HEMOLYTIC ANEMIA

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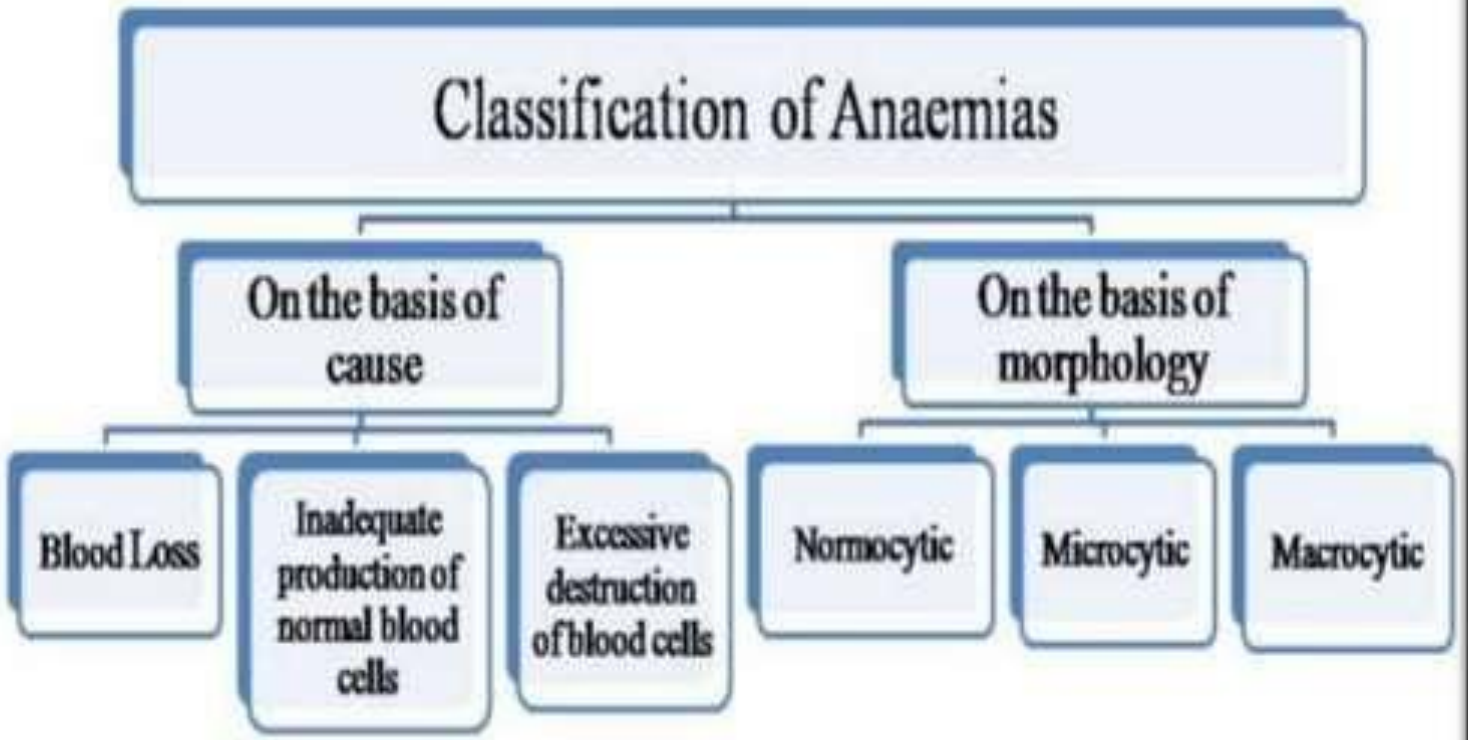
Surat

- ANEMIA - Anemia is defined as reduction of the total circulating red cell mass below normal limits.

- Anemia reduces the oxygen carrying capacity of blood, leading to tissue hypoxia.

- Anemia is usually diagnosed based on ***reduction in hematocrit and Hemoglobin concentration*** of the blood to levels that are below the normal range


Classification of Anaemias
On the basis of cause
On the basis of morphology
Blood Loss
Inadequate production of normal blood cells
Excessive destruction of blood cells
Normocytic
Microcytic
Macrocytic

HEMOLYTIC ANEMIA

- Hemolytic anemias are characterised by increase red cell destruction

- It shares the following features

1. A shortened red cell life span below the normal 120 days
2. Elevated erythropoietin level and compensatory increase in erythropoiesis
3. Accumulation of hemoglobin degradation products that are created as a part of process of red cell hemolysis

PATHOGENESIS

RED CELL DESTRUCTION

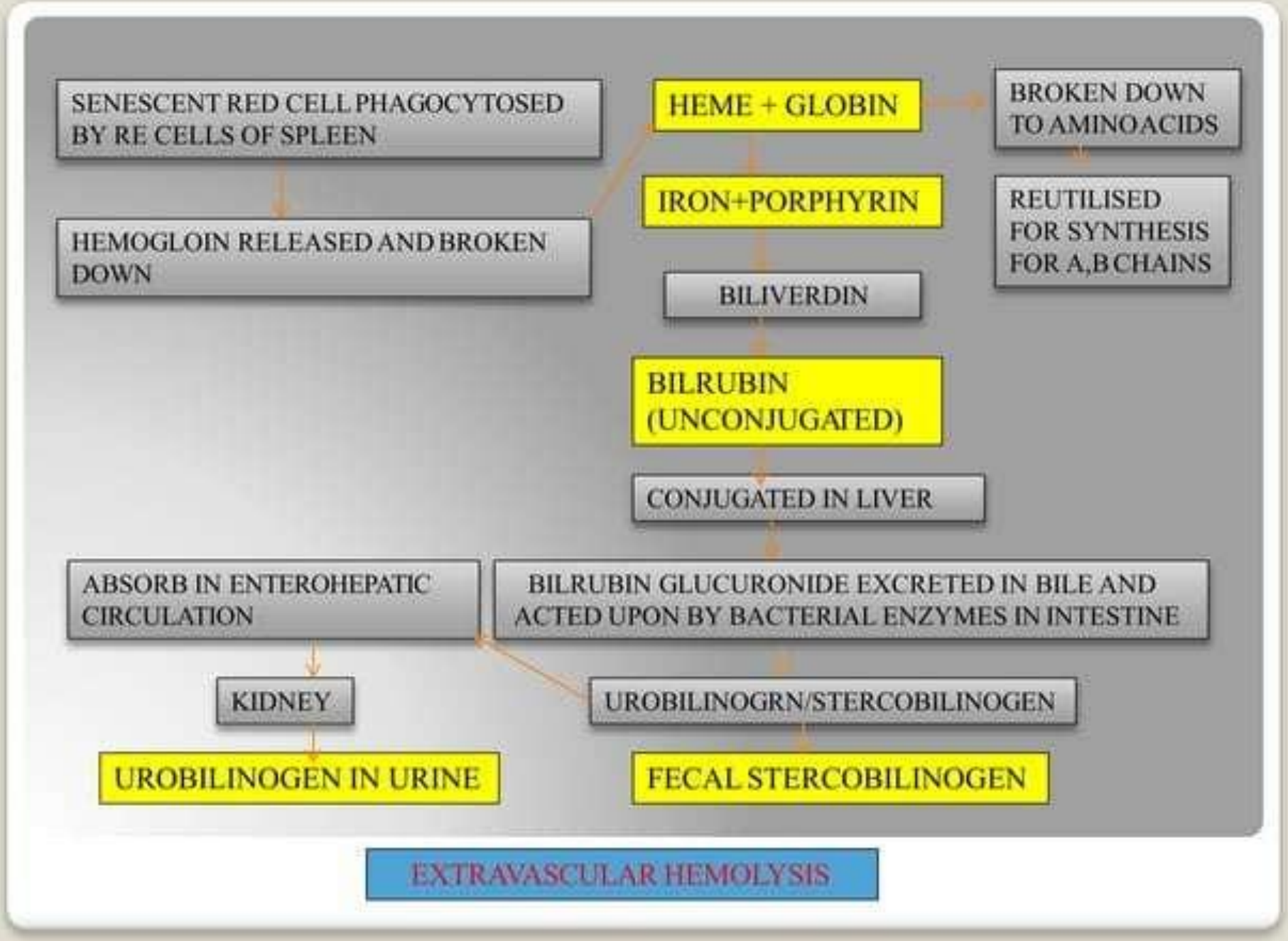
- The physiological destruction of senescent red cells takes place with in macrophages, which are abundant in spleen, liver and bone marrow

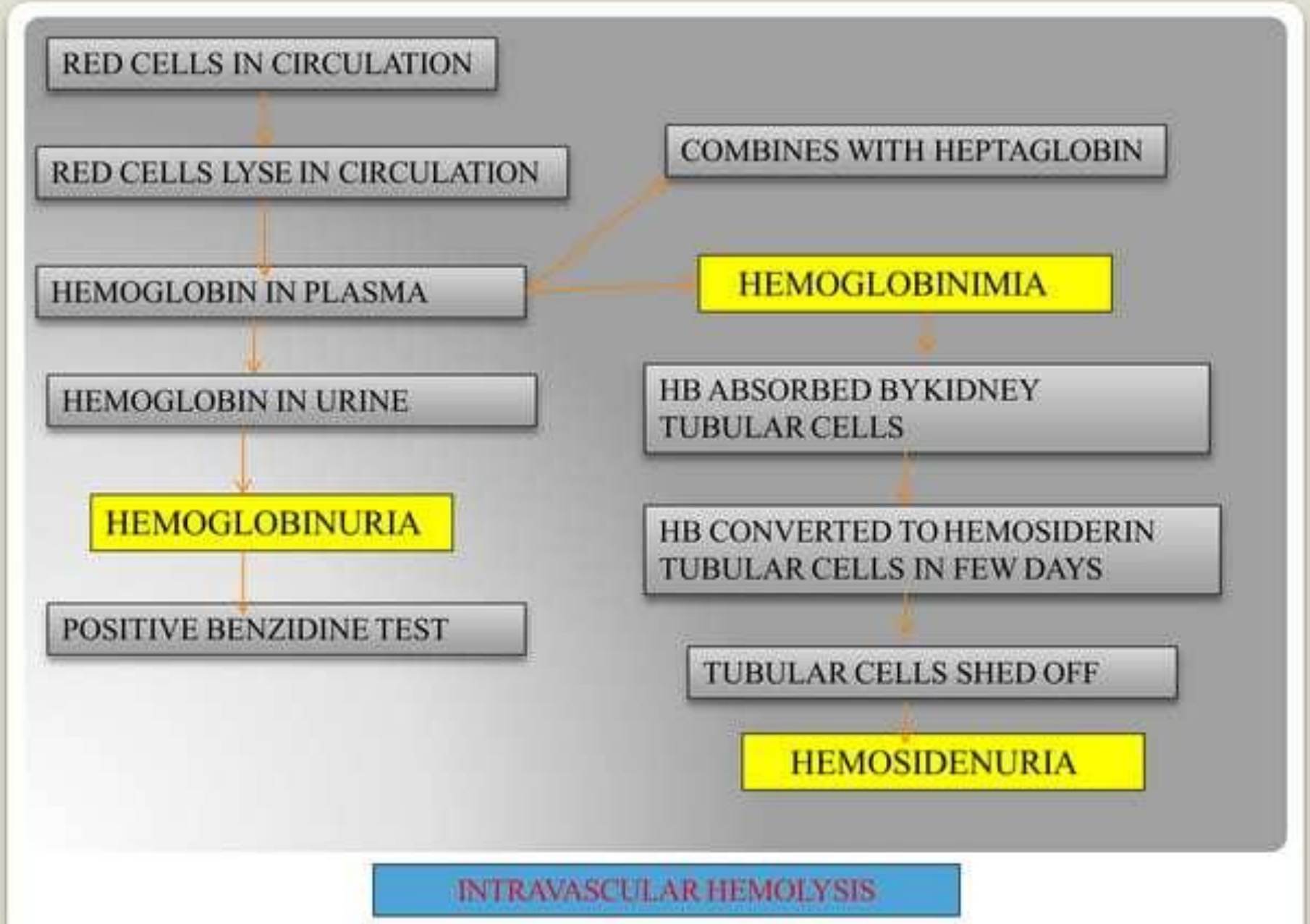
- This process appears to be triggered by age- dependent changes in red cell surface proteins, which lead to their recognition and phagocytosis

- Red cell destruction occur by 2 mechanisms-

- **Extravascular Hemolysis** – The site of destruction is mainly spleen and this is the major mechanism of red cell hemolysis. Red cells are taken up by the cells of RE system where they are destroyed and digested

- **Intravascular Hemolysis**– This is the minor pathway of red cell destruction and red cells are destroyed in circulation releasing hemoglobin.


SENESCENT RED CELL PHAGOCYTOSED BY RE CELLS OF SPLEEN
HEME + GLOBIN
BROKEN DOWN TO AMINO ACIDS
HEMOGLOIN RELEASED AND BROKEN DOWN
IRON+PORPHYRIN
REUTILISED FOR SYNTHESIS FOR A,B CHAINS
BILIVERDIN
BILRUBIN (UNCONJUGATED)
CONJUGATED IN LIVER
ABSORB IN ENTEROHEPATIC CIRCULATION
BILRUBIN GLUCURONIDE EXCRETED IN BILE AND ACTED UPON BY BACTERIAL ENZYMES IN INTESTINE
KIDNEY
UROBILINOGRN/STERCOBILINOGEN
UROBILINOGEN IN URINE
FECAL STERCOBILINOGEN
EXTRAVASCULAR HEMOLYSIS


RED CELLS IN CIRCULATION
RED CELLS LYSE IN CIRCULATION
HEMOGLOBIN IN PLASMA
HEMOGLOBIN IN URINE
HEMOGLOBINURIA
POSITIVE BENZIDINE TEST
COMBINES WITH HEPTAGLOBIN
HEMOGLOBINIMIA
HB ABSORBED BY KIDNEY TUBULAR CELLS
HB CONVERTED TO HEMOSIDERIN TUBULAR CELLS IN FEW DAYS
TUBULAR CELLS SHED OFF
HEMOSIDENURIA
INTRAVASCULAR HEMOLYSIS

LAB EVALUATION OF HEMOLYSIS

	EXTRAVASCULAR	INTRAVSCULAR
S.BILRUBIN	UNCONJUGATED++	UNCONJUGATED+
S.HEPTAGLOBIN	NORMAL	DECREASE
PLASMA HEMOGLOBIN	ABSENT	PRESENT
S. METHEMALBUMIN	ABSENT	PRESENT
LACTATE DEHYDROGENASE	VARIABLE+	INCREASE++
URINE BILRUBIN	PRESENT	PRESENT
U. HEMOGLOBIN	ABSENT	PRESENT
U. HEMOSIDERIN	ABSENT	PRESENT

CLASSIFICATION OF HEMOLYTIC ANEMIAS

The course of the disease	acute	chronic
The place of RBC distraction	intravascular	extravascular
The whence	acquired	inherited

Haemolytic anaemia
Intravascular vs. Extravascular

Intravascular

- red cells lyse in the circulation and release their products into the plasma fraction.
- Anemia
- Decreased Haptoglobin
- Hemoglobinemia
- Hemoglobinuria
- Urine hemosiderin
- Increased LDH

Extravascular

- ingestion of red cells by macrophages in the liver, spleen and bone marrow
- Little or no hemoglobin escapes into the circulation
- Anemia
- Decreased Haptoglobin
- Normal plasma hemoglobin

CLINICAL FEATURES –

Clinical sign and symptoms of hemolytic anemia depend upon the severity as well as duration of hemolysis. These are

- Pallor
- Jaundice
- Splenomegaly
- Gall stones
- Skeletal abnormalities in severe hemolysis
- Leg ulcers
- Dyspnoea
- Tachycardia and systolic murmur

DIAGNOSIS

- 1. History of the patient
- 2. Peripheral blood film
- 3. Bone marrow findings
- 4. Biochemical tests
- 5. Other screening tests

Evidence of Hemolysis

- Low RBC survival with chromium tagging study
- Unconjugated bilirubin
- Plasma Hb
- Decreased serum haptoglobin

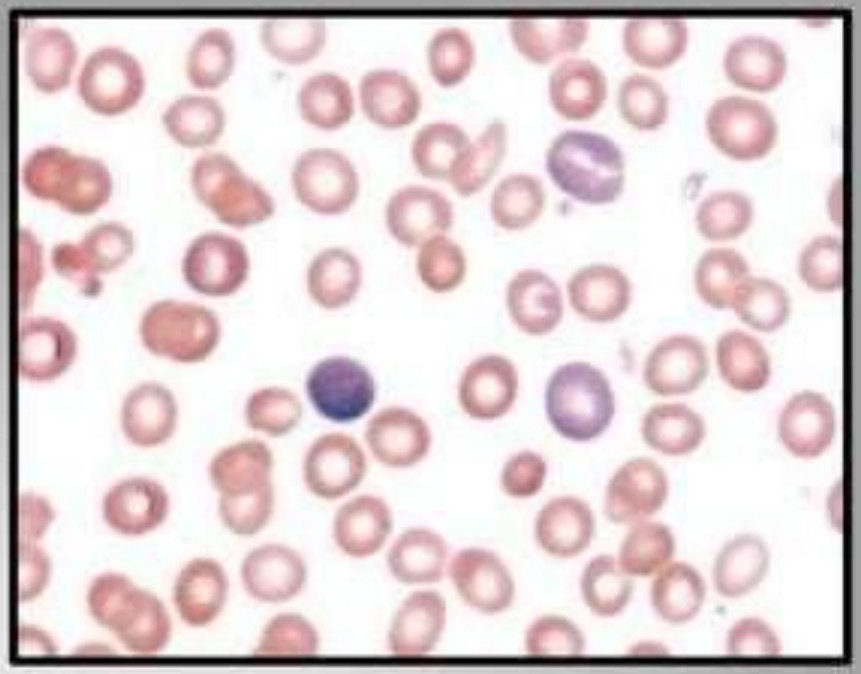
- **Coombs' test** is used to detect antibodies that act against the surface of red blood cells

Evidence of Erythropoiesis

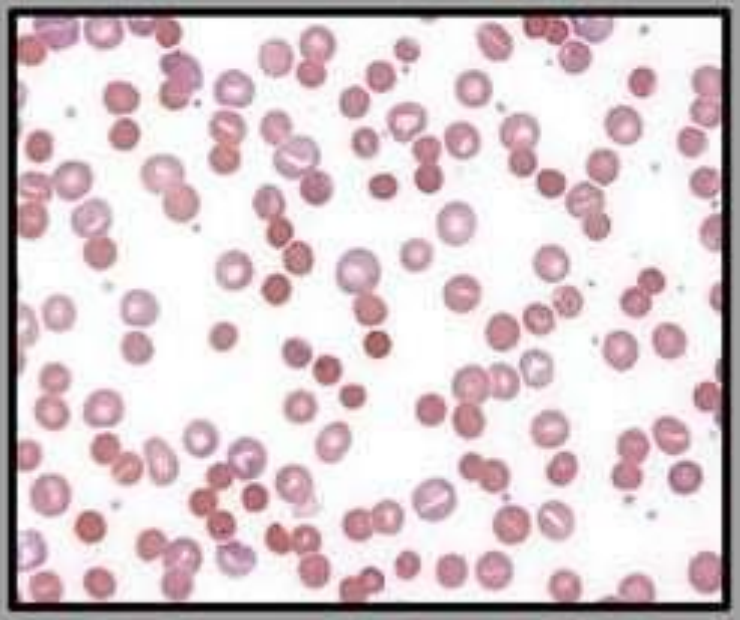
- Polychromasia
- Increased reticulocyte
- “Shift” macrocytosis
- Hypercelluar BM

- **PERIPHERAL BLOOD FINDINGS** – Peripheral smear evaluation is the most important investigation in hemolytic anemias
- The following morphological findings alone or in combination are suggestive of hemolysis : Polychromatophilia, nucleated red cells, thrombocytosis and neutrophilia with mild shift to left

- Red cell morphologic abnormalities provide a clue to underlyng disorder. Some are Spherocytes, Sickle cell, Target cells, Schistocytes (fragmented red cells, helmet cells, traingular cells) and acanthocytes



Peripheral blood film with Romanowsky stain demonstrating polychromatophilic cells. The polychromatophilic cells are basophilic because of increased RNA content. The cells are usually larger than normocytic red blood cells

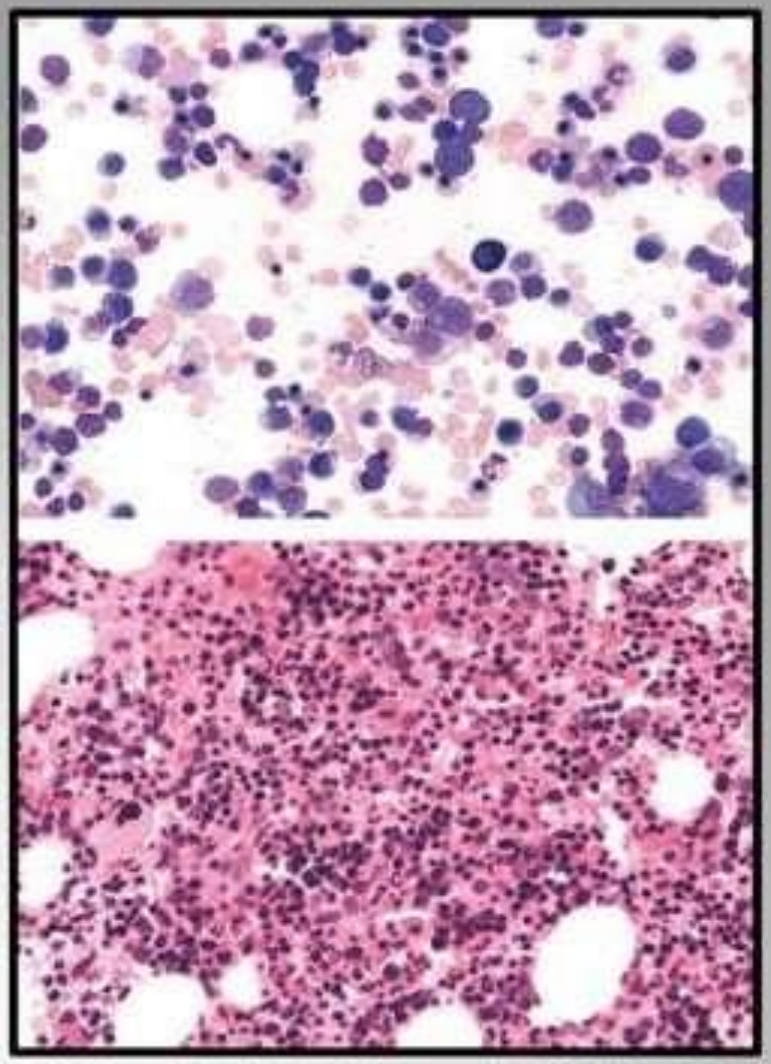


Autoimmune hemolytic anemia. Numerous spherocytes, small round RBCs lacking central pallor, are shown in this blood smear from a case of Coombs-positive hemolytic anemia.

2. Bone marrow findings- Compensatory mechanism to hemolysis

- *Erythroid hyperplasia of bone marrow-* Erythroid hyperplasia with normoblastic reaction. Reversal of M:E ratio

- *Reticulocytosis* – Increase variabley
  - Mild (2-10%)- Hemogobinopathies
  - Moderate to marked (10-60%)-
    Immune hemolytic anemias,
    Hereditary spherocytosis ,
    G6PD deficient states



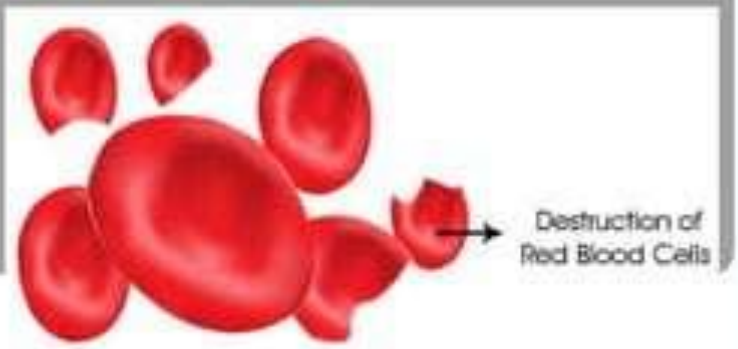
Bone marrow findings in hemolytic anemia.
Top panel: Erythroid hyperplasia is present with a predominance of erythroid precursors. The normal myeloid to erythroid ratio in a bone marrow aspirate is 3 to 5:1. In this case, there occurs a reversal of the myeloid to erythroid ratio of 1:4.
Bottom panel: Bone marrow biopsy in a patient with hemolytic anemia. Erythroid hyperplasia is seen with a predominance of erythroid precursors

CLASSIFICATION OF HEMOLYTIC ANEMIA


HEREDITARY HEMOLYTIC ANEMIA
ACCQUIRED HEMOLYTIC ANEMIA
PAROXYSMAL NOCTURNAL HEMOGLOBNURIA
DRUGS AND CHEMICALS
OTHERS
A. DEFECT IN RED CELL MEMBRANE
• HERDITARY SPHEROCYTOSIS
• H. ELLIPTOCYTOSIS
• H.PYROPOIKLIOCYTOSIS
• STOMATOCYTOSIS
• ABETALIPOPROTENIMIA
A. DEFECT IN GLOBIN SYNTHESIS
• THALASSEMIA
• SICKELING SYNDROMES
• ALPHA THALASSEMIA
• UNSTABLE HB DISEASE
A. ENZYME DEFICIENCIES
1. GLYCOLYTIC PATHWAY-
• PYRUVATE KINASE DEFICIENCY
• HEXOKINAS DEFICIENCY
2 . PPP PATHWAY-
• GLUCOSE6-PO4 DHYDROGENASE DEFICIENCY
3 RED CELL NUCLEOTIDE
• METABOLISM
PYRIMIDINE 5 NUCLEATIDASE DEFICIENCY
B. IMMUNE HEMOLYTIC SYNDROMES
1. AUTOIMMUNE HEMOLYTIC ANEMIA
• DUE TO WARM ANTIBODIES
• IDIOPATHIC
• SECONDARY
• DUE TO COLD ANTIBODIES-
• CAD
• PCH
2. HEMOLYTIC DISEASE OF NEW BORN, TRANSFUSION REACTION
B. FRAGMENTATION SYNDROMES
• HUS
• TTP
• DIC
• PCV
•OXIDANT DRUGS
•PRIMAQUINE
•DAPSONE
•VITAMIN E DEFICIENCY
•CHEMICALS – NAPTHELENE, NITRATES
•SPUR CELL ANEMIA IN LIVER
•CANCER INDUCED
THERMAL INJURY
BURNS
INFECTIONS
•C. PERFRINGENS
•C. WELICHII
•BARTONELLA
•CHOLERA
•MALARIA
•LEISHMANIA
•TRYPANOSOMA
•TOXOPLASMA
•TYPHOID FEVER

HEMOLYTIC ANEMIA

- INTRACORPUSCULAR HEMOLYSIS
  - Membrane Abnormalities
  - Metabolic Abnormalities
  - Hemoglobinopathies
- EXTRACORPUSCULAR HEMOLYSIS
  - Nonimmune
  - Immune



Intrinsic causes of hemolysis

Major causes:

- Defective **hemoglobin**
- Defective **structural proteins**
- Defective **surface proteins**
- Defective **enzymes**

INTRACORPUSCULAR HEMOLYSIS

Membrane Defect

- **Hereditary spherocytosis**
- **Hereditary elliptocytosis**
- **Hereditary pyropoikilocytosis**
- PNH (sensitivity to complement lysis -- sugar water test, Ham's test)
- **Hereditary stomatocytosis** (possibly Rh null)

INTRACORPUSCULAR HEMOLYSIS

Metabolic Defect (enzyme deficiency)

- **G6PD deficiency**
  - Hexose monophosphate shunt
  - Most common RBC enzyme defect, >50 variants
  - X-linked
  - Low glutathione due to low NADPH
  - Oxidative lysis, Heinz bodies, spherocytic
  - Primaquine, fava beans
- **Pyruvate kinase deficiency**
  - Glycolysis
  - Low RBC ATP level
  - Non-spherocytic
- **B12 and folate deficiency**
  - Macrocytic
  - HJ bodies
- **Hemoglobinopathies**
  - Poikilocytosis
  - Abnormal Hb

INTRACORPUSCULAR HEMOLYSIS

Hemoglobin Abnormalities

- Unstable hemoglobin disease
- **Sickle cell anemia**
- **Thalassemia major**
- Hemoglobin H disease
- Doubly heterozygous disorders (such as hemoglobin SC disease and sickle thalassemia)

EXTRACORPUSCULAR HEMOLYSIS

IMMUNE

- Drug-Related Hemolysis

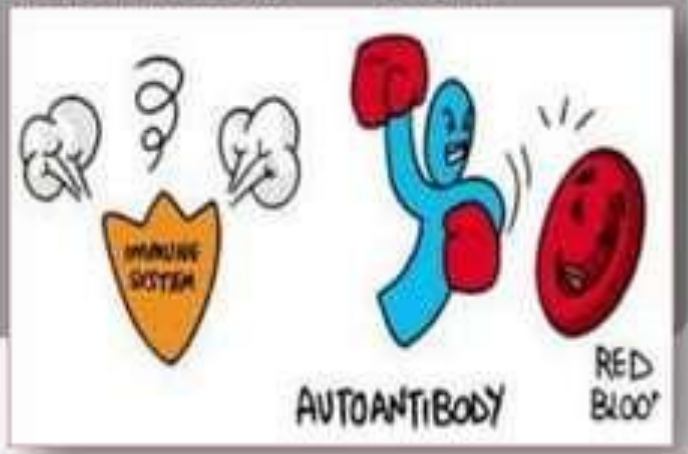
  PENICILLIN,
  CEFTRIAXONE,
  SULFA DRUGS
  QUINIDINE,
  ALPHA- METHYLDOPA,LEVODOPA
  PROCAINAMIDE,

- Alloimmune Hemolysis
  - Hemolytic Transfusion Reaction
  - Hemolytic Disease of the Newborn

EXTRACORPUSCULAR HEMOLYSIS

IMMUNE

- Autoimmune Hemolysis
  - Warm Autoimmune (WAIHA)70-80%
  - Cold Autoimmune (CAIHA) 20-30%
  - Mixed 7-8%
  - Paroxysmal Cold Hemoglobinuria - rare



EXTRACELLULAR DEFECTS

- Fragmentation Hemolysis
  - DIC, TTP, HUS
  - Extracorporeal membrane oxygenation
  - Prosthetic heart valve
  - Burns—thermal injury
  - Hypersplenism
  - Venom - Snake, Spider, Bee

Plasma Factors

- **Liver disease** (Spur-cell)
- Hypophosphatemia
- Vitamin E deficiency in newborns
- **Abetalipoproteinemia**
- **Infections**
  - Malaria
  - Babesia
  - Clostridium
  - Gram negative endotoxin
- **Wilson Disease**

AN APPROACH TO HEMOLYTIC ANEMIAS

HEREDITARY SPHEROCYTOSIS

- Hereditary spheroytosis is an inherited hemolytic anemia resultimg from red cell mebrane defect leading to microspherocytosis, splenomegaly and jaundice

- ETIOPATHOGENESIS-

- Spectrin deficiency is the most common abnormality
- Mutation of b spectrin gene and point mutations affect the binding of spectrin to protein 4.1

The gene mutations that cause hereditary spherocytosis cause red blood cells to have an abnormal, spherical shape with decreased flexibility.

The misshapen red blood cells are called spherocytes. The spherocytes are taken out of circulation and sent to the spleen to be destroyed (hemolysis).

This results in a shortage of red blood cells in the blood, and too many in the spleen

CLINICAL FEATURES-

- Seen all over the world
- Autosomal dominent with variable penetrance
- M=F ; present in neonate, childhood or adulthood
- Intermittent jaundice is usual presentation
- O/E- splenomegaly is a constant feature
- Gall stones (pigment type)
- Chronic leg ulcers (rare)

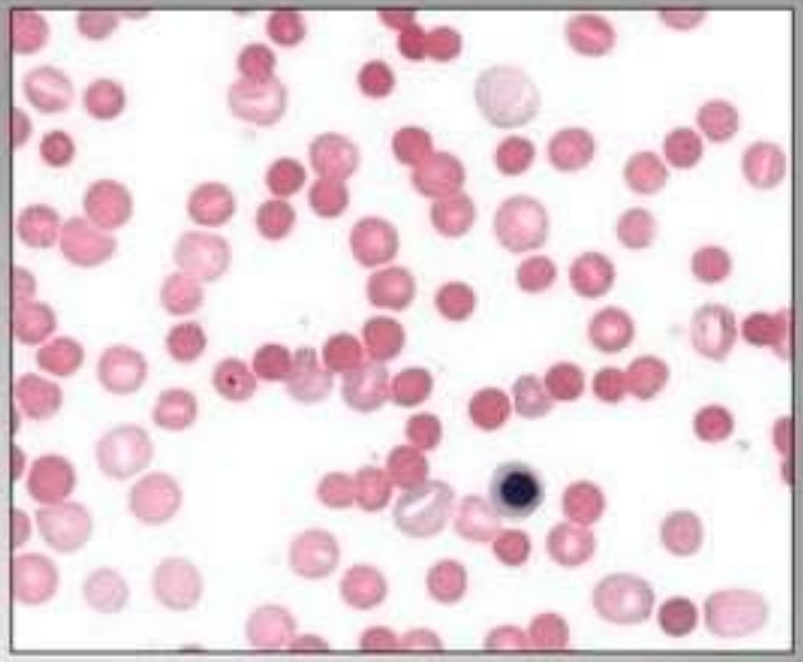
LAB FINDINGS

- PBF Findings- Microspherocytes which are small dense rbc without pallor
- MCV- Normal
- Reticulocytes- Increased
- Bone marrow- Erythroid hyperplasia with normoblastic reaction
- S. bilrubin- Increased (unconjugated)

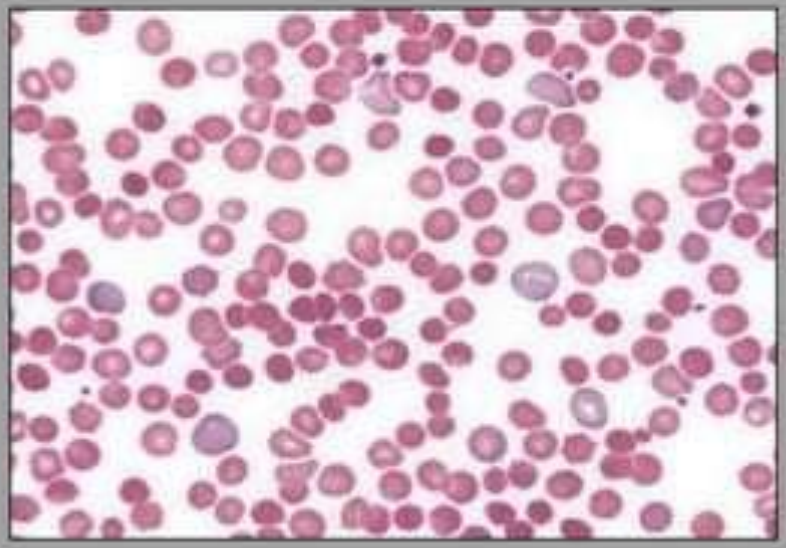
U. bilrubin – Increased

Fecal stercobilinogen- increased

S. haptoglobins- Reduced



Hereditary spherocytosis. Peripheral blood film of spherocytic hemolysis. Spherocytes are round, are slightly smaller than normal red blood cells, and lack central pallor. Note the nucleated red blood cells and polychromatophilic cells. It is important to look in the area of the slide where red blood cells are nearly touching each other to properly identify spherocytes. Red blood cells normally have a spherical appearance at the tail (thin) end of the blood smear.



Peripheral blood film of microspherocytes seen in *Clostridium perfringens sepsis. Although regular spherocytes are* usually smaller than normocytic red blood cells, microspherocytes are even smaller than that. This finding is usually seen in critically ill, septic patients with severe *C. perfringens infection.*

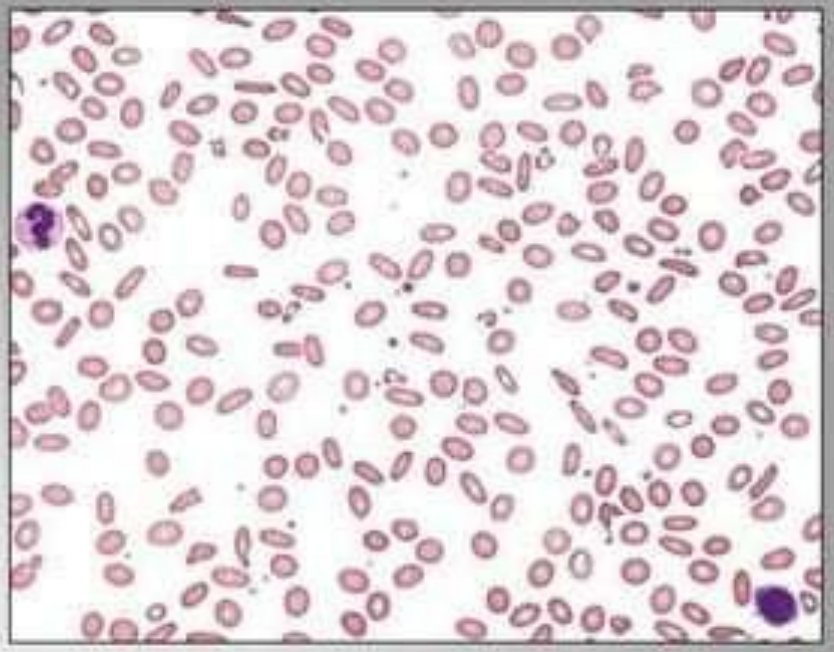
- Other diagnostic tests-

- Osmotic fragility test- shift of curve to right
- Incubated osmotic fragility test
- Glycerol lysis test – Increased (rate of lysis)
- Flow cytometry based on EMA (Eosin5-malemide)- lower in HS (mean fluooscnt intensity of EMA tagged cells)

HEREDITARY ELLIPTOCYTOSIS

- Group of anemias characterised by the presence of elliptical or oval RBCs in the peripheral blood. Such cells should be more than 25%
- Autosomal dominent disorder
- Membrane protein abnormalities like a b-spectrin defect, structural defectsor deficiency of protein 4.1 lead to elliptical shape of rbcs. membrane dysfunction and mild hemolysis

- Clinically patient are asymptomatic and mild hemolytic anemia is fully compensated in most cases
- Case is diagnosed incidentally when the blood film is examined for other ailment
- Peripheral smear demonstrates presence of elliptocytes (cigar shaped) which vary from 20-90% of cells. Osmotic fragility normal



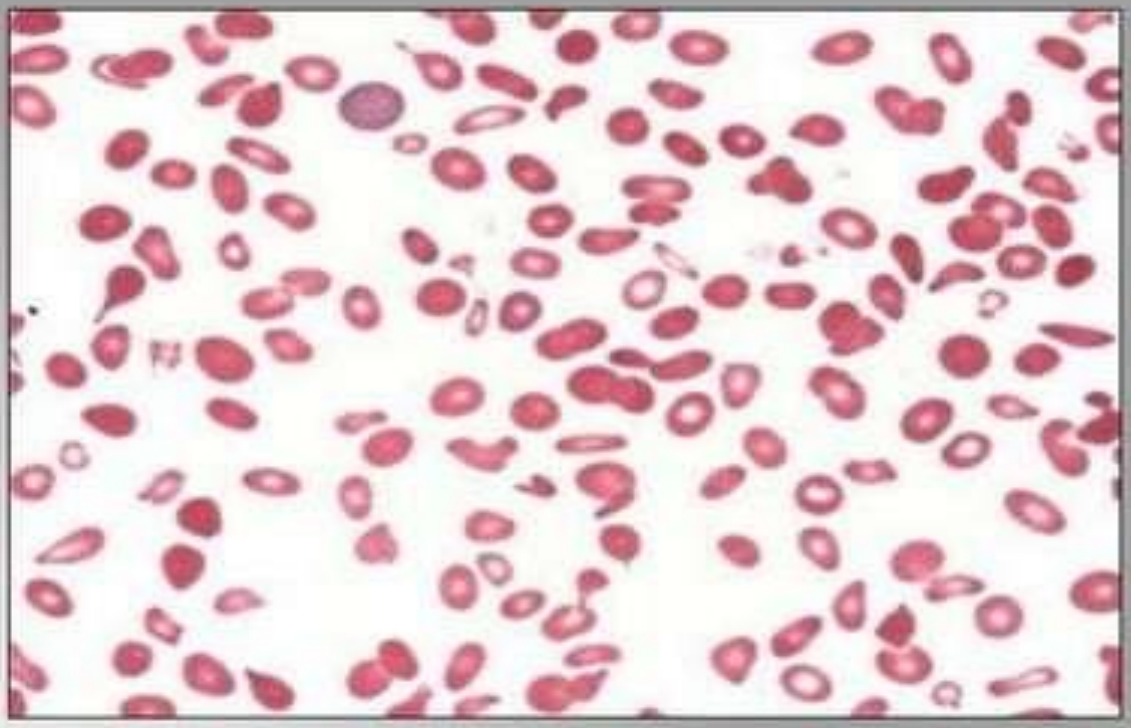
Hereditary elliptocytosis. Elliptocytes and ovalocytes are present in this blood film from a case of hereditary elliptocytosis. Elliptocytes are elongated with rounded edges (as opposed to sharp edges in sickle cells).

- ***Large numbers of elliptocytes***
- Hereditary elliptocytosis

- ***Small numbers of elliptocytes***
- Iron deficiency
- Thalassemia trait and major
- Megaloblastic anemia
- Myelodysplastic syndrome
- Myelofibrosis
- Southeast Asian ovalocytosis

Hereditary pyropoikliocytosis

- Hereditary pyropoikliocytosis is a rare hemolytic anemia
- There is a defective spectrin gene transmitted by one parent and also an elusive thalassemia like defect of spectrin synthesis inherited from normal parent
- This results in a compound inheritance in which a spectrin abnormality is superimposed upon spectrin deficiency

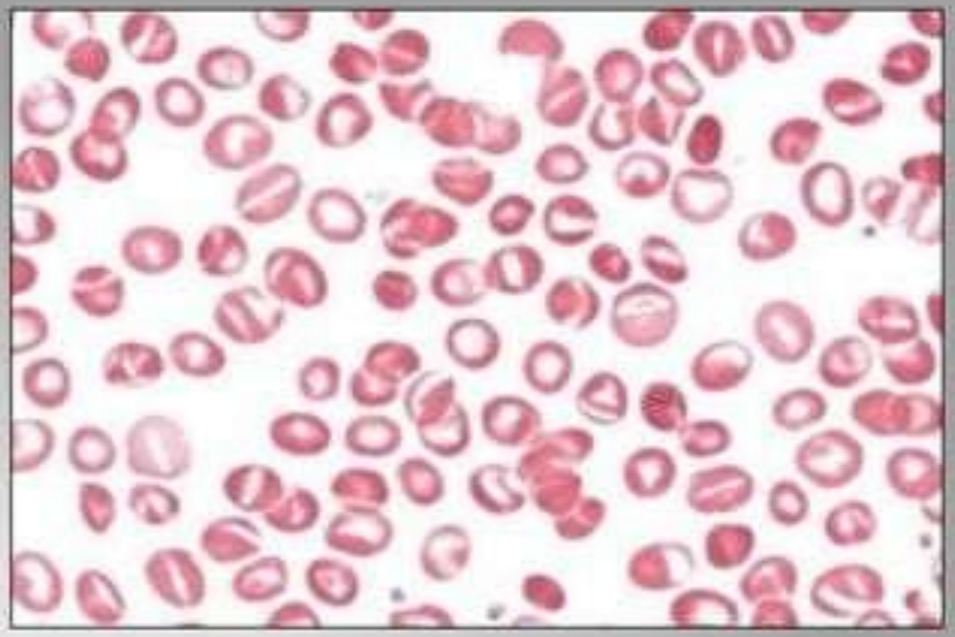


Hereditary pyropoikilocytosis. Peripheral blood film in patient with hereditary pyropoikilocytosis. Significant variations in size and shape are present: poikliocytes, teardrops, fragments, microspherocytes, elliptocytes, and small pieces and buds of red blood cells. The cells are microcytic with low MCV . Incubted osmotic fragility increased

Stomatocytosis

- Stomatocytes are red cells with a slit like central pallor and these are uniconcave/bowel shape in wet suspensions

Disorder	Stomatocytes %
Normal individual	<5%
Hereditary stomatocytosis	>30%
Accquired stomatoctosis	5-50%



Hereditary stomatocytosis. The red blood cells in this blood smear demonstrate slit-like central pallor, creating the appearance of a mouth (*stoma in Greek), from which the name* stomatocytes derives. Hereditary stomatocytosis may demonstrate 10% to 50% stomatocytes on the peripheral blood film. Ovalocytes and macrocytes also may be present.

- STOMATOCYTES

- Artifact
- Alcoholism
- Alcoholic liver disease
- Obstructive liver disease
- Hereditary stomatocytosis
- Hereditary xerocytosis
- Southeast Asian ovalocytosis
- Tangier disease
- Rh-null phenotype
- Drugs (hydroxyurea)

MANAGEMENT

- **Folate therapy**

- **Red blood cell transfusions** may be required in severe cases of anemia, particularly in the first years of life or during infections and pregnancy

- If red blood cell transfusions are needed repeatedly, **iron chelating therapy** may be required to reduce iron overload.

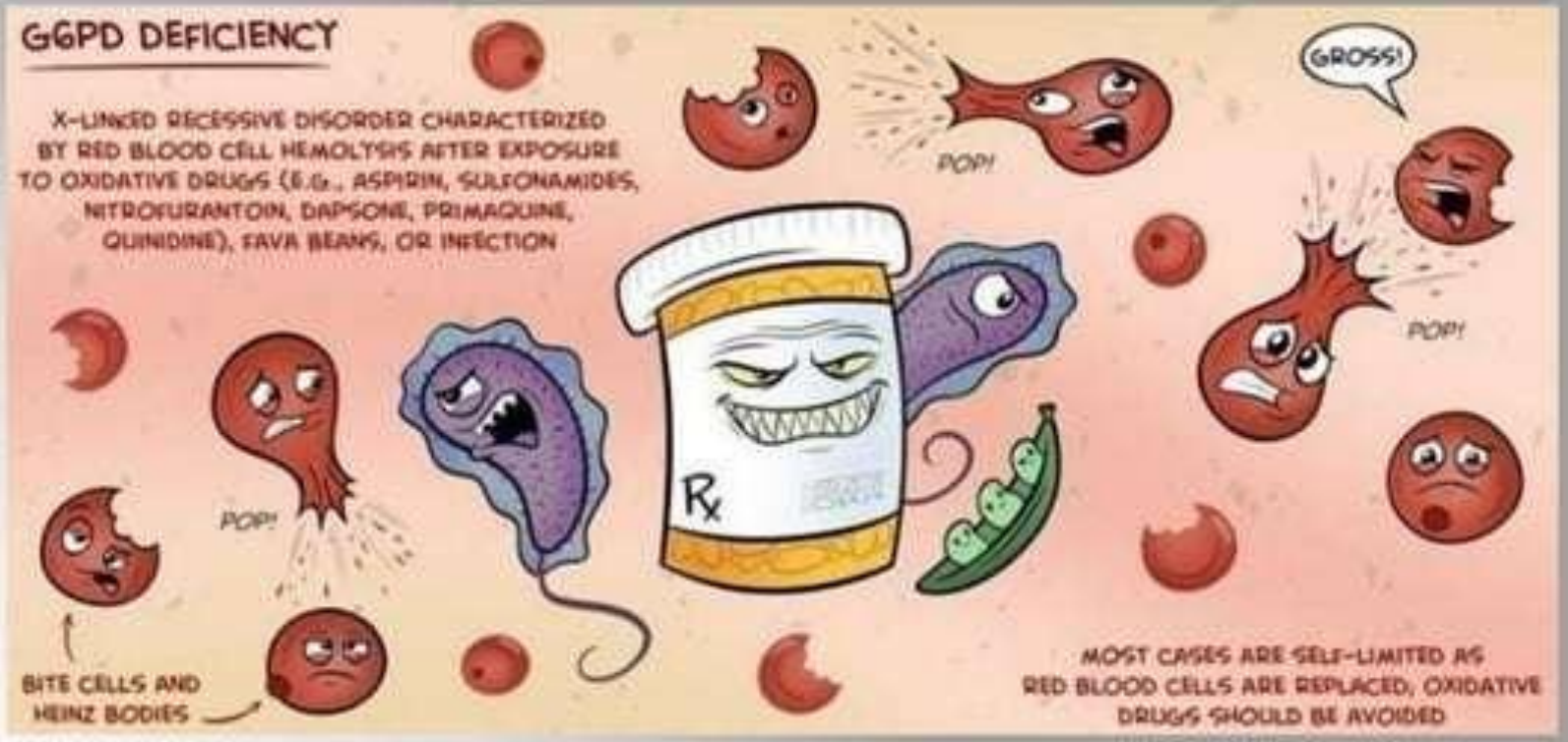
  Regular monitoring for anemia and gallstones is advised.

MANAGEMENT

Removal of the spleen (**SPLENECTOMY**) is usually only performed in severe HS or in moderate to severe cases with significant anemia and gallstone complications.

Splenectomy is not recommended in cases of mild HS except in specific cases.

ENZYMOPATHIES



GLUCOSE 6-PHOSPHATE DEHYDROGENASE DEFICIENCY

- Glucose6-phosphate dehydrogenase is the first enzyme in the hexose monophosphate shunt pathway (HMP) which protects red cells from oxidant injury
- Deficiency of G6PD may result in episodes of hemolysis following certain drug intake or chemical exposure or infection
- G6PD deficiency is a sex linked disease. Its prevalance is higher in tropical eastern countries. Prevalance is higher in kurdish jews (60-70%) and lower in japan (.1%)

Clinical and hematological presentation of G6PD deficiency

- ***Acute hemolytic anemia***- Occurs following exposure to drugs like primaquine, infections like pneumonia, typhoid and oxidative chemicals.

  CF- appears 1-3 hours after drug adiministration. Sudden development of pallor, passage of dark urine, jaundice and severe backache

- ***Chronic non-spherocytic anemia***- There is moderately severe enyme deficiency, hemolysis continues throughout life. Seen in neonatal period.

  CF- hemolysis is compensated so milder symptoms

Clinical and hematological presentation of G6PD deficiency

- ***Neonatal hyperbilrubinimia***- Jaundice, kernicterus

- ***Favism***- Common in children caused by consumption of fava beans.
  Resulting in acute severe hemolysis within few hours .
  CF-headache, fever, chills and back pain.

Diagnostic tests-

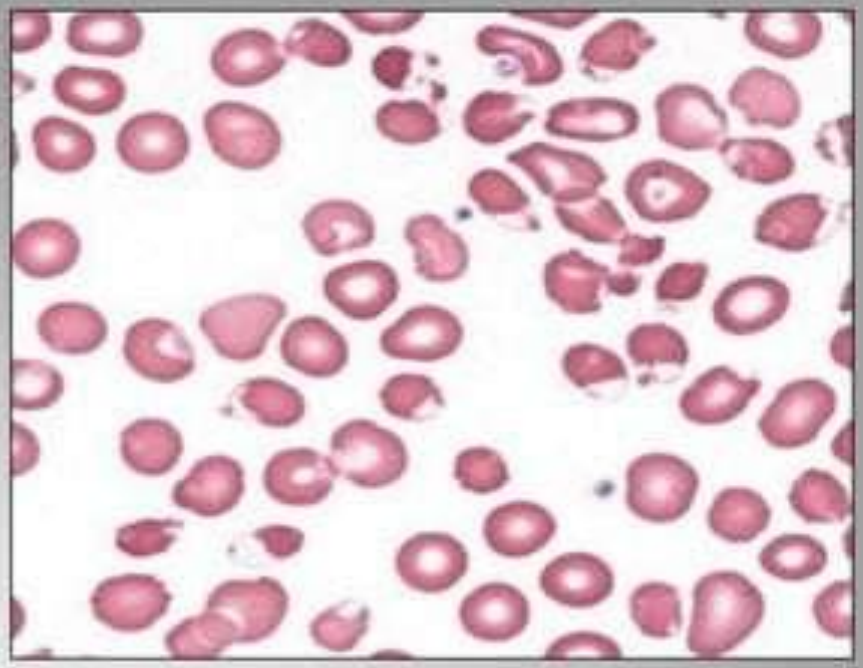
1. **Peripheral blood film evaluation, history and biochemical finding-**

- Moderate anisopoikliocytosis with polychromatophilia
- Microspherocytes and bite cell (removel of heinz bodies)
- Reticulocytosis (20-50%)
- Hemogobinuria and increase urobilinogen in urine

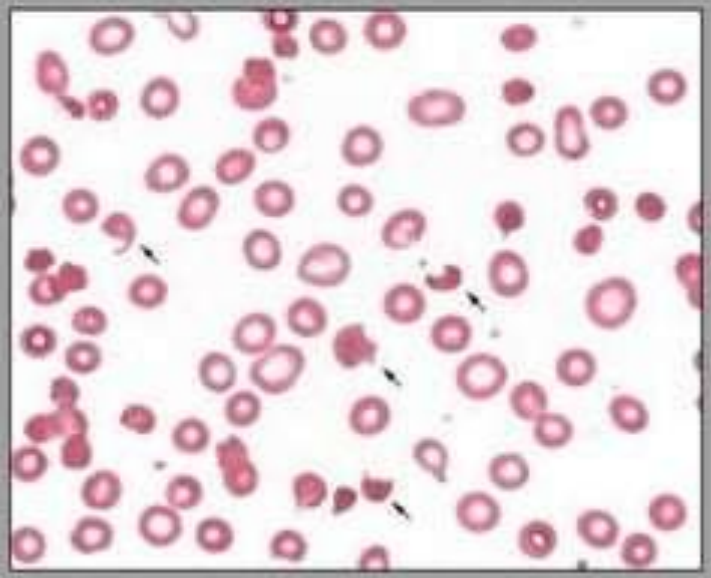
2. **Screening tests for G6PD deficiency** are-

- Methemaglobin reduction test (MRT)
- Ascorbate –cyanide test
- Fluooscent spot test
- Dye decolourisation test

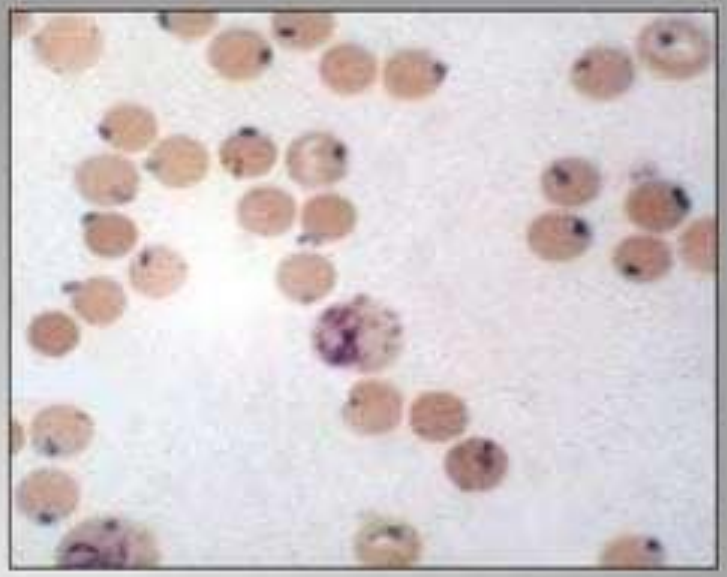
3. **Quantitative G6-PD assay and DNA analysis by PCR**



Peripheral blood film demonstrating blister cells in a patient with glucose-6-phosphate dehydrogenase deficiency. The blister appears as a vacuole in the erythrocyte's hemoglobin at the edge of the red blood cell surface. A thin rim of cytoplasm seems to enclose this vacuole. This cell is usually a precursor to a bite cell.



Bite cells. The red blood cells in this peripheral smear appear bitten. The erythrocyte may retain or lose central pallor, depending on the size and numbers of bites. In some cases, the bite cell may be mistaken for *helmet cells, a type of fragmented erythrocyte.*. A double bite cell is displayed in the center of the figure.



Heinz bodies. Peripheral blood stained with crystal violet supravital stain demonstrating Heinz-body inclusions, which are not visible with Romanowsky stains alone. Heinz bodies are purple-blue, large, single or multiple inclusions attached to the inner surface of the red blood cellmembrane. They represent precipitated normal or unstable hemoglobins..

Reticulocytes do not stain with crystal violet.

- Heinz bodies

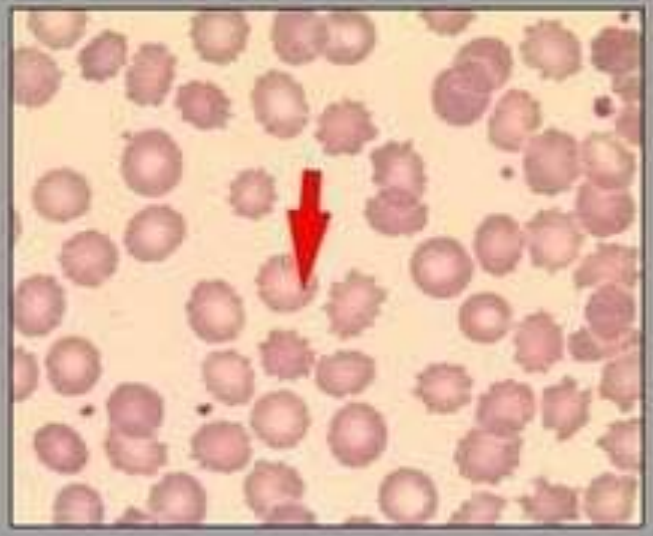
- *Oxidative stress*
  - glucose-6-phosphate dehydrogenase deficiency, glutathione synthetase deficiency
  - Drugs
  - Toxins

- *Unstable hemoglobins*

Pyruvate kinase deficiency

- This is the second common enzyme deficiency involving the glycolytic pathway of red cell metabolism.
- Autosomal recessive conditon
- Pyruvate kinase has 2 isoenzymes- PK-L (Liver) and PK-M (Muscles).
  There is accumulation of G-3-P, and 2,3-DPG and glucose

- Clinical features- Neonatal jaundice to compensated hemolytic process. Pallor , jaundice, gall stones and/or splenomegaly may be present



- Hematological findings- moderate anemia with reticulocytosis. Peripheral smear demostrates- Presence of prickle cells (red cells having sharp thorn like projections), a few echinocytes and tailed poikliocytes

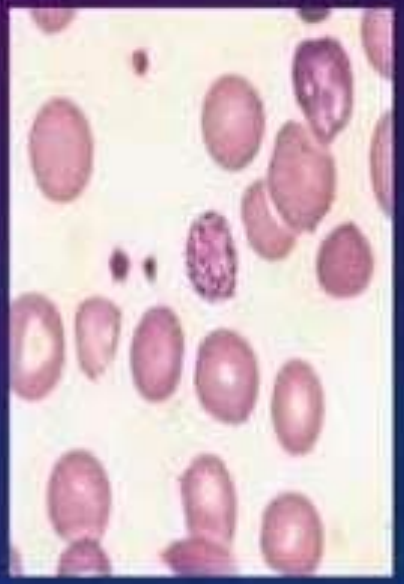
Pyrimidine 5 nucleotidase deficiency:

Characterised by the presence of marked basophilic stippling of RBCs and echinocytes

- Clinically, Mild spleomegaly wih intermittent jaundice

BASOPHILIC STIPPLING

- Presence of irregular basophilic granules with in Rbc which are variable in size .
- Stain deep blue with Wright's stain
- Fine stippling seen with
  - Increased polychromatophilia
  - Increased production of red cells.
- Coarse stippling
  - Lead and heavy metal poisoning
  - Disturbed erythropoiesis
    - Megaloblastic anemia
    - Thalassaemia
    - Infection
    - liver disease
  - Unstable Hb
  - Pyrimidine-5'-nucleotidase deficency



HEMOGLOBINOPATHIES

The Thalassemias

- Thalassemia syndrome are autosomal recessive disorders
- Thalassemia results from defects in the rate of synthesis of a or b chains, lead to reduced hemoglobin production and accumulation of a or b chains
- Thalassemia is considered to be quantitative hemogolobinopathy, since no structural abnormal hb is synthsised

Sickle cell disorders

- Sickling syndromes are characterized by the presence of HbS which imparts sickle shape to red cells in a state of reduced oxygen tension
- HbS is prevalant in Africa, Mediterranean countries and India. In India, seen common in tribals and in ethnic groups of MP, Orissa, AP, Maharashtra (vidharba region), TN (chetti tribes) and Kerala
- There is high prevelance of HbS in areas endemic to malaria falciperum

Genetics –

- Sickle mutation is caused by substitution of *valine* in place of *glutamic acid* in the 6th position (*b6 glu-val*) ofb-chain

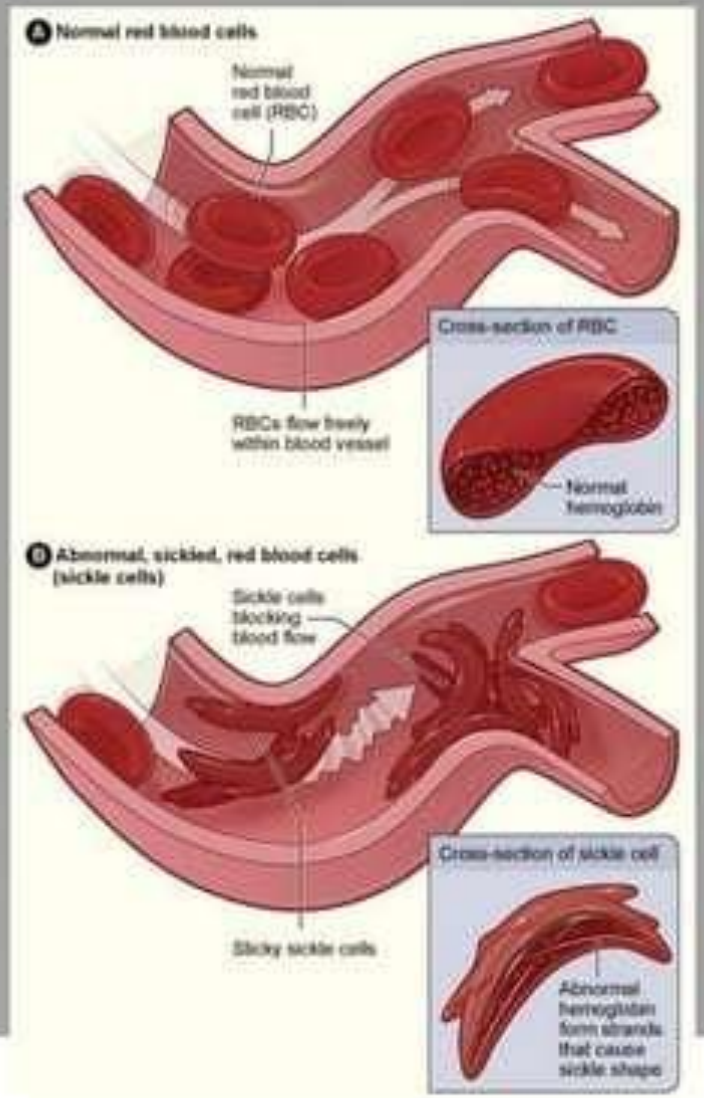
- Mutation results in clinical presentation

1. ***Sickle cell anemia-*** HbS-HbS, Homozygous state
2. ***Sickle cell trait*** - HbA-HbS, heterozygous state
3. ***Sickle cell disease-*** Refer to all diseases with HbS in combination with – normal (HbA), abnormal gene of b-thalassemia, a-thalassemia, HbD, HbE, HbC,HbQ

Pathophysiology of vascular occlusion and hemolysis

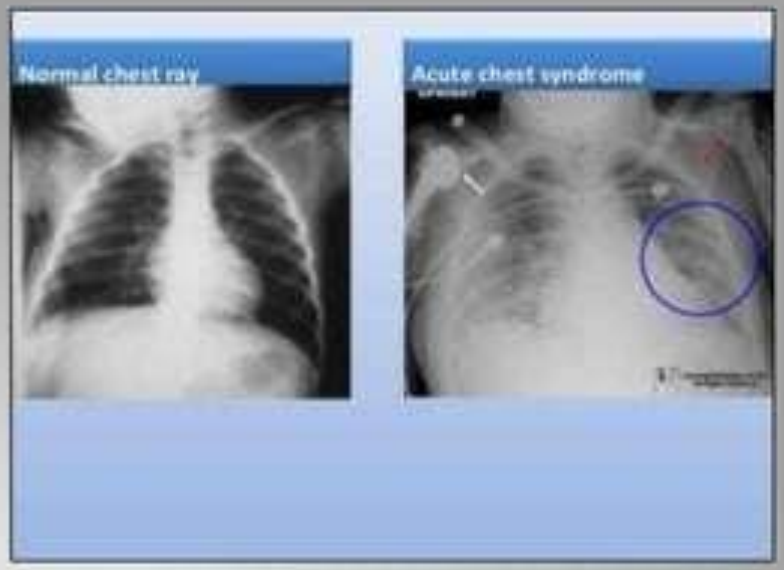
- Polymerisation of deoxygenated HbS is the primary event in the pathogenesis of the disease

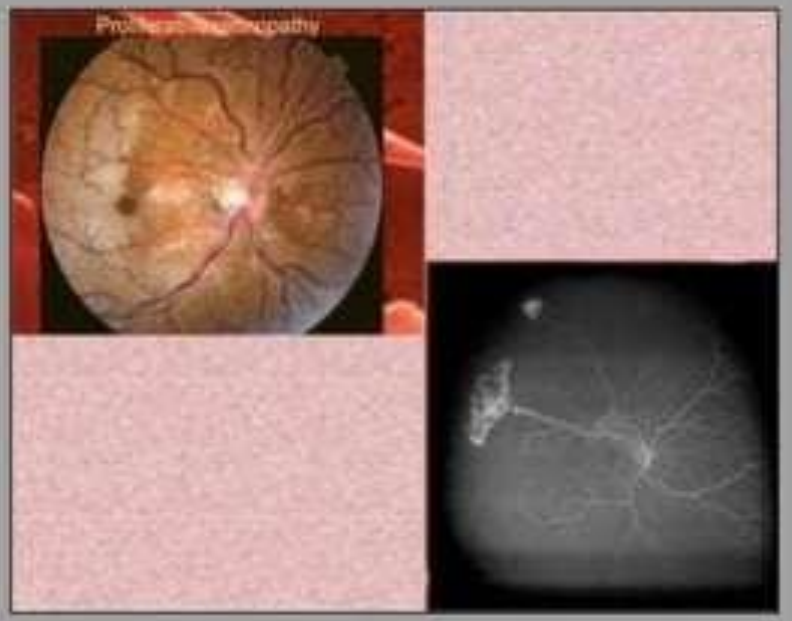
- Red cell containing HbS pass through microcirculation of spleen – various cycles of sickling and desickling – Irreversible sickeled RBCs
– Extravascular hemolysis in spleen – Vascular stasis – vascular occlusion – splenic infarcts – hyposplenism (lead to infection) and autosplenectomy



Clinical features-

- Delay in puberty, growth and development
- Recurrent leg ulcers
- Avascular necrosis of femur head
- Dactylitis (Hand –Foot syndrome)
- Pneumonia, meningitis, Osteomylitis
- Jaundice and liver enlargement
- Pigment gall stones
- Acute abdominal pain (infarcts of abdominal viscera)
- Priapism
- Acute chest syndrome (fever, chest pain, leucocytosis, appearance of pulmonary infilterate with sickle anemia)
- Sickle retinopathy- Salmon patches- intra retinal hemmorhages


Normal chest ray
Acute chest syndrome




Hand Foot syndrome -
Dactylitis

Crisis in sickling syndrome

- 1. Sickling crisis (vaso-occlusive crisis)
- 2. Hemolytic crisis
- 3. Aplastic crisis
- 4. Sequestration crisis

Sickle cell trait

- Sickle cell trait usually do not manifest any clinical findings
- Hemoglobin varies from 11-13 gm/dl
- Red cells are normocytic normochromic and very target cells and mild degree of anisopoikliocytosis
- Clinical and hematological picture is milder in comparison to HbSS state
- Diagnosis is confirmed by Hb electrophoresis, HPLC and sickling test

Hematological findings –

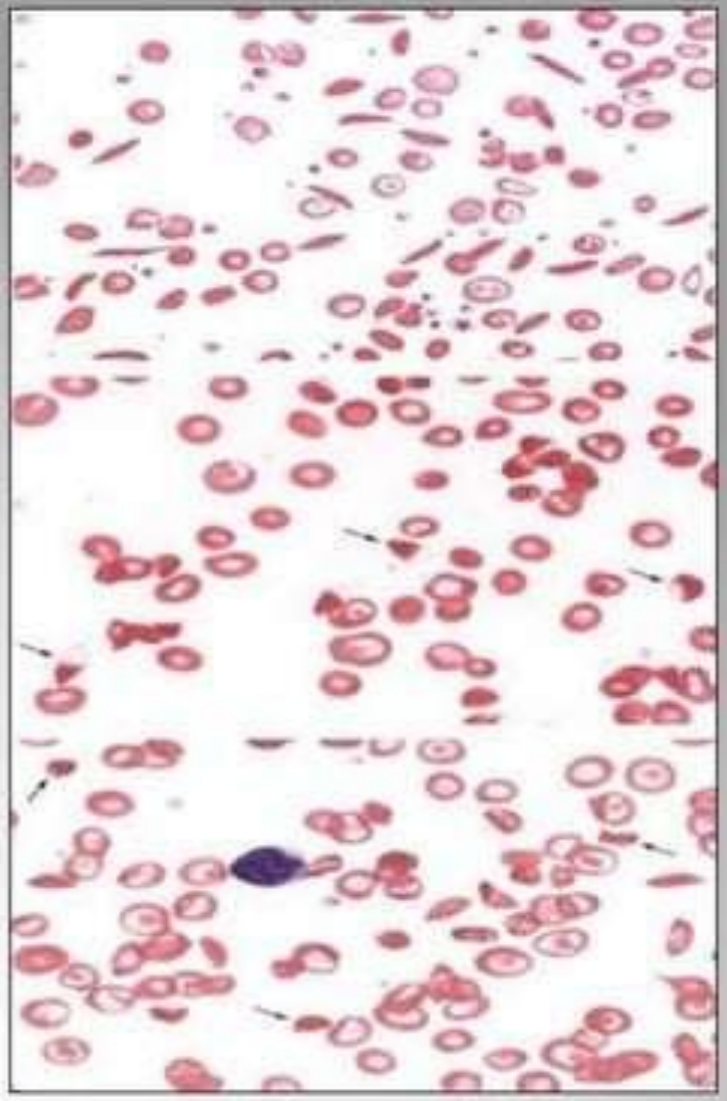
- Anemia- moderately severe anemia with Hb 5- 10 gm

- PBF demonstrates –

  Red cells- Normocytic normochromic to mildly hypochromic
  Moderate to severe degree of anisopoikliocytosis.
  Sickle cells, target cells, ovalocytes,
  Polychromtophila with nucleted RBCs.
  Howell-jolly bodies alo seen
  TLC- Mildly elevated ; Platlets- Increased

  Reticulocytosis- 3%-10%

- Bone marrow- Erythroid hyperplasia with normoblastic reaction



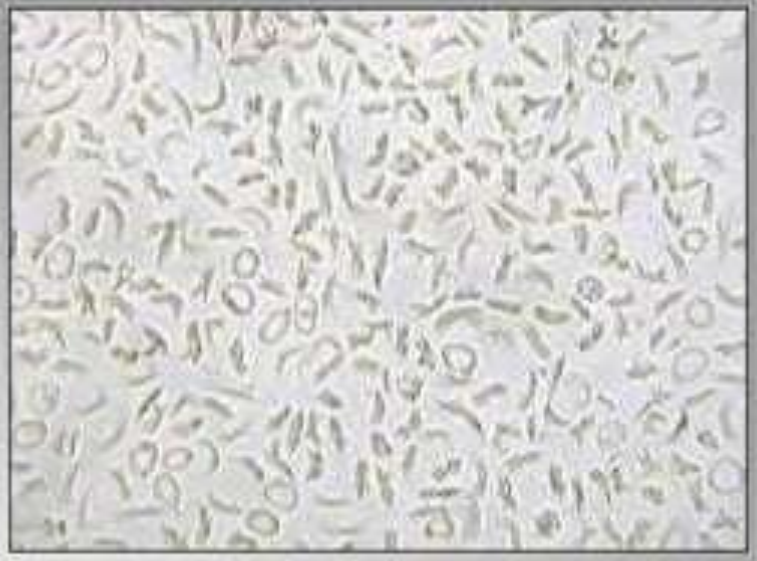
Sickle cell anemia. *Top panel: Peripheral blood film of* hemoglobin SS (HbS disease). The numerous elongated erythrocytes with sharp points are classic sickle cells. Sickle cells that appear folded over are called *envelope cells. Target cells are present,* in this case because of hyposplenism from the splenic infarction that occurs in HbSS patients. Howell-Jolly bodies may be seen as well. *Middle panel: Peripheral blood film in patient with HbSS,* demonstrating sickle cells with Hb concentrated at one end and absent at the other, called hemi-lunes(*arrows), a finding seen in* HbSS or HbSC. *Bottom panel: Peripheral blood film in patient with* HbSS, demonstrating short, stubby, and rhomboid-shaped sickle cells called oat and boat cells (*arrows).*

- Other diagnostic tests-

- **SICKLING TESTS-** Presence of HbS demostrated by using reducing agent like 2% sodium metabisulphite

- **SICKLING SOLUBILITY TEST**

- **Hb electrophoresis-** Hb electrophoresis can be carried out on cellulose acetate membrane (pH8.9) or starch agarose (pH 8.6). HbS is a slow moving Hb as compared to HbA and HbF. Howeever, electrophoretic mobility of HbD/HbQ india is similar to HbS , therefore sickling test is essential to differentiate.



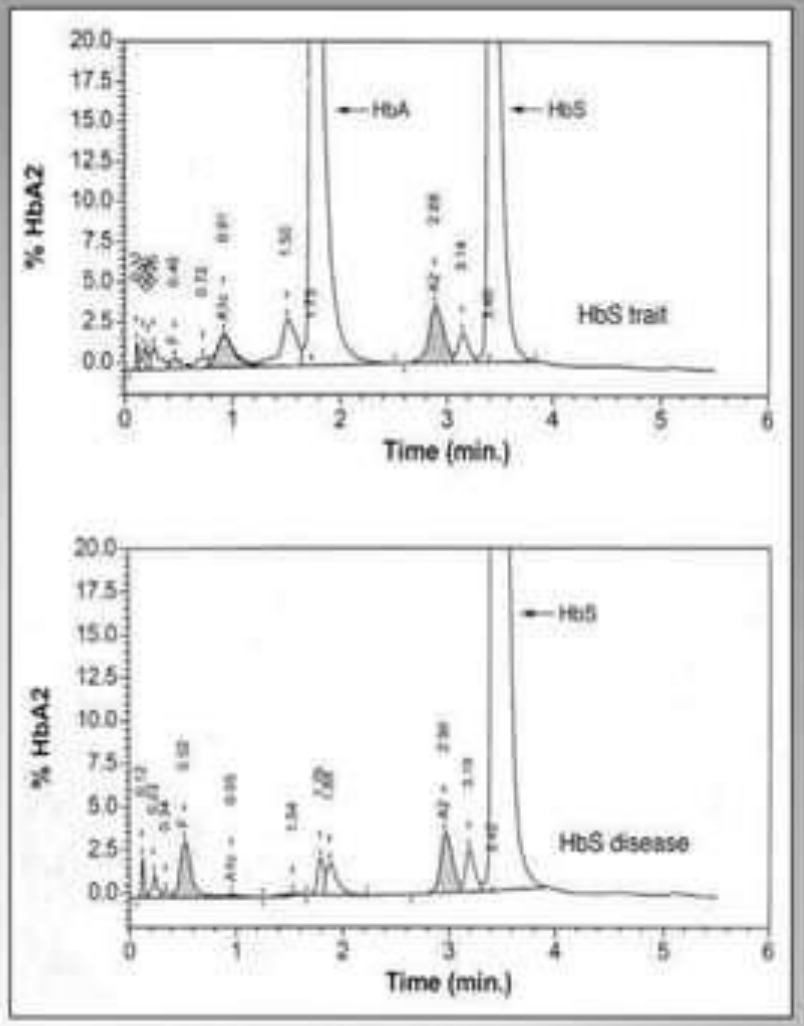
Sickling test – 2% metabisulphite prepration show sickled red cells

Sickle cell solubility test. In this test, whole blood is added to a high phosphate buffer with saponin and sodium dithionite, which causes the hemoglobin to become deoxyhemoglobin. Deoxyhemoglobin S is insoluble. The turbidity of the sample on the left indicates the presence of HbS. The clear sample onthe right contains no HbS.

3. HPLC (HIGH PERFORMANCE LIQUID CHROMATOGRAPHY)

- On HPLC, HbS has a retention time of 4.40 to 4.50 min, while HbD punjab is is 4.50-4.15 min. HbSS/HbSA- In HbSS, major abnormal Hb is HbSconstituting 70-90% of total Hb, HbF is 10-30% but HbA is nil. This differentiates homozygous state from heterozygous state, since the latter demonstrates 2 bands of HbS and HbA

- HPLC is a **sensitive method for confirmation of HbS**



High-performance liquid chromatography (HPLC) sample demonstrating hemoglobin S trait (HbA 60%, HbS 40%). HPLC can separate HbS from HbD/G/Lepore, which are seen in the same band on alkaline Hb electrophoresis. *Lower panel: HPLC sample demonstrating hemoglobin S disease (HbS* 90%). Note the absence of hemoglobin A.

Management of sickle cell anemia

Is usually aimed at

1. Avoiding pain episodes,
2. Relieving symptoms and
3. Preventing complications.

Treatments might include medications and blood transfusions.

For some children and teenagers, a stem cell transplant might cure the disease.

Medications

1. **HYDROXYUREA (DROXIA, HYDREA, SIKLOS).**
   Daily hydroxyurea reduces the frequency of painful crises and might reduce the need for blood transfusions and hospitalizations. It can also increase risk of infections. C/I pregnancy.
2. **L-GLUTAMINE ORAL POWDER (ENDARI).**
   The FDA recently approved this drug for treatment of sickle cell anemia.
   It helps in reducing the frequency of pain crises.
3. **CRIZANLIZUMAB (ADAKVEO).**
   The FDA recently approved this drug for treatment of sickle cell anemia. Given IV, it helps reduce the frequency of pain crises.
   Side effects can include nausea, joint pain, back pain and fever.

Medications

4) **VOXELOTOR (OXBRYTA).**

The Food and Drug Administration (FDA) recently approved this oral drug to improve anemia in people with sickle cell disease.

Side effects can include headache, nausea, diarrhea, fatigue, rash and fever

5) **PAIN-RELIEVING MEDICATIONS.**

Level of Pain	Suggested Medications
Mild pain	Non-opioid ± adjuvant
Moderate pain	Weak opioid (or low dose of strong opioid) ± non-opioid ± adjuvant
Severe pain	Strong opioid ± non-opioid ± adjuvant

Preventing infections

- ✓ Children with sickle cell anemia might receive penicillin between the ages of about 2 months old until at least age 5.
- ✓ Adults who have sickle cell anemia may need to take penicillin throughout their lives, if they've had pneumonia or surgery to remove the spleen.
- ✓ VACCINES
  - ✓ recommended childhood vaccinations
  - ✓ vaccines against pneumonia and meningitis and an annual flu vaccines.

Surgical and other procedures

- **Blood transfusions**
- **Stem cell transplant.** Also known as bone marrow transplant

ROLE OF PHYSIOTHERAPIST

- Role in education, treatment and possible prevention of exacerbations.
- Patient education is extremely important for individuals with sickle cell. They should be educated on the importance of physical activity and remaining mobile in order to combat serious pulmonary and other systemic complications.
- Furthermore, the patient should be taught breathing techniques and incentive spirometry to also prevent acute chest syndrome and atelectasis, as well as retain adequate lung capacity.
- Wound care to stasis ulcers that often occur on the hands, legs, and feet may also be indicated for pt management.

ROLE OF PHYSIOTHERAPIST

- Physical therapists may also work with individuals, especially young children, who have had an acute stroke secondary to sickle cell disease. Therapists can address any weakness, loss of function and neuromuscular complications that may have occurred due to the stroke.

- May have an intolerance to exercise and may fatigue quickly due to anemia. Pt's should be mindful of this and gradually work up to moderate levels of exercise with frequent rest breaks.
- During painful episodes, therapists should avoid overexerting the patient, and should look out for stressors that may include dehydration or cold.

THANK YOU

For more updates:

thepainkillerMD