Haemolytic Anaemia

Hereditary Spherocytosis
Haemoglobinopathies
Thalassaemias

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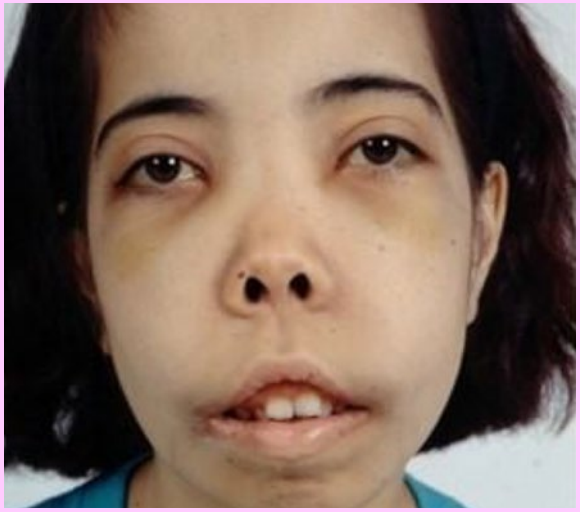
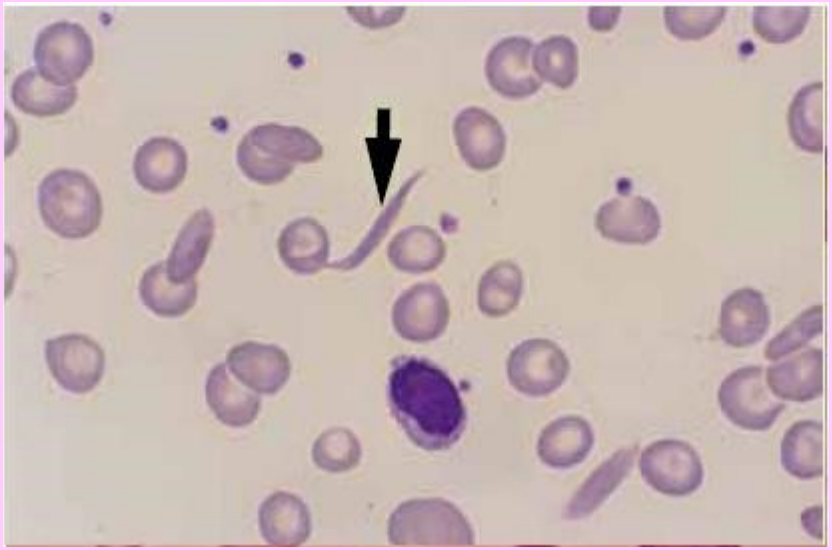




Haemolytic anaemia

Haemolysis indicates that there is shortening of the normal red cell lifespan of 120 days.

To compensate, the bone marrow may :

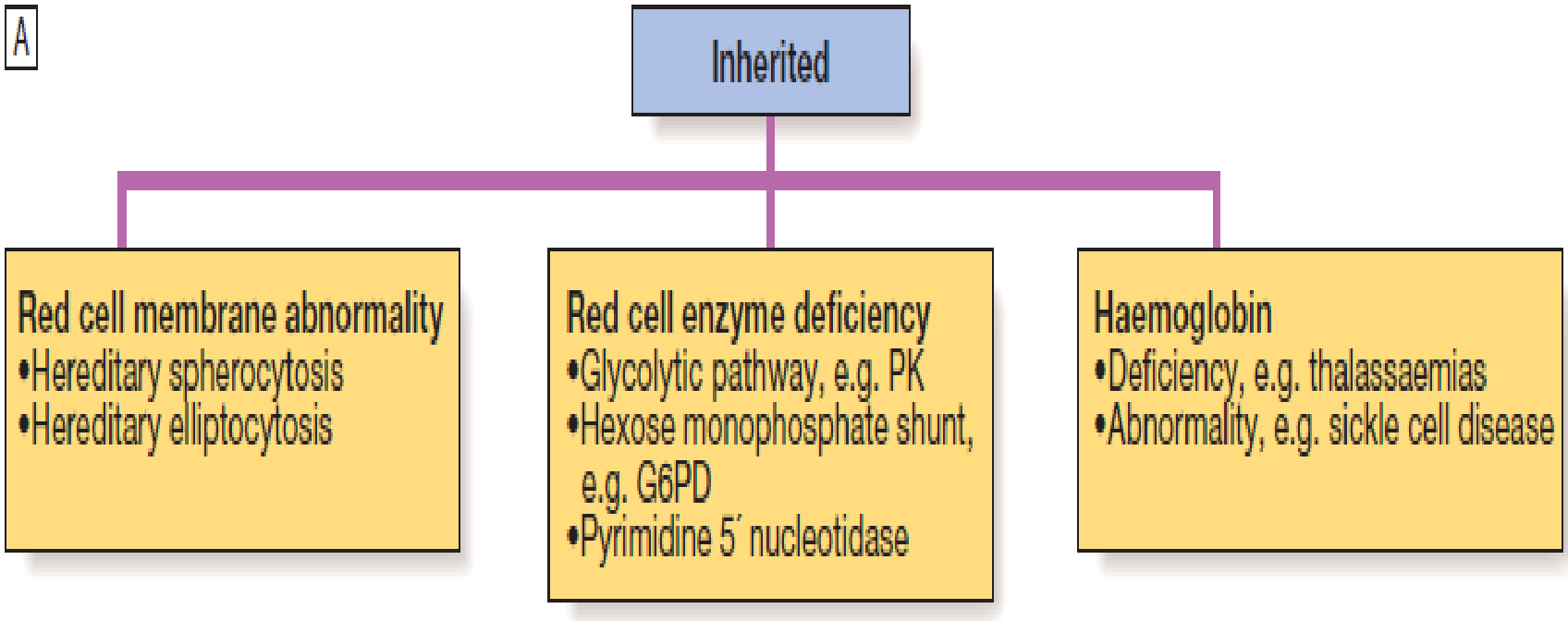
1-increase its output of red cells six- to eightfold by increasing the proportion of red cells produced.

2- expanding the volume of active marrow.

3-releasing reticulocytes prematurely.

Anaemia occurs only if the rate of destruction exceeds this increased production rate.

A


Inherited
Red cell membrane abnormality
•Hereditary spherocytosis
•Hereditary elliptocytosis
Red cell enzyme deficiency
•Glycolytic pathway, e.g. PK
•Hexose monophosphate shunt, e.g. G6PD
•Pyrimidine 5′ nucleotidase
Haemoglobin
•Deficiency, e.g. thalassaemias
•Abnormality, e.g. sickle cell disease

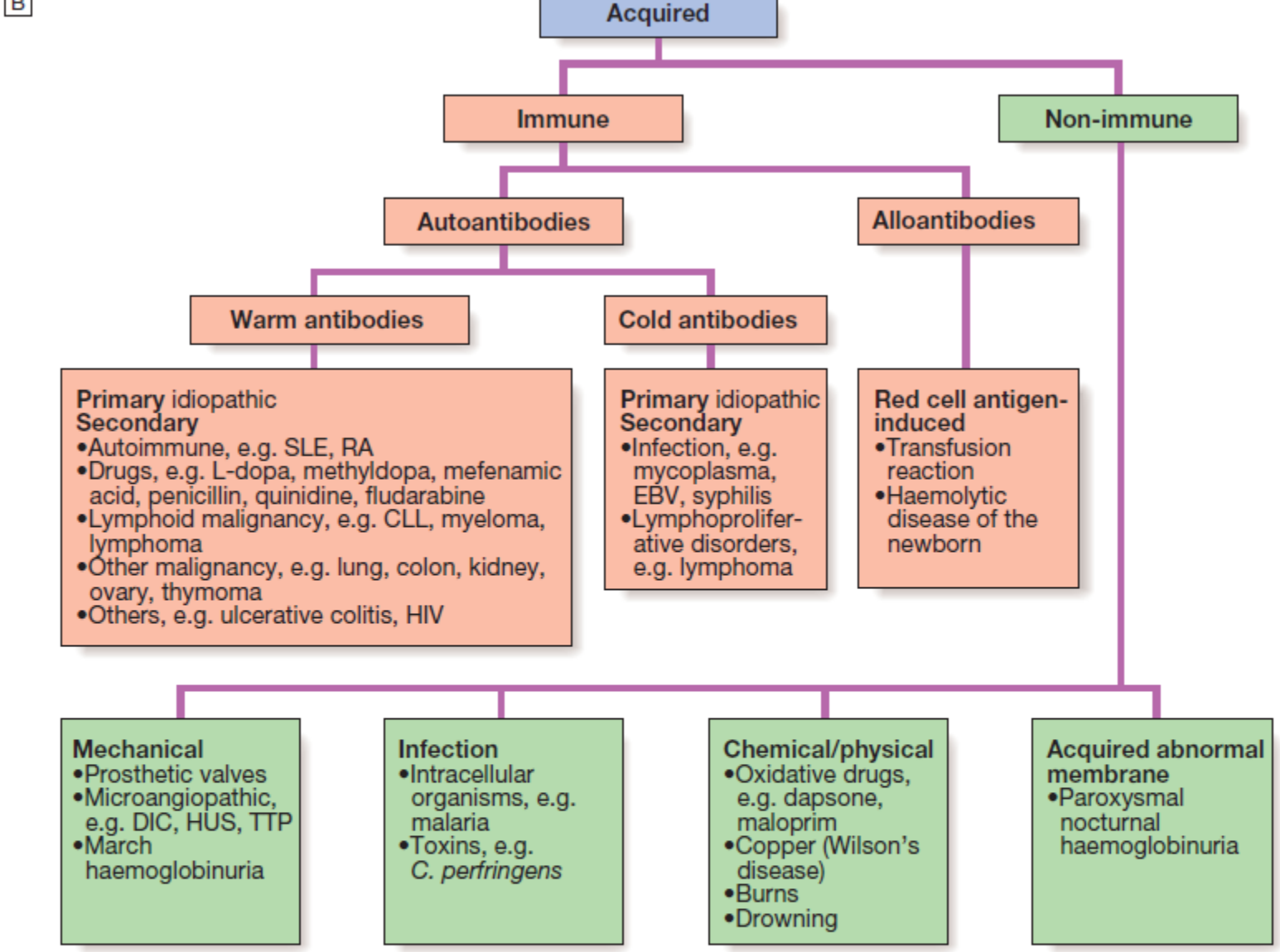


Fig. 24.21 Causes of haemolysis. A Inherited causes. B Acquired causes. (CLL = chronic lymphatic leukaemia; DIC = disseminated intravascular coagulation; EBV = Epstein–Barr virus; G6PD = glucose-6-phosphate dehydrogenase; HUS = haemolytic uraemic syndrome; PK = pyruvate kinase; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; TTP = thrombotic thrombocytopenic purpura)

mechanical trauma (heart valves, DIC) or oxidative damage (e.g. drugs such as dapsone and maloprim). When intravascular red cell destruction occurs, free hae-

degrade it and store the iron as haemosiderin. When the tubular cells are subsequently sloughed into the urine, they give rise to haemosiderinuria, which is always

Red cell destruction overloads pathways for haemoglobin breakdown in the liver , causing a modest rise in unconjugated bilirubin in the blood and mild jaundice.
Increased reabsorption of urobilinogen from the gut results in an increase in urinary urobilinogen .
Red cell destruction releases LDH into the serum.

The bone marrow compensation results in a reticulocytosis, and sometimes nucleated red cell precursors appear in the blood.
Increased proliferation of the bone marrow can result in a thrombocytosis, neutrophilia and, if marked, immature granulocytes in the blood, producing a leucoerythroblastic blood film.

Investigation results indicating

active haemolysis

Hallmarks of haemolysis

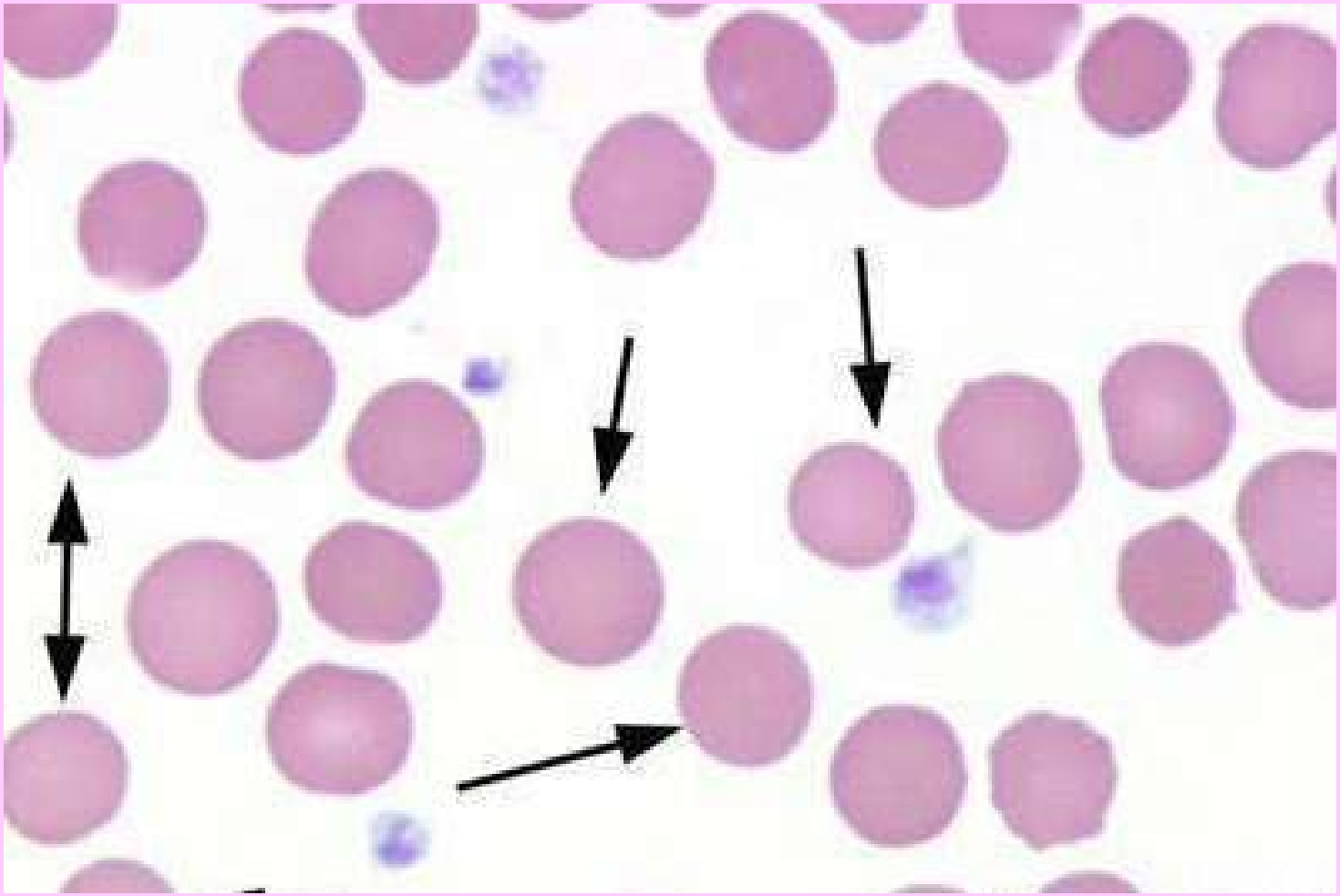
- **↓Haemoglobin**
- **↑Unconjugated bilirubin**
- **↑Lactate dehydrogenase**
- **↑Reticulocytes**
- **↑Urinary urobilinogen**

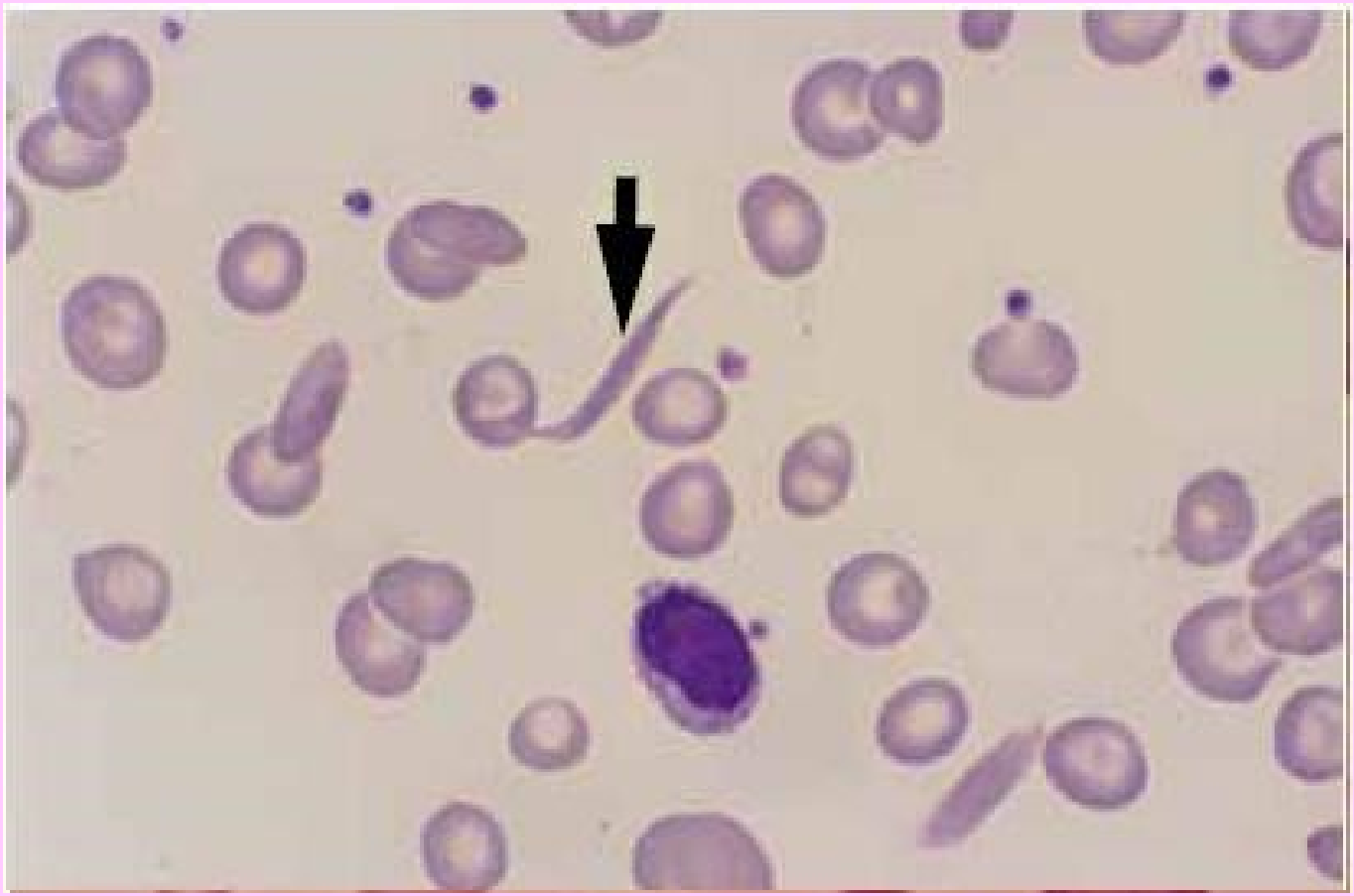
Additional features of intravascularhaemolysis

- **↓Haptoglobin**
- **↑Methaemalbumin**
- **Positive urinary haemosiderin**
- **Haemoglobinuria**

The apperance of the red cells may give an indication of the likely cause of the haemolysis:

- Spherocytes are small, dark red cells that suggest autoimmune haemolysis or hereditary spherocytosis.
- Sickle cells suggest sickle-cell disease.
- Red cell fragments indicate microangiopathic haemolysis.
- Bite cells (normal-sized red cells that look as if they have been partially eaten) suggest oxidative haemolysis .





extravascular hemolysis:

Physiological red cells destruction occurs in the reticulo-endothelial cells in the liver or spleen so avoiding free hemoglobin in the plasma. In most haemolytic states, haemolysis is predominantly extravascular.

To confirm the haemolysis, patients' red cells can be labelled with 51chromium. When re-injected, they can be used to determine red cell survival; when combined with body surface radioactivity counting, this test may indicate whether the liver or the spleen is the main source of red cell destruction.

Intravascular haemolysis

Less commonly, red cell lysis occurs within the blood stream due to membrane damage by complement (ABO transfusion reactions, paroxysmal nocturnal haemoglobinuria), infections (malaria, Clostridium perfringens), mechanical trauma (heart valves, DIC) or oxidative damage (e.g. enzymopathies such as glucose- 6-phosphate dehydrogenase deficiency, which may be triggered by drugs such as dapsone and maloprim).

1-When intravascular red cell destruction occurs, free haemoglobin is released into the plasma. Free haemoglobin is toxic to cells and binding proteins have evolved to minimise this risk. Haptoglobin is an α2-globulin produced by the liver, which binds free haemoglobin, resulting in a fall in its levels during active haemolysis

2-Once haptoglobins are saturated, free haemoglobin is oxidised to form methaemoglobin, which binds to albumin, in turn forming methaemalbumin, which can be detected spectrophotometrically in Schumm's test.

3-Methaemoglobin is degraded and any free haem is bound to a second binding protein called haemopexin.

4-If all the protective mechanisms are saturated, free haemoglobin may appear in the urine (haemoglobinuria).

When fulminant, this gives rise to black urine, as in severe falciparum malaria infection .

In smaller amounts, renal tubular cells absorb the haemoglobin, degrade it and store the iron as haemosiderin. When the tubular cells are subsequently sloughed into the urine, they give rise to haemosiderinuria, which is always indicative of intravascular haemolysis.

Causes of haemolytic anaemia

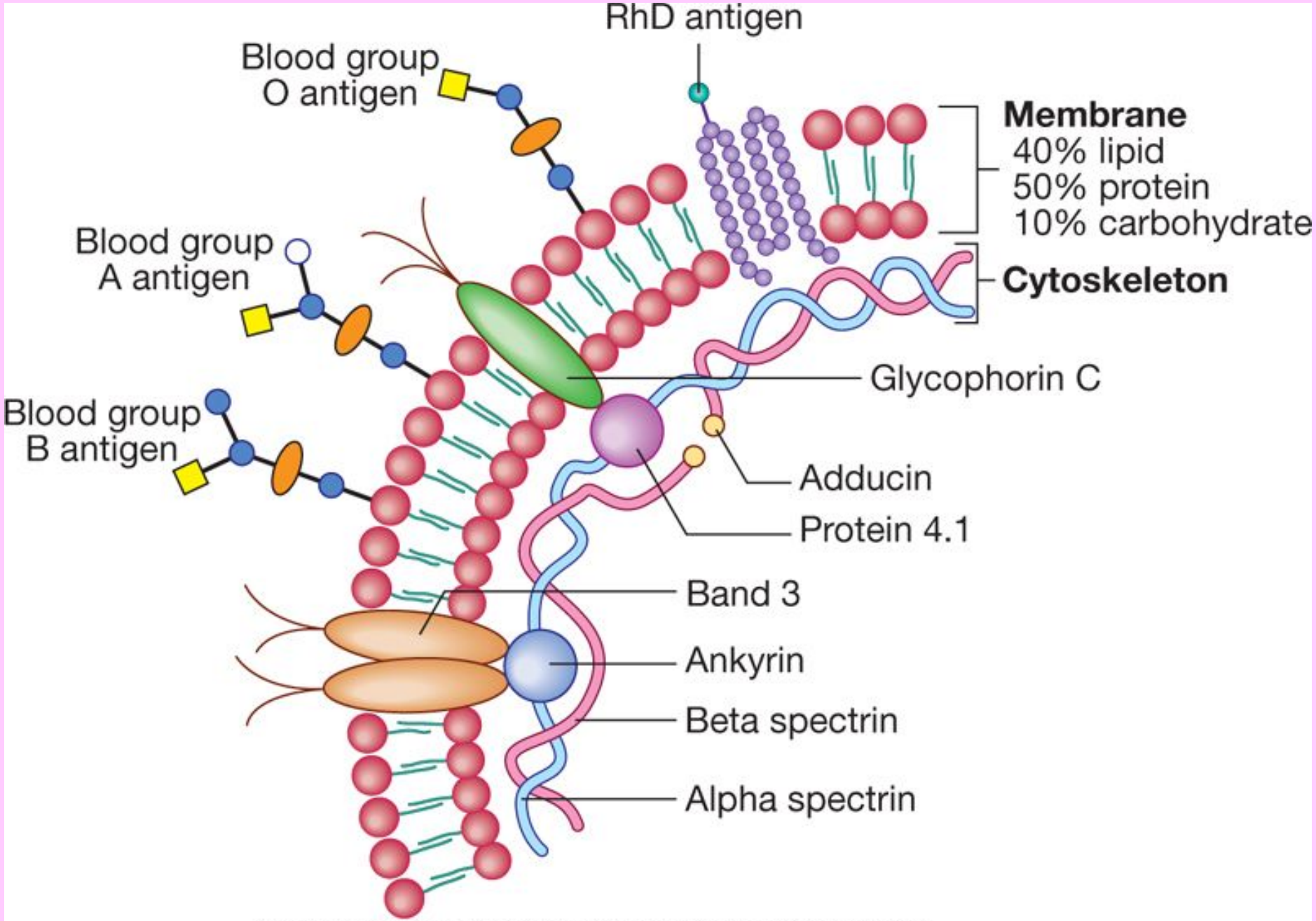
These can be classified as inherited or acquired .

• Inherited red cell abnormalities resulting in chronic haemolytic anaemia may arise from pathologies of the red cell membrane (hereditary spherocytosis or elliptocytosis), haemoglobin (haemoglobinopathies), or protective enzymes that prevent cellular oxidative damage, such as glucose-6-phosphate dehydrogenase (G6PD).

• Acquired causes include auto- and alloantibody-mediated destruction of red blood cells and other mechanical, toxic and infective causes.

Red cell membrane defects

The basic structure is a cytoskeleton 'stapled' on to the lipid bilayer by special protein complexes. This structure ensures great deformability and elasticity; the red cell diameter is 8 μm but the narrowest capillaries in the circulation are in the spleen, measuring just 2 μm in diameter.



Colledge et al: Davidson's Principles and Practice of Medicine, 21st Edition

When the normal red cell structure is disturbed, usually by a quantitative or functional deficiency of one or more proteins in the cytoskeleton, cells lose their elasticity..

Each time such cells pass through the spleen, they lose membrane relative to their cell volume. This results in an increase in mean cell haemoglobin concentration (MCHC), abnormal cell shape and reduced red cell survival due to extravascular haemolysis

Hereditary Spherocytosis

Autosomal dominant disorder.
25% of cases have no Family History presenting new Mutation.
The incidence is approximately 1:5000 in developed countries .
The pathogenesis varies between families.
The Most common abnormality is Defect of Beta Spectrin or ankyrin.

Deficiency of Spectrin, which is RBC membrane protein, the RBC loses its biconcave shape and become spherical, more susceptible to osmotic lysis and most of them destroyed by the spleen.
The type of hemolysis is extravascular.

The severity of spontaneous haemolysis varies.
Most cases are associated with an asymptomatic compensated chronic haemolytic state with spherocytes present on the blood film, a reticulocytosis and mild hyperbilirubinaemia.

Pigment gallstones are present in up to 50% of patients and may cause symptomatic cholecystitis.

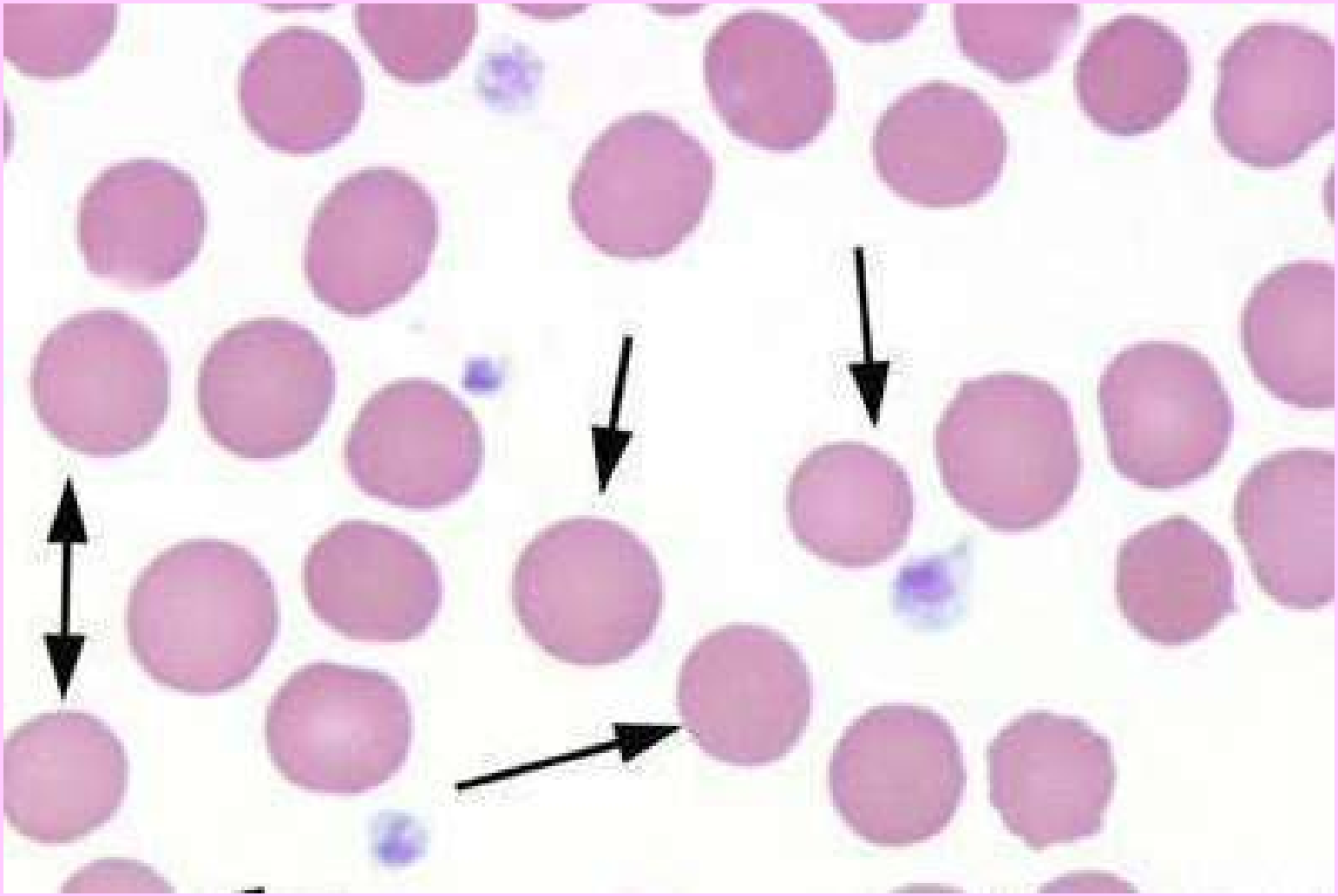
The clinical course may be complicated by crises:

- **A haemolytic crisis** occurs when the severity of haemolysis increases; this is rare, and usually associated with infection.
- **A megaloblastic crisis** follows the development of folate deficiency; this may occur as a first presentation of the disease in pregnancy.
- **An aplastic crisis** occurs in association with parvovirus (erythrovirus) infection . Parvovirus causes a common exanthem in children, but if individuals with chronic haemolysis become infected, the virus directly invades red cell precursors and temporarily switches off red cell production. Patients present with severe anaemia and a low reticulocyte count

Investigations

The patient and other family members should be screened for features of compensated haemolysis This may be all that is required to confirm the diagnosis. Haemoglobin levels are variable, depending on the degree of compensation.

The blood film will show spherocytes but the direct Coombs test is negative, excluding immune haemolysis.
An osmotic fragility test may show increased sensitivity to lysis in hypotonic saline solutions but is limited by lack of sensitivity and specificity. More specific flow cytometric tests, detecting binding of eosin-5-maleimide to red cells, are recommended in border line cases.



Management

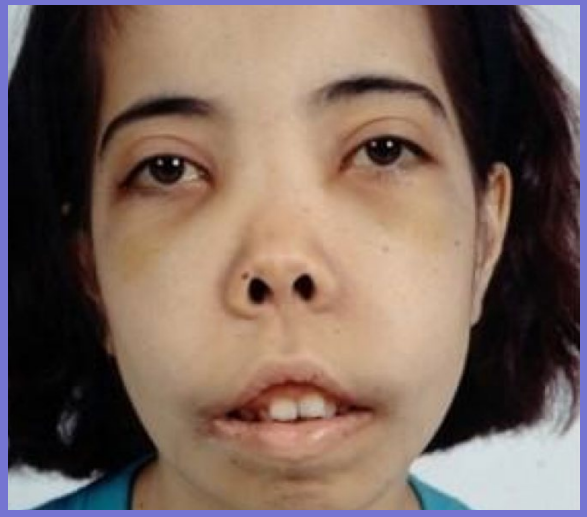
1-Folic acid prophylaxis, 5 mg daily, should be given for life.

2-splenectomy: in sever cases consideration may given to splenectomy which improves but does not normalise red cell survival.

Potential indications for splenectomy include moderate to severe haemolysis with complications (anaemia and gallstones), although splenectomy should be delayed where possible until after 6 years of age in view of the risk of sepsis.

3-Acute, severe haemolytic crises require transfusion support, but blood must be cross-matched carefully and transfused slowly as haemolytic transfusion reactions may occur

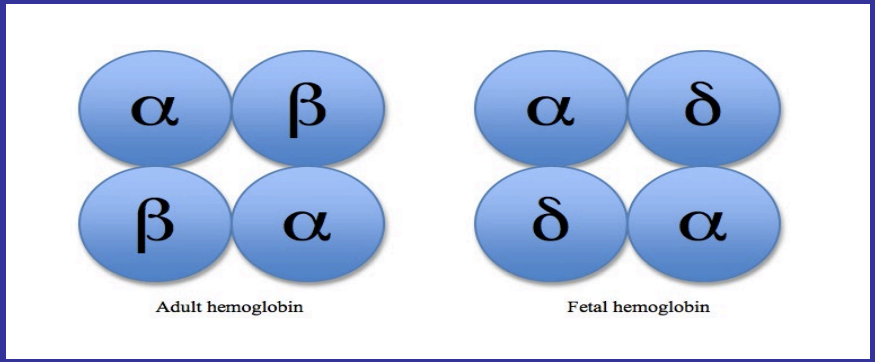
HAEMOGLOBINOPATHIES



HAEMOGLOBINOPATHIES

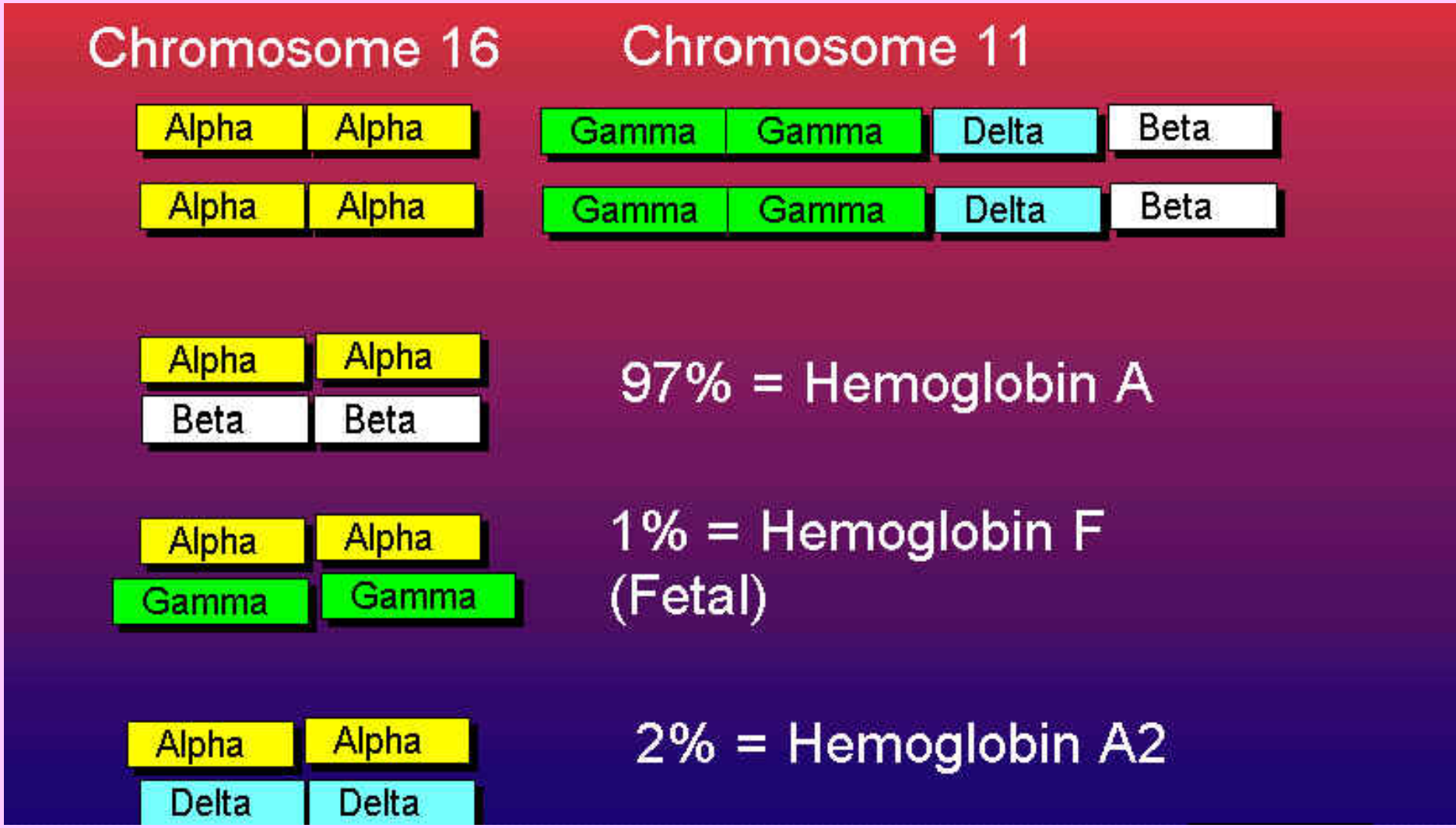
These diseases are caused by mutations affecting the genes encoding the globin chains of the haemoglobin molecule.

Normal haemoglobin is comprised of two alpha and two non-alpha globin chains



Alpha globin chains are produced throughout life, including in the fetus, so severe mutations in these may cause intrauterine death. Production of non-alpha chains varies with age; fetal haemoglobin (HbF-αα/γγ) has two gamma chains, while the predominant adult haemoglobin (HbA-αα/ββ) has two beta chains.
Thus, disorders affecting the beta chains do not present until after 6 months of age.
A constant small amount of haemoglobin A2 (HbA2-αα/δδ, usually less than 2%) is made from birth.

Normal hemoglobins in the red cell consist of Hb A, Hb F, and Hb A2. The protein sequences are DNA coded on Chromosome 11 for the beta, delta and gamma chains. The alpha chains are coded on Chromosome 16. The beta variants such as Hb S, Hb C, and Hb D all occur from a mutation on Chromosome 11.


Chromosome 16
Chromosome 11
Alpha
Alpha
Alpha
Alpha
Gamma
Gamma
Delta
Beta
Gamma
Gamma
Delta
Beta
Alpha
Alpha
Beta
Beta
97% = Hemoglobin A
Alpha
Alpha
Gamma
Gamma
1% = Hemoglobin F
(Fetal)
Alpha
Alpha
Delta
Delta
2% = Hemoglobin A2

Quantitative abnormalities – thalassaemias

In quantitative abnormalities (the thalassaemias), there are mutations causing a reduced rate of production of one or other of the globin chains, altering the ratio of alpha to non-alpha chains. The excess chains precipitate, causing red cell membrane damage and reduced red cell survival Due to haemolysis.

The thalassaemias

Thalassaemia is an inherited impairment of haemoglobin production, in which there is partial or complete failure to synthesise a specific type of globin chain.

In alpha-thalassaemia, disruption of one or both alleles on chromosome 16 may occur, with production of some or no alpha globin chains.

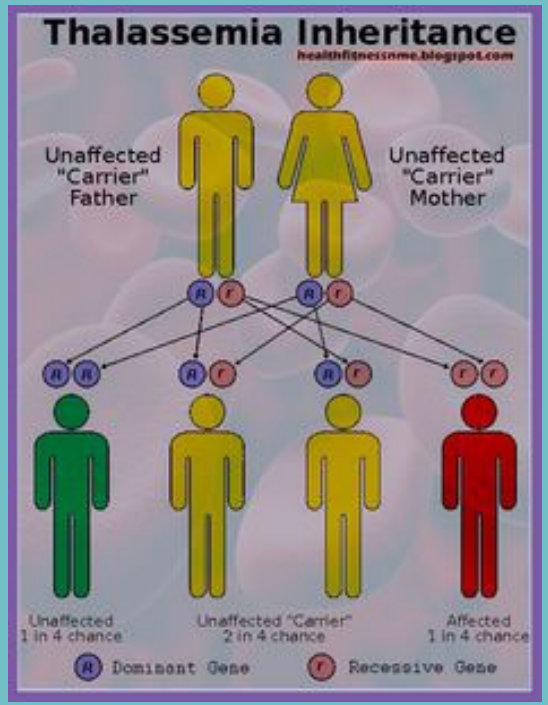
In beta-thalassaemia, defective production usually results from disabling point mutations causing no (β0) or reduced (β–) beta chain production.

Beta -thalassaemia

Failure to synthesise beta chains (beta-thalassaemia) is the most common type of thalassaemia, most prevalent in the Mediterranean area.
Heterozygotes have thalassaemia minor, a condition in which there is usually mild anaemia and little or no clinical disability, which may be detected only when iron therapy for a mild microcytic anaemia fails.

Homozygotes (thalassaemia major) either are unable to synthesise haemoglobin A or at best produce very little; after the first 4-6 months of life they develop profound hypochromic anaemia.

Thalassemia inherited in an autosomal recessive pattern



Pathogenesis

1-Defective globin-chain synthesis in β-thalassemia causes both decreased normal hemoglobin production and the production of a relative excess of α chains.

2-The decrease in normal hemoglobin synthesis results in a hypochromic anemia.

3-the excess α chains form insoluble α-chain complexes and cause hemolysis.

In mild thalassemic syndromes, the excess αchains are insufficient to cause significant hemolysis, and the primary finding is a microcytic anemia.

In severe forms of thalassemia, hemolysis occurs both in the periphery and in the marrow, with intense secondary expansion of the marrow production of red cells.

4-The expansion of the marrow space causes severe skeletal abnormalities.

5- the ineffective erythropoiesis also provides a powerful stimulus to absorb iron from the intestine

CLINICAL FEATURES:

1.Sever anaemia:- overlap after the first 4 months of life, many pt with B-Thalassaeinia major (Coolley s Anaemia) are transfusion dependent, the pt develop iron overlapped, in untreated pt this usually lead to death in 2nd decade.

2. Bone changes:- due to expansion of bone marrow space and growth retardation

3. Chipmunk facies:- due to increase erythropoiesis

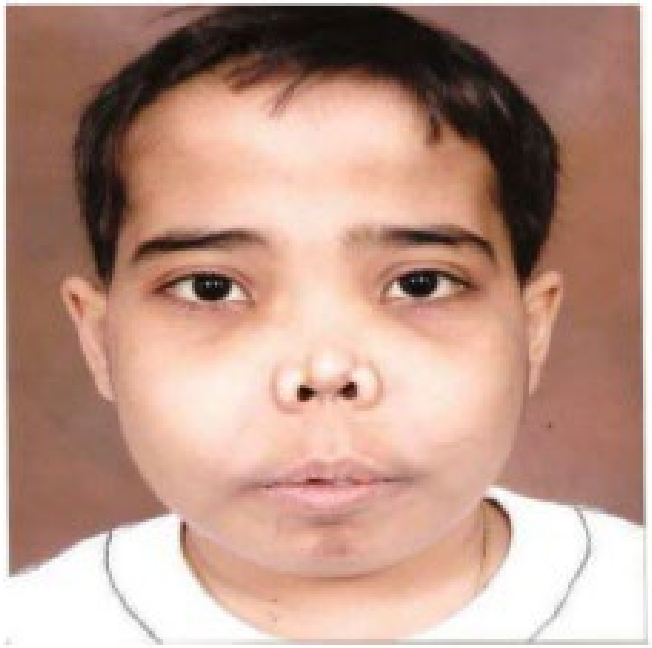
4. Skin:- copper colour from paller,icterus and melanin deposition.

5. hepatosplenomegally:- may be massive

- **Bone abnormalities**

1.Abnormal facies :

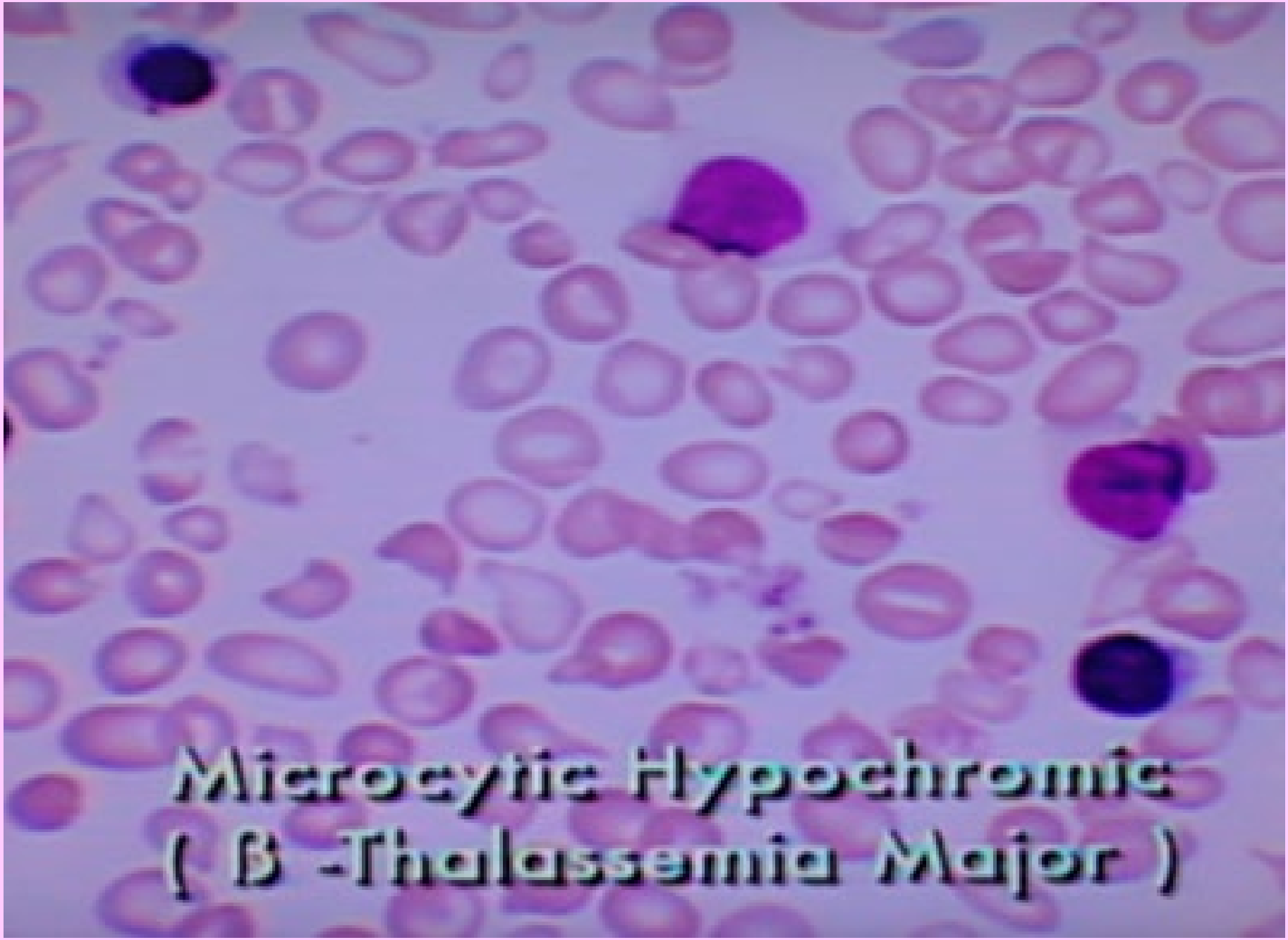
- prominence of malar eminences,
- frontal bossing,
- depression of bridge of the nose,
- exposure of upper central teeth.

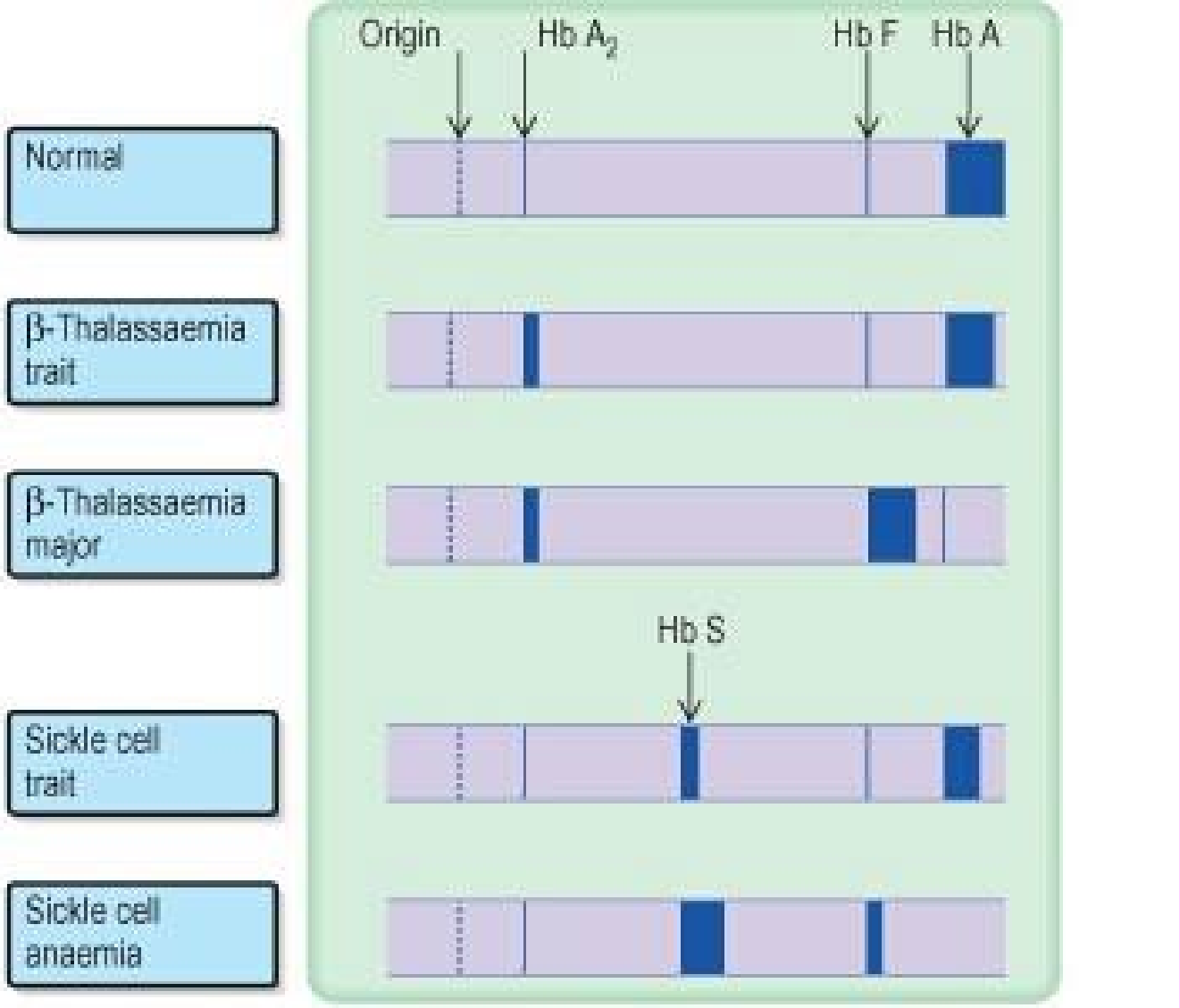


DIAGNOSTIC FEATURES:-

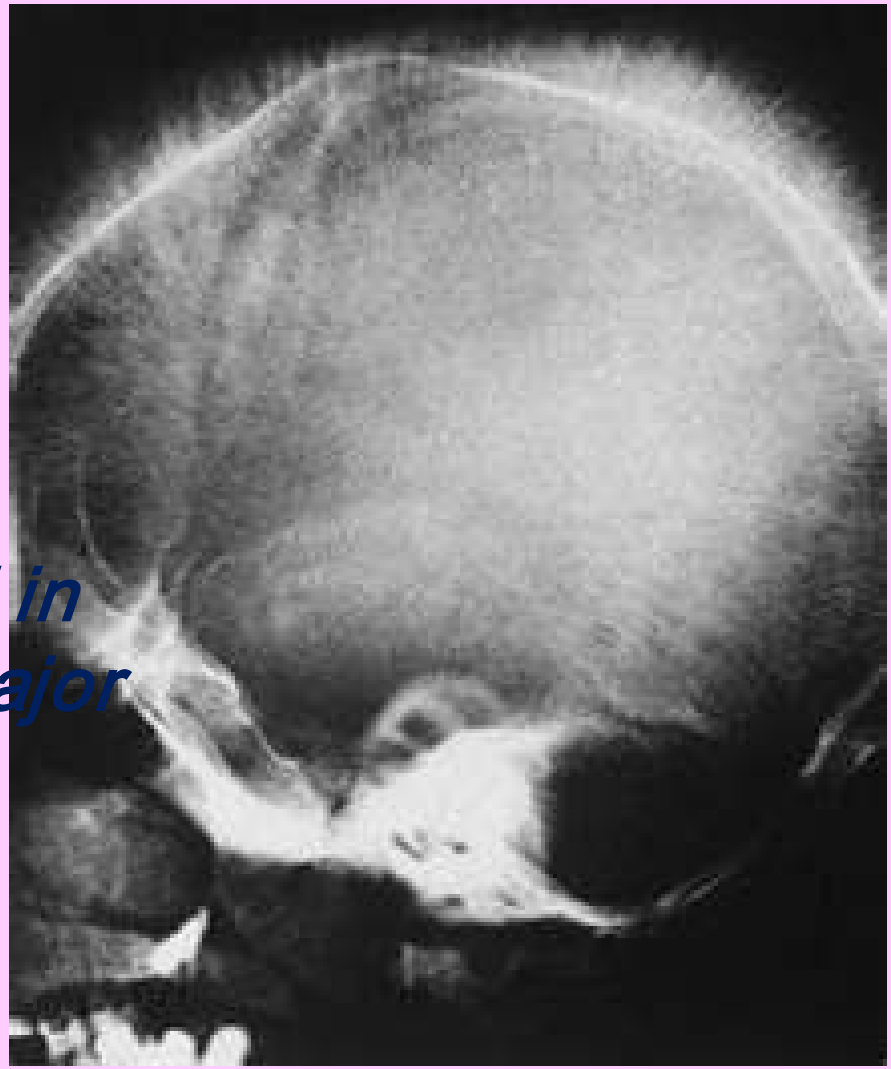
**major:*

. *Profound hypochromic anaemia*
- *Evidence of RBC dysplasia*
- *Erythroblastosis*
- *Absence or gross reduction ofHbA*
- *Raised level HbF*
- *Evidence that both parents have Thalassaemia minor.*


Microcytic Hypochromic
(β -Thalassemia Major)


Origin
Hb A2
Hb F
Hb A
Normal
β-Thalassaemia trait
β-Thalassaemia major
Hb S
Sickle cell trait
Sickle cell anaemia

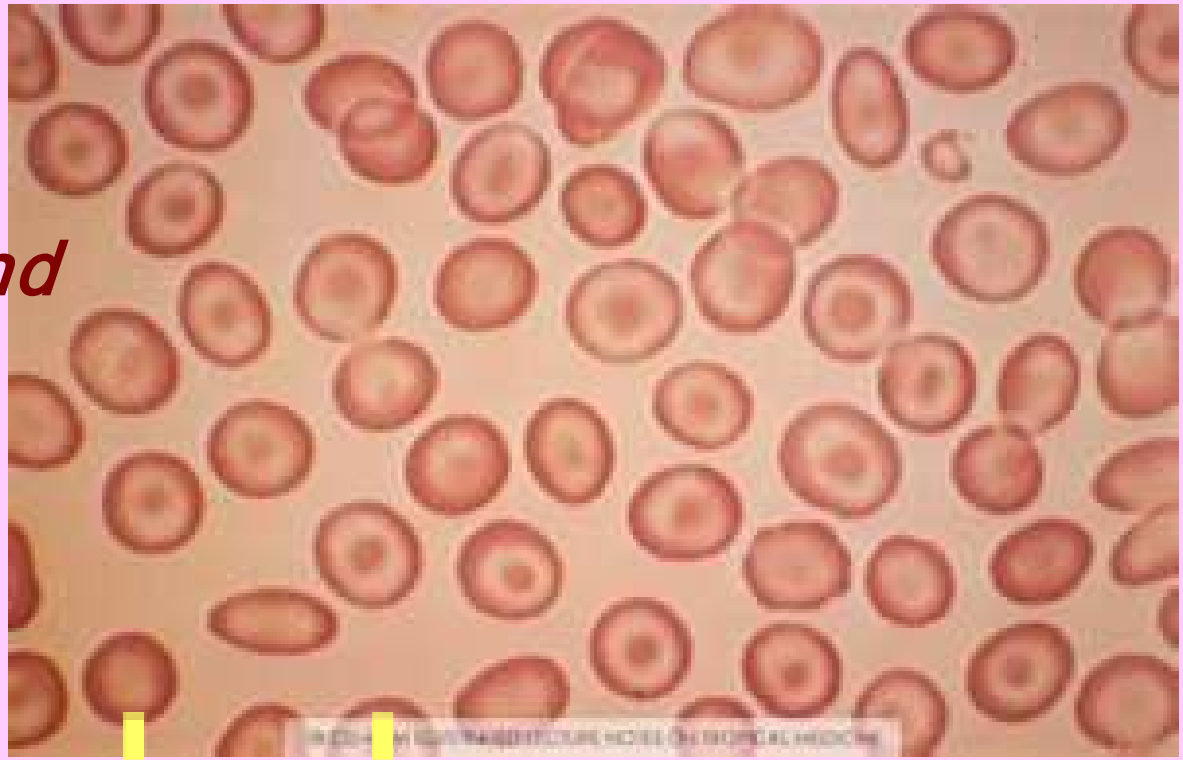
Hair on end skull in B-thalassemia major



Beta-thalassaemia minor (heterozygotes)

- *Mild anaemia*
- *Microcytic hypochromic erythrocytes (not iron-deficient)*
- *Some target cells*
- *Punctate basophilia*
- *Raised haemoglobin A2 fraction*

Target cells and microcytosis



Thalassaemia minor

TREATMENT of B-Thalassaemia MAJOR:

-Erythropoiesis failure

Allogenic bone marrow transplantation

From human leukocyte antigen (HLA)-c compatible sibling

Transfusion to maintain Hb>10g/dl

folic acid 5mg daily

- Iron Overload

***iron therapy forbidden*

***desfenioxamine therapy*

-Splenomegaly causing mechanical problems or excessive transfusion needs, the treatment will be Splenctomy.

** TREATMENT of B-Thalassaemia MINOR:

Do not need to be treated but in certain regions in which the incidence increased, screening for B-Thalassaemia combined with counseling and it is an important role to decrease the incidence of the disease

**Prevention:

It is possible to identify a fetus with homozygous B-Thalassaemia by obtaining chorionic villous material for DNA analysis sufficiently early in pregnancy to allow termination. This examination is only appropriate if both parents are known to be carrier (beta -Thalassaemia minor) and will accept a termination.

Alpha-thalassaemia:

The reduction or absence of alpha-chain synthesis is common in Southeast Asia. There are two alpha gene loci on chromosome 16 and therefore four alpha genes. If one is deleted there is no clinical effect. If two are deleted there may be a mild hypochromic anaemia. If three are deleted the patient has haemoglobin H disease and if all four are deleted the baby is stillborn (hydrops fetalis).

Haemoglobin H is a beta-chain tetramer formed from the excess of chains. It is functionally useless. Treatment of haemoglobin H disease is similar to that of beta-thalassaemia of intermediate severity

involving

1-folic acid supplementation,

2-transfusion if required and

3-avoidance of iron therapy.

ALPHA-THALASSAEMIA

Cause

•Failure of production of haemoglobin alpha chains due to gene deletion

Age and sex incidence

•Both sexes from birth onward

Genetics

•Two alpha-chain genes from each parent

Presentation

•Hydrops fetalis if all genes deleted
•Haemoglobin H if three genes deleted
•Mild hypochromic microcytic anaemia if two genes deleted

Treatment

•Hydrops fetalis: none available
•Haemoglobin H: no specific therapy required; avoid iron therapy; folic acid if

THANK YOU