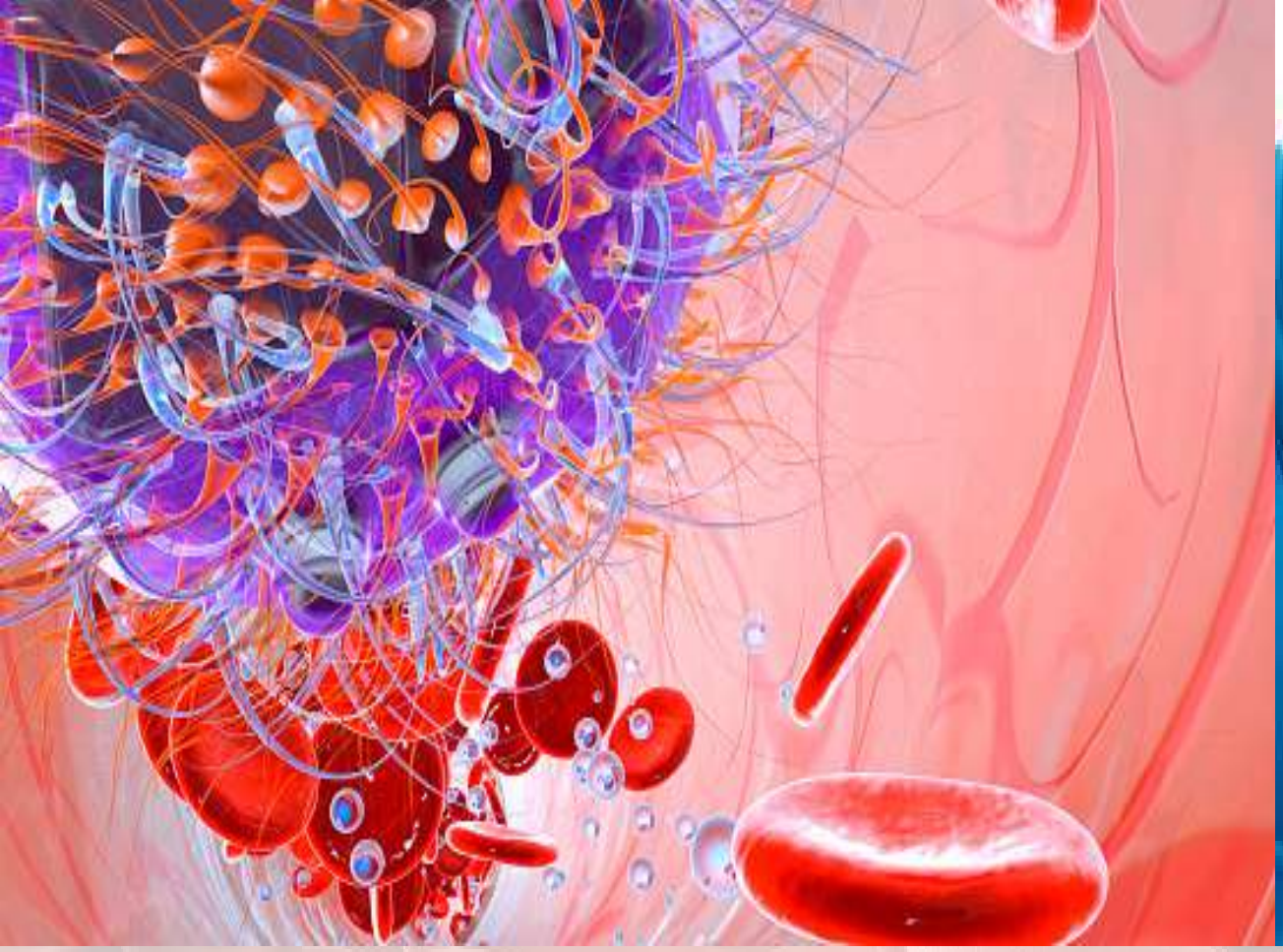
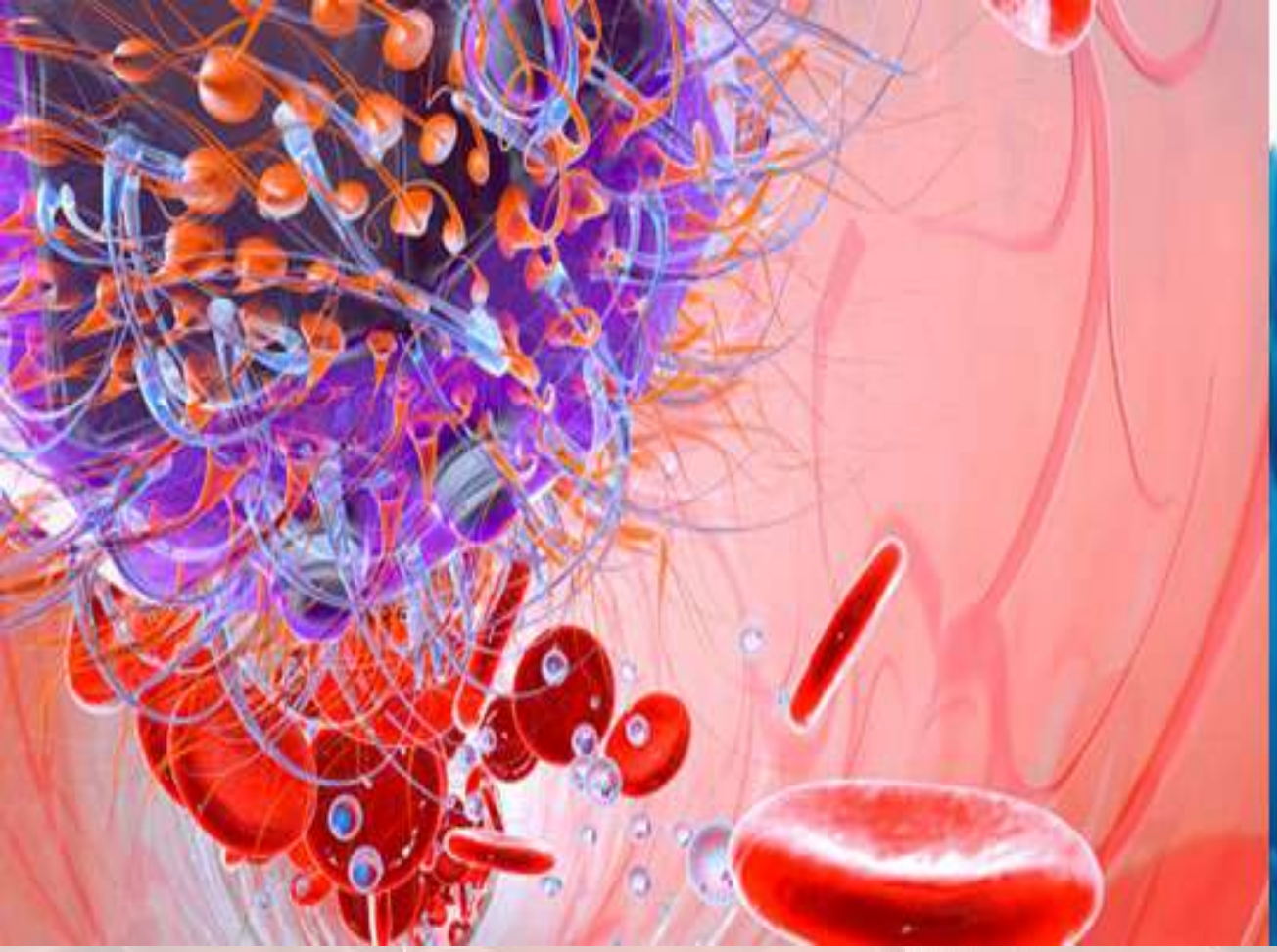


Hematology

"Haematology"

Dr. Abdulsalam A. Al-Ani
4th Year- Under Graduate
Medical College
University of Anbar



Haematology

Hematology

Dr. Abdulsalam Al-Ani
4th Year – Under Graduate
College of Medicine
University of Anbar

Objectives

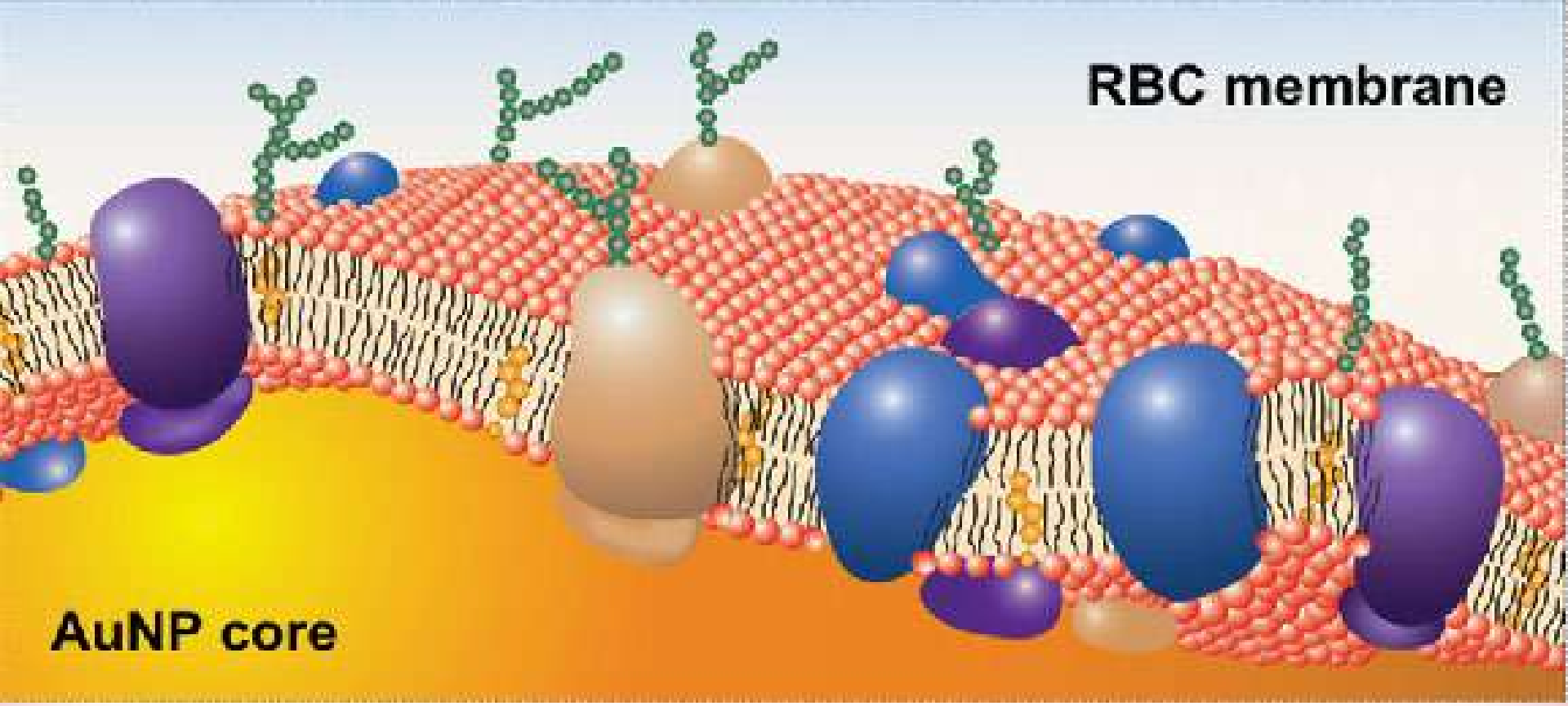
1. Hemopoiesis.
2. **Anemia, Types and Related Disorders.**
3. Granulopoiesis and White Blood Cell Disorders.
4. Hematological Malignancies.
5. Hemostasis.
6. Transfusion Medicine.

Hemolytic Anemia (cont'd):

HEREDITARY HEMOLYTIC ANEMIA:

The inherited HA divided into;

1. Red cell membrane Defects; (eg; spherocytosis (HS), elliptocytosis (HE), pyropoikylocytosis (HPP) and acanthocytosis (HA).
2. Red cell enzymes Defects; (eg; Glocose-6-phosphate dehydrogenase (G6PD) deficiency, and Pyruvate kinase deficiency PK).
3. Hb abnormalities (hemoglobinopathies); thalassemias and sickle cell.

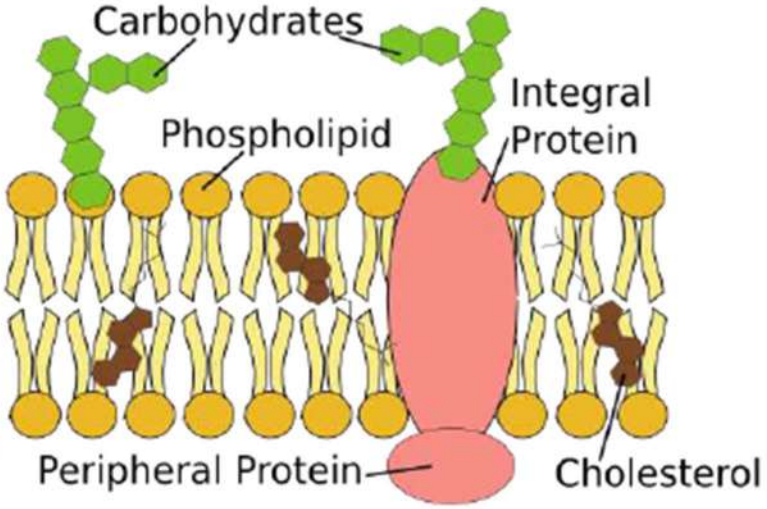


1. Red Cell Membrane Defects Hemolytic Anemia

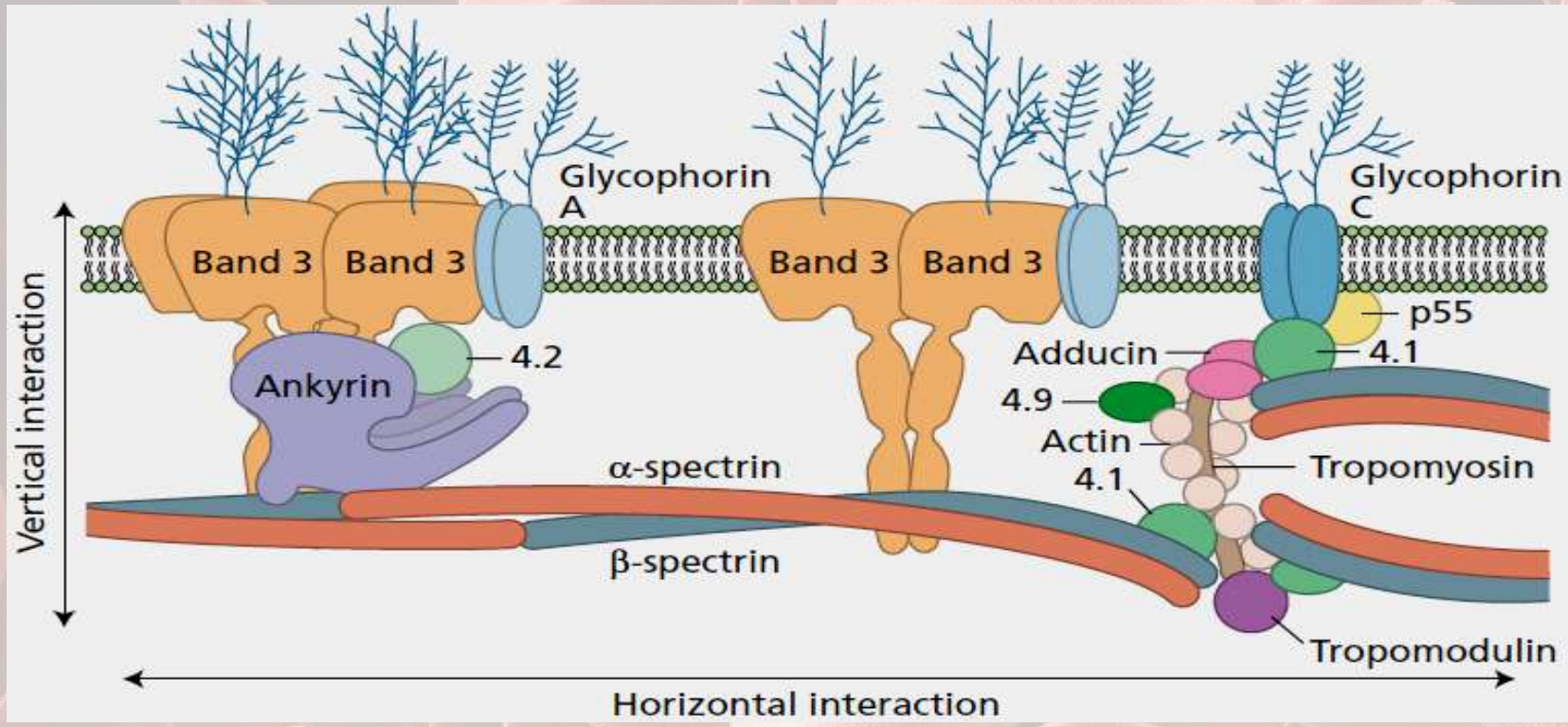
RBC CELL MEMBRANE:

CONSIST OF:

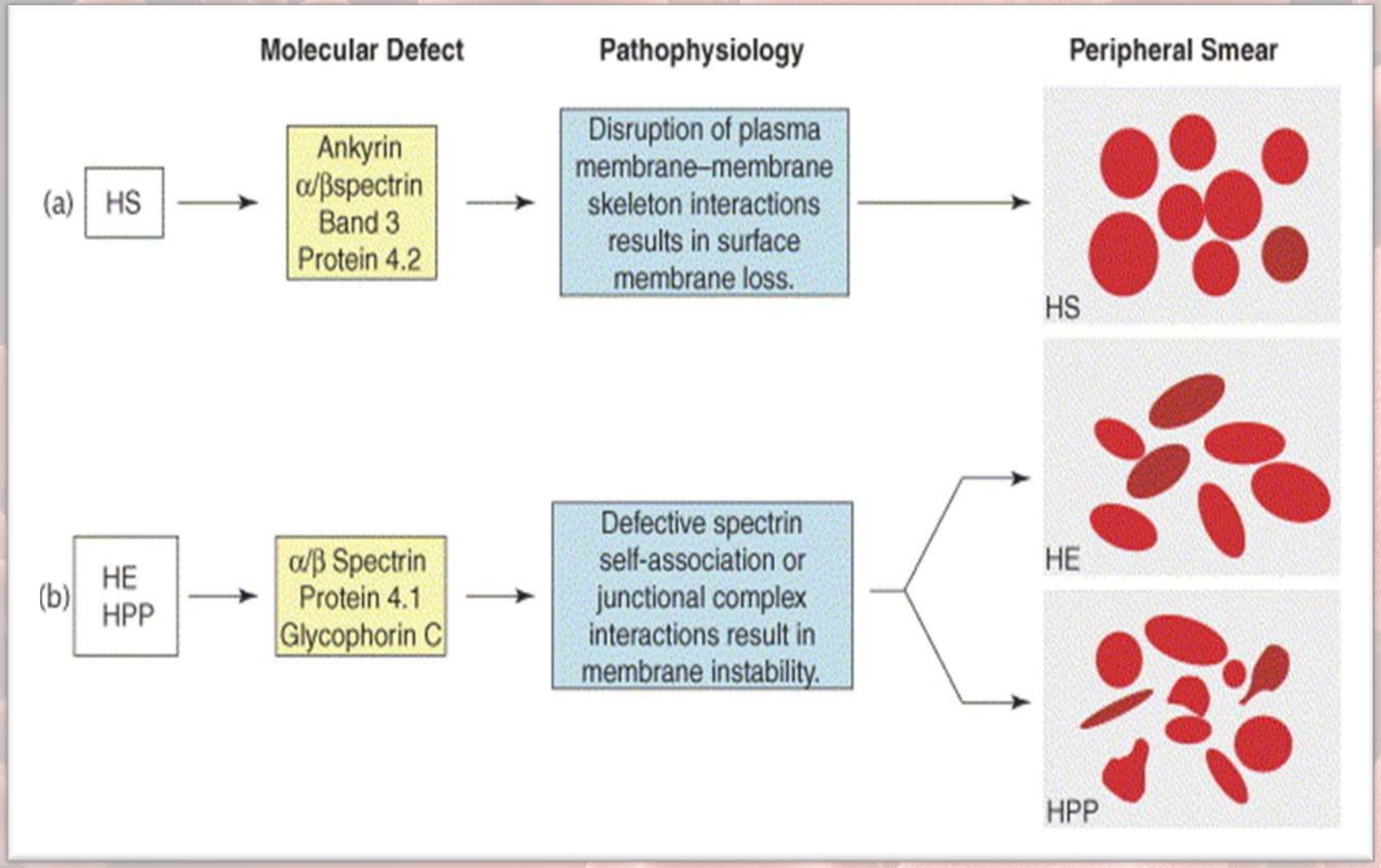
- PROTEIN 50%
- PHOSPHOLIPID 20%
- CHOLESTROL MOLECULES 20%
- CARBOHYDRATE 10%



Normal Red Cell Membrane



- Spectrin consists of two forms; α and β, joined to form a heterodimer with a hairpin structure.
- Ankyrin binds the β spectrin chains to band 3, a large integral membrane protein, while the tail end of spectrin binds to protein 4.1, thus forming spectrin oligomers.
- Protein 4.1 also binds to glycophorin A or aminophospholipids to serve as secondary attachment sites of the cytoskeleton to the inner surface of the bilayer.

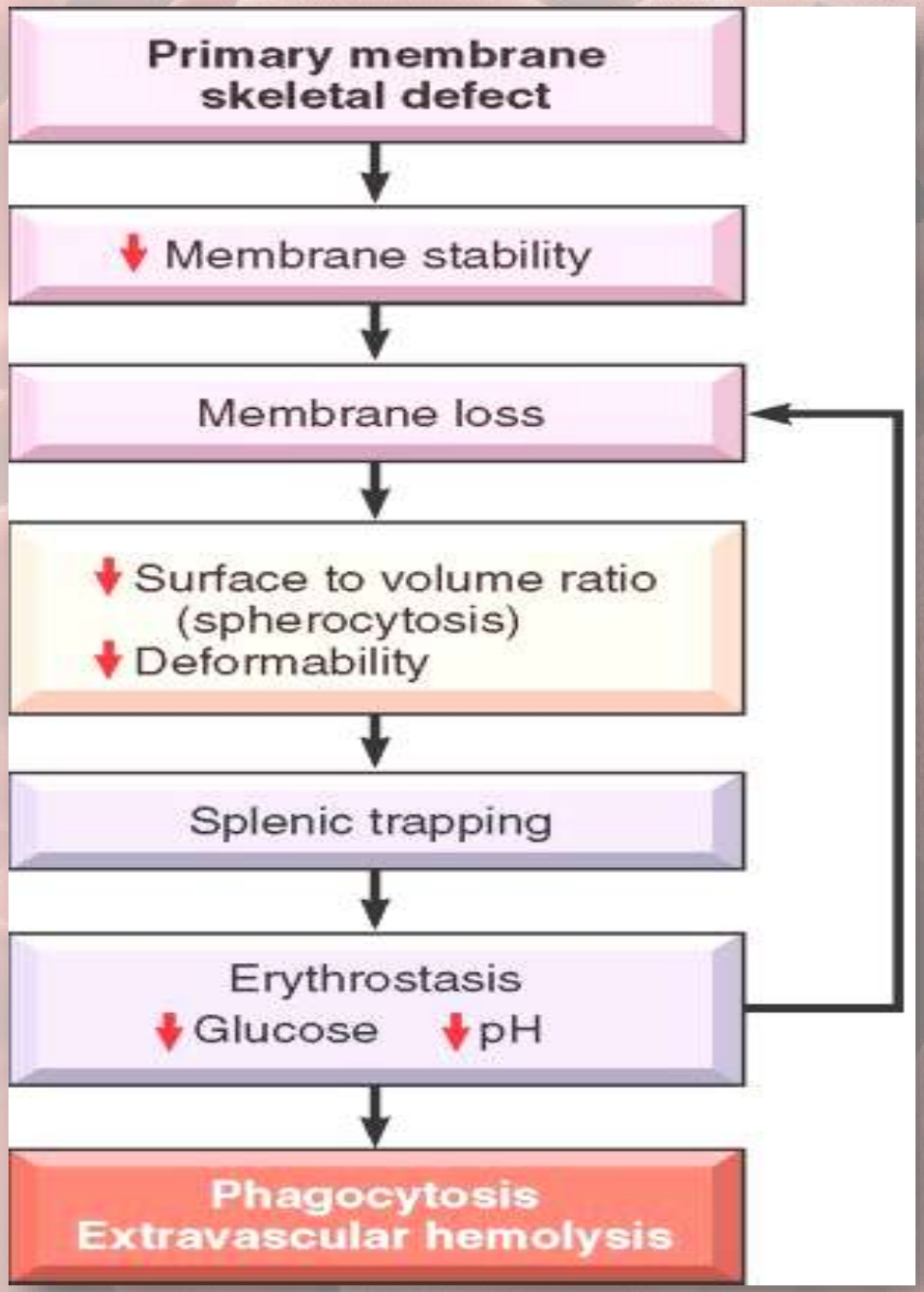


HS; Hereditary spherocytosis, HP; Hereditary Elliptocytosis, HPP; Hereditary Pyropoikylocytosis.

➢ Hereditary Spherocytosis (HS):

- Autosomal dominant (rarely, may be autosomal recessive) inherited hemolytic anemia.
- Usually caused by defects in the proteins (mainly mutation of Ankyrin leads to reduced Spectrin) involved in the vertical interactions between the membrane skeleton and the lipid bilayer of the red cell.
- Characterized by spherocytic RBCs, losing its normal biconcave shape with a low surface area (reduced surface area in relation to the volume) and loss of ability to pass through microcirculation mainly of the spleen and subsequent premature death.

❖ Pathophysiology of HS



❖ Clinical Features:

1- Moderate form; is the most common (70%), the typical type.

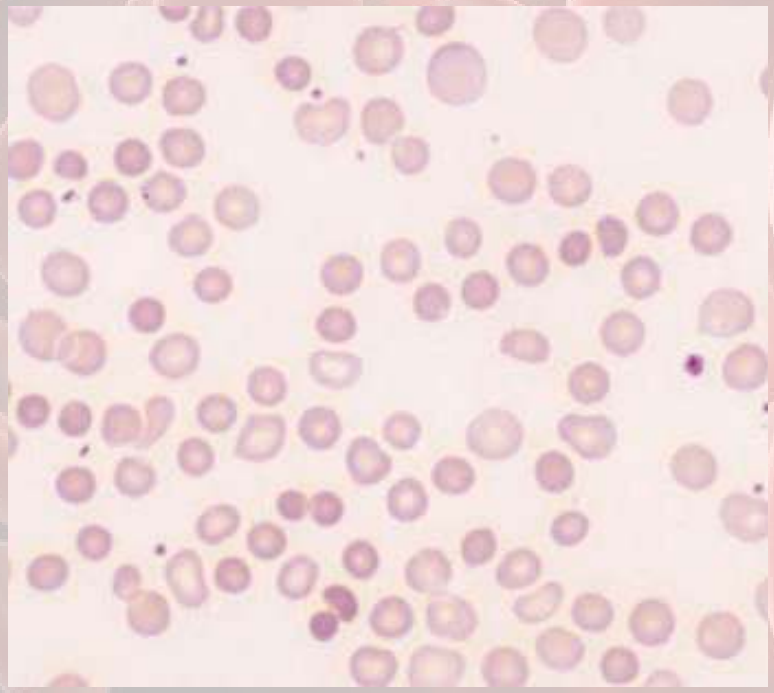
2- Mild HS (20%); no anemia (erythropoiesis compensates for production).

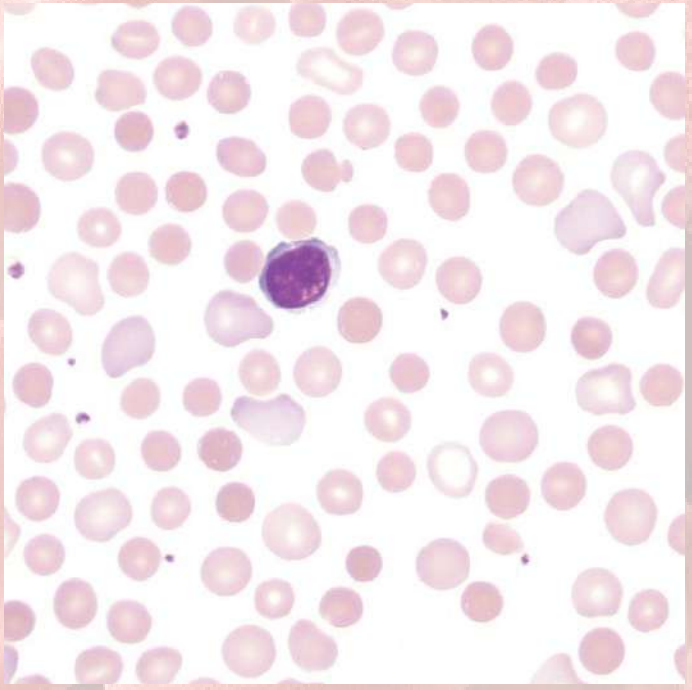
3- Sever form (10%); transfusion dependent.

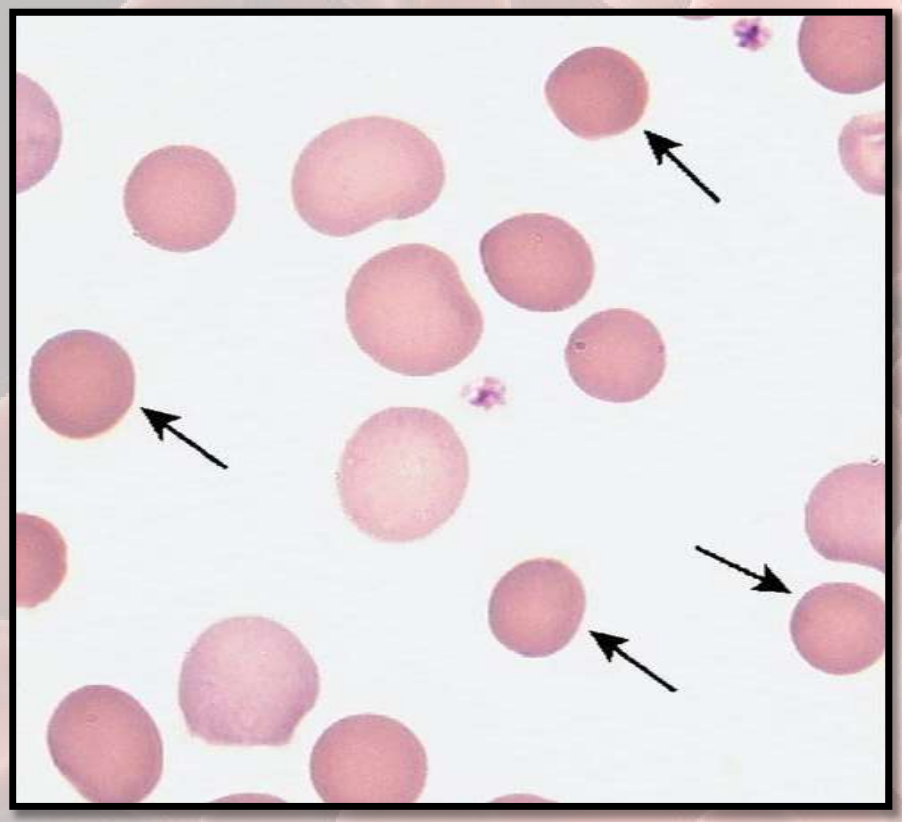
- Anemia at any age. Its severity correlates with the abnormality
- Jaundice.
- Slenomegaly.
- Gall stones.
- May developes; 1- Foot and lower leg ulcers.
  2- A plastic crisis.
  3- Skeletal abnormalities (severe cases).

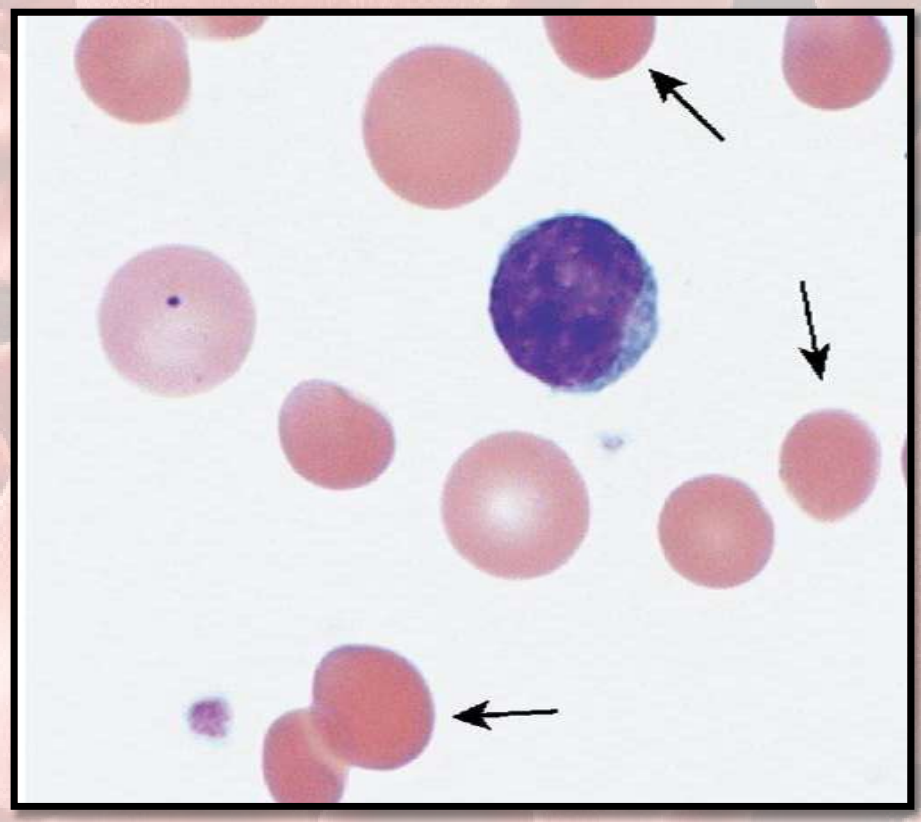
❖ Laboratory Features:

- Low Hb level (nearly similar in the affected family members).
- Reticulocyte count usually between 5-20%.
- Blood film; densely stained microspherocytes and polychromatic cells









Densely stained microspherocytes (arrows) and there small size when compared to a mature lymphocyte

Osmotic fragility test; Its used to measure the ability of the cell to resist lysis in different concentrations of buffer saline

The spherocytic, whether due to HS or other cause are more liable for hemolysis than normal.

Reticulocytes for a tail due to its resistant, while normally 50% conc. the all cells are lysed.

Fluorescent flow cytometric assay (Eosin-maleimide, EMA)

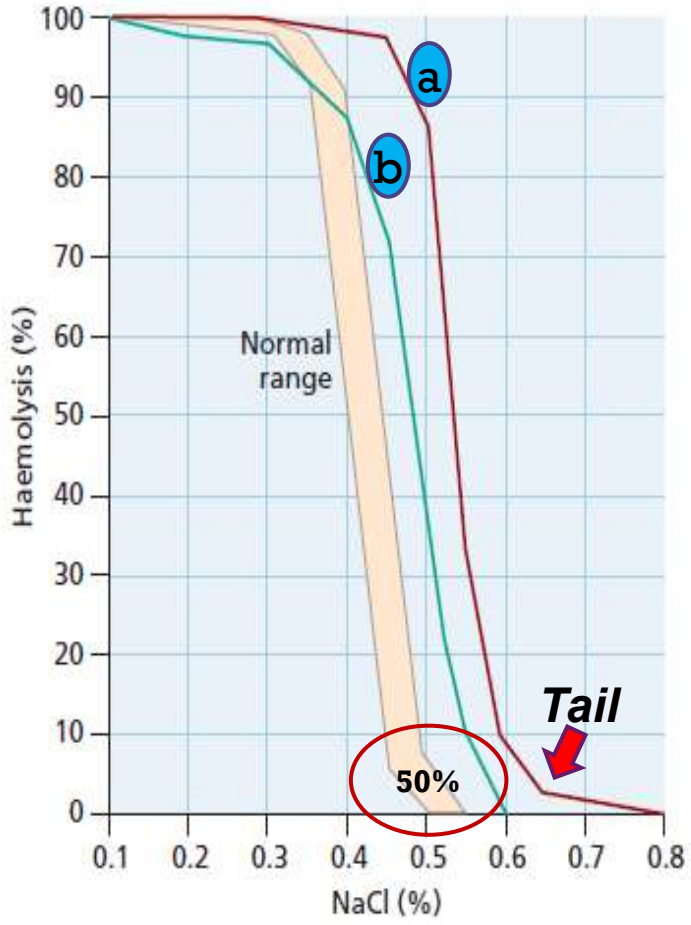
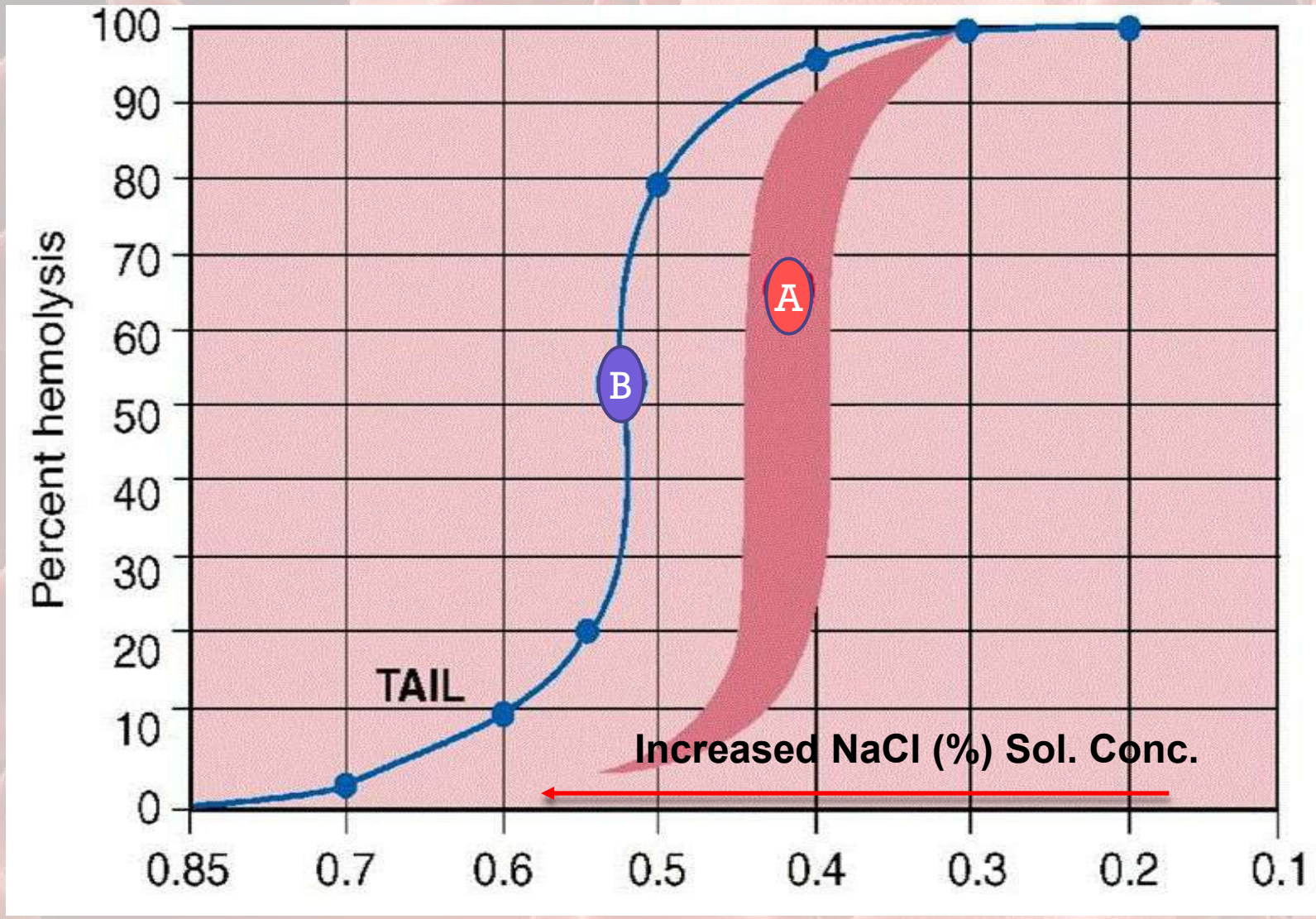
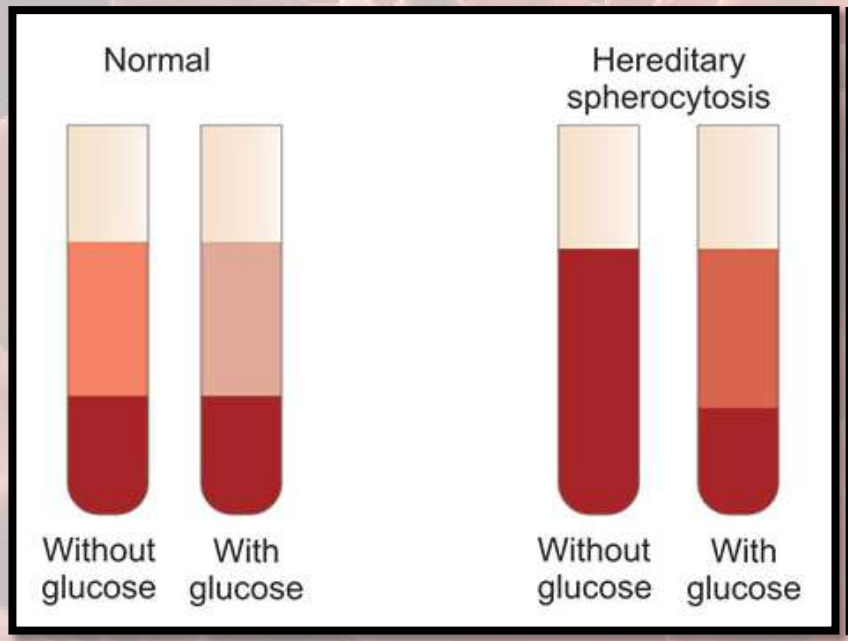
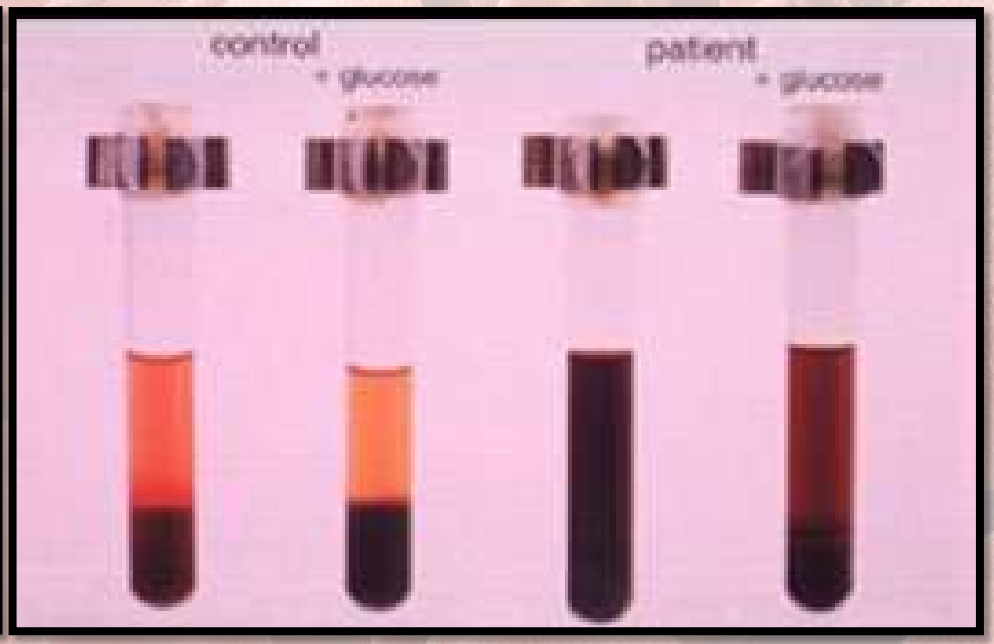


Chart of: Osmotic fragility test in hereditary spherocytosis. Osmotic fragility is increased in the microspherocytes (right shift), but there is also a small population of resistant cells due to increased reticulocytes (a). After splenectomy, the microspherocytes remain, but the proportion of reticulocytes is reduced to normal values and the resistant cells are not seen (b).


Percent hemolysis
100
90
80
70
60
50
40
30
20
10
0
0.85
0.7
0.6
0.5
0.4
0.3
0.2
0.1
A
B
TAIL
Increased NaCl (%) Sol. Conc.

- Autohemolysis test; shows increased lysis of red cells with partially correction by glucose.
- Direct Coombs test (negative, -ve).





Autohemolysis test; hemolysis after incubation of samples at 37°C for 24 hrs. There is increased hemolysis in the patient in comparison with the control. Glucose has given partial correction.

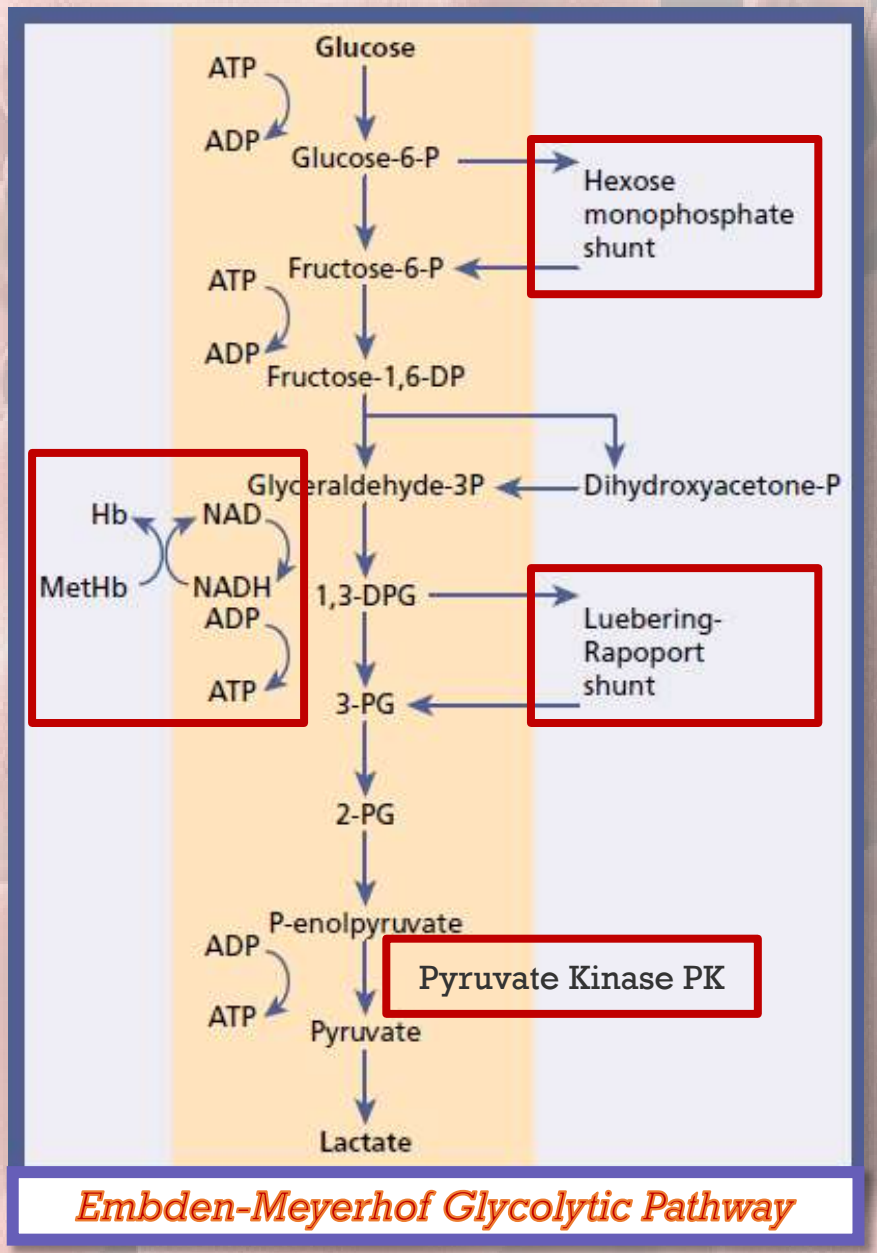
❖ Treatment:

- Splenectomy (laparoscopic); in clinical indications, such as; anemia, gall stone, leg ulcer or growth retardation.
- Avoided as much as possible in early childhood (below 5 years), because the possibility of sepsis and if performed, vaccination for serious bacteria highly recommended.
- Cholecystectomy (gallstones).

2. Red Cell Metabolism Defects Hemolytic Anemia

Normal Red Cell Metabolism:

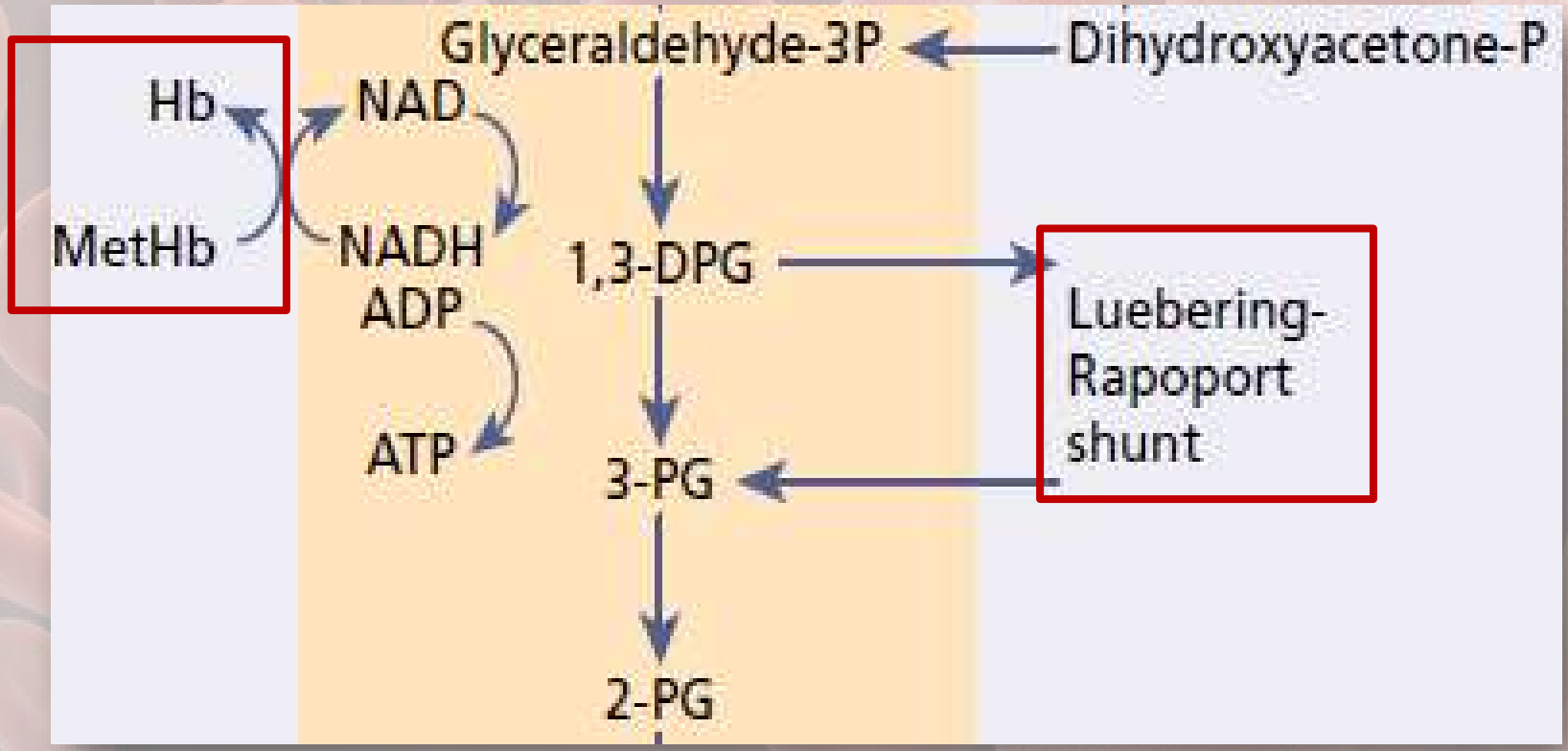
Erythrocyte has no nucleus, no mitochondria, and no organelles to allow it to undergo aerobic respiration. As a result, the cell is dependent on glycolysis (*Embden-Meyerhof glycolytic pathway)* to produce energy in the form of ATP and make energy to support the cell during its 120-day life cycle, maintaining cell shape and flexibility as well as cation and water content through the action of sodium and calcium pumps.



Embden-Meyerhof Glycolytic Pathway

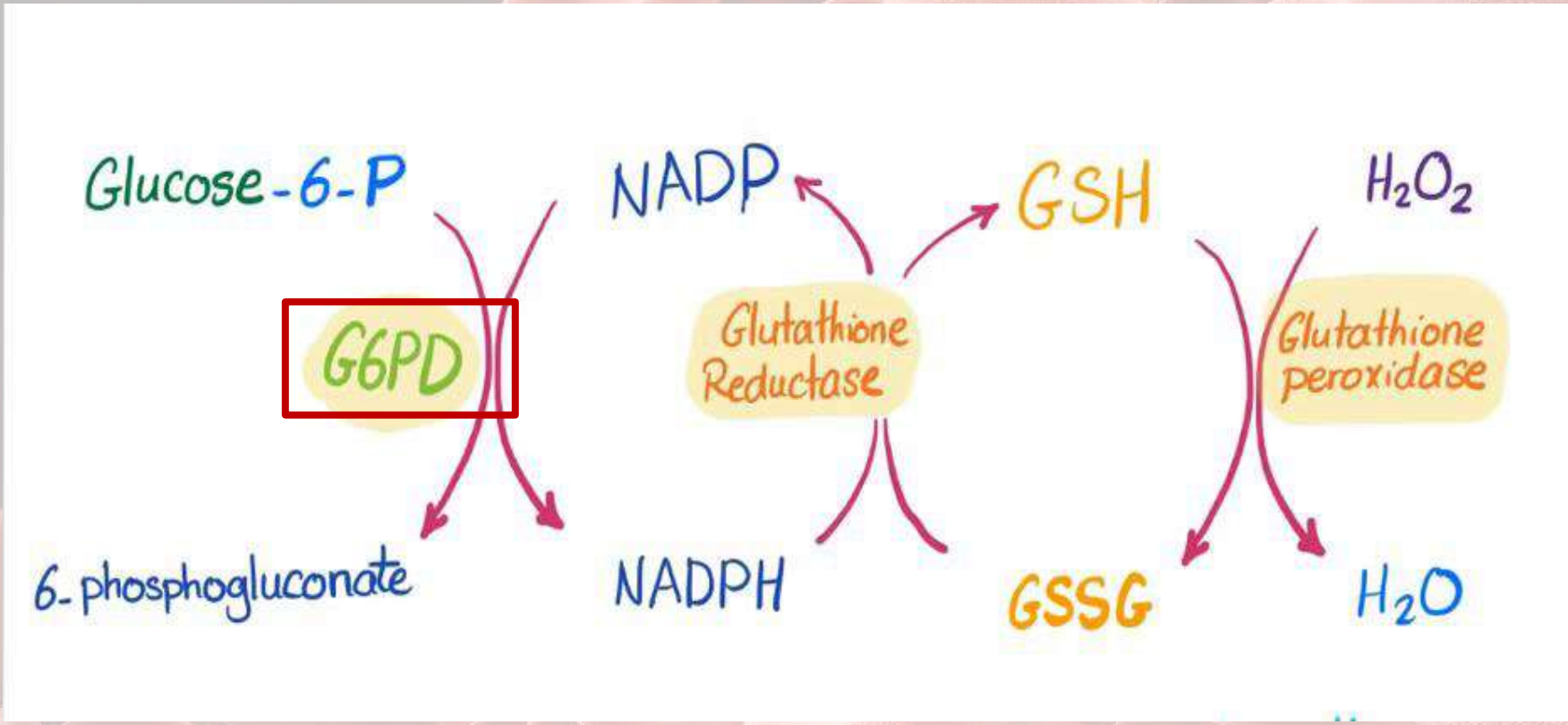
Under normal conditions, some oxidation of Hb to methemoglobin occurs, but an enzyme system, NADH-methemoglobin reductase, in the RBC converts methemoglobin back to Hb.

The **Luebering-Rapoport shunt** provides 2,3-DPG for control of hemoglobin oxygen affinity.

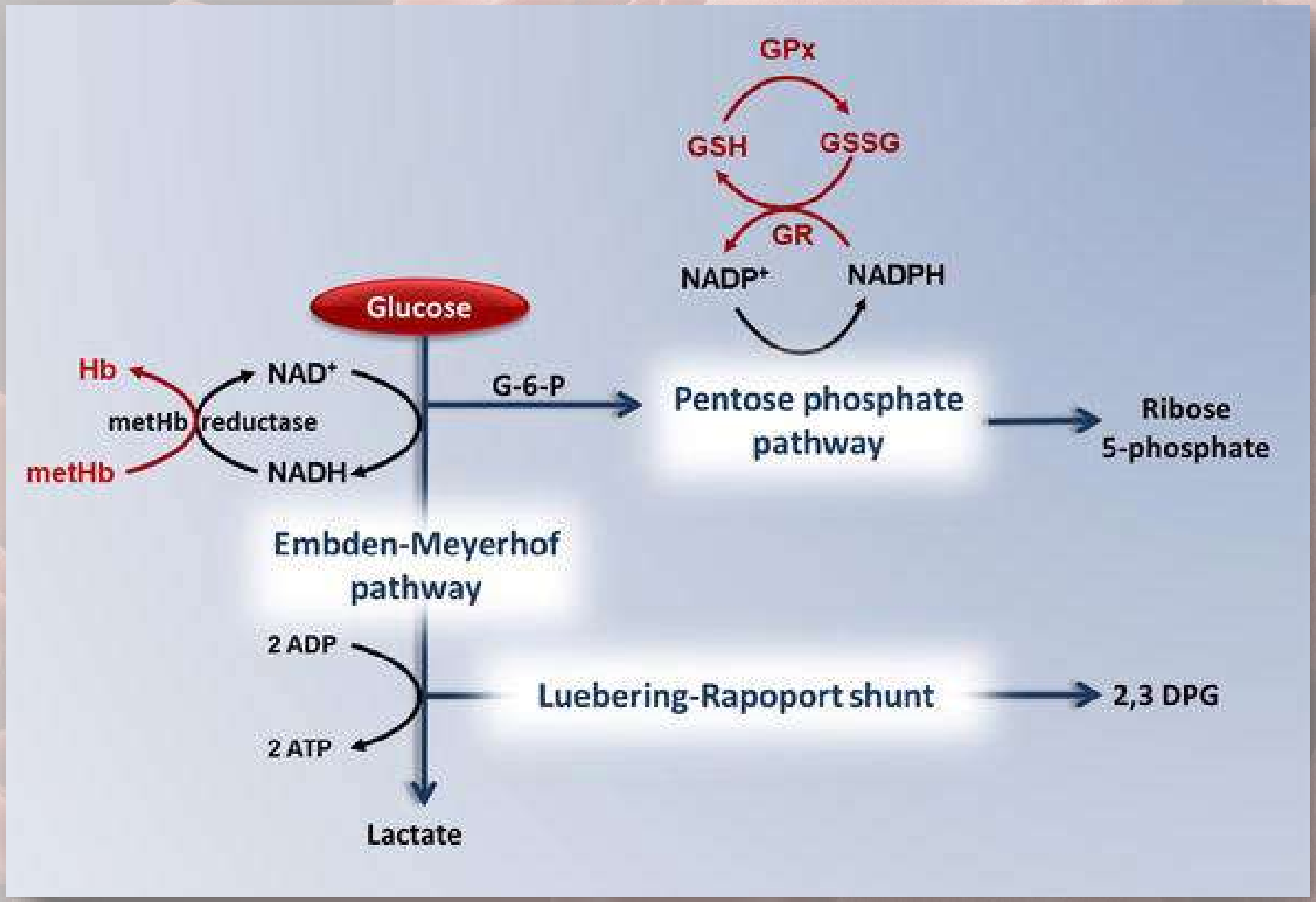


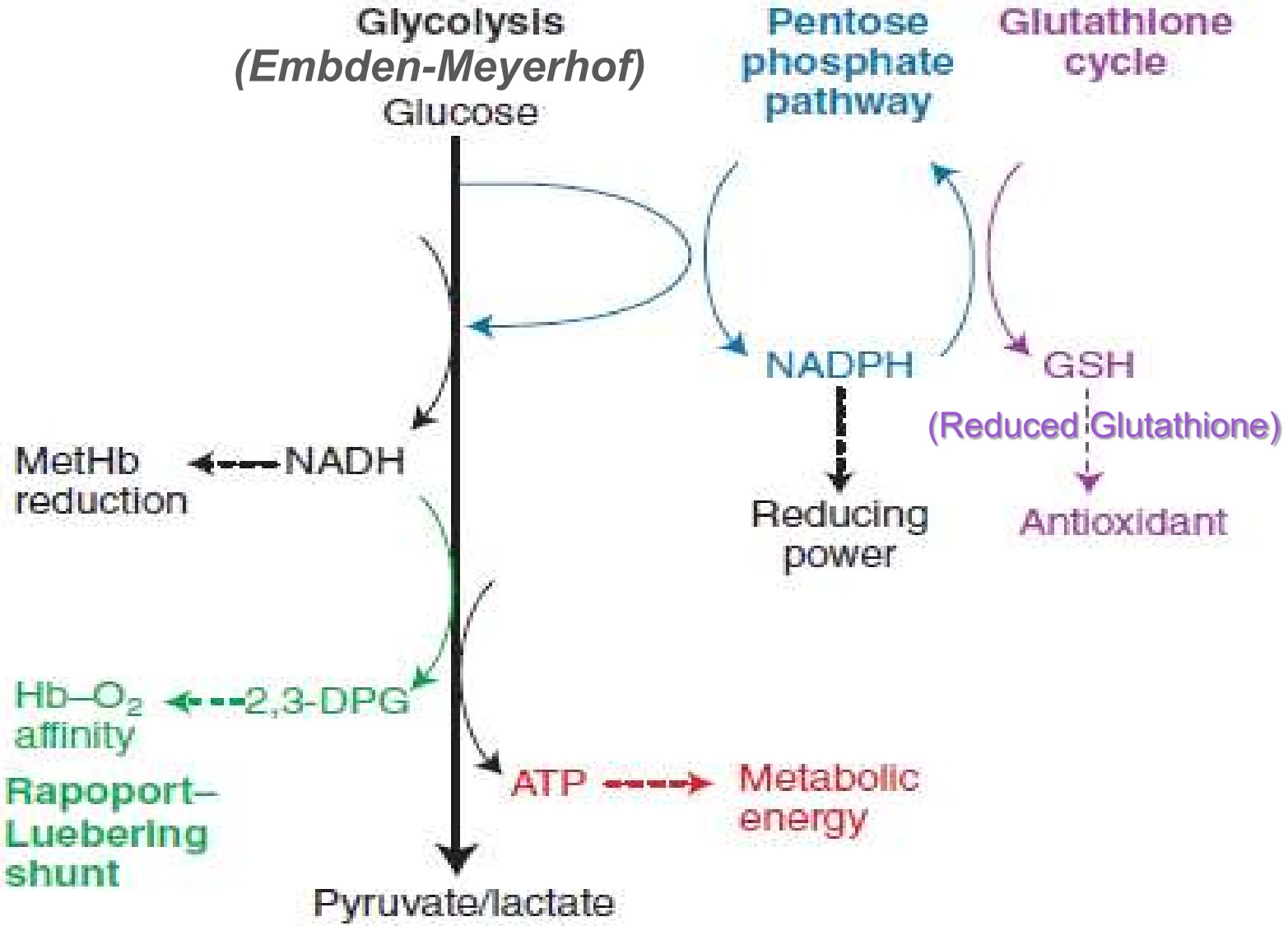
Pentose phosphate pathway (hexose monophosphate shunt); by which the red blood cells are capable of limited aerobic glycolysis. Its major role is the generation of reduced nicotinamide adenine dinucleotide phosphate (NADPH). Erythrocyte NADPH converts oxidized glutathione (GSSG) to reduced glutathione (GSH), the major red blood cell antioxidant.

Red blood cell hemoglobin, are protected from oxidant damage through the action of glutathione, which maintains hemoglobin in a reduced, active form, preventing its oxidizing effects.



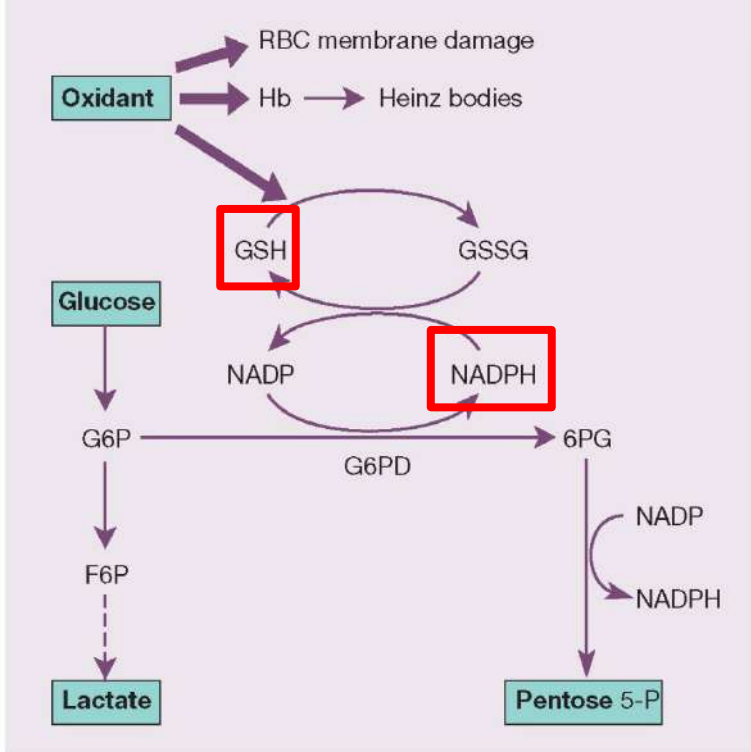
Reducing power is produced by the pentose phosphate pathway which linked to redox reactions through the glutathione cycle. The disposal of H_2O_2, a potential oxidant, is dependent on the adequacy of reduced glutathione (GSH), which is generated by the action of the reduced form of nicotinamide adenine dinucleotide (NADPH). The synthesis of NADPH is dependent on the activity of G6PD.

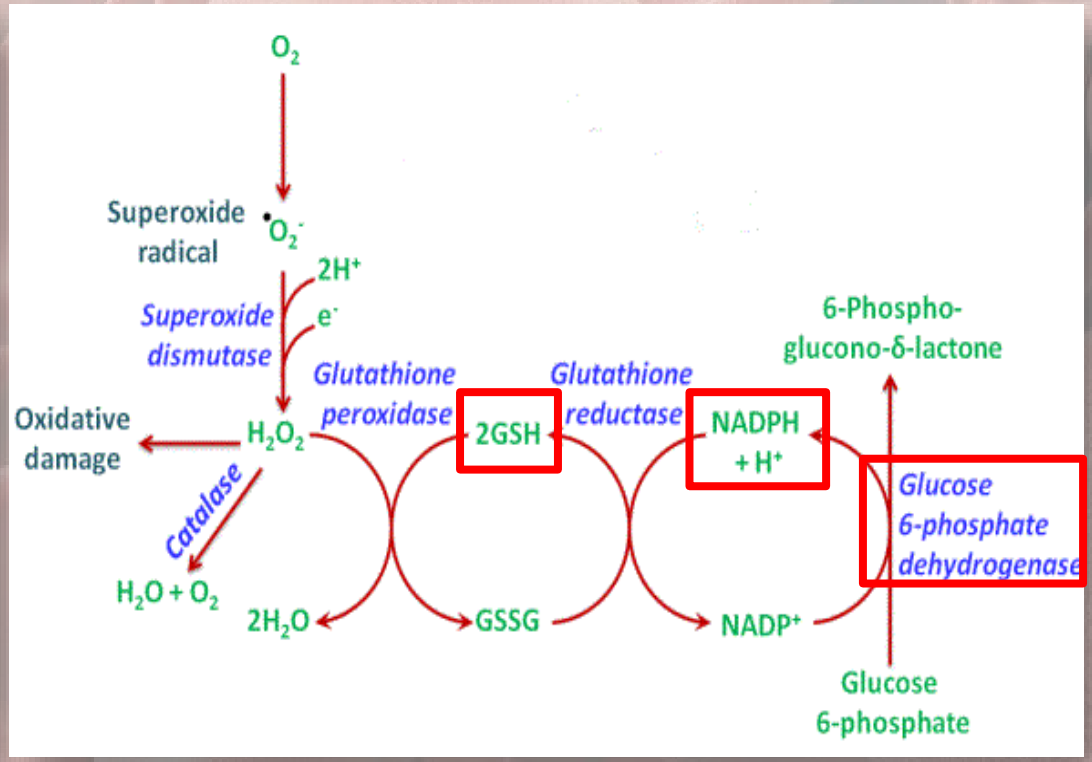

GPx
GSH
GSSG
GR
NADP+
NADPH
Glucose
Hb
NAD+
metHb
reductase
metHb
NADH
G-6-P
Pentose phosphate pathway
Ribose 5-phosphate
Embden-Meyerhof pathway
2 ADP
2 ATP
Luebering-Rapoport shunt
2,3 DPG
Lactate


Glycolysis
(Embden-Meyerhof)
Glucose
Pentose phosphate pathway
Glutathione cycle
NADPH
GSH
(Reduced Glutathione)
MetHb reduction
NADH
Reducing power
Antioxidant
Hb–O2 affinity
2,3-DPG
Rapoport–Luebering shunt
ATP
Metabolic energy
Pyruvate/lactate

➢ Glucose-6-phosphate Dehydrogenase Deficiency (G6PD):

- Commonest hereditary defective RC metabolism all over the world (400 million), in Iraq about 6.5-8.0%.
- Sex-linked inheritance (affected males and carried by females
- Variable G6PD level according to the genetic variant, mostly A in African and B in Western, in addition to more than 400 variants. In Iraq the most common type called Mediterranean variant.
- Main effect of this deficiency related to the cell susceptibility to the oxidant stress (free radical formation). This due to the reduction of NADPH (reduce nicotinamide adenine dinucleotide phosphate), which is important for the formation of GSH (reduced glutathione).





Hemoglobin and red blood cell (RBC) membranes are usually protected from oxidant stress by reduced glutathione (GSH). In G6PD deficiency, NADPH and GSH synthesis is impaired.

F6P;fructose-6-phosphate, G6P;glucose-6-phosphate, G6PD; glucose-6-phosphate dehydrogenase, GSSG; glutathione (oxidized form), NADP; nicotinamide adenine dinucleotide phosphate.

❖ Clinical Features:

Can be in one of the following forms;

- Chronic non-spherocytic HA (CNSHA); occurs in cases with sever deficiency with chronic HA and attacks of exacerbations.

- Favism; in moderate to sever deficiency. Characterized by cute attack of HA, mostly of intravascular, due to the oxidative effect of fava beans. Affect any age with variable degrees according to the level of the enzyme. Associated with features of hemolysis and in sever cases with loin pain. Mostly of intravascular hemolysis, which can be fatal due to acute renal failure. It also may induced by infection or use of the oxidative drugs (long list, mostly; antimalarial, sulphonamides ..etc.)

In this form also presented as a neonatal jaundice.

- Asymptomatic, in certain variants usually if there is no oxidant stress.

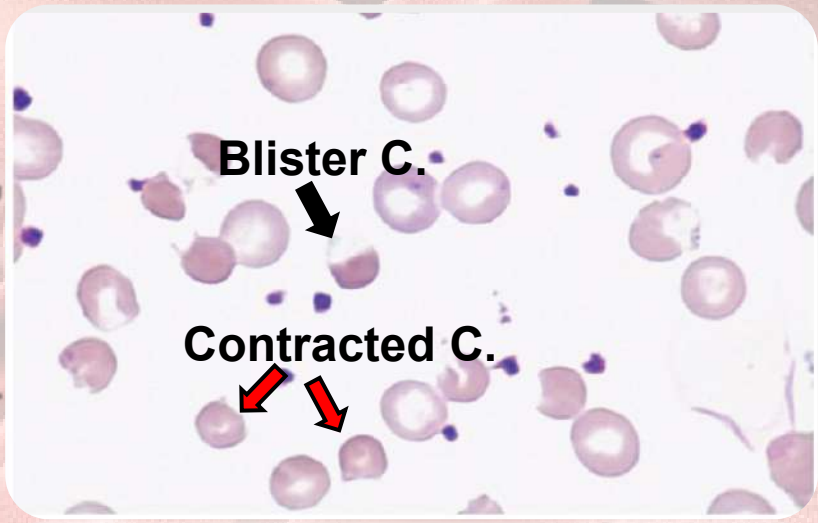
World Health Organization classification of G6PD deficiency (1989).

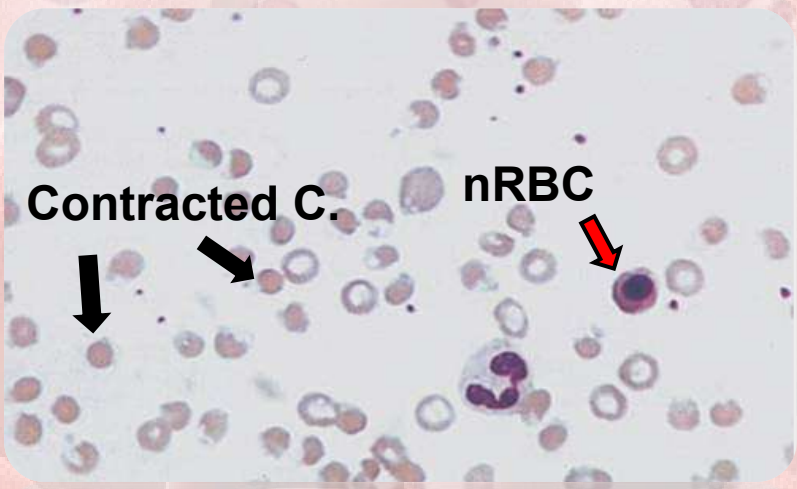
Class	Enzyme activity (% normal)	Examples	Clinical effects
I	Severe (usually <2)	Santiago de Cuba (Gly447Arg)	CNSHA, acute exacerbations
II	<10	Mediterranean (Ser188Phe) Canton (Arg459Leu) Orissa (Ala44Gly)	Favism, acute intravascular haemolysis (drug induced), neonatal jaundice
III	Moderate (>10, <60)	A− (Val68Met, Asn126Asp)	Acute intravascular haemolysis (drug induced), neonatal jaundice
IV	100	B (wild type) A (Asn126Asp)	None None
V	150	//	None

CNSHA, congenital non-spherocytic haemolytic anaemia.

❖ Laboratory Features:

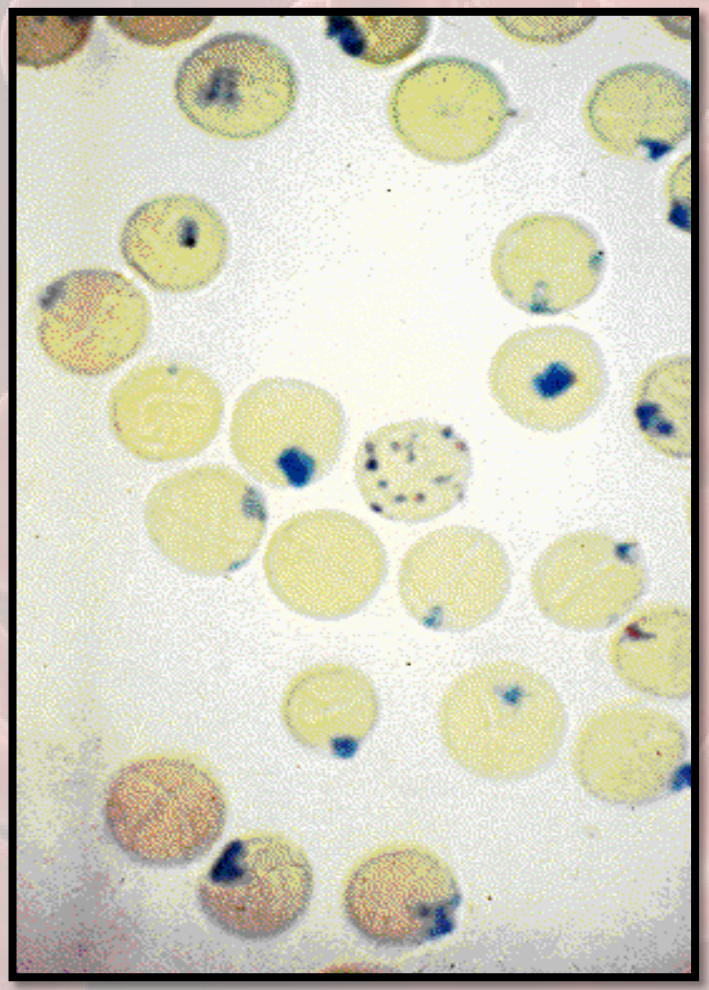
- Normal between the attacks, except of low G6PD level.
- Blood film; irregular contracted cells, fragmented, blister cells.
- Nucleated RBCs/erythroblastemia may be seen.
- Heinz bodies (oxidized denatured Hb) a feature
- High reticulocyte count.

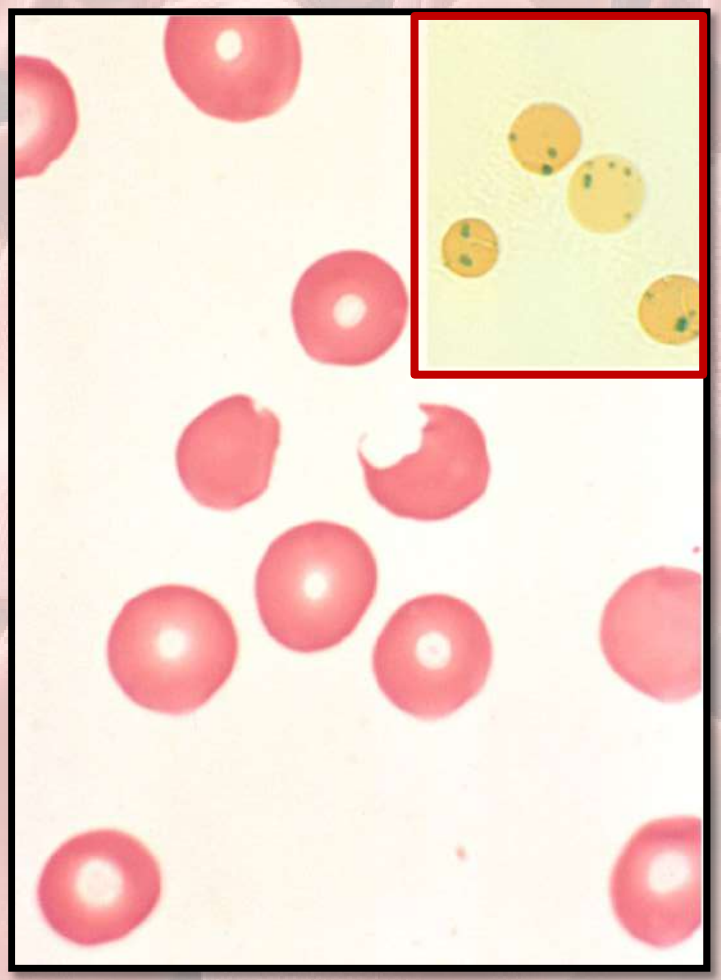




- Intravascular hemolytic features; Hbemia and Hburia.
- Normal G6PD level, during the attack of hemolysis (crisis),because of it's high level in the young erythrocytes.

Heinz body preparation is positive. Heinz bodies represent denatured hemoglobin; multiple blue–green spherical inclusions develop on exposure to brilliant cresyl blue or New Methylene blue as in reticulocyte preparations.





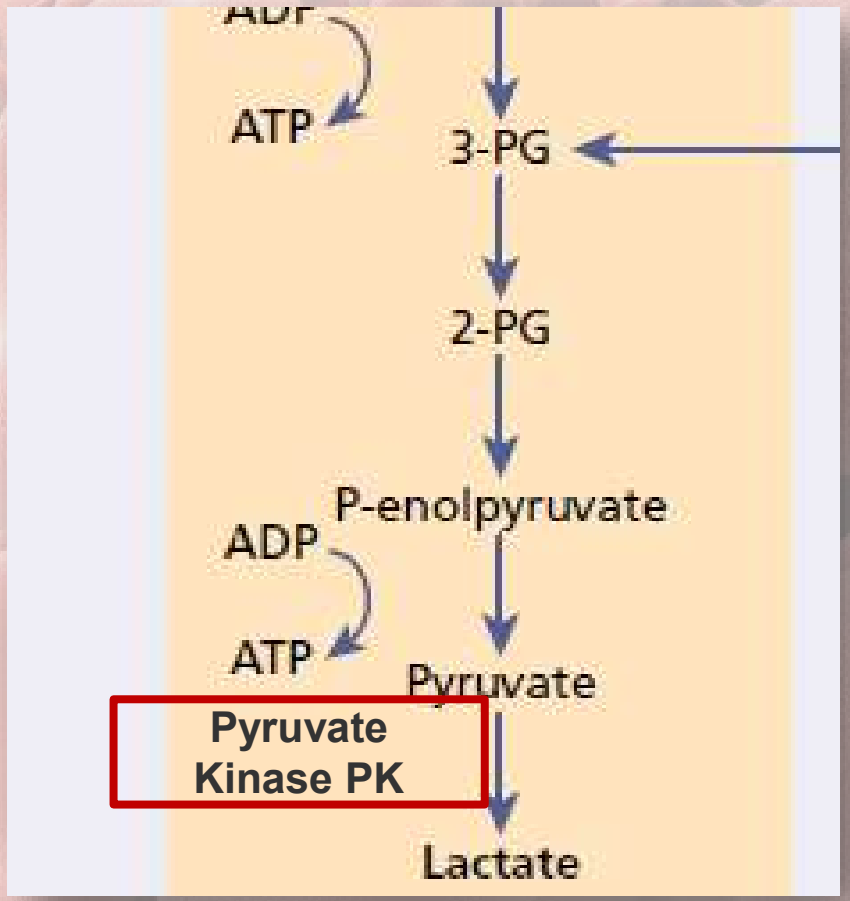
❖ Treatment:

- Avoid the cause (Fava or drugs).
- Close observation of urine output.
- Blood transfusion (may be in severe life-threatening hemolysis).
- Neonatal jaundice may treated by phototherapy or exchange transfusion.

➢ Pyruvate Kinase Deficiency

Disease of genetic heterogeneity with wide variations in the phenotype.

Its deficiency leads to accumulation of 2,3-DPG with shifts of the oxygen dissociation curve to the right, indicating low oxygen affinity.



The presenting features ranging from very mild or fully compensated anemia to life-threatening neonatal anemia and jaundice.

The hemolysis is nearly always extravascular.

Red cell morphology is often unremarkable (no profound changes), with some degree of anisocytosis, poikilocytosis and polychromasia (reticulocytosis).


thank you
danke
謝謝
merci
gracias
obrigado
dziękuję
bedankt
mauruuru
hvala
sukriya
kop khun krap
go raibh maith agat
teşekkür ederim
ngiyabonga
شكراً جزيلاً
спасибо
рахмат
Баярлалаа
dank je
tapadh leat
mochchakkeram
merci
grazie
arigatô
dakujem
terima kasih
sagolun
tack
barka
mersi
welalin
spas
mahalo
paldies
grazzi
misaotra
matondo
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dèkuji
mèsi
didi madloba
kam sah hamnida
najis tuke
rahmat
তোমাকে ধন্যবাদ
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xièxie
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dhanyavadagalu
shukriya
merce
мерси
trugarez
takk
taiku