HEMOGLOBINOPATHIES

BIOCHEMISTRY

- A large number of mutations have been described in the globin genes. These mutations can be divided into two distinct types:

- Those that cause **qualitative** abnormalities (e.g. sickle cell anemia) and those that cause **quantitative** abnormalities (the thalassemias). Taken together these disorders are referred to as the **hemoglobinopathies**.

Sickle Cell disease

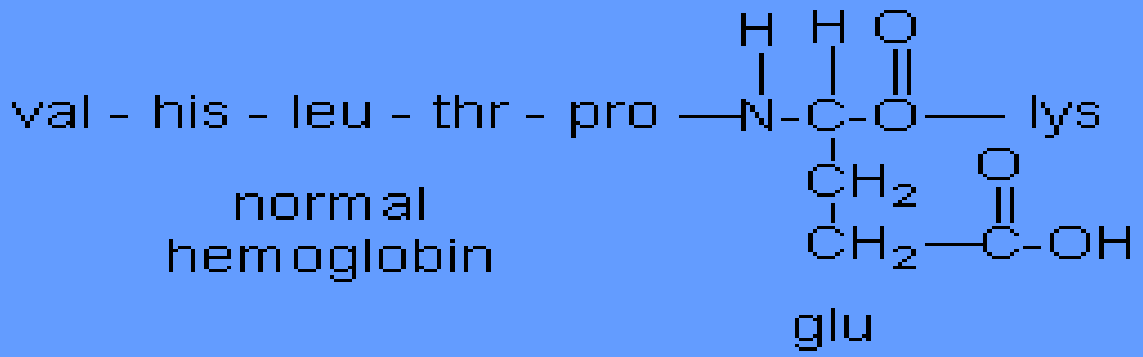
- The mutation causing sickle cell anemia is a single nucleotide substitution (A to T) in the codon for amino acid 6. The change converts a glutamic acid codon (GAG) to a valine codon (GTG). The form of hemoglobin in persons with sickle cell anemia is referred to as HbS.

- Sickle cell anemia is an autosomal recessive disorder. This means that in order for full disease symptoms to manifest in an individual they must carry two copies (homozygous genotype = SS) of the HbS gene.

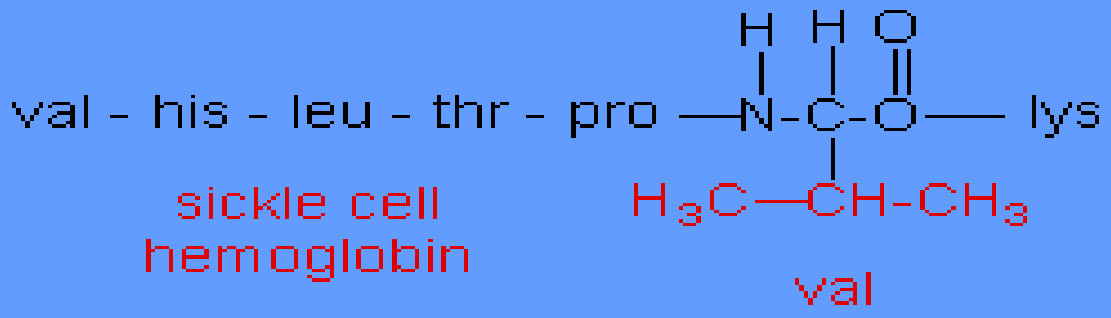
- However, individuals who are heterozygous (genotype = AS) have what is referred to as sickle cell trait.

- The underlying problem in sickle cell anemia is that the **valine** for **glutamic acid** substitution results in hemoglobin tetramers that aggregate into arrays upon deoxygenation in the tissues.
- This aggregation leads to deformation of the red blood cell into a sickle-like shape making it relatively inflexible and unable to traverse the capillary beds.

Sickle Cell Anemia

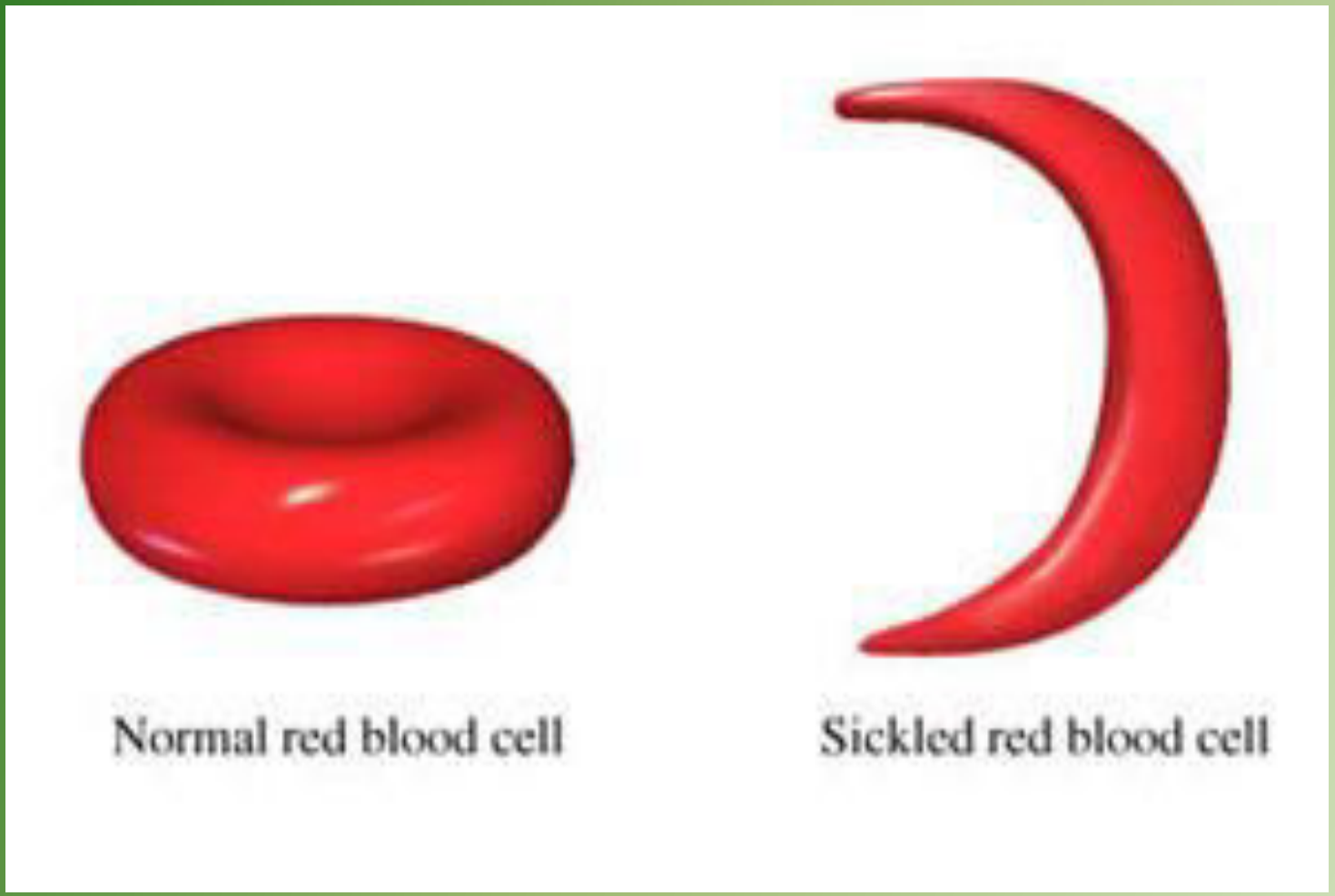


normal hemoglobin



sickle cell hemoglobin

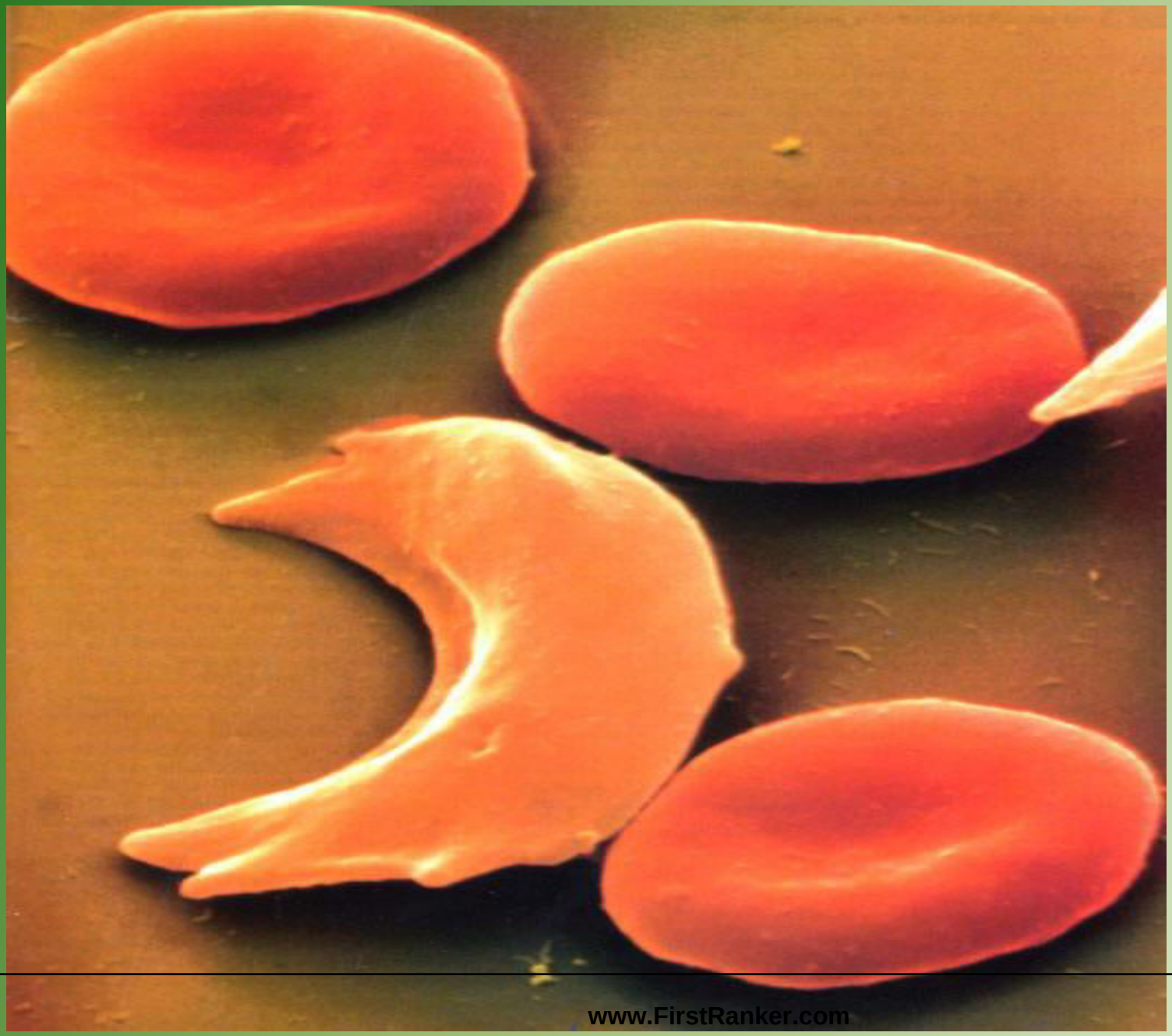
C. Ophardt, c. 2003

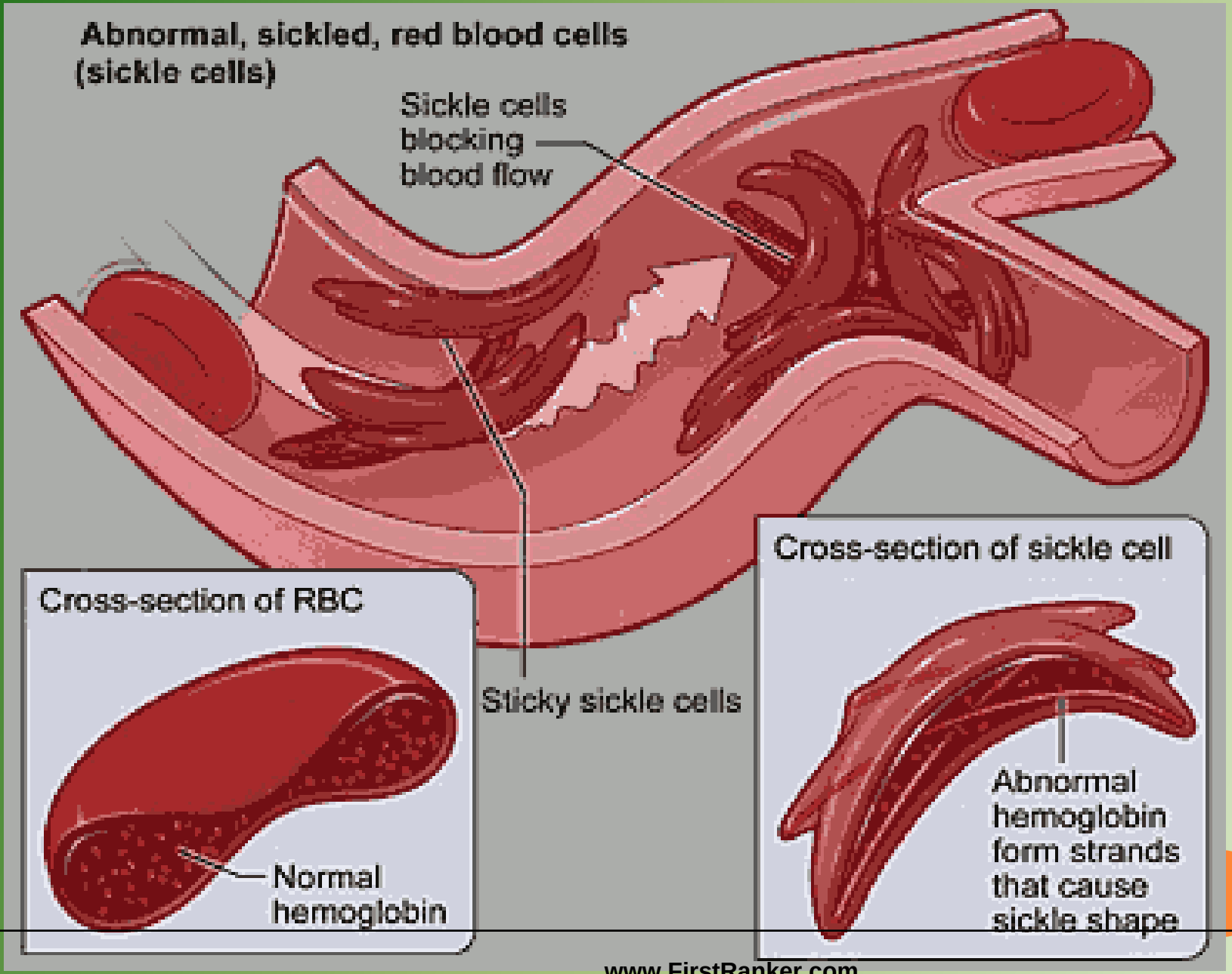


- Hb S contains two normal alpha globin chains and two mutant beta globin chains (B^s).
- Altered mobility on electrophoresis due to less negative charges.

- Valine residue forms a protrusion on the beta chain that fits into the complementary site on the alpha chain of another hemoglobin molecule.

- At low oxygen tension deoxyHb S polymerizes inside the cell, that distort the cell.





- Sickling caused by:

1. High altitude
2. Increased pCO2
3. Decreased pH
4. Dehydration
5. Increased concentration of 23BPG.

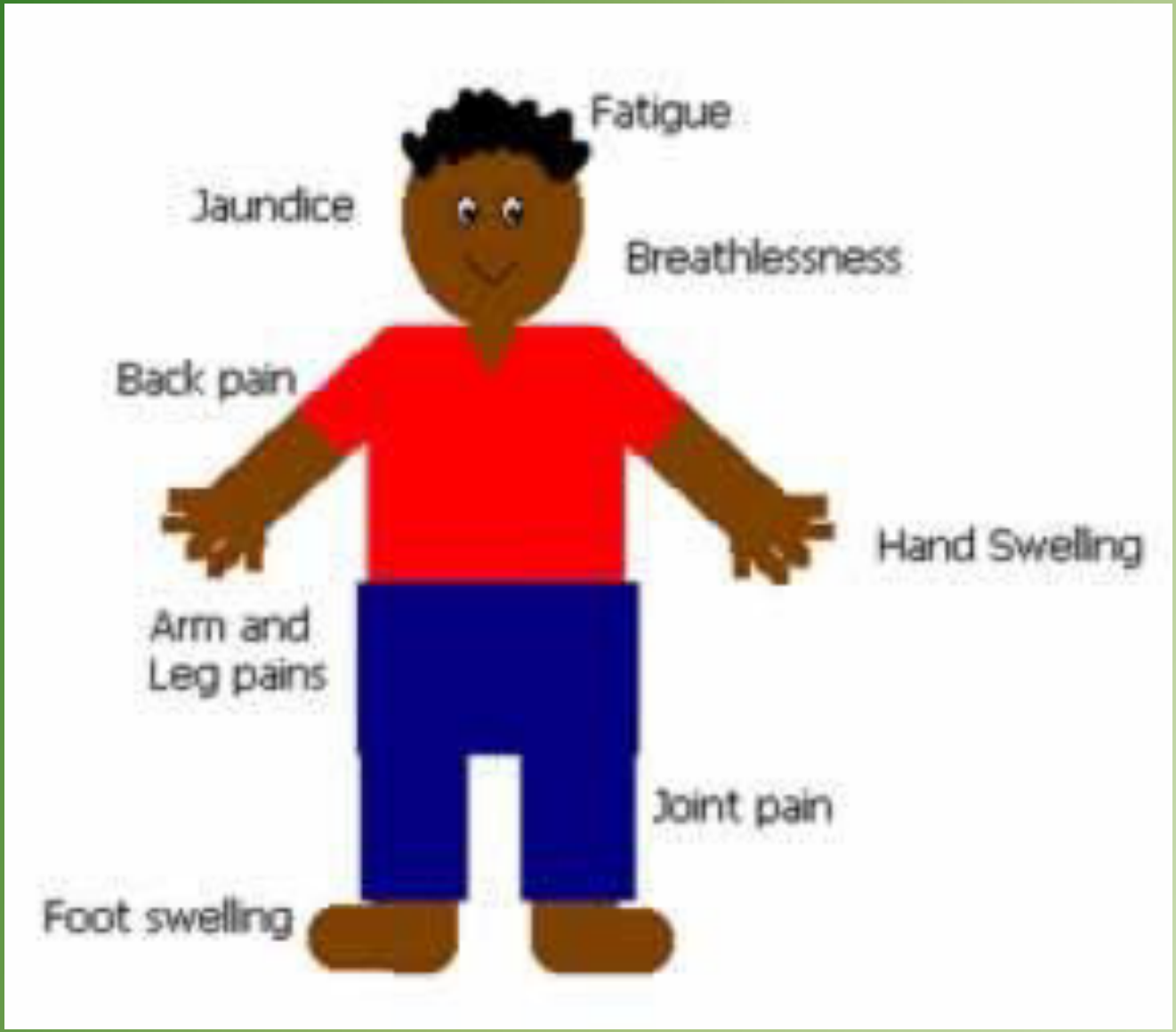
Pathophysiology of Sickle Cell Anemia

- Sickle cell anemia is characterized by persistent episodes of hemolytic anemia and the occurrence of acute episodes referred to as sickling crises.
- The sickling red cells result in clogging of the fine capillary beds.

- In addition, due to these recurrent vasculo-occlusive episodes there are a series of complications:

1. Because bones are particularly affected by the reduced blood flow, frequent and severe bone pain results. This is the typical symptom during a sickle cell crisis.

2. Long term, the recurrent clogging of the capillary beds leads to damage to the internal organs, in particular the kidneys, heart and lungs.
3. The continual destruction of the sickled red blood cells leads to chronic anemia and episodes of hyperbilirubinemia.



Individual homozygous for sickle-cell allele

Sickle-cell (abnormal) hemoglobin

Abnormal hemoglobin crystallizes, causing red blood cells to become sickle shaped

Sickle cells

Breakdown of red blood cells

Clumping of cells and clogging of small blood vessels

Accumulation of sickled cells in spleen

Physical weakness

Anemia

Heart failure

Pain and fever

Brain damage

Damage to other organs

Spleen damage

Impaired mental function

Paralysis

Pneumonia and other infections

Rheumatism

Kidney failure

Treatment of sickle cell disease

- Hydration
- Analgesics
- Antibiotics
- Transfusions(risks- hemosiderosis)
- Hydroxyurea

ADVANTAGE

- Selective advantage for heterozygotes.
- Less susceptible to malaria-(plasmodium falciparum).

THALASSEMIAS

- The **thalassemias** are the result of abnormalities in hemoglobin synthesis and affect both clusters.

- Deficiencies in ß-globin synthesis result in the ß-thalassemias and deficiencies in α-globin synthesis result in the α-thalassemias.

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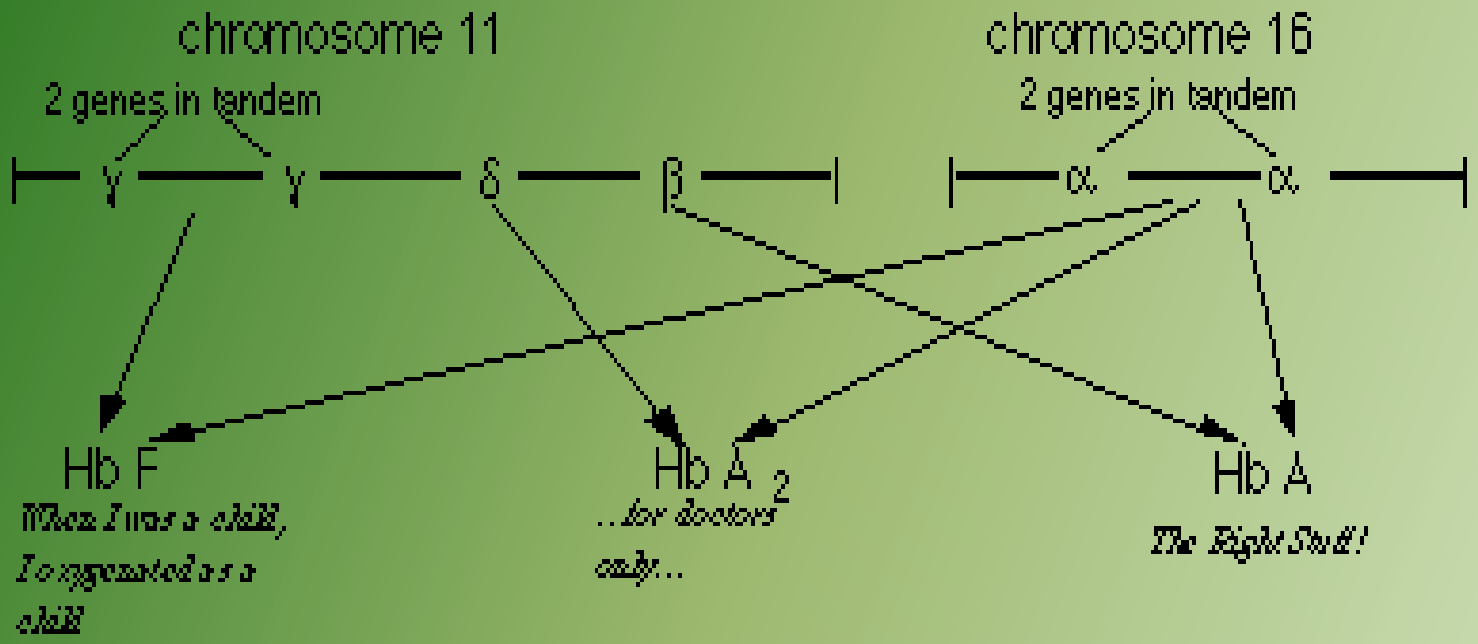

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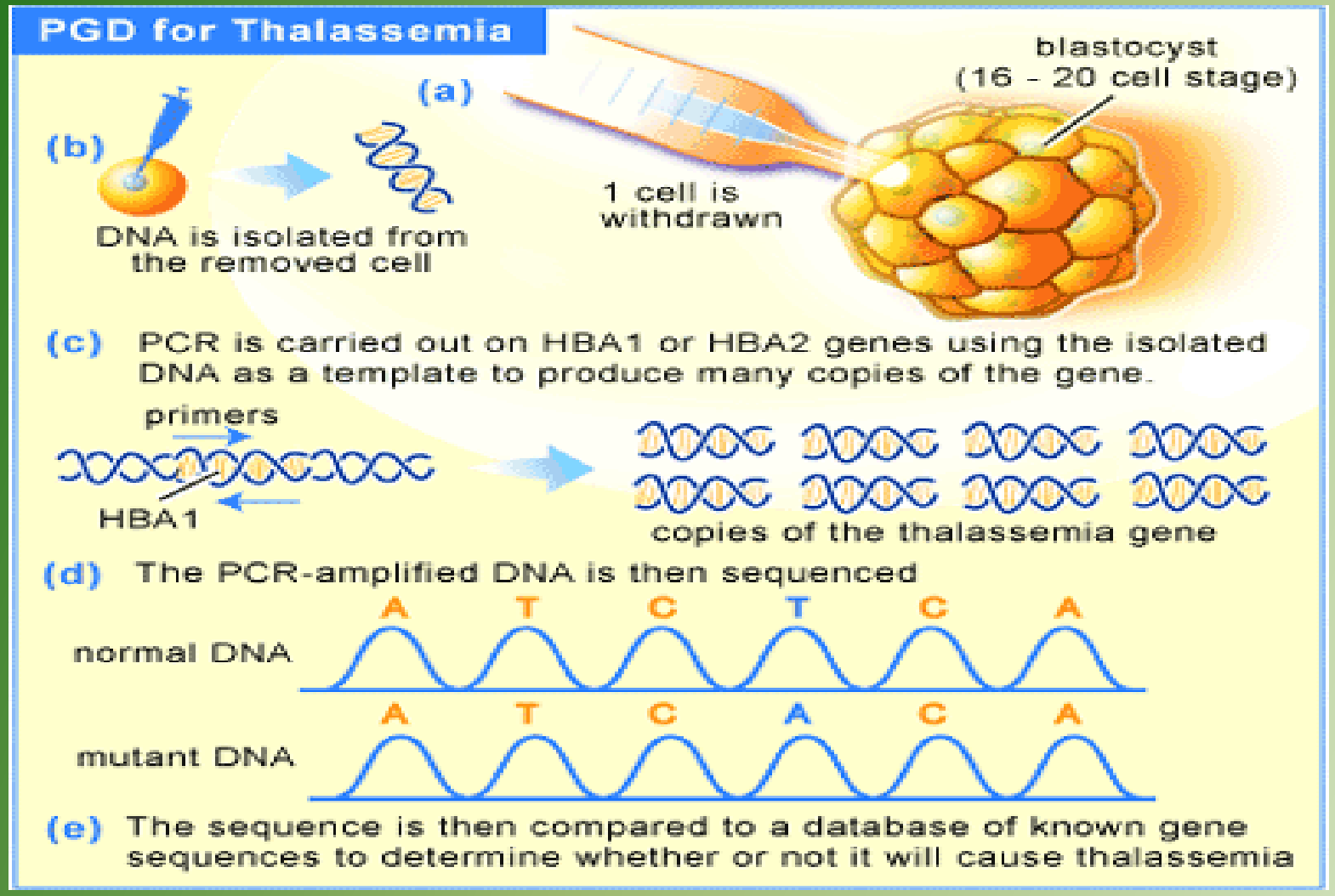


β-THALASSEMIAS

- A large number of mutations have been identified leading to decreased or absent production of β-globin chains resulting in the β-thalassemias.
- Alpha chains production is normal
- But cannot form stable tetramers
- And precipitate and prematurely cells die without forming RBCs.

- If both the beta globin genes are defective then it is called**Thalassemia major.**

- Thalassemia major patients require frequent blood transfusions for survival.

- **Thalassemia minor** patients are heterozygous for ß-thalassemia. Afflicted individuals harbor one normal ß-globin gene and one that harbors a mutation leading to production of reduced or no ß-globin.
- Individuals that do not make any functional ß-globin protein from 1 gene are termed $ß^0$ heterozygotes. If ß-globin production is reduced at one locus the individuals are termed $ß^+$ heterozygotes. Thalassemia minor individuals are generally asymptomatic.

- Mutations include :

1.Gene deletions

2.Point mutations in the promoter

3. Mutations in the coding region leading to defective initiation, insertions and deletions resulting in Frameshifts and Nonsense mutations

4. Splicing abnormalities.

Clinical and Hematological Findings

- At birth most thalassemia major infants are asymptomatic. However, because fetal hemoglobin (HbF) production declines following birth symptoms of severe anemia will begin to present.

- If left untreated these children will show a marked retardation in growth rate. As a consequence of the anemia the bone marrow dramatically increases its' effort at blood production.

- The cortex of the bone becomes thinned leading to pathologic fracturing and distortion of the bones in the face and skull.

- Progressive hepatosplenomegaly is a constant clinical finding as the liver and spleen act as additional sites of blood production.

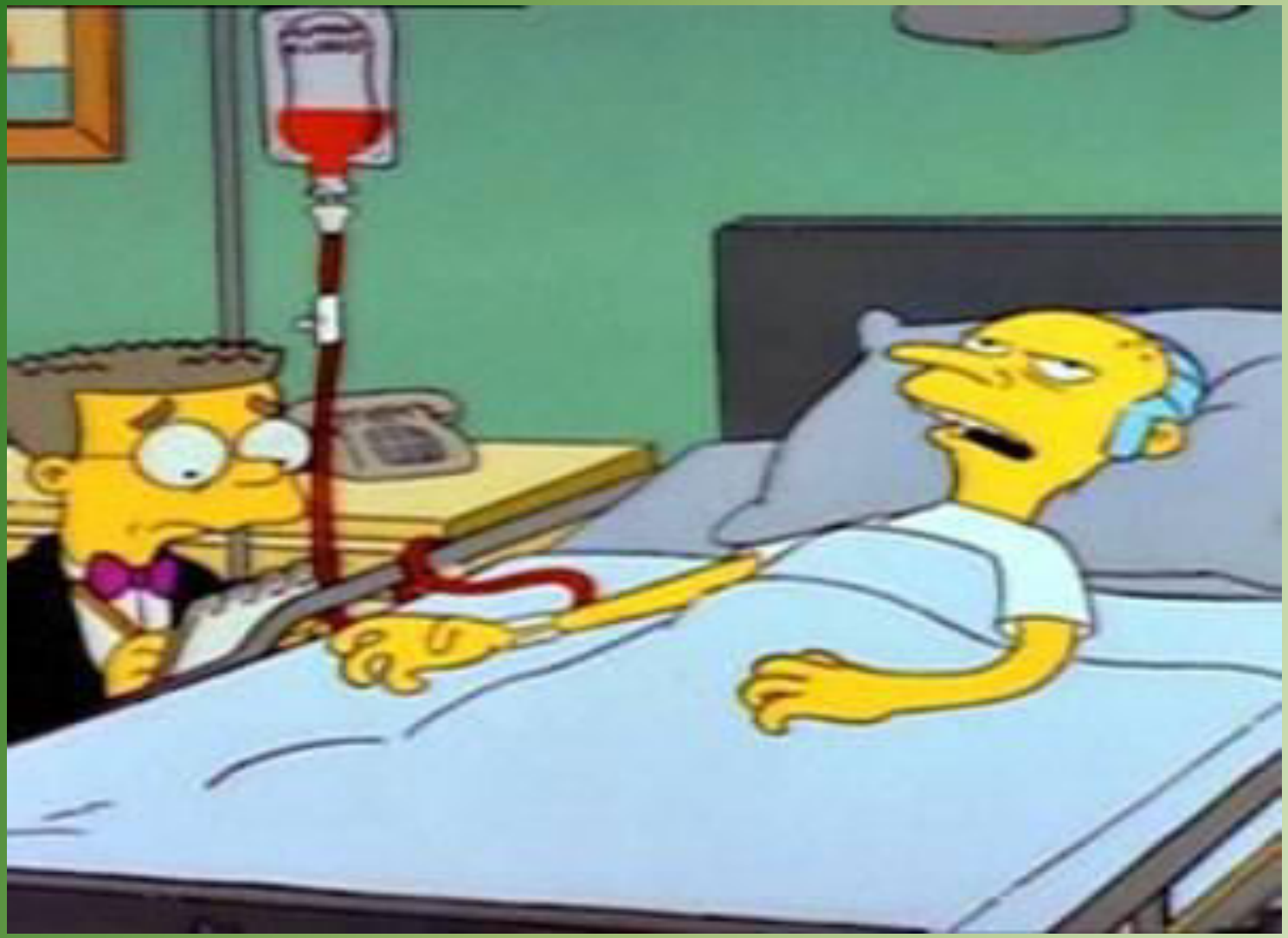
- The hepatosplenomegaly leads to leukopenia (decreased white blood cell count) and thrombocytopenia (low platelet count).

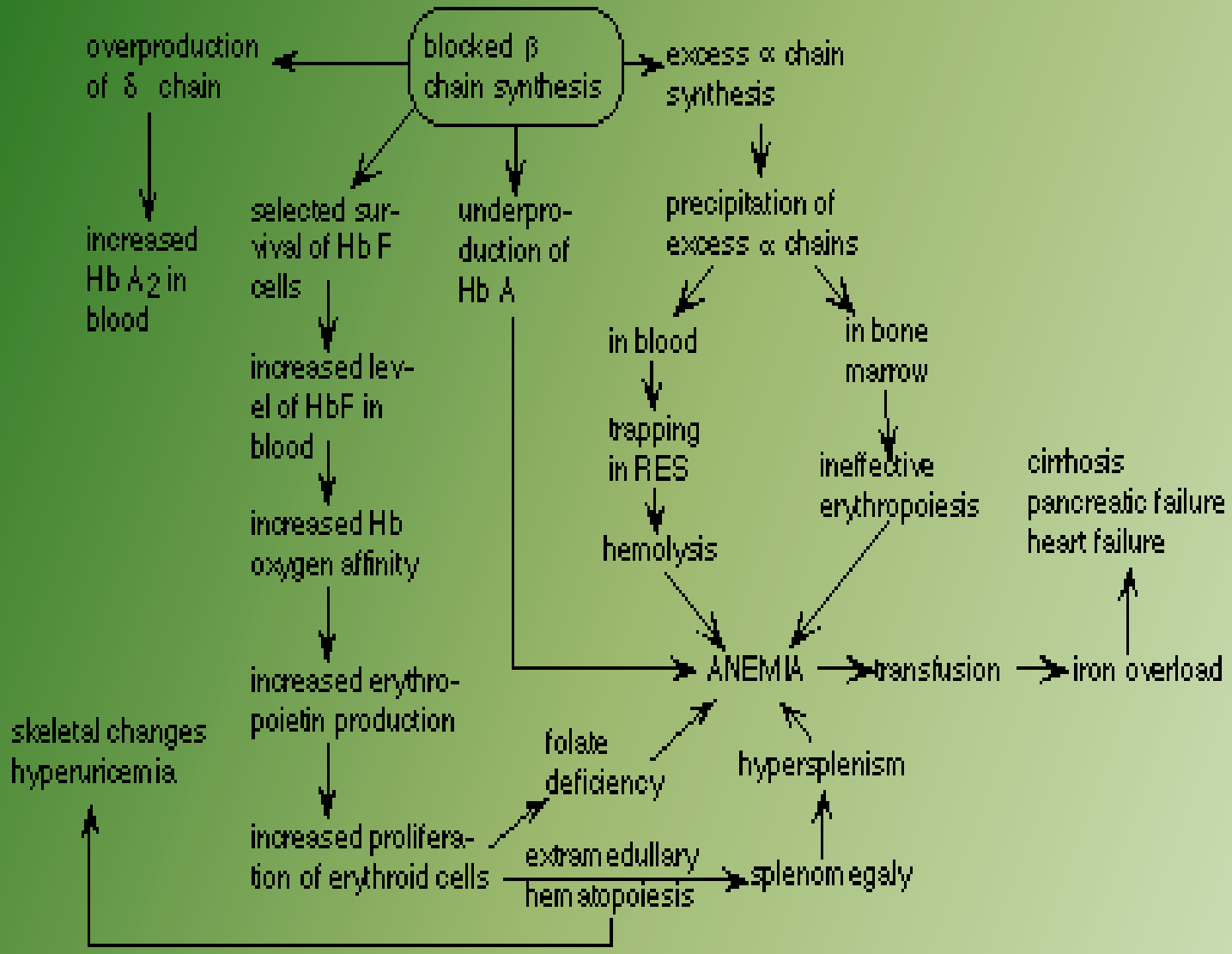
- Recurrent infections are a frequent complication in thalassemia major and are the leading cause of morbidity and mortality in this disease.

- Frequent blood transfusions are required to maintain a hemoglobin level of 9 to 11g/dl.

- In the long term these transfusions lead to the accumulation of iron in the organs, particularly the heart, liver and pancreas. Organ failure ensues with death in the teens to early twenties.

- Iron chelation therapies appear to improve the outlook for ß-thalassemia major patients but this requires continuous infusion of the chelating agent.





Control of thalassemia

- Early diagnosis — By Hb electrophoresis
- Proper management — By appropriate blood transfusion
- Counseling when think of marriage
- Antenatal care — Amniocentesis if needed for early diagnosis

α-THALASSEMIAS

- With the α-thalassemias the level of α-globin production can range from none to very nearly normal levels.

- This is due in part to the fact that there are 2 identical α-globin genes on chromosome 16. Thus, the α-thalassemias involve inactivation of 1 to all 4 α-globin genes.

- If **3 of the 4 α-globin** genes are functional, individuals are completely asymptomatic. This situation is identified as the "**silent carrier**" state or sometimes as α-thalassemia 2.

- If **2 of the 4 genes** are inactivated individuals are designated as "**α-thalassemia trait**"

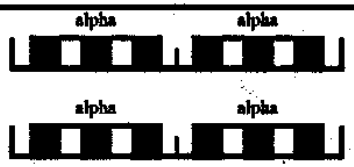
- The clinical situation becomes more severe if only **1 of the 4 α-globin genes** is functional.
- Because of the dramatic reduction in α-globin chain production in this latter situation, a high level of $\beta_4$tetramer is present. Clinically this is referred to as **hemoglobin H disease** (HbH).

- The most severe situation results when **no α-globin chains** are made .This leads to prenatal lethality or early neonatal death.

- The predominant fetal hemoglobin in afflicted individuals is a tetramer of γ-chains and is referred to as **hemoglobin Bart's**..

- This hemoglobin has essentially no oxygen carrying capacity resulting in oxygen starvation in the fetal tissues.
- Heart failure results as the heart tries to pump the unoxygenated blood to oxygen starved tissues leading to marked edema. This latter situation is called **hydrops fetalis.**

Normal:



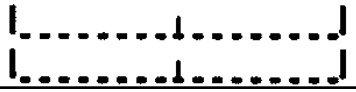
Alpha Thalassemia Genotypes (Classic):

Alpha-Thal2 Trait (Mild trait, silent carrier):

Alpha– Thal1 Trait (Severe alpha-Thal trait):

Hemoglobin H Disease:

Hb Bart's-hydrops fetalis:



α-thalassemia

1 in 9,000 births — α-thalassemia
1 in 55,000 births — ß-thalassemia

Frequency of carriers is higher in Africa, Asia (south and southeast), Mediterranean and Middle East.

Compiled by steven.chan@ucd.edu, 2009.08.11.
Handouts and references available at www.stevenchan.us/alphathal

CHROMOSOME 16	HEMOGLOBIN PRODUCED	SYMPTOMS & LABS	MANAGEMENT
Four genes control α-globin chain synthesis. **Normal.**	~95% HbA $\alpha_2\beta_2$ ~2% HbA_2 $\alpha_2\delta_2$ ~2% HbF $\alpha_2\gamma_2$	Normality.	No therapy required.
1 gene is deleted in **α-thalassemia minima, α-thalassemia-2 trait, silent carrier of α-thalassemia.**	HbA $\alpha_2\beta_2$ HbA_2 $\alpha_2\delta_2$ HbF $\alpha_2\gamma_2$	**Asymptomatic.** Slight hypochromia. Slight microcytosis. Dx only by DNA analysis.	No therapy required.
2 genes are deleted in **α-thalassemia minor, α-thalassemia-1 trait.** trans African cis Asian	↓HbA $\alpha_2\beta_2$ ↓HbA_2 $\alpha_2\delta_2$ ↓HbF $\alpha_2\gamma_2$ Risk for producing offspring with **Hb Barts.**	**Hypochromia.** **Microcytosis.** **Target cells.** MCV < 80 fL.	No therapy required.
3 genes are deleted in **Hemoglobin H disease.**	↓HbA $\alpha_2\beta_2$ ↓HbA_2 $\alpha_2\delta_2$ ↓HbF $\alpha_2\gamma_2$ 5–30% HbH $-\beta_4$	**Microcytic. Target cells.** HbH can't release O2 to tissues, because affinity is greater than HbA + HbH insoluble → Precipitates form inclusion bodies. → **Chronic hemolytic anemia** (hepatosplenomegaly, indirect hyperbilirubinemia, ↑LDH, ↓haptoglobin, ↓leg ulcers) → **Neonatal jaundice, occasionally hydrops fetalis.**	Most don't require chronic transfusion in 1st decade of life. **Splenectomy, transfusion** in 2nd, 3rd decade of life. **Avoid oxidants that may exacerbate HbH** (e.g. antimalarials, some sulfa drugs).
All 4 genes are deleted in **Hb Barts.**	~~HbA $\alpha_2\beta_2$~~ ~~HbA_2 $\alpha_2\delta_2$~~ ~~HbF $\alpha_2\gamma_2$~~ Hb Barts $-\gamma_4$ Both HbH and Hb Barts can't release O2 to tissues → ischemia.	**Hydrops fetalis:** High output heart failure → excess fluid accumulation → fetal demise, neonatal mortality.	Almost always lethal in utero. Consider therapeutic termination of pregnancy in mothers at risk. **Chronic intensive hypertransfusion, iron chelation, hematopoietic cell transplantation.**