**Introduction and classification**

**Definition**

The term 'anaemia' refers to a reduction of haemoglobin or red cell concentration in the blood. With the widespread introduction of automated equipment into haematology laboratories the haemoglobin concentration has replaced the haematocrit (or 'packed cell volume') as the key measurement. Haemoglobin concentration can be determined accurately and reproducibly and is probably the laboratory value most closely correlated with the pathophysiological consequences of anaemia. Thus, anaemia is simply defined as a haemoglobin concentration below the accepted normal range.

The normal range for haemoglobin concentration varies in men and women and in different age groups (Table 1). The definition of normality requires accurate haemoglobin estimation in a carefully selected reference population. Subjects with iron deficiency (up to 30% in some unselected populations) and pregnant women must be excluded or the lower level of normality will be misleadingly low. Normal haemoglobin ranges may vary between ethnic groups and between populations living at different altitudes.

**Prevalence**

The prevalence of anaemia and the aetiologies vary in different populations. In developed countries where most studies have been performed, anaemia is more common in women than in men. Particularly susceptible groups include pregnant women, children under 5 years and the elderly. The majority of cases in younger people are caused by iron deficiency. Anaemia is surprisingly common in the elderly, affecting roughly 10% of people over 65 years. Up to a third of these cases remain unexplained. In developing countries, factors influencing the prevalence of anaemia include climate, socio-economic conditions and, most importantly, the incidence of coexistent diseases.

**General features**

In anaemia the blood’s reduced oxygen-carrying capacity can lead to tissue hypoxia. The clinical manifestations of significant anaemia (see also p. 14) are to a large extent due to the compensatory mechanisms mobilised to counteract this hypoxia. Cardiac overactivity causes palpitations, tachycardia and heart murmurs. The dyspnoea of severe anaemia may be a sign of incipient cardio-respiratory failure. Pallor is due primarily to skin vasoconstriction with redistribution of blood flow to tissues with higher oxygen dependency such as the brain and myocardium.

Anaemia is one of the most common clinical problems presenting in general practice, hospitals and in medical examinations. Usually characteristic symptoms and signs prompt a blood count to confirm the diagnosis but on occasion an unexpectedly low haemoglobin estimation in a 'routine' blood count precedes the clinical consultation. Whatever the sequence of events, anaemia is not in itself an adequate diagnosis further enquiry to establish the underlying cause is essential.

A logical approach to anaemia demands a clear understanding of both its possible causes and its clinical and laboratory features. There are two major classifications – both have advantages and they are best used together.

**Classification**

**Morphological classification**

As already discussed (p. 18), modern electronic laboratory equipment can provide estimations of red cell indices in addition to haemoglobin concentration. Abnormal red cell indices should be confirmed by microscopic examination of blood films. The 'morphological' classification is based on a correlation between red cell indices and the underlying cause of anaemia. The most important measurements are of red cell size (mean cell volume or MCV) and red cell haemoglobin concentration (mean cell haemoglobin (MCH) or mean cell haemoglobin concentration (MCHC)).

Anaemias with raised, normal and reduced red cell size (MCV) are termed macrocytic, normocytic and microcytic respectively. Anaemias associated with a reduced haemoglobin concentration within red cells are termed hypochromic and those with a normal MCH are termed normochromic. Characteristic combinations are of microcytosis and hypochromia, and normocytosis and normochromia. As can be seen in Figure 1, this terminology is helpful in narrowing the differential diagnosis of anaemia. It is perhaps least helpful in normocytic anaemia as the possible causes are numerous and diverse.

The value of the blood film in diagnosis should not be underestimated. For instance, combined iron deficiency (a cause of microcytosis) and folate deficiency (a cause of macrocytosis) may cause an anaemia with a normal MCV. However, inspection of the film will reveal a dual population of microcytic hypochromic red cells and macrocytic red cells.

**Aetiological classification**

Figure 2 illustrates a classification of anaemia based on cause. It is less immediately helpful than the morphological classification in forming a differential diagnosis but it does illuminate the pathogenesis of anaemia. The fundamental division is between excessive loss or destruction of mature red cells and inadequate production of red cells by the marrow.

Loss of red cells occurs in haemorrhage and excessive destruction in haemolysis. A normal bone marrow will respond by increasing red cell production with accelerated discharge of young red cells (reticulocytes) into the blood. Inadequate red cell production may result from insufficient erythropoiesis (i.e. a quantitative lack of red cell precursors) or ineffective erythropoiesis (i.e. defective erythrocytes destroyed in the marrow). Examples of insufficient

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**Table 1 Normal haemoglobin concentrations at different ages**

<table>
<thead>
<tr>
<th>Age</th>
<th>Mean haemoglobin (g/L)</th>
<th>Lower limit of normal (g/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth (cord blood)</td>
<td>165</td>
<td>135</td>
</tr>
<tr>
<td>1–3 days (capillary)</td>
<td>185</td>
<td>145</td>
</tr>
<tr>
<td>1 month</td>
<td>140</td>
<td>100</td>
</tr>
<tr>
<td>2–6 months</td>
<td>115</td>
<td>75</td>
</tr>
<tr>
<td>6 months–2 years</td>
<td>120</td>
<td>95</td>
</tr>
<tr>
<td>2–6 years</td>
<td>125</td>
<td>115</td>
</tr>
<tr>
<td>6–12 years</td>
<td>135</td>
<td>115</td>
</tr>
<tr>
<td>12–18 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>140</td>
<td>120</td>
</tr>
<tr>
<td>male</td>
<td>145</td>
<td>130</td>
</tr>
<tr>
<td>Adult</td>
<td></td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>140</td>
<td>115</td>
</tr>
<tr>
<td>male</td>
<td>155</td>
<td>135</td>
</tr>
</tbody>
</table>

Normal haemoglobin concentration probably slightly lower after 65 years.
Characteristics of bacteria

Anaemia: introduction and classification

- Anaemia is defined as a haemoglobin concentration below the accepted normal range.
- The normal range for haemoglobin is affected by sex, age, ethnic group and altitude.
- The clinical features of anaemia are largely caused by compensatory measures mobilised to counteract hypoxia.
- Anaemia can be classified according to red cell morphology or aetiology.
- Red cell indices and morphology correlate with the underlying cause of anaemia.
- Wherever possible the cause of anaemia should be determined before treatment is started.
- Blood transfusion is only required in a minority of cases.

Management

The treatment of specific types of anaemia is discussed in subsequent sections. However, some general statements can be made. Whenever possible, the cause of anaemia should be determined before treatment is instituted. Blood transfusion should only be used where the haemoglobin is dangerously low, where there is risk of a further dangerous fall in haemoglobin (e.g. rapid bleeding), or where no other effective treatment of anaemia is available. Prompt blood transfusion can be life-saving in a profoundly anaemic patient but it should be undertaken with great caution as heart failure can be exacerbated. Mild anaemia in the elderly should not be overlooked as it is a frequent cause of debility and has been linked with increased mortality.
Iron deficiency anaemia

Iron

Iron is a constituent of haemoglobin and rate limiting for erythropoiesis. The metabolism of iron in the body is dominated by its role in haemoglobin synthesis (Fig. 1). Normally, the total iron content of the body remains within narrow limits: absorption of iron from food (usually 10–30 mg/day) must replace any iron losses. Iron is not excreted as such but is lost in desquamated cells, particularly epithelial cells from the gastrointestinal tract. Menstruating women will lose an additional highly variable amount of iron, and in pregnancy the rate of iron loss is about 3.5 times greater than in normal men. The storage forms of iron, ferritin and haemosiderin, constitute about 13% of total body iron.

Iron deficiency

Clinically significant iron deficiency is characterised by an anaemia which can usually be confidently diagnosed on the basis of the clinical history and simple laboratory tests. It cannot be overstressed that the diagnosis of iron deficiency is not adequate in itself – a cause for the deficiency must always be sought.

Causes

The likely cause will vary with the age, sex and geographic location of the patient (Table 1). Iron deficiency is usually caused by long-term blood loss, most often gastrointestinal or uterine bleeding and less commonly bleeding in the urinary tract or elsewhere. Particularly in elderly patients, deficiency may be the presenting feature of gastrointestinal malignancy (Fig. 2). Hookworm infection is the commonest cause of iron deficiency worldwide. Malabsorption and increased demand for iron as in pregnancy are other possible causes. Poor diet may exacerbate iron deficiency but is rarely the sole cause outside the growth spurs of infancy and teenage years.

Clinical features

These can be conveniently grouped into three categories:

- General symptoms and signs of anaemia (see pp. 14 and 22).

Table 1 Causes of iron deficiency

<table>
<thead>
<tr>
<th>Very common</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Bleeding from the gastrointestinal tract (e.g. benign ulcer, malignancy)</td>
<td>● Menorrhagia</td>
</tr>
<tr>
<td>● Pregnancy</td>
<td>● Malabsorption (e.g. coeliac disease, atrophic gastritis)</td>
</tr>
<tr>
<td>● Malnutrition</td>
<td>● Bleeding from urinary tract</td>
</tr>
<tr>
<td></td>
<td>● Pulmonary haemosiderosis</td>
</tr>
</tbody>
</table>

Fig. 1 The normal iron cycle. Iron is absorbed from the gut into plasma where it is transported to the bone marrow for haemoglobin synthesis. Dying red cells are engulfed by macrophages in the reticuloendothelial system, and iron is recycled into the plasma for reuse. Iron is transported in the plasma bound to the glycoprotein, transferrin. Transferrin receptors exist on most cells in the body. Of the total 4–5 g of iron in the body only about 0.1% is being recycled at any given time. The rest is in tissue-specific proteins such as haemoglobin (66% of total body iron) and myoglobin, or stored in ferritin.

Fig. 2 Carcinoma of the colon. A 53-year-old man presented to his doctor complaining only of tiredness. A blood count was consistent with iron deficiency (Hb 76 g/L, MCV 69 fl) and this was confirmed by a low serum ferritin level. History and examination revealed no obvious cause for his iron deficiency. Colonoscopy revealed a large bowel carcinoma which was successfully resected.

Fig. 3 Glossitis and angular stomatitis in iron deficiency.
Further tests are helpful in confirming the diagnosis (Table 2) and excluding other causes of a hypochromic microcytic anaemia (see p. 23). Measurement of serum ferritin is probably the most useful of these tests: a low level always indicates iron deficiency but a normal level does not guarantee normal stores as ferritin is increased in chronic inflammation and liver disease. In occasional difficult cases (e.g. where the patient has recently been transfused) a bone marrow aspirate is helpful in showing absence of iron stores. In practice the most likely confusion is with the anaemia of chronic disease (p. 36).

### Management

This is divisible into investigations of the underlying cause and the correction of iron deficiency.

#### Investigation of underlying cause

Where the likely cause is apparent, further investigations can be highly selective. Thus in a young woman with severe menorrhagia and no other symptoms it can be assumed that uterine bleeding is the cause of iron deficiency, and investigation of the gastrointestinal (GI) tract is not necessary. A gynaecological referral would be adequate. Complaints of indigestion or a change in bowel habit should prompt an endoscopy (GI) tract is not necessary. A gynaecological referral would be adequate. Complaints of indigestion or a change in bowel habit should prompt an endoscopy.

#### Correction of iron deficiency

Oral iron is given to correct the anaemia. Oral iron is given to correct the anaemia. The normal regimen is ferrous sulphate 200 mg three times a day (providing 195 mg elemental iron daily). Side-effects, including nausea, epigastric pain, diarrhoea and constipation, are best managed by reducing the dosage rather than stopping the medication. An adequate response to oral iron is an increase in haemoglobin of 20 g/L every 3 weeks. Iron is given for at least 6 months to replete body stores. There are several possible causes of a failure to respond to oral iron (Table 3). Parenteral iron (intramuscular or intravenous) can be used where oral therapy is unsuccessful because of poor tolerability or compliance or where there is continuing blood loss or malabsorption. Iron gluconate and iron sucrose appear to cause less severe side-effects (e.g. anaphylactic reactions) than iron dextran.

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**Iron deficiency anaemia**

- Iron is a constituent of haemoglobin and is essential for erythropoiesis.
- Iron deficiency is most often caused by long-term blood loss.
- Iron deficiency causes a hypochromic microcytic anaemia.
- The anaemia is usually easily corrected with oral iron supplements.
- It is important to establish the cause of iron deficiency – it may be the presenting feature of gastrointestinal malignancy.

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**Table 2** Tests to confirm iron deficiency

<table>
<thead>
<tr>
<th>Test</th>
<th>Result in iron deficiency</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferritin</td>
<td>Low</td>
<td>Level increased in chronic inflammation/liver disease</td>
</tr>
<tr>
<td>Transferrin saturation</td>
<td>Low</td>
<td>Low levels also in elderly and chronic disease</td>
</tr>
<tr>
<td>Serum iron</td>
<td>Low</td>
<td>Levels fluctuate significantly and low in chronic disease</td>
</tr>
<tr>
<td>Transferrin concentration</td>
<td>High</td>
<td>Useful test as low in anaemia of chronic disease</td>
</tr>
<tr>
<td>Zinc protoporphyrin</td>
<td>High</td>
<td>Late finding only</td>
</tr>
<tr>
<td>BM iron</td>
<td>Low</td>
<td>Informative but invasive investigation</td>
</tr>
<tr>
<td>Serum transferrin receptor level</td>
<td>Low</td>
<td>Also high in haemolysis</td>
</tr>
<tr>
<td>Percentage of hypochromic red cells</td>
<td>High</td>
<td>Limited availability</td>
</tr>
<tr>
<td>Reticulocyte haemoglobin content</td>
<td>Low</td>
<td>Limited availability</td>
</tr>
</tbody>
</table>

BM, bone marrow.
Megaloblastic anaemia

The megaloblastic anaemias are characterised by delayed maturation of the nucleus of red cells in the bone marrow due to defective synthesis of DNA. Red cells either die in the marrow ('ineffective haematopoiesis') or enter the bloodstream as enlarged, misshapen cells with a reduced survival time. In clinical practice megaloblastic anaemia is almost always caused by deficiency of vitamin B₁₂ (cobalamin) or folate (pteroyl monoglutamate). It is one of the most common causes of a macrocytic anaemia.

Why does deficiency of vitamin B₁₂ or folate lead to megaloblastic anaemia?

Key characteristics of these essential vitamins are summarised in Table 1. Both folate and vitamin B₁₂ are necessary for the synthesis of DNA (Fig. 1). Folate is needed in its tetrahydrofolate form (FH₄) as a cofactor in DNA synthesis. Deficiency of B₁₂ leads to impaired conversion of homocysteine to methionine causing folate to be ‘trapped’ in the methyl form. The resultant deficiency in methylene FH₄ deprives the cell of the coenzyme necessary for DNA formation.

All dividing cells in the body suffer from the impaired DNA synthesis of B₁₂ and folate deficiency. However, the actively proliferating cells of the bone marrow are particularly affected. As RNA synthesis progresses unhindered in the cytoplasm, the erythroid cells develop nuclear–cytoplasmic imbalance with abundant basophilic cytoplasm and enlarged nuclei. The chromatin pattern in the nucleus is characteristically abnormal: one author has described it as resembling ‘fine scroll work’, another as ‘sliced salami’ (Fig. 2). The slowed synthesis of DNA leads to prolonged cell cycling and the cells being discharged into the blood without the normal quota of divisions. Red cells are enlarged and egg-shaped and the neutrophils hypersegmented due to retention of surplus nuclear material (Fig. 3).

Clinical syndromes

Vitamin B₁₂ deficiency

Pernicious anaemia

This classic cause of vitamin B₁₂ deficiency is an autoimmune disorder. Most patients have IgG autoantibodies targeted against gastric parietal cells and the B₁₂ transport protein intrinsic factor. The precise pathogenesis, and particularly the role of the autoantibodies, is incompletely understood but B₁₂ deficiency ultimately arises from reduced secretion of intrinsic factor (IF) by parietal cells and, hence, reduced availability of the B₁₂–IF complex which is absorbed in the terminal ileum.

The clinical hallmarks of pernicious anaemia are gastric parietal cell atrophy and achlorhydria, a more generalised epithelial cell atrophy and megaloblastic anaemia. The disease is most common in northern Europe in women greater than 50 years of age and is familial. Affected patients classically have premature greying of the hair and blue eyes and may develop other autoimmune disorders including vitiligo, thyroid disease and Addison’s disease. Slight jaundice is caused by the haemolysis of ineffective erythrocytes. Patients usually have symptoms of anaemia and the generalised epithelial abnormality can manifest as glossitis (Fig. 4) and angular stomatitis. The archetypal neurological complication – ‘subacute combined degeneration’ – arises from demyelination of the dorsal and lateral columns of the spinal cord. Patients most commonly complain of an unsteady gait, and if B₁₂ deficiency is not corrected there can be progression to irreversible damage of the central nervous system. There is a possible increased incidence of carcinoma of the stomach and colorectal cancer in pernicious anaemia.

<table>
<thead>
<tr>
<th>Vitamin B₁₂ and folate</th>
<th>Characteristic</th>
<th>Vitamin B₁₂</th>
<th>Folate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average dietary intake/day (µg)</td>
<td>250</td>
<td>2500</td>
<td></td>
</tr>
<tr>
<td>Minimum adequate intake/day (µg)</td>
<td>1–2</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Major food sources</td>
<td>Animal produce only</td>
<td>Liver, vegetables</td>
<td></td>
</tr>
<tr>
<td>Normal body stores</td>
<td>Sufficient for several years</td>
<td>Sufficient for a few months</td>
<td></td>
</tr>
<tr>
<td>Mode of absorption</td>
<td>Combined with transport protein (IF) secreted by gastric parietal cells</td>
<td>Dietary folate converted to methyl THF and absorbed in duodenum and jejunum</td>
<td></td>
</tr>
</tbody>
</table>

THF: tetrahydrofolate; IF: intrinsic factor.

Fig. 1 The cause of megaloblastic anaemia. Both vitamin B₁₂ and folate (FH₄) are necessary for normal synthesis of DNA (see text).

Fig. 2 Bone marrow aspirate in megaloblastic anaemia. The immature red cells show nuclear–cytoplasmic imbalance with enlarged abnormal nuclei and basophilic cytoplasm.
Vitamin B12 deficiency should be excluded or corrected before increased dietary requirements as in pregnancy. Folate deficiency is more often due to frank dietary deficiency or dietary history patients may need investigations for malabsorption (e.g. jejunal biopsy).

Folate deficiency is treated with oral folic acid 5 mg once daily. This is given for several months at least, the precise duration of therapy depending on the underlying cause. Folate is prescribed prophylactically in pregnancy (400 μg daily) and in groups of patients at high risk of deficiency (Table 2). Before folate is prescribed, vitamin B12 deficiency must be excluded (or corrected) as subacute combined degeneration of the cord can be precipitated.

In practice patients with megaloblastic anaemia are often started on both B12 and folate supplements after a blood sample has been taken for assay of the vitamins. When the results are known the unnecessary vitamin can be stopped. Blood transfusion is best avoided as it may lead to circulatory overload – where judged necessary to correct hypoxia it is undertaken with extreme caution. Hypokalaemia occasionally requires correction.

Other causes of vitamin B12 deficiency
These are mostly abnormalities of the stomach and ileum (Table 2). As normal body stores are sufficient for 2 years, clinically apparent deficiency from any cause will develop slowly.

Folate deficiency
Folate deficiency is caused by dietary insufficiency, malabsorption, excessive utilisation or a combination of these (Table 2). Patients may complain of symptoms of anaemia or of an underlying disease. The increased risk of thrombosis is because of associated hyperhomocysteinaemia (see p. 79). There is a macrocytic anaemia and a megaloblastic bone marrow. In significant deficiency both serum and red cell folate are usually low but the latter is the better measure of tissue stores. In addition to a thorough dietary history patients may need investigations for malabsorption (e.g. jejunal biopsy).

Folate deficiency is treated with oral folic acid 5 mg once daily. This is given for several months at least, the precise duration of therapy depending on the underlying cause. Folate is prescribed prophylactically in pregnancy (400 μg daily) and in groups of patients at high risk of deficiency (Table 2). Before folate is prescribed, vitamin B12 deficiency must be excluded (or corrected) as subacute combined degeneration of the cord can be precipitated.
General features of haemolysis

The term 'haemolytic anaemia' describes a group of anaemias of differing aetiology that are all characterised by abnormal destruction of red cells. The hallmark of these disorders is reduced lifespan of the red cells rather than underproduction by the bone marrow.

In classification of the haemolytic anaemias there are three main considerations:

- The mode of acquisition of the disease: is it an inherited disorder or a disorder acquired in later life?
- The location of the abnormality: is the abnormality within the red cell (intrinsic) or outside it (extrinsic)?
- The site of red cell destruction: red cells may be prematurely destroyed in the bloodstream (intravascular haemolysis) or outside it in the spleen and liver (extravascular haemolysis).

The simple classification in Table 1 relies upon division of the main clinical disorders into inherited and acquired types. In general, it can be seen that inherited disorders are intrinsic to the red cell and acquired disorders extrinsic. The inherited disorders can be subdivided depending on the site of the defect within the cell – in the membrane, in haemoglobin, or in metabolic pathways. Acquired disorders (discussed in the next section) are broadly divided depending on whether the aetiology has an immune basis.

Diagnosis of a haemolytic anaemia

Recognition of the general clinical and laboratory features of haemolysis usually precedes diagnosis of a particular clinical syndrome. Where haemolysis leads to significant anaemia the resultant symptoms are as for other causes of anaemia. However, the increased red cell breakdown of the haemolytic anaemias causes an additional set of problems. Accelerated catabolism of haemoglobin releases increased amounts of bilirubin into the plasma such that patients may present with jaundice (Fig. 1). Where the spleen is a major site of red cell destruction there may be palpable splenomegaly. Severe prolonged haemolytic anaemia in childhood can lead to expansion of the marrow cavity and associated skeletal abnormalities including frontal bossing of the skull.

Initial laboratory investigations of haemolysis will include an automated blood count, a blood film and a reticulocyte count. The blood count will show low haemoglobin. Many cases of haemolysis have ‘normochromic normocytic’ red cell indices although some are moderately macrocytic. The latter observation is caused by the increased number of large immature red cells (reticulocytes) in the peripheral blood following a compensatory increase in red cell production by the bone marrow. Reticulocytes have a characteristic blue tinge with Romanowsky stains and their presence in the film causes ‘polychromasia’. A reticulocyte count is performed either manually on a blood film stained with a supravital stain or by the automated cell counter.

Simple laboratory tests to detect increased breakdown of red cells are also useful indicators of haemolysis. In addition to moderately raised serum bilirubin (often 30–50 μmol/L), there may be raised levels of urine urobilinogen and faecal stercobilinogen. Bilirubin itself is unconjugated and therefore does not appear in the urine. Haptoglobin, a glycoprotein bound to free haemoglobin in the plasma, is depleted in haemolysis. In intra-vascular haemolysis, haemoglobin and haemosiderin can be detected in the urine. Haemosiderin is present for several weeks after a haemolytic episode and is simply demonstrated by staining urine sediment for iron.
Examination of the bone marrow is not usually necessary in the work-up of haemolysis but, where performed, will show an increased number of immature erythroid cells. Formal demonstration of reduced red cell survival by tagging of cells with radioactive chromium ($^{51}$Cr) and in vivo surface counting of radioactivity to identify the site of red cell destruction are other possible investigations infrequently performed in practice.

**Inherited disorders**

**Disorders of the red cell membrane**

**Hereditary spherocytosis**

This is the most common cause of inherited haemolytic disease in northern Europeans. The disease is heterogeneous with a variable mode of inheritance. There are many possible gene mutations with alterations in spectrin, ankyrin and other membrane proteins. In a blood film the red cells are spheroidal (‘spherocytes’) with a reduced diameter and more intense staining than normal red cells (Fig. 2). These abnormal red cells are prone to premature destruction in the microvasculature of the spleen.

The severity of haemolysis is variable and the disease may present at any age. Fluctuating levels of jaundice and palpable splenomegaly are common features. Occasionally, patients develop severe anaemia associated with the transient marrow suppression of a viral infection; this so-called ‘aplastic crisis’, which may intervene in any form of chronic haemolysis, is often caused by parovirus B19. Prolonged haemolysis may lead to bilirubin gallstones.

Diagnosis is facilitated by the presence of a family history. The combination of general features of haemolysis and spherocytes in the blood is suggestive of hereditary spherocytosis but not diagnostic as spherocytes may also be seen in autoimmune haemolysis. The two haemolytic disorders are distinguished by the direct antiglobulin test, which is negative in hereditary spherocytosis and nearly always positive in immune haemolysis. Useful screening tests for hereditary spherocytosis include measurement of osmotic fragility (Fig. 3), the cryohaemolysis test, and flow cytometric analysis of eosin-5-maleimide binding.

In difficult cases, gel electrophoretic analysis of red cell membranes is helpful.

No treatment is required in patients with mild disease. In more serious cases the spleen is removed. This should ideally be performed after 6 years of age with counselling regarding the infection risk.

**Hereditary elliptocytosis**

This disease has many similarities to hereditary spherocytosis but the cells are elliptical in shape and the clinical course is usually milder. Splenectomy helps in the rare severe cases. There are various gene mutations with the most common structural change being a defective spectrin molecule.

**Abnormalities of haemoglobin**

These disorders are referred to collectively as the ‘haemoglobinopathies’. Thalassaemia and sickle cell syndromes are discussed in later sections.

**Abnormalities of red cell metabolism**

The red cell has metabolic pathways to generate energy and also to protect it from oxidant stress (Fig. 4). Loss of activity of key enzymes may lead to premature destruction; there are two common examples.

**Glucose-6-phosphate dehydrogenase (G6PD) deficiency**

G6PD is a necessary enzyme in the generation of reduced glutathione which protects the red cell from oxidant stress. Deficiency is X-linked, affecting males; female carriers show half normal G6PD levels. The disorder is most common in West Africa, southern Europe, the Middle East and South-East Asia. Patients are usually asymptomatic until increased oxidant stress leads to a severe haemolytic anaemia, often with intravascular destruction of red cells. Common triggers include fava beans, drugs (many including antimarials and analgesics) and infections. The disease can alternatively present as jaundice in the neonate. Diagnosis requires demonstration of the enzyme deficiency by direct assay – this should not be done during acute haemolysis as reticulocytes have higher enzyme levels than mature red cells and a ‘false normal’ level may result. Treatment is to stop any offending drug and to support the patient. Blood transfusion may be necessary.

**Pyruvate kinase (PK) deficiency**

In this autosomal recessive disorder patients lack an enzyme in the Embden–Meyerhof pathway. Red cells are unable to generate adequate ATP and become rigid. All general features of haemolysis can be present, but clinical symptoms are often surprisingly mild for the degree of anaemia as the block in metabolism leads to increased intracellular 2,3-DPG levels facilitating release of oxygen by haemoglobin. Spleenectomy may help in reducing transfusion requirements.

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**Haemolytic anaemia I – general features and inherited disorders**

- ‘Haemolytic anaemias’ are caused by abnormal destruction of red cells.
- Most inherited haemolytic disorders have a defect within the red cell whilst most acquired disorders have the defect outside the cell.
- Haemolysis causes characteristic clinical features and laboratory abnormalities. It may be intra- or extravascular.
- Hereditary spherocytosis and hereditary elliptocytosis are haemolytic disorders caused by a deficiency in the red cell membrane.
- Glucose-6-phosphate dehydrogenase and pyruvate kinase are key enzymes in red cell metabolism; inherited deficiency leads to haemolysis.
Autoimmune haemolytic anaemia

Autoimmune haemolytic anaemia (AIHA) is an example of an acquired form of haemolysis with a defect arising outside the red cell. The bone marrow produces structurally normal red cells and premature destruction is caused by the production of an aberrant autoantibody targeted against one or more antigens on the cell membrane. Once an antibody has attached itself to the red cell, the exact nature of the haemolysis is determined by the class of antibody and the density and distribution of surface antigens. IgM autoantibodies cause destruction by agglutination or by direct activation of serum complement. IgG class antibodies generally mediate destruction by binding of the Fc portion of the cell-bound immunoglobulin molecule by macrophages in the spleen and liver. The disparate behaviour of different types of autoantibody provides the explanation for a number of different clinical syndromes.

Classification

Table 1 shows a simple approach to the classification of autoimmune haemolytic anaemia. The disease can be divided into ‘warm’ and ‘cold’ types depending on whether the antibody reacts better with red cells at 37°C or 0–5°C. For each of these two basic types of autoimmune haemolysis there are a number of possible causes and these can be incorporated into the classification. A diagnosis of autoimmune haemolysis may precede diagnosis of the causative underlying disease.

Clinical presentation and management

Warm autoimmune haemolytic anaemia

Warm AIHA (Figs 1 and 2) is the most common form of the disease. The red cells are coated with either IgG alone, IgG and complement or complement alone. Premature destruction of these cells usually takes place in the reticuloendothelial system. Approximately half of all cases are idiopathic but in the other half there is an apparent underlying cause (Table 1). The autoantibody is usually non-specific with reactivity against basic membrane constituents present on virtually all red cells. Patients present with the clinical and laboratory features of haemolysis discussed in the last section. Splenomegaly is a frequent examination finding in severe cases. The most characteristic laboratory abnormality in warm AIHA is a positive direct antiglobulin test (DAT) sometimes known as the Coombs’ test (p. 83). A major priority in management is the identification and treatment of any causative disorder. It is particularly important to stop an offending drug – cephalosporin antibiotics are most commonly implicated. Where the haemolysis itself requires treatment, steroids are normally used (e.g. prednisolone 40–60 mg daily). In idiopathic AIHA most patients will respond to steroids with a significant rise in haemoglobin and diminished clinical symptoms. However, the disease is usually controlled rather than cured and relapses often occur when steroids are reduced or stopped. Where refractoriness to steroids develops, splenectomy is usually indicated. Other immunosuppressive drugs (e.g. azathioprine, ciclosporin) or cytotoxic agents or the monoclonal antibody rituximab may be helpful in supplementing the immunosuppressive effect of prednisolone.

Cold autoimmune haemolytic anaemia

In cold AIHA the antibody is generally of IgM type with specificity for the I red cell antigen. It attaches best to red cells in the peripheral circulation where the blood temperature is lower. As is seen in Table 1, this kind of haemolysis can occur in the context of a monoclonal (i.e. malignant) proliferation of B-lymphocytes in the so-called ‘idiopathic cold haemagglutinin syndrome’ or in a variety of lymphomas. The other major cause is infection.

The severity of haemolysis varies and agglutination (clumping) of red cells (Fig. 3) may cause circulatory problems such as acrocyanosis, Raynaud’s phenomenon and ulceration. The haemolysis, where longstanding, is often worse in the winter. On occasion red cell destruction is intravascular due to direct lysis by activated complement. Where this occurs free haemoglobin is released into the plasma (haemoglobinemia) and may appear in the urine (haemoglobinaemia), giving it a dark colour. Cold AIHA arising from infection is usually self-limiting. Where it is chronic the mainstay of treatment is keeping the patient warm, particularly in the extremities. In forms associated with lymphoproliferative disorders, cytotoxic drugs (e.g. chlorambucil) or rituximab may be helpful.

Isoimmune haemolytic anaemia

Here alloantibodies (isoantibodies) cause haemolysis as a result of transfusion or
transfer across the placenta. These antibodies are conventional antibodies specific for foreign antigens on incompatible red cells. Haemolytic blood transfusion reactions are discussed on page 84 and haemolytic disease of the newborn on page 90.

Microangiopathic haemolytic anaemia

Collectively, microangiopathic haemolytic anaemia (MAHA) is one of the most frequent causes of haemolysis. The term describes intravascular destruction of red cells in the presence of an abnormal microcirculation. There are many causes of MAHA (Table 2) but common triggers are the presence of disseminated intravascular coagulation (DIC), abnormal platelet aggregation and vasculitis. Characteristic laboratory findings include red cell fragmentation in the blood film (Fig. 4) and the coagulation changes seen in DIC (see p. 76). Two specific syndromes merit brief description.

Haemolytic uraemic syndrome (HUS)

HUS mainly affects infants and children. The three main features are MAHA, renal failure and thrombocytopenia. The disease can occur as seasonal epidemics caused by Escherichia coli producing verotoxin; it is then preceded by bloody diarrhoea. Treatment is essentially supportive with dialysis for renal failure. Mortality ranges from 5 to 30%.

Thrombotic thrombocytopenic purpura (TTP)

This rare congenital or acquired disorder has many similarities to HUS. It is characterised by MAHA, thrombocytopenia (often severe), fluctuating neurological symptoms, fever and renal failure. Platelet microvascular thrombi are mediated by ultra-large von Willebrand factor multimers which accumulate due to deficiency of a protease (ADAMTS 13). Daily plasma exchange is the mainstay of treatment; mortality rates are 10–30%.

Other acquired haemolytic anaemias

Haemolysis associated with red cell fragmentation may also occur due to the mechanical effects of defective heart valves or in long distance runners who effectively stamp repeatedly on a hard surface (‘march haemoglobinuria’). Certain drugs (e.g. dapsone and sulphasalazine) can cause oxidative intravascular haemolysis in normal people if taken in sufficient dosage. Many infections can cause haemolysis, either by direct invasion of red cells or via the circulatory changes already discussed. The anaemia of malaria often has a haemolytic component (pp. 96–97).

Paroxysmal nocturnal haemoglobinuria (PNH) (Fig. 5) is a rare example of acquired haemolysis caused by an intrinsic red cell defect. In this clonal disorder arising from a somatic mutation in the PIG-A gene in a stem cell, the mature blood cells have faulty anchoring of several proteins to membrane glycolipids containing phosphatidylinositol. Clinical features are highly variable and include intravascular haemolysis, pancytopenia and recurrent thrombotic episodes, including portal vein thrombosis. There is coexistent marrow damage and PNH is often associated with aplastic anaemia and may even terminate in acute leukaemia. The traditional diagnostic test exploits the cell’s unusual sensitivity to complement lysis (Ham test) but the cell’s characteristic lack of certain surface proteins (CD55, CD59) can also be demonstrated by flow cytometry. Treatment is generally supportive with blood transfusion and anticoagulation as required. In young patients with severe disease, allogeneic stem cell transplantation can be curative.

Haemolytic anaemia II – Acquired disorders

- Autoimmune haemolytic anaemia (AIHA) can be divided into ‘warm’ and ‘cold’ types dependent on the temperature at which the antibody reacts optimally with red cells.
- For each type of AIHA there are possible underlying causes which must be identified and treated.
- The term ‘microangiopathic haemolytic anaemia’ (MAHA) describes the intravascular destruction of red cells in the presence of an abnormal microenvironment. Clinical syndromes associated with MAHA include haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura.
- Paroxysmal nocturnal haemoglobinuria (PNH) is a rare example of acquired haemolysis caused by an intrinsic red cell defect.
The thalassaemias

The thalassaemias are a heterogeneous group of inherited disorders of haemoglobin synthesis. They are characterised by a reduction in the rate of synthesis of either alpha or beta chains and are classified accordingly (i.e. α-thalassaemia, β-thalassaemia). The basic haematological abnormality in the thalassaemias is a hypochromic microcytic anaemia of variable severity. Unbalanced synthesis of α- and β-globin chains can damage red cells in two ways. Firstly, failure of α and β chains to combine leads to diminished haemoglobinisation of red cells to levels incompatible with survival. Even those hypochromic cells released into the circulation transport oxygen poorly. The second mechanism for red cell damage is the aggregation of unmatched globin chains – the inclusion bodies lead to accelerated apoptosis of erythroid precursors in the bone marrow (ineffective erythropoiesis) and destruction of more mature red cells in the spleen (haemolysis). In general, the clinical severity of any case of thalassaemia is proportionate to the degree of imbalance of α- and β-globin chain synthesis.

Thalassaemias are amongst the most common inherited disorders. Gene carriers have some protection from falciparum malaria. Cases occur sporadically in most populations but the highest thalassaemia gene frequency is in a broad geographical region extending from the Mediterranean through the Middle East and India to South-East Asia.

**Classification**

The classification illustrated in Table 1 is based on the mode of inheritance of thalassaemia.

As the α-globin chain gene is duplicated on each chromosome there may be total loss of α-globin chain production (termed α0 or −/−haplotype) or partial loss of α-chain production resulting from loss of only one gene (termed α−/−α−/−haplotype).

The most important clinical syndromes are haemoglobin (Hb)–Barts hydrops syndrome (−/−−) which is incompatible with life and Hb H disease (−/−α−). At the molecular level the majority of cases of α-thalassaemia result from large deletions in the α-globin gene complex; occasionally mutations can depress expression of the gene.

**Clinical syndromes**

**α-Thalassaemias**

**Hb-Barts hydrops syndrome (−/−−)**

Here deletion of all four genes leads to complete absence of α-chain synthesis. As the α-globin chain is needed for fetal haemoglobin (HbF) as well as adult haemoglobin (HbA) (see p. 5) the disorder is incompatible with life and death occurs in utero (hydrops fetalis).

**HbH disease (−/−α−)**

This disorder arises from deletion of three of the four α-globin genes and is found most commonly in South-East Asia. The clinical features are variable but there is often a moderate chronic haemolytic anaemia (Hb 70–110 g/L) with splenomegaly and sometimes hepatomegaly. Severe bone changes and growth retardation are unusual. The blood film shows hypochromic microcytic red cells with poikilocytosis, polychromasia and target cells. The HbH molecule is formed of unstable tetramers of unpaired β chains (βα). It is best detected by electrophoresis (at pH 6–7) but may be demonstrated as red cell inclusion bodies in reticulocyte preparations.

**β-Thalassaemia traits**

Deletion of a single α-globin chain leads only to a slight lowering of red cell mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH) and even deletion of two genes usually only minimally lowers the haemoglobin with a raised red cell count and hypochromia and microcytosis. These carrier states can be difficult to identify in the routine laboratory as haemoglobin electrophoresis is normal. Occasional HbH bodies may be detected in reticuloocyte preparations. Definitive diagnosis requires DNA analysis.

**β-Thalassaemias**

**β-Thalassaemia major**

The characteristic severe anaemia (Hb less than 70 g/L) is caused by α-chain excess leading to ineffective erythropoiesis and haemolysis. Anaemia first becomes apparent at 3–6 months when production of HbF declines. The child fails to thrive and develops hepatosplenomegaly. Compensatory expansion of the marrow space causes the typical facies with skull bossing and maxillary enlargement (Fig. 1a). The ‘hair-on-end’ radiological appearance of the skull (Fig. 1b) is due to expansion of bone marrow into cortical bone. If left untreated further complications can include repeated infections, bone fractures and leg ulcers. Red cell membrane abnormalities contribute to hypercoagulability. Laboratory testing should precede blood transfusion. There is a severe hypochromic microcytic anaemia with a characteristic blood film (Fig. 2) and Hb electrophoresis demonstrates absence or near absence of HbA with small amounts of HbA2 and the remainder HbF (Fig. 3).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Classification of thalassaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of thalassaemia</strong></td>
<td><strong>Heterozygote</strong></td>
</tr>
<tr>
<td>α-thalassaemia</td>
<td></td>
</tr>
<tr>
<td>α−/α−</td>
<td>Thal minor</td>
</tr>
<tr>
<td>α−/−α−</td>
<td>Thal minor</td>
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<tr>
<td>β-thalassaemia</td>
<td></td>
</tr>
<tr>
<td>β−/β−</td>
<td>Thal minor</td>
</tr>
<tr>
<td>β−/−β−</td>
<td>Thal major or intermedia</td>
</tr>
</tbody>
</table>

*Compound heterozygosity (α−/−β−) leads to HbH disease.*
With intense supportive therapy, increasing numbers of patients in the developed world survive into adulthood. Blood transfusion remains the mainstay of management. Raising the haemoglobin concentration both reduces tissue hypoxia and suppresses endogenous haematopoiesis which is largely ineffective. There is improved growth and development and reduced hepatosplenomegaly. Transfusion is generally given to maintain a haemoglobin level of at least 90 to 100 g/L. Splenectomy can reduce the transfusion frequency. Without chelation, accumulation of iron damages the liver, endocrine organs and heart with death in the second or third decades. The most commonly used regimen is subcutaneous desferrioxamine given for 5–7 days per week. Compliance may be problematic (especially in teenagers) but where good there is a considerably improved life expectancy. Oral iron chelators (e.g. deferiprone) are emerging as an acceptable alternative. Endocrine disturbances related to iron overload will require appropriate therapy.

Allogeneic stem cell transplantation is a serious option. In ‘best risk’ patients the probability of survival exceeds 90%. Experimental approaches include drugs to stimulate fetal haemoglobin production and gene therapy (see p. 100).

Thalassaemia intermedia
Thalassaemia intermedia is a clinical syndrome which may result from a variety of genetic abnormalities (Table 2). The clinical features are less severe than in β-thalassaemia major as the α/β-globin chain imbalance is less pronounced. Patients usually present later than is the case for β-thalassaemia major (often at 2–5 years), and have relatively high haemoglobin levels (80–100 g/L), moderate bone changes and normal growth. Regular transfusion is not required.

β-Thalassaemia trait (minor)
Heterozygotes for β0 or β+ are usually asymptomatic with hypochromic microcytic red cells and slightly reduced haemoglobin levels. The red cell count is elevated. The key diagnostic feature is a raised HbA2 level (4–7%). The disorder may be confused with iron deficiency leading to unnecessary investigations. If both parents have β-thalassaemia trait there is a 25% chance of a child having β-thalassaemia major.

Prenatal diagnosis
Polymerase chain reaction (PCR) technology can detect point mutations or deletions in chorionic villus samples allowing first-trimester DNA-based tests for thalassaemia. Non-invasive methods using fetal cells or DNA in maternal blood are being explored.

The thalassaemias
- The thalassaemias are a heterogeneous group of inherited disorders where there is a reduction in the rate of synthesis of haemoglobin α chains (α-thalassaemia) or β chains (β-thalassaemia).
- There may be both ineffective erythropoiesis and haemolysis. The basic haematological abnormality is a hypochromic microcytic anaemia.
- There are several clinical syndromes. In general the severity is proportional to the degree of imbalance of α- and β-globin chains.
- Thalassaemia major leads to severe anaemia requiring regular blood transfusion and iron chelation.
- Thalassaemia trait is a symptomless clinical disorder which should not be confused with iron deficiency. Genetic counselling is required in selected cases.
Sickle cell syndromes

The sickle cell syndromes are a group of haemoglobinopathies which primarily affect the Afro-Caribbean population. The common feature of these diseases is inheritance of an abnormal haemoglobin β-chain gene – the gene is designated β*. Inheritance of two β* genes leads to a serious disorder termed sickle cell anaemia. A similar syndrome can result from inheritance of the β* gene with another abnormal β gene such as the haemoglobin C gene or β-thalassaemia gene. Inheritance of the β* gene with a normal β-chain gene (β+) causes the innocuous sickle cell trait (Fig. 1).

Pathophysiology

The abnormal β* gene has a high incidence in tropical and subtropical regions as the abnormal haemoglobin produced (HbS) gives some protection against falciparum malaria. HbS differs from normal haemoglobin (HbA) in that glutamic acid has been replaced by valine at the sixth amino acid from the N-terminus of the β-globin chain. The clinical features of sickle cell anaemia arise from the propensity of red cells containing haemoglobin S to undergo ‘sickling’. In the deoxygenated state HbS undergoes a conformational change leading to the creation of haemoglobin tetramers which aggregate to produce large polymers. The creation of haemoglobin tetramers which lead to increased rigidity and the ultimate sequestration of the red cell in the reticuloendothelial system causing haemolytic anaemia. The inflexible sickle cells also become lodged in the microcirculation causing stasis and obstruction.

Clinical syndromes

Sickle cell anaemia (HbSS)

This classic form of sickle cell syndrome is enormously variable in severity.

Haemolytic anaemia

The haemoglobin is generally in the range 60–100 g/L. Because HbS releases oxygen more readily than HbA, the symptoms of anaemia are often surprisingly mild. Intercurrent infection with parvovirus or folate deficiency can block erythropoesis and cause a sudden fall in haemoglobin – the ‘aplastic crisis’.

Vascular-occlusive crises

Acute, episodic, painful crises are a potentially disabling feature of sickle cell anaemia. They may be triggered by infection or cold. Patients complain of musculoskeletal pain which may be severe and require hospital admission. Hips, shoulders and vertebrae are most affected. Attacks are generally self-limiting but infarction of bone can occur and must be distinguished from salmonella osteomyelitis. Avascular necrosis of the femoral head is a crippling complication. Other organs are vulnerable to infarction; most serious is neurological damage which may manifest as seizures, transient ischaemic attacks (TIAs) and strokes. Vaso-occlusion in infancy is responsible for the ‘hand–foot syndrome’, a type of dactylitis damaging the small bones of hands and feet (Fig. 3).

Sequestration crises

These arise from sickling and infarction within particular organs. Specific syndromes include ‘acute chest syndrome’ with occlusion of the pulmonary vasculature, ‘girdle sequestration’ caused by occlusion of the mesenteric blood supply, and hepatic and splenic sequestration.

Other complications

These are multiple, usually caused by vascular stasis and local ischaemia.

- Genitourinary. Papillary necrosis with haematuria: loss of ability to concentrate urine; nephrotic syndrome; priapism.
- Skin. Lower limb ulceration.
- Eyes. Proliferative retinopathy; glaucoma.
- Hepatobiliary. Liver damage; pigment gallstones.

Diagnosis

Diagnosis depends on the following:

- Blood film appearance (Fig. 2).
- Screening tests for sickling. The blood sample is deoxygenated (e.g. with
sodium metabisulphate) to induce sickling.

Haemoglobin electrophoresis. In sickle cell anaemia (HbSS) there is no HbA detectable (Fig. 4).

Management

General. Patients need support in the community and easy access to centres experienced in the management of sickle cell anaemia. Prophylaxis is important. Patients should avoid factors known to precipitate crises, take folate supplements (because of chronic haemolysis) and be prescribed penicillin and pneumococcal vaccine (because of hypoplasmenism caused by infarction). Infections require prompt treatment.

Painful vascular-occlusive crises. First-line treatment is rest, increased fluids and adequate oral analgesia. Constitutional upset or pain not relieved by oral analgesia necessitates hospital admission with continued rest, warmth, intravenous fluids and opiate analgesia.

Blood transfusion. Clinical indications for blood transfusion are becoming better defined although there are few randomised clinical trials. Options are simple transfusion, chronic simple transfusion and exchange transfusion. Simple transfusion may be used for asymptomatic anaemia or in a range of complications benefiting from a relative reduction in Hbs-containing cells. Exchange transfusion is preferred for rapid reduction of Hbs levels or where simple transfusion would cause hyper-viscosity or circulatory overload. Blood is phenotypically matched to reduce the chance of alloimmunisation. Iron chelation may be required.

Pregnancy and surgery. Transfusion is not routinely indicated in an uncomplicated pregnancy but may be needed for severe anaemia or other sickle-cell-related complications. During surgery it is important to avoid hypoxia and dehydration. Preoperative simple transfusion or even exchange transfusion may be appropriate for high-risk procedures.

Hydroxy-carbamide. Increasing the level of fetal haemoglobin in red cells with the antimetabolite hydroxy-carbamide can reduce the severity of the disease. Recent studies have been encouraging, with a significant reduction in painful crises, major complications, blood transfusion and hospital admissions. There are concerns regarding the long-term toxicity of this drug and it should be reserved for patients with more severe disease and then be carefully monitored.

Stem cell transplantation. Stem cell transplantation offers the possibility of a cure in selected patients but it will not be widely applicable until the toxicity is reduced (see p. 56).

Gene therapy. Gene therapy has the potential to provide a cure without the risks of stem cell transplantation (see p. 100).

Prognosis

The risk of early death is inversely related to fetal haemoglobin levels. The most common causes of death are infection in infancy, cerebrovascular accidents in adolescence and respiratory complications in adult life.

Doubly heterozygous sickling disorders

Here patients inherit the β gene and another abnormal β gene – usually HbC or β-thalassaemia. HbSC disease is similar to HbSS but there is a tendency for fewer painful crises and a higher incidence of proliferative retinopathy and avascular necrosis. HbSβ-thalassaemia is often severe, with the entire range of sickling disabilities.

Sickle cell trait (HbAS)

Sickle cell trait normally causes no clinical problems as there is enough HbA in red cells (approximately 60%) to prevent sickling. However, haematuria occasionally occurs as a result of renal papillary necrosis and additional care is required during pregnancy and anaesthesia. Diagnosis is by a sickle test and Hb electrophoresis (Fig. 4).

Counselling and prenatal diagnosis

Genetic counselling is needed by those affected with either the homozygous disease, compound heterozygosity or the trait. Prenatal diagnosis is possible using mutation analysis on PCR-amplified DNA from chorionic villi (see p. 98).
Anaemia of chronic disease (ACD) is a term used to describe a type of anaemia seen in a wide range of chronic inflammatory, infective and malignant diseases (Table 1). The anaemia often becomes apparent during the first few months of illness and then remains fairly constant (Fig. 1). It is rarely severe (haemoglobin ≥ 90 g/L; packed cell volume (PCV) ≥ 0.30) but there is some correlation with the intensity of the underlying illness. For instance, in infection the anaemia is often more marked where there is a persistent fever and in malignancy where there is widespread dissemination. Patients may suffer no symptoms from their anaemia or have only slight fatigue. The importance of this type of anaemia arises not from its severity but from its ubiquity. It is widely misunderstood (for such a common disorder) and ill patients are frequently subjected to excessive haematological investigation and unnecessary treatment with haematinics. The term ACD should not be used to describe other causes of anaemia such as haemolysis or bleeding which may also complicate chronic disorders. It has been argued that the designation ACD is inappropriate but other suggested terms appear even less satisfactory.

**Incidence**

Because its causes are common, ACD is probably only second to iron deficiency as a cause of anaemia. It has been estimated to account for approximately half of all hospital cases of anaemia not explained by blood loss.

**Pathophysiology**

The causation of the anaemia of chronic disease has been extensively studied but questions remain. Key factors in aetiology are summarised in Figure 2. Inflammatory cytokines such as tissue necrosis factor (TNF) and interleukin-1 and -6 are implicated in all of these processes.

There is a modest shortening of red cell lifespan which leads to an increased demand for bone marrow production. The marrow struggles to respond adequately as there is blunting of the expected increase in erythropoietin secretion and also diminished responsiveness of erythroid precursor cells to erythropoietin. Hepcidin, a recently discovered peptide hormone, appears to be an important mediator of ACD. This acute phase reactant protein is released from the liver following stimulation by interleukin-6. Actions of hepcidin include inhibition of microbial infection, macrophage iron recycling and intestinal iron absorption. Patients with inflammation and anaemia have elevated levels of hepcidin in the urine. Abnormalities of iron metabolism are well documented in ACD. These include:

- reduced iron absorption from the gastrointestinal tract
- decreased plasma iron concentration
- excessive retention of iron in reticuloendothelial cells (macrophages) with diminished release to erythroid cells.

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**Table 1: Common causes of the anaemia of chronic disease**

- Malignancy
- Rheumatoid arthritis
- Various connective tissue disorders
- Chronic infection
- Extensive trauma

---

**Fig. 1** ACD in a patient with chronic infection. The rate of development of anaemia and its final severity are typical of ACD.

**Fig. 2** Overview of the aetiology of ACD. Cytokines such as TNF, interleukin-1 and interleukin-6 and the peptide hepcidin play key roles (see text).
The high prevalence of ACD has led to the suggestion that it may have some benefits for those with chronic inflammation. Perhaps withdrawal of iron by increased storage in the reticuloendothelial system limits its availability to microorganisms or tumour cells. Decreased haemoglobin levels reduce the oxygen-carrying capacity of the blood and might reduce the oxygen supply to unwelcome microorganisms and cells. Cell-mediated immunity is probably strengthened by reduced levels of metabolically active iron in the circulation as iron inhibits the activity of IFN-γ.

**Diagnosis**

Most patients will have a documented chronic disorder and a moderate anaemia. On occasion the anaemia is a more dominant feature and the underlying cause is not immediately apparent. The anaemia is usually of normochromic normocytic type although it can be slightly hypochromic microcytic. The blood film appearance is often unremarkable but there may be changes ‘reactive’ to the underlying disorder such as a neutrophil leucocytosis, thrombocytosis and rouleaux formation. There is a reticulocytopenia. Serum iron concentration and transferrin concentration are usually reduced. The serum ferritin level is normal or high (as an acute phase reactant). In practice, ACD is most commonly confused with mild iron deficiency anaemia, particularly if the MCV and MCH are reduced. However, the two forms of anaemia should be distinguishable as in uncomplicated iron deficiency the transferrin concentration is elevated and the ferritin level is low. In difficult cases the plasma transferrin receptor concentration and the plasma transferrin receptor/ferritin index are particularly useful (Table 2). Measurement of the percentage of hypochromic red cells or reticulocytes can be helpful in detecting coexistent iron-restricted red cell production in a patient with ACD.

It should be remembered that anaemia in a patient with a chronic medical disorder may be of multifactorial origin. It is important not to misdiagnose ACD as something else but equally it cannot be assumed that every patient with chronic medical disorder may be of multifactorial origin. It is a condition which can be difficult to distinguish from iron deficiency anaemia and requires careful consideration of clinical and laboratory findings.

**Management**

As the anaemia is usually non-severe and not progressive, the management is essentially that of the underlying disorder. Occasionally, patients cannot adequately compensate for the anaemia and require blood transfusion.

Erythropoietin can be effective in relieving anaemia, particularly in rheumatoid arthritis and malignancy. It should be considered for patients with more severe ACD which is unlikely to respond rapidly to treatment of the chronic disorder. Iron supplements should be reserved for absolute iron deficiency and selected patients with functional deficiency, particularly where there is no response to erythropoietin. Further studies are needed to evaluate the effect of amelioration of the anaemia on the course of the underlying disease. Possible future therapies for ACD include alternative stimulators of erythropoiesis and hepcidin antagonists.

**Table 2 Comparison of clinical and laboratory findings in ACD and iron deficiency anaemia**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ACD</th>
<th>Iron deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity of anaemia</td>
<td>Hb usually 250 g/L</td>
<td>Very variable</td>
</tr>
<tr>
<td>Symptoms of anaemia</td>
<td>Usually mild</td>
<td>May be severe</td>
</tr>
<tr>
<td>Coexistent chronic disease</td>
<td>Yes</td>
<td>Variable</td>
</tr>
<tr>
<td>Red cell indices (MCV, MCH)</td>
<td>Normochronic</td>
<td>Hypochromic</td>
</tr>
<tr>
<td></td>
<td>Normocytic</td>
<td>Microcytic</td>
</tr>
<tr>
<td>Blood film appearance</td>
<td>Often normal or</td>
<td>Hypochromia</td>
</tr>
<tr>
<td></td>
<td>reactive</td>
<td>Microcytosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Polikilocytes</td>
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<tr>
<td></td>
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<tr>
<td>Serum iron</td>
<td>Reduced</td>
<td>Reduced</td>
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<tr>
<td>Transferrin concentration</td>
<td>Reduced or normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Ferritin</td>
<td>Normal or increased</td>
<td>Reduced</td>
</tr>
<tr>
<td>Plasma transferrin receptor</td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Plasma transferrin receptor-ferritin index</td>
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<td>High</td>
</tr>
<tr>
<td>Marrow iron stores</td>
<td>Normal or increased</td>
<td>Reduced</td>
</tr>
</tbody>
</table>

1 May be slightly hypochromic microcytic
2 Reactive changes in a blood film may accompany the underlying disorder; possible abnormalities include rouleaux formation, a neutrophil leucocytosis and thrombocytosis.
3 Unless there is a coexistent acute phase response when the ferritin level may be normal.
4 Transferrin receptor concentration divided by plasma ferritin concentration (or log of plasma ferritin concentration).

**Fig. 3 Bone marrow aspirate stained with Perls stain showing increased reticuloendothelial iron stores in ACD.**

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**Anaemia of chronic disease (ACD)**

- ACD is seen in a wide range of chronic malignant, inflammatory and infective disorders.
- The pathogenesis of ACD is complex. There is a reduction in both red cell production and survival. Hepcidin is likely to be a key mediator.
- The anaemia is usually of normochromic, normocytic type, non-progressive and is rarely severe.
- Treatment is that of the underlying disorder. Blood transfusion and erythropoietin may help in selected cases. Iron supplementation has a limited role.