

6

Haematology

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6.1 Background

Learning objectives

You should:

- know what to ask about in the haematological history and what to look for on examination
- know when to measure and how to interpret a full blood count, film, differential white count, platelet count and erythrocyte sedimentation rate (ESR)
- understand the other main haematological investigations and when to carry them out
 - haematinics: iron and total iron-binding capacity, ferritin, vitamin B₁₂, folate and red cell folate
 - coagulation tests: international normalised ratio (INR), prothrombin time (PT), activated partial thromboplastin time (APTT), plasma fibrinogen, fibrin degradation products.
- know the indications for, and the information that can be gained from bone marrow examination and lymph node biopsy.
- know which situations commonly confront a house officer and understand how to manage them
- know enough about the other major haematological diseases to recognise them, make appropriate and timely referrals and explain them to your patients.

This chapter is structured around disorders of:

- red cells
- white cells
- platelets
- coagulation.

Remember, however, that individual diseases commonly affect more than one of them.

Physiology

The marrow is a large organ, approaching the size of the liver. In adults, most of it is in the flat bones, including the sternum, pelvis and vertebrae. White blood cell precursors form 75% of the marrow and most of the rest consists of erythroid precursors. Megakaryocytes (from which platelets are formed) are scattered throughout. It may seem surprising that so much of the marrow is devoted to the white cell series, given that there are 500 times as many red cells as white cells in the circulation. However, erythrocytes have a mean life of 120 days whereas white cells have a circulating lifespan measured in hours. Even in health, marrow is an extremely active tissue which is able to respond to sudden stresses like haemorrhage and infection. All blood cells are derived from multipotent, uncommitted stem cells. These differentiate into the lines of committed stem cells from which red cells, platelets, monocytes, granulocytes and lymphocytes are formed. The processes of differentiation and proliferation are controlled by growth factors, including interleukins, colony-stimulating factors and erythropoietin.

Clinical assessment

A clinical assessment begins as the patient walks into the room or you go to the bedside:

- look for pallor and signs of bruising/bleeding
- is the patient unkempt or thin and is there a smell of alcohol?
- take note of racial origin and gender.

History

Specific symptoms

Anaemia. The symptoms include:

- tiredness
- breathlessness
- chest pain
- ankle swelling.

Tiredness is thought of as the classical symptom of anaemia but most tired people are not anaemic and some patients (particularly elderly ones) have few symptoms despite profound anaemia. This is usually because the anaemia has developed slowly and their lifestyle does not make heavy demands for oxygen. Apart from tiredness, impaired oxygen delivery causes breathlessness, light-headedness and faints. It worsens angina and can precipitate heart failure, especially if it is superimposed on coronary artery disease.

Red cell excess (polycythaemia). The symptomatology is covered on page 266.

Leucopenia. The symptoms of leucopenia include:

- mouth ulceration
- infective symptoms.

Mouth ulceration must always be taken seriously in an at-risk patient. Infective symptoms occur with both neutropenia and lymphopenia.

White cell excess (leukaemia and lymphoma). The symptomatology is relatively specific to individual diseases, which are covered on pages 267–273.

Platelet/coagulation disease. Symptoms include:

- easy bruising
- bleeding
- thromboses.

Thrombocytopenia causes petechial haemorrhages and bruising. When it is severe, it also causes bleeding from the gums or into the gut. Impaired coagulation more commonly causes bleeding into soft tissues than overt external bleeding. Haemophilia may cause prolonged bleeding from minor injuries and surgery but often presents with bleeding into joints. Other hereditary clotting disorders are rare, apart from von Willebrand's disease, which most often causes skin and mucous membrane bleeding because the abnormality results in a defect of platelet function. Remember to ask about menorrhagia and bleeding problems after dental extractions and surgery. Thrombophilia (increased tendency to clot) causes recurrent venous and arterial thromboses.

General history

You should take a detailed drug history from every patient. Remember not just the prescription drugs but also medicines bought over the counter. Take a family history if the patient has haemolytic anaemia, a bleeding tendency or thrombophilia and construct a family tree if it is positive. Take a dietary and alcohol history. Note the length of history and take particular note if the symptoms suggest that more than one aspect of

haematological function is affected (e.g. symptoms of infection, bruising *and* anaemia). Be alert to symptoms of systemic disease, such as weight loss, dyspepsia, change in bowel habit, night sweats and pruritus.

Examination

Your examination (Fig. 64) should include

- a thorough and systematic examination of the skin
- careful palpation of all groups of lymph nodes (including deep palpation of the abdomen)
- inspection of the conjunctivae and mouth
- palpation of the spleen and liver
- a thorough search for signs of infection.

Red cell disorders

The physical signs of anaemia are extremely subjective. Examine the conjunctivae, which are less affected by variations in capillary blood flow than the skin or nail beds. *Definite* conjunctival pallor is

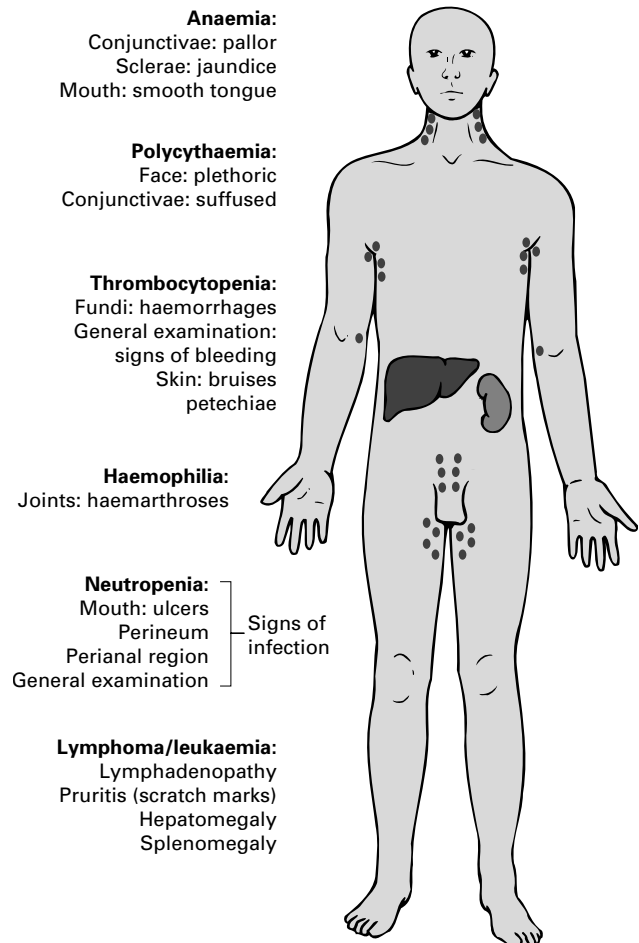


Fig. 64 Physical signs of haematological disease. Uncommon signs are omitted.

relatively specific for moderate-to-severe anaemia. Examine the sclerae carefully for jaundice (not detectable until serum bilirubin is raised to three times normal); it is present in haemolytic but not other types of anaemia. Look at the patient's face: a plethoric complexion with suffusion of the conjunctivae may be a sign of polycythaemia. Examine the abdomen for splenomegaly, which is a prominent feature of chronic extravascular haemolysis, and is a key finding in polycythaemia vera.

White cell disorders

Neutropenia should be considered in any patient with severe oral ulceration/candidiasis. Examination for lymphadenopathy requires skill, not just in knowing where and how to palpate but in interpreting the findings. If there are palpable lymph nodes, note:

- whether they are hard, firm or soft
- whether they are tender or non-tender
- their approximate size
- whether they are mobile and discrete or matted together.

Axillary and inguinal lymphadenopathy is commonly found in normal people, particularly if they have a history of injury or infection. Pathological lymph nodes are larger, present in the neck and epitrochlear region of the elbow and sometimes coalescent or matted. Lymph nodes that are enlarged because of infection are smaller than those of lymphoma (usually less than 2 cm) and more likely to be discrete. The distribution of lymphadenopathy in Hodgkin's and non-Hodgkin's lymphoma (NHL) is considered on page 271. Assess the size of the spleen and liver and search for para-aortic and pelvic nodes. Mild splenomegaly may be caused by an infection but moderate or massive splenomegaly suggests lymphoma, myelofibrosis or chronic leukaemia. Hepatomegaly may be found in myeloproliferative diseases. Tissue infiltration (particularly of the gums) occurs in some leukaemias.

Platelet and coagulation disorders

Petechial haemorrhages are a sign of thrombocytopenia. They are characteristically seen first over the lower legs, where capillary pressure is highest. Later they become generalised, and may coalesce as bruises (ecchymoses); particularly over the arms. Inspect the gums for bleeding and the fundi for retinal haemorrhages, which should be taken very seriously as a sign of impending cerebral haemorrhage. Joint swelling caused by bleeding (haemarthrosis) is an important feature of haemophilia and other coagulation disorders.

Thrombocytosis and other hypercoagulable states have no specific physical signs other than those of arterial or venous thrombosis.

Investigation

There are a large number of investigations in haematology, some routine and some for more specialised parameters. Box 10 lists the more common tests and the abbreviations for these tests.

Blood count and film

When you take blood, you can affect the result by:

- excessive cuffing: a prolonged increase in venous pressure artificially increases the haematocrit
- being slow to put blood in the tube or not mixing it thoroughly: coagulation in the tube gives a falsely low platelet count and abnormal coagulation results.

Automated counters measure concentrations (per unit volume) of red cells, haemoglobin, platelets and leucocytes (lymphocytes, monocytes, neutrophils, eosinophils and basophils). They also measure the percentage of red cells present as reticulocytes (newly released cells) and calculate indices which describe the size of red cells and platelets and the degree of haemoglobinisation. Normal values for adults are shown in Table 1 (p. 7). In addition, a dried and stained blood film can be inspected to assess the morphology of the cells and detect abnormal cells. Some of the terms you will come across on blood film reports are given in Table 60.

Box 10 Investigations in haematology

Blood count and film

Full blood count; red cell count (RCC), white cell count (WCC)
Blood film
Differential white cell count
Platelet count
Erythrocyte sedimentation rate (ESR)
Mean cell volume (MCV)
Red cell width distribution (RDW)

Haematinics

Iron and total iron-binding capacity
Ferritin
Vitamin B₁₂
Folate and red cell folate

Coagulation

International normalised ratio (INR)
Prothrombin time (PT)
Activated partial thromboplastin time (APTT)
Plasma fibrinogen
Fibrin degradation products (FDPs)
D-dimer

Bone marrow

Lymph node biopsy

Table 60 Terms used to describe abnormalities of red blood cells

Term	Description
Hypochromia	Defective haemoglobinisation, as in some anaemias
Anisochromia	Variable haemoglobinisation, as in haemolysis
Polychromasia	Bluish tinge to the red cells, reflects increased haemopoiesis
Microcytosis	Small size (p. 259)
Macrocytosis	Large size (p. 259)
Anisocytosis	Variable size, as in iron deficiency
Poikilocytosis	Abnormal shape; as in myelofibrosis (p. 271)
Erythrocytosis Spherocytosis, elliptocytosis	Increased number of red cells Abnormal shape resulting from congenital or acquired cell membrane defect
Sickle cells	Abnormal shape resulting from abnormal haemoglobin
Target cells	Increased surface:volume ratio; as in liver disease
Fragmented or damaged cells	Trauma to red cells (p. 264)
Inclusions	
Basophilic stippling	Immature cells resulting from accelerated haemopoiesis
Iron granules (siderocytes)	Seen with special stain in sideroblastic anaemia
Howell–Jolly bodies	Nuclear remnants seen after splenectomy

Interpreting the haemoglobin and red cell indices

Anaemia is diagnosed when there is a reduction in the concentration of haemoglobin caused by a reduced number of red cells or a reduced amount of haemoglobin within the cells. An *increase* in haemoglobin concentration resulting from an increased number of red cells per unit volume is termed erythrocytosis.

Whenever you are told that a patient is anaemic, you should ask for the mean cell volume (MCV), by which anaemias are classified (explained further on page 259). The cell counter also tells you how similar the red cells are to one another in size. This is expressed as the red cell distribution width (RDW). A low RDW signifies a normal, homogeneous population of cells. An increased RDW signifies heterogeneity in cell size as a result of:

- active haemopoiesis, because immature red cells (reticulocytes) are large
- treatment of iron deficiency, resulting in a mixture of microcytic and normocytic cells

- mixed deficiency, giving both small and large 'diseased' cells.

Reticulocytes can be counted automatically and are expressed as a percentage of the total red cell count.

White cells and platelets

Changes in cell counts are diagnosed by the automated counter. Examination of the film gives an accurate differential count and detects cells such as leukaemic blast cells. It also detects morphological changes such as the degree of lobulation of the neutrophil nuclei, which depends on their age. In infection, neutrophils are relatively immature and may appear as bands rather than with the normal multilobulated appearance; a 'left shift'. Conversely, the neutrophils are hypermature ('right shifted') in megaloblastic anaemia because vitamin B₁₂ deficiency impairs haemopoiesis (p. 261). There may also be cytoplasmic abnormalities, e.g. vacuolation or heavy granulation of neutrophils during bacterial infection. Abnormalities of neutrophils, such as hypogranularity, are seen in myelodysplasia.

Platelets

A simple platelet count is the clue to most platelet diseases.

Erythrocyte sedimentation rate

The erythrocyte sedimentation rate (ESR) is a very crude test which measures the rate (in mm/h) at which red cells sediment. Abnormal proteins in inflammatory conditions and myeloma cause rapid sedimentation. The ESR is, therefore, a non-specific marker of infection, inflammation and neoplasia. It may be non-specifically raised in anaemia and some non-inflammatory diseases such as uraemia. In some hospitals, blood viscosity or **acute-phase proteins** is measured as more reliable markers of inflammation.

Haematinics

The blood count must always be checked before measuring haematinics because it is unlikely that a patient has significant iron, vitamin B₁₂ or folate deficiency if the count is normal. An extremely high index of suspicion (e.g. suspected subacute combined degeneration of the cord, p. 236) would be needed to justify these extra measurements in the face of a normal blood count. Similarly, it is wasteful to measure serum iron or ferritin if the diagnosis of iron deficiency is obvious from the clinical context and blood count. With those provisos, measure:

- vitamin B₁₂ and folate in patients with macrocytic anaemia
- iron in patients with microcytosis
- all three in a patient with anaemia and a normal MCV but a high RDW (to exclude a mixed deficiency).

The diagnosis of iron, vitamin B₁₂ and folate deficiencies are considered on pages 260 and 262.

Tests of coagulation and fibrinolysis

These are discussed on page 276.

Bone marrow examination

Bone marrow can be examined either as an aspirate from the sternum or iliac crest or as a trephine biopsy from the iliac crest. Marrow aspirate is useful for detailed cytology, cell counts and assessment of iron stores. Trephine biopsies are useful for judging cellularity, detecting tumour and diagnosing myelofibrosis (p. 271).

Remember that marrow examination is not infallible in detecting tumour deposits because they may be absent from the area sampled. Marrow aspiration is a painful procedure which should not be done without good indications. These include:

- to confirm iron deficiency or megaloblastic anaemia, if the diagnosis is in doubt or the patient does not respond to treatment
- to investigate unexplained anaemia
- to investigate suspected leukaemia, myeloma or other haematological malignancy
- to monitor response to the treatment of leukaemia
- to diagnose cancer, where there is circumstantial evidence of marrow involvement
- to investigate agranulocytosis or thrombocytopenia
- to stain and obtain cultures for suspected tuberculosis, histoplasmosis and leishmaniasis.

In some conditions—notably myelofibrosis and malignant infiltration of the marrow—bone marrow aspiration may be unsuccessful. A ‘dry tap’ is pathological and of diagnostic value.

Lymph node biopsy

Lymph node biopsy is the definitive investigation to diagnose lymphoma and identify its histological type. It is also used to diagnose disseminated cancer and other causes of lymphadenopathy. The features of lymph nodes that make them ‘suspicious’ are described on page 257, and other clinical features suggesting lymphoma are described on page 269. Which node should be biopsied is partly a surgical decision and partly determined by their ‘feel’. Lymph node biopsies are usually taken under general anaesthesia. The specimen will be ruined for some analyses if it is put straight into formalin. It should be promptly handled by a skilled histology technician. Remember to request culture if tuberculosis is suspected.

6.2 Red cell disorders

Learning objectives

You should:

- understand the range of diseases that cause anaemia and how they do so
- know how to diagnose and treat anaemias
- know the indications for blood transfusion and how to avoid complications
- know what polycythaemia is, what can cause it and how it causes symptoms and signs.

Erythropoiesis:

- is controlled by erythropoietin, which is secreted by the kidneys
- is stimulated by hypoxia
- requires an adequate supply of folic acid, vitamin B₁₂ and iron
- is inhibited by poor nutrition, systemic disease and local disease within the marrow.

Anaemias

Think of anaemias in terms of:

- decreased red cell production
- increased loss.

This classification is expanded in Table 61. Note that the commonest form, iron-deficiency anaemia, often results from a combination of both. The MCV is central to the diagnosis of anaemia. Remember that:

- iron deficiency causes microcytosis
- vitamin B₁₂ and folate deficiency cause macrocytosis (other causes are covered on p. 261)
- the anaemia of marrow suppression is often normocytic.

Exceptions to these rules are discussed under individual diseases. Given the haemoglobin and MCV, white cell count, platelet and reticulocyte counts and a description of the blood film, you can make a working diagnosis in most cases.

Iron-deficiency anaemia

Iron-deficiency anaemia is the most common and, to the generalist, most important anaemia because it:

- is a significant public health problem

Table 61 A classification of the anaemias

	Decreased production	Increased destruction/loss
Acute haemorrhage		+
Haematinic deficiency		
Iron deficiency	+	±
B ₁₂ deficiency	+	
Folate deficiency	+	
Hypoplastic anaemias		
Idiopathic	+	
Secondary	+	
Anaemia of chronic disease	+	
Marrow replacement		
Leukaemias	+	
Myeloma	+	
Other tumours	+	
Congenital haemolysis		
Spherocytosis and elliptocytosis	±	+
Sickle cell disease		+
Thalassaemia		+
Glucose 6-phosphate dehydrogenase deficiency		+
Acquired haemolysis		
Autoimmune		+
Microangiopathic		+
Hypersplenism		+

- may be the presentation of an occult gastrointestinal (GI) carcinoma at a curable stage
- is eminently treatable whatever its cause.

Iron deficiency is caused by an imbalance between dietary availability and blood loss, so much of the population is iron deficient in areas of the developing world where GI parasites are endemic. Active growth, pregnancy and lactation increase the demand for iron and may unmask deficiency. The prevalence of depleted iron stores in women of menstrual age may be as high as 20% and that iron deficiency can persist into the post-menopausal years if they have a poor diet and do not replete their iron stores. Iron deficiency is much less prevalent in adult men and, therefore, more likely to be caused by an occult carcinoma or other underlying disease.

There are sizeable iron stores in the liver, reticulo-endothelial system and marrow, as well as in the erythrocytes themselves, so negative iron balance must exist for some time before anaemia develops. For the same reason, replenishment of iron stores takes longer than the restoration of haemopoiesis, and iron treatment should be continued after the haemoglobin has returned to normal.

Causes

These are:

- blood loss

- dietary deficiency
- malabsorption.

Iron may be malabsorbed as a result of small intestinal disease or after gastrectomy.

Sources of blood loss, in order of frequency, are:

- menstruation
- the GI tract (Ch. 3)
- the urinary tract.

In practice, it may be difficult to decide whether menorrhagia is the sole cause of blood loss. If in doubt, suspect another disease.

Common causes of GI blood loss are:

- gastritis, peptic ulcer or oesophagitis, particularly in patients taking aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) or steroids
- diverticular disease
- carcinoma of the stomach, caecum or colon
- angiodysplasia of the colon, an increasingly recognised cause in elderly people
- oesophageal varices.

A less common cause is Meckel's diverticulum.

Although only a small minority of iron-deficient patients have GI tumours, it is worthwhile identifying them because diagnosis at the stage of a predominantly mucosal lesion may allow curative surgery.

Clinical and haematological signs

Symptoms and signs were covered earlier and in Figure 64. Early signs on the blood film are variability in size and shape of the red cells. In established iron deficiency, they are hypochromic and microcytic and 'pencil cells' may be seen.

Diagnosis and further investigation

Iron deficiency is overwhelmingly the most common UK cause of microcytosis but it also occurs in thalassaemia trait and, sometimes, in the anaemia of chronic disease. If there is doubt, iron deficiency is diagnosed by measuring serum iron and total iron-binding capacity. These are measured together because binding protein deficiency may lower the serum iron concentration without signifying true iron deficiency; < 10% saturation of iron-binding capacity is diagnostic of iron deficiency. Measurement of serum ferritin is a better reflection of iron stores (particularly to detect iron overload, as in haemochromatosis). Absence of stainable marrow iron stores and a significant improvement in the blood count with iron replacement are definitive evidence of iron deficiency.

Stool samples are often tested for occult blood to confirm or exclude the GI tract as the site of blood loss, but they may be falsely positive or negative. Dietary assessment and tests for malabsorption (p. 127) may be indi-

cated. The investigations are not complete until a patient with undiagnosed iron deficiency has had gastroscopy, colonoscopy (or barium studies) to look for a site of blood loss.

Management

There is little to choose between the many formulations of oral iron. Ferrous sulphate is usually prescribed. It may cause nausea, abdominal pain, diarrhoea or constipation, in which case the dose should be reduced or a different iron salt given. A response should be seen within 1 week of starting treatment and a rise in haemoglobin of 10 g/l each week is to be expected. Treatment is continued for 3 months after the haemoglobin has returned to normal to replenish iron stores.

Megaloblastic anaemias

Vitamin B₁₂ (cobalamin) and folic acid are coenzymes for cellular metabolism, particularly haemopoiesis. Deficiency affects DNA synthesis in all marrow cell lines and the red cell precursors develop 'megaloblastic' morphological changes. Ineffective erythropoiesis reduces the production of mature red cells and they are enlarged (macrocytic). Formation of platelets and granulocytes is also impaired.

Vitamin B₁₂ and folate deficiency are not the only causes of macrocytosis; others, in approximate order of frequency, are:

- common causes
 - alcohol abuse
 - liver disease
 - active haemopoiesis (immature red cells are large): haemolytic anaemias, blood loss
- less common causes
 - myelodysplasia
 - aplastic anaemia
 - antifolate drugs: methotrexate, phenytoin.

However, vitamin B₁₂ and folate deficiency are the only common conditions to produce the typical megaloblastic bone marrow appearances. They have identical haematological features but differ in their causes and non-haematological manifestations. This section will first present the common features and then the differences between them.

Clinical and haematological features

Patients typically present with symptoms of anaemia and malaise. These develop insidiously and the anaemia may be very severe by the time the diagnosis is made. Elderly people, in particular, may tolerate it surprisingly well until they present with heart failure or angina resulting from tissue hypoxia. There may be

- mild jaundice caused by haemolysis of the defective red cells
- fever
- glossitis
- splenomegaly (very unusually).

Although moderate neutropenia and thrombocytopenia are common, they are not usually symptomatic. Vitamin B₁₂ deficiency may, uncommonly, present with its neurological complications (see Ch. 5). There may be features of an underlying GI disease in vitamin B₁₂, folate or a mixed deficiency anaemia.

Whatever the cause, the blood film shows:

- pancytopenia
- macrocytosis: large oval red cells
- hypersegmentation of the neutrophil nuclei (termed a 'right shift')
- megaloblasts in peripheral blood in severe cases.

This haematological picture is so characteristic that the diagnosis can generally be made without bone marrow examination, the definitive way of demonstrating megaloblastic change.

Vitamin B₁₂ deficiency

Vitamin B₁₂ is present in meat and dairy produce. It is absorbed as a complex with intrinsic factor (IF) produced by the gastric parietal cells. Pure dietary deficiency is exceptionally rare because there are large hepatic stores but can occur in alcoholics. More commonly, deficiency is caused by

- autoimmune damage to the gastric parietal cells: pernicious anaemia
- destruction of vitamin B₁₂ by bacterial overgrowth in diverticulae, blind loops or fistulae
- disease of the terminal ileum where the B₁₂-IF complex is absorbed: usually Crohn's disease
- pancreatic exocrine deficiency
- gastrectomy.

Pernicious anaemia

Pernicious anaemia is an organ-specific autoimmune disease caused by antibodies to gastric parietal cells and intrinsic factor. It

- is commoner in women than men
- may develop from adolescence onwards but is most common in middle to old age.

It is associated with:

- blood group A
- failure of gastric acid secretion
- an increased risk of gastric acid carcinoma

- an increased incidence of the other organ-specific autoimmune diseases, including vitiligo, diabetes mellitus, hypothyroidism and Addison's disease.

The diagnosis is made by demonstrating a reduced serum vitamin B₁₂ concentration, and IF antibodies. It is confirmed by the Schilling test, in which radiolabelled B₁₂ is given on two occasions, first on its own and then with oral IF. Urinary excretion of the label is measured. In pernicious anaemia, there is malabsorption which is correctable by IF. Other causes of malabsorption are not correctable.

Neurological effects of B₁₂ deficiency

Full blood counts are now so widely available that B₁₂ deficiency is usually recognised and treated before it has any significant neurological effects; however, some individuals may develop neurological effects with little or no anaemia. These include:

- optic atrophy
- dementia
- subacute combined degeneration of the cord (Ch. 5).

Treatment

One simple rule is that folate and vitamin B₁₂ should always be given together in megaloblastic anaemia, at least until the haematinic results are known, because folate treatment alone can increase haemopoiesis in patients with pure vitamin B₁₂ deficiency and actually precipitate neurological complications. Patients with vitamin B₁₂ deficiency should be given injections of vitamin B₁₂ weekly for 6 weeks and then 3-monthly indefinitely thereafter. The reticulocyte response should be checked after 7 days. Potassium supplements are needed in some cases, as well as iron and folate, because cellular anabolism requires potassium. Whether or not patients with severe megaloblastic anaemia should be transfused is controversial because even careful transfusion can precipitate heart failure. If it is done, it should be slow and with diuretic cover and should not aim to restore haemoglobin immediately to normal.

Folate deficiency

Folate is absorbed in the upper small intestine. The body stores are relatively small so folate deficiency develops earlier in malabsorption syndromes than does iron or vitamin B₁₂ deficiency. For the same reason, folate deficiency is more likely to have a purely dietary cause, to develop during pregnancy or to be precipitated by active haemopoiesis in haemolytic states. Folate metabolism is vulnerable to a wide range of drugs and is actually the target of some chemotherapeutic agents, e.g. methotrexate. These are the main causes of folate deficiency:

- dietary, for example in:
 - alcoholism
 - elderly or neglected people
- increased demand
 - pregnancy
 - active haemopoiesis, e.g. haemolytic anaemia
- malabsorption
 - coeliac disease
 - pancreatic insufficiency
 - postgastrectomy
 - Crohn's disease
- drugs which interfere with folate absorption:
 - phenytoin
- drugs which interfere with folate metabolism:
 - methotrexate, phenytoin, trimethoprim.

Investigation of the cause of folate deficiency will depend on the context in which it is diagnosed. If there is a clear dietary or drug cause, no further investigation is needed. Otherwise, investigation for malabsorption is indicated.

Diagnosis

A low serum or red cell folate concentration confirms the diagnosis. Of the two, red cell folate more accurately reflects total body folate stores.

Prevention and treatment

Pregnant women are routinely given prophylactic oral folate. Alcoholic or poorly nourished patients should be given folate as part of their rehabilitation. Proven folate deficiency is treated with oral folic acid. As explained above, this must never be given alone in macrocytic anaemia unless vitamin B₁₂ deficiency has been excluded. If there is evidence of iron deficiency, oral iron should also be given.

Aplastic/hypoplastic anaemia

Aplastic anaemia is a rare condition which may be congenital or acquired. It may be primary (no cause identified) or secondary to:

- drugs, e.g. chloramphenicol, chemotherapy, zidovudine, ganciclovir, phenylbutazone
- irradiation
- chemicals
- infection, e.g. viral hepatitis
- autoimmune disease.

There is usually leucopenia and thrombocytopenia as well as anaemia, although pure red cell aplasia may occur. The aplasia may be *transient* or *chronic*, and *partial* (hypoplastic) or *complete* (aplastic). The symptoms and signs depend on the relative degrees of anaemia, thrombocytopenia and neutropenia. The red cells are normocytic or slightly macrocytic. The marrow trephine

biopsy is hypoplastic. The differential diagnosis is with other causes of pancytopenia, particularly marrow replacement/fibrosis. Severe aplastic anaemia has a high mortality. A significant number of patients respond to antilymphocyte globulin, but the best chance of cure lies in bone marrow transplantation from an HLA-identical sibling donor. Androgens and corticosteroids have occasionally been effective. Supportive care of the neutropenic patient (p. 268) and transfusions of platelet and red cells are needed. With time, platelet and red cell antibodies develop and may complicate management.

Leucoerythroblastic anaemia

Leucoerythroblastic anaemia is used to describe a condition in which the blood film shows immature leucocytes and erythroblasts. It has many causes, notably marrow infiltration with a solid tumour, myeloma, lymphoma, leukaemia or myelofibrosis. It is investigated by marrow aspiration/biopsy.

Anaemia of chronic disease

Anaemia caused by chronic disease is, second to iron deficiency, the most common anaemia you are likely to encounter. Common causes are:

- chronic infection
- renal failure
- liver disease
- malignancy
- autoimmune disease.

The typical pattern is a normocytic or microcytic anaemia with reduced serum iron and total iron-binding capacity, intact marrow iron stores and reduced erythroblast haemosiderin. It is usually caused by suppressed erythropoiesis, although other mechanisms such as haemolysis may contribute. The anaemia is often relatively mild. There is no specific treatment other than management of the causative disease.

Haemolytic anaemias

Destruction of red cells by a disease process either intrinsic or extrinsic to the cell causes:

- shortened red cell survival
- increased erythropoiesis
- anaemia if erythropoiesis cannot keep pace with red cell destruction.

There may be morphological changes in the red cells, giving a clue to the cause of haemolysis.

In most haemolytic anaemias, red cells are removed by macrophages of the reticuloendothelial system, chiefly in the spleen. This process is termed **extravascu-**

lar haemolysis. Breakdown of haemoglobin increases the plasma level of unconjugated bilirubin, causing clinically overt jaundice in severe haemolysis. Splenomegaly and pigment gall stones may occur.

When there is rapid breakdown of red cells within the circulation (**intravascular haemolysis**), haemoglobin is liberated. Initially, it is bound to plasma proteins called haptoglobins. When the binding capacity of haptoglobins is exceeded, free haemoglobin is filtered in the kidneys and converted to haemosiderin in renal tubular cells. Haemosiderin can be detected in urine.

The haemolytic anaemias are a heterogeneous group of disorders which can be classified into congenital and acquired forms. Congenital haemolytic anaemias include:

- haemoglobinopathies
 - sickle cell disease
 - thalassaemia
- membrane defects
 - spherocytosis
 - elliptocytosis
- red cell enzyme defects
 - glucose 6-phosphate dehydrogenase deficiency.

Acquired haemolytic anaemias include:

- autoimmune (p. 264)
- non-immune
 - microangiopathic haemolytic anaemia
 - prosthetic heart valve
 - drug or toxin induced.

Diagnosis

The clinical features of haemolytic anaemias are those of the anaemia, the sequelae of haemolysis and any underlying cause. In addition to haematological features, patients with chronic haemolytic anaemia are prone to leg ulceration as well as pigment gall stones.

Laboratory features of haemolysis are:

- evidence of increased erythropoiesis: reticulocytosis, polychromasia, erythroid hyperplasia of bone marrow
- evidence of increased red cell breakdown: increased plasma unconjugated bilirubin and urinary urobilinogen, reduced plasma haptoglobin.

Congenital haemolytic anaemias

The only congenital haemolytic anaemias covered here are those that you might expect to encounter as a house officer.

Sickle syndromes Sickle syndromes are caused by a recessively inherited amino acid substitution in the haemoglobin A molecule, which causes it to become insoluble and cross-link under hypoxic conditions. This

causes haemolysis, 'stickiness' and microvascular occlusion.

Africans are most often affected, so heterozygotes are common in areas with a high African population. They may develop symptoms after surgery or during any situation that causes hypoxia.

'Sickle trait' can be diagnosed by the *in vitro* 'sickle test' and by haemoglobin electrophoresis.

Homozygotes are more severely affected. They have a chronic haemolytic anaemia and may have sickling crises precipitated by:

- hypoxia
- dehydration
- infection
- other systemic stresses.

During crises, microvascular occlusion causes infarcts of bone and soft tissues. Patients experience severe pain, fever and malaise. Splenic infarcts lead to hyposplenism and an increased risk of pneumococcal septicaemia. Salmonella osteomyelitis is common in areas of infarcted bone. There may be soft tissue complications, including retinopathy, acute renal papillary necrosis, acute pulmonary syndrome, and leg ulcers. Pigment gall stones are common. Pregnancy is hazardous. Prophylactic penicillin is required to prevent pneumococcal septicaemia.

Sickling crises are treated by

- keeping the patient warm
- oxygen
- intravenous fluids
- opiate analgesia
- antibiotics.

The thalassaemias The thalassaemias are a group of congenital haemolytic anaemias caused by mutations or gene deletions affecting the α - and β -globin chains (α - and β -thalassaemia, respectively). They vary in severity from a chance finding in an asymptomatic individual to a disease that is incompatible with life. Synthesis of abnormal haemoglobin causes 'ineffective erythropoiesis'. There is microcytosis and the cells are irregular in size, shape and degree of haemoglobinisation.

Heterozygotes (thalassaemia trait) usually remain asymptomatic but may become mildly anaemic during intercurrent infection or pregnancy. Remember thalassaemia trait in the differential diagnosis of microcytic anaemia. Thalassaemia major is not considered further here.

Acquired haemolytic anaemia

Autoimmune haemolytic anaemia Autoimmune haemolytic anaemia (AIHA) is most commonly idiopathic but may be caused by:

- autoimmune disease, e.g. systemic lupus erythematosus (SLE)
- neoplasia, e.g. chronic lymphocytic leukaemia
- infection, e.g. infectious mononucleosis, mycoplasma
- drugs, e.g. methyldopa.

The anti-red cell antibody involved may cause haemolysis at body temperature ('warm AIHA': usually IgG) or only at temperatures well below 37°C ('cold AIHA': usually IgM) and the clinical picture varies accordingly.

Cold AIHA (cold haemagglutinin disease). Haemolysis is mediated by complement and usually intravascular, classically causing episodes of dark urine (haemoglobinuria) after cold exposure. At the same time, agglutination of red cells in peripheral capillaries may cause peripheral cyanosis, Raynaud's-like symptoms and even gangrene. Cold AIHA may occur as a transient problem after infectious diseases such as infectious mononucleosis or mycoplasma pneumonia. Red cell agglutinates can be seen on a blood film at room temperature.

Warm AIHA. Haemolysis is usually extravascular, particularly in the spleen, and leads to jaundice and splenomegaly. The blood film shows spherocytosis.

Direct antiglobulin test. In either case, the definitive test for AIHA is the direct antiglobulin test, in which antibodies are demonstrated on the red cell surface by the addition of anti-human globulin, which will cause agglutination.

Management of warm AIHA. Warm AIHA can be treated with:

- steroids
- splenectomy
- immunosuppressive therapy.

Management of cold AIHA. Patients with cold agglutinins should be kept warm; they respond less well to steroids and splenectomy. Blood transfusion may be needed for haemolytic crises, but cross-matching can be difficult.

Non-immune acquired haemolytic anaemias The non-immune acquired haemolytic anaemias are caused by:

- fibrin deposited in the microcirculation, as in disseminated intravascular coagulation (DIC) (p. 279)
- heart valves or other mechanical prostheses
- toxic causes, including uraemia, lead poisoning and some drugs
- paroxysmal nocturnal haemoglobinuria, a rare condition in which deficiencies of membrane proteins make the red cells susceptible to the lytic actions of serum complement.

In the case of DIC and mechanical red cell damage, schistocytes (fragmented red cells) are seen on the blood film.

Blood transfusion

There are two quite distinct indications for blood transfusion:

- to restore volume after acute blood loss
- to restore the red cell mass in a patient with anaemia and a normal blood volume (compensated anaemia).

An excellent, 'official' guide is available at <http://www.show.scot.nhs.uk/sbts/webpages/01aud.htm>.

Acute blood loss

Acute blood loss is caused by trauma, haemorrhage, usually from the GI tract, and surgery. If haemorrhage is severe, there is circulatory collapse. The physical signs are from the blood loss itself and from volume depletion (p. 188).

You should transfuse red cells (with other fluids, if needed) as quickly as necessary to restore the circulation, monitoring the pulse, blood pressure and urine output. Remember that the haemoglobin concentration is no guide to the severity of acute blood loss because it takes time for haemodilution to occur.

Transfusion for anaemia

In anaemia, plasma volume is normal despite lack of red cells. This process of compensation takes hours or days after acute blood loss. The indications for transfusion are less strong than after acute blood loss because:

- the patient is not shocked
- treating the underlying cause of anaemia is a more permanent (albeit slower) solution than transfusing red cells, which have a short lifespan
- transfusion increases blood volume and may cause volume overload (heart failure).

Transfusion may nevertheless be indicated to:

- relieve symptoms
- prepare anaemic patients for surgery

- increase the red cell mass in case of further bleeding.

As a rule of thumb, blood transfusion:

- is rarely indicated if the haemoglobin concentration is above 100 g/l
- may be indicated between 80 and 100 g/l
- is likely to be needed below 80 g/l.

In general, iron, vitamin B₁₂ or folate deficiency should be treated with haematinics. Transfusion for anaemia is particularly hazardous if the patient is in heart failure, when red cells should be given with an i.v. loop diuretic and close observation of the patient's haemodynamic state. Blood transfusion is expensive and potentially hazardous. It should not be 'dished out' carelessly.

Blood groups

The main ABO system consists of two markers inherited as Mendelian dominant traits from the parents. The red cells of an individual may carry the A antigen (group A), the B antigen (group B), both (group AB) or neither (group O). The antigens are carried on many tissues other than red cells and individuals are exposed early in life to those antigens that they do not carry. Thus group A individuals have agglutinins to the B antigen and vice versa; group O individuals have agglutinins to both antigens and group AB individuals have agglutinins to neither. The importance of this system to blood transfusion is that donated cells may be lysed by host agglutinins; lysis of host cells by donor agglutinins is not usually a problem. Table 62 summarises the system and reminds you that group O subjects are 'universal donors' because their cells have neither antigen and will not be lysed if they are transfused into group A, B or AB recipients. Group AB subjects are 'universal recipients' because they have agglutinins against neither antigen.

The rhesus (D) blood group system is also conceptually very simple. About 85% of the Caucasian population (and a higher proportion of Asians) carry the D (or rhesus) antigen on their red cells. Those who are rhesus negative may develop antibodies against the D antigen

Table 62 The ABO and rhesus blood group systems

Blood group	Relative frequency (%)	Alleles	Agglutinins present	Plasma will agglutinate cell types	Comment
O	45	Null, null	Anti-A, Anti-B	A, B, AB	Universal donor
A	40	A, A or A, null	Anti-B	B, AB	
B	10	B, B or B, null	Anti-A	A, AB	
AB	5	A, B	None	None	Universal recipient
Rh ⁺	85	D ⁺	None	None	
Rh ⁻	15	D ⁻	None or anti-D	None or Rh ⁺	

but only if exposed to it by blood transfusion or, in pregnancy, by placental leakage.

Cross-matching

After determining the patient's ABO and rhesus blood groups, donor red cells of an appropriate group are then cross-matched, both at room temperature and at 37°C against patient's serum, to detect cold and warm antibodies. Positive results in these tests mandate further investigation, and a significant delay before compatible blood can be made available. There is an increasing move towards storing the patient's own blood in preparation for elective surgery, eliminating the risks of cross-infection and incompatibility (autologous transfusion).

Complications of transfusion

The major risks of HIV and hepatitis B and C infection can largely be eliminated by careful screening of donor blood. Other potential complications are:

- minor febrile reactions
- haemolytic reactions
- severe allergic reactions
- transfusion-related lung injury
- problems caused by massive transfusions
- chronic iron overload.

Minor febrile reactions

Minor febrile reactions are not uncommon, particularly in patients who have developed platelet and/or white cell antibodies from repeated transfusions. They may be prevented by leucodepleting the red cells before transfusion, or using a filter to trap white cells and platelets during transfusion.

Acute, severe haemolytic reactions

Severe acute haemolytic reactions are fortunately rare, invariably caused by ABO incompatibility (e.g. a group O recipient receiving group A blood) and almost always caused by elementary errors like the incorrect labelling of blood samples or incomplete pretransfusion checks. They are likely to lead to undefendable litigation. The patient may develop pyrexia, chest or abdominal pain and pass black urine, rapidly progressing to shock, acute renal failure and DIC. If a haemolytic reaction is suspected, you should:

- stop the transfusion immediately
- give intravenous hydrocortisone and chlorphenamine
- check the patient's identity and details of the donor blood
- return the blood to the transfusion laboratory with a fresh sample of the patient's blood

- call for senior help and resuscitate as needed.

Severe allergic reactions

Severe allergic reactions occur occasionally. Patients who are deficient in IgA (1 in 600) and produce anti-IgA antibodies are particularly at risk.

Transfusion-related acute lung injury

Acute lung injury can be caused by aggregation of neutrophils in lung capillaries precipitated by anti-white cell antibodies in donor plasma; it may result in acute respiratory distress.

Massive transfusion

Massive transfusions may lead to particular problems. Hypocalcaemia can result from the chelating action of citrate, particularly if there is liver disease, which impairs citrate metabolism. Dilution of platelets and clotting factors by stored blood leading to an increased risk of bleeding is another potential complication.

Iron overload

Repeated blood transfusions can eventually lead to cardiac, liver and endocrine damage.

Polycythaemia

The term polycythaemia (increased number of red cells) is frequently used to mean erythrocytosis (increased haemoglobin concentration). That is not strictly correct but has become accepted in medical parlance. Polycythaemia and erythrocytosis are therefore both defined as an increased red cell mass. You will recognise it on the blood count as an increased haemoglobin concentration, red cell count and haematocrit. It may be *absolute*, or *relative* to a reduced plasma volume.

Absolute polycythaemia may be:

- primary: termed polycythaemia vera
- secondary to increased erythropoietin.

Causes of secondary polycythaemia include:

- compensatory increased erythropoietin secretion as a result of:
 - tissue hypoxia
 - lung disease
 - cyanotic heart disease
 - altitude
 - hypoventilation (Pickwickian syndrome)
- non-compensatory increased erythropoietin secretion from:
 - renal tumour or cysts
 - other tumours.

Only lung disease is a common cause of clinical polycythaemia.

Polycythaemia increases the oxygen-carrying capacity of blood but it also increases viscosity and impairs blood flow. Many of its clinical effects are the result of stasis and impaired tissue oxygenation.

Polycythaemia vera

Polycythaemia vera is a neoplastic stem cell proliferation which increases the formation primarily of red cells but also of leucocytes and platelets. Clinical manifestations result from:

- hyperviscosity
- tissue hypoxia
- vascular occlusive events resulting from stasis and thrombocytosis.

Paradoxically, patients may also bleed easily because their platelets are dysfunctional.

Clinical presentation

Patients may present with:

- systemic symptoms such as pruritus (particularly after a warm bath) or malaise
- an arterial or deep venous thrombosis
- neurological symptoms, including headache, tinnitus and visual disturbance
- cardiovascular symptoms, including angina and intermittent claudication
- dyspepsia or non-specific abdominal pain signifying GI mucosal ulceration
- episodes of epistaxis or GI haemorrhage
- gout.

On examination, there is plethora, cyanosis, injection of the conjunctivae and, in most cases, splenomegaly. There may also be hepatomegaly. The blood count shows a haematocrit in the range 50–70%, with leucocytosis and an increased platelet count. The red cell mass, measured isotopically, is increased. The marrow is active but normoblastic. Serum uric acid and vitamin B₁₂ are usually raised.

Management

Treatment is with:

- venesection to reduce hyperviscosity
- phosphorus-32 or an alkylating agent to reduce stem cell proliferation.

The aim is to reduce both the haematocrit and the platelet count. Life expectancy is reduced despite treatment, and the disease may transform into acute leukaemia or myelofibrosis.

Relative polycythaemia

Relative polycythaemia is far more common than polycythaemia vera. It is a disorder often seen in middle-

aged hypertensive men who drink and smoke too much. The primary abnormality is a reduced plasma volume. The aetiology is unknown.

Faced with an apparently polycythaemic patient:

- measure the haematocrit more than once to be sure the apparent erythrocytosis is not a cuffing artefact
- consider the possibility of secondary polycythaemia, of which the common cause is chronic lung disease; measure the blood gases
- check that the patient is truly polycythaemic (i.e. exclude *relative* polycythaemia) by measuring the red cell mass.

If the patient has a leucocytosis, thrombocytosis or splenomegaly, the diagnosis is likely to be polycythaemia vera.

6.3 White cell disorders

Learning objectives

You should:

- understand the causes of neutropenia
- know what infections to be concerned about in the neutropenic patient and what to do if such a patient gets a fever
- know the diseases of white cell proliferation and how they are diagnosed and treated.

A simple way of approaching white cell disorders is to think in terms of white cell numbers. They may be:

- reduced, increasing susceptibility to infection
- increased, signifying systemic disease or marrow proliferation.

Physiology

Granulocytes

Granulocytes are the most abundant white cells in peripheral blood.

Neutrophils. Most granulocytes are neutrophils, a key element of defence against most bacteria and some fungi. Most neutrophils in the normal person are present in the blood loosely adherent to the walls of vessels (marginating pool). When the appropriate stimulus comes along (such as a bacterial infection) they are released from the marginating pool and attracted to sites of inflammation by chemotactic factors including complement. Once a neutrophil comes into contact with a microbe or foreign body it attaches itself, ingests it into a vacuole called a phagosome and kills it.

Eosinophils. These are the next most abundant form. They attack parasites which are too large to be phagocytosed, and also have a role in mucosal immunity.

Basophils. These are the least abundant form. They release histamine and other inflammatory mediators during immediate hypersensitivity reactions.

Monocytes

Monocytes are large non-granulated white cells that are released from the bone marrow, circulate for several days and then enter tissues to become the tissue macrophages, including pulmonary alveolar macrophages, osteoclasts and the Kupffer cells of the liver. They engulf and kill bacteria in tissues and, as antigen-presenting cells, play a key role in immunity.

Lymphocytes

Lymphocytes are derived from the same stem cells of the bone marrow as the other cell lines. During fetal development, they migrate out to populate the thymus, liver, spleen, lymph nodes and other lymphoid tissues. In adult life, some lymphocytes are formed in the marrow but most are formed in lymphoid tissues elsewhere. There are two distinct cell lines, morphologically identical but distinguishable by cell-surface markers. The B cells — plasma cells and memory cells — are responsible for humoral immunity. T cells are responsible for cell-mediated immunity and for activating B cells. The subtypes of T cells are not discussed further here but an understanding of them is crucial to an understanding of AIDS (p. 381).

Leucopenia

Leucopenia is a reduction in the number of white blood cells.

Lymphopenia is caused by:

- HIV infection
- autoimmune disease
- lymphoma
- irradiation

Neutropenia is caused by:

- decreased production
 - drugs, e.g. cytotoxic therapy, carbimazole,
 - phenylbutazone
 - vitamin B₁₂ or folate deficiency
 - irradiation
 - marrow aplasia, fibrosis, malignant invasion, acute myeloid leukaemia (AML)
 - marrow dysplasia (p. 270)
 - infection
- increased consumption
 - hypersplenism
 - antineutrophil antibodies.

Neutropenia is relatively rare except in haematological malignancies and as a result of their treatment, the subject of the next section.

Management of neutropenia

The normal neutrophil count is around 2×10^9 cells/l. There is an increasing risk of infection when the count falls below 1×10^9 cells/l and the risk of invasive infections rises substantially when the count falls below 0.5×10^9 cells/l. A longer duration of neutropenia (e.g. more than 7 days) also puts the patient at substantially greater risk of life-threatening infection. Infections include:

- streptococci
- Gram-negatives, including *Pseudomonas aeruginosa*
- *Staphylococcus epidermidis* (usually related to indwelling central venous lines, and not immediately life-threatening)
- mucosal and invasive candidiasis
- invasive pulmonary aspergillosis
- herpes simplex virus (especially mouth ulcers).

A typical clinical scenario is that you are on call for haematology patients and summoned to the ward because a patient with no circulating neutrophils has developed a new fever 7–14 days after chemotherapy for leukaemia. You need to:

- assess whether there are any localising symptoms such as cough, skin rash, nasal symptoms, abdominal pain, etc.
- examine the mouth, chest, skin and rectal area and any other sites that are symptomatic
- assess whether the patient is in shock or going into respiratory failure
- order a portable chest radiograph if the illness has any respiratory features
- check the notes and recent results for any positive microbiology
- take at least one blood culture and collect any other microbiological specimens that are indicated by the patient's symptoms
- start broad-spectrum i.v. antibiotics according to the policy of the unit; typically these will include coverage for *Ps. aeruginosa* and streptococcal infections as a minimum (e.g. ceftazidime)
- if there are any unusual features, or the patient is very ill, you should contact a senior member of staff responsible for the patient.

Expert microbiological advice is needed if the patient remains profoundly neutropenic and has persistent fever.

Ceasing therapy. Antibiotics can usually be stopped when the neutrophil count has risen above 0.5×10^9 cells/l.

Leucocytosis

Causes of leucocytosis include:

- neutrophilia
 - infection, usually bacterial
 - inflammation
 - connective tissue disease
 - myeloproliferative disease
 - non-haematological malignancy
 - corticosteroid therapy
 - diabetic ketoacidosis
- eosinophilia
 - parasitic infection
 - allergy
 - drug reaction
 - connective tissue disease, e.g. microscopic polyarteritis (Churg–Strauss syndrome)
 - cancer
- lymphocytosis
 - viral infection
 - connective tissue disease
 - lymphoproliferative disease
- basophilia: rare and usually caused by myeloproliferation
- monocytosis
 - infection, particularly during convalescence
 - connective tissue disease
 - myeloproliferative disease.

In many cases, the cause is obvious. In others, detailed haematological investigation is needed. Remember the common causes and remember that diabetic ketoacidosis and steroid therapy cause leucocytosis in the absence of infection.

The leukaemias, myeloproliferative disorders and lymphomas

These neoplastic diseases may seem hard to understand and remember but a few simple principles provide a framework on which the diseases hang:

- all of them are neoplastic clonal proliferations but they differ in their degree of malignancy
- the more chronic diseases tend to become increasingly malignant with time
- a distinction can be drawn between *lymphoproliferative* and *myeloproliferative* diseases
- the myeloproliferative group, particularly the more chronic types (polycythaemia vera, essential thrombocythaemia and chronic granulocytic leukaemia (CGL)) usually involve proliferation of more than one cell line
- other marrow tissues that are not derived from stem cells proliferate reactively to myeloproliferation and lymphoproliferation, as in myelofibrosis and lymphoma.

Figure 65 shows the relationship between the diseases. In general, the more malignant the disease, the more intense the treatment required and the higher the chance of cure. Low-grade diseases tend to be chronic and incurable.

The acute leukaemias

Classification and risk factors

There are two broad categories of acute leukaemia, **acute lymphoblastic leukaemia (ALL)** and **acute myeloid leukaemia (AML)**, the latter including several subtypes, shown in Figure 65. The incidence of ALL peaks in childhood. It is more common in males. AML is a disease of both children and adults, with a rapidly rising incidence in old age and no gender difference. Radiation exposure, genetic factors, viral infections and toxins, including chemotherapeutic drugs, have been implicated as risk factors for leukaemia, although the cause in an individual case is usually unknown.

Clinical and haematological features

Acute leukaemia may arise *de novo* or in patients with chronic myeloproliferative disease or myelodysplasia. The clinical manifestations result from marrow dysfunction and tissue infiltration. They include:

- symptoms and signs of anaemia
- bruising, bleeding and purpura
- increased susceptibility to infection.

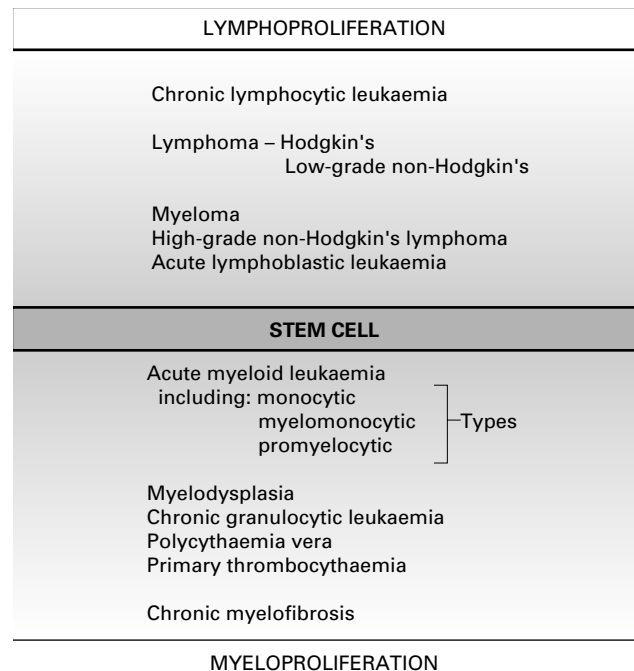


Fig. 65 Schematic representation of the lymphoproliferative and myeloproliferative diseases. The darkest shading indicates the highest degree of malignancy.

Tissue infiltration may cause:

- bone and joint pain
- gum infiltration
- skin rashes.

There is occasionally hepatosplenomegaly and, in ALL, lymphadenopathy. The diagnosis is made on blood film and bone marrow examination. There is usually anaemia and thrombocytopenia. There may be leucopenia or a leucocytosis with blasts (primitive cells) in peripheral blood. The marrow is hypercellular and infiltrated with blasts. AML and ALL are distinguished and subclassified on morphological, cytochemical, immunological and cytogenetic characteristics. Rod-shaped cytoplasmic bodies, named Auer rods, are a virtually pathognomonic feature of AML.

Management

The treatment of ALL has been one of the success stories of oncology because two-thirds of children (fewer adults) are cured. Most forms of acute leukaemia are amenable to chemotherapy, but equally important is the intensive supportive treatment with antibiotics and blood products, and sympathetic management of the patient and his/her family. The aim is to eliminate the abnormal clone from blood, bone marrow and other sites and allow repopulation with normal haemopoietic cells. This is termed **remission**. A discussion of the specific drugs and regimens is beyond the scope of this chapter but treatment may include the following phases.

1. Remission induction: elimination of neoplastic tissue, allowing recovery of normal marrow
2. Consolidation of remission
3. Prevention of recurrence in extramedullary sites (as in ALL) and maintenance of remission
4. Treatment of relapses.

There are some important differences between the treatment of ALL and AML. More intensive myelosuppression is used in AML; consequently the risks of infection and bleeding are greater. In ALL, there is a high risk that systemic chemotherapy will not eradicate malignant cells from certain extra medullary 'sanctuary' sites, including the brain, spinal cord and testes; therefore, additional local treatment (e.g. intrathecal chemotherapy) is given. Relatively low-dose maintenance therapy is often continued for 2 to 3 years in ALL, whereas induction in AML is followed by several further courses of very intensive chemotherapy over a much shorter period of time in an attempt to prevent relapse.

If a suitable donor is available (preferably an HLA-identical sibling), allogeneic bone marrow or peripheral blood stem cell transplantation may be performed in both AML and ALL, in an attempt to reduce the

chance of relapse. This offers a 'graft versus leukaemia' effect, in addition to the benefits of the chemotherapy given, but may at the same time cause graft-versus-host disease, which has a significant morbidity and mortality. Alternatively, autologous transplantation, using the patient's own bone marrow or peripheral blood stem cells, collected during remission, may be employed. This avoids the risk of graft-versus-host disease but does not have the benefit of a graft-versus-leukaemia effect, and there is a chance that the transplanted marrow may still contain leukaemic cells.

Over 90% of children and 80% of adults with ALL achieve remission; the 5-year survival for children is over 60%, but unfortunately the majority of adults relapse and die of leukaemia. The remission rate with intensive chemotherapy in AML is over 70%, but the 5-year survival is only 20%. Many patients are elderly and not treated intensively, which results in a 5-year survival for all patients with AML of approximately 5%. Increasing age has an adverse prognostic effect on all types of leukaemia and a high white count at presentation predicts a bad outcome. Specific cytogenetic defects in the leukaemic cells are closely related to either a good (e.g. t(8; 21) in AML) or bad (e.g. t(9; 22) in ALL) prognosis.

There is increasing interest in directing specific treatments towards molecular genetic defects newly identified in haematological malignancies. A big success story in this regard has been the treatment of acute promyelocytic leukaemia, a subtype of AML that carries a high risk of early death from bleeding in DIC. The genetic abnormality (t(15; 17)) involves a retinoic acid receptor gene, and it has been found that complete remission can be achieved by administration of all-*trans*-retinoic acid. Intensive chemotherapy still has to be used, but the risk of early death and incidence of relapse have been markedly reduced; as a result, the cure rate is now approximately 70%.

Myelodysplastic syndrome

Myelodysplastic syndrome describes a group of disorders characterised by cytopenias of one or more cell lines with a cellular marrow and morphological abnormalities in both marrow and peripheral blood. Cytogenetic abnormalities can often be demonstrated. The cytopenias are presumed the result of ineffective haemopoiesis. Myelodysplastic syndrome progresses, at a variable rate, to AML. Management is supportive until leukaemia develops, when cytotoxic therapy may be indicated although the outlook is poor at this stage. Many patients are elderly and unsuitable for intrusive treatment. Allogeneic bone marrow transplantation can be considered in younger patients.

Myeloproliferative diseases

Chronic granulocytic leukaemia

Chronic granulocytic leukaemia (CGL, also known as chronic myeloid leukaemia (CML)), is an uncommon disease which may occur at any age but peaks in the 50–60 age group. It is characterised by uncontrolled proliferation of myeloid progenitor cells, generally most noticeable in granulopoietic cells but also affecting red cells and platelets. The characteristic feature, present in 95% of patients, is the **Philadelphia chromosome**, resulting from a reciprocal translocation between the long arms of chromosomes 9 and 22 (t(9;22)).

These are the clinical features and some modes of presentation of CGL:

- patients typically present with symptoms of anaemia, weight loss fatigue, anorexia, drenching sweats or abdominal discomfort
- palpable splenomegaly in 50%, which may be massive, and there may be symptomatic splenic infarction
- there may be symptoms and signs of haemorrhage
- the diagnosis may be made by chance on a blood count.

There is marked leucocytosis including, especially, neutrophils and myelocytes and, in many cases, basophils and eosinophils. The platelet count is usually normal or raised at presentation. The bone marrow shows granulopoietic hyperplasia.

CGL can be distinguished from other causes of leucocytosis by:

- symptoms and signs
- blood film
- Philadelphia chromosome
- reduced leucocyte alkaline phosphatase score on a blood film.

CGL progresses over about 3 years to a more malignant phenotype, culminating in an accelerated phase. This may be marked by rapid transformation to acute leukaemia (AML or ALL), or more gradual deterioration involving such features as anaemia, massive splenomegaly, myelofibrosis, marked basophilia or thrombocytosis. Response to treatment is generally poor and the outlook is bleak.

During the chronic phase, the disease is easily controlled by simple oral chemotherapy, usually hydroxyurea. Nevertheless, the Philadelphia chromosome is not eradicated. Alpha interferon can produce good haematological remissions, and occasional cytogenetic remissions. At present, allogeneic bone marrow transplantation during the chronic phase (if a suitable donor is available) is the only reliable means of achieving this key objective. However, new treatment

directed against the gene product of the Philadelphia translocation has been developed and may become an important part of management in the future.

Polycythaemia vera and thrombocythaemia

Although polycythaemia vera and thrombocythaemia are myeloproliferative disorders, they are described in the red cell (p. 267) and platelet (p. 274) sections of this chapter because their clinical features are determined by the predominant cell type in peripheral blood rather than their progenitor cell.

Myelofibrosis

Myelofibrosis describes a disease in which proliferation of fibrous tissue in the marrow is the main feature. It may be the final result of other myeloproliferative diseases or may present as a primary disorder in middle-aged or elderly people. There is anaemia — which may be leucoerythroblastic (p. 263) — and massive splenomegaly. It can be impossible to aspirate marrow. Trepine biopsy shows extensive fibrosis. The treatment is supportive, sometimes with splenectomy to improve red cell, white cell and platelet survival. It may progress to acute leukaemia.

Lymphoproliferative diseases

Hodgkin's disease

There are incidence peaks of Hodgkin's disease in early adulthood and old age. The two main clinical characteristics of lymphomas are lymphadenopathy and systemic symptoms.

A cardinal feature of Hodgkin's disease (which distinguishes it from NHL) is that, when more than one group of nodes is involved, they are always contiguous, suggesting lymphatic spread of malignant cells. The cervical nodes are most often involved. With disseminated disease, there may be hepatosplenomegaly and extra-lymphatic involvement. Systemic symptoms include pruritus, fever, night sweats and weight loss. Anaemia is common. There may be neutrophilia and eosinophilia. Impaired cell-mediated immunity predisposes to infection, most typically herpes zoster. Alcohol-induced pain at the site of the disease is a quite specific symptom.

The diagnostic feature on lymph node biopsy is the presence of multinucleated **Reed–Sternberg cells**.

There are several histological subtypes of Hodgkin's disease, which vary, among other things, in the relative proportion of lymphocytes and reactive elements in the malignant tissue. Staging, however, is the most important determinant of treatment and prognosis. This is based on the Ann Arbor system' which, in its simplest form, is:

stage I: involvement of one group of lymph nodes only
stage II: involvement of more than one group of lymph

nodes on one side of the diaphragm
 stage III: involvement of lymph nodes on both sides of the diaphragm
 stage IV: presence of extra lymphatic disease (e.g. bone marrow, liver).

The disease is also subclassified as:

A: no systemic symptoms.

B: presence of fever, night sweats or significant weight loss.

Staging therefore involves:

- a careful history and examination
- liver function tests
- computed tomographic (CT) scanning of chest, abdomen and pelvis
- bone marrow trephine biopsy.

Less favourable prognosis is associated with:

- lymphocyte depleted histology
- higher stage
- B subtype symptoms
- increasing age
- very bulky lymphadenopathy (e.g. massive mediastinal enlargement).

Broadly speaking, treatment is with local radiotherapy for stages IA and IIA disease, and with chemotherapy, with or without radiotherapy, for higher stages. Depending on the above factors, Hodgkin's disease has a 50–90% 5-year survival.

Non-Hodgkin's lymphoma

NHL is a more heterogeneous group of disorders with varying malignancy and prognoses. It differs from Hodgkin's disease in four ways:

- higher prevalence
- older mean age at diagnosis
- non-contiguous, multicentric spread
- extranodal involvement is more common.

Several types of NHL are known to be caused by viruses, including Epstein–Barr virus (Burkitt's lymphoma), human T cell leukaemia-1 virus and human immunodeficiency virus (HIV). Like Hodgkin's disease, NHL may present with lymphadenopathy and systemic symptoms, although the symptomology is more diverse.

Remember that lymphadenopathy must always be taken seriously. In younger people, it is more likely to be caused by infection than malignancy. In older people, there is a high likelihood of cancer (usually localised lymphadenopathy), lymphoma or chronic lymphocytic leukaemia (generalized lymphadenopathy). The diagnosis of NHL is made by biopsy. It is staged as for Hodgkin's disease.

There are two broad histological categories:

- **low-grade NHL:** this is indolent, but may become more aggressive with time; it is essentially without cure but survival may be prolonged (> 5 years)
- **high-grade NHL:** This form carries a much higher early mortality but is more responsive to treatment, with an approximately 30% 5-year disease-free survival.

Treatment Because NHL is usually more widespread than Hodgkin's disease at presentation, treatment is more often with chemotherapy, although localised disease is treated with radiotherapy. Stem cell or bone marrow transplantation is used in some patients.

Chronic lymphocytic leukaemia

Chronic lymphocytic leukaemia (CLL) is the least malignant of the leukaemias and is characteristically a disease of elderly people. It is more common in men than women. It may be a chance finding on a blood film or may present with lymphadenopathy or anaemia. Typically, there is hepatosplenomegaly. The blood film shows (sometimes massively) increased numbers of mature lymphocytes. Because the lymphocytes are B cells in over 95% of patients, there may be:

- a 'paraprotein' (see Myeloma, below)
- depression of normal immunoglobulins and increased susceptibility to infection
- autoimmune phenomena such as haemolytic anaemia or thrombocytopenia.

Cytotoxic therapy or corticosteroids may be given for symptoms or complications, although many patients need no treatment. Progressive disease causes:

- worsening lymphocytosis
- increasing hepatosplenomegaly and lymphadenopathy
- eventually, bone marrow failure.

There is a 50% five-year survival.

Multiple myeloma

Multiple myeloma is a malignant proliferation of plasma cells (B cells), which are relatively highly differentiated and secrete a monoclonal immunoglobulin. Myeloma is predominantly a disease of old people, although it may arise at any time in adult life. The plasma cells may secrete:

- IgG, with or without free light chains (50% of patients)
- IgA, with or without free light chains (20%)
- free light chains only (20%)
- Other patterns of paraprotein (10%).

The clinical features result from:

- plasma cell proliferation
- systemic effects of the paraprotein
- impairment of normal haematological function.

There is bone destruction caused by humorally mediated activation of osteoclasts without the normal osteoblastic response. This may cause diffuse osteopenia or, radiologically, punched-out lesions at the site of plasma cell deposits. Pathological fractures may result. Such deposits may present as mass lesions: plasmacytomas. Bone destruction mobilises calcium; consequently hypercalcaemia (p. 355) is a common complication of myeloma.

Apart from its skeletal features, two other characteristics of myeloma are hyperviscosity and renal failure. Hyperviscosity occurs because the paraprotein alters the surface charge of the red cells and thus leads to aggregation. It may impair cerebral and peripheral blood flow, typically causing lethargy, confusion and impaired consciousness. It does not usually present a clinical problem in myeloma but is seen more often in **Waldenström's macroglobulinaemia**, a rare plasma cell proliferative disease with an IgM paraprotein.

Renal failure in myeloma results from:

- a direct nephrotoxic effect of free light chains
- hypercalcaemia
- hyperuricaemia and urate nephropathy
- infection
- amyloid deposition in the kidneys
- plasma cell infiltration of the kidneys.

The effects upon normal haematological function include:

- increased susceptibility to bacterial infection (typically septicaemia or pneumonia) as a result of reduced leucocyte numbers of function together with reduced secretion of normal immunoglobulins
- anaemia or pancytopenia because of marrow replacement or suppression of haemopoiesis.

Clinical presentation

Patients may present with bone pain or fractures (particularly involving the spine and ribs), weight loss, anaemia, infective episodes and renal failure. Other typical symptoms include thirst, polyuria, nocturia (owing to hypercalcaemia and/or renal failure), constipation (from hypercalcaemia), lethargy and confusion.

The diagnosis is based upon finding:

- a high ESR (except in those with only light chain secretion)
- the paraprotein, by immunoelectrophoresis of blood and/or urine

- reduced concentrations of normal immunoglobulins (immune paresis)
- radiological evidence of generalised osteopenia or local bone destruction
- increased plasma cell numbers in a bone marrow aspirate.

Other laboratory features include:

- anaemia, thrombocytopenia and leucopenia
- renal failure
- hypercalcaemia.

It should be noted that the term **Bence-Jones proteinuria** is of historical interest only. It describes the behaviour of light chains in boiled urine, now superseded by immunoelectrophoresis of concentrated urine.

Management

Patients may become caught in a vicious spiral of hypercalcaemia, volume depletion and renal failure. The first step for such patients is i.v. fluid therapy (described under acute renal failure, p. 175). Infection should be sought and treated, pain controlled, and hypercalcaemia treated with corticosteroids and/or i.v. bisphosphonate if fluid alone does not control it. Plasma exchange may occasionally be needed to control hyperviscosity. Long-term treatment is with chemotherapy such as oral melphalan, an alkylating agent, or more aggressive regimens in younger patients. Bone pain may be controlled with radiotherapy. Despite treatment, the 50% survival is about 2 years.

6.4 Platelet disorders

Learning objectives

You should:

- be able to understand the clinical presentations of platelet disorders
- understand the indications for platelet transfusions
- understand how increased platelet numbers can cause thrombophilia.

Physiology

The role of platelets is to 'plug' defects in damaged vessels, initiate coagulation and promote healing. They:

- adhere to the vessel wall
- become activated
- degranulate
- aggregate.

This can best be thought of as a cascade process, which becomes self-perpetuating as they activate one another.

The cascade may be triggered by:

- damage to the vessel wall, which exposes platelets to collagen and von Willebrand factor (vWF)
- blood coagulation, which leads to thrombin formation
- the activation of other platelets, which causes discharge of ADP, thromboxane A₂ and platelet-derived growth factor
- inflammation, which leads to release of platelet-activating factor from neutrophils and monocytes.

The process of adherence and aggregation is promoted by the prostaglandin thromboxane A₂. This is derived from arachidonic acid within platelets and held in check by prostacyclin, which is synthesised from arachidonic acid in the endothelium.

Adherence leads to platelet degranulation. The contents of the granules attract other platelets, cause platelet aggregation and trigger blood coagulation. Uncontrolled platelet adhesion and thrombosis are prevented by secretion of prostacyclin and activation of protein C (p. 275) from adjacent healthy endothelium.

Platelet numbers can easily be measured with an automated counter. Their function can be assessed crudely by measuring how long a patient bleeds after 'nicking' the skin (bleeding time) and more accurately by platelet aggregation tests in the laboratory.

Conceptually, platelet disorders are straightforward. Patients may have too many or too few platelets or platelets that do not work properly. Changes in platelet number are caused by increased or reduced thrombopoiesis or platelet consumption. Moderate thrombocytopenia (e.g. count $< 50 \times 10^9$ cells/l) or decreased platelet function may result in easy bruising. Severe thrombocytopenia (e.g. count $< 10 \times 10^9$ cells/l) can cause mucosal or intracerebral haemorrhage, in which case urgent platelet transfusion is indicated. Transfused platelets have such a short life that transfusions may need to be repeated daily. Thrombocytosis or increased platelet activity raise the coagulability of blood, causing arterial and venous thromboses. Thrombocytosis is treated with antiplatelet drugs or chemotherapy.

Thrombocytopenia

Decreased platelet production is usually caused by one of the major haematological diseases or its treatment. Other causes include:

- bone marrow infiltration
- myelosuppressive drugs
- radiation exposure
- megaloblastic anaemia.

Increased platelet loss may be caused by:

- increased activity of the spleen causing 'sequestration' of platelets
- entrapment of platelets in fibrin deposited in small vessels (see DIC, p. 279)
- immunity or autoimmunity.

The two immune mechanisms of platelet destruction are:

- antibodies formed against platelet antigens
- antigen-antibody complexes (e.g. precipitated by a drug), which bind to platelets and accelerate their destruction.

Idiopathic (immune) thrombocytopenic purpura, marrow suppression and DIC are the most important conditions to know about.

Idiopathic thrombocytopenic purpura

Idiopathic thrombocytopenic purpura may occur acutely, often in infants or young adults, sometimes soon after a viral infection and with a self-limited course. It may also have a less acute presentation, typically in a young adult or middle-aged woman, and a chronic course.

The presentation is with purpura and bleeding, which may be severe. In its subacute form, it may be a chance laboratory finding. The disease is frequently benign but may lead to serious bleeding, such as GI haemorrhage, or (rarely) to cerebral haemorrhage. Platelet antibodies can be demonstrated in some patients and the marrow is active, signifying compensatory thrombopoiesis. Steroids or high-dose immunoglobulin infusions may be used. In the chronic form, steroid therapy may induce a lasting remission. If it does not and thrombocytopenia is severe, splenectomy may be effective by removing the site of platelet destruction.

Thrombocytosis

Thrombocytosis may result from decreased platelet consumption after splenectomy, although it is usually only transient. Increased production may be secondary to any marrow stimulus such as bleeding, haemolysis surgery or as a reaction to inflammation or malignancy. The one primary disease is **essential thrombocythaemia**, an uncommon myeloproliferative disease characterised by increased numbers of variably active platelets. As has been explained above, patients may either develop arterial/venous thromboses or bleed. It is characteristically a disease of middle or old age. As well as thrombocytosis, there may be normocytic anaemia and leucocytosis

(caused by myeloproliferation) and either splenomegaly or hyposplenism owing to splenic infarction. The marrow shows megakaryocyte proliferation with other myeloproliferative features. Treatment is with antiplatelet drugs or chemotherapy. Leukaemic transformation or myelofibrosis may be late complications.

Antiplatelet therapy

Particularly in ischaemic heart disease and transient ischaemic attacks, antiplatelet therapy is of proven value in preventing arterial thromboses. It may also protect against venous thrombo-embolism. Aspirin is the most effective drug. It works by irreversible inhibition of cyclo-oxygenase, the key enzyme in prostaglandin synthesis. Since cyclo-oxygenase inhibition prevents synthesis of endothelial prostacyclin as well as platelet thromboxane, aspirin has prothrombotic as well as antithrombotic effects. These effects are dose related and the balance can be shifted towards antithrombosis by giving lower doses. The main side-effects are dyspepsia, peptic ulceration and GI haemorrhage. Other platelet inhibitors such as sulfinpyrazone and dipyridamole may also be used but there is less evidence that they are clinically effective. Platelet glycoprotein receptor antagonists are a new class of drug currently undergoing controlled clinical trial for treatment of cardiovascular disease.

Whether **antiplatelet** or **anticoagulant** therapy is more appropriate depends on the pathophysiology of the disease in question: platelet activation is central to the arterial thrombo-embolism of cerebrovascular (p. 225) and ischaemic heart disease (p. 14), so aspirin is the treatment of choice to prevent them. Intracardiac thrombosis and venous thrombo-embolism are more dependent on the coagulation pathways and are, therefore, treated with anticoagulants.

6.5 Coagulation disorders

Learning objectives

You should:

- understand how coagulation defects are acquired
- know how warfarin and heparin work, when to use them, and their potential dangers
- understand the concept of hypercoagulability (thrombophilia) and its causes.

Physiology

The functions of the coagulation and fibrinolytic system are to:

- maintain the fluidity of blood
- plug damaged vessels
- prevent the uncontrolled propagation of blood clot
- remove clot as healing proceeds.

Coagulation is a complex process, triggered by damage to tissue or the vessel wall. This exposes collagen or releases tissue thromboplastin, which activate the coagulation cascade, summarised in Figure 66. Platelet activation also triggers coagulation. The final result is conversion of fibrinogen to an insoluble fibrin plug. This is catalysed by thrombin formed from its precursor prothrombin. Within the cascade, there are the intrinsic and extrinsic systems. These converge on a common pathway that activates the final two steps of thrombin and fibrin formation. Calcium is essential to coagulation. The coagulation factors are synthesised in the liver; a number of them are dependent on vitamin K.

There are also mechanisms that restrain coagulation, notably the thrombin inhibitor antithrombin III. Protein C is another. This protein is activated by thrombin formation and feeds back to suppress the coagulation cascade. Protein S is a cofactor for that inhibitory pathway.

Once formed, clots are lysed by plasmin with the release of fibrin degradation products (FDPs). The conversion of plasminogen to plasmin is promoted by tissue plasminogen activator (tPA). The dynamic

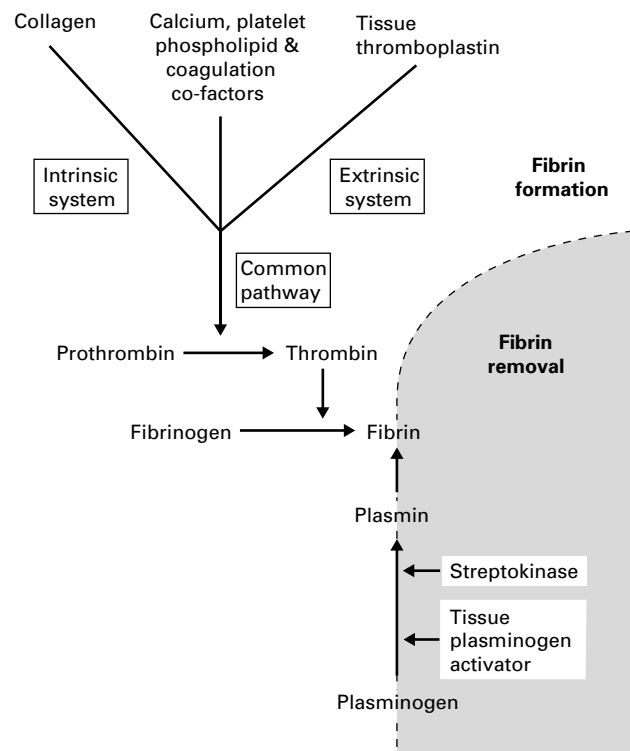


Fig. 66 The coagulation and fibrinolytic systems.

equilibrium between the formation of fibrin and its removal maintains haemostasis.

Warfarin prolongs coagulation by preventing the hepatic synthesis of vitamin K-dependent clotting factors. Heparin potentiates antithrombin III. Fibrinolytic drugs include **streptokinase** and **recombinant tPA**, both of which potentiate plasmin formation and the breakdown of fibrin.

Tests of coagulation and fibrinolysis

Two tests are in general use (Fig. 67): the prothrombin time (PT) and activated partial thromboplastin time (APTT). The PT tests the extrinsic system, common pathway and fibrin formation. It is sensitive to deficiency of the vitamin K-dependent clotting factors and is prolonged by:

- malnutrition
- warfarin
- hepatocellular dysfunction
- fat malabsorption
- consumption of clotting factors, in DIC.

When the prothrombin time is used to measure the effect of warfarin, it is performed with standardised reagents (so that it is reproducible from one laboratory to another) and expressed as the international normalised ratio (INR).

The APTT tests the intrinsic system, common pathway and fibrin formation. It is affected by:

- liver disease
- circulating inhibitors of coagulation, including heparin
- DIC.

The APTT is prolonged by deficiency of the vitamin K-dependent clotting factors but less so than the PT. If prolongation of either the PT or APTT is caused by deficiency of a factor, or factors, it can be 'corrected' in the laboratory by mixing normal plasma (replete with those factors) with the patient's plasma. If the prolonged PT or

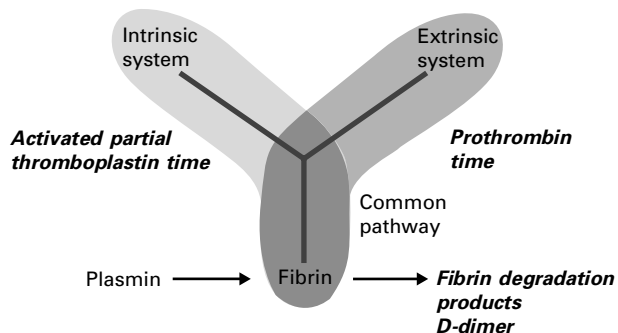


Fig. 67 Tests of coagulation and fibrinolysis.

APTT is caused by an inhibitor, it cannot be 'corrected' in this way. The APTT is more sensitive than the PT to circulating inhibitors and is used to monitor heparin therapy.

The only fibrinolytic test that is widely used is measurement of FDPs. This detects excess fibrinolysis but is so insensitive that it can only detect DIC. There is also a sensitive test for a specific breakdown product of fibrin, **D-dimer**.

Coagulation defects

Inherited coagulation defects

Only von Willebrand disease is common enough to be described here.

Von Willebrand disease

Von Willebrand factor (vWF) is a large protein released by endothelium that plays an important role in platelet adhesion and aggregation; it is also necessary as a carrier for factor VIII in plasma. Von Willebrand disease is by far the commonest inherited disorder of coagulation and a variety of types have now been described. These differ in whether vWF is present in reduced quantity (type I, type III) or is functionally defective (type II, subtypes A, B, M, N). The commonest (type I) is inherited as an autosomal dominant trait. Typically, there is a lifelong history of mild-to-moderate bleeding, usually from mucosal surfaces, but patients may not be aware that they have a bleeding disorder until they undergo surgery or have an accident, when bleeding may be excessive.

Diagnosis and classification of von Willebrand disease is not always easy, because results of laboratory investigations often vary day-to-day. Classically, patients have a prolonged bleeding time and APTT, but both may be normal. Generally, quantitative abnormalities are detected by measuring plasma vWF concentration; functional defects produce abnormal platelet aggregation in response to ristocetin (ristocetin cofactor activity). Treatment depends upon the situation and the type of von Willebrand disease but may involve tranexamic acid (an inhibitor of fibrinolysis), desmopressin (a synthetic analogue of antidiuretic hormone (arginine vasopressin; see p. 299), which causes release of vWF from endothelial stores), vWF concentrate or, occasionally (type IIB), platelet transfusions.

Acquired coagulation defects

The causes of acquired coagulation disorders are listed under the coagulation tests above. You should remember that any GI disease that affects fat absorption may cause vitamin K deficiency. Hepatocellular dysfunction

impairs coagulation factor synthesis to such an extent that the PT is a very sensitive test of hepatocellular failure. Clinical implications of this are considered under liver disease (p. 139).

The effects of warfarin and heparin are discussed in the next section and 'consumption coagulopathy' is discussed under DIC (p. 279). Vitamin K is given parenterally to treat malabsorption and to reverse the action of warfarin. It may also improve clotting factor synthesis in mild liver disease. Otherwise, the treatment for coagulation factor deficiencies is infusion of fresh frozen plasma.

Anticoagulation and fibrinolytic therapy

Anticoagulation and fibrinolytic therapies are primarily used in cardiovascular disease. Anticoagulation is considered here and fibrinolysis under acute myocardial infarction (p. 17).

Heparin

Unfractionated heparin consists of natural polysaccharides of various molecular weights, which have an almost immediate anticoagulant effect. It markedly potentiates the action of antithrombin III and inhibits serine proteases such as activated Factor X (Xa). It has to be given parenterally, and either by continuous infusion or as several injections per day because it has a short half-life. It prevents the formation of new clot and shifts the balance of fibrin formation/lysis in the direction of lysis, but it is not primarily a fibrinolytic drug. It is indicated whenever an immediate anticoagulant effect is required. It may also be used to prevent thrombosis (usually venous). There are two common schedules:

- prophylaxis: heparin 5000 units subcutaneously 8- or 12-hourly
- treatment: heparin 5000 units as an i.v. loading dose followed by 1000–2000 units hourly by continuous i.v. infusion.

Sensitivity to heparin varies from patient to patient. You should check the APTT every 6–12 hours until it is prolonged approximately twofold (depending upon the indication) and stable. Warfarin can be introduced while the patient is on heparin. Heparin should be continued at least until the patient is stabilised on warfarin, and for a minimum of 5 days in venous thrombo-embolism. Prolonged heparin treatment (> 5 days) can cause thrombocytopenia. More prolonged treatment (as in pregnancy) can cause osteoporosis. Unfractionated heparin is now being superseded by the newer low-molecular-weight heparin (LMWH) preparations, which may eventually replace it entirely. These compounds act mainly by inhibition of factor Xa and have a much more predictable effect for a standard dose in dif-

ferent patients. This enables treatment to be given by once or twice daily subcutaneous injections, often without need for laboratory monitoring. It also allows outpatient treatment of venous thrombo-embolism in selected patients.

Warfarin

Warfarin and other coumarins are used for long-term anticoagulation. They take about 48 hours to become effective, governed by the half-lives of the vitamin K-dependent factors. Warfarin is strongly protein bound. Anything that affects this binding will affect sensitivity to it. Liver function and levels of the vitamin K-dependent factors also affect sensitivity to warfarin to such an extent that patients may be 'autoanticoagulated'. For this reason, you must always check the PT before starting therapy. Warfarin is given as loading doses over 2 days and a maintenance dose adjusted to prolong the PT (reported as the INR, see p. 276) by a factor of 1.5–4 (depending upon the indication). The effect of warfarin is unpredictable in alcoholism and liver disease. Important drug interactions are:

- potentiation of warfarin by displacement from protein binding, e.g. salicylates, sulphonamides
- potentiation of warfarin by inhibiting warfarin metabolism, e.g. metronidazole, amiodarone, cimetidine, isoniazid
- potentiation of the effect of warfarin on the liver, e.g. tetracycline
- reduced effect of warfarin by inducing warfarin metabolism, e.g. phenobarbitol, carbamazepine, rifampicin.

Indications for anticoagulation

There are a number of indications for anticoagulation therapy;

- short-term prophylaxis (usually low-dose heparin)
 - prolonged recumbency
 - immobilisation, e.g. traction
 - severe heart failure
 - malignant pelvic disease or impediment to venous flow
 - postoperatively, especially after major lower limb orthopaedic surgery
 - in pregnancy in women at high risk of venous thrombo-embolism.
- acute (usually heparin)
 - venous thrombo-embolism: deep venous thrombosis, pulmonary embolism
 - arterial disease: peripheral arterial thrombosis or embolism, cardiac mural thrombo-embolism, unstable angina
- chronic (usually warfarin)
 - continued treatment of acute indications

- prophylactically in cardiac dysrhythmia (e.g. atrial fibrillation, especially if intermittent or associated with mitral stenosis), poor cardiac function (cardiomyopathy), prosthetic heart valve or vascular prosthesis, after full-thickness anterior myocardial infarct.

Contraindications to anticoagulation

There are both absolute and relative contraindications to anticoagulation therapy:

- absolute
 - cerebral haemorrhage
 - GI, urinary tract or other haemorrhage
 - active peptic ulceration
- relative
 - liver disease
 - alcoholism
 - likely poor compliance
 - concomitant drug therapy likely to cause instability.

Side-effects of anticoagulation

Even if the contraindications listed above are observed, over-anticoagulation may occur and directly cause haemorrhage from the mucosae, into the skin or into the tissues (e.g. cerebral haemorrhage). That should be rare provided the dosage schedule and degree of anticoagulation are appropriately chosen and monitored. Warfarin can be reversed within a few hours by giving i.v. vitamin K or immediately by infusion of fresh frozen plasma or clotting factor concentrate. Heparin action will wear off after about 4 hours but can be reversed rapidly by i.v. protamine.

Sometimes, a decision has to be taken to give anticoagulation therapy to a patient at risk of haemorrhage because the risk of not providing anticoagulation is even more unacceptable. Your responsibilities as a prescriber are to:

- vet *all* patients' suitability for anticoagulation in terms of compliance and understanding
- screen for underlying diseases which may complicate treatment
- advise patients about the risks and benefits of treatment and the need to abstain from alcohol and drugs (including over-the-counter drugs) which may complicate anticoagulation
- ensure adequate monitoring of the INR.

Thrombophilic states

Thrombophilic states may be inherited or acquired.

Inherited thrombophilia

The most common cause of inherited thrombophilia is a point mutation in the gene encoding factor V (factor V

Leiden), which causes resistance to activated protein C and allows thrombosis to progress uninhibited. Antithrombin III deficiency is an autosomal dominant condition that is incompatible with life in its homozygous form. The prevalence of heterozygosity is about 1 per 2000. Protein C and protein S deficiency are similarly inherited but are less common. A prothrombotic variant of the prothrombin gene is also well documented.

Acquired thrombophilia

Antiphospholipid syndrome is an uncommon autoimmune disorder in which an autoantibody triggers coagulation. It may be associated with lupus (lupus anticoagulant) and can cause recurrent fetal loss in young women. Anticardiolipin antibodies are often present. Lesser degrees of thrombophilia occur in any illness that increases fibrinogen levels, in pregnancy and in women taking the oral contraceptive, (which is particularly prone to cause thrombosis in women with the factor V Leiden mutation).

Clinical presentation

Inherited thrombophilia presents with thrombosis at an early age, recurrent thrombosis, thrombosis at unusual sites (e.g. mesenteric vein) and/or a positive family history. The thromboses are usually venous but may be arterial.

Screening for thrombophilia

The following are indications to screen a patient for thrombophilia:

- venous or arterial thrombo-embolism in a young person (aged < 40 years)
- recurrent venous thrombosis
- family history of venous thrombo-embolism
- recurrent fetal loss.

Investigation

You should check a full blood count to exclude polycythaemia (p. 266) and thrombocytosis (p. 274): measure plasma fibrinogen and the PT and APTT. Other investigations include anticardiolipin antibodies and direct measurements of activated protein C resistance, protein C, protein S and antithrombin III. These should be done before starting anticoagulants.

Management

Significant thrombophilia requires anticoagulation to cover high-risk situations (e.g. pregnancy, surgery) and, sometimes, life long.

6.6 Disseminated intravascular coagulation

Learning objectives

You should:

- know the causes of DIC
- understand its clinical effects and treatment.

Pathophysiology

DIC describes widespread activation of the coagulation pathways secondary to a severe illness. There is intravascular fibrin deposition, which may cause microvascular occlusion. Clotting factors and platelets are consumed and may become so depleted that the patient bleeds. Fibrin in the microvasculature may cause mechanical damage to the red cells (microangiopathic haemolysis) leading to haemolytic anaemia, with schistocytes (fragmented cells, p. 258) on the blood film.

Causes

DIC can occur as a result of a number of underlying causes:

- severe sepsis (p. 403)
- incompatible blood transfusion (p. 266)
- trauma
 - particularly crush injury
- systemic diseases
 - disseminated malignancy
 - acute pancreatitis
 - acute promyelocytic leukaemia
- obstetric situations
 - retained fetal products
 - antepartum haemorrhage
 - amniotic fluid embolism.

These factors all have in common the systemic release of toxins which trigger coagulation.

Clinical effects

The dominant clinical features are usually those of the underlying illness. Often a fall in the platelet count is the first sign that the patient is developing DIC. The accom-

panying features of DIC can be worked out if you think system by system of the effects of small vessel occlusion:

- CNS: impaired consciousness, fits, focal neurological signs
- lungs: acute respiratory distress syndrome
- kidneys: acute renal failure
- gut: bowel infarction
- skin: ischaemic ulceration, digital gangrene.

In addition, there may be haemorrhage into any or all of these tissues. Petechial skin haemorrhages, purpura and bleeding from the mucosae may develop.

Investigations

The investigations follow directly from the pathophysiology. The diagnostic features of DIC are:

- thrombocytopenia ($< 100 \times 10^9$ cells/l)
- prolonged PT and APTT
- raised FDPs and D-dimer
- reduced plasma fibrinogen
- signs of microangiopathic haemolytic anaemia (p. 263).

Treatment and natural history

The development of DIC is a bad prognostic sign in a disease that often already has a bad prognosis. The main aim of treatment is to control the underlying disease; without that, treating the DIC is unlikely to be of value. The treatment of DIC consists of replacing the coagulation factors (as fresh frozen plasma) and platelets. This narrative has described severe, fulminating DIC. Low-grade DIC may develop in association with malignant disease, vasculitis and other illnesses. Again, treatment is aimed at the underlying disease, and prognosis is determined by the disease itself more than the DIC.

Other related diseases

Detailed knowledge of the haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura and other such rare diseases is not 'core'. You should simply be aware that the pathophysiological processes of consumption coagulopathy and microangiopathic haemolysis can occur in settings other than classical DIC.

Self-assessment: questions

Multiple choice questions

- The following statements are true:
 - Hypocalcaemia causes prolongation of the prothrombin time
 - The prothrombin time is a sensitive test of hepatocellular dysfunction
 - The activated partial thromboplastin time (APTT) is prolonged by unfractionated heparin therapy
 - The effect of heparin is reversed by vitamin K
 - Deep venous thrombosis can be reliably diagnosed by measuring fibrin degradation products (FDPs)
- In a patient with severe thrombocytopenia:
 - Rectal bleeding is usually the first symptom
 - Examination of the optic fundi should be performed regularly
 - There is a risk of cerebral haemorrhage
 - Corticosteroids are given to prevent haemorrhage, whatever the cause
 - Platelet transfusions can be expected to cause prompt normalisation of the platelet count
- The following may cause a microcytic anaemia:
 - Sickle cell disease
 - The thalassaemias
 - Anaemia of chronic disease
 - Anticonvulsant therapy
 - Haemolysis, whatever the cause
- In lymphoma:
 - If a newly presenting patient has generalised lymphadenopathy, the diagnosis is more likely to be non-Hodgkin's lymphoma than Hodgkin's disease
 - Early stages of Hodgkin's disease can be cured by radiotherapy alone
 - Lymphocyte predominance is a favourable histological sign in Hodgkin's disease
 - Pain in lymph nodes after alcohol is very typical of non-Hodgkin's lymphoma
 - Bone marrow transplantation has greatly improved the prognosis of low-grade non-Hodgkin's lymphoma
- The following statements are true:
 - A neutrophil count of only 0.8×10^9 cells/l is a major risk for infection
 - A neutrophil count in a febrile patient of 25×10^9 cells/l reflects mostly the production of new neutrophils from the bone marrow
 - In a patient with less than 0.1×10^9 cells/l neutrophils and a fever, treatment with antibiotics should await the results of blood culture
 - Neutropenia is common in AIDS
 - Neutropenia can be caused by carbimazole therapy

Case history questions

Case history 1

Your consultant is concerned that a 73-year-old man in atrial fibrillation is at risk of stroke and asks you to anticoagulate him. You are aware that the patient is vaguely confused and the nursing staff on the ward have received a telephone call from a neighbour stating that he has become increasingly reclusive. He has often been noted to be unsteady on his feet and has once been found lying in the road. At visiting time you have a chance to meet his wife to discuss the plan to use anticoagulation therapy and to give further information.

- Suggest two important questions which you should ask
- Name two haematological investigations which it would be appropriate to perform
- Name two possible contraindications to anticoagulation in this case
- If a decision were made to proceed with anticoagulation, describe two pieces of advice that you would give to the patient and his wife

Case history 2

You are called on a Sunday to see a 63-year-old man with non-Hodgkin's lymphoma and a fever of 38.6°C . He is in reverse barrier nursing because his total white cell count is $0.2 \times 10^9/\text{l}$ and his platelets are $15 \times 10^9/\text{l}$ despite daily platelet transfusions. He received intensive chemotherapy (fludarabine) 15 days previously and has been leukopenic for 7 days. You put on your gown, mask and gloves to examine the patient and find that he has no symptoms except those of the fever, mild headache, sweating and an uncomfortable feeling around his bottom.

- Which of the following actions would be appropriate:

- Order a chest X-ray
- Take a blood culture
- Do a blood count
- Do a digital rectal examination
- Start him on oral amoxicillin

The senior nurse on the ward encourages you to start him on the 'usual' antibiotics (ceftazidime and gentamicin). His fever is still elevated 6 hours later despite antibiotics and he looks more toxic. The consultant suggests that you add metronidazole to his regimen. Four days later you are also on call and are asked to see him again. He has had fever up to 38.3°C for 4 days despite ceftazidime, gentamicin, metronidazole and 2 days of vancomycin. He now has a dry cough, in addition to a painful bottom.

- What actions should you now take?
 - Look at his white cell and platelet counts from that morning
 - Arrange for transfer to an intensive care unit (ITU)
 - Examine him again carefully
 - Treat him for a possible fungal infection
 - Do blood cultures, including a fungal blood culture

On examination, you find crackles at the left base that do not clear on coughing and a black and red perianal area about 2 cm across with surrounding erythema.

- Should you:
 - Speak to his consultant at home
 - Arrange a chest X-ray
 - Arrange an induced sputum
 - Call the physiotherapist in
 - Arrange for a special mattress to help his developing pressure sore
- Give a differential diagnosis and your thoughts on management

Table 63 Data obtained for six patients

	A	B	C	D	E	F
Hb (g/dl)	42	78	185	91	87	84
MCV (fl)	123	69	96	85	80	86
WBC ($\times 10^9/l$)	2.3	13.6	15.3	8.7	63.0	1.7
Platelets ($\times 10^9/l$)	60	200	600	180	140	48

Data interpretation

- Suggest a cause for the findings described in Table 63 for each of six patients.
- A 22-year-old patient is admitted to hospital 48 hours after a paracetamol overdose, complaining of haematuria. The prothrombin time is 60 s (control 18 s). What is the likely diagnosis?
- A 70-year-old man is referred to hospital because he is anaemic (Hb 82 g/dl, MCV 90 fl, platelets 150×10^9 cells/l ESR 130 mm/h. Name a possible haematological diagnosis. What biochemical tests should be performed?

Picture questions

- This skull radiograph (Fig. 68) was taken from a 73-year-old patient who presented in acute renal failure.
 - What abnormality do you see?
 - How could the skull radiograph be relevant to the renal failure? Be as precise as you can.
 - Name one rapid biochemical test which might establish a link.
 - What would be your immediate management?

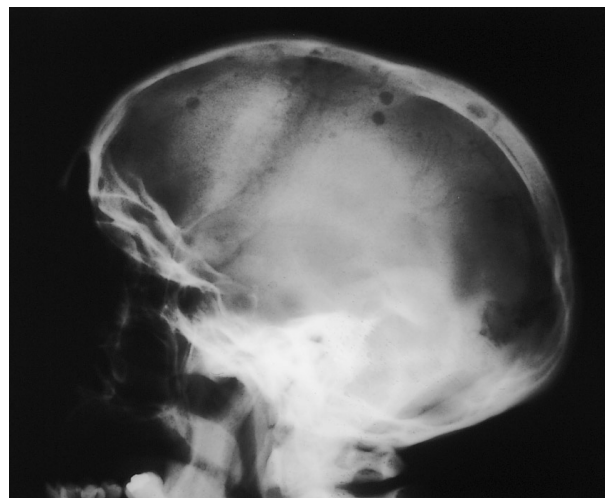


Fig. 68 A skull radiograph of a patient in acute renal failure.

- A previously fit 28-year-old woman has lost weight. She has night sweats, pruritus and weight loss. She has noticed pain in the cervical region after drinking alcohol. Her GP arranged a chest radiograph which was thought to show hilar enlargement. Figure 69 shows thoracic computed scans before (a) and after (b) an intravenous contrast agent. T, trachea; A, aortic arch, B, left brachiocephalic vein.
 - What abnormality is shown?
 - Suggest, in order of likelihood, a differential diagnosis

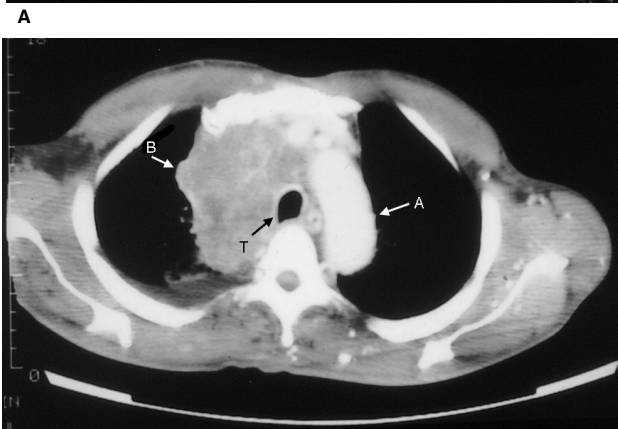
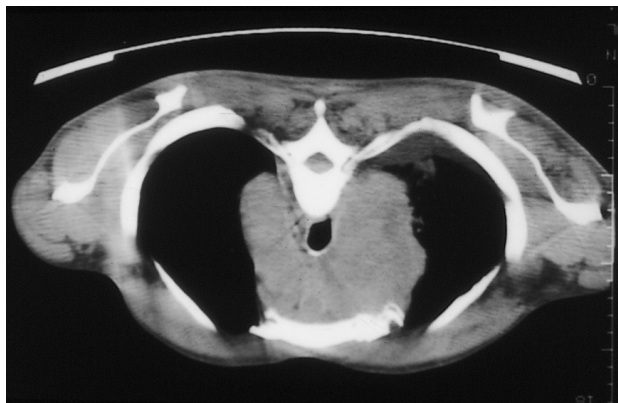


Fig. 69 Thoracic computed tomographic scans before (a) and after (b) an intravenous contrast agent.

Viva questions

1. What complications might you expect in a patient with aplastic anaemia and how would you prevent them?
2. How would you decide whether to use antiplatelet or anticoagulant therapy?

Extended matched questions

EMQ 1

Theme: Haematological diagnoses

Options:

1. Hodgkin's disease
2. Acute lymphoblastic leukaemia
3. Myelofibrosis
4. Chronic granulocytic (myeloid) leukaemia
5. von Willebrand's disease
6. Iron-deficiency anaemia
7. Thalassemia trait
8. Anaemia of chronic disease
9. Hereditary spherocytosis
10. Acute myeloid leukaemia
11. Pernicious anaemia
12. Non-Hodgkin's lymphoma

13. Multiple myeloma

For each of the following patients, select the most likely final diagnosis given the clinical feature(s) (more than one may be correct). Each item can be used once, more than once, or not at all.

- A. An anaemic elderly patient with a palpable spleen has a 'dry tap' on attempted bone marrow aspiration.
- B. A 35-year-old woman with weight loss, fever and pruritis has masses of large lymph nodes only in the neck and axillae.
- C. A 53-year-old man has an increased count of neutrophil leucocytes showing the 'Philadelphia chromosome'.
- D. An otherwise healthy woman with menorrhagia and mild anaemia has a reduced mean red cell volume.
- E. An elderly patient with acute renal failure has severe hypercalcaemia.

EMQ 2

Theme: Drug treatments

Options:

1. Unfractionated heparin
2. Dipyridamole
3. Reteplase
4. Sinthron
5. Aspirin
6. Warfarin adjusted to achieve an INR ≥ 2
7. Intravenous streptokinase
8. Low-molecular-weight heparin
9. Intranasal prostacyclin

For each of the following patients not currently on any of the drugs on the list above, select the most appropriate drug (more than one may be correct). Each item can be used once, more than once, or not at all.

- A. A 65-year-old woman with repeated carotid transient ischaemic attacks (TIAs) who has a $< 70\%$ stenosis of the internal carotid artery and intimal plaque seen on carotid doppler.
- B. A 40-year-old man newly admitted with an acute pulmonary embolism 14 days after fracturing his femur.
- C. A 59-year-old patient admitted to the coronary care unit with unstable angina on no treatment.
- D. A 72-year-old man with atrial fibrillation and a small stroke, which resolved completely within 5 days, whose echocardiogram shows left atrial thrombus.
- E. An 88-year-old man with early dementia and in atrial fibrillation who is to be discharged to live alone having been admitted after a fall.

Objective structured clinical examination (OSCE)

This is a 5 minute station with a normal volunteer on a couch.

Examiner: This 35-year-old man has been found to have

a mediastinal mass and lymphoma is suspected. Please examine him.

After you have examined him:

Examiner: What features of any lymph nodes found on examination would help your differential diagnosis?

Self-assessment: answers

Multiple choice answers

- False.** This is true in vitro but hypocalcaemia severe enough to have the same effect in vivo would be incompatible with life.
 - True.** Because hepatocellular dysfunction impairs the synthesis of vitamin K-dependent clotting factors.
 - True.** This is used as a measure of heparinisation.
 - False.** Vitamin K reverses the action of warfarin; protamine reverses heparin action.
 - False.** FDPs are raised by massive intravascular fibrin formation, as in disseminated intravascular coagulation (DIC), and may be increased in thrombotic conditions but are not sensitive or specific enough to be a useful diagnostic test. Measurement of D-dimer is sensitive enough to detect venous thrombosis but is not specific.
- False.** A purpuric rash or easy bruising on the limbs or trunk are more likely first symptoms.
 - True.** The appearance of retinal haemorrhages indicates that the patient is at risk of haemorrhage.
 - True.**
 - False.** Corticosteroids are given to some patients with idiopathic thrombocytopenic purpura but thrombocytopenia is often not steroid responsive.
 - False.** The goal is to prevent bleeding, not to normalise the blood count.
- False.**
 - True.** Thalassaemia is one of the causes of microcytosis.
 - True.**
 - False.** Anticonvulsants may cause macrocytosis.
 - False.** Haemolysis increases the reticulocyte count which, since reticulocytes are large, causes macrocytosis.
- True.** In Hodgkin's disease, the lymphadenopathy is often confined to a single site, most commonly the neck, at presentation.
 - True.**
 - True.**
 - False.** Alcohol-related pain is typical of Hodgkin's disease.
 - False.** There is no evidence for this in clinical trials to date.
- False.** A minor risk. It is when the count falls below 0.5×10^9 cells/l and particularly 10^9 cells/l that the risk becomes major.
 - False.** Mostly neutrophil release from the marginating pool. The left shift (or band forms) is the proportion of new neutrophils from the marrow.
 - False.** Immediate intravenous broad-spectrum antibiotics are indicated.
 - True.** Especially caused by the drugs zidovudine and ganciclovir.
 - True.** Neutropenia occurs in 1:10 000 patients treated with carbimazole for thyrotoxicosis.

Case history answers

Case history 1

- Whilst anticoagulation is indicated to prevent cerebral embolism in patients with atrial fibrillation, you must not initiate it unless you are sure it will be safe. Age, in itself, is not a contraindication, but there are aspects of the history which suggest there are other contraindications. There are strong hints that he may be abusing alcohol. The confusion is worrying because someone who is having falls and becomes confused could have a subdural haematoma, which is an absolute contraindication to anticoagulation. You should ask about:

 - his alcohol intake
 - dyspepsia or history of blood loss
 - his likelihood of taking tablets and attending for anticoagulant monitoring reliably.
- You should measure his prothrombin time *before starting anticoagulants*; autoanticoagulation is common and would affect your choice of loading dose. It would also increase your anxiety about the possibility of alcohol abuse (prolonging the PT by causing hepatocellular damage). You should also check the haemoglobin concentration; anaemia would be a relative contraindication to anticoagulation or should, at least, be investigated before anticoagulation.
- These might include

 - alcohol abuse
 - dementia (if it would interfere with compliance)
 - difficulty attending for anticoagulant monitoring
 - inability of wife or carer to supervise treatment
 - history of GI bleeding or anaemia
 - history of cerebral haemorrhage
 - concomitant drug therapy affecting the stability of warfarin levels
 - falls.

4. Advice would include:

- avoid alcohol
- avoid non-steroidal analgesics and aspirin
- report any excessive or unusual bleeding immediately
- attend regularly for anticoagulant monitoring.

You should give the patient and his wife an information sheet about anticoagulants, listing drugs to be avoided.

Case history 2

1. a. **True.** This is always appropriate in febrile neutropenia, even in the absence of chest signs or symptoms.
 - b. **True.** Very important.
 - c. **False.** Unnecessary if done that morning, which it will have been to see whether platelet transfusions were required.
 - d. **False.** You must inspect his anal area as he has a symptom there, but a formal rectal examination is not appropriate as it may cause bacteraemia.
 - e. **False.** Not appropriate; i.v. therapy required with broader coverage.
2. a. **True.**
 - b. **False.** He is not that ill and you would take him out of protective isolation. In fact, even if he were so ill and requiring ventilation, neutropenic leukaemic patients do so badly in ITU that it is used rarely.
 - c. **True.** Always true in this group of patients. Especially mouth, chest, skin and rectal area (p. 268).
 - d. **True.** Candidaemia or invasive aspergillosis are now more likely. This group of patients with persistent fever during neutropenia have a 30% mortality, mostly as a result of fungal infection.
 - e. **True.** It is always worth repeating blood cultures, even though he is on antibiotics, as these patients get breakthrough bacteraemia.
3. a. **True.** Now you have a complex problem with two possible sites of infection.
 - b. **True.** If one was not done that day. A CT scan of his chest is a much better investigation and should be done within the next 24 hours.
 - c. **False.** Not useful in febrile neutropenia (unlike AIDS), although pneumocystis pneumonia is a diagnostic possibility because fludarabine therapy 'paralyses' T cells.
 - d. **False.** As the cough is not productive, of no benefit.
 - e. **False.** His lesion is almost certainly not a pressure sore but a developing infection called ichthyma gangrenosum (*Pseudomonas aeruginosa*).

4. He probably has two focal infections: one in his lungs and the other perirectally. The perirectal infection is likely to be caused by *Pseudomonas aeruginosa*, other bacteria including anaerobes, *Aspergillus* or mucormycosis. His lung disease may be caused by any of these or other bacteria or possibly *Pneumocystis*. He needs large doses of antifungals (amphotericin), a CT scan of the lung, which is helpful diagnostically, bronchoscopy, with lavage, to obtain material for microscopy and culture, and a biopsy of his rectal lesion, all as soon as possible.

Data interpretation answers

1. **Patient A.** This is a fairly typical picture of megaloblastic anaemia caused by vitamin B₁₂ or folate deficiency with severe macrocytosis, leucopenia and thrombocytopenia; hypersegmented neutrophils on the blood film would confirm the diagnosis, as would bone marrow aspiration although this is not done as a routine. Haematinics should be measured.

Patient B. This is a moderately severe microcytic anaemia (the differential diagnosis is given on p. 260). Iron deficiency is the most likely cause. The leucocytosis may be caused by infection or inflammation but could signify acute or subacute blood loss, a possible cause for the iron deficiency.

Patient C. There is erythrocytosis, thrombocytosis and leucocytosis, suggestive of polycythaemia vera. The red cell mass is likely to be increased and splenomegaly may be present.

Patient D. There is a normocytic anaemia with normal white cell and platelet counts. This would be typical of the anaemia of chronic disease (e.g. renal failure) but could also be caused by a mixed deficiency. This would be suggested by an increased: red cell distribution width (RDW) and a 'dimorphic' blood film. You should examine and investigate the patient for an underlying disease.

Patient E. Here, there is a normochromic anaemia with mild thrombocytopenia, but the striking abnormality is the marked leucocytosis; this is typical of a chronic leukaemia. A differential white cell count and blood film would be crucial.

Patient F. This shows moderate pancytopenia and could be seen in a patient with acute leukaemia, hypoplastic anaemia or after chemotherapy (see p. 262 for a fuller list of causes).

2. Prolongation of the prothrombin time may be caused by warfarin, consumption of clotting factors as in DIC, vitamin K deficiency or deficiency of the vitamin K-dependent clotting factors owing to liver disease. At 48 hours after a massive paracetamol

overdose is about the time when hepatocellular damage becomes apparent, and the prothrombin time is quite a sensitive test for this. The likely diagnosis is acute hepatocellular necrosis caused by paracetamol.

3. An extremely high ESR is usually caused by multiple myeloma, giant cell arteritis or chronic/severe infection/inflammation. This patient also has a moderate normochromic anaemia. Multiple myeloma is a likely diagnosis. Renal failure and hypercalcaemia are common in myeloma. You should measure plasma urea, creatinine and calcium. The definitive diagnosis is made by plasma and urine immunoelectrophoresis, bone marrow examination and skeletal survey.

Picture answers

1. a. Figure 68 shows multiple 'punched-out' lesions, in keeping with multiple myeloma or another cause of osteolytic metastases.
 - b. Hypercalcaemia is a common cause of acute renal failure in multiple myeloma. Volume depletion is an important and reversible effect of hypercalcaemia. 'Myeloma kidney' may cause renal failure without hypercalcaemia. This is because of tubular damage by the paraprotein, secondary hyperuricaemia, amyloidosis and infection.
 - c. With the history given, you should immediately measure serum calcium. You should also arrange serum and urine immunoelectrophoresis to identify a paraprotein but that is not an emergency investigation.
 - d. You should assess the patient's volume status, using a central venous pressure line if necessary, and give saline to increase urinary calcium excretion. Corticosteroid and/or bisphosphonate therapy may be needed as second-line treatment for hypercalcaemia.
2. a. There is a large soft tissue attenuation mass within the mediastinum abutting the trachea and aortic arch and compressing the superior vena cava (which cannot be seen). This is almost certainly a large lymph node mass.
 - b. Although you are not told that she has cervical lymphadenopathy, the scenario makes it very likely that she is describing alcohol-related lymph node pain, which is very specific to Hodgkin's disease. The combination with mediastinal lymphadenopathy makes the diagnosis of Hodgkin's by far the most likely diagnosis. Other causes of a mediastinal soft tissue mass include non-Hodgkin's lymphoma (not associated with

alcohol-related pain) or sarcoidosis (the second most likely possibility in this case). Unlikely causes are tuberculosis, retrosternal thyroid (unlikely), thymic tumour, dermoid or lung cancer nodes (especially small cell).

Viva answers

1. Aplastic anaemia usually affects the red cells, white cells and platelets. Patients are anaemic, thrombocytopenic and neutropenic. The anaemia may be symptomatic; it may precipitate symptoms of coronary, cerebrovascular or peripheral vascular ischaemia and may cause heart failure. Thrombocytopenia may cause purpura, bruising and – in severe cases – mucosal or GI bleeding or cerebral haemorrhage. Neutropenia causes mouth ulceration, perineal infection and susceptibility to opportunistic infection. Anaemia is treated with periodic blood transfusions. Platelet transfusions are given if the patient is severely thrombocytopenic and at risk of haemorrhage. Granulocyte transfusions are relatively ineffective and so the treatment of neutropenia is prophylaxis against infection and aggressive treatment of the earliest signs of it.
2. The choice of antiplatelet or anticoagulation therapy depends upon the pathophysiology of the disease (see p. 275).

Extended matched answers

EMQ 1

- A. 3. The dry tap suggests myelofibrosis and splenomegaly is characteristic.
- B. 1. This patient has 'B' symptoms and pathological lymphadenopathy; the fact that it is in adjacent areas (on only one side of the diaphragm) suggests Hodgkin's disease.
- C. 4. The Philadelphia chromosome is pathognomonic of chronic granulocytic leukaemia
- D. 6. Either thalassaemia trait or chronic disease could also give a microcytic anaemia, but the clinical details strongly favour iron deficiency
- E. 13. Of course there are many causes of renal failure, but the heading makes it clear that you should be making a haematological diagnosis; myeloma is the haematological disease most closely associated with renal failure.

EMQ 2

- A. 5. TIAs are caused by platelet emboli so aspirin is the treatment of choice.

- B. 8. Fibrinolytic therapy is of no proven value, and may cause him to bleed into the fracture site. He will certainly need to take warfarin but must be treated with heparin first. Clinical trials consistently show low-molecular-weight heparin to be superior to unfractionated heparin so that should be your choice.
- C. 8, 5. Either aspirin or heparin would be correct, but low-molecular-weight heparin is the better answer.
- D. 6 or 4. Unlike carotid TIAs, arterial thromboembolism from cardiac clot should be treated with warfarin (or sinthron, although it is less commonly used). Depending on your perception of the danger of recurrence, you might give heparin, but medium-to-long term warfarin is the mainstay of preventing recurrence.
- E. 5. Warfarin is indicated for preventing cerebral embolism in atrial fibrillation unless there are contraindications. Age, falls and concern about this patient's ability to care for himself are relative contraindications. Depending on likely compliance, you might prescribe aspirin.

Response to OSCE

Do not waffle on about 'taking a history' because your instruction is clear and do not attempt to perform a 'general' physical examination. You must use your knowledge to focus the examination on examining:

- all possible sites of lymphadenopathy: the epitrochlear region of the elbow, neck, axillae, and groins
- the abdomen for para-aortic nodes (by deep palpation), hepatomegaly and splenomegaly
- the conjunctivae for anaemia.

It is reasonable to examine the chest if you have time, but make less of a play of this than the parts of the examination listed above because chest examination may well be normal, and these other features will be much more informative, whether negative or positive.

The character and distribution of the nodes are both important; see page 257.