**Haemolytic anaemias**

**Normal red cell destruction:**

Red cell destruction usually occurs after a mean life span of 120 days when the cells are removed extravascularly by the macrophages in the bone marrow ,liver and spleen.

The breakdown of the haem from red cells liberates iron for re circulations via plasma transferrin to marrow erythroblasts, and protoporphyrin which is broken down to bilirubin

Bilirubin circulates to the liver where it is conjugated to glucoronides which are excreted into the gut via bile and converted to stercobilinogen and stercobilin which are excreted in faeces, stercobilinogen and stercobilin are partly reabsorbed and exerted in urine as urobilinogen and uribilin.

Globin chains are broken down to amino acids which are reutilized for general protein synthesis in the body, intravascular haemolysis(break down of red cells with in blood vessels ) plays little or no role in normal red cells destruction.

**Definition of haemolytic anaemias:**

Haemolytic anaemias are defined as those anaemias that results from an increase in the rate of red cells destruction.

**Classification of haemolytic anaemias:**

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| Acquried | Hereditary |
| 1-immune (autoimmune,alloimmune and drug associated | 1-membrane defects |
| 2- red cell fragmentation syndrome | 2-defective red cell metabolism. |
| 3-march haemoglobinuria | 3-genetic disorder of haemoglobin. |
| 4- infections |  |
| 5-chemical and physical agents |  |
| 6- secondary to renal and liver disease |  |
| 7-paraxysmal nocturnal haemoglobinuria |  |

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**Clinical features :**

1-pallor of the mucous membrane.

2- mild jaundice.

3- splenomegaly.

4-pigment gallstones may complicates the condition.

5-aplastic crises may occur, usually precipitated by infection with parvovirus.

**Laboratory finding :**

The laboratory finding can be divided into three groups:

1- features of increased red cell break down:

a-serum bilirubin raised.

b-urine urobilinogen increased.

c-fecal stercobilinogen increased.

d- serum haptoglobin absent(haptoglobin is a protein found in normal plasma capable of binding haemoglobin)

2-features of increased red cell production:

a-reticulocytosis.

b- bone marrow erythroid hyperplasia.

3-damged red cells:

a-morphology(spherocytes,elliptocytes)

b-osmotic fragility.

c-shortened red cell survival by51 Cr

**Intravascular and extravascular haemolysis**:

These are tow main mechanisms where by red cell destroyed in haemolytic anaemias,in extravascular haemolysis there is excessive removal of red cells by macrophages while intravascular haemolysis ,the red cells are directly destroyed in the circulation. **The main laboratory features of intravascular haemolysis are:**

1-haemoglobinuria(free haemoglobin in the plasma)

2-haemosidrinuria(iron storage protein in the urine)

3-methaemoglobinaemia.

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**Hereditary haemolytic anaemias:**

***1-membrane defects:***

***a- Hereditary spherocytosis(HS)***: the mode of inheritance is autosomal dominant,rarly it may be autosomal recessive,it results from defects in red cell membrane cytoskeleton .

**Clinical features:**

●Anaemia :can be present at any age.

Fluctuating jaundice.●

Splenomegaly occurs in most patients. ●

Pigment gall stones are frequent. ●

Aplastic crisis precipitated by parvovirus infection.●

**Investigations:**

1-usually low haemoglobin.

2-reticulocytosis.

3-the blood film shows spherocytes.

4-Osmotic fragility test is increased.

5-direct antiglobulin test (coombs test )is negative.

**Treatment:**

The principle form of treatment is splenectomy ,folic acid is given in sever cases to prevent folate deficiency.

***b-hereditary elliptocytosis***: this has similar clinical and laboratory features to HS, except for the appearance of blood film which has a characteristic elliptical cells ,but it is clinically mild disorder and occasionally require splenectomy.

***2- Defective red cells metabolism***

***a-glucose 6 phosphate dehydrogenase deficiency(G6PD)***

G6PD function is reduction of nicotineamide adenine dinucleotide phosphate (NADP) while oxidizing glucose6phospate,it is the only source of NADP in the red cells and as NADP is needed for the production of reduced glutathione which protect the red cell membrane and haemoglobin from oxidant stress. .

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**Red cell membrane damage**

**Oxidant**

**Hb Heinz body**

GSH GSSG

**GLUCOSE**

NADP NADPH

G6P 6PG

G6PD

NADP

F6P

NADPH

**Lactate** Pentose 5-P

The inheritance of G6PD is sex-linked ,affecting males and carried by females who show approximately half the normal red cellG6PD values, there is a wide variety of normal genetic variants of the enzyme G6PD ,the most common being type B in western and type A in Africans, in addition more than 400 variants caused by point mutations or deletion of the enzyme.

The degree of deficiency varies often being mild 10-15 % of normal activity in black African, more sever in Orientals and most sever in Mediterranean.

**Clinical features :**

G6PD deficiency is usually a symptomatic, the main syndrome occurs are:

♦ *Acute haemolytic anaemia* in response to oxidant stress for examples: drugs such as antimalarial drugs, sulphonamide and sulphones,analgesia and antihelminthic drugs , other oxidant stress fava beans and infection. The acute haemolytic syndrome is caused by rapidly developing intravascular haemolysis and haemoglobinuria ,the anaemia may be self limiting as new young red cells are made with near normal enzyme level.

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♦ *Neonatal jaundice.*

♦*Rarely congenital non spherocytic haemolytic anaemia*.

**Diagnosis:**

Between crises the blood count is normal, the enzyme deficiency is detected by screening test or by direct enzyme assay on red cells, during the crises the blood film shows contracted and fragmented red cells and Heinz body seen , which is denatured and oxidized haemoglobin .there are also features of intravascular haemolysis.

**Treatment :**

The offending drugs is stopped , the underlying infection is treated, a high urine output is maintained and blood transfusion is undertaken for sever anaemia.  
***b-pyruvate kinase deficiency***: inherited as autosomal recessive , the severity of the anaemia varies widely , jaundice is usual and gall stones is frequent, frontal bossing may be present .

**Laboratory finding:**

● blood film shows poikilocytosis, distorted cells (prickle cells) .

● auto haemolysis test is increased.

●enzyme assay to make the diagnosis .

**Treatment**: Splenectomy may alleviate the anemia but does not cure it, and is indicated in those patients who need frequent transfusion.

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**Acquired haemolytic anaemia:**

♦ *Immune haemolytic anaemia*: classification

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| --- | --- |
| **A-Autoimmune** | |
| *Cold type:* | *Warm type:* |
| Idiopathic | Idiopathic |
| Secondary : Lymphoma, infections(mycoplasma pneumonia and infectious mononucleosis), paroxysmal cold haemoglobinuria. | Secondary : SLE, CLL, Lymphoma, drugs(methyldopa) |
| **B-Alloimmune** | |
|  | *1- Induced by red cells antigens* Haemolytic transfusion reaction , Haemolytic disease of newborn. |
|  | *2- Induced by drugs* |

*Autoimmune haemolytic anaemias*: are caused by antibody production by the body against its own red cells. They are characterized by appositive direct antiglobulin test( coombs test ) and divided into warm and cold type according to whether the antibody reacts more strongly with red cells at

37oC or 4oC.

*Warm autoimmune haemolytic anemia* :the red cells are coated with immunoglobulin(Ig) usually immunoglobulin G (IgG) alone or with complement, and are therefore taken up by macrophages which have receptors for immunoglobulin ,part of the red cell membrane is lost so it becomes progressively more spherical and ultimately prematurely destroyed ,predominantly in the spleen.

**Clinical features** :

The disease occur any age in either sex and present as haemolytic anaemia in varying severity ,the spleen enlarge and the disease tends to remit and relapse , it may occur alone or with other disease or arise a result of methyldopa therapy .

**Laboratory finding**:

The peripheral blood film shows prominent spherocytosis and the direct antihuman globulin test is positive as a result of IgG or IgG with complement on the cells .   
**Treatment** :

1-Remone the underlying cause (methyldopa).

2- corticosteroid ,(prednisolone) is the first line of treatment.

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3-splenectomy may be of value in those who fail to respond well to steroid.  
4-immunsupression may be tried after other measure have failed .  
5-monoclonal antibodies ( anti CD20) has produced prolong remission.

6- folic acid is given in few cases.

7-blood transfusion may be needed in sever cases.

*Cold autoimmune haemolytic anaemia*: in these syndromes the autoantibody attaches to red cells mainly in peripheral circulation where the blood temperature is cooled, the antibody is usually IgM and bind to red cells at4oC.IgM antibody is high efficient in fixing the complement and both intravascular and extravasculer haemolysis can occur.

**Clinical features:**

The patient may have chronic haemolytic anaemia aggravated by the cold and often associated with intravascular haemolysis, mild jaundice and splenomegaly may present, the patient may develops acrocyanosis(purplish skin discoloration) at the tips of nose, ears and fingers due to agglutination of red cells in small blood vessels.

**Laboratory finding:**

Are similar to those in warm type but spherocytosis is less marked.

**Treatment :**

1-Keep the patient warm.

2- Treatment of the underlying cause.

3-Alkalyting agents such chlorambucil in chronic cases.

4-monoclonal antibody.

5-splenectomy and steroid are usually not helpful.

*Paroxysmal cold haemoglobinuria*:

It is a rare syndrome of intravasculer haemolysis after exposure to the cold, it is caused by IgG antibody with specificity for the P blood group antigens which bind the red cells in the cold and lysis by complement in the warm condition. Viral infection and syphilis is predisposing causes and the condition is self limiting.

*Alloimmune haemolytic anaemia*:

In those anaemias the antibody produced by one individual reacts with red cells of another. Two important situations are transfusion of incompatible blood and rhesus haemolytic disease of newborn.

*Drugs induced immune haemolytic anaemia:*

Drugs may cause immune haemolytic anaemia by three mechanisims:

1-antibody directed against a drug-red cell membrane complex(pencillin).

2-deposition of complement via a drug-protein(antigen)-antibody complex on to red cell surface(quinidine)

3-true autoimmune haemolytic anaemia(methyldopa).

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♦ *Red cell fragmentation syndrome* , caused by:

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| --- | --- |
| 1-Cardiac haemolysis:(arise through physical damage to red cells on abnormal surface) | a-prosthetic heart valve  b-arterial grafts |
| 2- arterioveneous malformation |  |
| 3-microangiopathic : (caused by red cells passing through abnormal small vessels). | a-thrombotic thrombocytopenic purpura (TTP)  b-haemolytic uraemic sundrom(HUS)  c-disseminated intravascular coagulation(DIC)  d-malignant disease.  e-vasculitis.  f-pre-eclampsia/HELLP syndrome. |

♦*March haemoglobinurea*: Is caused by damage to red cells between the small bones of the feet, usually during prolonged marching or running.

♦*Infections* may cause haemolysis in variety of ways :

a-precipitate acute haemolytic crises in G6PD deficiency.

b-cause microangiopathic haemolytic anaemia(meningococcal septicemia)

c-malaria may cause haemolysis by extravascular destruction of parasitized cells and direct intravascular haemolysis.

♦*Chemical and physical agents*:

a-drugs (dapsone and salazopyrin) cause intravascular haemolysis in high doses.

b-chemical poisoning by lead can cause sever haemolysis.

c-sever burn damage red cells causing spherocytosis.

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