Haemolytic anaemias
An Introduction to hemolytic anaemia
Normal red cell destruction

Red cell destruction usually occurs after a mean lifespan of 120 days when the cells are removed extravascularly by the macrophages of the reticuloendothelial (RE) system, especially in the marrow but also in the liver and spleen.
### Extravascular

- **RBC**
- Globin
  - Iron
  - Protoporphyrin
  - Binds to transferrin
  - Amino acids
  - Unconjugated bilirubin
- Liver
  - Bilirubin glucuronides
  - Reabsorbed
  - Gut
  - Kidney
  - Urobilinogen (urine)
  - Stercodobilinogen (faeces)

### Intravascular

- **RBC**
  - Lysis
  - Haemoglobin
    - Metheamoglobin
    - Methaemalbumin
  - Kidney
    - Haemoglobinuria
    - Haemosiderinuria
Red cell metabolism gradually deteriorates as enzymes are degraded and the cells become non-viable.

The breakdown of haem from haemoglobin liberates iron for recirculation via plasma transferrin mainly to marrow erythroblasts, and protoporphyrin, which is broken down to bilirubin.
Bilirubin circulates to the liver where it is conjugated to glucuronides, which are excreted into the gut via bile and converted to stercobilinogen and stercobilin (excreted in faeces). Stercobilinogen and stercobilin are partly reabsorbed and excreted in urine as urobilinogen and urobilin.
Globin chains are broken down to amino acids which are reutilized for general protein synthesis in the body.

**Haptoglobin**s are proteins in normal plasma which bind haemoglobin.

The haemoglobin–haptoglobin complex is removed by the RE system.
Intravascular haemolysis (breakdown of red cells within blood vessels) plays little or no part in normal red cell destruction.
Haemolysis

Definitions

**Haemolysis** indicates that the destruction of red cells is accelerated.

**Haemolytic anaemias** are defined as anaemias that result from an increase in the rate of red cell destruction.
Normally, in adults, the bone marrow output is well below its maximal capacity. Red cell production can be increased more than ten fold in the adult by increasing the cellularity of existing haemopoietic marrow, as well as by expansion of haemopoietic marrow into the long bones.
In the newborn, and during infancy, marrow expansion depends on expanding the medullary cavity of bones, leading to thinning of cortical bone.

These bony changes are most extreme in the β-thalassaemia syndromes, but some skeletal changes, usually some bossing of the frontal bones, may be seen in more extreme hereditary haemolytic anaemias of other causes.
Bony changes
Increased red cell destruction is often completely matched by increased production, resulting in

*Compensated haemolysis.*
When the rate of haemolysis exceeds the maximum erythropoietic capacity of the bone marrow,
or
when the latter is limited (e.g. because of inadequate supply of iron or folate or by ineffective erythropoiesis), the result is

**Haemolytic anaemia**
Anaemia due to haemolysis may not be seen until the red cell lifespan is less than 30 days.
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<th>Hereditary</th>
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<td>Paroxysmal nocturnal haemoglobinuria (see Chapter 22)</td>
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Hereditary haemolytic anaemias are the result of ‘intrinsic’ red cell defects, whereas acquired haemolytic anaemias are usually the result of an ‘extracorpuscular’ or ‘environmental’ change. Paroxysmal nocturnal haemoglobinuria (PNH) is the exception because, although it is an acquired disorder, the PNH red cells have an intrinsic defect
General features of haemolysis

The clinical and laboratory aspects of haemolysis depend on the consequences of increased red cell destruction and production as well as the main process by which destruction takes place...
In the presence of haemolysis, serum haptoglobin levels are greatly reduced or absent. However, haptoglobin is an acute-phase protein and levels will increase in the presence of inflammation. Haemopexin is another haem-binding protein produced by the liver that is decreased in haemolysis.
Chronic haemolytic anaemia may increase the iron content of the body through increased iron absorption as a result of anaemia coupled to the retention of the haem iron following binding to haptoglobin and haemopexin. In rare cases of inherited haemolytic anaemia, this iron overload may be sufficient to produce clinically important effects, particularly if there is coinheritance of a haemochromatosis gene.
In most haemolytic anaemias, owing to membrane defects, the destruction of red cells takes place extravascularly in the reticuloendothelial system, particularly in the spleen, and the iron is retained.

When destruction is intravascular, free haemoglobin will be released into the plasma, producing haemoglobinaemia and methaemalbuminaemia, and will pass through the glomerulus to produce haemoglobinuria and haemosiderinuria.
Iron deficiency is thus more likely than overload in intravascular haemolysis
Clinical features

- pallor
- Mild fluctuating jaundice and splenomegaly.
- There is no bilirubin in urine but this may turn dark on standing because of excess urobilinogen.
- Pigment (bilirubin) gallstones may complicate the condition.
- Some patients (particularly with sickle cell disease) develop ulcers around the ankle.
Jaundice, anemia, and hemoglobinemia from intravascular hemolysis
Sickle cell anemia skin ulcers
Aplastic crises may occur, usually precipitated by infection with parvovirus which ‘switches off’ erythropoiesis, and are characterized by a sudden increase in anaemia and drop in reticulocyte count.

-Rarely, folate deficiency may cause an aplastic crisis in which the bone marrow is megaloblastic.
Laboratory findings

1. Features of increased red cell breakdown:

(a) Raised serum unconjugated bilirubin.
(b) Urine urinobilinogen increased;
(c) Serum haptoglobins absent because the haptoglobins become saturated with haemoglobin and the complex is removed by RE cells.
2 Features of increased red cell production:

a. Marrow expansion: bone changes
b. Increased erythropoiesis: ↓ myeloid/erythroid ratio
c. Reticulocytosis: polychromasia
d. Increased folate requirements: macrocytosis.
Bony changes include bossing of the skull; hypertrophy of the maxilla, exposing the upper teeth; depression of nasal bridge; and periorbital puffiness
Bone marrow findings (upper: B.M. aspirate, lower: B.M. biopsy) in hemolytic anemia. Erythroid hyperplasia is present with a predominance of erythroid precursors.
Reticulocytes
Reticulocytes
3 Damaged red cells:

(a) morphology (e.g. microspherocyttes, elliptocytes, fragments);
(b) osmotic fragility;
(c) specific enzyme, protein or DNA tests
Blood film in hereditary spherocytosis.
Blood film in hereditary elliptocytosis
**Figure 6.8** Blood film in G6PD deficiency with acute haemolysis after an oxidant stress. Some of the cells show loss of cytoplasm with separation of remaining haemoglobin from the cell membrane (‘blister’ cells). There are also numerous contracted and deeply staining
Sickle cell anemia
Warm autoimmune haemolytic anaemia. Blood film showing spherocytosis (arrows), polychromasia and a nucleated red blood cell
Cold haemagglutinin disease. Blood film showing gross haemagglutination
Figure 6.11  Blood film in microangiopathic haemolytic anaemia (in this patient Gram-negative septicaemia). Numerous contracted and deeply staining cells and cell fragments are present.
Osmotic fragility curves of normal and hereditary spherocytosis red blood cells
Intravascular and extravascular
Haemolysis

Two mechanisms:
1. Extravascular haemolysis

excessive removal of red cells by cells of the RE system.

2. Intravascular haemolysis

RBC are broken down directly in the circulation.
Whichever mechanism dominates will depend on the pathology involved.
The main laboratory features of intravascular haemolysis:

1. Haemoglobinaemia and haemoglobinuria.
2. Haemosiderinuria.
3. Methaemalbuminaemia (detected spectrophotometrically).
Figure 6.3  (a) Progressive urine samples in an acute episode of intravascular haemolysis showing haemoglobinuria of decreasing severity. (b) Prussian blue-positive deposits of haemosiderin in a urine spun deposit (Perls' stain).
Causes of intravascular haemolysis

- Mismatched blood transfusion (usually ABO)
- G6PD deficiency with oxidant stress
- Red cell fragmentation syndromes
- Some severe autoimmune haemolytic anaemias
- Some drug- and infection-induced haemolytic anaemias
- Paroxysmal nocturnal haemoglobinuria
- March haemoglobinuria
- Unstable haemoglobin
Features of extravascular haemolysis

- jaundice.
- gallstones
- splenomegaly
- raised reticulocytes, unconjugated bilirubin and absent haptoglobins.