# ABC OF CLINICAL HAEMATOLOGY: Second Edition

*Edited by*
*DREW PROVAN*

**BMJ Books**

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DREW PROVAN

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# Contents

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# Preface

As with most medical specialties, haematology has seen major changes since this book was first published in 1998. We now have greater understanding of the molecular biology of many diseases, both malignant and non-malignant. This new knowledge has helped us to develop more sensitive assays for many conditions, and has been taken into the clinic, with the engineering of new drugs, such as STI571 used in the treatment of chronic myeloid leukaemia, amongst others.

As with the first edition, the intention has been to encompass all aspects of haematology but with perhaps a greater emphasis on basic science than previously. Readers will note that the writing team is almost identical to that for the first edition, which provides continuity of style.

I would like to express my gratitude to all my haematology colleagues for updating their sections and bringing the entire text up to date. Key reading lists are provided for all topics for those wishing to read about haematology in greater detail. Thanks must also go to the BMJ and in particular Mary Banks, Senior Commissioning Editor, and Sally Carter, Development Editor, who have been key players in the development of the second edition.

I would welcome any comments concerning the book, and perhaps readers may have suggestions for the next edition. I can be contacted at *a.b.provan@qmul.ac.uk*.

# 1 Iron deficiency anaemia

Drew Provan

Iron deficiency is the commonest cause of anaemia worldwide and is frequently seen in general practice. The anaemia of iron deficiency is caused by defective synthesis of haemoglobin, resulting in red cells that are smaller than normal (microcytic) and contain reduced amounts of haemoglobin (hypochromic).

## Iron metabolism

Iron has a pivotal role in many metabolic processes, and the average adult contains 3-5 g of iron, of which two thirds is in the oxygen-carrying molecule haemoglobin.

A normal Western diet provides about 15 mg of iron daily, of which 5-10% is absorbed (~1 mg), principally in the duodenum and upper jejunum, where the acidic conditions help the absorption of iron in the ferrous form. Absorption is helped by the presence of other reducing substances, such as hydrochloric acid and ascorbic acid. The body has the capacity to increase its iron absorption in the face of increased demand—for example, in pregnancy, lactation, growth spurts, and iron deficiency.

Once absorbed from the bowel, iron is transported across the mucosal cell to the blood, where it is carried by the protein transferrin to developing red cells in the bone marrow. Iron stores comprise ferritin, a labile and readily accessible source of iron, and haemosiderin, an insoluble form found predominantly in macrophages.

About 1 mg of iron a day is shed from the body in urine, faeces, sweat, and cells shed from the skin and gastrointestinal tract. Menstrual losses of an additional 20 mg a month and the increased requirements of pregnancy (500-1000 mg) contribute to the higher incidence of iron deficiency in women of reproductive age.

## Clinical features of iron deficiency

The symptoms accompanying iron deficiency depend on how rapidly the anaemia develops. In cases of chronic, slow blood loss, the body adapts to the increasing anaemia, and patients can often tolerate extremely low concentrations of haemoglobin—for example, <70 g/l—with remarkably few symptoms. Most patients complain of increasing lethargy and dyspnoea. More unusual symptoms are headaches, tinnitus, and taste disturbance.

On examination, several skin, nail, and other epithelial changes may be seen in chronic iron deficiency. Atrophy of the skin occurs in about a third of patients, and (rarely nowadays) nail changes such as koilonychia (spoon shaped nails) may result in brittle, flattened nails. Patients may also complain of angular stomatitis, in which painful cracks appear at the angle of the mouth, sometimes accompanied by glossitis. Although uncommon, oesophageal and pharyngeal webs can be a feature of iron deficiency anaemia (consider this in middle aged women presenting with dysphagia). These changes are believed to be due to a reduction in the iron-containing enzymes in the epithelium and gastrointestinal tract.

Tachycardia and cardiac failure may occur with severe anaemia irrespective of cause, and in such cases prompt remedial action should be taken.

**Table 1.1 Daily dietary iron requirements per 24 hours**

| | |
|---|---|
| Male | 1 mg |
| Adolescence | 2-3 mg |
| Female (reproductive age) | 2-3 mg |
| Pregnancy | 3-4 mg |
| Infancy | 1 mg |
| Maximum bioavailability from normal diet about | 4 mg |

**Box 1.1 Risk factors in development of iron deficiency**

- **Age:** infants (especially if history of prematurity); adolescents; postmenopausal women; old age
- **Sex:** increased risk in women
- **Reproduction:** menorrhagia
- **Renal:** haematuria (rarer cause)
- **Gastrointestinal tract:** appetite or weight changes; changes in bowel habit; bleeding from rectum/melaena; gastric or bowel surgery
- **Drug history:** especially aspirin and non-steroidal anti-inflammatories
- **Social history:** diet, especially vegetarians
- **Physiological:** pregnancy; infancy; adolescence; breast feeding; age of weaning

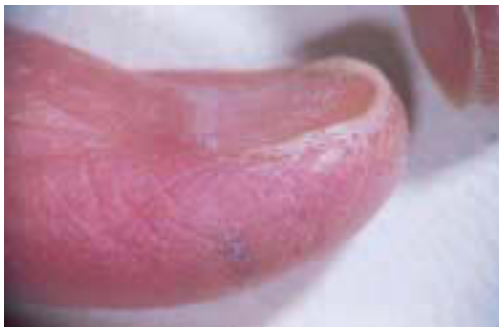

**Figure 1.1** Nail changes in iron deficiency anaemia (koilonychia)

**Box 1.2 Causes of iron deficiency anaemia**

**Reproductive system**
- Menorrhagia

**Gastrointestinal tract**

*Bleeding*
- Oesophagitis
- Oesophageal varices
- Hiatus hernia (ulcerated)
- Peptic ulcer
- Inflammatory bowel disease
- Haemorrhoids (rarely)
- Carcinoma: stomach, colorectal
- Angiodysplasia
- Hereditary haemorrhagic telangiectasia (rare)

*Malabsorption*
- Coeliac disease
- Atrophic gastritis (also may result *from* iron deficiency)

**Physiological**
- Growth spurts (especially in premature infants)
- Pregnancy

**Dietary**
- Vegans
- Elderly

Worldwide commonest cause of iron deficiency is hookworm infection

When iron deficiency is confirmed a full clinical history including leading questions on possible gastrointestinal blood loss or malabsorption (as in, for example, coeliac disease) should be obtained. Menstrual losses should be assessed, and the importance of dietary factors and regular blood donation should not be overlooked.

Diet alone is seldom the sole cause for iron deficiency anaemia in Britain except when it prevents an adequate response to a physiological challenge—as in pregnancy, for example.

## Laboratory investigations

A full blood count and film should be taken. These will confirm the anaemia; recognising the indices of iron deficiency is usually straightforward (reduced haemoglobin concentration, reduced mean cell volume, reduced mean cell haemoglobin, reduced mean cell haemoglobin concentration). Some modern analysers will determine the percentage of hypochromic red cells, which may be high before the anaemia develops (it is worth noting that a reduction in haemoglobin concentration is a *late* feature of iron deficiency). The blood film shows microcytic hypochromic red cells. Hypochromic anaemia occurs in other disorders, such as anaemia of chronic disorders and sideroblastic anaemias and in globin synthesis disorders, such as thalassaemia. To help to differentiate the type, further haematinic assays may be necessary. Difficulties in diagnosis arise when more than one type of anaemia is present—for example, iron deficiency and folate deficiency in malabsorption, in a population where thalassaemia is present, or in pregnancy, when the interpretation of red cell indices may be difficult.

Haematinic assays will demonstrate reduced serum ferritin concentration in straightforward iron deficiency. As an acute phase protein, however, the serum ferritin concentration may be normal or even raised in inflammatory or malignant disease.

A prime example of this is found in rheumatoid disease, in which active disease may result in a spuriously raised serum ferritin concentration masking an underlying iron deficiency caused by gastrointestinal bleeding after non-steroidal analgesic treatment. There may also be confusion in liver disease as the liver contains stores of ferritin that are released after hepatocellular damage, leading to raised serum ferritin concentrations. In cases where ferritin estimation is likely to be misleading, the soluble transferrin receptor (sTfR) assay may aid the diagnosis. Transferrin receptors are found on the surface of red cells in greater numbers in iron deficiency; a proportion of receptors are shed into the plasma and can be measured using commercial kits. Unlike the serum ferritin, the sTfR does not rise in inflammatory disorders, and hence can help differentiate between anaemia due to inflammation from iron deficiency.

Diagnostic bone marrow sampling is seldom performed in simple iron deficiency, but if the diagnosis is in doubt a marrow aspirate may be carried out to demonstrate absent bone marrow stores.

When iron deficiency has been diagnosed, the underlying cause should be investigated and treated. Often the history will indicate the likely source of bleeding—for example, menstrual blood loss or gastrointestinal bleeding. If there is no obvious cause, further investigation generally depends on the age and sex of the patient. In male patients and postmenopausal women possible gastrointestinal blood loss is investigated by visualisation of the gastrointestinal tract (endoscopic or barium studies). Faecal occult bloods are of no value in the investigation of iron deficiency.

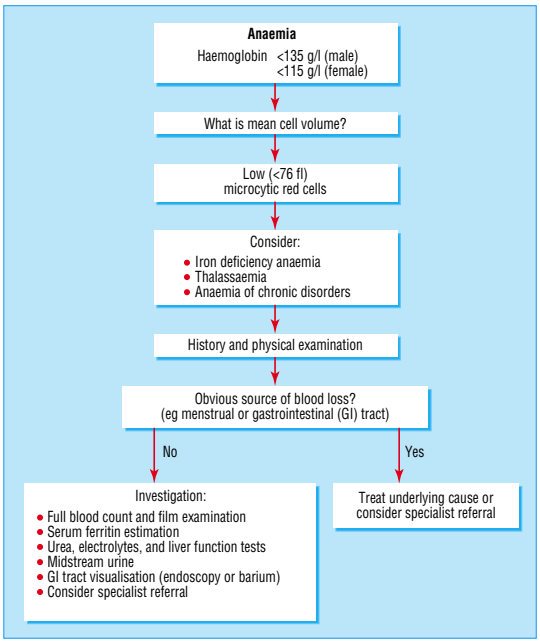


**Figure 1.2** Diagnosis and investigation of iron deficiency anaemia

**Box 1.3 Investigations in iron deficiency anaemia**

- Full clinical history and physical examination
- Full blood count and blood film examination
- Haematinic assays (serum ferritin, vitamin $B_{12}$ folate)
- % hypochromic red cells and soluble transferrin receptor assay (if available)
- Urea and electrolytes, liver function tests
- Fibreoptic and/or barium studies of gastrointestinal tract
- Pelvic ultrasound (females, if indicated)

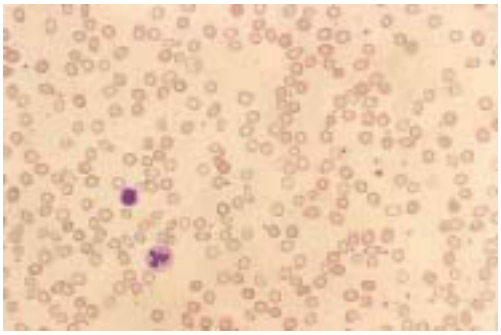

**Figure 1.3** Blood film showing changes of iron deficiency anaemia

**Table 1.2 Diagnosis of iron deficiency anaemia**

| | |
|---|---|
| Reduced haemoglobin | Men <135 g/l, women <115 g/l |
| Reduced mean cell volume | <76 fl |
| Reduced mean cell haemoglobin | 29.5 ± 2.5 pg |
| Reduced mean cell haemoglobin concentration | 325 ± 25 g/l |
| Blood film | Microcytic hypochromic red cells with pencil cells and target cells |
| Reduced serum ferritin* | Men <10 μg/l, women (postmenopausal) <10 μg/l (premenopausal) <5 μg/l |
| Elevated % hypochromic red cells (>2%) | |
| Elevated soluble transferrin receptor level | |

*Check with local laboratory for reference ranges

## Management

Effective management of iron deficiency relies on (a) the appropriate management of the underlying cause (for example, gastrointestinal or menstrual blood loss) and (b) iron replacement therapy.

Oral iron replacement therapy with gradual replenishment of iron stores and restoration of haemoglobin is the preferred treatment. Oral ferrous salts are the treatment of choice (ferric salts are less well absorbed) and usually take the form of ferrous sulphate 200 mg three times daily (providing 65 mg × 3 = 195 mg elemental iron/day). Alternative preparations include ferrous gluconate and ferrous fumarate. All three compounds, however, are associated with a high incidence of side effects, including nausea, constipation, and diarrhoea. These side effects may be reduced by taking the tablets after meals, but even milder symptoms account for poor compliance with oral iron supplementation. Modified release preparations have been developed to reduce side effects but in practice prove expensive and often release the iron beyond the sites of optimal absorption.

Effective iron replacement therapy should result in a rise in haemoglobin concentration of around 1 g/l per day (about 20 g/l every three weeks), but this varies from patient to patient. Once the haemoglobin concentration is within the normal range, iron replacement should continue for three months to replenish the iron stores.

## Failure to respond to oral iron therapy

The main reason for failure to respond to oral iron therapy is poor compliance. However, if the losses (for example, bleeding) exceed the amount of iron absorbed daily, the haemoglobin concentration will not rise as expected; this will also be the case in combined deficiency states.

The presence of underlying inflammation or malignancy may also lead to a poor response to therapy. Finally, an incorrect diagnosis of iron deficiency anaemia should be considered in patients who fail to respond adequately to iron replacement therapy.

### Intravenous and intramuscular iron preparations

Parenteral iron may be used when the patient cannot tolerate oral supplements—for example, when patients have severe gastrointestinal side effects or if the losses exceed the daily amount that can be absorbed orally.

Iron sorbitol injection is a complex of iron, sorbitol and citric acid. Treatment consists of a course of deep intramuscular injections. The dosage varies from patient to patient and depends on (a) the initial haemoglobin concentration and (b) body weight. Generally, 10-20 deep intramuscular injections are given over two to three weeks. Apart from being painful, the injections also lead to skin staining at the site of injection and arthralgia, and are best avoided. An intravenous preparation is available (Venofer®) for use in selected cases, and under strict medical supervision, for example, on haematology day unit (risk of anaphylaxis or other reactions).

### Alternative treatments

Blood transfusion is not indicated unless the patient has decompensated due to a drop in haemoglobin concentration and needs a more rapid rise in haemoglobin—for example, in cases of worsening angina or severe coexisting pulmonary

**Table 1.3 Characteristics of anaemia associated with other disorders**

| | Iron deficiency | Chronic disorders | Thalassaemia trait (α or β) | Sideroblastic anaemia |
|---|---|---|---|---|
| Degree of anaemia | Any | Seldom <9.0 g/dl | Mild | Any |
| MCV | ↓ | N or ↓ | ↓ ↓ | N or ↓ or ↑ |
| Serum ferritin | ↓ | N or ↑ | N | ↑ |
| Soluble transferrin receptor assay | ↑ | N | ↑ | N |
| Marrow iron | Absent | Present | Present | Present |

N = norm

**Figure 1.4** Oral iron replacement therapy

**Table 1.4 Elemental iron content of various oral iron preparations**

| Preparation | Amount (mg) | Ferrous iron (mg) |
|---|---|---|
| Ferrous fumarate | 200 | 65 |
| Ferrous gluconate | 300 | 35 |
| Ferrous succinate | 100 | 35 |
| Ferrous sulphate | 300 | 60 |
| Ferrous sulphate (dried) | 200 | 65 |

**Box 1.4 Intravenous iron preparations**

- Iron dextran no longer available (severe reactions)
- Iron-hydroxide sucrose is currently available in the UK
- Useful in selected cases
- Must be given under close medical supervision and where full resuscitation facilities are available

**The rise in haemoglobin concentration is no faster with parenteral iron preparations than with oral iron therapy**

disease. In cases of iron deficiency with serious ongoing acute bleeding, blood transfusion may be required.

**Prevention**

When absorption from the diet is likely to be matched or exceeded by losses, extra sources of iron should be considered—for example, prophylactic iron supplements in pregnancy or after gastrectomy or encouragement of breast feeding or use of formula milk during the first year of life (rather than cows' milk, which is a poor source of iron).

Drs AG Smith and A Amos provided the photographic material and Dr A Odurny provided the radiograph. The source of the detail in the table is the British National Formulary, No 32(Sep), 1995.

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# 2 Macrocytic anaemias

Victor Hoffbrand, Drew Provan

Macrocytosis is a rise in the mean cell volume of the red cells above the normal range (in adults 80-95 fl (femtolitres)). It is detected with a blood count, in which the mean cell volume, as well as other red cell indices, is measured. The mean cell volume is lower in children than in adults, with a normal mean of 70 fl at age 1 year, rising by about 1 fl each year until it reaches adult volumes at puberty.

The causes of macrocytosis fall into two groups: (a) deficiency of vitamin $B_{12}$ (cobalamin) or folate (or rarely abnormalities of their metabolism) in which the bone marrow is megaloblastic, and (b) other causes, in which the bone marrow is usually normoblastic. In this chapter the two groups are considered separately. The reader is then taken through the steps to diagnose the cause of macrocytosis, and subsequently to manage it.

**Megaloblastic bone marrow is exemplified by developing red blood cells that are larger than normal, with nuclei more immature than their cytoplasm. The underlying mechanism is defective DNA synthesis**

## Deficiency of vitamin $B_{12}$ or folate

### Vitamin $B_{12}$ deficiency

The body's requirement for vitamin $B_{12}$ is about 1 μg daily. This is amply supplied by a normal Western diet (vitamin $B_{12}$ content 10-30 μg daily) but not by a strict vegan diet, which excludes all animal produce (including milk, eggs, and cheese). Absorption of vitamin $B_{12}$ is through the ileum, facilitated by intrinsic factor, which is secreted by the parietal cells of the stomach. Absorption is limited to 2-3 μg daily.

In Britain, vitamin $B_{12}$ deficiency is usually due to pernicious anaemia, which now accounts for up to 80% of all cases of megaloblastic anaemia. The incidence of the disease is 1:10 000 in northern Europe, and the disease occurs in all races. The underlying mechanism is an autoimmune gastritis that results in achlorhydria and the absence of intrinsic factor. The incidence of pernicious anaemia peaks at age 60; the condition has a female:male incidence of 1.6:1.0 and is more common in those with early greying, blue eyes, and blood group A, and in those with a family history of the disease or of diseases that may be associated with it—for example, vitiligo, myxoedema, Hashimoto's disease, Addison's disease of the adrenal gland, and hypoparathyroidism.

Other causes of vitamin $B_{12}$ deficiency are infrequent in Britain. Veganism is an unusual cause of severe deficiency, as most vegetarians and vegans include some vitamin $B_{12}$ in their diet. Moreover, unlike in pernicious anaemia, the enterohepatic circulation for vitamin $B_{12}$ is intact in vegans, so vitamin $B_{12}$ stores are conserved. Gastric resection and intestinal causes of malabsorption of vitamin $B_{12}$—for example, ileal resection or the intestinal stagnant loop syndrome—are less common now that abdominal tuberculosis is infrequent and $H_2$-antagonists have been introduced for treating peptic ulceration, thus reducing the need for gastrectomy.

### Folate deficiency

The daily requirement for folate is 100-200 μg, and a normal mixed diet contains about 200-300 μg. Natural folates are largely in the polyglutamate form, and these are absorbed through the upper small intestine after deconjugation and conversion to the monoglutamate 5-methyl tetrahydrofolate.

Body stores are sufficient for only about four months. Folate deficiency may arise because of inadequate dietary

**Box 2.1 Causes of megaloblastic anaemia**

**Diet**
- Vitamin $B_{12}$ deficiency: veganism, poor quality diet
- Folate deficiency: poor quality diet, old age, poverty, synthetic diet without added folic acid, goats' milk

**Malabsorption**
- Gastric causes of vitamin $B_{12}$ deficiency: pernicious anaemia, congenital intrinsic factor deficiency or abnormality gastrectomy
- Intestinal causes of vitamin $B_{12}$ deficiency: stagnant loop, congenital selective malabsorption, ileal resection, Crohn's disease
- Intestinal causes of folate deficiency: gluten-induced enteropathy, tropical sprue, jejunal resection

**Increased cell turnover**
- Folate deficiency: pregnancy, prematurity, chronic haemolytic anaemia (such as sickle cell anaemia), extensive inflammatory and malignant diseases

**Renal loss**
- Folate deficiency: congestive cardiac failure, dialysis

**Drugs**
- Folate deficiency: anticonvulsants, sulphasalazine

Defects of vitamin $B_{12}$ metabolism—eg transcobalamin II deficiency, nitrous oxide anaesthesia—or of folate metabolism (such as methotrexate treatment), or rare inherited defects of DNA synthesis may all cause megaloblastic anaemia

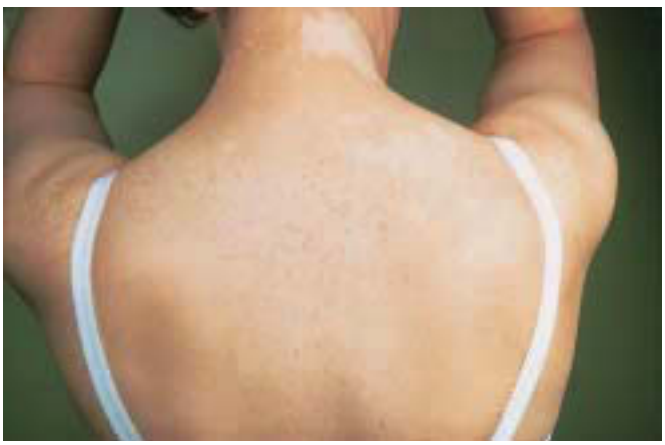

**Figure 2.1** Patient with vitiligo on neck and back

intake, malabsorption (especially gluten-induced enteropathy), or excessive use as proliferating cells degrade folate. Deficiency in pregnancy may be due partly to inadequate diet, partly to transfer of folate to the fetus, and partly to increased folate degradation.

**Consequences of vitamin $B_{12}$ or folate deficiencies**

*Megaloblastic anaemia*—Clinical features include pallor and jaundice. The onset is gradual, and a severely anaemic patient may present in congestive heart failure or only when an infection supervenes. The blood film shows oval macrocytes and hypersegmented neutrophil nuclei (with six or more lobes). In severe cases, the white cell count and platelet count also fall (pancytopenia). The bone marrow shows characteristic megaloblastic erythroblasts and giant metamyelocytes (granulocyte precursors). Biochemically, there is an increase in plasma of unconjugated bilirubin and serum lactic dehydrogenase, with, in severe cases, an absence of haptoglobins and presence in urine of haemosiderin. These changes, including jaundice, are due to increased destruction of red cell precursors in the marrow (ineffective erythropoiesis).

*Vitamin $B_{12}$ neuropathy*—A minority of patients with vitamin $B_{12}$ deficiency develop a neuropathy due to symmetrical damage to the peripheral nerves and posterior and lateral columns of the spinal cord, the legs being more affected than the arms. Psychiatric abnormalities and visual disturbance may also occur. Men are more commonly affected than women. The neuropathy may occur in the absence of anaemia. Psychiatric changes and at most a mild peripheral neuropathy may be ascribed to folate deficiency.

*Neural tube defects*—Folic acid supplements in pregnancy have been shown to reduce the incidence of neural tube defects (spina bifida, encephalocoele, and anencephaly) in the fetus and may also reduce the incidence of cleft palate and hare lip. No clear relation exists between the incidence of these defects and folate deficiency in the mother, although the lower the maternal red cell folate (and serum vitamin $B_{12}$) concentrations even within the normal range, the more likely neural tube defects are to occur in the fetus. An underlying mechanism in a minority of cases is a genetic defect in folate metabolism, a mutation in the enzyme 5, 10 methylenetetra hydrofolate reductase.

*Gonadal dysfunction*—Deficiency of either vitamin $B_{12}$ or folate may cause sterility, which is reversible with appropriate vitamin supplementation.

*Epithelial cell changes*—Glossitis and other epithelial surfaces may show cytological abnormalities.

*Cardiovascular disease*—Raised serum homocysteine concentrations have been associated with arterial obstruction (myocardial infarct, peripheral vascular disease or stroke) and venous thrombosis. Trials are under way to determine whether folic acid supplementation reduces the incidence of these vascular diseases.

**Other causes of macrocytosis**

The most common cause of macrocytosis in Britain is alcohol. Fairly small quantities of alcohol—for example, two gin and tonics or half a bottle of wine a day—especially in women, may cause a rise of mean cell volume to >100 fl, typically without anaemia or any detectable change in liver function.

The mechanism for the rise in mean cell volume is uncertain. In liver disease the volume may rise due to excessive lipid deposition on red cell membranes, and the rise is particularly pronounced in liver disease caused by alcohol.

**Figure 2.2** Patient with celiac disease: underweight and low stature

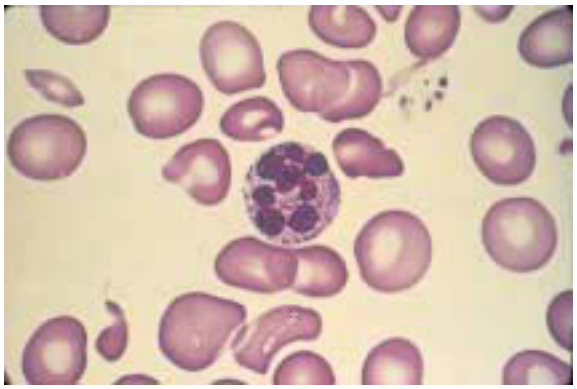

**Figure 2.3** Blood film in vitamin $B_{12}$ deficiency showing macrocytic red cells and a hypersegmented neutrophil

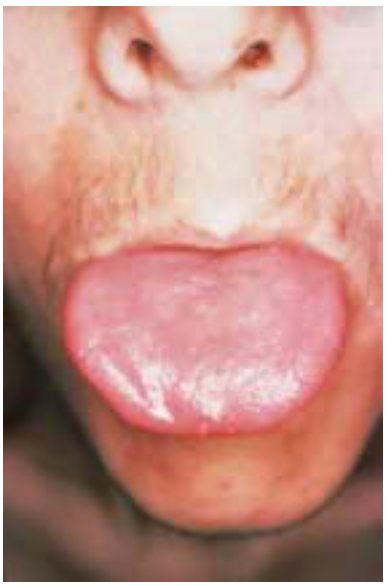

**Figure 2.4** Glossitis due to vitamin $B_{12}$ deficiency

A modest rise in mean cell volume is found in severe thyroid deficiency.

In other causes of macrocytosis, other haematological abnormalities are usually present—in myelodysplasia (a frequent cause of macrocytosis in elderly people) there are usually quantitative or qualitative changes in the white cells and platelets in the blood. In aplastic anaemia, pancytopenia is present; pure red cell aplasia may also cause macrocytosis. Changes in plasma proteins—presence of a paraprotein (as in myeloma)—may cause a rise in mean cell volume without macrocytes being present in the blood film. Physiological causes of macrocytosis are pregnancy and the neonatal period. Drugs that affect DNA synthesis—for example, hydroxyurea and azathioprine—can cause macrocytosis with or without megaloblastic changes. Finally, a rare, benign familial type of macrocytosis has been described.

**Box 2.2 Other causes of macrocytosis***

- Alcohol
- Liver disease
- Hypothyroidism
- Reticulocytosis
- Aplastic anaemia
- Red cell aplasia
- Myelodysplasia
- Cytotoxic drugs
- Paraproteinaemia (such as myeloma)
- Pregnancy
- Neonatal period

*These are usually associated with a normoblastic marrow

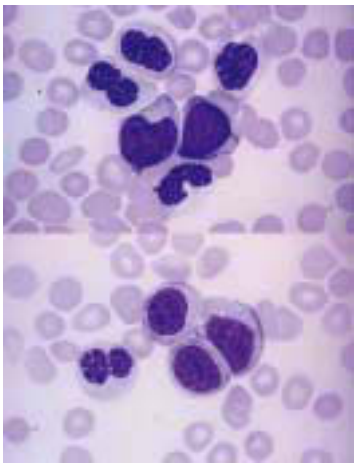

**Figure 2.5** Bone marrow aspirate in myelodysplasia showing characteristic dysplastic neutrophils with bilobed nuclei

## Diagnosis

### Biochemical assays

The most widely used screening tests for the deficiencies are the serum vitamin $B_{12}$ and folate assays. A low serum concentration implies deficiency, but a subnormal serum concentration may occur in the absence of pronounced body deficiency—for example, in pregnancy (vitamin $B_{12}$) and with recent poor dietary intake (folate).

Red cell folate can also be used to screen for folate deficiency; a low concentration usually implies appreciable depletion of body folate, but the concentration also falls in severe vitamin $B_{12}$ deficiency, so it is more difficult to interpret the significance of a low red cell than serum folate concentration in patients with megaloblastic anaemia. Moreover, if the patient has received a recent blood transfusion the red cell folate concentration will partly reflect the folate concentration of the transfused red cells.

### Specialist investigations

Assays of serum homocysteine (raised in vitamin $B_{12}$ or folate deficiency) or methylmalonic acid (raised in vitamin $B_{12}$ deficiency) are used in some specialised laboratories. Serum homocysteine levels are also raised in renal failure, with certain drugs, e.g. corticosteroids, and increase with age and smoking.

### Autoantibodies

For patients with vitamin $B_{12}$ or folate deficiency it is important to establish the underlying cause. In pernicious anaemia, intrinsic factor antibodies are present in plasma in 50% of patients and in parietal cell antibodies in 90%. Antigliadin, anti-endomysial and antireticulin antibodies are usually positive in gluten-induced enteropathy.

### Other investigations

A bone marrow examination is usually performed to confirm megaloblastic anaemia. It is also required for the diagnosis of myelodysplasia, aplastic anaemia, myeloma, or other marrow disorders associated with macrocytosis.

Radioactive vitamin $B_{12}$ absorption studies—for example, Schilling test—show impaired absorption of the vitamin in pernicious anaemia; this can be corrected by giving intrinsic factor. In patients with an intestinal lesion, however, absorption of vitamin $B_{12}$ cannot be corrected with intrinsic factor. Human intrinsic factor is no longer licensed for this test because of concern about transmission of prion disease.

Endoscopy should be performed to confirm atrophic gastritis and exclude gastric carcinoma or gastric polyps, which

**Box 2.3 Investigations that may be needed in patients with macrocytosis**

- Serum vitamin $B_{12}$ assay
- Serum and red cell folate assays
- Liver and thyroid function
- Reticulocyte count
- Serum protein electrophoresis
- For vitamin $B_{12}$ deficiency: serum parietal cell and intrinsic factor antibodies, radioactive vitamin $B_{12}$ absorption with and without intrinsic factor (Schilling test), possibly serum gastrin concentration
- For folate deficiency: antigliadin, anti-endomysial and antireticulin antibodies
- Consider bone marrow examination for megaloblastic changes suggestive of vitamin $B_{12}$ or folate deficiency, or alternative diagnoses—eg myelodysplasia, aplastic anaemia, myeloma
- Endoscopy—gastric biopsy (vitamin $B_{12}$ deficiency); duodenal biopsy (folate deficiency)
- Serum antigliadin and anti-endomysial antibodies

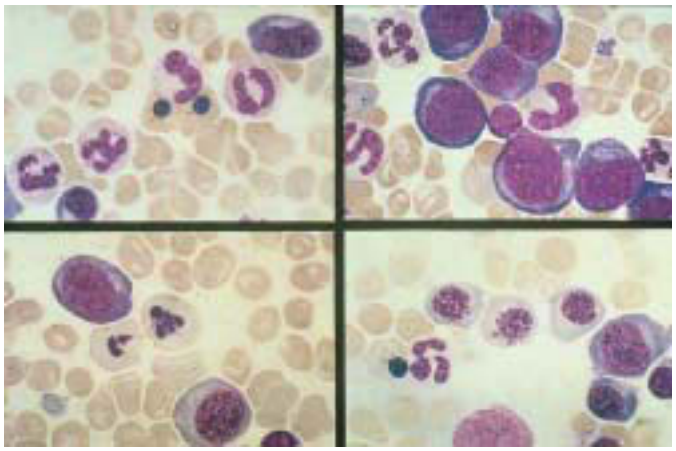

**Figure 2.6** Bone marrow appearances in megaloblastic anaemia: developing red cells are larger than normal, with nuclei that are immature relative to their cytoplasm (nuclear:cytoplasmic asynchrony)

are two to three times more common in patients with pernicious anaemia than in age and sex matched controls.

If folate deficiency is diagnosed, it is important to assess dietary folate intake and to exclude gluten induced enteropathy by tests for serum antigliadin and anti-endomysial antibodies, endoscopy and duodenal biopsy. The deficiency is common in patients with diseases of increased cell turnover who also have a poor diet.

## Treatment

Vitamin $B_{12}$ deficiency is treated initially by giving the patient six injections of hydroxo-cobalamin 1 mg at intervals of about three to four days, followed by four such injections a year for life. For patients undergoing total gastrectomy or ileal resection it is sensible to start the maintenance injections from the time of operation. For vegans, less frequent injections—for example, one or two a year—may be sufficient, and the patient should be advised to eat foods to which vitamin $B_{12}$ has been added, such as certain fortified breads or other foods.

Folate deficiency is treated with folic acid, usually 5 mg daily orally for four months, which is continued only if the underlying cause cannot be corrected. As prophylaxis against folate deficiency in patients with a severe haemolytic anaemia—such as sickle cell anaemia—5 mg folic acid once weekly is probably sufficient. Vitamin $B_{12}$ deficiency must be excluded in all patients starting folic acid treatment at these doses as such treatment may correct the anaemia in vitamin $B_{12}$ deficiency but allow neurological disease to develop.

**Table 2.1 Results of absorption tests of radioactive vitamin $B_{12}$**

| | Dose of vitamin $B_{12}$ given alone | Dose of vitamin $B_{12}$ given with intrinsic factor† |
|---|---|---|
| Vegan | Normal | Normal |
| Pernicious anaemia or gastrectomy | Low | Normal |
| Ileal resection | Low | Low |
| Intestinal blind-loop syndrome | Low* | Low* |

*Corrected by antibodies.
†Human intrinsic factor no longer licensed for this test because of concern about prion transmission

**Box 2.4 Preventing folate deficiency in pregnancy**

- As prophylaxis against folate deficiency in pregnancy, daily doses of folic acid 400 μg are usual
- Larger doses are not recommended as they could mask megaloblastic anaemia due to vitamin $B_{12}$ deficiency and thus allow $B_{12}$ neuropathy to develop
- As neural tube defects occur by the 28th day of pregnancy, it is advisable for a woman's daily folate intake to be increased by 400 μg/day at the time of conception
- The US Food and Drugs Administration announced in 1996 that specified grain products (including most enriched breads, flours, cornmeal, rice, noodles, and macaroni) will be required to be fortified with folic acid to levels ranging from 0.43 mg to 1.5 mg per pound (453 g) of product. Fortification of flour with folic acid is currently under discussion in the UK
- For mothers who have already had an infant with a neural tube defect, larger doses of folic acid—eg 5 mg daily—are recommended before and during subsequent pregnancy

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The illustration of the bone marrow (Figure 2.6) is reproduced with permission from *Clinical haematology* (AV Hoffbrand, J Pettit), 3rd ed, St Louis: CV Mosby, 2000.

# 3 The hereditary anaemias

David J Weatherall

Hereditary anaemias include disorders of the structure or synthesis of haemoglobin; deficiencies of enzymes that provide the red cell with energy or protect it from chemical damage; and abnormalities of the proteins of the red cell's membrane. Inherited diseases of haemoglobin—haemoglobinopathies—are by far the most important.

The structure of human haemoglobin (Hb) changes during development. By the 12th week embryonic haemoglobin is replaced by fetal haemoglobin (Hb F), which is slowly replaced after birth by the adult haemoglobins, Hb A and Hb $A_2$. Each type of haemoglobin consists of two different pairs of peptide chains; Hb A has the structure $\alpha_2\beta_2$ (namely, two α chains plus two β chains), Hb $A_2$ has the structure of $\alpha_2\delta_2$, and Hb F, $\alpha_2\gamma_2$.

The haemoglobinopathies consist of structural haemoglobin variants (the most important of which are the sickling disorders) and thalassaemias (hereditary defects of the synthesis of either the α or β globin chains).

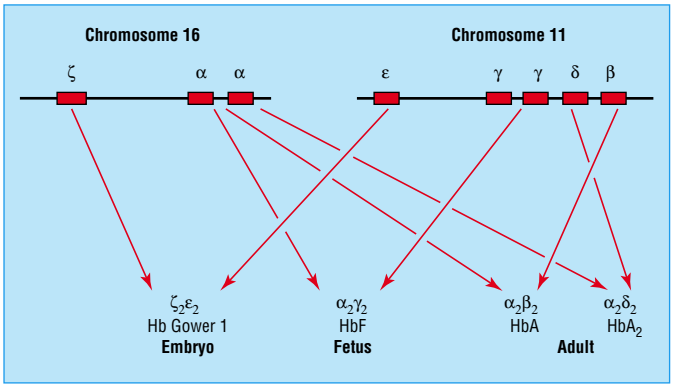


**Figure 3.1** Simplified representation of the genetic control of human haemoglobin. Because α chains are shared by both fetal and adult Hb, mutations of the α globin genes affect Hb production in both fetal and adult life; diseases that are due to defective β globin production are only manifest after birth when Hb A replace Hb F

## The sickling disorders

### Classification and inheritance

The common sickling disorders consist of the homozygous state for the sickle cell gene—that is, sickle cell anaemia (Hb SS)—and the compound heterozygous state for the sickle cell gene and that for either Hb C (another β chain variant) or β thalassaemia (termed Hb SC disease or sickle cell β thalassaemia). The sickle cell mutation results in a single amino acid substitution in the β globin chain; heterozygotes have one normal ($\beta^A$) and one affected β chain ($\beta^S$) gene and produce about 60% Hb A and 40% Hb S; homozygotes produce mainly Hb S with small amounts of Hb F. Compound heterozygotes for Hb S and Hb C produce almost equal amounts of each variant, whereas those who inherit the sickle cell gene from one parent and β thalassaemia from the other make predominantly sickle haemoglobin.

**Box 3.1 Sickling syndromes**

- Hb SS (sickle cell anaemia)
- Hb SC disease
- Hb S/$\beta^+$ thalassaemia
- Hb S/$\beta^\circ$ thalassaemia
- Hb SD disease

### Pathophysiology

The amino acid substitution in the β globin chain causes red cell sickling during deoxygenation, leading to increased rigidity and aggregation in the microcirculation. These changes are reflected by a haemolytic anaemia and episodes of tissue infarction.

**Box 3.2 Sickle cell trait (Hb A and Hb S)**

- Less than half the Hb in each red cell is Hb S
- Occasional renal papillary necrosis
- Inability to concentrate the urine (older individuals)
- Red cells do not sickle unless oxygen saturations <40% (rarely reached in venous blood)
- Painful crises and splenic infarction have been reported in severe hypoxia—such as unpressurised aircraft, anaesthesia

Sickling is more severe where Hb S is present with another β globin chain abnormality—such as Hb S and Hb C (Hb SC) or Hb S and Hb D (Hb SD)

### Geographical distribution

The sickle cell gene is spread widely throughout Africa and in countries with African immigrant populations; some Mediterranean countries; the Middle East; and parts of India. Screening should not be restricted to people of African origin.

### Clinical features

Sickle cell carriers are not anaemic and have no clinical abnormalities. Patients with sickle cell anaemia have a haemolytic anaemia, with haemoglobin concentration 60-100 g/l and a high reticulocyte count; the blood film shows polychromasia and sickled erythrocytes.

Patients adapt well to their anaemia, and it is the vascular occlusive or sequestration episodes ("crises") that pose the main threat. Crises take several forms. The commonest, called the painful crisis, is associated with widespread bone pain and is usually self-limiting. More serious and life threatening crises

**Box 3.3 Sickle cell anaemia (homozygous Hb S)**

- Anaemia (Hb 60-100 g/l): symptoms milder than expected as Hb S has reduced oxygen affinity (that is, gives up oxygen to tissues more easily)
- Sickled cells may be present in blood film: sickling occurs at oxygen tensions found in venous blood; cyclical sickling episodes
- Reticulocytes: raised to 10-20%
- Red cells contain ⩾80% Hb S (rest is maily fetal Hb)
- Variable haemolysis
- Hand and foot syndrome (dactylitis)
- Intermittent episodes, or crises, characterised by bone pain, worsening anaemia, or pulmonary or neurological disease
- Chronic leg ulcers
- Gall stones

include the sequestration of red cells into the lung or spleen, strokes, or red cell aplasia associated with parvovirus infections.

**Diagnosis**

Sickle cell anaemia should be suspected in any patient of an appropriate racial group with a haemolytic anaemia. It can be confirmed by a sickle cell test, although this does not distinguish between heterozygotes and homozygotes.
A definitive diagnosis requires haemoglobin electrophoresis and the demonstration of the sickle cell trait in both parents.

**Prevention and treatment**

Pregnant women in at-risk racial groups should be screened in early pregnancy and, if the woman and her partner are carriers, should be offered either prenatal or neonatal diagnosis. As soon as the diagnosis is established babies should receive penicillin daily and be immunised against *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, and *Neisseria meningitidis*. Parents should be warned to seek medical advice on any suspicion of infection. Painful crises should be managed with adequate analgesics, hydration, and oxygen. The patient should be observed carefully for a source of infection and a drop in haemoglobin concentration. Pulmonary sequestration crises require urgent exchange transfusion together with oxygen therapy. Strokes should be treated with a transfusion; there is good evidence now that they can be prevented by regular surveillance of cerebral blood flow by Doppler examination and prophylactic transfusion. There is also good evidence that the frequency of painful crises can be reduced by maintaining patients on hydroxyurea, although because of the uncertainty about the long term effects of this form of therapy, it should be restricted to adults or, if it is used in children, this should be only for a short period. Aplastic crises require urgent blood transfusion. Splenic sequestration crises require transfusion and, because they may recur, splenectomy is advised.

**Sickling variants**

Hb SC disease is characterised by a mild anaemia and fewer crises. Important microvascular complications, however, include retinal damage and blindness, aseptic necrosis of the femoral heads, and recurrent haematuria. The disease is occasionally complicated by pulmonary embolic disease, particularly during and after pregnancy; these episodes should be treated by immediate exchange transfusion. Patients with Hb SC should have annual ophthalmological surveillance; the retinal vessel proliferation can be controlled with laser treatment.

**Box 3.4 Complications of sickle cell disease**

- Hand and foot syndrome: seen in infancy; painful swelling of digits
- Painful crises: later in life; generalised bone pain; precipitated by cold, dehydration but often no cause found; self limiting over a few days
- Aplastic crisis: marrow temporarily hypoplastic; may follow parvovirus infection; profound anaemia; reduced reticulocyte count
- Splenic sequestration crisis: common in infancy; progressive anaemia; enlargement of spleen
- Hepatic sequestration crisis: similar to splenic crisis but with sequestration of red cells in liver
- Lung or brain syndromes: sickling of red cells in pulmonary or cerebral circulation and endothelial damage to cerebral vessels in cerebral circulation
- Infections: particularly *Streptococcus pneumoniae* and *Haemophilus influenzae*
- Gall stones
- Progressive renal failure
- Chronic leg ulcers
- Recurrent priapism
- Aseptic necrosis of humoral/femoral head
- Chronic osteomyelitis: sometimes due to *Salmonella typhi*

**Box 3.5 Treatment of major complications of sickle cell disease**

- Hand and foot syndrome: hydration; paracetamol
- Painful crises: hydration; analgesia (including graded intravenous analgesics); oxygen (check arterial blood gases); blood cultures; antibiotics
- Pulmonary infiltrates: especially with deterioration in arterial gases, falling platelet count and/or haemoglobin concentration suggesting lung syndrome requires urgent exchange blood transfusion to reduce Hb S level together with oxygenation
- Splenic sequestration crisis: transfusion; splenectomy to prevent recurrence
- Neurological symptoms: immediate exchange transfusion followed by long term transfusion
- Prevention of crises: ongoing trials of cytotoxic agent hydroxyurea show that it raises Hb F level and ameliorates frequency and severity of crises; long term effects unknown

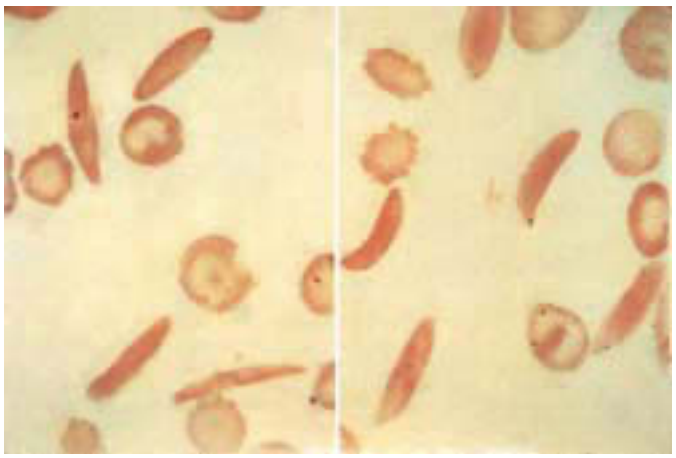

**Figure 3.2** Peripheral blood film from patient with sickle cell anaemia showing sickled erythrocytes

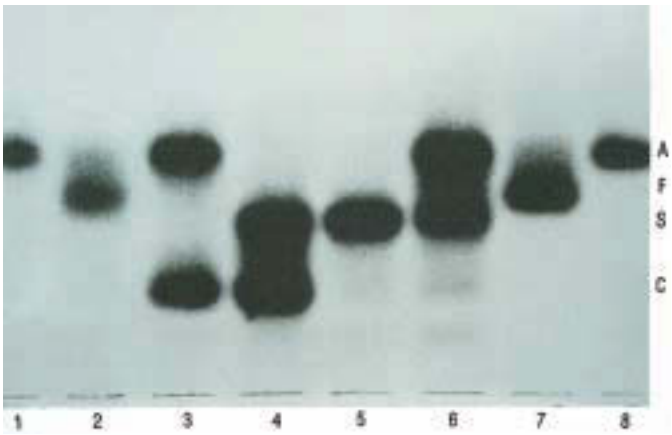


**Figure 3.3** Haemoglobin electrophoresis showing (1) normal, (2) newborn, (3) Hb C trait (A-C), (4) Hb SC disease (SC), (5) sickle cell disease (SS), (6) sickle cell trait (A-S), (7) newborn, (8) normal

The management of the symptomatic forms of sickle cell β thalassaemia is similar to that of sickle cell anaemia.

## The thalassaemias

### Classification

The thalassaemias are classified as α or β thalassaemias, depending on which pair of globin chains is synthesised inefficiently. Rarer forms affect both β and δ chain production—δβ thalassaemias.

### Distribution

The disease is broadly distributed throughout parts of Africa, the Mediterranean region, the Middle East, the Indian subcontinent, and South East Asia, and it occurs sporadically in all racial groups. Like sickle cell anaemia, it is thought to be common because carriers have been protected against malaria.

### Inheritance

The β thalassaemias result from over 150 different mutations of the β globin genes, which reduce the output of β globin chains, either completely (β° thalassaemia) or partially ($\beta^+$ thalassaemia). They are inherited like sickle cell anaemia; carrier parents have a one in four chance of having a homozygous child. The genetics of the α thalassaemias is more complicated because normal people have two α globin genes on each of their chromosomes 16. If both are lost (α° thalassaemia) no α globin chains are made, whereas if only one of the pair is lost ($\alpha^+$ thalassaemia) the output of α globin chains is reduced. Impaired α globin production leads to excess γ or β chains that form unstable and physiologically useless tetramers, $\gamma_4$ (Hb Bart's) and $\beta_4$ (Hb H). The homozygous state for α° thalassaemia results in the Hb Bart's hydrops syndrome, whereas the inheritance of α° and $\alpha^+$ thalassaemia produces Hb H disease.

### The β thalassaemias

Heterozygotes for β thalassaemia are asymptomatic, have hypochromic microcytic red cells with a low mean cell haemoglobin and mean cell volume, and have a mean Hb $A_2$ level of about twice normal. Homozygotes, or those who have inherited a different β thalassaemia gene from both parents, usually develop severe anaemia in the first year of life. This results from a deficiency of β globin chains; excess α chains precipitate in the red cell precursors leading to their damage, either in the bone marrow or the peripheral blood. Hypertrophy of the ineffective bone marrow leads to skeletal changes, and there is variable hepatosplenomegaly. The Hb F level is always raised. If these children are transfused, the marrow is "switched off", and growth and development may be normal. However, they accumulate iron and may die later from damage to the myocardium, pancreas, or liver. They are also prone to infection and folic acid deficiency. Milder forms of β thalassaemia (thalassaemia intermedia), although not transfusion dependent, are sometimes associated with similar bone changes, anaemia, leg ulcers, and delayed development.

### The α thalassaemias

The Hb Bart's hydrops fetalis syndrome is characterised by the stillbirth of a severely oedematous (hydropic) fetus in the second half of pregnancy. Hb H disease is associated with a moderately severe haemolytic anaemia. The carrier states for α° thalassaemia or the homozygous state for $\alpha^+$ thalassaemia result in a mild hypochromic anaemia with normal Hb $A_2$ levels. They can only be distinguished with certainty by DNA analysis in a

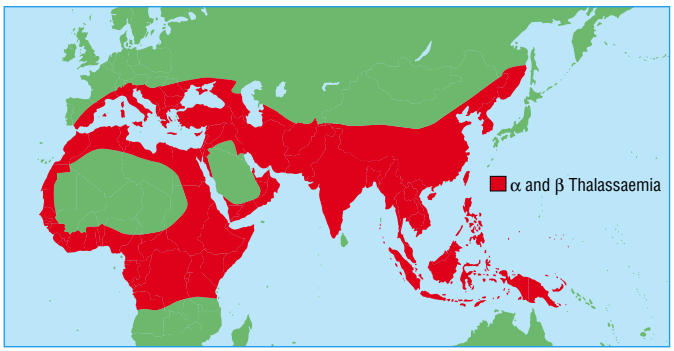


**Figure 3.4** Distribution of the thalassaemias (red area)

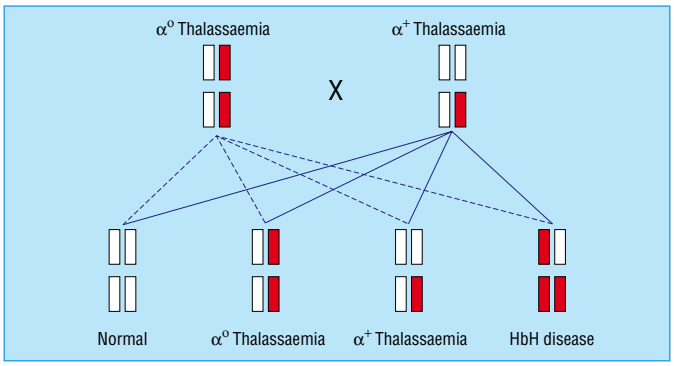


**Figure 3.5** Inheritance of Hb disease (open boxes represent normal α globin genes and red boxes, deleted α globin genes)

**Box 3.6 β Thalassaemia trait (heterozygous carrier)**

- Mild hypochromic microcytic anaemia
  - Haemoglobin 90-110 g/l
  - Mean cell volume 50-70 fl
  - Mean corpuscular haemoglobin 20-22 pg
- No clinical features, patients asymptomatic
- Often diagnosed on routine blood count
- Raised Hb $A_2$ level

**Box 3.7 β Thalassaemia major (homozygous β thalassaemia)**

- Severe anaemia
- Blood film
  - Pronounced variation in red cell size and shape
  - Pale (hypochromic) red cells
  - Target cells
  - Basophilic stippling
  - Nucleated red cells
  - Moderately raised reticulocyte count
- Infants are well at birth but develop anaemia in first few months of life when switch occurs from γ to β globin chains
- Progressive splenomegaly; iron loading; proneness to infection

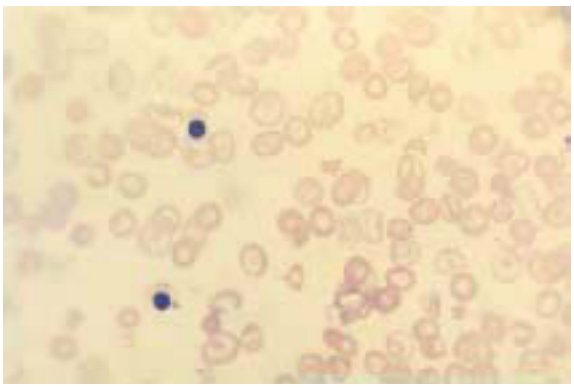

**Figure 3.6** Peripheral blood film in homozygous β thalassaemia showing pronounced hypochromia and anisocytosis with nucleated red blood cells

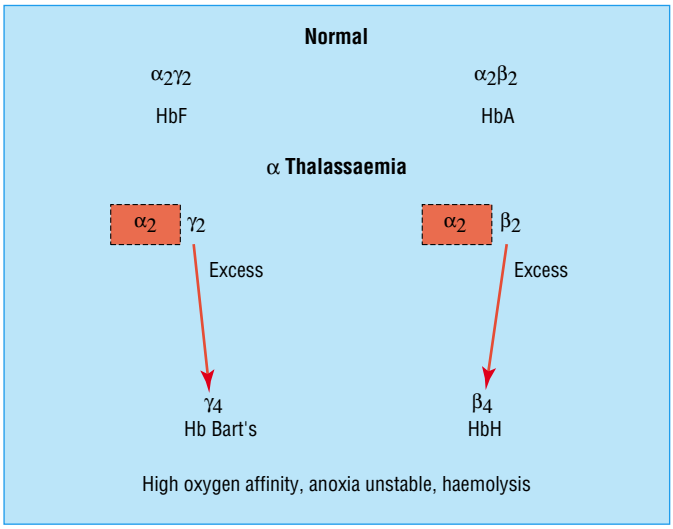


**Figure 3.7** Pathophysiology of α thalassaemia

specialised laboratory. In addition to the distribution mentioned above, α thalassaemia is also seen in European populations in association with mental retardation; the molecular pathology is quite different to the common inherited forms of the condition. There are two major forms of α thalassaemia associated with mental retardation (ATR); one is encoded on chromosome 16 (ATR-16) and the other on the X chromosome (ATRX). ATR-16 is usually associated with mild mental retardation and is due to loss of the α globin genes together with other genetic material from the end of the short arm of chromosome 16. ATRX is associated with more severe mental retardation and a variety of skeletal deformities and is encoded by a gene on the X chromosome which is expressed widely in different tissues during different stages of development. These conditions should be suspected in any infant or child with retarded development who has the haematological picture of a mild α thalassaemia trait.

**Box 3.8 The α thalassaemias**

**-α/αα 1α gene deleted**
- Asymptomatic
- Minority show reduced mean cell volume and mean corpuscular haemoglobin

**-α/-α or αα/- - 2α genes deleted**
- Haemoglobin is normal or slightly reduced
- Reduced mean cell volume and mean corpuscular haemoglobin
- No symptoms

**- -/ -α 3α genes deleted, Hb H disease**
- Chronic haemolytic anaemia
- Reduced α chain production with formation of $\beta_4$ tetramers ($\beta_4$ is termed Hb H)
- Hb H is unstable and precipitates in older red cells
- Haemoglobin is 70-110 g/l, though may be lower
- Reduced mean cell volume and mean corpuscular haemoglobin
- Clinical features: jaundice, hepatosplenomegaly, leg ulcers, gall stones, folate deficiency

**- -/- - 4α genes deleted, Hb Bart's hydrops**
- No α chains produced
- Mainly γ, forms tetramers ($\gamma_4$ = Hb Bart's)
- Intrauterine death or stillborn at 25-40 weeks or dies soon after birth

αα/αα represents 2α globin genes inherited from each parent
Changes due to α thalassaemia are present from birth unlike in β thalassaemia

**Box 3.9 Women with thalassaemia**
- Women with the haematological features of thalassaemia trait with normal Hb $A_2$ levels should be referred to a centre able to identify the different forms of α thalassaemia
- Those with α° thalassaemia trait—if their partners are similarly affected—should be referred for prenatal diagnosis
- This is because the haemoglobin Bart's hydrops syndrome is associated with an increased risk of toxaemia of pregnancy and postpartum bleeding due to a hypertrophied placenta

**Prevention and treatment**

As β thalassaemia is easily identified in heterozygotes, pregnant women of appropriate racial groups should be screened; if a woman is found to be a carrier, her partner should be tested and the couple counselled. Prenatal diagnosis by chorionic villus sampling can be carried out between the 9th and 13th weeks of pregnancy. If diagnosis is established, the patients should be treated by regular blood transfusion with surveillance for hepatitis C and related infections.

To prevent iron overload, overnight infusions of desferrioxamine together with vitamin C should be started, and the patient's serum ferritin, or better, hepatic iron concentrations, should be monitored; complications of desferrioxamine include infections with *Yersinia* spp, retinal and acoustic nerve damage, and reduction in growth associated with calcification of the vertebral discs. The place of the oral chelating agent deferiprone is still under evaluation. It is now clear that it does not maintain iron balance in approximately 50% of patients and its long term toxicity remains to be evaluated by adequate controlled trials. It is known to cause neutropenia and transient arthritis. Current studies are directed at assessing its value in combination with desferrioxamine. Bone marrow transplantation—if appropriate HLA-DR matched siblings are available—may carry a good prognosis if carried out early in life. Treatment with agents designed to raise the production of Hb F is still at the experimental stage.

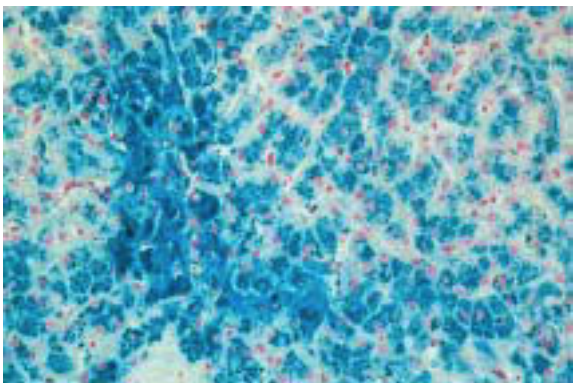

**Figure 3.8** Liver biopsy from patient with β thalassaemia showing pronounced iron accumulation

In β thalassaemia and Hb H disease progressive splenomegaly or increasing blood requirements, or both, indicate that splenectomy may be beneficial. Patients who undergo splenectomy should be vaccinated against *S pneumoniae*, *H influenzae*, and *N meningitidis* preoperatively and should receive a maintenance dose of oral penicillin indefinitely.

## Red cell enzyme defects

Red cells have two main metabolic pathways, one burning glucose anaerobically to produce energy, the other generating reduced glutathione to protect against injurious oxidants. Many inherited enzyme defects have been described. Some of those of the energy pathway—for example, pyruvate kinase deficiency—cause haemolytic anaemia; any child with this kind of anaemia from birth should be referred to a centre capable of analysing the major red cell enzymes.

Glucose-6-phosphate dehydrogenase deficiency (G6PD) involves the protective pathway. It affects millions of people worldwide, mainly the same racial groups as are affected by the thalassaemias. Glucose-6-phosphate dehydrogenase deficiency is sex linked and affects males predominantly. It causes neonatal jaundice, sensitivity to fava beans (broad beans), and haemolytic responses to oxidant drugs.

**Box 3.10 Drugs causing haemolysis in patients with G6PD deficiency**

**Antimalarials**
Primiquine
Pamaquine

**Analgesics***
Phenacetin
Acetyl salicylic acid

**Others**
Sulphonamides
Nalidixic acid
Dapsone

*Probably only at high doses

## Red cell membrane defects

The red cell membrane is a complex sandwich of proteins that are required to maintain the integrity of the cell. There are many inherited defects of the membrane proteins, some of which cause haemolytic anaemia. Hereditary spherocytosis is due to a structural change that makes the cells more leaky. It is particularly important to identify this disease because it can be "cured" by splenectomy. There are many rare inherited varieties of elliptical or oval red cells, some associated with chronic haemolysis and response to splenectomy. A child with a chronic haemolytic anaemia with abnormally shaped red cells should always be referred for expert advice.

## Other hereditary anaemias

Other anaemias with an important inherited component include Fanconi's anaemia (hypoplastic anaemia with skeletal deformities), Blackfan-Diamond anaemia (red cell aplasia), and several forms of congenital dyserythropoietic anaemia.

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