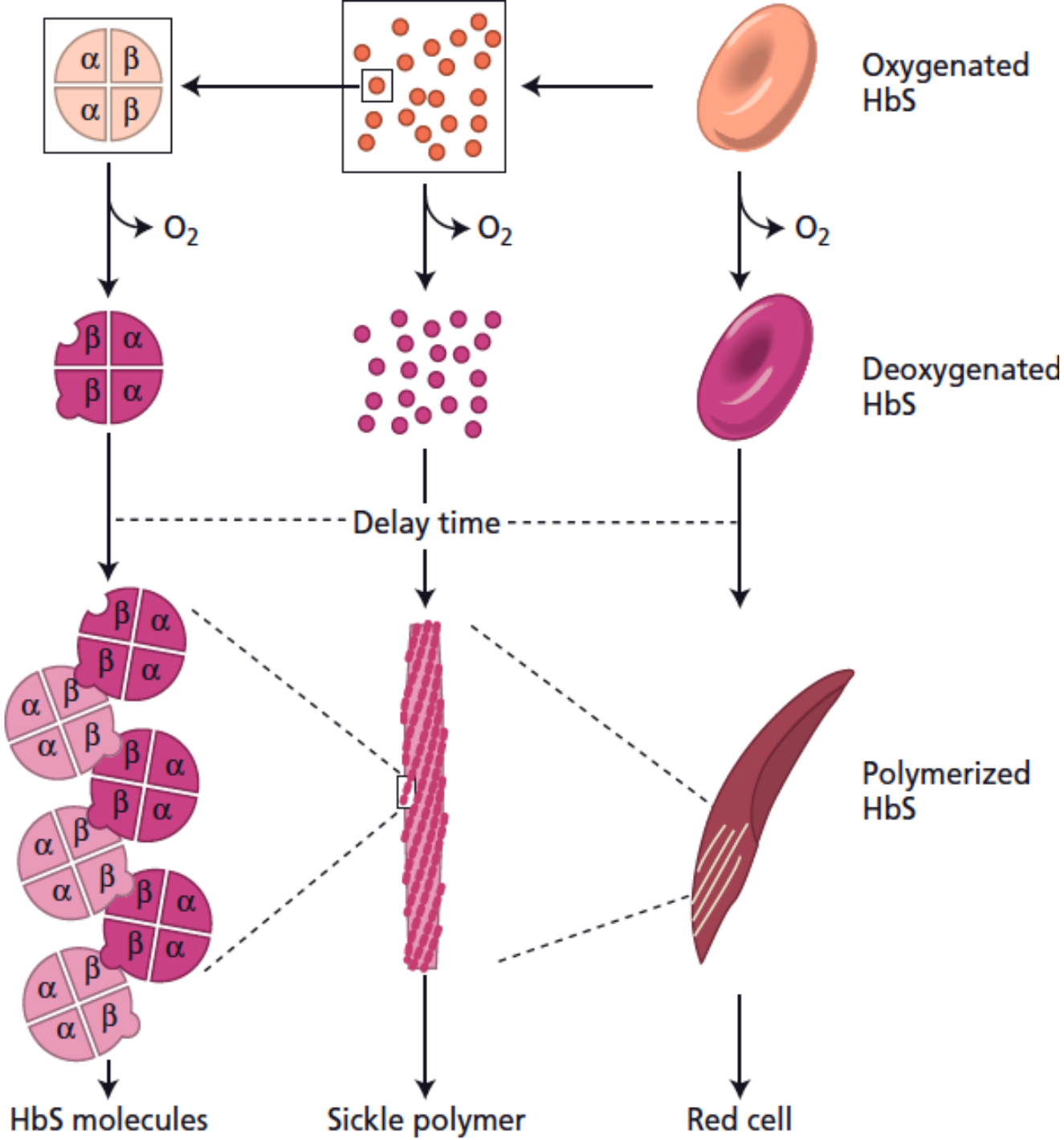
The sickling disorders are found in Africa, Mediterranean, India & the Middle East. This distribution is due to the immunity granted against Plasmodium falciparum. The disease is inherited in autosomal recessive pattern.

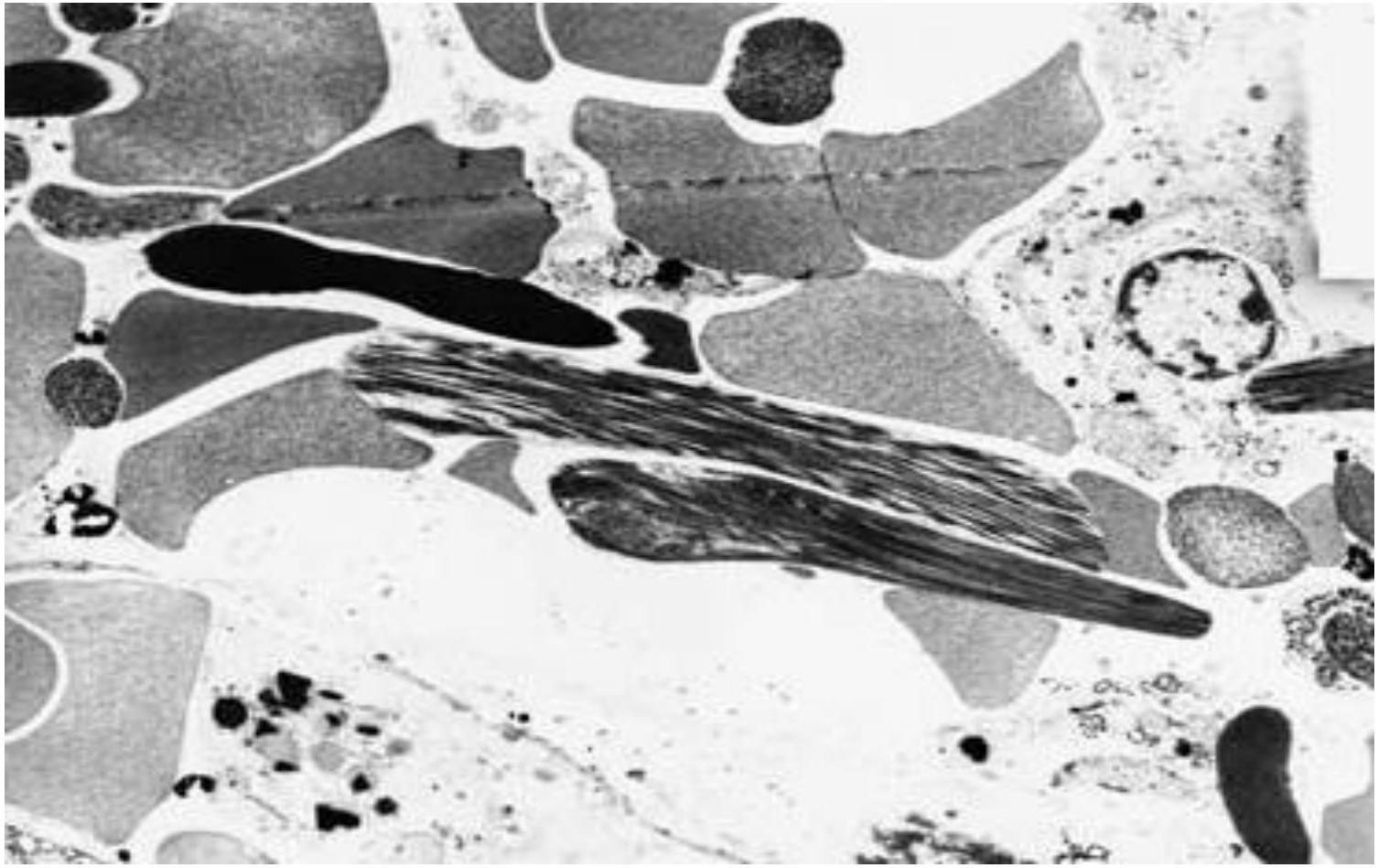

Typical
(No Blood Disorder)
Sickle Cell Trait
Sickle Cell Disease

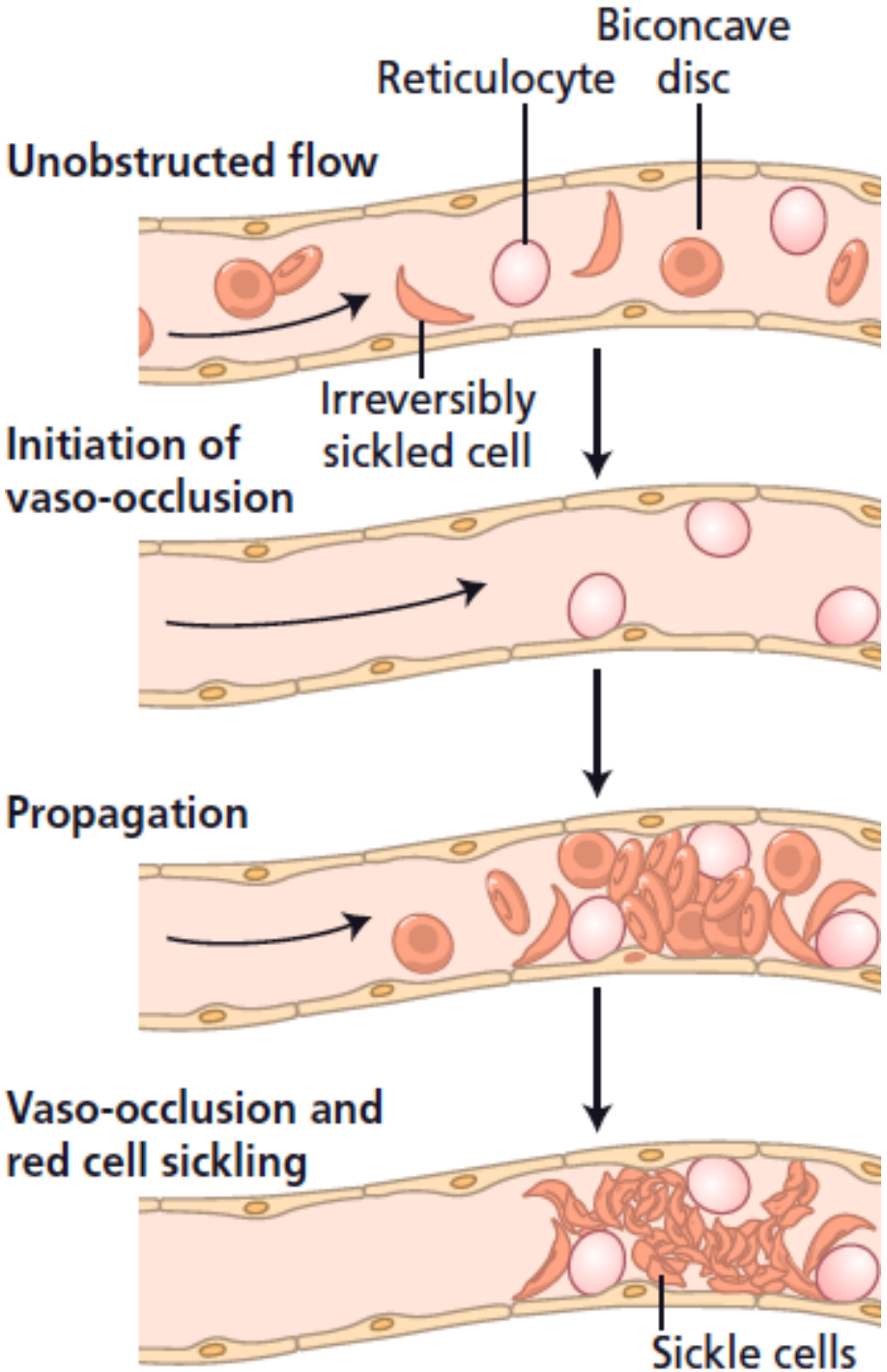
Pathophysiology:

Hb S results from substitution of glutamic acid by valine at position 6 of β chain. Hb S will form crystals upon deoxygenation & the red cells will assume sickle shape. This process is reversible in the beginning but repeated cycles of sickling & desickling will lead to formation of irreversibly sickled cells. Sickle cells have shortened survival leading to hemolytic anemia. Also because of their rigidity they block the small vessels leading to vaso -occlusive crises.


Wild-type haemoglobin DNA
3'
5'
C
T
C
Mutant haemoglobin DNA
3'
5'
C
A
C
mRNA
5'
3'
G
A
G
mRNA
5'
3'
G
U
G
Normal haemoglobin
Glu
Sickle cell haemoglobin
Val


α β
α β
Oxygenated HbS
O2
O2
O2
β α
β α
Deoxygenated HbS
Delay time
Polymerized HbS
HbS molecules
Sickle polymer
Red cell

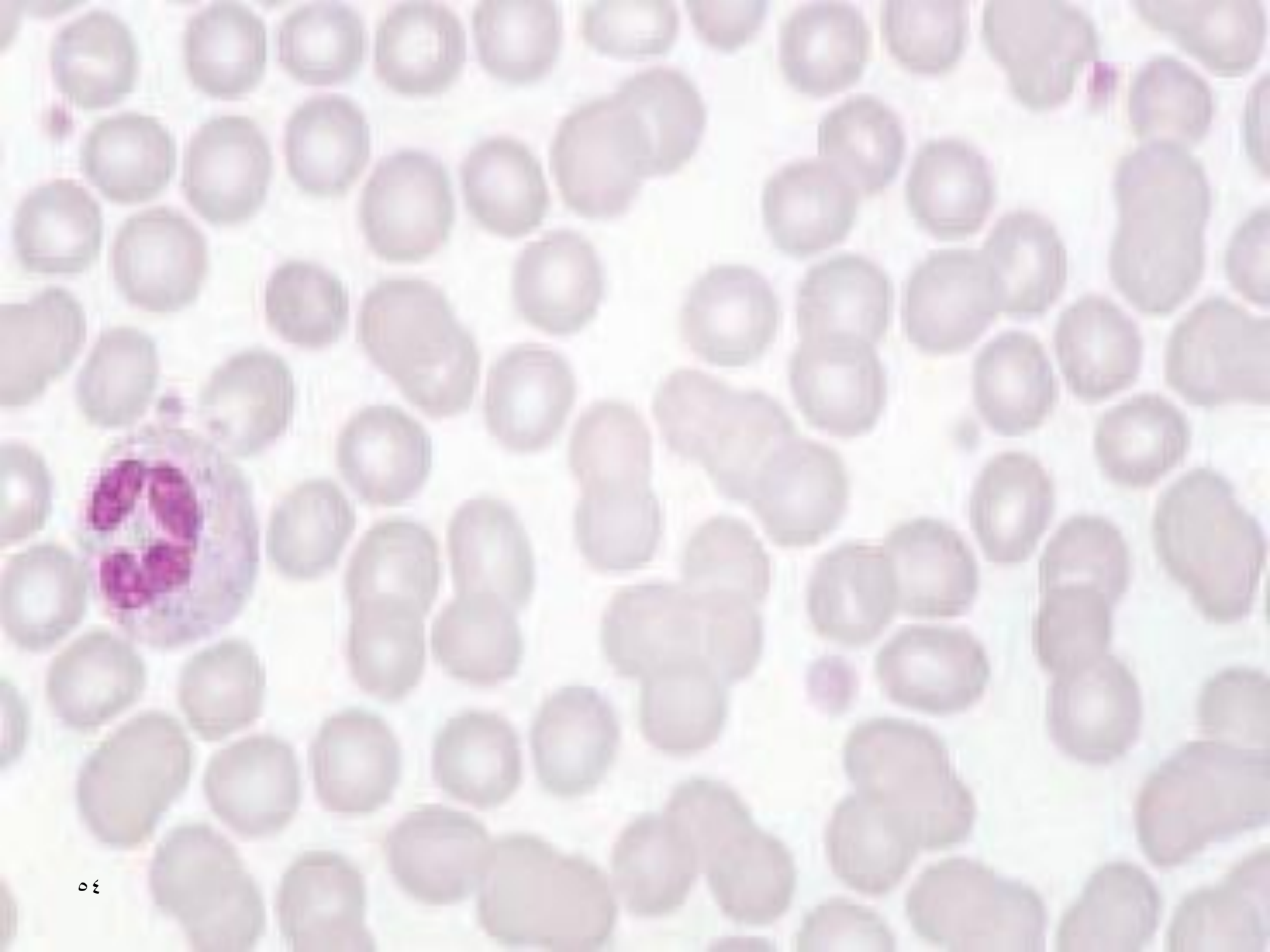


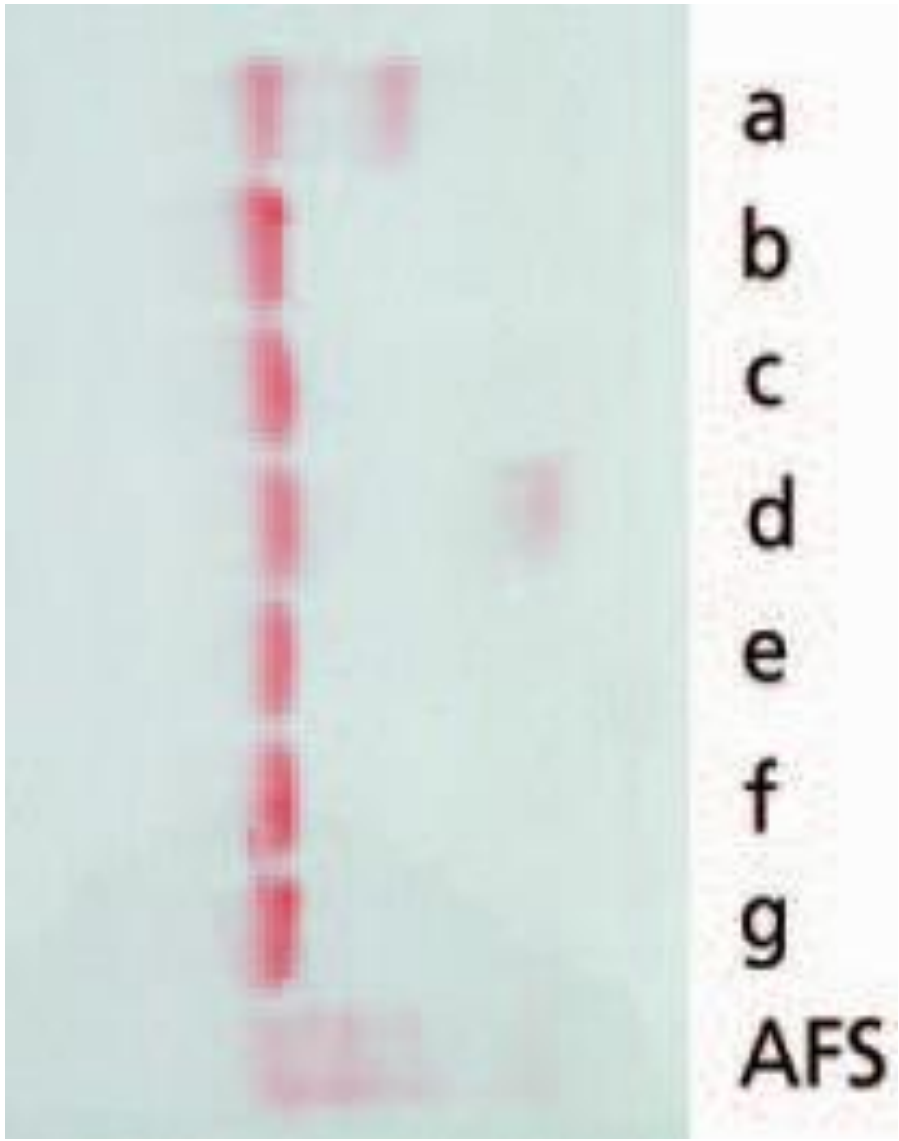

Biconcave
Reticulocyte
disc
Unobstructed flow
Irreversibly
sickled cell
Initiation of
vaso-occlusion
Propagation
Vaso-occlusion and
red cell sickling
Sickle cells

Sickle cell trait: genotype AS

The carriers are usually asymptomatic except under hypoxic conditions like anesthesia & unpressurized aircraft. The complete blood picture is normal.

Diagnosis is confirmed by a positive sickling test & Hb electrophoresis which will reveal both Hb A & Hb S.

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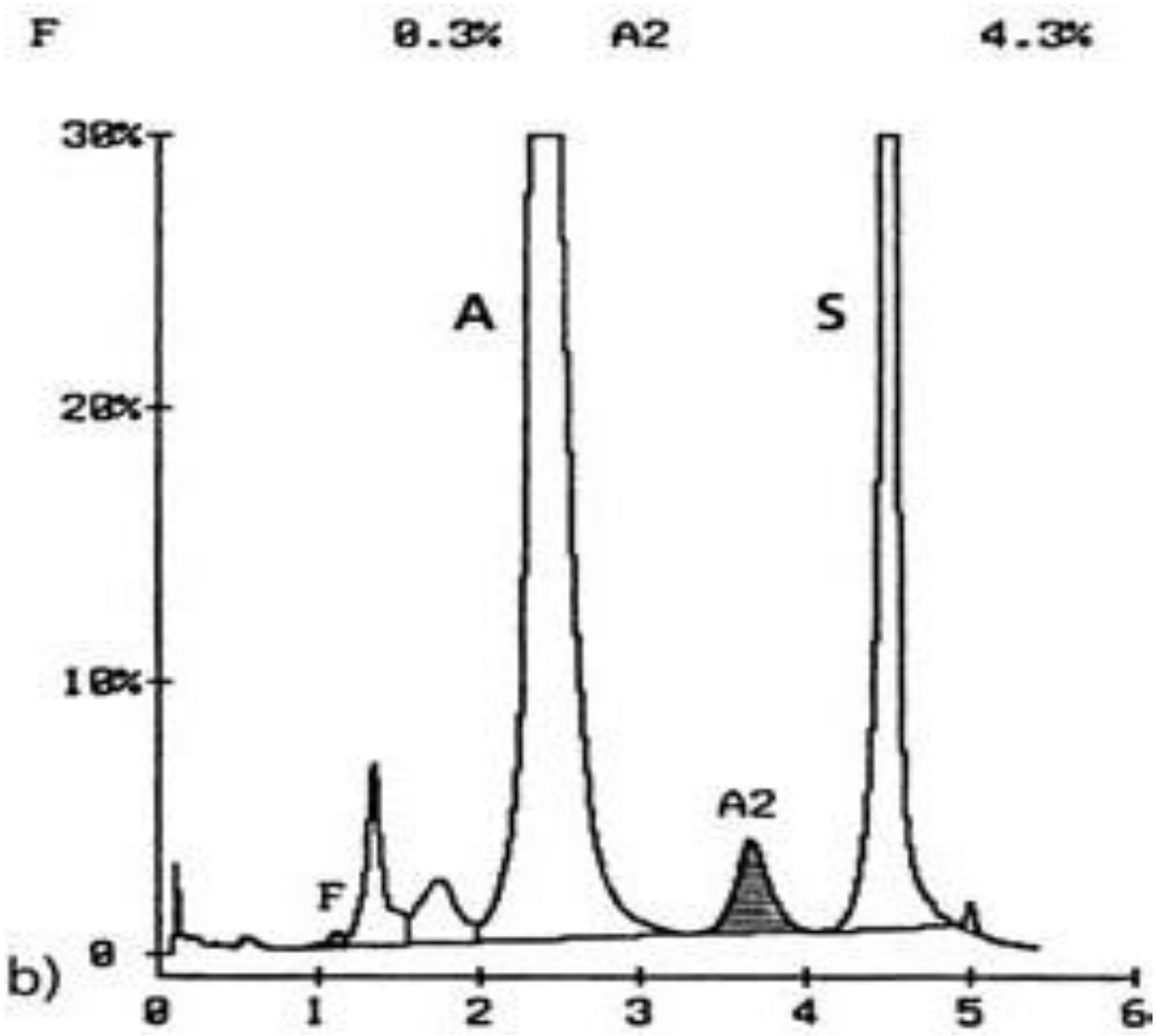
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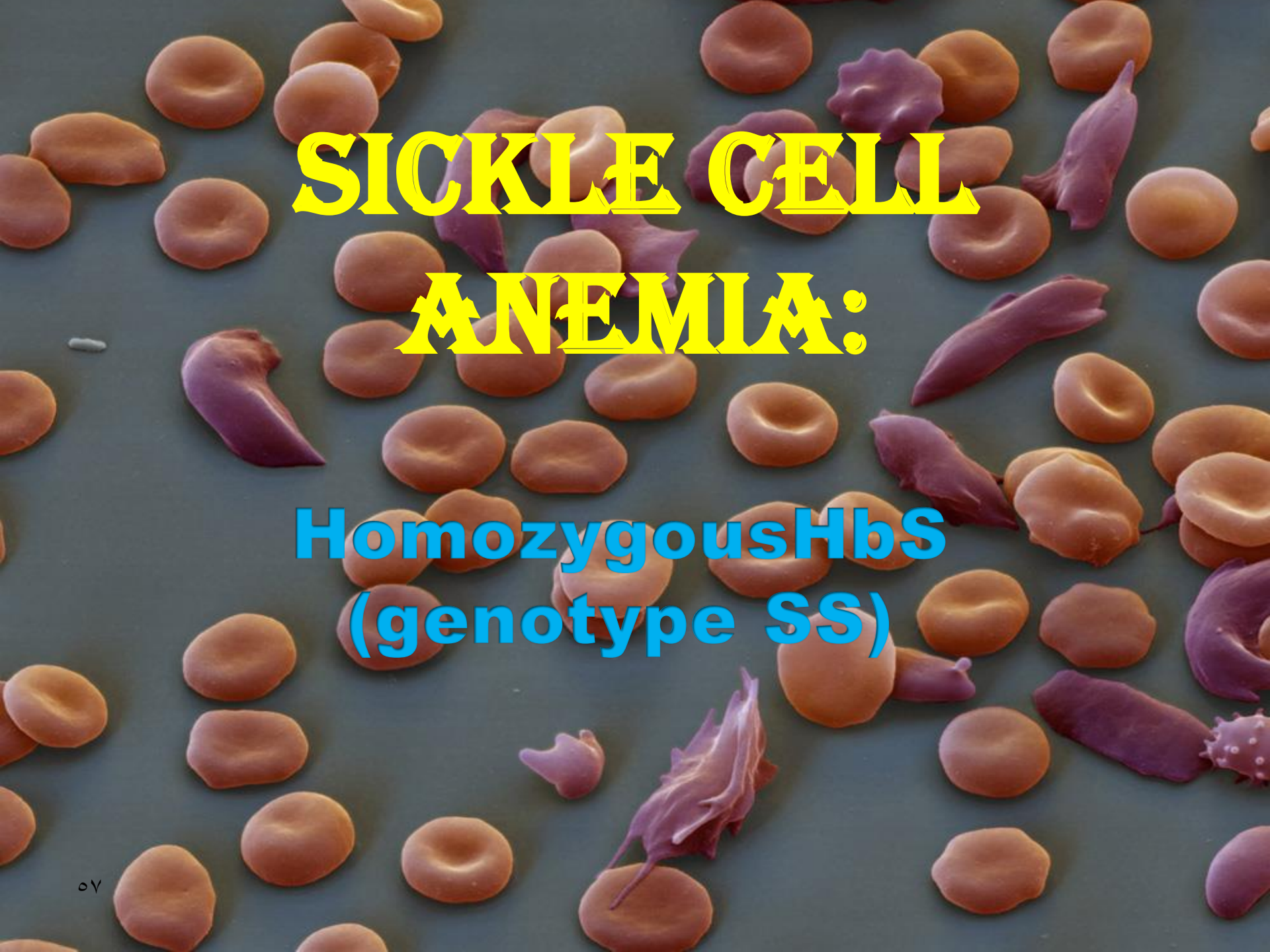

SICKLE CELL ANEMIA:
HomozygousHbS (genotype SS)

Clinical features:

Symptoms start towards the end of first year of life as the protective effect of Hb F is lost (Hb A becomes the main Hb after 6 months of age). The patients suffer from chronic hemolytic anemia with complications called crises. Growth & development are usually normal. The disease can manifest as:

*Vaso-occlusive crises: result from blockage of the microcirculation by sickled cells. The may present as one of the following:

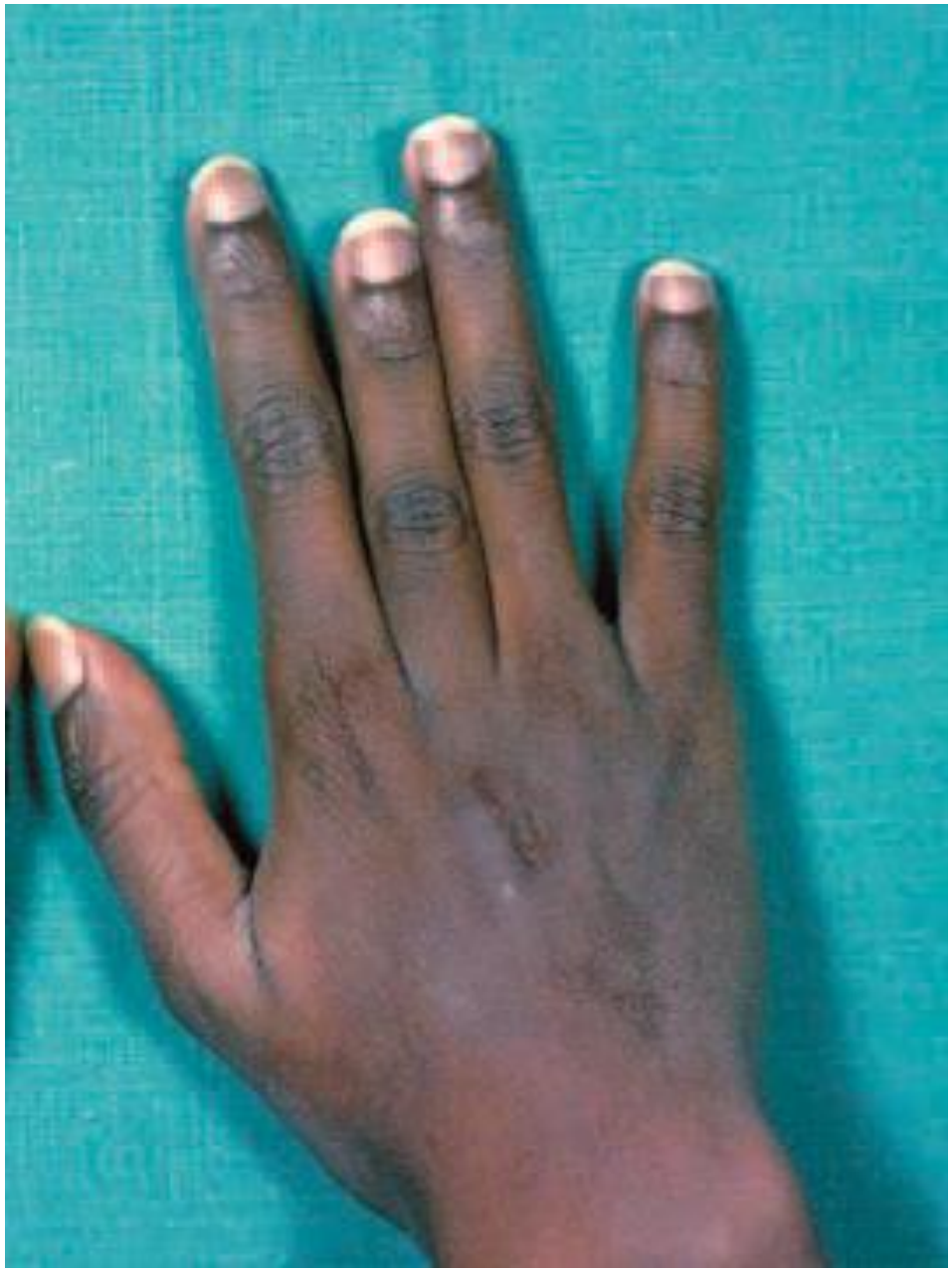
.Hand & foot syndrome: painful dactylitis, may lead to shortened digits.

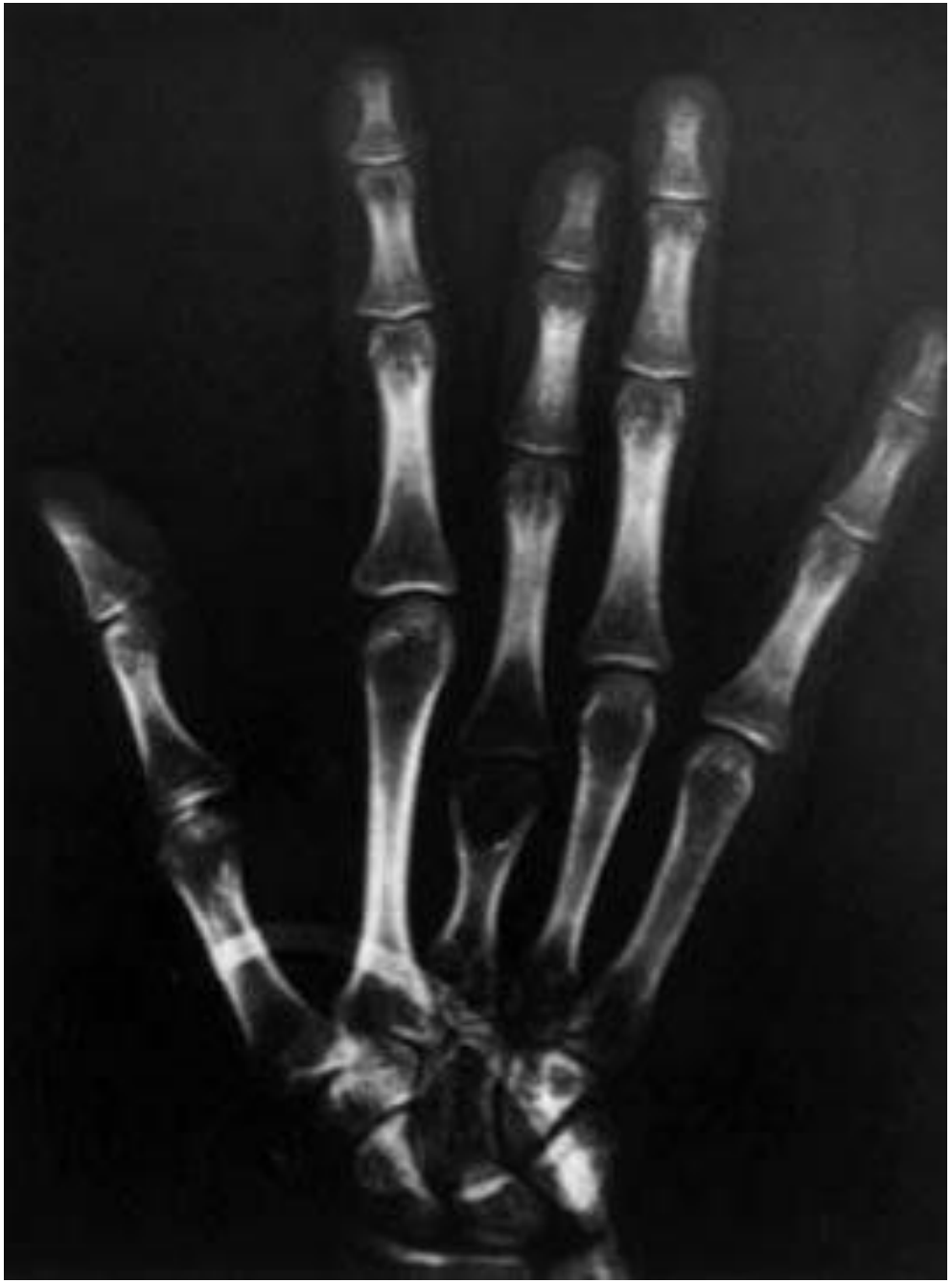
.Brain syndrome: present as stroke.

.Chest syndrome: present like chest infection.

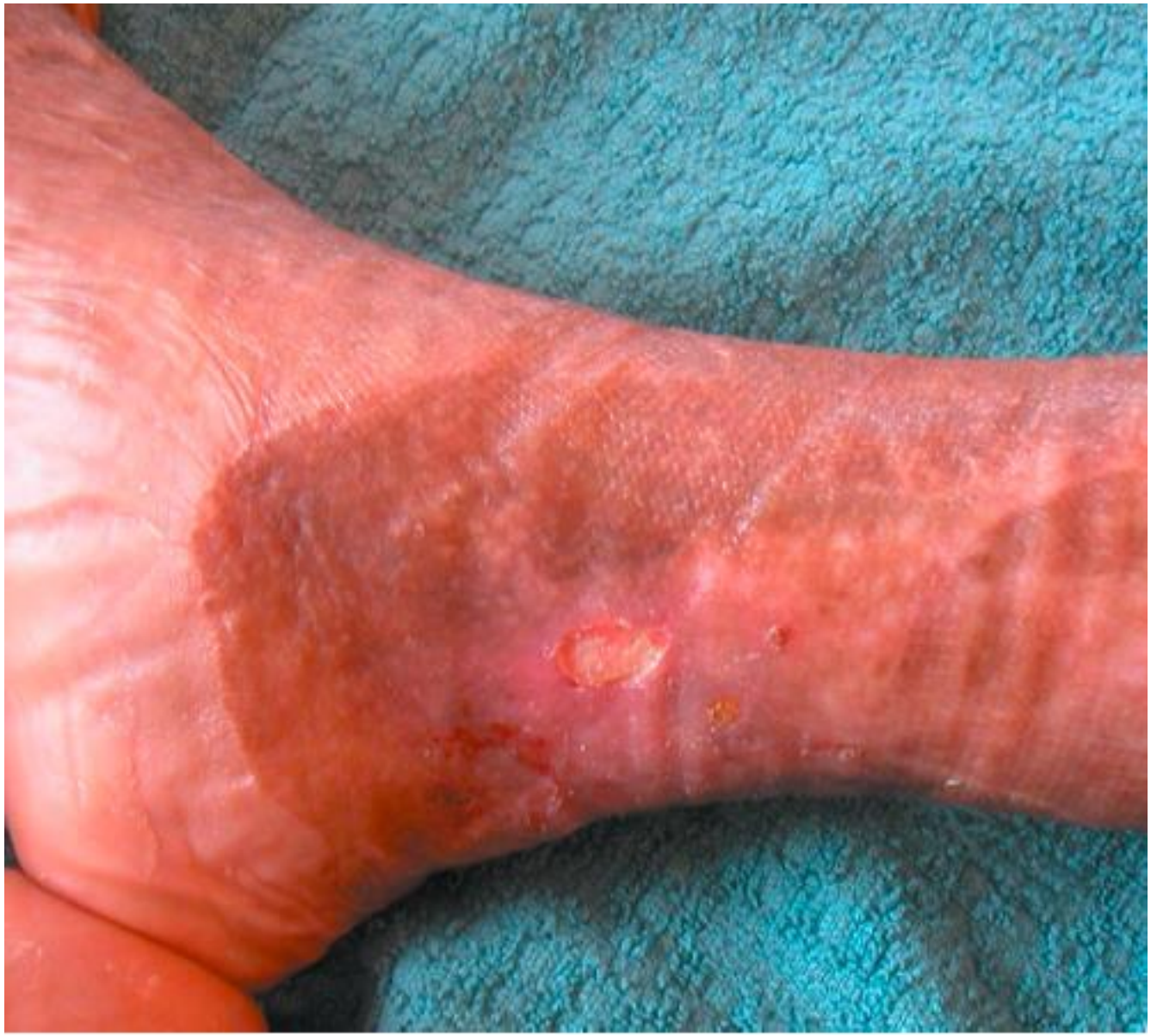
.Priapism: can lead to permenant disfigurement & loss of function if not treated soon enough.

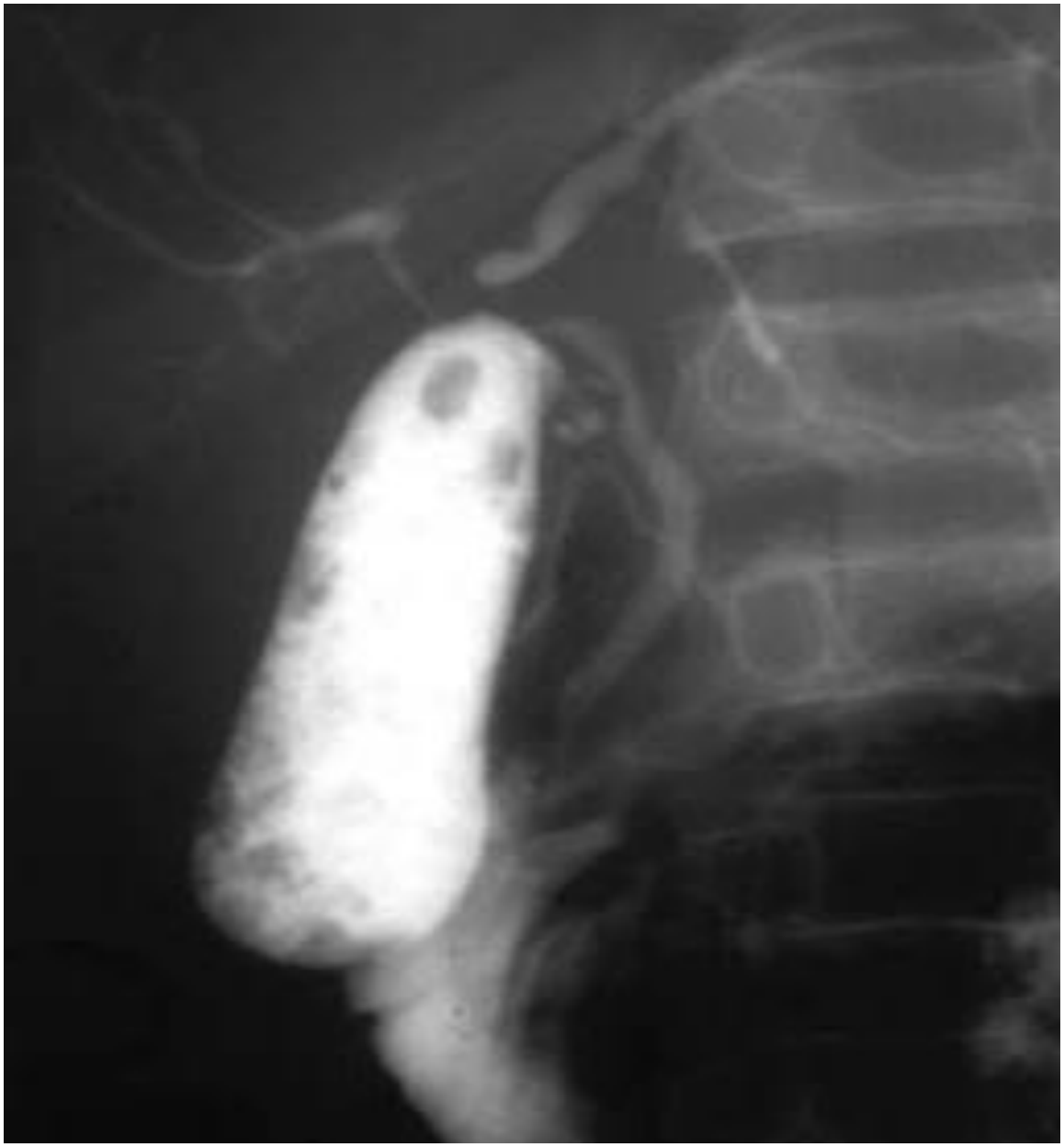
.Autosplenectomy due to repeated infarction of the splenic artery.





* **Aplastic crises:** erythropoiesis stops temporarily due to parvovirus infection. May need blood transfusion. Usually recover spontaneously.
* **Sequestration crises:** there is a rapid enlargement of the liver or spleen due to entrapment of the sickled cells.
* **Infections:** the commonest cause of mortality,
* **Pigment gallstone.**
* **Leg ulcers** over the medial malleolus.

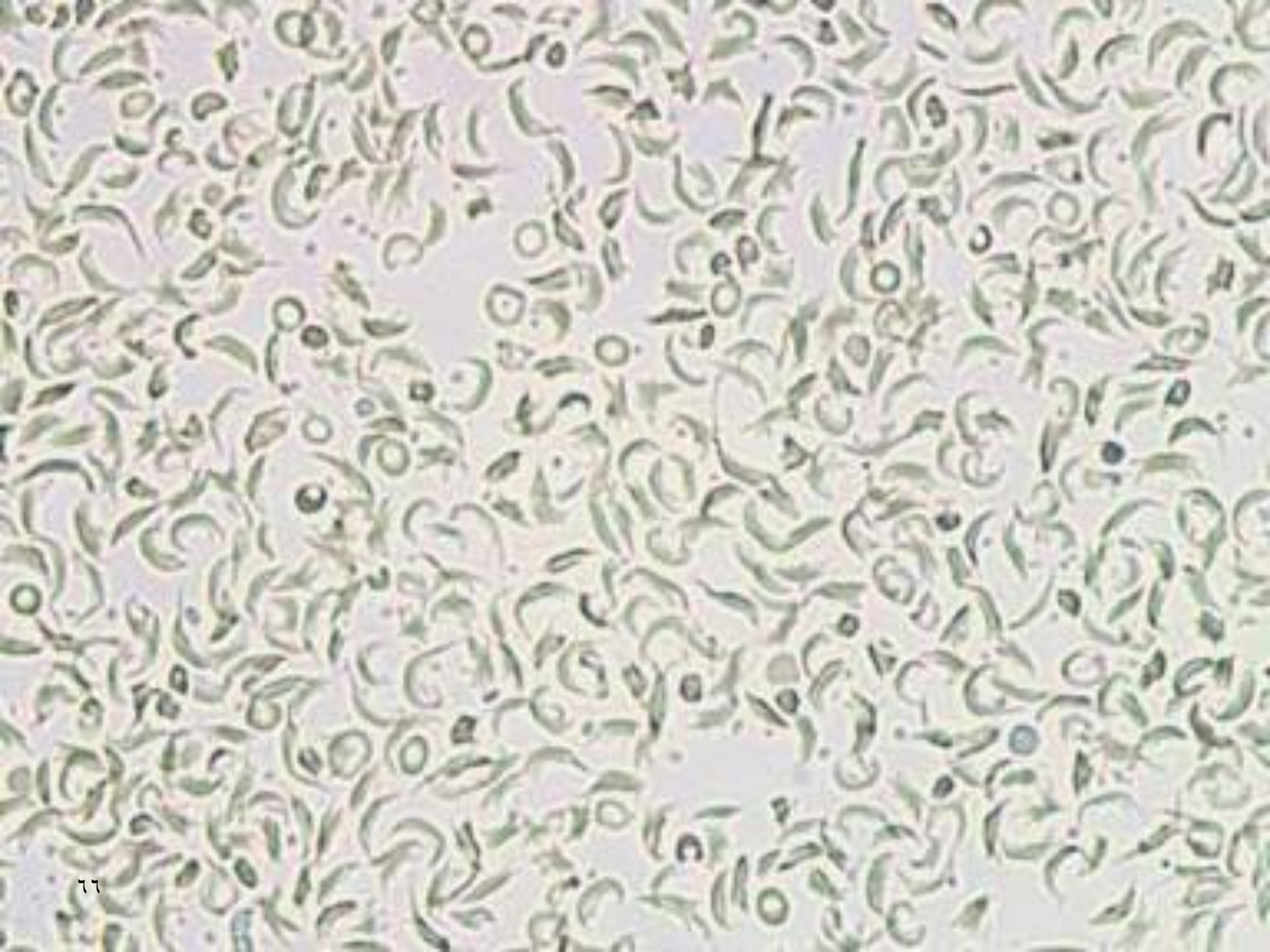


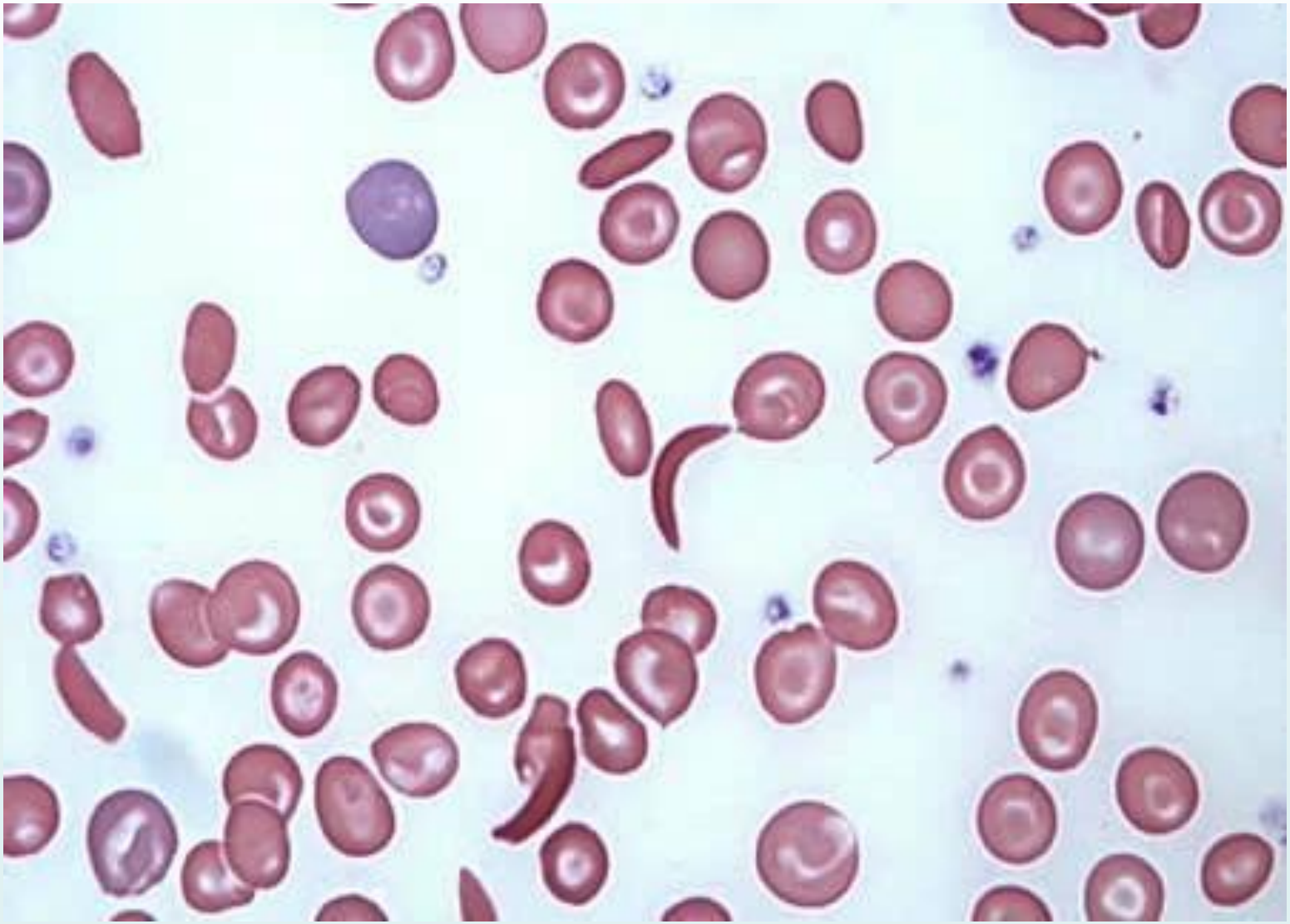


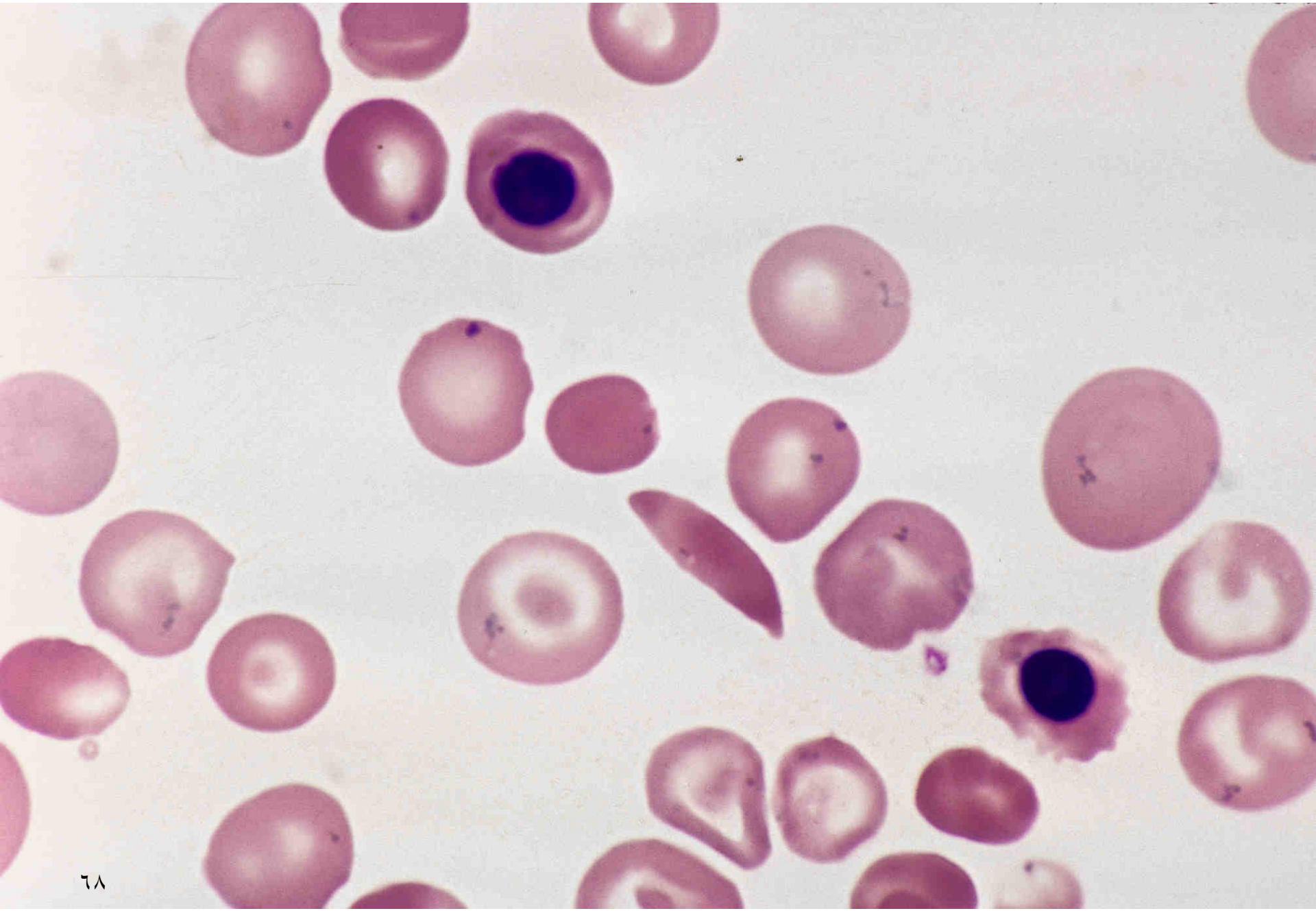
Laboratory findings:

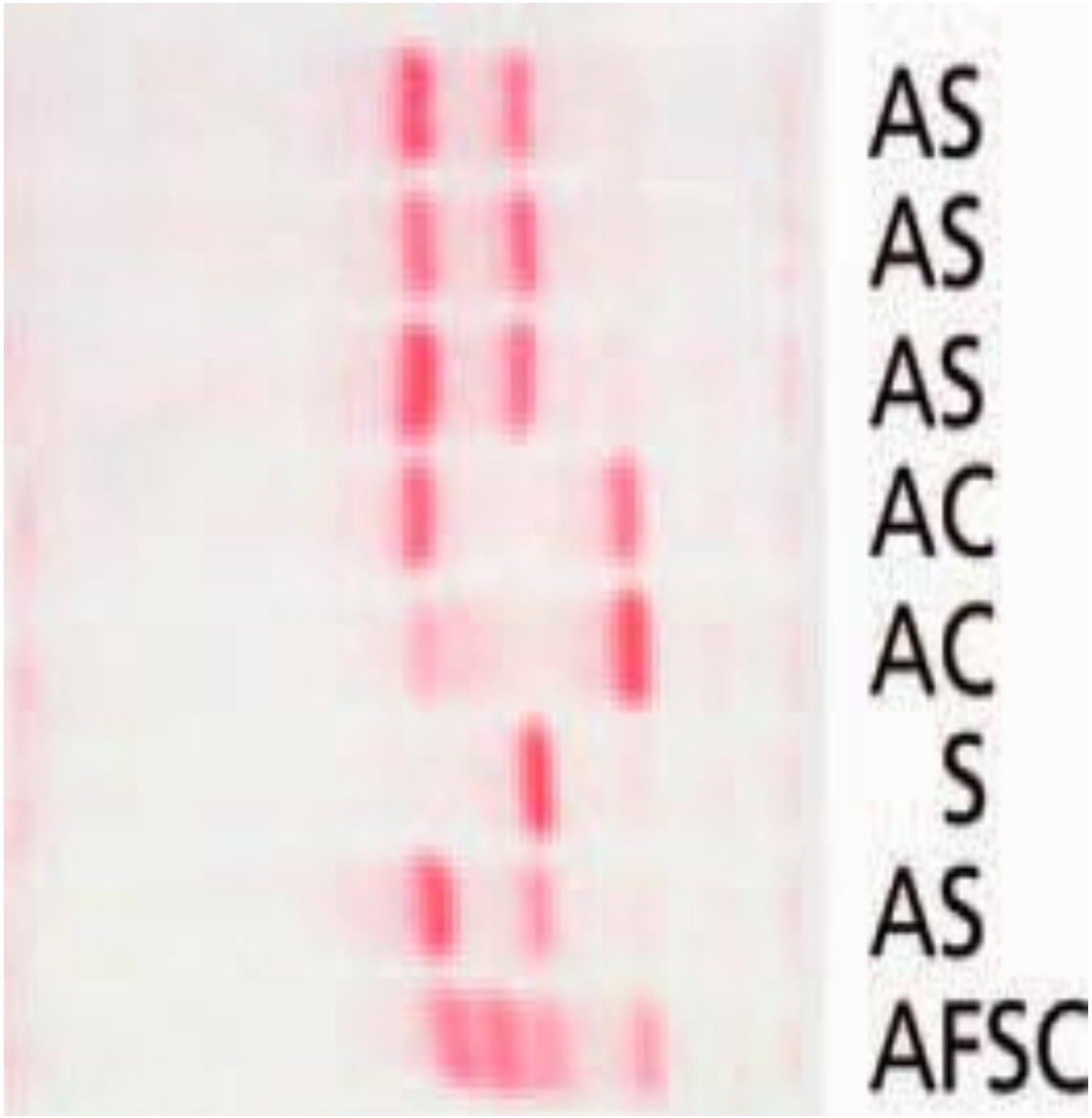
1. Anemia: HB is around 6-8 g/dL.
2. Reticulocytosis up to 20 %.
3. Blood film shows sickle cells.
4. Sickling test is positive
5. Hb electrophoresis: the major Hb is Hb S with a variable amount of Hb F.

There is no Hb A. H F interferes with the sickling process, so the higher it is, the less severe the disease will be.





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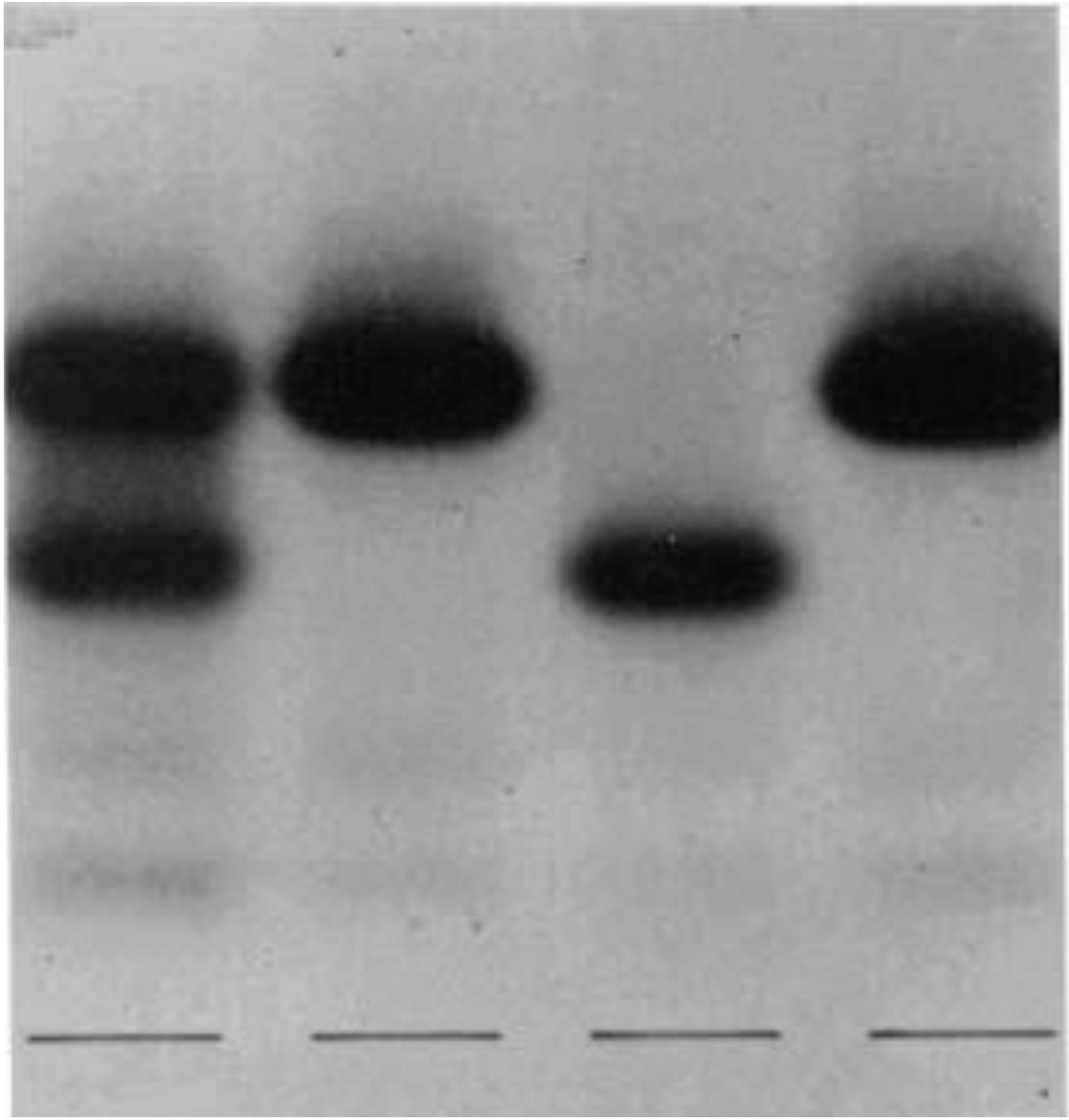
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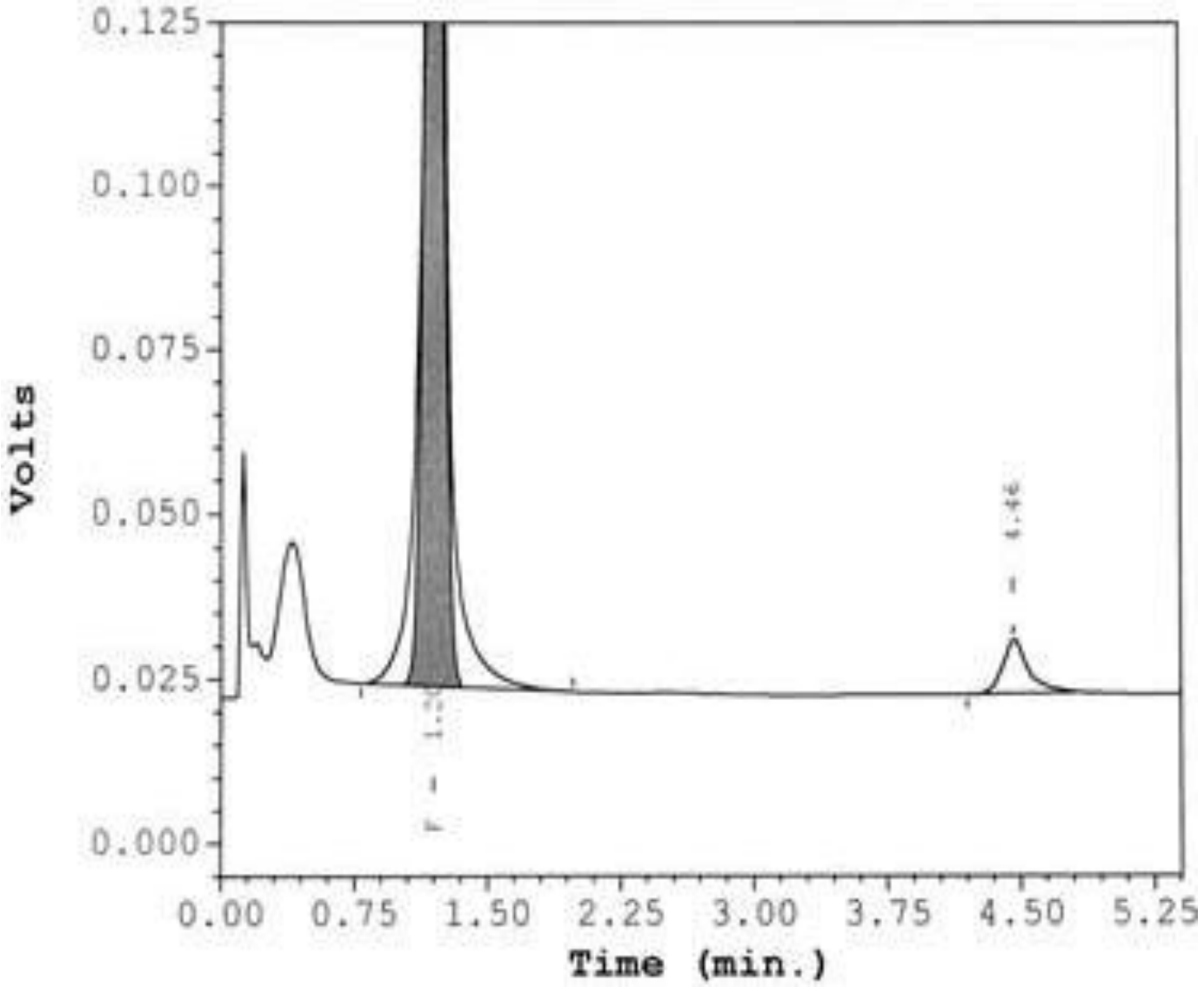
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thank you