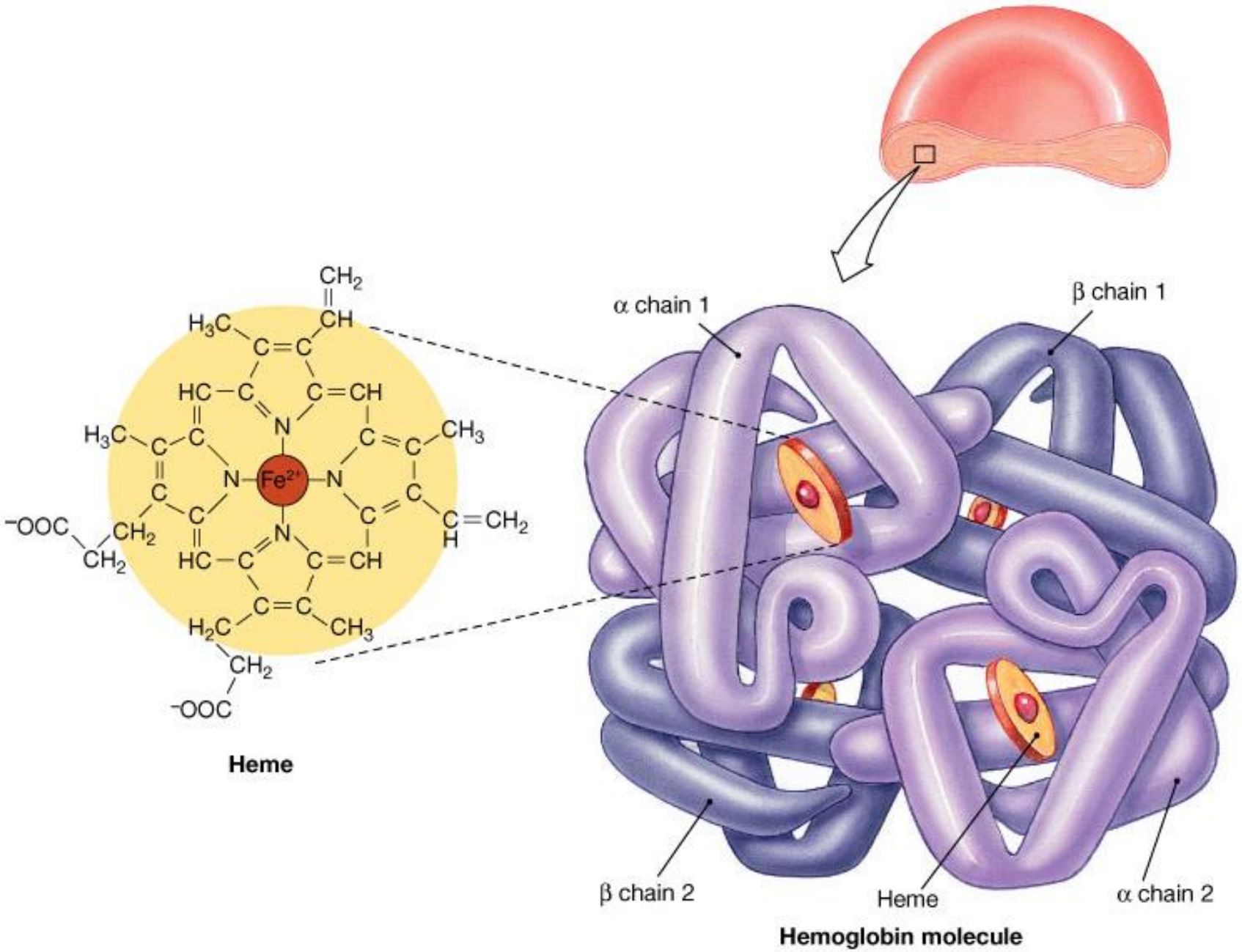
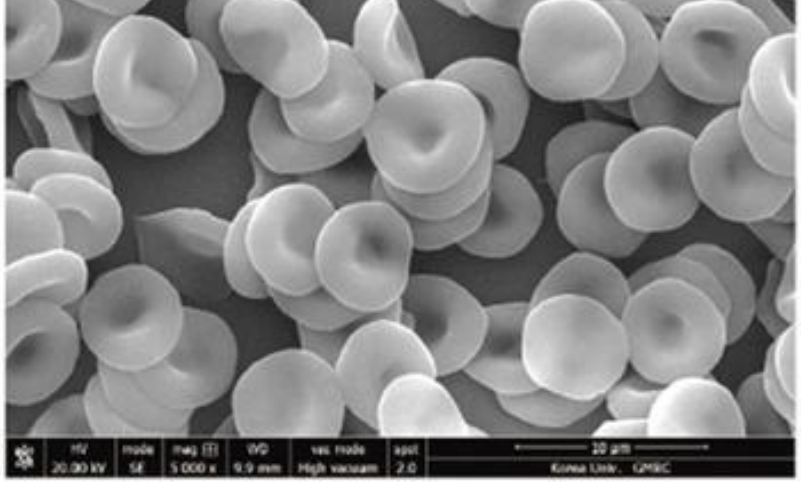
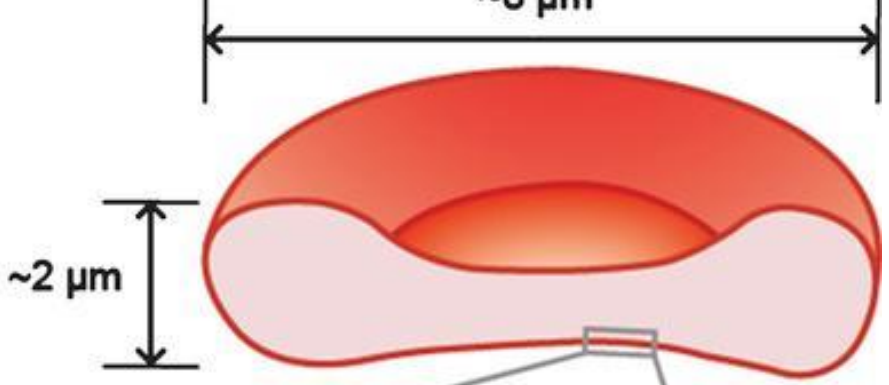
RBC disorders 4

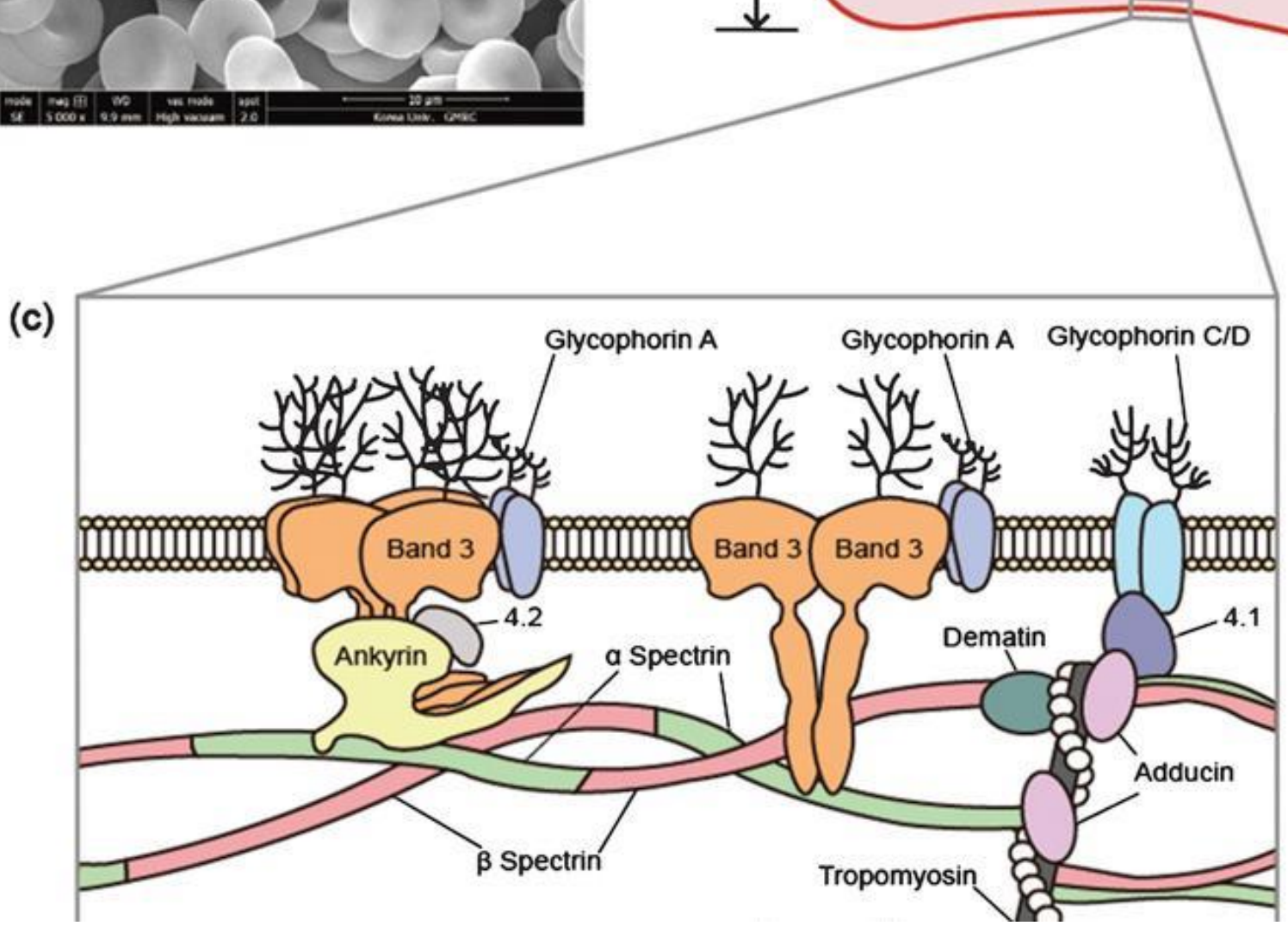
Ahmad Mansour, MD

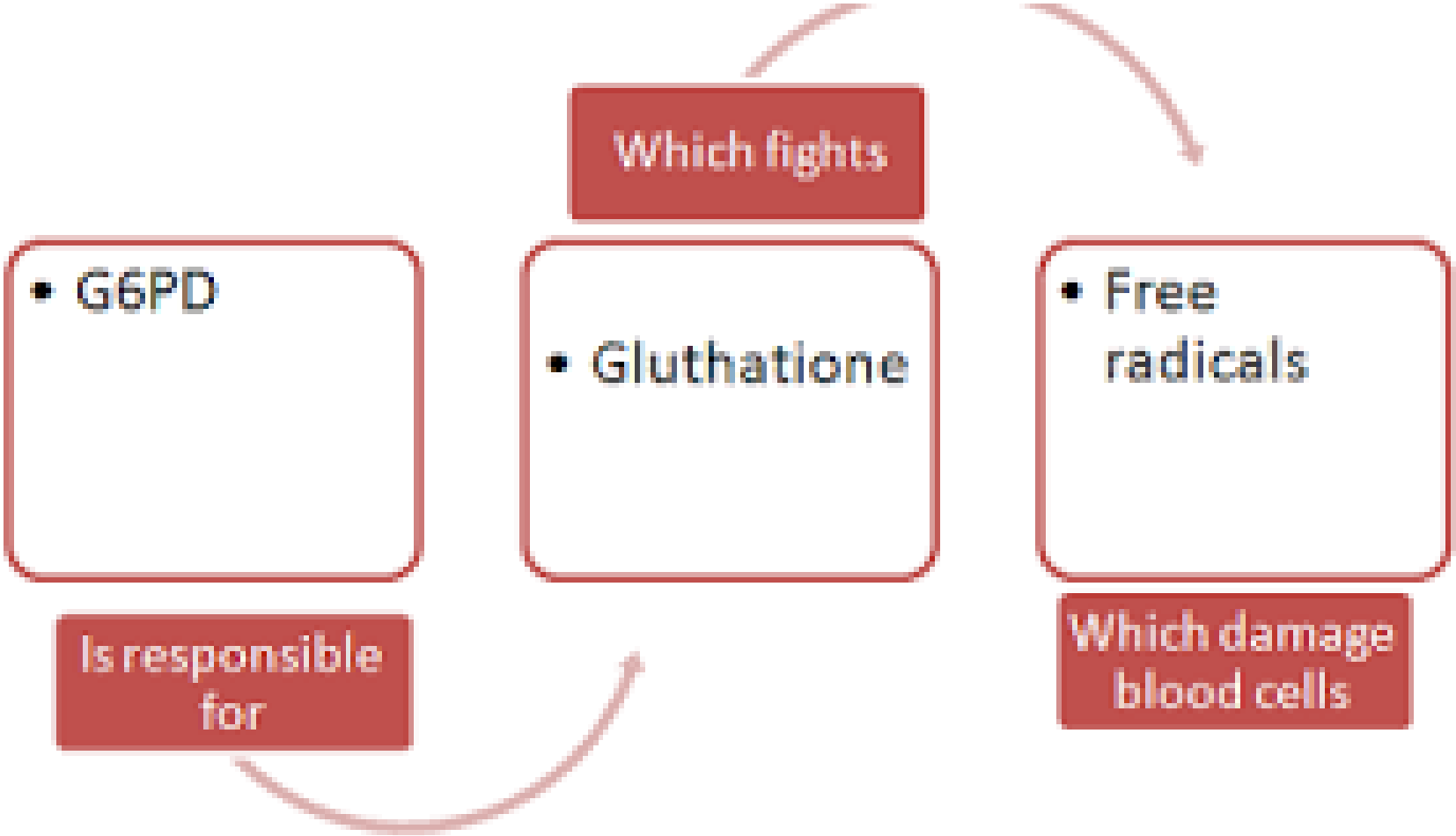
Anemia of blood loss (2)

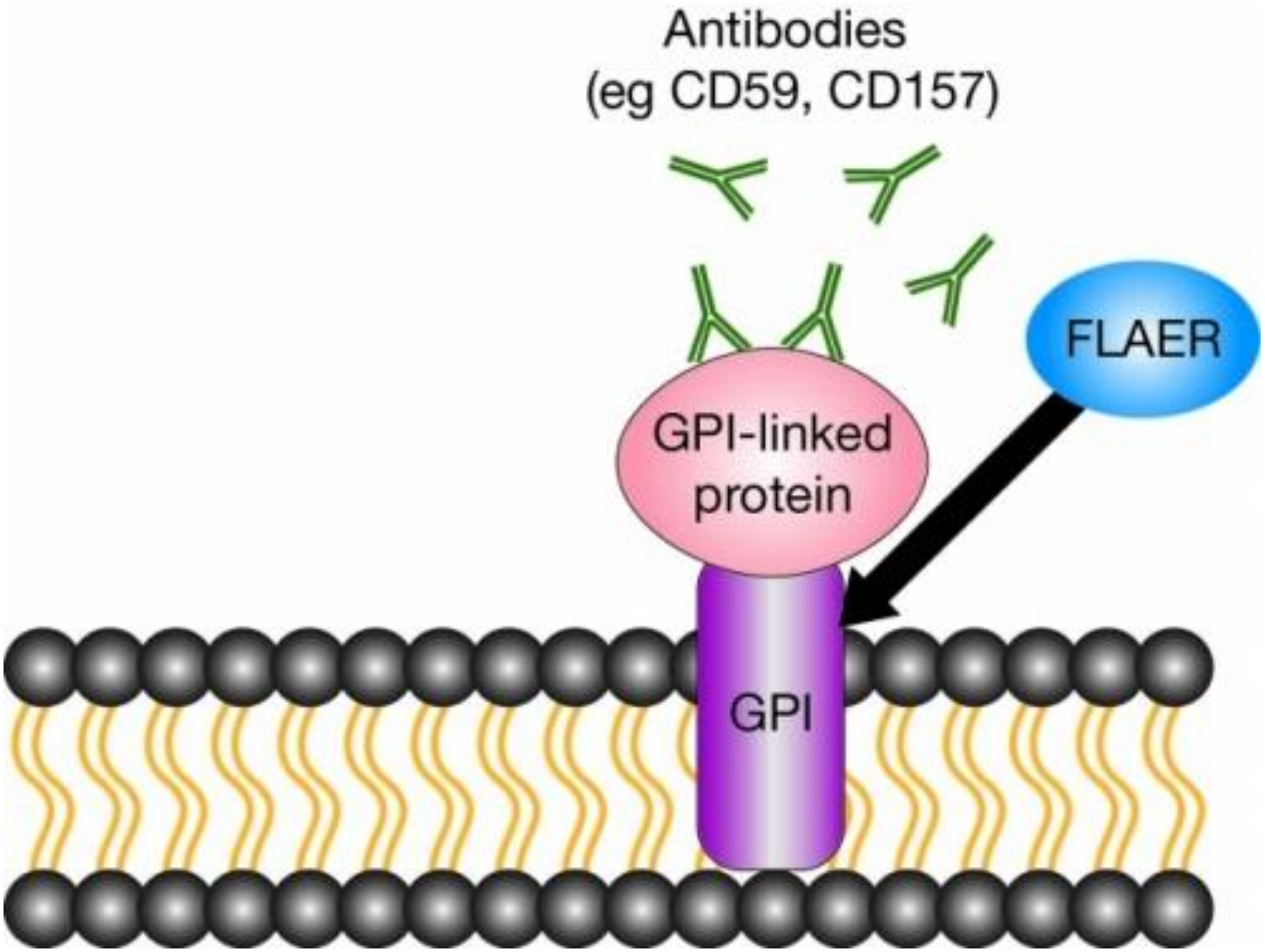

α chain 1
β chain 1
β chain 2
Heme
α chain 2
Heme
Hemoglobin molecule




~2 μm


(c)
Glycophorin A
Glycophorin A
Glycophorin C/D
Band 3
Band 3
Band 3
4.2
Ankyrin
α Spectrin
Dematin
4.1
Adducin
β Spectrin
Tropomyosin


• G6PD
Is responsible for
• Gluthatione
Which fights
• Free radicals
Which damage blood cells


Antibodies
(eg CD59, CD157)
FLAER
GPI-linked
protein
GPI

1- what is the mode of inheritance in the vast majority f spherocytosis cases?

A. Autosomal dominant
B. Autosomal recessive
C. X-linked dominant
D. X linked recessive

2- The amino acid present at the sixth position of the normal alpha-globin chain is replaced by which one of the following amino acids in sickle cell disease?

A. Lysine
B. Valine
C. Serine
D. Alanine
E. None of the above

3- In thalassemia disorders, when only one alpha gene is affected, what do we call that?

A. Normal
B. Silent carrier
C. Thalassemia trait-*cis*
D. Thalassemia trait-*trans*
E. HbH disease

4- gallbladder stones are a frequent complication of G6PD deficiency?

TRUE FALSE

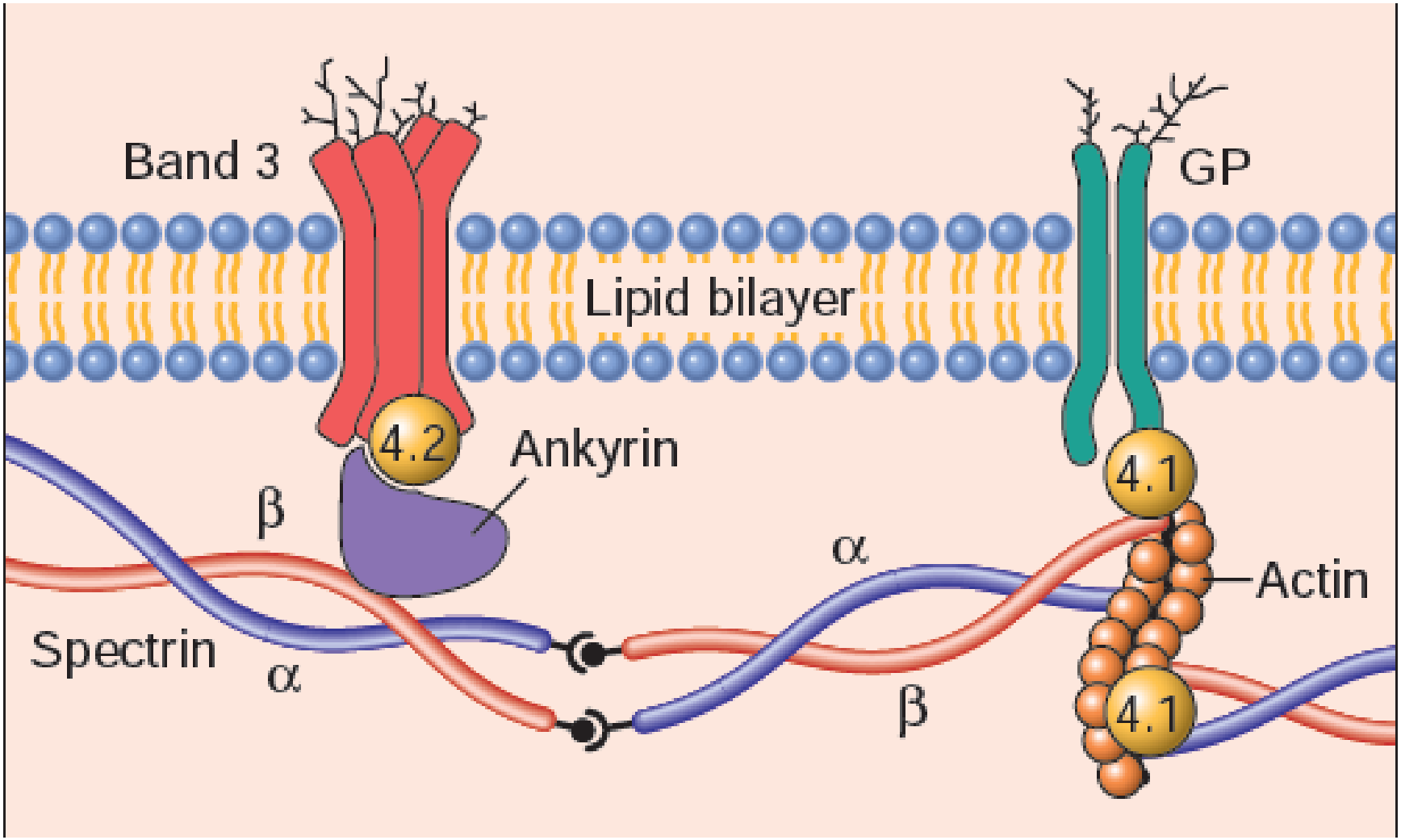
5- Paroxysmal nocturnal hemoglobinuria results from an acquired mutation in which of the following genes:

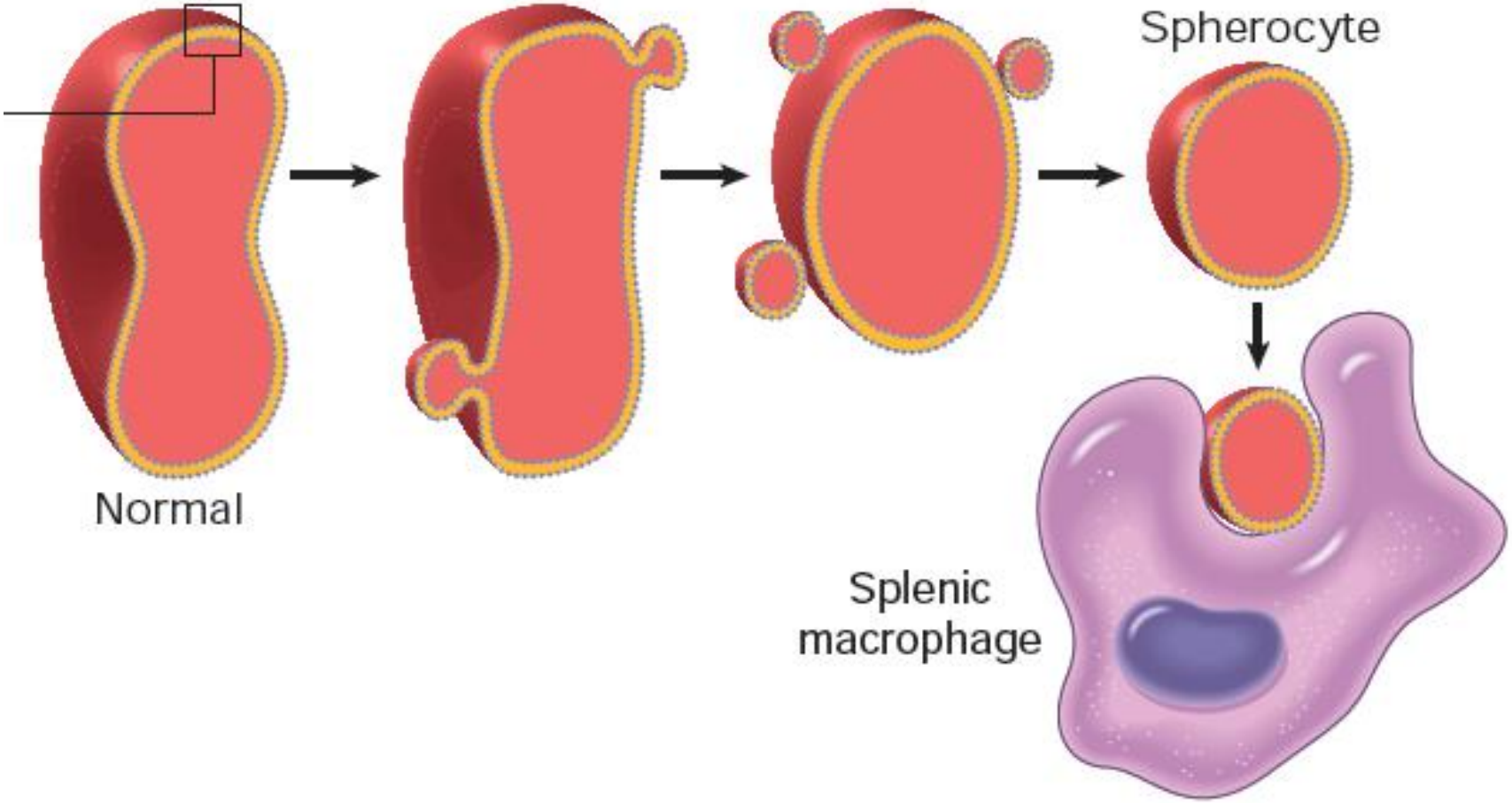
A. Alpha hemoglobin
B. Beta hemoglobin
C. Erythropoietin
D. PIGA
E. G6PD

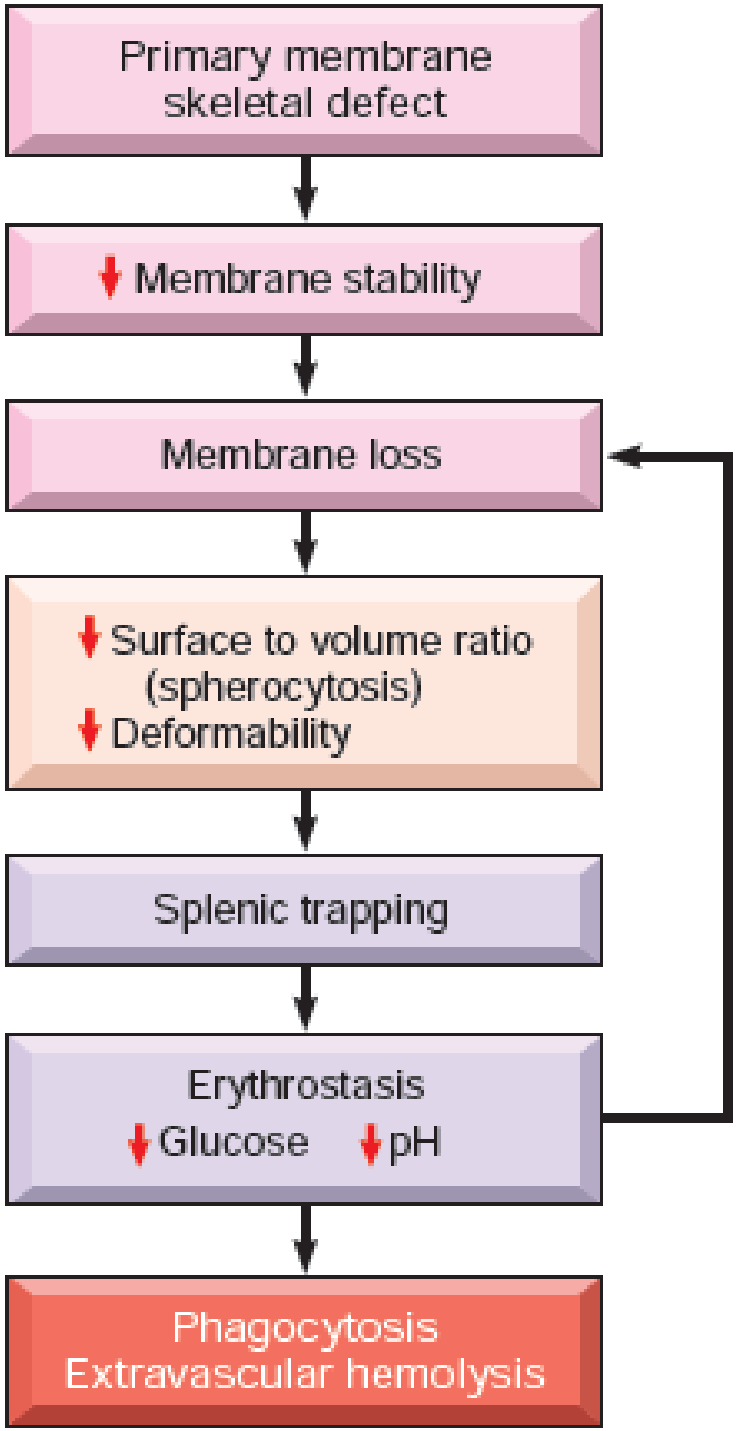
- Anemia of blood loss, hemorrhage
- Hemolysis
  - extrinsic
    - Immune hemolytic anemia
    - Hemolytic anemia resulting from mechanical trauma to the red cells
    - Infection

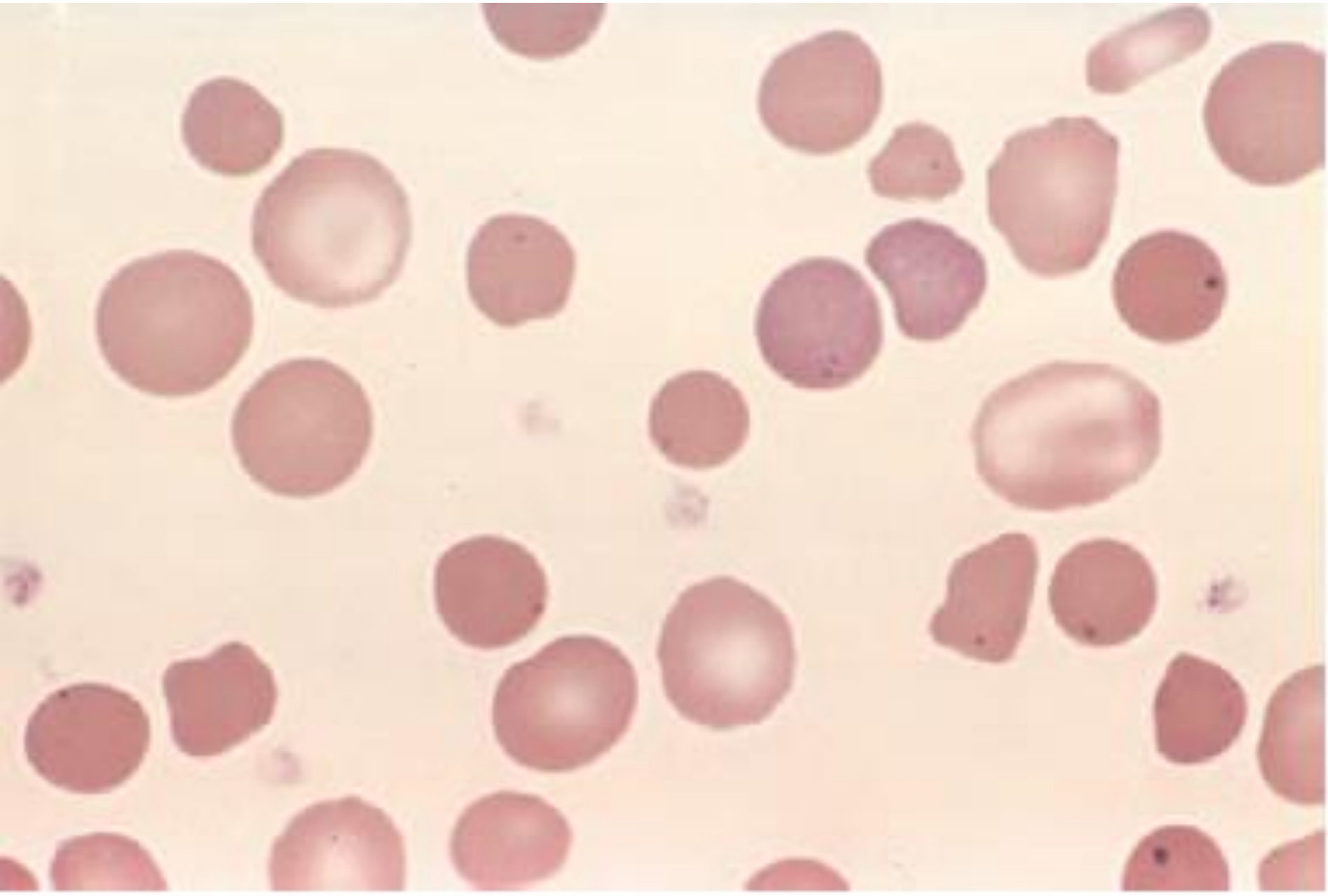
- intrinsic
  - Hereditary
    - Membranopathies-spherocytosis
    - Hemoglobinopathies-thalassemia and sickle cell disease
    - Enzymopathies-G6PD deficiency
  - Acquired
    - Paroxysmal nocturnal hemoglobinuria.

Hereditary spherocytosis




Spherocyte
Normal
Splenic
macrophage

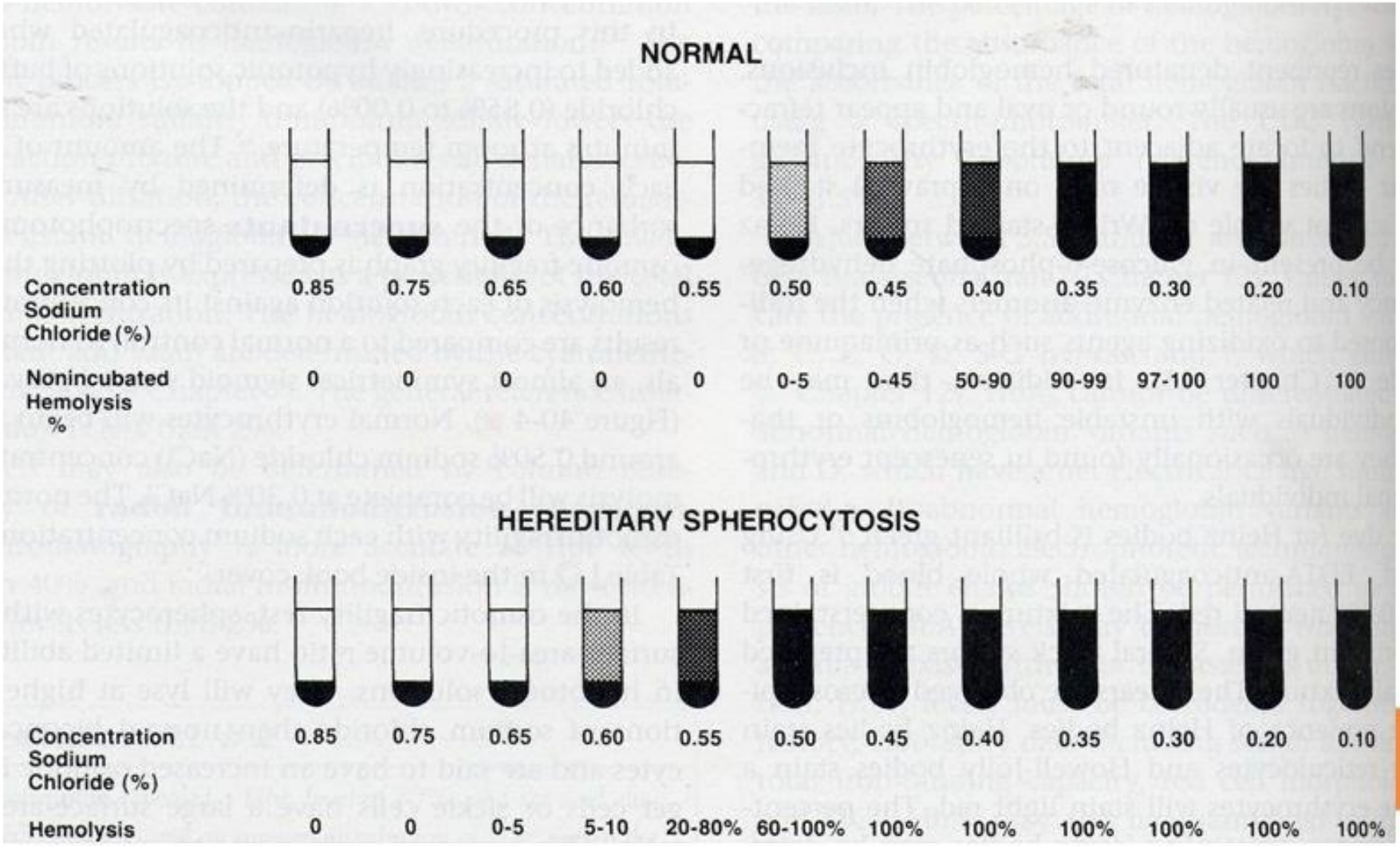

Primary membrane skeletal defect
↓ Membrane stability
Membrane loss
↓ Surface to volume ratio (spherocytosis)
↓ Deformability
Splenic trapping
Erythrostasis
↓ Glucose ↓ pH
Phagocytosis
Extravascular hemolysis



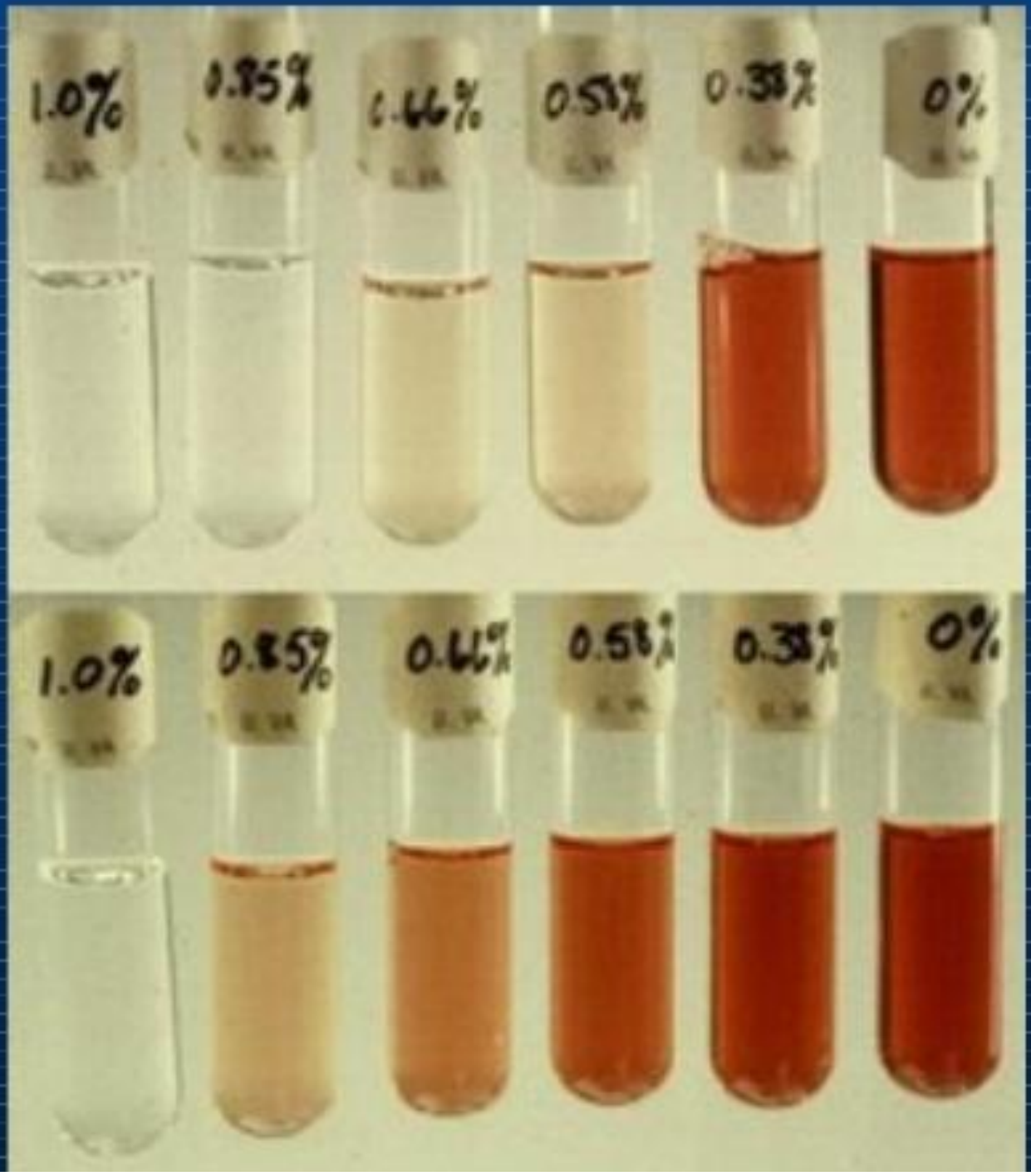
- Mostly autosomal dominant
- Prevalent in north Europe
- Mutation in ankyrin, band 3, and spectrin.

- Moderate clinical course, mostly.
- Can be complicated by aplastic crisis (parvo B19).
- Anemia, jaundice, gallbladder stones, splenomegaly.
- MCHC is high.
- Diagnosis involves osmotic fragility test
- No definitive treatment
  - Symptomatic treatment with splenectomy.

OSMOTIC FRAGILITY TEST



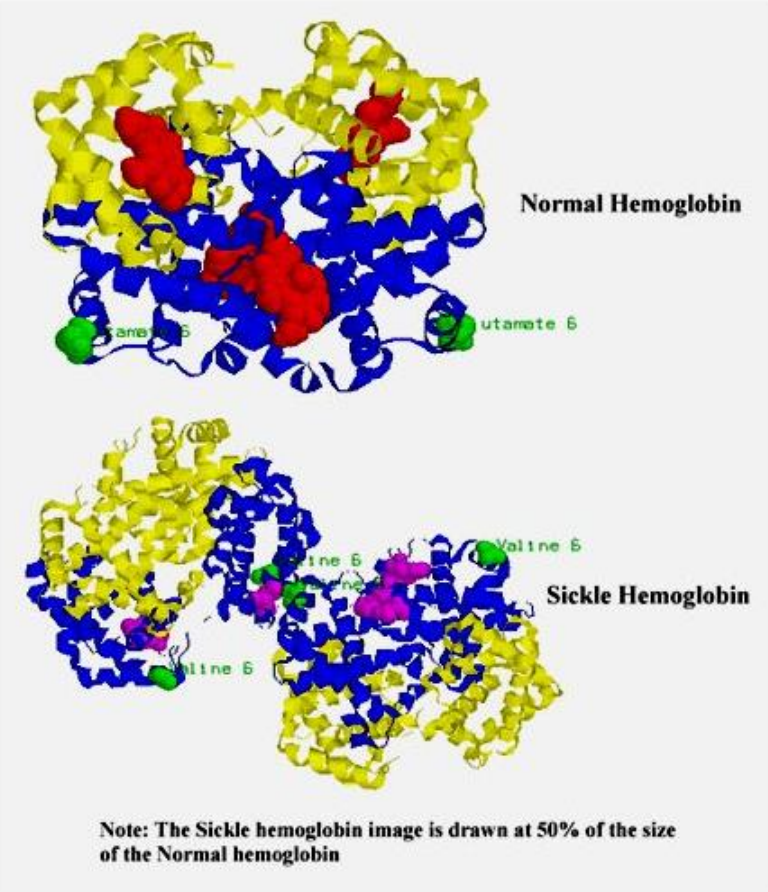
Normal



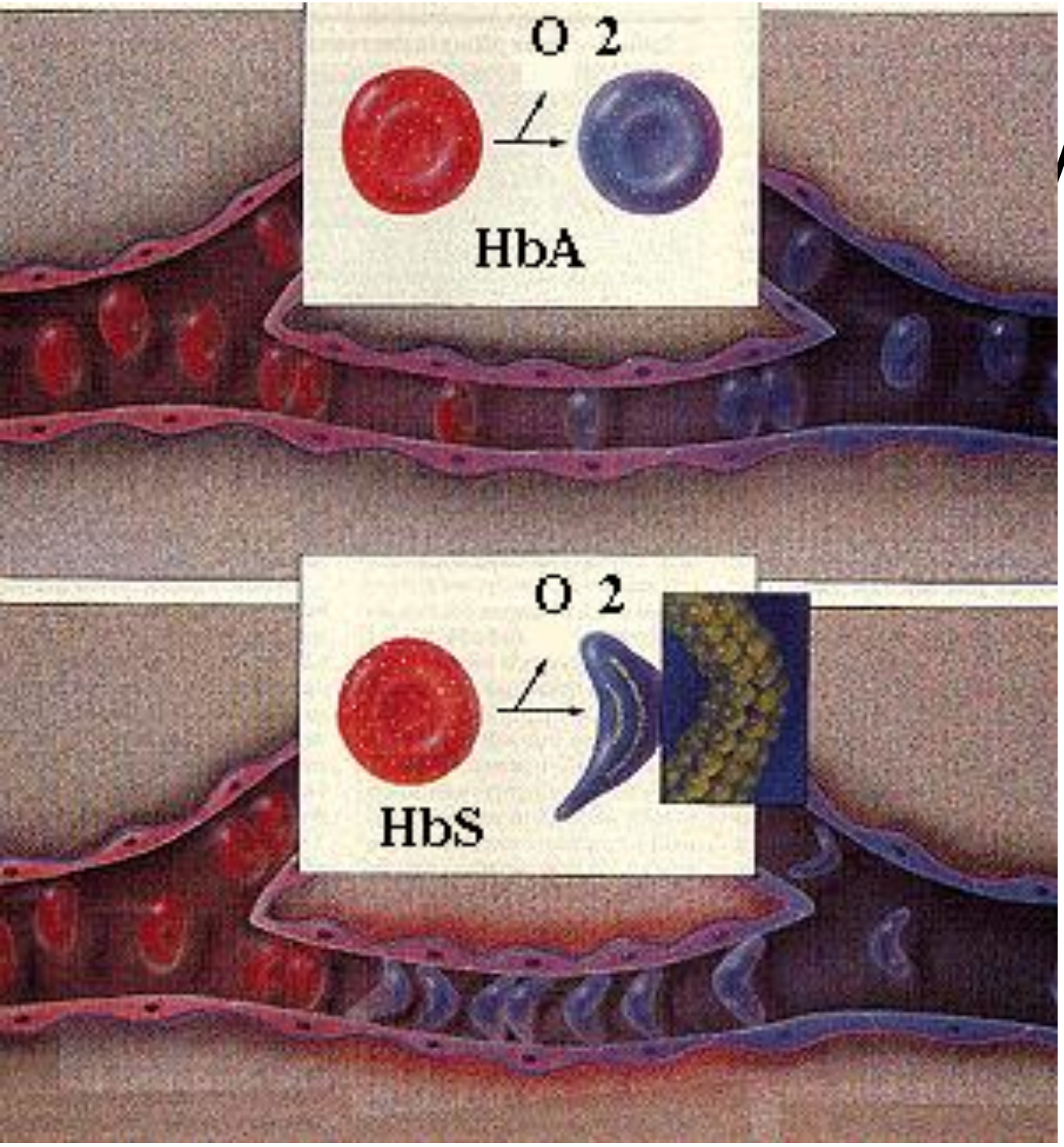
Abnormal-
HS cells lyse more readily at low ionic strength

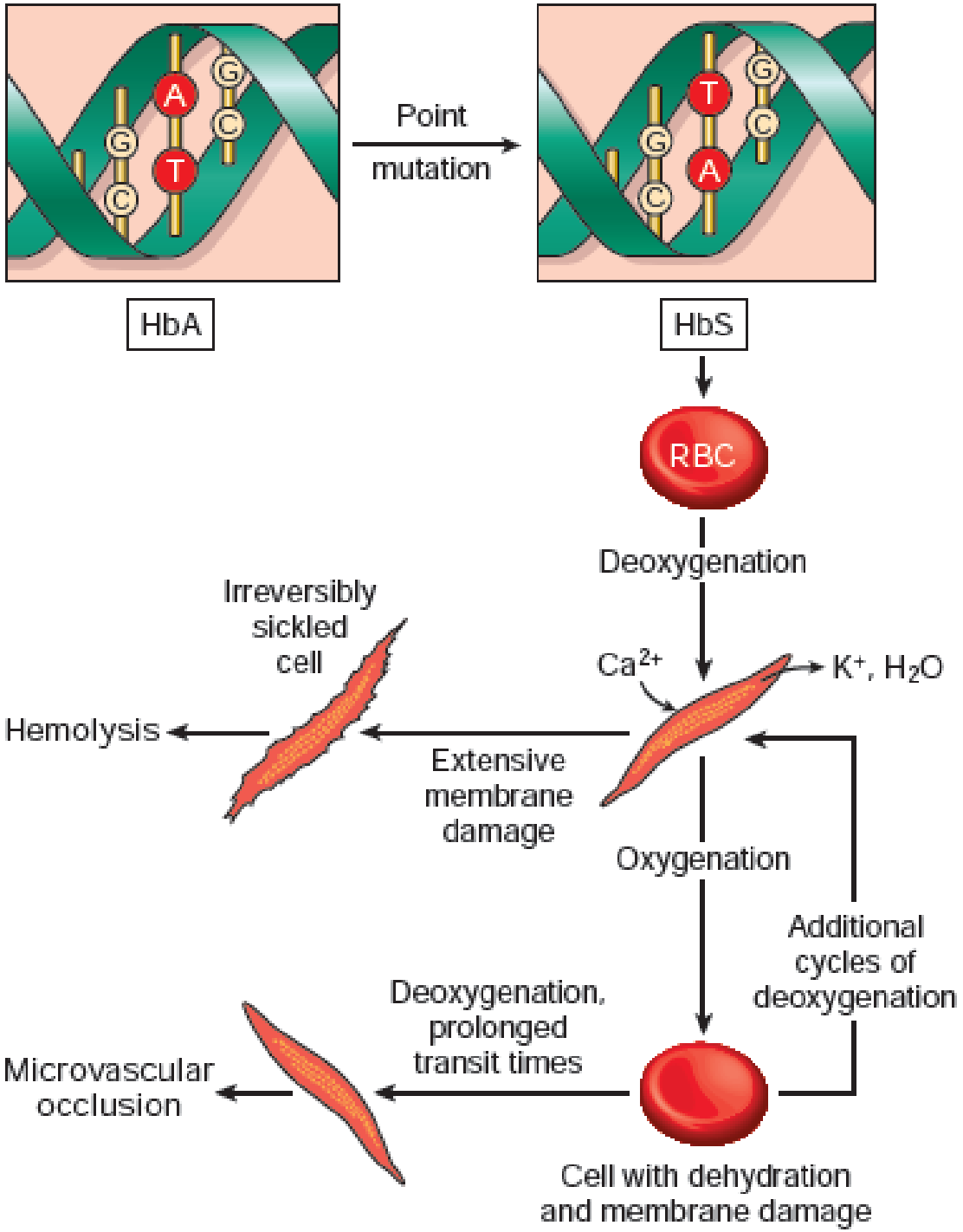
- intrinsic
  - Hereditary
    - Membranopathies-spherocytosis
    - Hemoglobinopathies-thalassemia and sickle cell disease
    - Enzymopathies-G6PD deficiency
  - Acquired
    - Paroxysmal nocturnal hemoglobinuria.

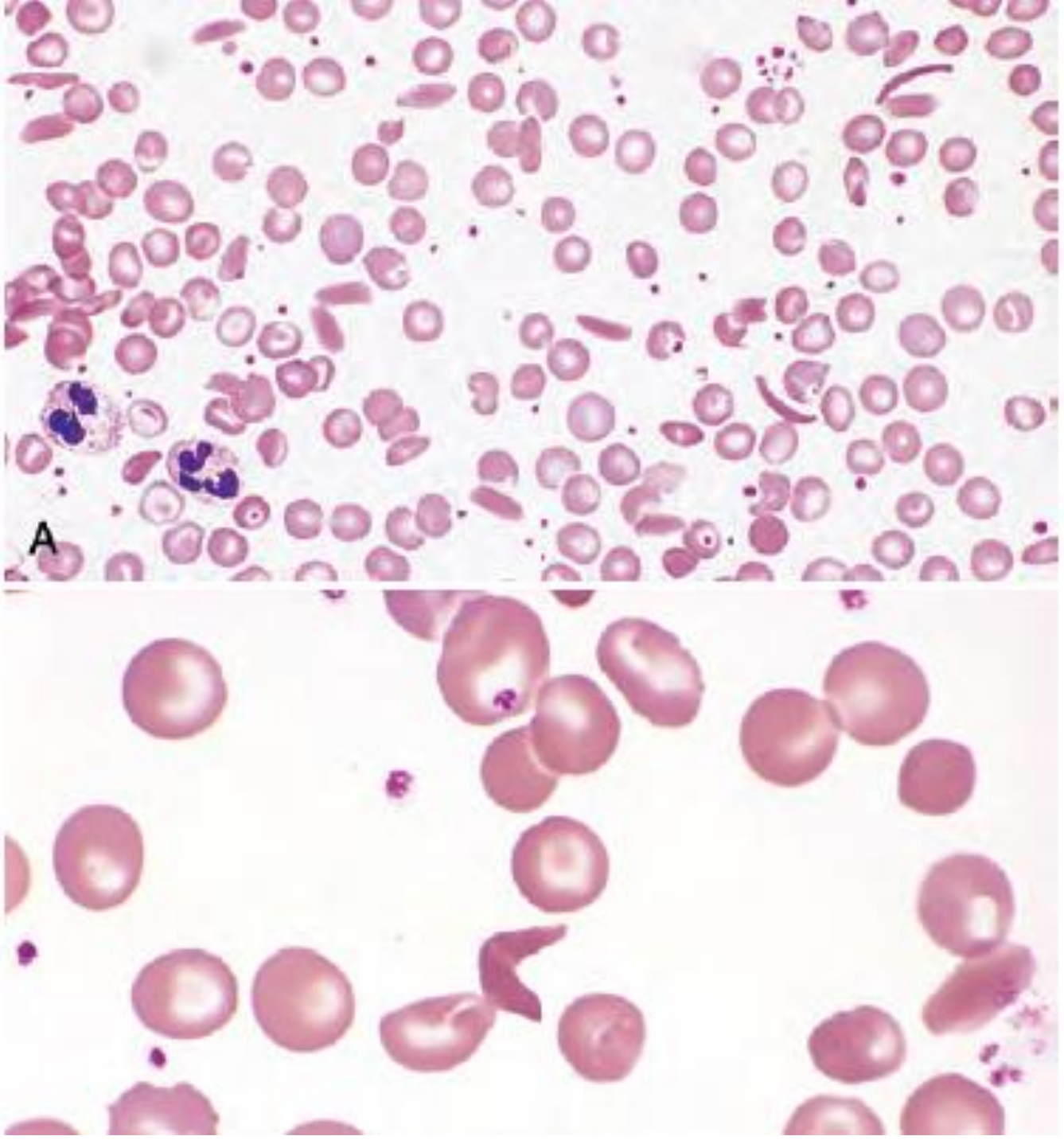
Sickle cell anemia



- The most common hemoglobinpathy
- In homozygotes all HB is replaced by HbS
- In heterozygotes half is replaced.
- Gene frequency is ~30%
- 8% in black Americans.


O 2
HbA
O 2
HbS


A
G
C
T
G
C
Point
mutation
T
G
C
A
G
C
HbA
HbS
RBC
Deoxygenation
Irreversibly
sickled
cell
Ca2+
K+, H2O
Hemolysis
Extensive
membrane
damage
Oxygenation
Additional
cycles of
deoxygenation
Deoxygenation,
prolonged
transit times
Microvascular
occlusion
Cell with dehydration
and membrane damage


A

- Three important factors influence sicling in the body
  - Presence of hemoglobins other than HbS
  - Intracellular concentration of hemoglobin
  - Transit time for RBCs within the vasculature

Presence of hemoglobins other than HbS

- HBA ($\alpha_2\beta_2$)…weak
- HbF($\alpha_2\gamma_2$)…weak
- HbC…strong

Intracellular concentration of hemoglobin

- Dehydration…..high conc.
- Alpha thalassemia….low conc.

Transit time for RBCs within the vasculature

- Short time….no sickling
- Long time….sickling

- Chronic hemolytic anemia
- Fatty change in the heart, liver and renal tubules
- Reticulocytosis and erythroid hyperplasia in bone marrow
- Bone changes, prominent cheekbones and crew-cut skull
- Extramedullary hematopoiesis in liver and spleen.

- Mild splenic congestion, autosplenectomy in adults.
- Increased risk of infections, salmonella osteomyelitis.
- Vessel occlusion, bone pain, acute chest syndrome, stroke.
- Aplastic crisis

- Diagnosis with electrophoresis to demonstrate HbS and fetal DNA via amniocentesis or chorionic villi biopsy.

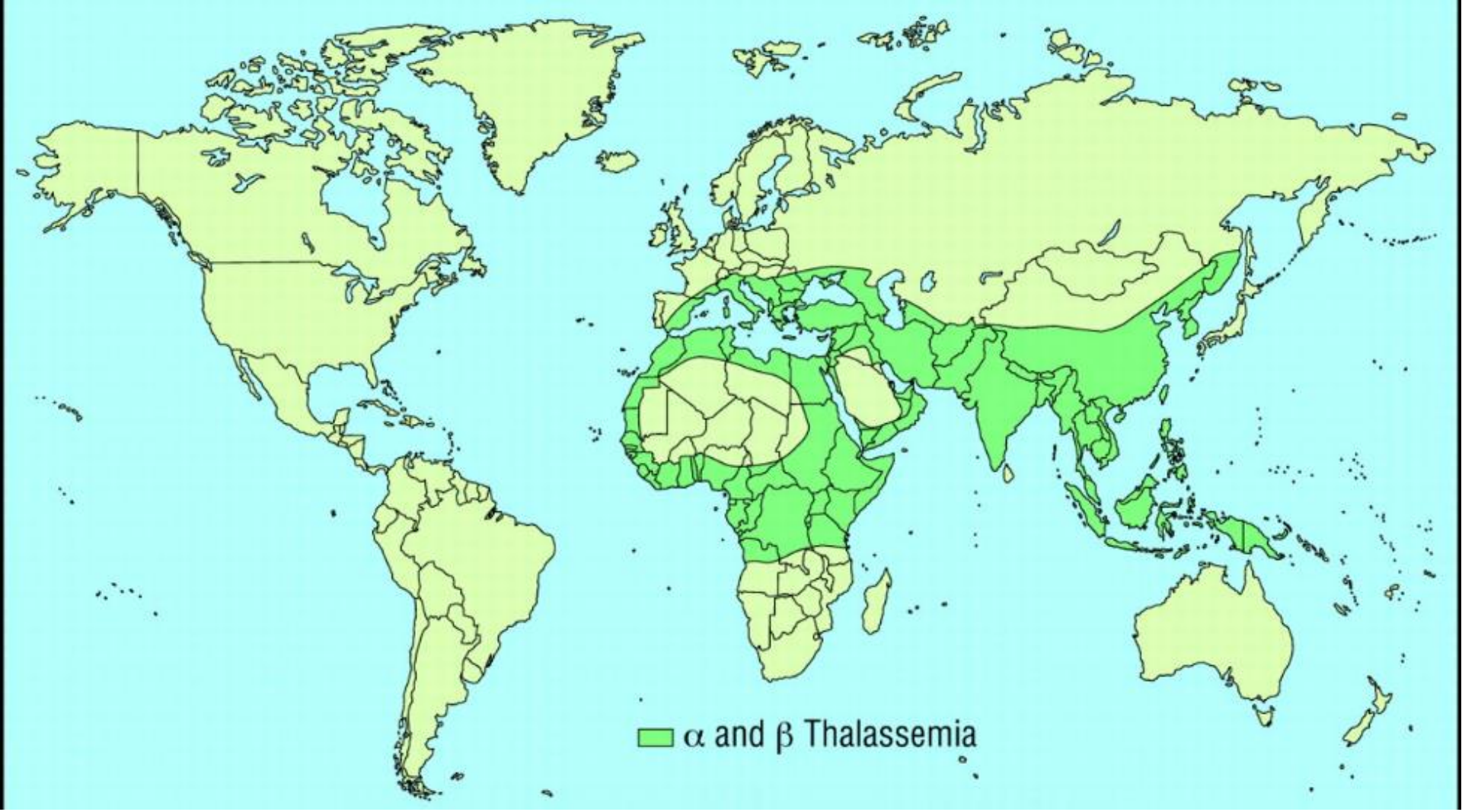
- Variable clinical course
  - SICKLE CELL TRAIT IS MOSTLY ASYMPTOMATIC.

- HYDROXYUREA
  - Increase HbF
  - Anti inflammatory due to decrease WBC production
  - Increase MCV
  - Production of NO
- BONE MARROW TRANSPLANT

Thalassemia

The thalassemia syndromes are a heterogeneous group of disorders caused by inherited mutations that ***decrease the synthesis*** *of either the α-globin or β-globin chains that compose adult hemoglobin, HbA (α2β2), leading to anemia, tissue hypoxia, and* ***red cell hemolysis*** *related to the imbalance in globin chain synthesis*

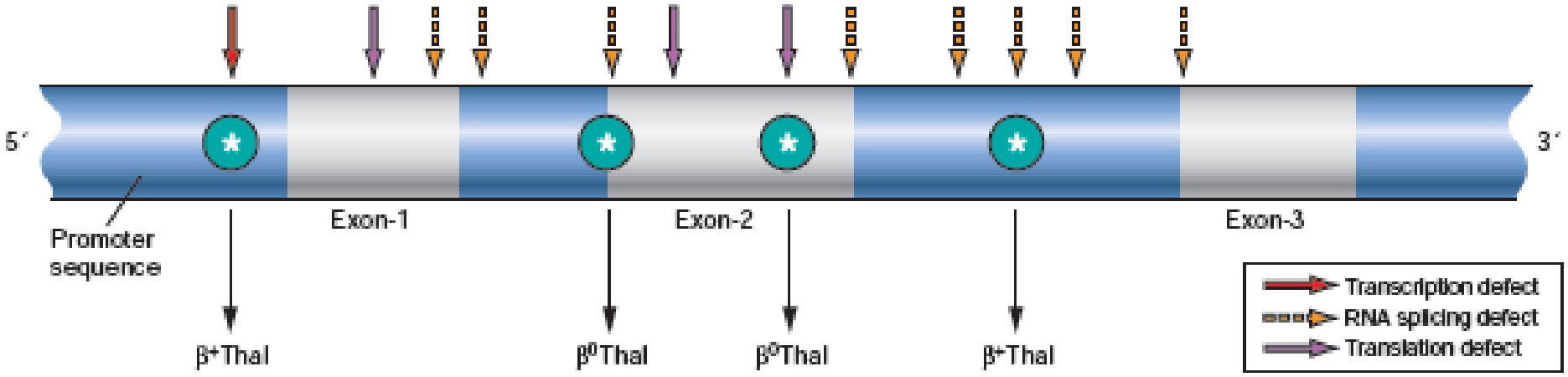
- 4 alpha genes, chromosome 16
- 2 beta genes, chromosome 11


α and β Thalassemia

B thalassemia

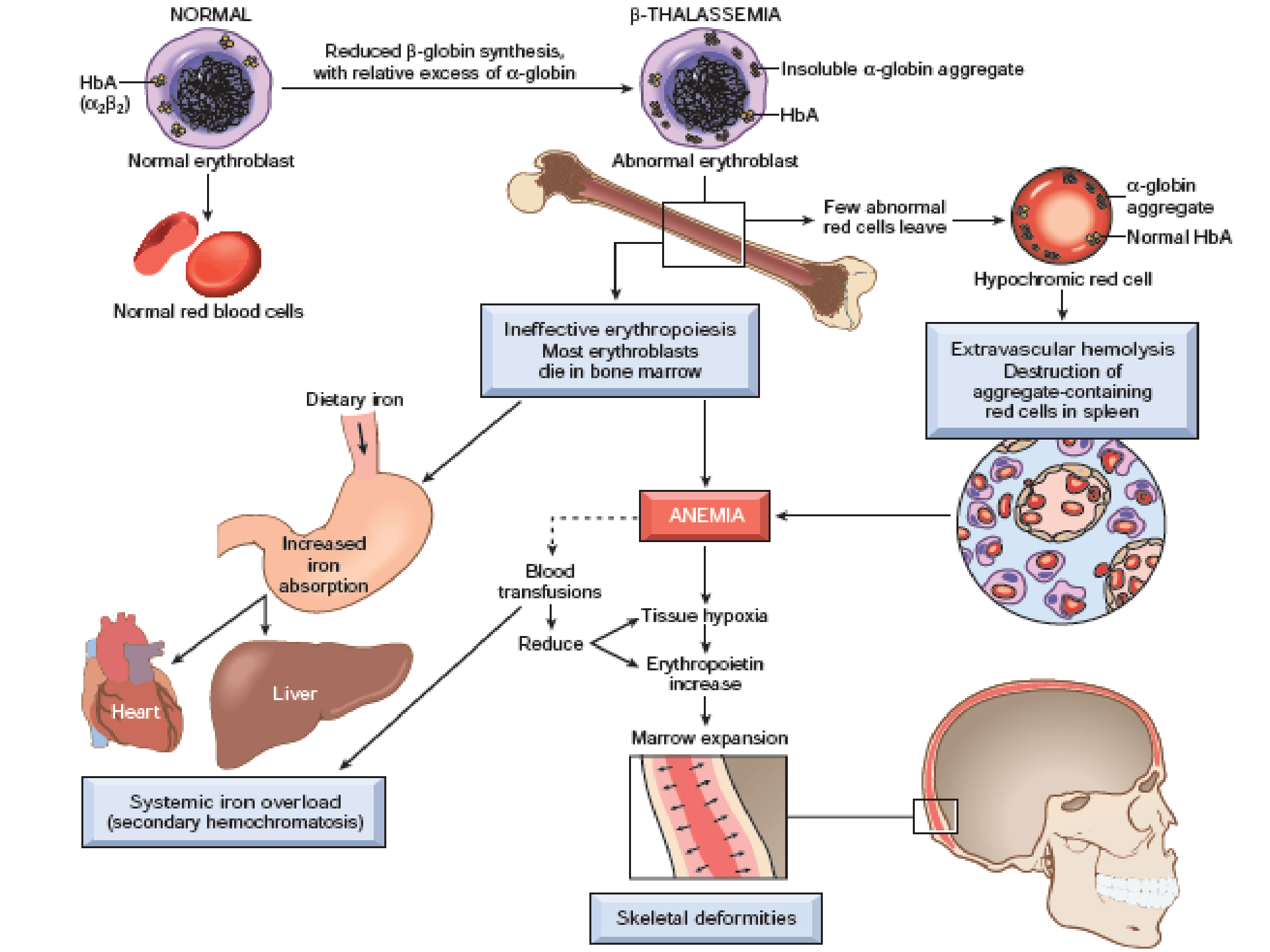
- The β-thalassemias are caused by mutations that diminish the synthesis of β-globin chains.
- Two categories of causative mutations
  - (1) β^0mutations, associated with absent β-globin synthesis
  - (2) β^+mutations, characterized by reduced (but detectable) β-globin synthesis.

unlike sickle cell disease, the amino acid sequence is **INTACT!



-Promoter region mutation
-Splicing mutations
-Chain termination mutations

- Two mechanisms of anemia
  - Underhemoglobinization
  - Decreased red cell survival due to chain imbalance.


NORMAL
β-THALASSEMIA
HbA
($\alpha_2\beta_2$)
Reduced β-globin synthesis, with relative excess of α-globin
Insoluble α-globin aggregate
HbA
Normal erythroblast
Abnormal erythroblast
Normal red blood cells
Few abnormal red cells leave
α-globin aggregate
Normal HbA
Hypochromic red cell
Ineffective erythropoiesis
Most erythroblasts die in bone marrow
Extravascular hemolysis
Destruction of aggregate-containing red cells in spleen
Dietary iron
ANEMIA
Increased iron absorption
Blood transfusions
Tissue hypoxia
Reduce
Erythropoietin increase
Heart
Liver
Marrow expansion
Systemic iron overload (secondary hemochromatosis)
Skeletal deformities

- *B* thalassemia major (Homozygousβ-thalassemia) (β0/β0, β+/β+, β0/β+)
- *B* thalassemia minor (Heterozygousβ-thalassemia) (β0/β, β+/β)
- *B* thalassemia intermedia (Variable)

  (β0/β+, β+/β+, β0/β, β+/β)

B-Thalassemia Major.

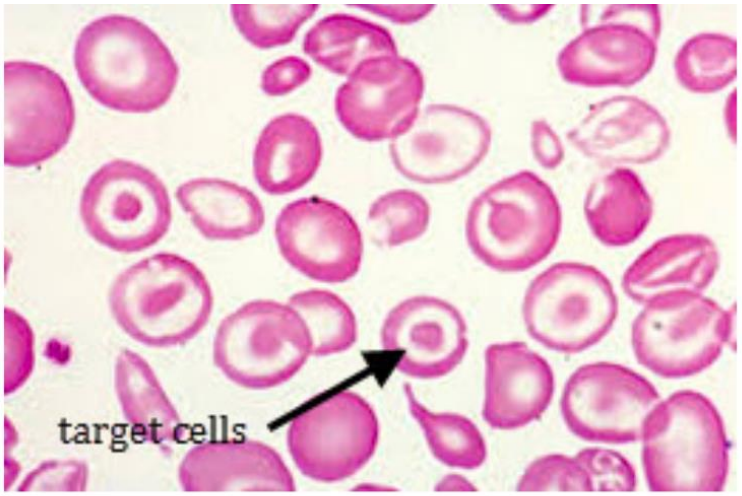
-common in the Mediterranean areas and the Middle East

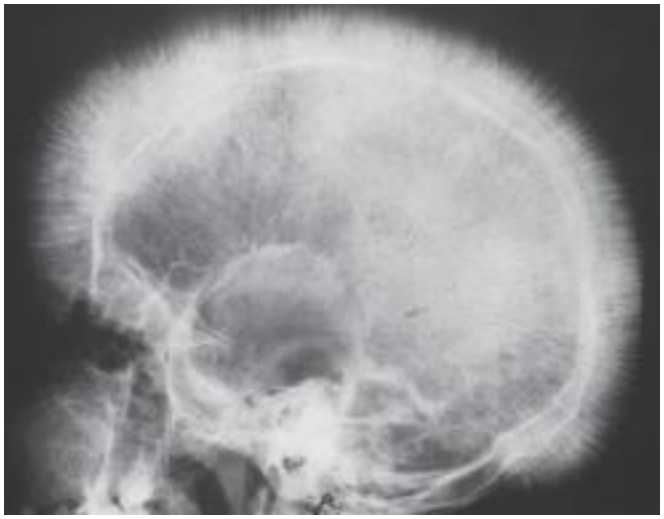
-anemia manifests 6-9months of life after as hemoglobin synthesis switches from HbF ($\alpha_2\gamma_2$) to hemoglobin A ($\alpha_2\beta_2$)

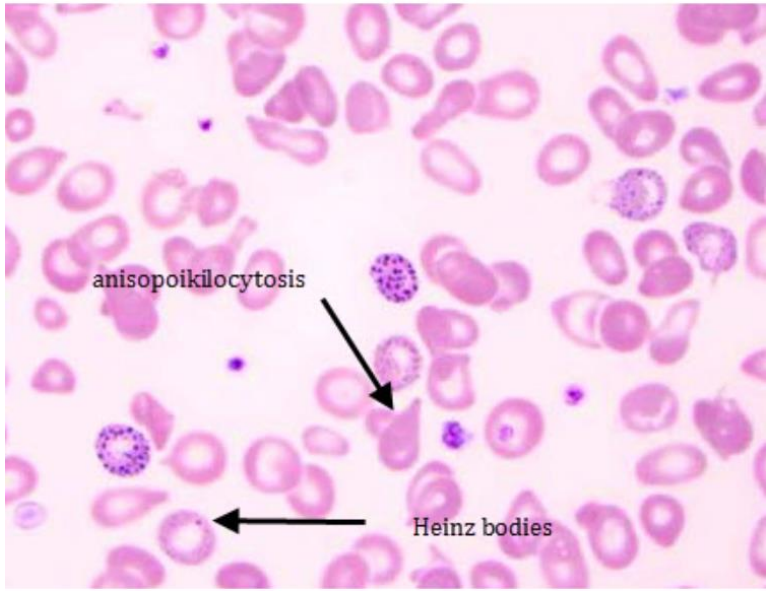
Low hemoglobin 3-6g/dL

Elevated HbF and HbA2($\alpha_2\delta_2$)

Morphology







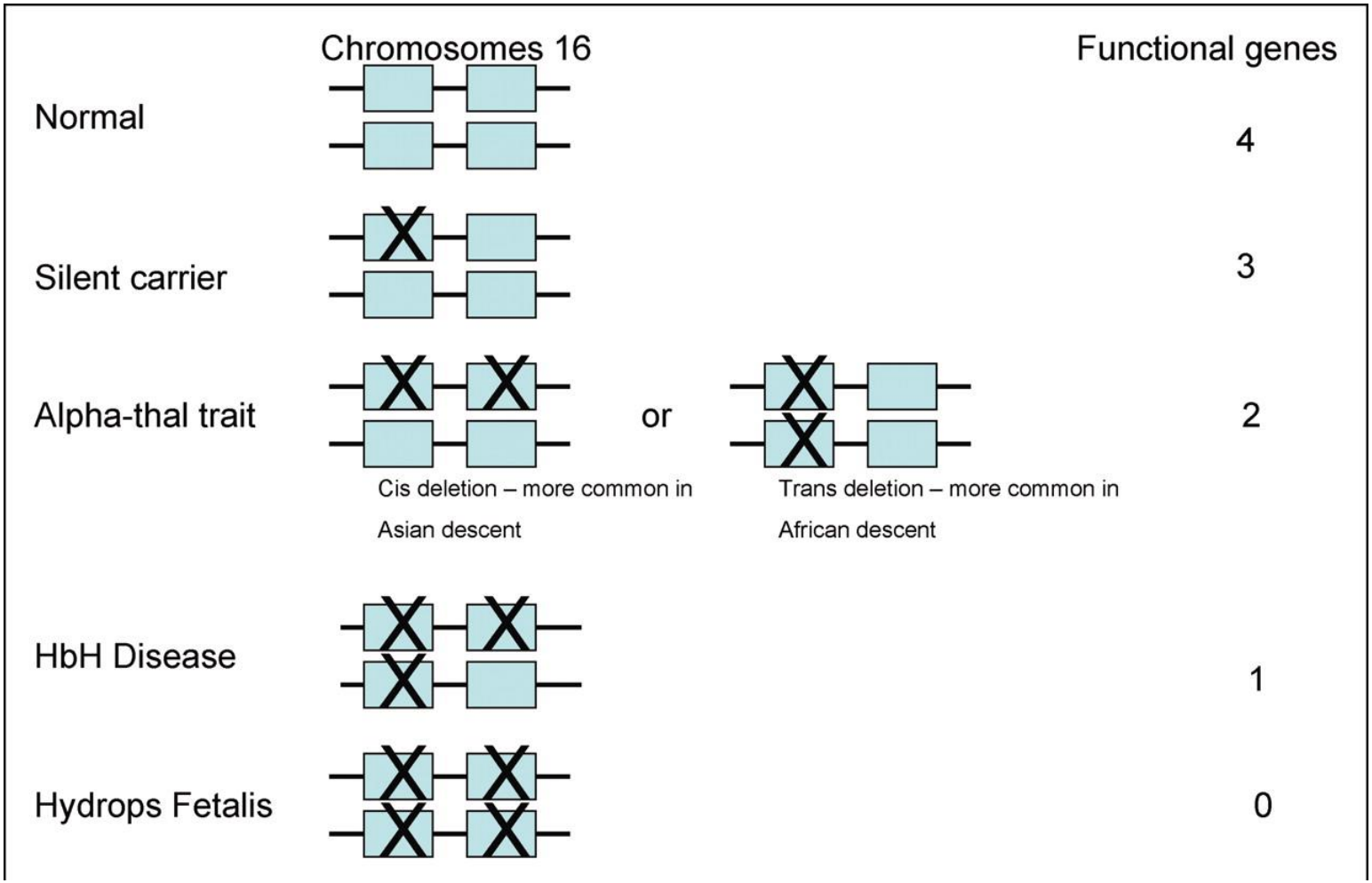
- Hepatosplenomegaly
- Cardiac disease
- Transfusion dependent, role of chelation therapy
- Guarded prognosis
- Stem cell transplantation is the only hope for cure.

B-thalassemia minor

- Same ethnic groups as B major
- Usually asymptomatic
- Mild PB smear findings
- Bone marrow EP hyperplasia
- Elevated HbA2

- Important to recognize due to
  - Differentiate from IDA
  - Genetic counseling

Alpha thalassemia



- Silent Carrier State: asymptomatic, microcytosis.
- Alpha thalassemia trait: microcytosis and mild to no anemia
- HbH: moderately severe anemia similar to B-thalassemia intermedia
- Hydrops fetalis: lethal without in utero transfusion.

- The mutations in B thalassemia are **point mutations** or small deletions while in alpha thalassemia they are **large deletions.**

- intrinsic
  - Hereditary
    - Membranopathies-spherocytosis
    - Hemoglobinopathies-thalassemia and sickle cell disease
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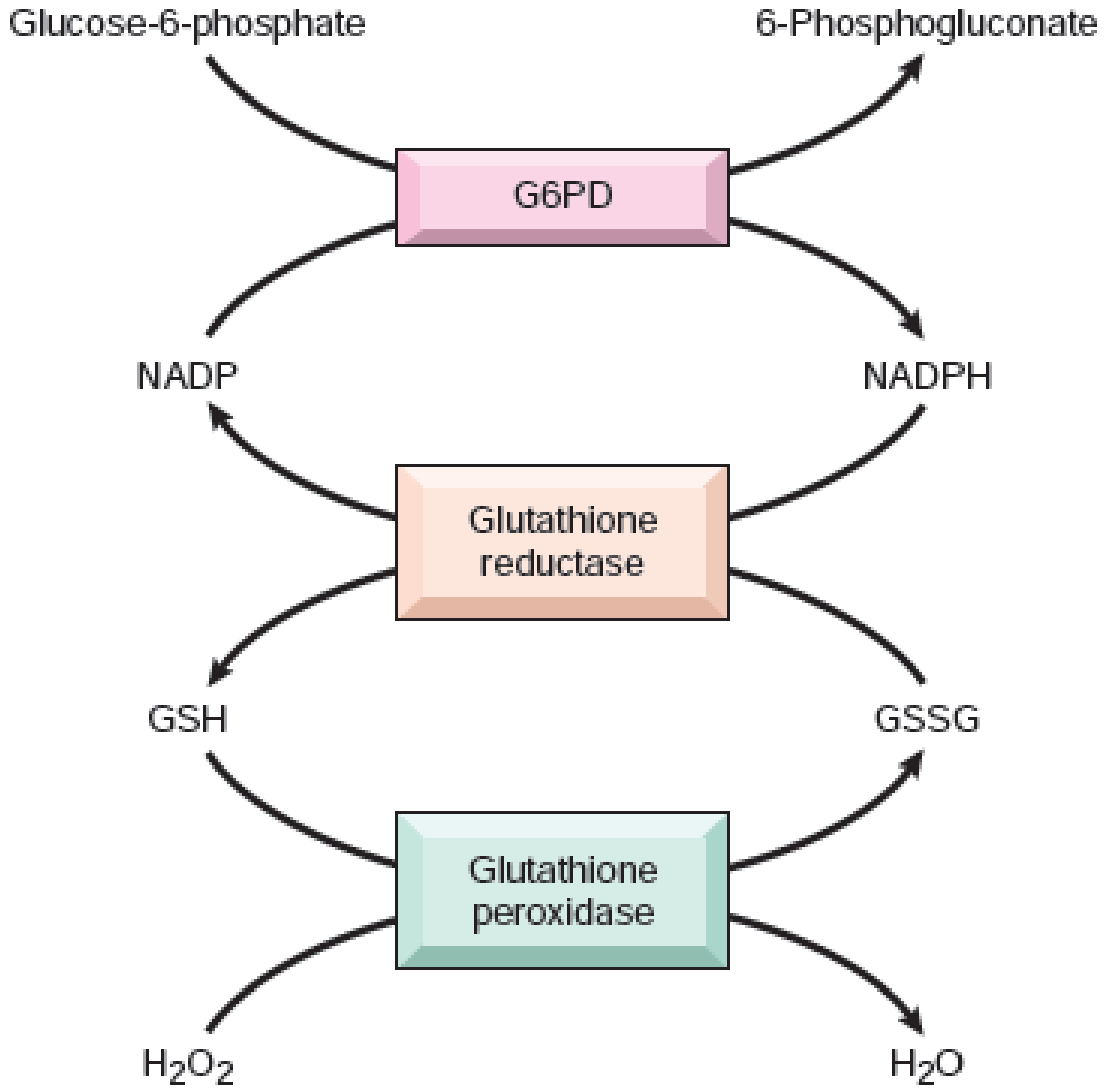
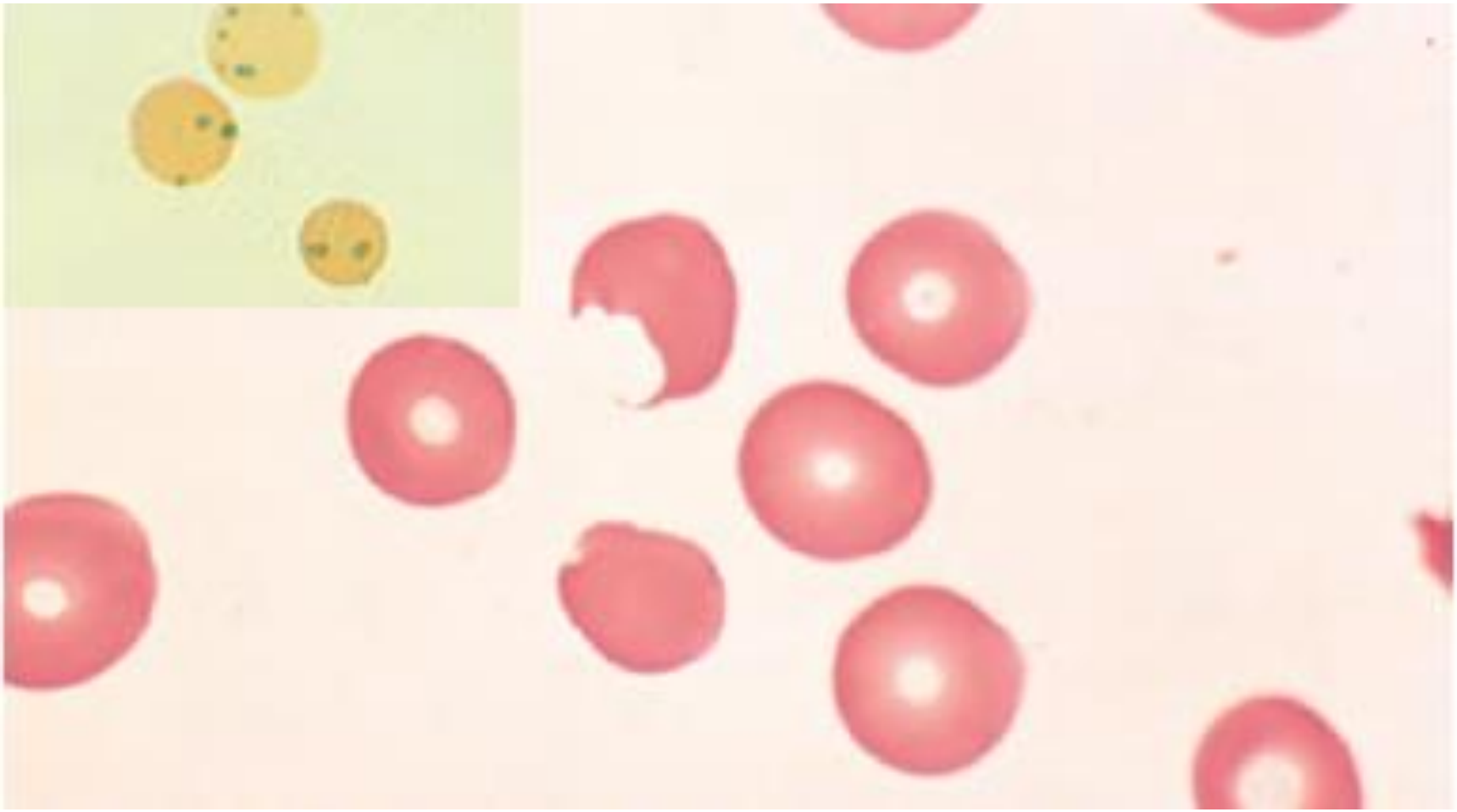
Glucose 6-phosphate dehydrogenase deficiency



- X-linked disorder
- More common in males
- Numerous mutations
- G6PD A- and G6PD Mediterranean

- Presents most commonly as episodic hemolysis
  - Infections: most common cause.
  - Drugs: antimalarials, nitofurantoin
  - Certain foods: fava beans



- Hemolysis can be either intra- or extravascular hemolysis
- Hemolysis stops after old RBC hemolyze even if the offending agent is still effective.
- Since it's **episodic acute (rather than chronic)** hemolysis, features related to chronic hemolysis (splenomegaly and gallbladder stones) are typically **absent.**

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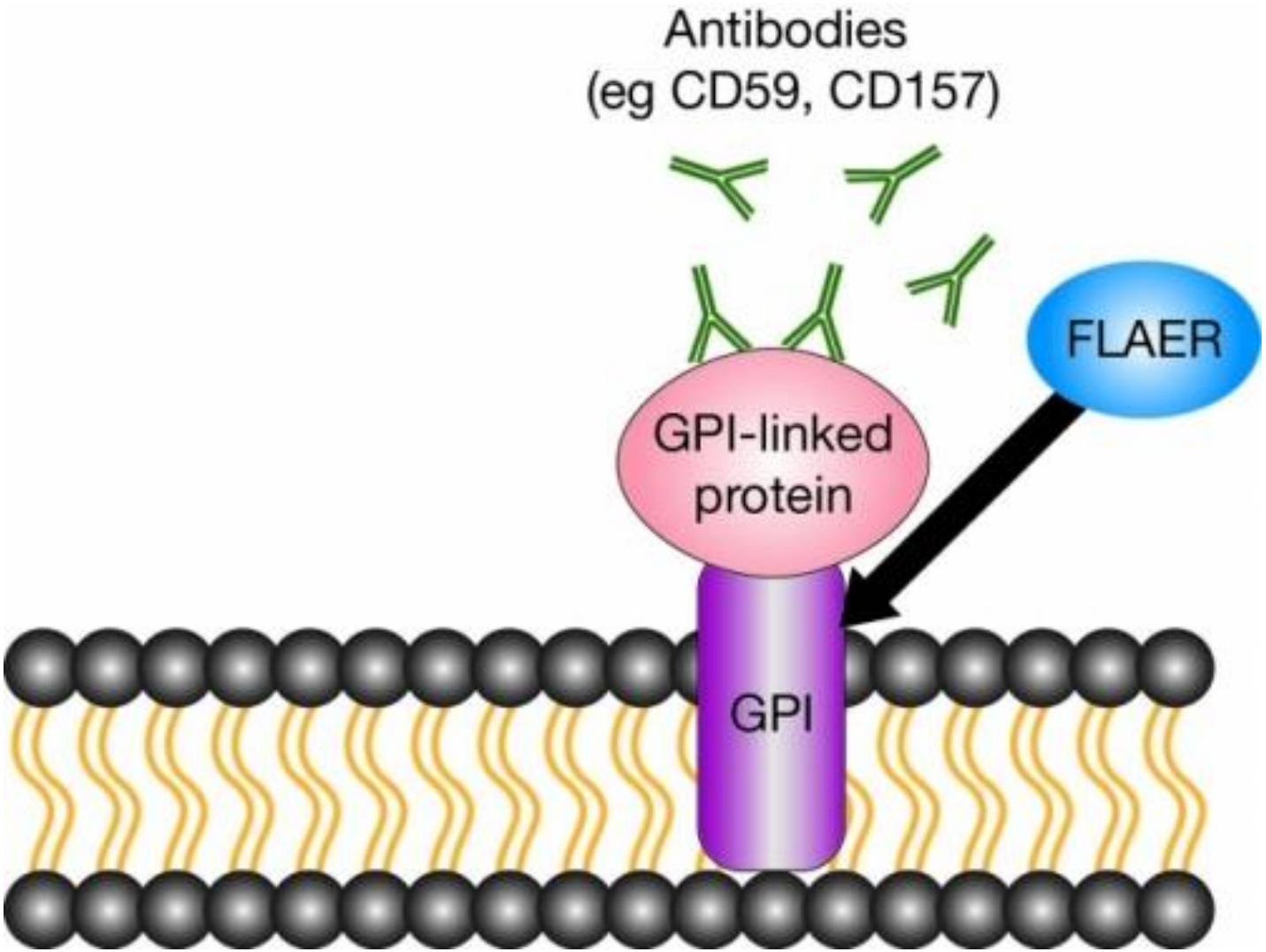
Paroxysmal nocturnal hemoglobinuria (PNH)



- Paroxysmal nocturnal hemoglobinuria (PNH) is a disease that results from **acquired mutations** in the phosphatidylinositol glycan complementation group A gene (PIGA), an enzyme that is essential for the synthesis of certain membrane-associated **complement regulatory proteins**

- It is the only hemolytic anemia resulting from an acquired genetic defect.
- Mutation in the *PIGA* gene, present on the X chromosome.

Clinical manifestations

- Low level chronic hemolytic anemia
- NOCTURNAL!!!
- Increased risk of thrombosis
- Association with aplastic anemia
- Treatment may place the patient at risk of Niesseria infections.

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D. Thalassemia trait-trans
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4- gallbladder stones are a frequent complication of G6PD deficiency?

TRUE FALSE

5- Paroxysmal nocturnal hemoglobinuria results from an acquired mutation in which of the following genes:

A. Alpha hemoglobin
B. Beta hemoglobin
C. Erythropoietin
D. PIGA
E. G6PD

Thank you