Anaemia

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Introduction

- Group of diseases characterized by decrease in either Hgb or RBCs, resulting in reduced oxygen carrying capacity of the blood

- Anaemias can result from inadequate RBC production, increased RBC destruction, accelerated loss of RBC mass, or they can be a manifestation of a host of systemic disorders like infection, chronic renal disease or malignancy

- Anaemia is second only to TB as the world's most prevalent and costy public health issue
- Worldwide over 50% pregnant women and over 40% infants are anaemic

Etiopathogenesis

- ⇩ Haemoglobin synthesis
- ⇧ Haemoglobin loss

- 1. **<u>Decreased Hb synthesis:</u>** due to lack of nutrients or bone marrow failure
- Reduced proliferation of precursors – Iron deficiency, anaemia of chronic disease, anaemia due to renal failure, aplastic anaemia, infiltration of bone marrow (leukaemia, metastasis)
- Defective maturation of precursors – Vitamin B12 deficiency, folate deficiency, Iron deficiency, thalassemias, Sideroblastic anaemia

- Normal Erythropoiesis:
- Pluripotent stem cells mature through various stages – synthesize Hb, DNA & RNA
- Pluripotent stem cell > Erythroid burst forming unit (BFU-E) > Erythoid colony forming unit (CFU-E) > Erythroblast (Normoblast) > Reticulocyte > Mature red cell

- Erythropoietin help in differentiation & division of BFU-E & CFU-E, increased erythropoiesis
- In case of hypoxia/anaemia – stimulation of erythropoietin
- Survival of erythrocytes - 120 days
- **IRON** – removed from haem component back to bone marrow
- Pyrrole ring of **GLOBIN** is excreted as bilirubin
- Polypeptide **PROTEIN** enters body's protein pool

Clinical Manifestations

- Tiredness, lethargy, pallor, fainting, exertional dyspnoea, tachycardia, palpitation, worsening of angina, worsening of cardiac failure etc

- **Investigations:**
- Haemoglobin concentration; size-shape-colour of RBCs
- ***Hypochromic, microcytic*** – Iron deficiency, Sideroblastic, Thalassaemia
- ***Macrocyctic*** – Folate deficiency, Vitamin B 12 deficiency
- ***Normochromic, normocytic*** – Haemolytic anaemia, acute blood loss anaemia, anaemia of chronic disease

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- **Complete Blood Count -**
- **RBC :** 4.6-6.2 millions cells/mm3 (males)
  4.2-5.4 millions cells/mm3 (females)

- **Hb :** 14-18g/dl for males; 12-16g/dl for females

- **Hct :** Percentage volume of blood that contains erythrocytes
  42-52% for males; 37-47% for females

- **MCV (Mean cell volume) :** Average volume of RBCs
- MCV = Hct / no. of RBC ; 80-98 fl.
- MCV > 100 fL (macrocytic anaemia); 81-99fL (normocytic anaemia)
- < 80 fL (microcytic anaemia)

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- **MCH (Mean cell haemoglobin) :** Percent volume of Hgb per RBC. Hgb/RBC ; 27-33pg/cell (decreases in iron deficiency anaemia)
- **MCHC (Mean Cell Haemoglobin Concentration) :** Hgb / Hct
- 31-35 g/dl (decreases in iron deficiency anaemia)
- **Reticulocyte :** An indirect measurement of recent RBC production
- 0.5-25% of RBCs; use to monitor an anemic patients response to vitamin or iron therapy.
- **Red Blood Cell Distribution Width :** An indication of the variation in red cell volume. As this value increases, so does the variability in the size of the RBCs. 11-16%
- Used primarily with other tests to diagnose iron deficiency anaemia.

Iron deficiency anaemia

- 20% of world population
- **Etiology:**
- 1. Blood loss – menstrual loss, hookworm infestation, gastrointestinal bleeding, haemorrhoids, postpartum haemorrhage etc
- 2. Inadequate iron absorption – dietary deficiency, malabsorption
- 3. Increased physiological demand – heart failure, pregnancy

- **Pathophysiology:**
- Anaemia results from a mismatch between body's iron requirements & iron absorption
- Elimination of iron is not controlled physiologically so the homeostasis is maintained by controlling iron absorption
- Iron is necessary for Hb synthesis. Daily requirements are approximately 1 mg of elemental iron for each 1ml of RBCs produced.
- Hence daily requirements are approx. 20-25 mg for erythropoiesis
- Most required iron is obtained by recycling.
- Only about 5% of the daily requirement (1mg) is newly absorbed

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- Approx. 2.5 g of iron exists in the form of Hgb, whereas 400 mg exists as iron containing proteins; another 3-7 mg of iron is bound to transferrin in plasma while the remaining iron exists as storage iron in the form of ferritin
- Tetracyclins, penicillamine & fluoroquinolones bind to iron in GI & reduce absorption of iron from supplements
- Adult male – 0.9 mg, Menstruating adult female - 2.0 mg
- Pregnant female – 3-5 mg, Postmenopausal female – 0.9 mg

- Clinical manifestations:
- Pale skin & mucous membrane, painless glossitis, angular stomatitis, koilonychia, dysphagia, pica, atropic gastritis

- Investigations:
- RBC, Hb, RBC indices, Iron, TIBC, Ferritin.
- Peripheral evaluation of blood shows microcytic & hypochromic cells with poikilocytes & occassional target cells.

- **Serum Iron :** 50-150 µg/dl (measures iron bound to transferrin)
- **Total Iron Binding Capacity (TIBC) :** measures the iron-binding capacity of transferrin protein. 250-410 µg/dl
- In iron deficiency anaemia, TIBC is increased due to a compensatory increase in transferrin synthesis.
- **Serum ferritin :** > 10-20 ng/ml
- Markedly reduced in iron deficiency anaemia (3-6 µg/L)
- *when old erythrocytes are taken up by phagocytic cells in the liver, spleen, the Hgb molecule is broken down and iron is extracted and stored with proteins. This iron-protein complex within the macrophage is known as ferritin. Its concentration reflects total body iron stores*

Treatment

- **Oral Iron :**
- Ferrous sulphate 200 mg = 65 mg of elemental iron
- Ferrous gluconate 300 mg = 35 mg of elemental iron
- Ferrous fumarate 200 mg = 65 mg of elemental iron
- Treatment should be continued for 6 months. (200 mg tid)
- Response : ↑ 1 g/dl in 1-2 weeks

  reticulocytes appears in 2-3 days

Parenteral iron:

- who fail oral therapy, gastrectomy, severe deficiency with chronic bleeding etc
- Iron requirements (mg) = 4.4 X body weight (kg) X Hb deficit (g/dl)
- Iron dextran : colloidal solution containing 50 mg iron/ml

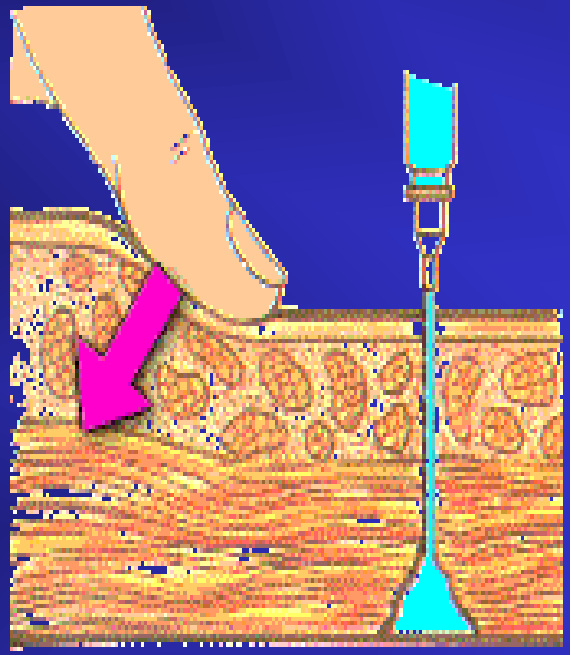
  iron sorbitol : 50 mg iron/ml

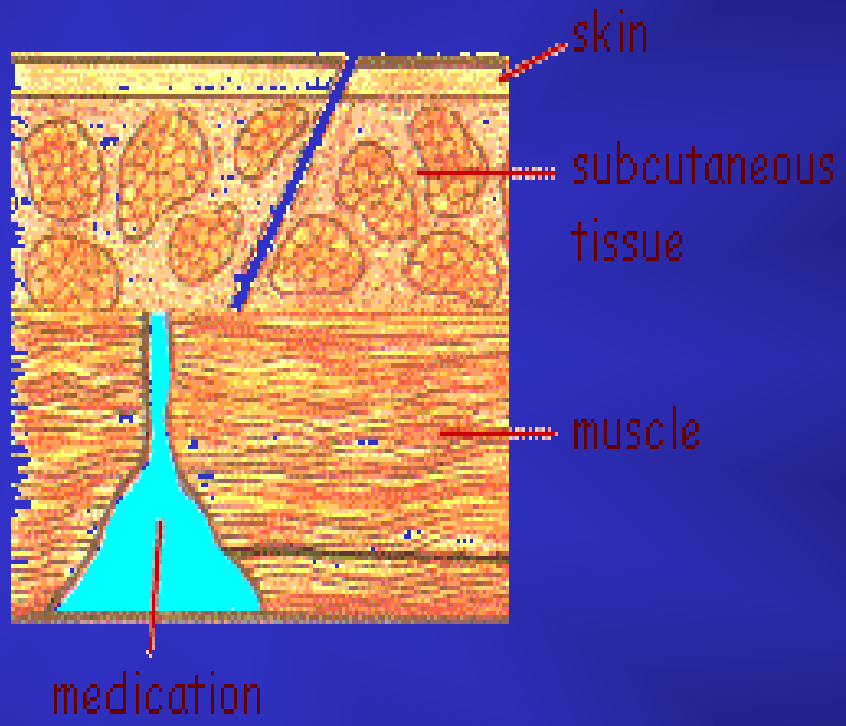
Parenteral Iron contd…

- A test dose of the preparation (few drops) must be injected first to screen sensitive patients
- To avoid staining of the skin, Intramuscularly iron is injected deeply in the gluteal region using Z TRACT technique (it handles IM injections of irritating substances with minimal tracking of medications through surrounding tissues)
- Iron dextran can be injected 2 ml daily, or on alternate days, or 5 ml each side on the same day. More than 1.5-2 ml of iron-sorbitol should not be injected at one time.
- **ADRs** : local- pain at site of i.m injection, pigmentation of skin
- systemic – fever, headache, joint pains, metallic taste, discoloration of stools

Z-tract injection

A technique in which the skin and subcutaneous tissue are displaced laterally before inserting the needle intramuscularly; used to prevent leakage along the track of the needle and consequent tissue irritation.

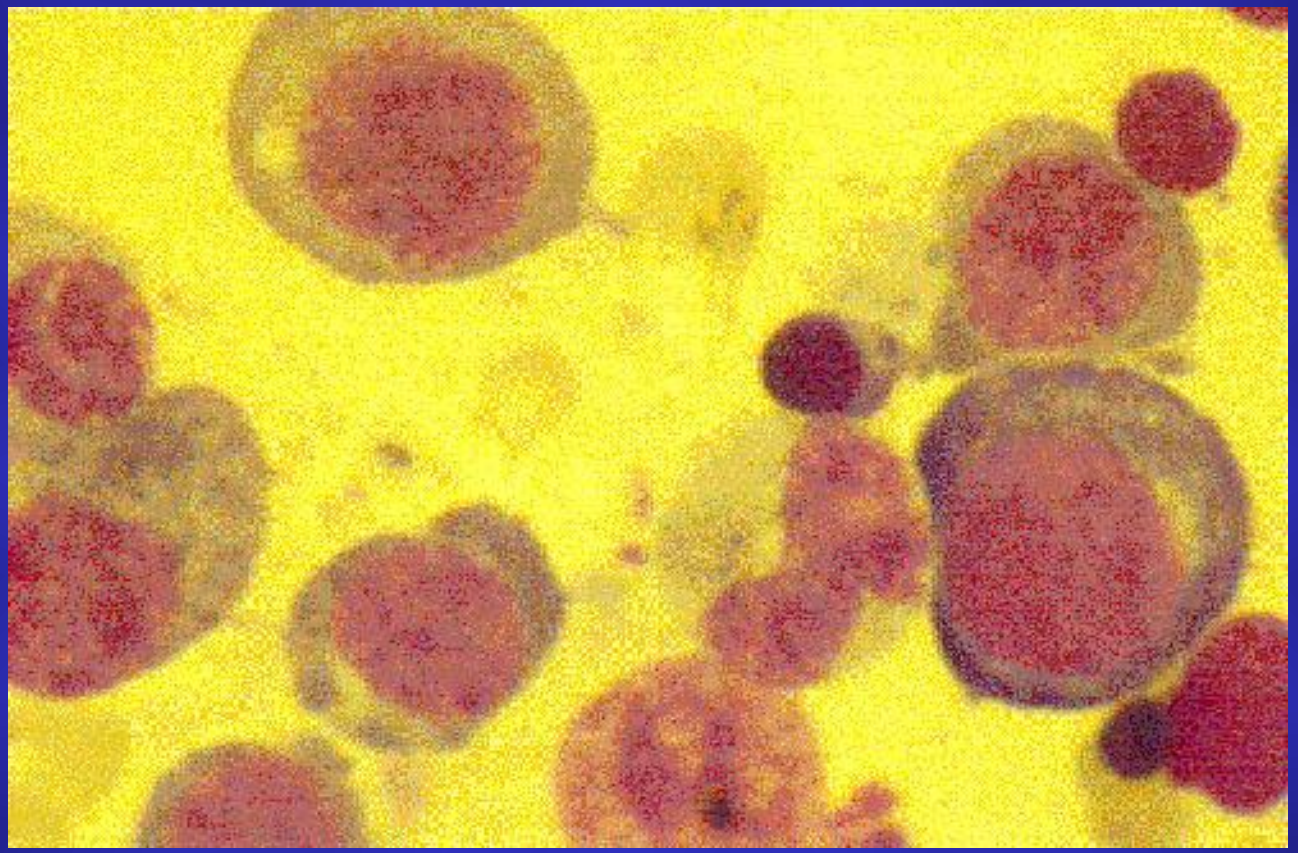




- **Blood transfusion**
- **Patient counseling points:**
- Take iron products with or after meals
- Faeces may become dark
- Length of treatment and adherence

- **ADRs :**
- nausea, abdominal pain, heart burn, change in bowel habits (constipation / diarrhea)

Megaloblastic Anaemia



Megaloblastic Anaemia

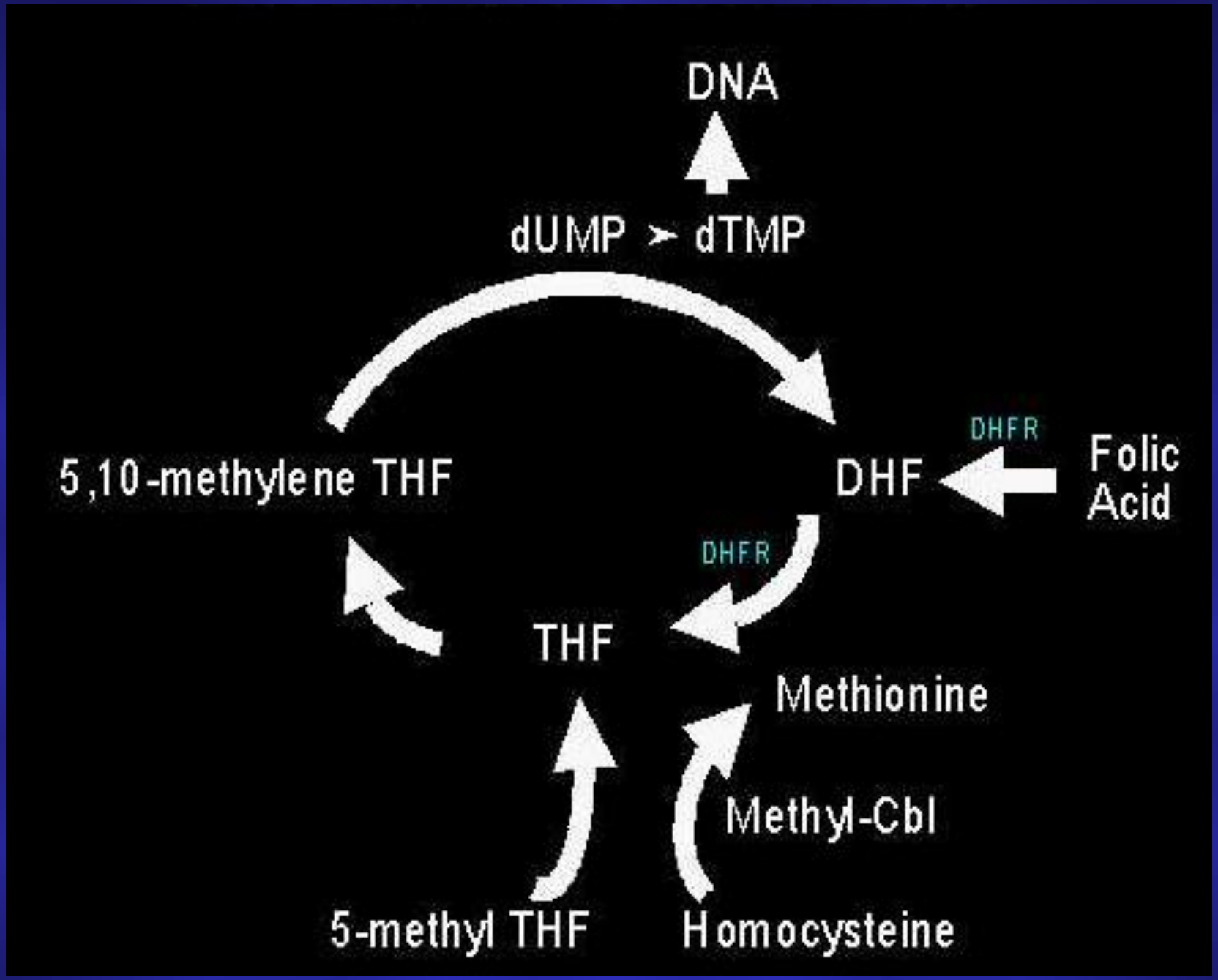
- **Deficiency of vit B12 and folic acid which are B group vitamins results in megaloblastic anaemia characterized by the presence of large red cell precursors in bone marrow and their large and short-lived progeny in peripheral blood**

- **Pernicious anaemia is a specific disease caused by malaborption of vit B12**

- **Folate is an important substrate of , and vitamin B12 a cofactor for, the enzymatic generation of the essential AA methionine from homocysteine. This reaction produces tetrahydrofolate which is converted to thymidine monophosphate for incorporation into DNA.**
- **Deficiency of either vitamin B 12 or folate will therefore produce high plasma levels of homocysteine and impaired DNA synthesis.**

- **Basic defect is in DNA synthesis**

- **Folate deficiency : dietary deficiency immediately causes folate deficiency**
- **Vitamin B12 deficiency : in strict vegetarians, total gastrectomy patients**
- **Pernicious anaemia : intrinsic factor deficiency (elderly)**


DNA
dUMP ➢ dTMP
DHFR
Folic Acid
5,10-methylene THF
DHF
DHFR
THF
Methionine
Methyl-Cbl
5-methyl THF
Homocysteine

Etiology…

- **Folate deficiency :** inadequate dietary intake, malabsorption, chronic alcoholism, increased demand (pregnancy, lactation etc), drug induced (phenytoin, methotrexate, trimethoprim, primidone, phenobarbitone, oral contraceptives etc)

- **Vitamin B12 deficiency** : Addisonian pernicious anaemia (autoimmune disorder which results in destruction of gastric parietal cells > absence of intrinsic factor in gastric juice > inability to absorb B 12), malabsorption, pregnancy, infancy

- Daily requirements : folic acid < 0.1-0.8 mg ; vit B12 1-5 µg/d

Pathophysiology

- Folic acid deficiency anaemia:
- Folate found in food is mainly conjugated to polyglutamic acid. Polyglutamate form prevents the folate leaking out of the cells.
- The folate acts as a co-enzyme involved in various reaction including DNA & RNA synthesis. Defective DNA synthesis mainly affects cells with rapid turnover.

Pathophysiology

- Vitamin B12 deficiency anaemia:
- Absorption is by active process (enzymes in the stomach release vit B12 from protein complexes. One molecule of vit B12 then combines with one molecule of a glycoprotein called intrinsic factor)
- Intrinsic factor protects vit B12 from breakdown
- Total gastrectomy always leads to vit B12 deficiency
- Onset is delayed as body stores 2-5 mg of vit B12 sufficient for 2-3 years
- Lack of vit B12 traps folate as methyltetrahydrofolate and prevents DNA synthesis.

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- Pernicious anaemia:
- Autoimmune origin, gastric parietal cell antibodies are found in 90% of patients

- Clinical manifestations:
- Folate deficiency anaemia-
- Glossitis, angular stomatitis, altered bowel habits, anorexia, mild jaundice, sterility, peripheral neuropathy, skin pigmentation, fever
- Vitamin B12 deficiency-
- Anisocytosis, poikilocytosis, mild thrombocytopenia, neuropathy.

Investigations

- Megaloblastic anaemia- RBC, ⬇ Hb, Hct, ⬆ MCV
- In Folic acid deficiency anaemia- symptomless, diagnosis is made following a full blood count carried out for another reason
- folic acid > 3.3 mg/ml

- In Vitamin B12 deficiency anaemia-
- (205-876 pg/ml)
- Schilling test : the test is based on giving a radiolabelled oral dose of vit B12 and an unlabelled parenteral dose that saturates the vit B12 binding proteins. The amount of labelled vitamin in the urine gives a measure of absorption

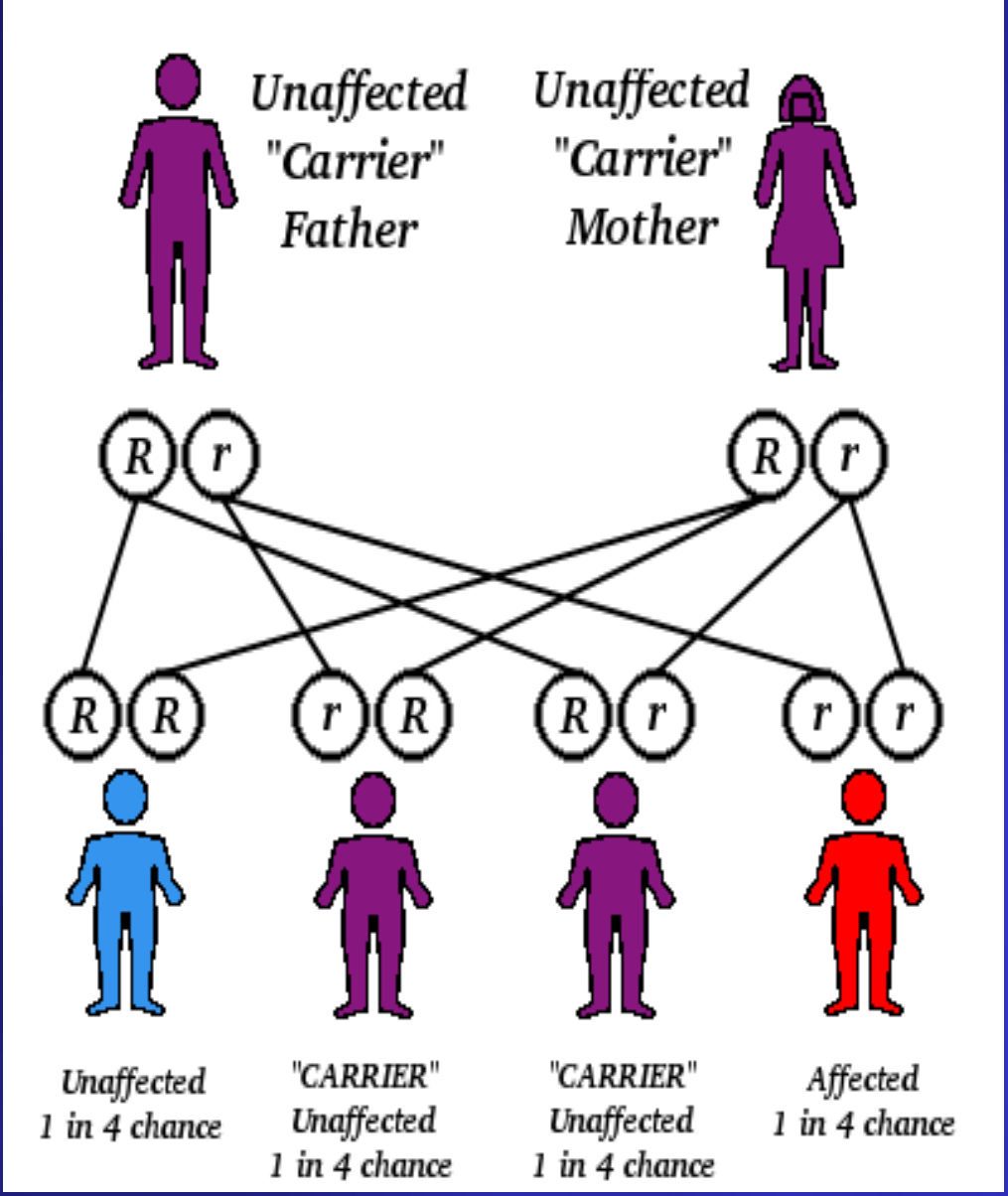
Treatment

- Folate deficiency anaemia -
- Normal dietary requirement : 100 µg/day; Pregnancy: 350-500 µg/day
- Usual treatment dose (folic acid) : 5-15 mg/day; prophylactic 0.5 mg/day
- Treatment for a duration of 4 months
- Folic acid therapy should be started after excluding vit B12 deficiency

- Vitamin B12 deficiency anemia -
- Require life long therapy
- Hydroxycobalamine 1mg (IM) repeated five times at 3 day intervals followed by maintenance dose of 1mg (IM) once in 3 months
- Red blood count returns to normal after 7-10 days; Hb by 1g/dl every week; neuropathy may take 6-12 months to correct

Sideroblastic anaemias

- Sideroblastic anaemias are a group of conditions that are diagnosed by finding ring sideroblasts in the bone marrow
- Hereditary : X chromosome linked pattern of inheritance; main defect is a reduced activity of the enzyme 5-aminolevulinate synthetase (ALAS) which is involved in haem synthesis
- Acquired : Idiopathic, Myeloproliferative disorders and forms secondary to the ingestion of drugs (Isoniazid, chloramphenicol, pyrazinamide, cycloserine etc)
- Low levels of ALAS (required in the first step of haem synthesis and needs pyridoxal phosphate as a co-factor; pyridoxine is a precursor for pyridoxal)



- INHERITED AS AN AUTOSOMAL RECESSIVE TRAIT
- HOMOZYGOUS ONLY PRODUCES ABNORMAL BETA CHAINS RESULTING IN CLINICAL SYNDROME
- HETEROZYGOUS PRODUCES MIX OF NORMAL & ABNORMAL BETA CHAINS (CLINICALLY ASYMTOMATIC SICKLE TRAIT)

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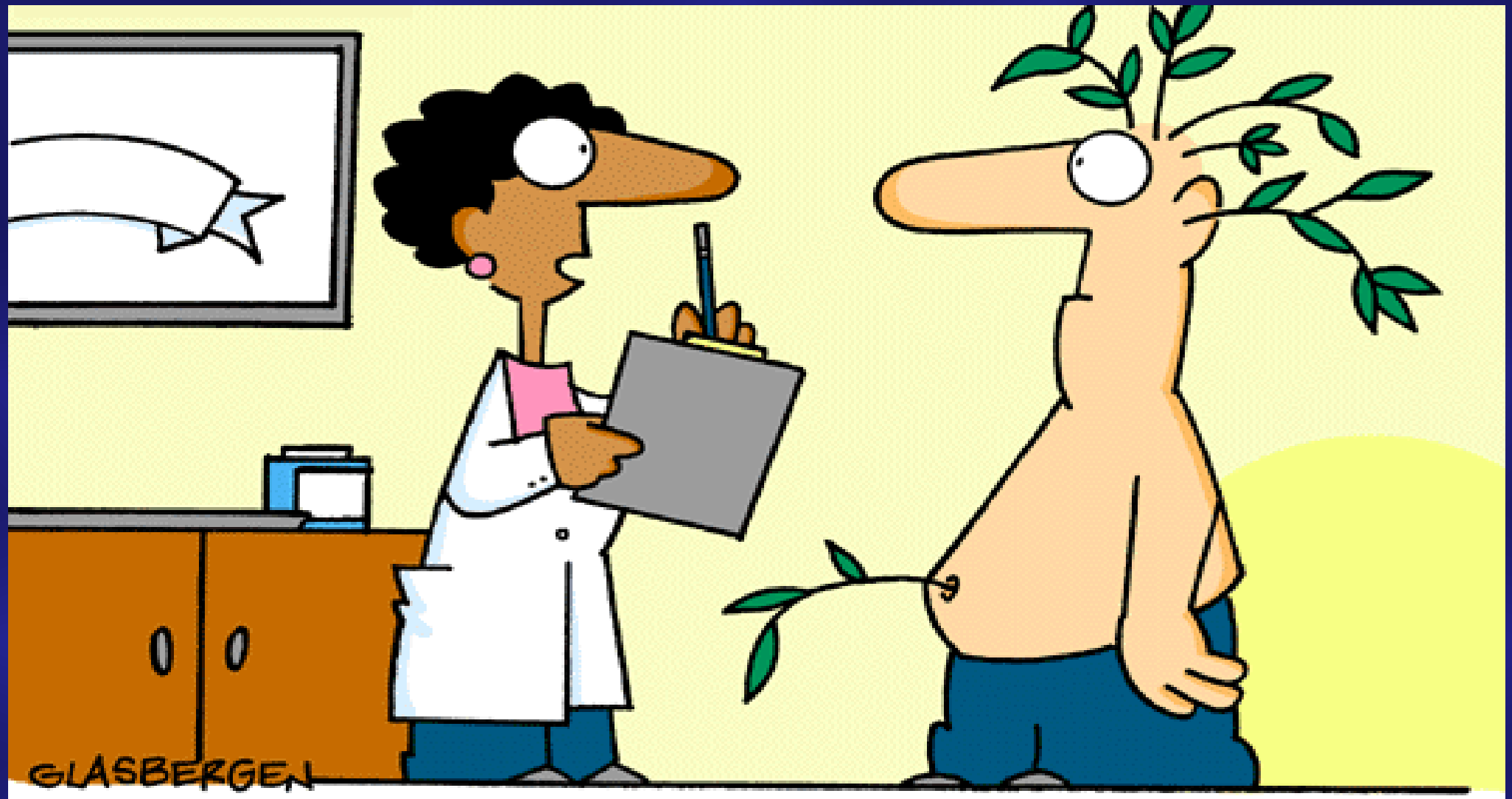
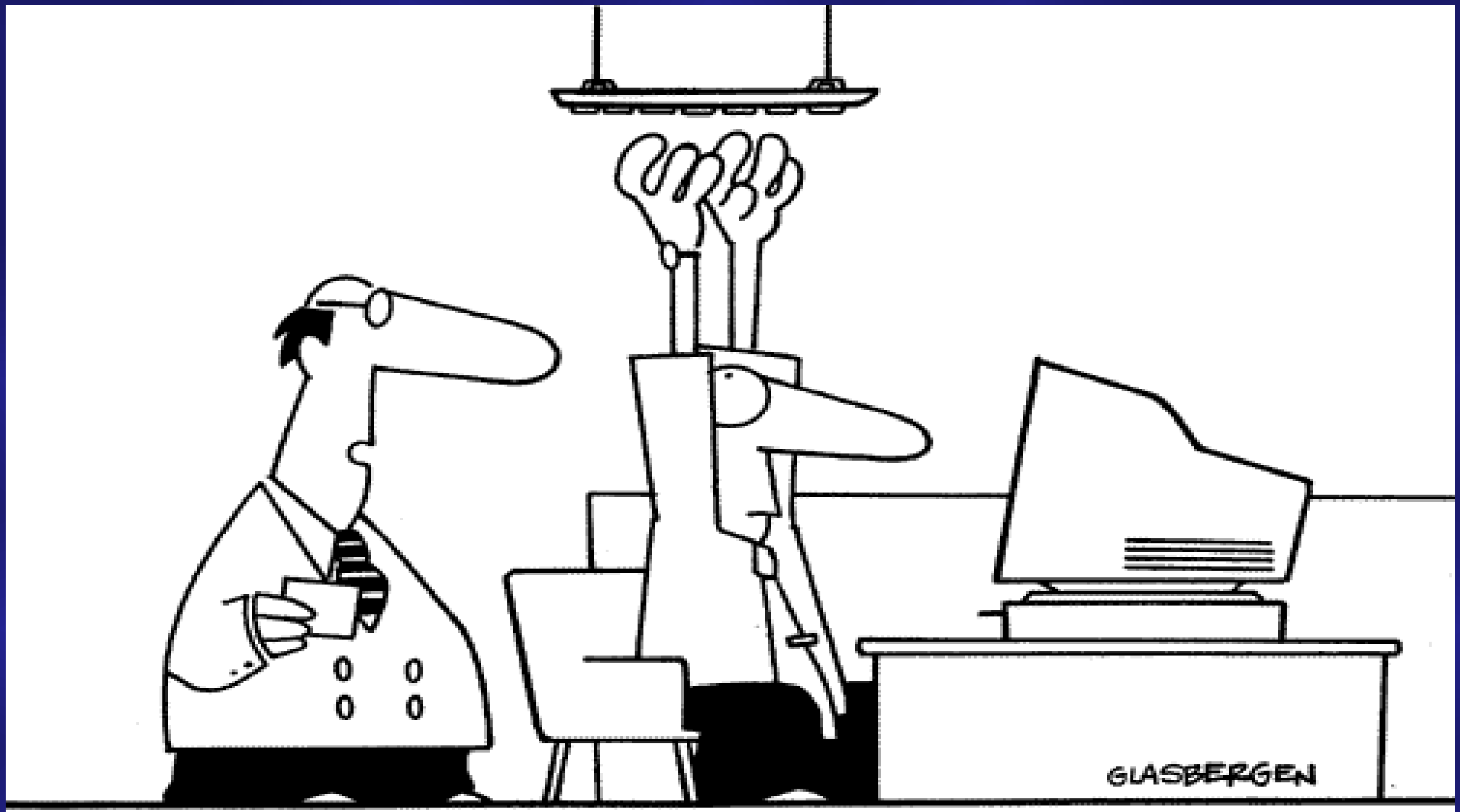
- Clinical manifestations:
- Hereditary forms typically develop in infancy or childhood; there may be splenomegally which can lead to mild thrombocytopenia
- Idiopathic/Acquired forms tend to develop insidiously (middle age or later)
- Presence of sideroblasts in bone marrow is the common finding
- Hereditary: hypochromic and microcytic; high serum iron & ferritin
- Acquired: hypochromic and normo / macrocytic

- Treatment:
- Large doses of pyridoxine (200mg daily)
- Peripheral neuropathy due to long term high dose
- Parenteral pyridoxal-5-pyrophosphate : who fails on oral therapy
- Folate supplements in case of increased turnover of cells in the bone marrow
- Non responsive groups : Blood transfusions (chelating agent desferrioxamine by i/v or s/c infusion)
- Oral agent: Deferiprone (may cause reversible neutropenia)
- It may lead to complications of iron overload, sensitization and risk of blood borne virus transmission.



"It's good that you're eating more fresh fruit and vegetables, but be careful to chew more thoroughly."

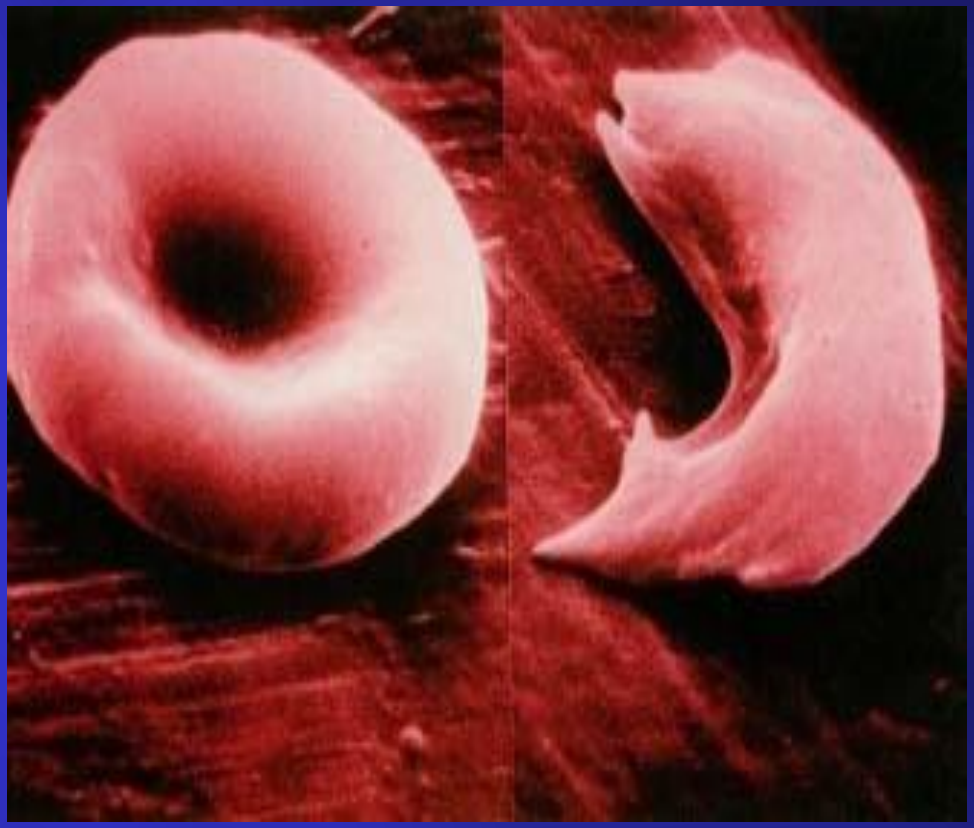


"Suspending your keyboard from the ceiling forces you to sit up straight, thus reducing fatigue."

Haemolytic anaemias

- Reduced lifespan of the erythrocytes.
- Sickle cell anemia:
- A hereditary condition with abnormal haemoglobin (HbS) valine substituted for glutamic acid as the 6^{th} amino acid in the beta-polypeptide
- Damaged membrane of red cells containing Hb S leading to intracellular dehydration.
- When the patient's blood is deoxygenated a semisolid gel forms leading to formation of sickle cells.
- Sickle cells are less flexible leading to impaired blood flow through the microcirculation resulting in local tissue hypoxia.

Sickle cell anaemia



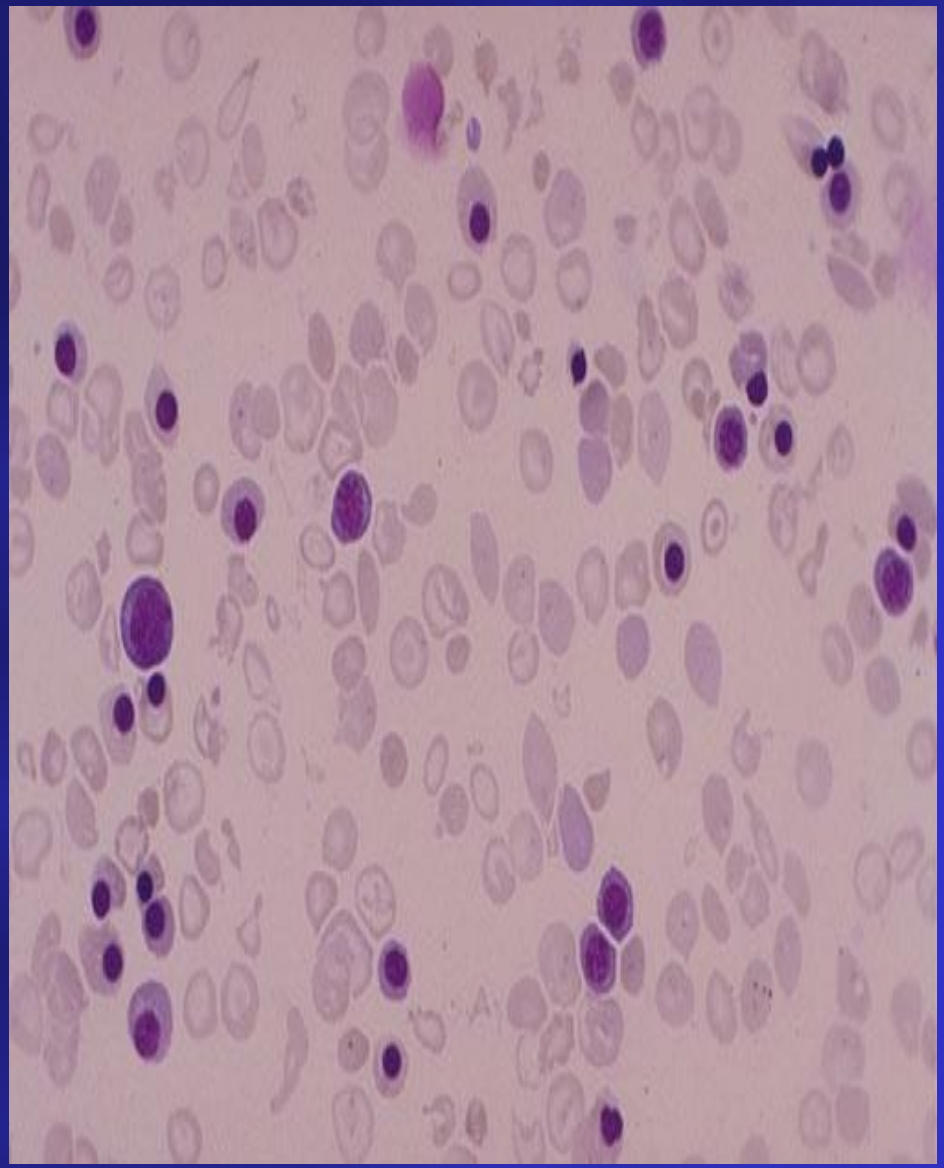
- Clinical manifestations:
- Chronic anaemia, arthralgia, anorexia, fatigue and splenomegaly
- Crises can be precipitated by infection and fever, dehydration, hypoxia or acidosis, infarction of the long bones/organ
- Management:
- Requires prompt and effective treatment; removal of the trigger factor, hydration and effective pain relief are the mainstays of treatment
- For pneumococcal infections: prophylactic antibiotics (penicillin V 250 mg twice daily); vaccination
- Increase Hb F levels : Cytarabine, Vinblastine, hydoxyurea, erythropoeitin
- Hydroxyurea in crises (cytoreduction in bone marrow leading to alteration in RBC differentiation and Hb F production)
- Transfusions

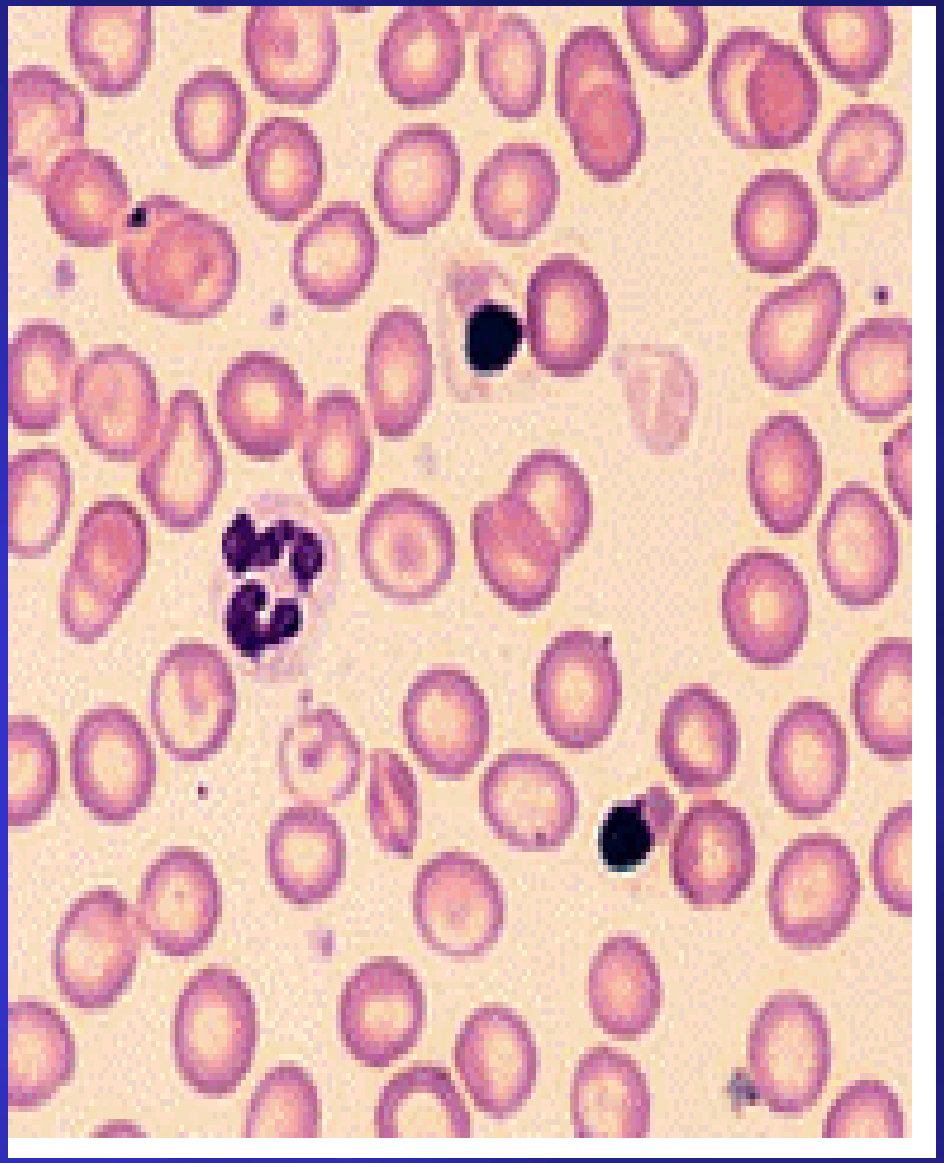
Thalassaemias

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

- α and ß thalassaemias
- In ß thalassaemias there is a reduced or absent production of the globin ß chain leading to a excess of alpha chain which, when unpaired, become unstable and precipitates in the red cell precursors causing ineffective erythropoietin
- Deficiency of alpha chains leads to an excess of γ or ß chains ; haemoglobin produced is unstable (Hb Barts or Hb H) and physiologically useless (Common in South East Asia)
- Bone marrow deformity and growth retardation

- Haemoglobin electrophoresis is used to determine the amounts of abnormal haemoglobin





- Management:
- Blood transfusion. Desferrioxamine & Deferiprone are routinely needed.
- Splenectomy
- Combination of hydroxycarbamide and erthropoietin may provide clinical improvement.

Glucose-6-phosphate dehydrogenase deficiency anaemia

- G6PD is essential for the production of the reduced form of phosphorylated nicotinamide-adenine dinucleotide (NADPH) in erythrocytes.
- NADPH is needed to keep glutathione in a reduced form which maintains Hb in a reduced form and helps erythrocytes deal with oxidative stress
- In G6PD deficiency, if the erythrocytes are exposed to oxidizing agents, the haemoglobin becomes oxidized and forms HEINZ BODIES
- Drugs causing G6PD deficiency: ciprofloxacin, dapsone, primaquine, nalidixic acid, sulphonamide, quinidine, chloroquine, chloramphenicol, aspirin etc

- Drug history and measuring G6PD activity

- Management:
- Avoid the causative factor (e.g., drug)
- No specific drug treatment
- Adequate hydration
- Blood transfusions may be necessary
- Vitamin E (an antioxidant)

THANK YOU