Diyala University – collage of medicine
Hematology -5th stage

Hemolytic disorders part 2

By:
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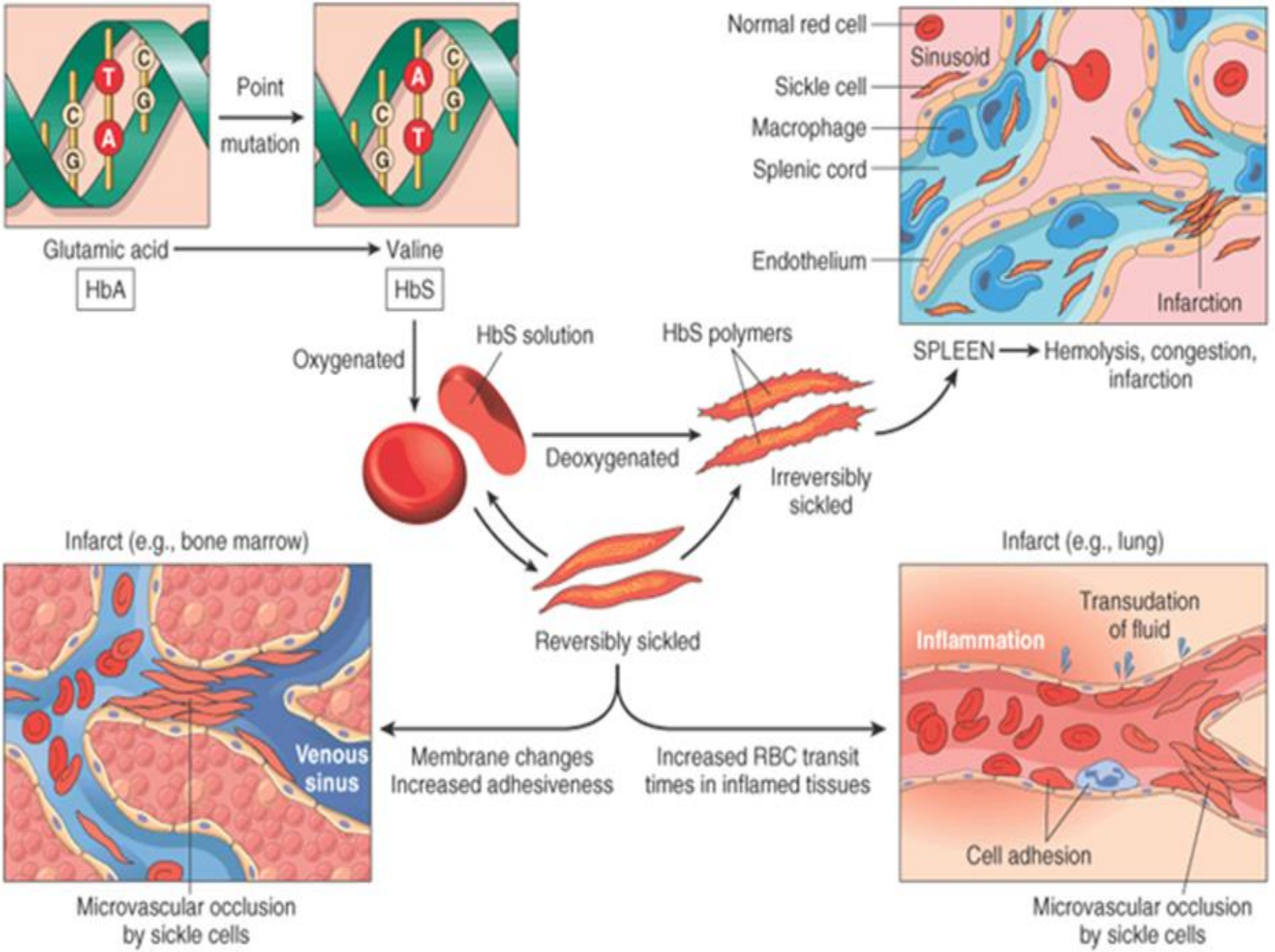
Sickle cell Disorders

* Disorders characterized by red cells which undergo sickling upon deoxygenation
* Sickling is due to presence of Hemoglobin S
* It is common in Black population, and in Southern Iraq, especially in basrah

Normal β- chain	Amino acid	pro	glu	glu
	Base composition	CCT	GAG	GAG
Sickle β- chain	Base composition	CCT	GTG	GAG
	Amino acid	pro	val	glu

Pathophysiology of Sickling syndromes

1. Vaso-occlusion result from deoxygenation of HbS
2. Repeated or prolonged sickling progressively damages the red cell membrane
3. dehydration of red cells producing increase intracellular hemoglobin concentration
4. the red cells become abnormally adherent to the vascular endothelium
5. membrane of RC may be sufficiently damage lead to irreversible sickling and these cells are destructed by spleen leading to HA.


T
C
C
G
A
G
Point
mutation
C
A
C
G
T
G
Glutamic acid
Valine
HbA
HbS
Normal red cell
Sinusoid
Sickle cell
Macrophage
Splenic cord
Endothelium
Infarction
SPLEEN
Hemolysis, congestion, infarction
Oxygenated
HbS solution
HbS polymers
Deoxygenated
Irreversibly sickled
Reversibly sickled
Infarct (e.g., bone marrow)
Venous sinus
Microvascular occlusion by sickle cells
Membrane changes
Increased adhesiveness
Increased RBC transit times in inflamed tissues
Infarct (e.g., lung)
Inflammation
Transudation of fluid
Cell adhesion
Microvascular occlusion by sickle cells

Forms of sickling syndromes:

1. Sickle cell anemia (HbSS)
2. Sickle cell trait (HbSA)
3. Sickle cell thalassemia
4. Sickle cell/Hb C (SC)
5. HbS/ other variant of Hb

Clinical features of SCD

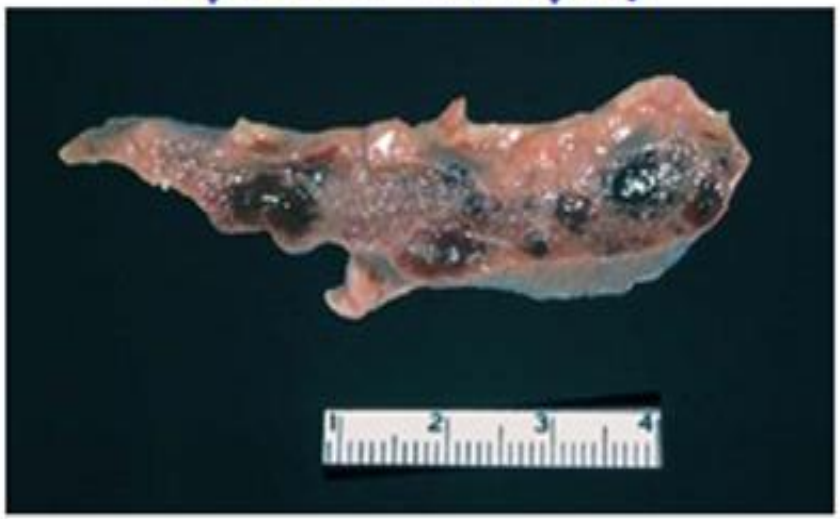
- Extremely variable, features will not be apparent until the age of 4-6 months, and is characterized by variable degree of anemia, jaundice and splenomegaly, extenuated by episodes of sickle cell crisis
- Splenomegaly occurs initially followed by auto splenctomy by gradual infarction
- In Iraq SCA is milder with more SM than that in Africa, but less leg ulceration.
- SC trait is resistant to Falciparum malaria.

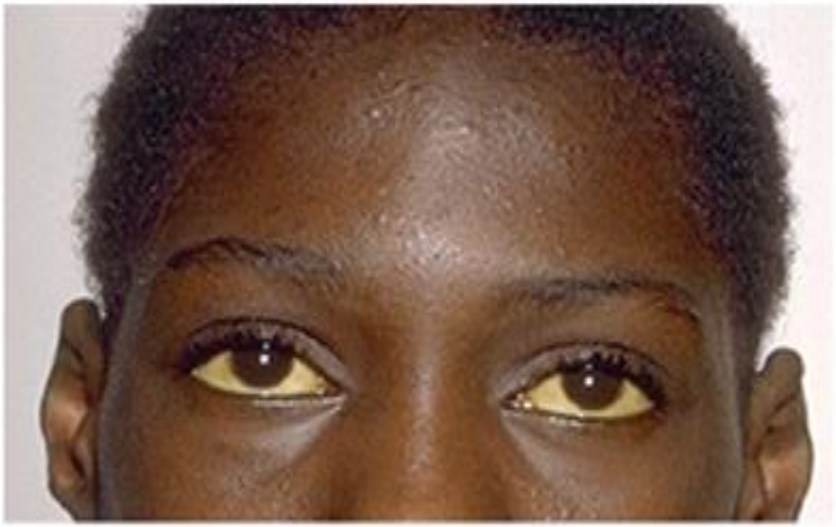
- **Sickle cell crisis** is any new syndrome developing rapidly in a patient with sickle cell disease, they include:
  - Vaso - occlusive crises
  - Acute Sequestration Crisis
  - Aplastic Crisis
  - Hemolytic crisis

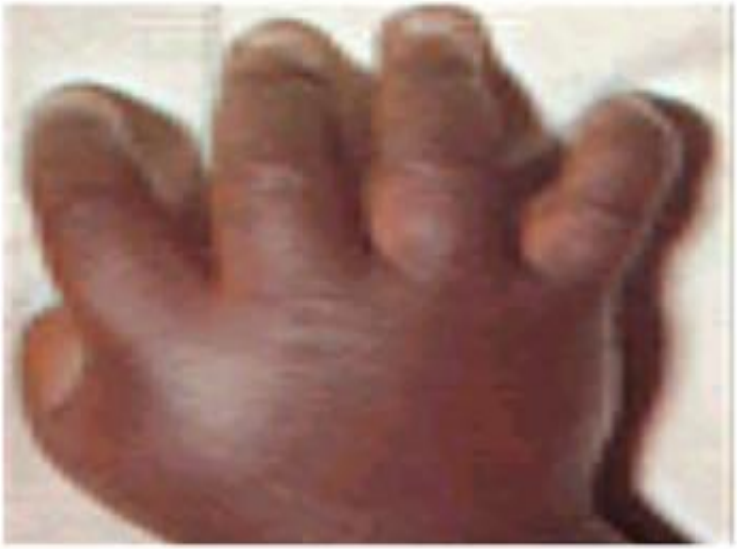
❑Other features of SCD

- Infections: especially by pneumococci, meningococci and H-influenzae.
- Proliferative sickle retinopathy.
- Cholelithesis (Due to indirect hyperbilirubinaemia), liver abscess.
- Avascular necrosis of femoral head, disfigurement, joint swelling.
- Leg ulceration.
- Decrease in growth and development.
- Renal complication.

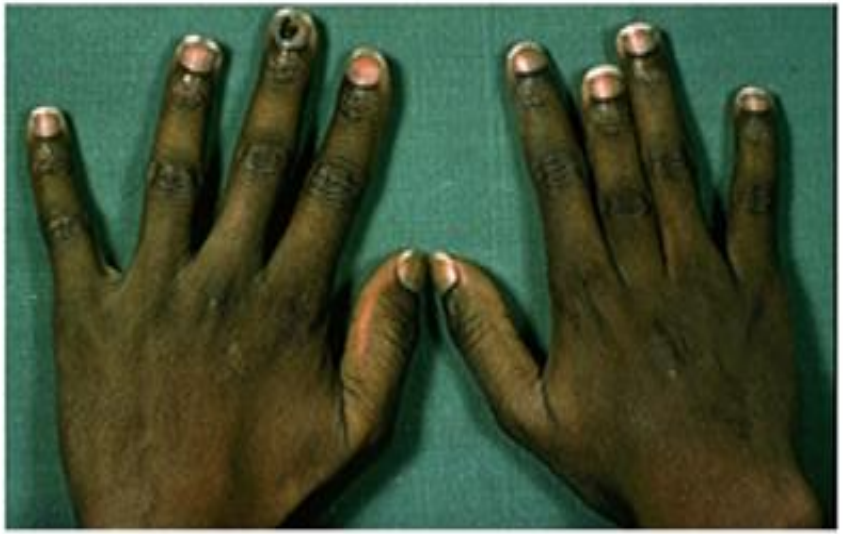
Splenic atrophy





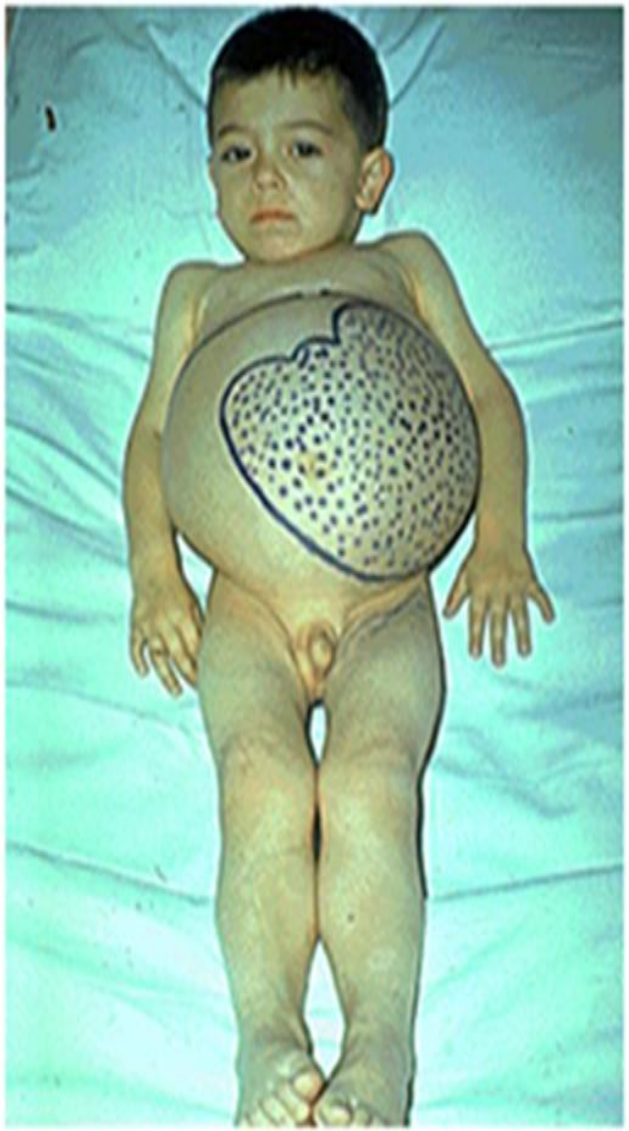


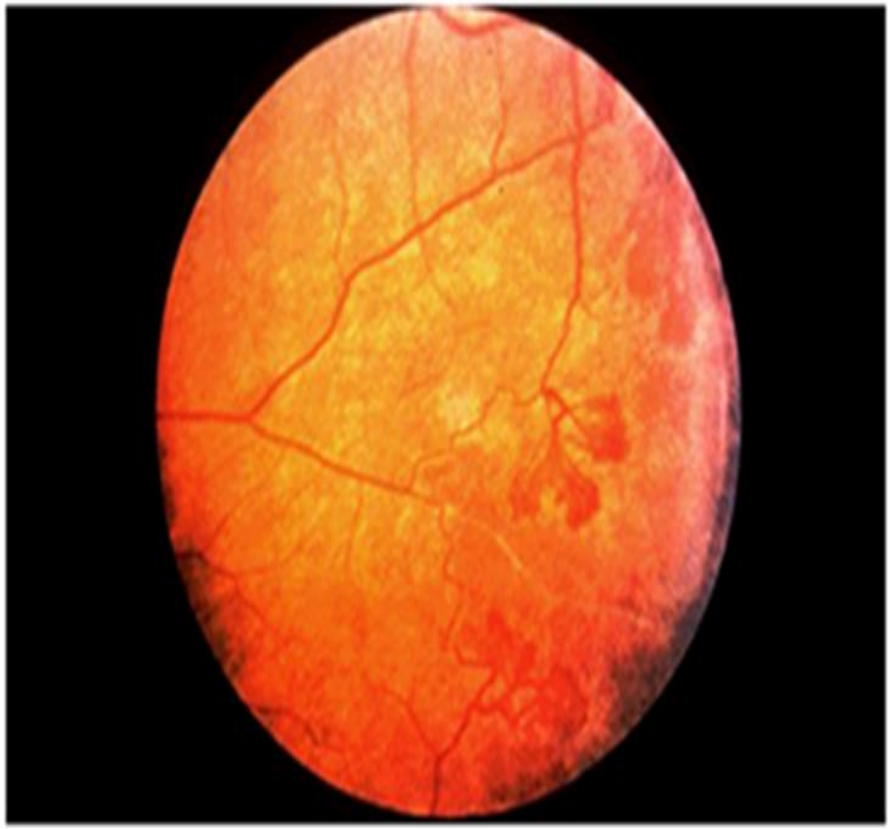
Hand foot syndrome



Sequel of Hand foot syndrome

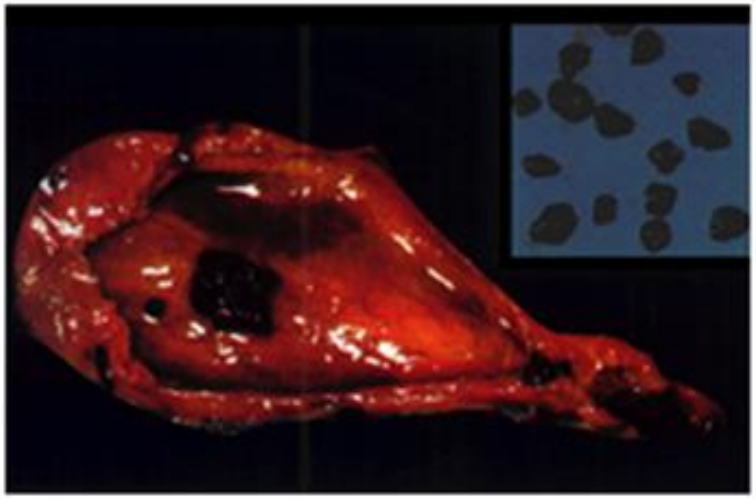
Sequestration Crisis

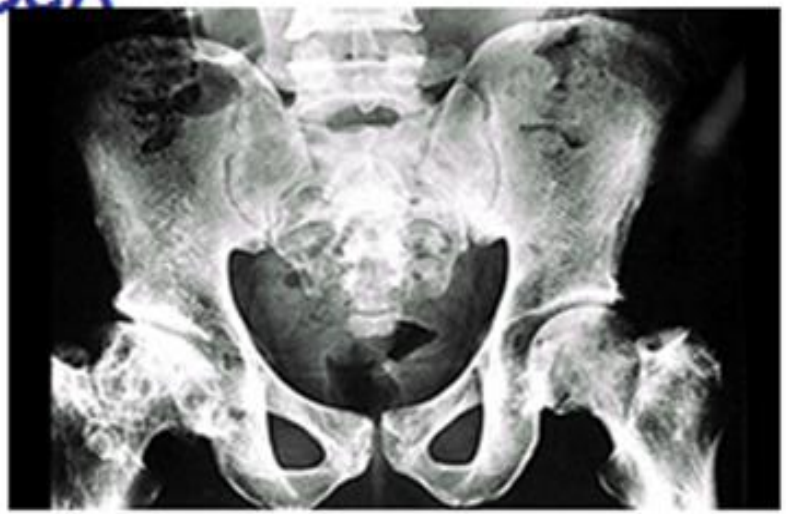




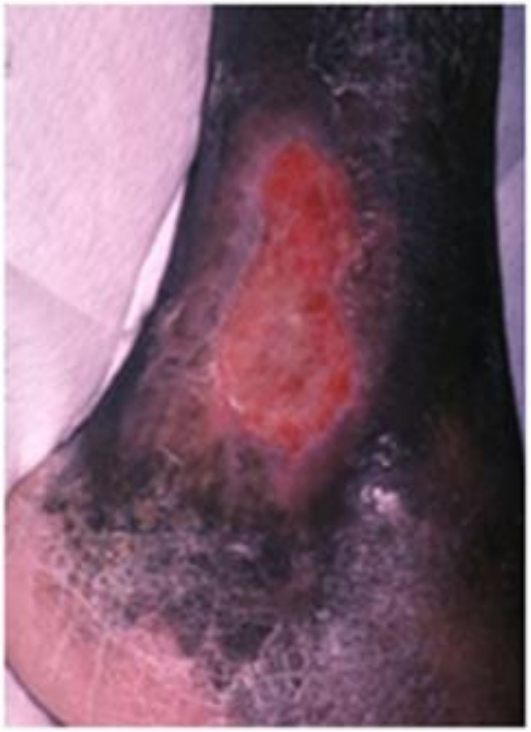
Optical complication in SCA

Gall stones in SCA





Avascular necrosis in SCA

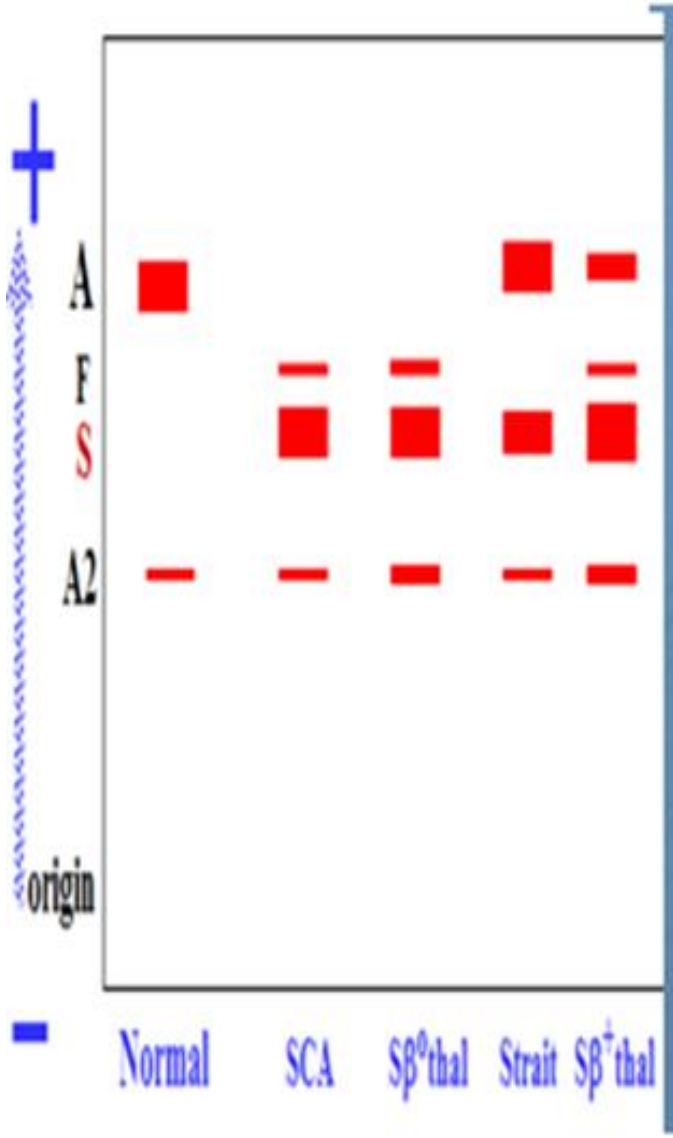


Leg ulceration

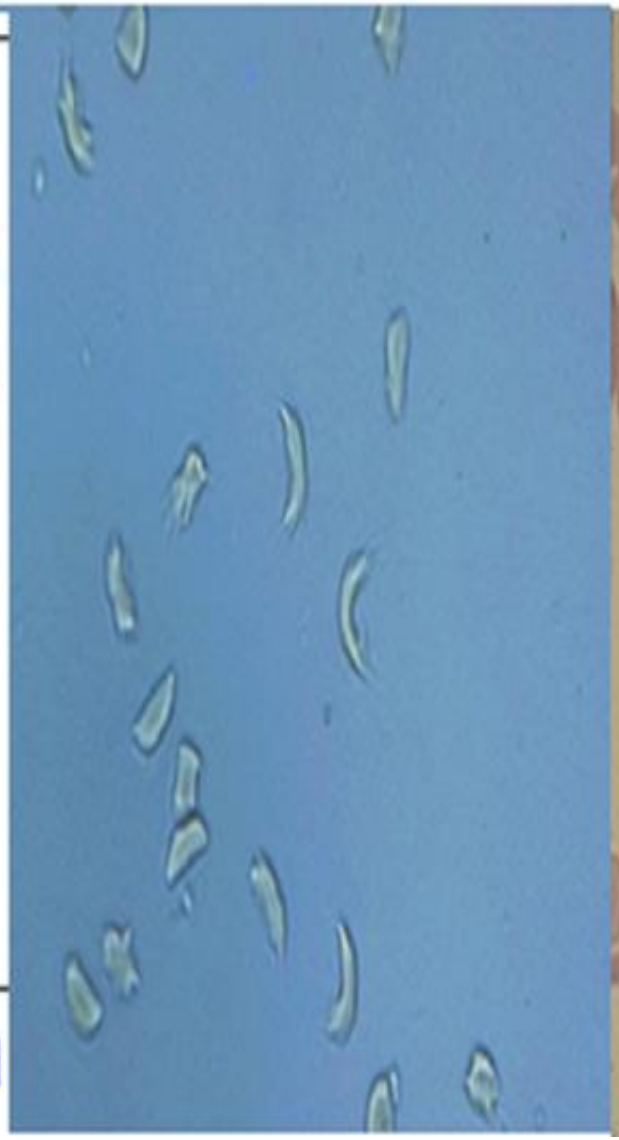
Lab. Findings:

* **CBC** : Variable anemia (6-8g/dl)
* **B.F** :Sickle cells, target cells and feature of splenic atrophy may see on blood film.
* **Retics** usually increased 10-20%.
* **Sickling** test positive, Solubility test positive.
* **Hb electrophoresis**: HbS 80-90%, HBF 2-20%, no HbA and normal HbA2.
* **Antenatal screening** as approach to thalassemia syndromes.

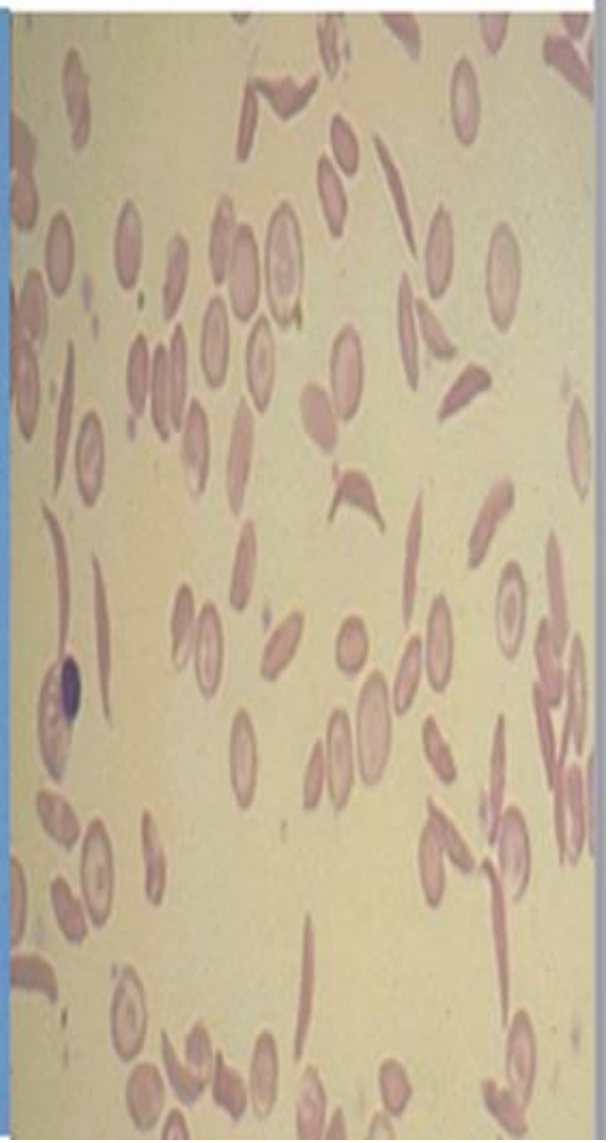
Hb- electrophoresis



Positive Sickling test



Blood Film in Sickle cell Anemia



Course and Prognosis :

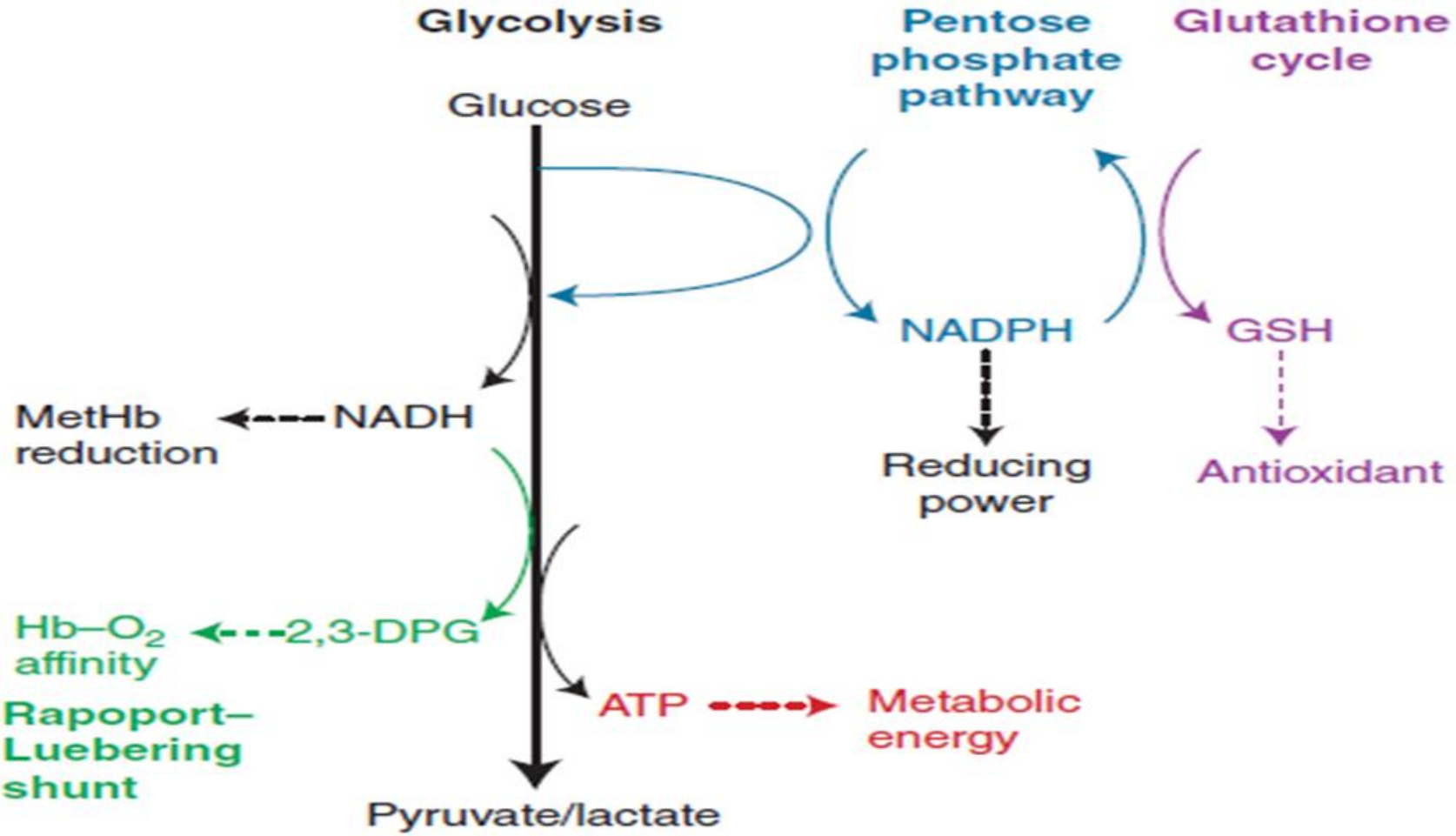
* High mortality in first few years, (especially in under-developed countries), is due to pneumonia and meningitis, splenic sequestration.
* Most patients however survive well into adult life.

Managements:

- ✓ **Avoid** precipitating factors.
- ✓ **FA** supplementation.
- ✓ Good **general nutrition** and hygiene.
- ✓ **Vaccinatio**n to many M.O.
- ✓ **Crisis management** with: rest, warming, rehydration, Ab, analgesia, and exchange transfusion in indicated cases.
- ✓ **Regular blood transfusion** usually not required unless indications are present.
- ✓ **Hydroxyurea** can increase HbF.
- ✓ Stem cells **transplantation** can cure the disease.
- ✓ **Gene therapy**.
- ✓ **Management of complications**.

Hemolysis due to Enzymopathies

- Disorders of Glycolytic pathway as PK def.
- Disorders of PP (HMP) pathway as G6PD def.
- Disorders of Nucleotide metabolism as P5-N def.



Oxidant agent
(free radicals formation)

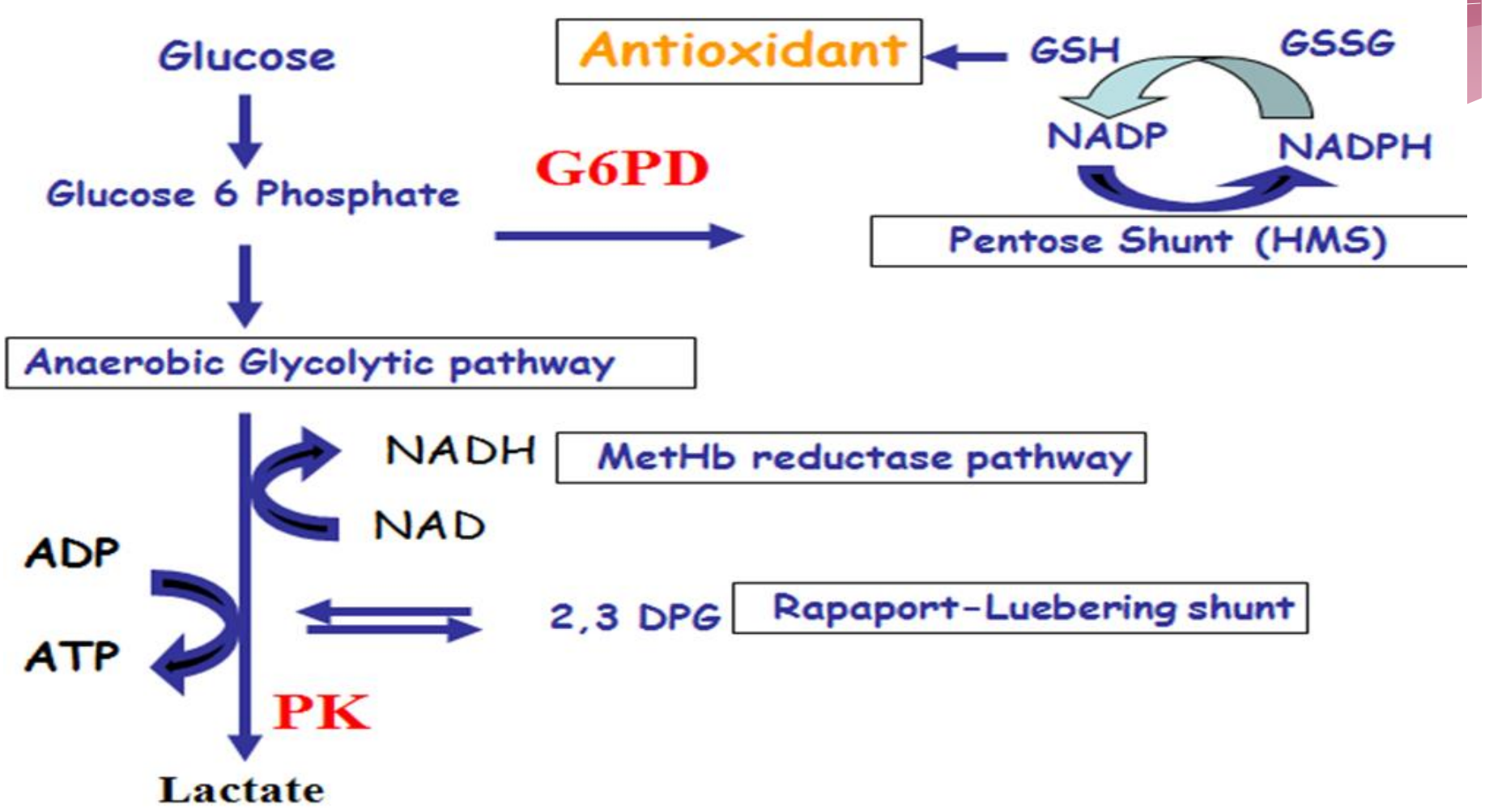
→ Peroxidation of membrane lipid / IVH

→ Hb denaturation (H. body) / EVH

G6PD Deficiency

- **Definition**: Sex-linked inherited disorder characterized usually by acute hemolytic episodes following exposure to oxidant stress (infection, drugs or fava beans) due to deficiency of RBC enzyme G6PD.
- All RBC, WBC and platelets have this enzyme under same genetic control, but clinically consequent is confined to RBC.
- **Prevalence**:
  - More than 400 million people effected worldwide.
  - Most races are West Africa, Medit., Middle East, and South East Asia.
  - Quite frequent in Iraq with 8-13% of the population affected more in south area

Pathophysiology of hemolysis



Clinical features:

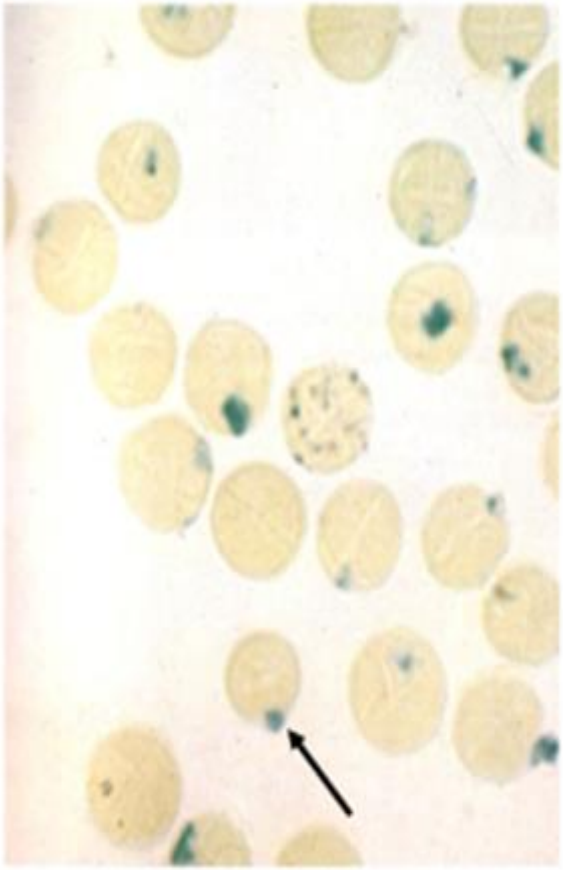
- X-Linked dis., more in Male, carried in female.
- More common among black races.
- Acute hemolytic attack characterize by Sudden Pallor, Jaundice, red or dark urine due to Hemoglobinuria, fever and abdominal pain Lasts usually for 2-6 days followed by spontaneous recovery.
- **4 main syndromes** are Favism, drug/infection induce, NNJ, and rarely CNSHA.
- Spontaneous anemia is rare but hemolytic crises are frequent precipitate by triggering factors

- **Favism**:
  - Occurs on consumption of Fava beans, usually occurs within few hrs to 1-2 days of ingestion, most frequent in spring (March-May), 2/3 of cases occur in 1-6 year old children with males predominate
  - 10-20% of deficient patient suffer from favism when exposed.
- **NJ**: 10-20% of deficient infants are affected.
- **CNSHA**: rare type, chronic life long hemolysis (extravascular), splenomegaly, chronic jaundice, susceptibility to infection.

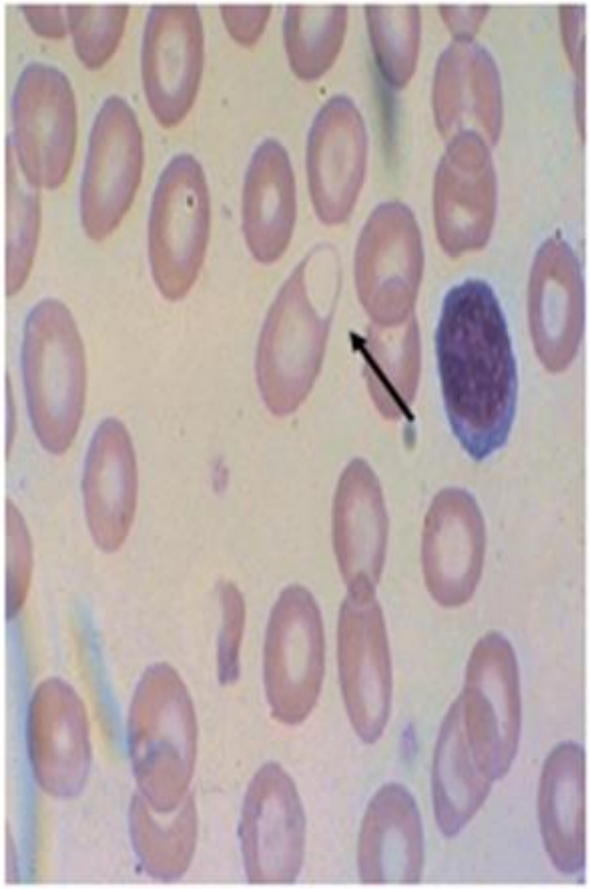
Laboratory findings:

- ✓ Variable anaemia during the hemolytic episode with findings of IV hemolysis.
- ✓ Blood film during acute hemolysis showing polychromasia, bitten cell, blister cells and Heinz body. Blood picture normal between the hemolytic crises.
- ✓ Screening test: Fluorescent screening test, Methemoglobin reduction test, MetHb elusion test.
- ✓ Specific Assay for red cell G6PD (best to done 2 wks after the attack) due to high enzyme level in young red cells and reticulocytes

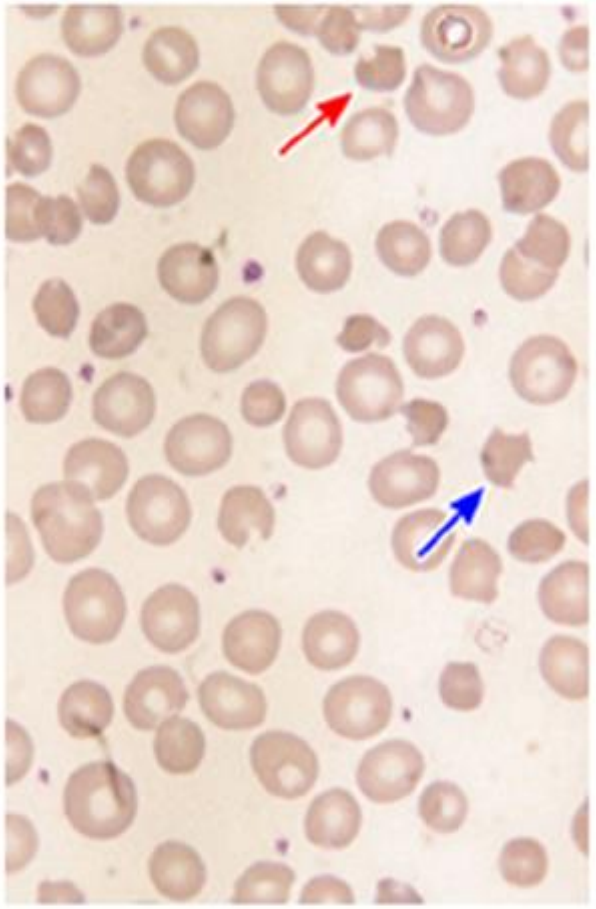
Blood Film in acute hemolysis



Heinz body



Blister Cell



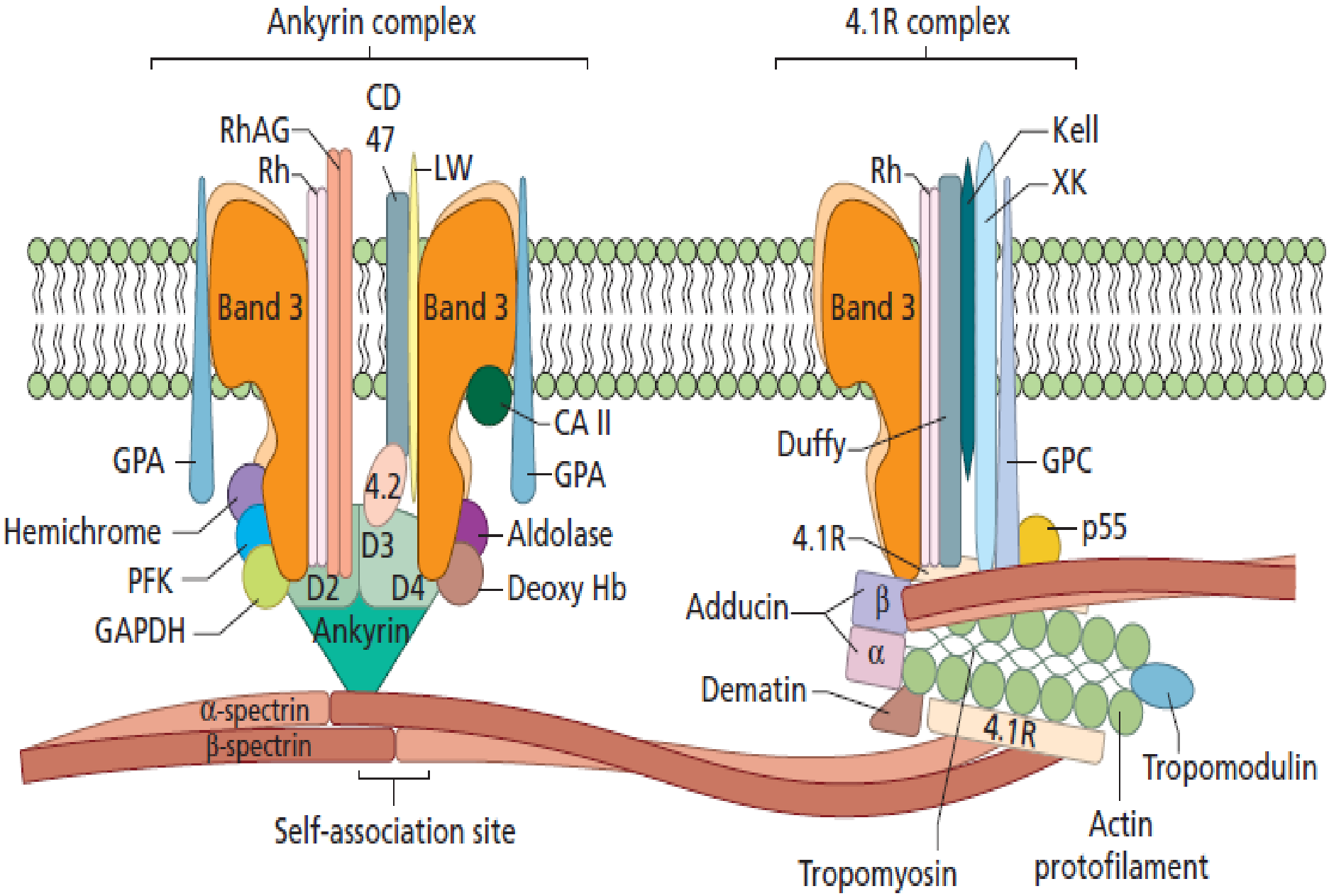
Bitten cell

Management

- ✓ Spontaneous recovery.
- ✓ Blood transfusion if required.
- ✓ Avoid precipitating factors.
- ✓ NNJ treatment (phototherapy, exchange transfusion).
- ✓ Vitamin E trail

Disorders of red cell membrane

* The erythrocyte membrane plays a critical role in the function and structure of the red cell.
* It is a key determinant of the unique biconcave disk shape and provides the cell with a finely tuned combination of flexibility and durability.
* The red cell membrane maintains a nonreactive surface so that erythrocytes do not adhere to the endothelium or aggregate and occlude capillaries
* . It provides a barrier with selective permeability, which retains vital components inside the cell and permits the efflux of metabolic waste.


Ankyrin complex
4.1R complex
CD
47
RhAG
Rh
LW
Band 3
Band 3
Rh
Kell
XK
Band 3
CA II
GPA
GPA
4.2
Duffy
GPC
Hemichrome
D3
Aldolase
4.1R
p55
PFK
D2
D4
Deoxy Hb
Adducin
β
GAPDH
Ankyrin
α
Dematin
α-spectrin
4.1R
β-spectrin
Tropomodulin
Self-association site
Tropomyosin
Actin
protofilament

. Erythrocyte Membrane Protein Defects in Inherited Disorders of Red Cell Shape**2–46TABLE**

Protein	**Disorder**	**Comment**
Ankyrin	HS	Most common cause of typical dominant HS
3Band	HS, SAO, NIHF, HAc	Pincered" HS spherocytes seen on blood film " -amino-acid 9presplenectomy; SAO results from deletion
β-Spectrin	HS, HE, HPP, NIHF	Acanthocytic" spherocytes seen on blood film " presplenectomy; location of mutation in β-spectrin determines clinical phenotype
α-Spectrin	HS, HE, HPP, NIHF	Location of mutation in α-spectrin determines clinical phenotype; α-spectrin mutations most common cause of typical HE
4.2Protein	HS	Primarily found in Japanese patients
4.1Protein	HE	Found in certain European and Arab populations
GPC	HE	deficiency is basis of HE in 4.1 Concomitant protein GPC defects

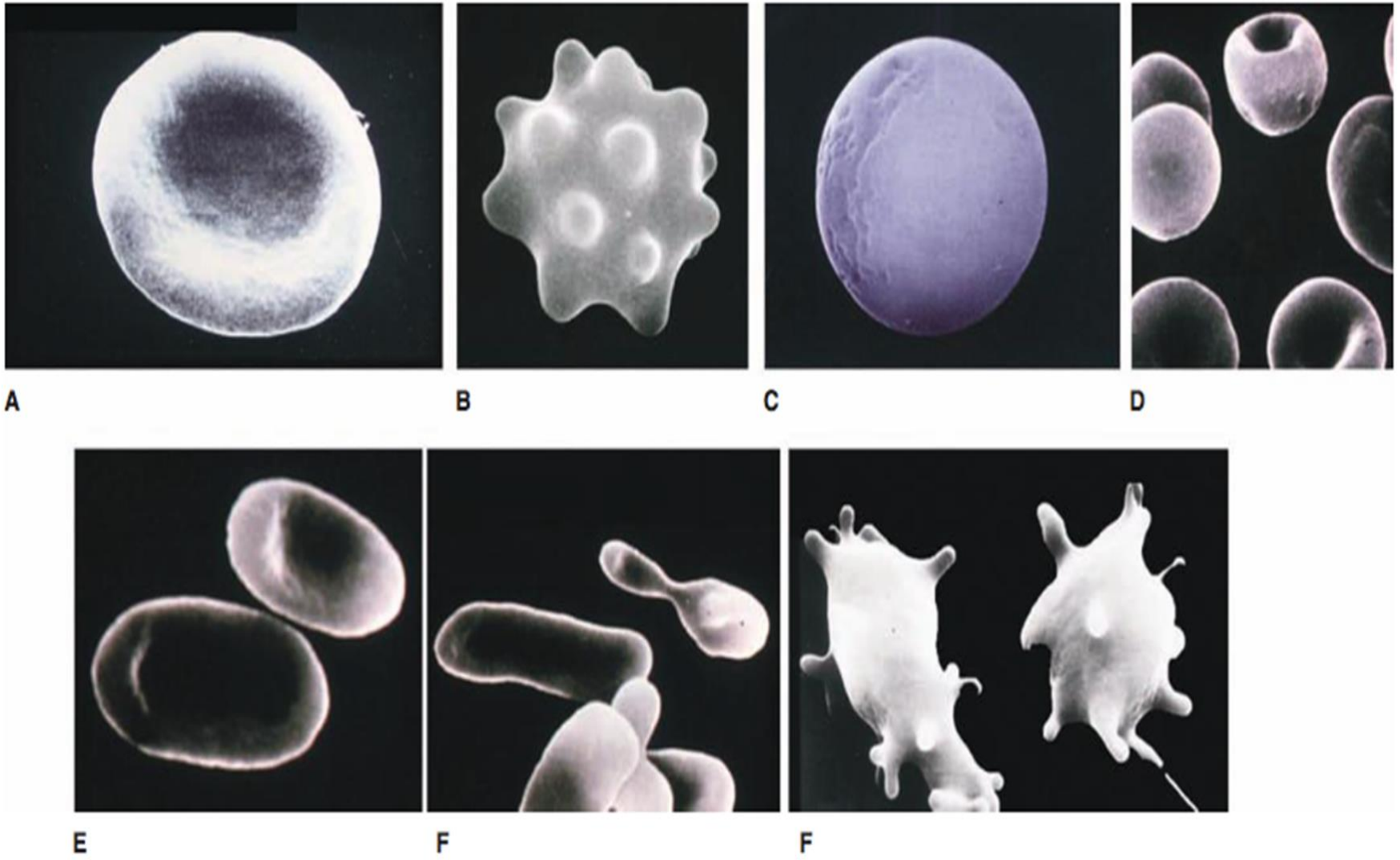
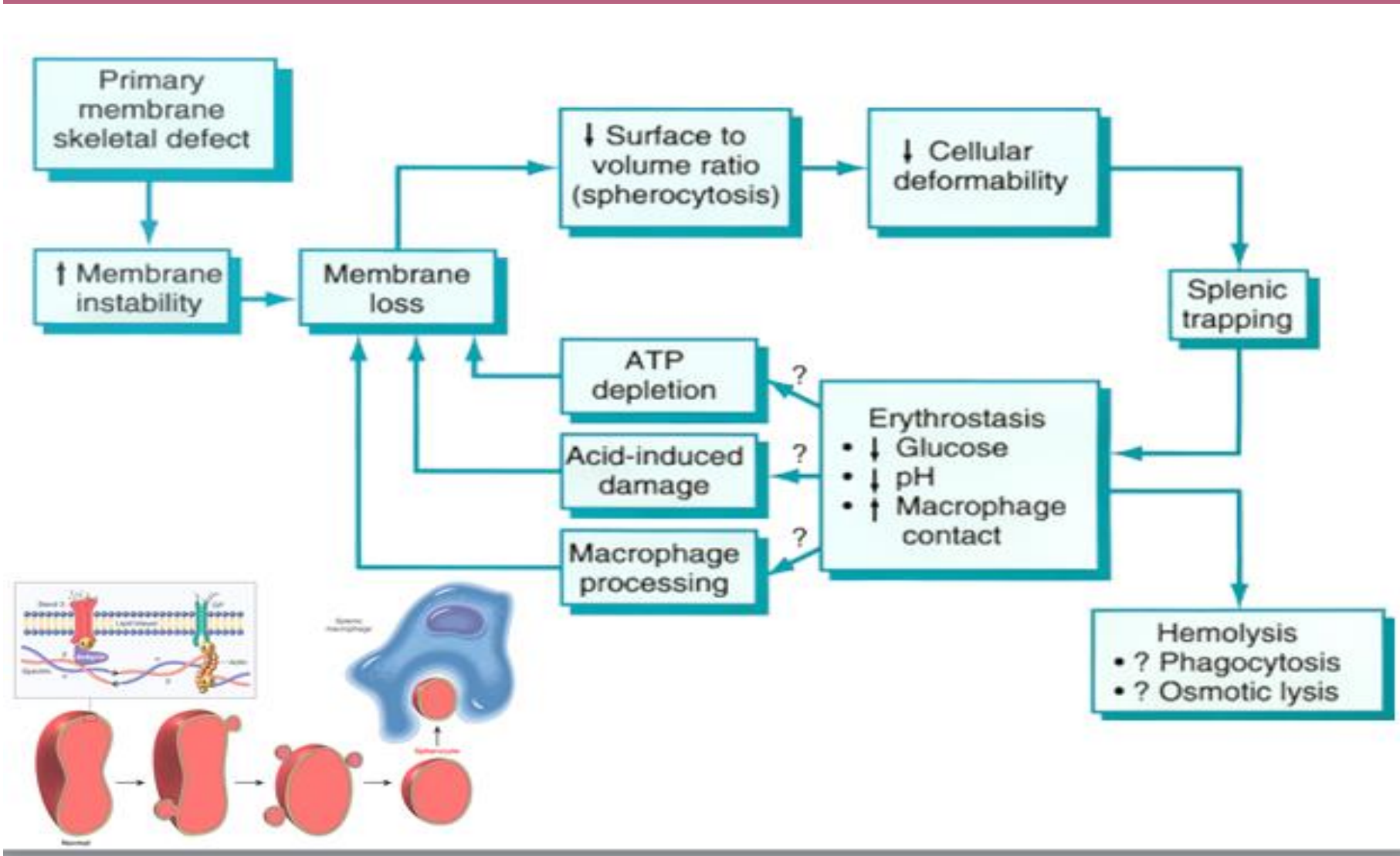


Figure 46–11. Scanning electron micrographs of erythrocytes with abnormal morphology due to membrane defects. **A.** Normal discocyte. **B.** Echinocyte. **C.** Spherocyte. **D.** Stomatocytes. **E.** Ovalocytes. **F.** Elliptocytes. **G.** Acanthocytes. *(Reproduced with permission from* Lichtman's Atlas of Hematology, *www.accessmedicine.com.)*

Hereditary Spherocytosis

* Definition: Inherited disorder resulting from an intrinsic defect involving red cell membrane, making the RBC osmotically fragile and spherocytic in shape.
* Usually inherited as Autosomal dominant (75%), may be AR or de-novo mutation.
* Not common in Iraq, is the common hereditary HA in North Europe.
* Defect in proteins involved in vertical interaction between membrane skeleton and lipid bilayer of RBC.
* So the lipid bilayer not supported by the skeleton proteins.

Pathophysiology of HS

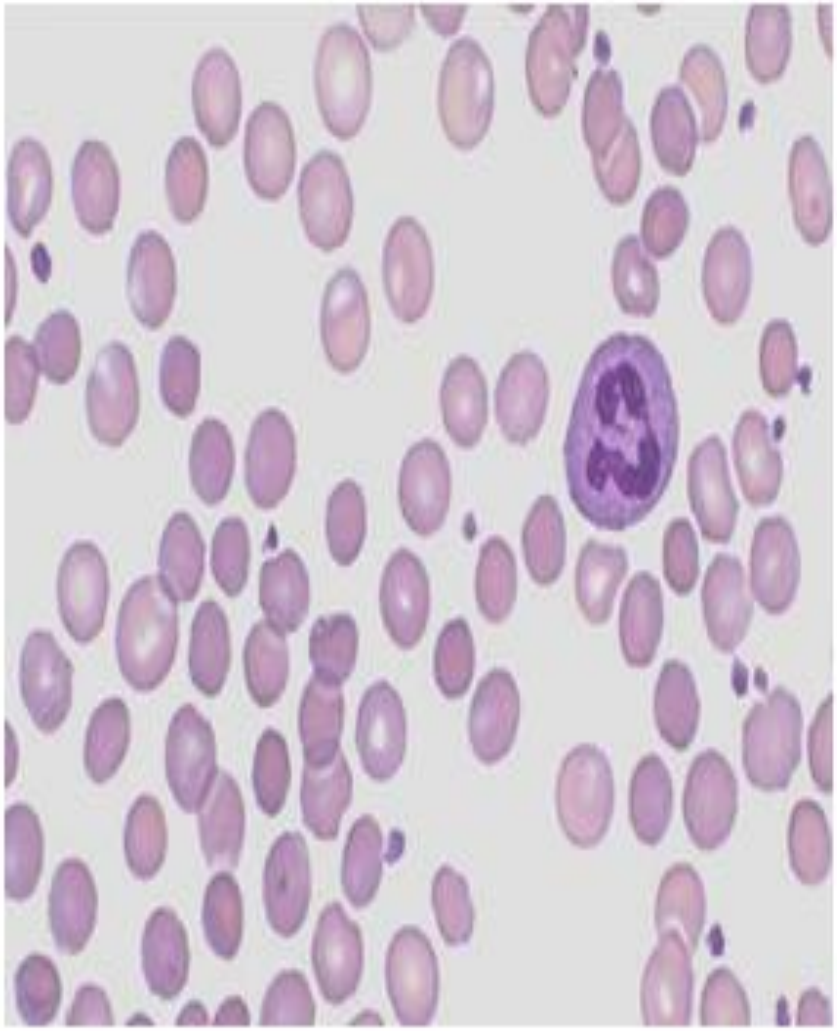


Clinical features

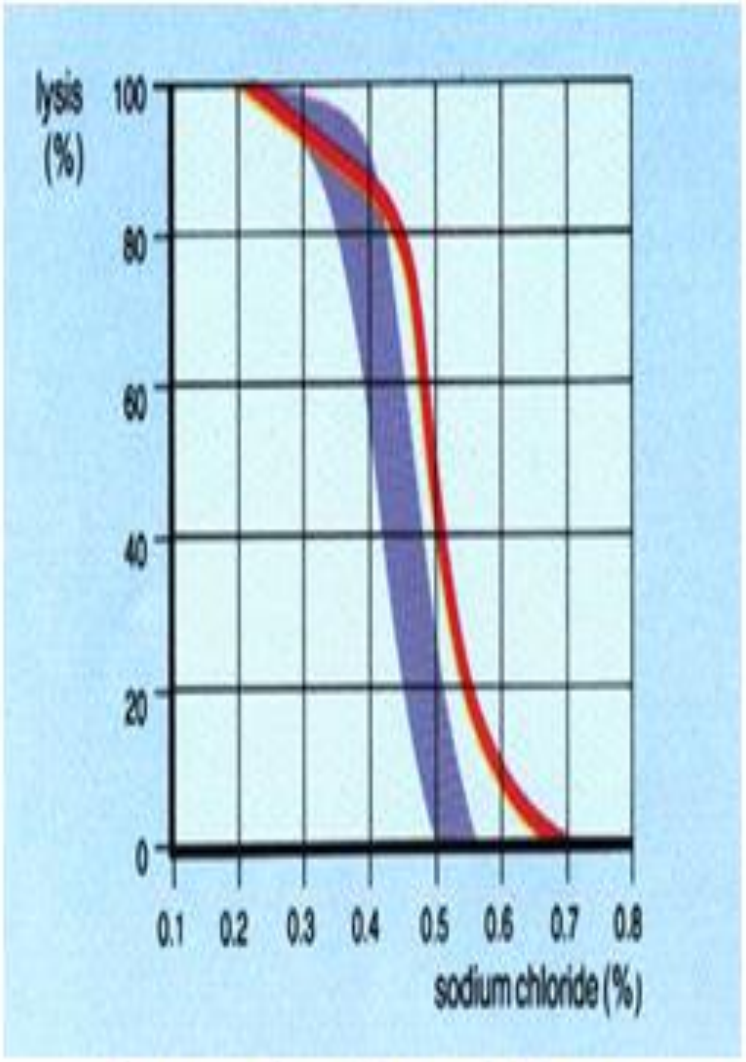
* HS may present at birth,severe anaemia in utero is rare.
* Majority present in first 10 years of life, with pallor, Jaundice and splenomegaly.
* Anemia may present at any age.
* As the main site of increased red cell destruction in HS is the spleen.
* Jaundice typically fluctuated, and SM in most patient.
* HA may aggravate by infections, pregnancy.
* Complications as gall stones, leg ulceration and crisis (hemolytic, aplastic, sequestration crisis).

Lab.findings

* Variable anemia, peripheral spherocytosis or microspherocytes, reticulocytosis,
* The typical findings of extravascular haemolysis are present
* Right shift on Osmotic Fragility Test (OFT).
* Normal direct coomb's test (exclude AIHA).
* An alternate to the osmotic fragility test is to measure the extent of membrane surface area loss by flow cytometry following labelling with eosin-5-maleimide (EMA binding test).
* Membrane protein analysis (Diagnostic test).



Blood film



Osmotic Fragility test

Management

* No Cure, aim is to minimize consequences of disease.
* Uncomplicated HS always response to splenctomy that done under indications.
* All should receive folate supplements.


Thank You!