SECTION 2

Communication

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CHAPTER 4

The blood

ANIMATIONS

Blood is a fluid connective tissue. It circulates constantly around the body, allowing constant communication between tissues distant from each other. It transports:

- oxygen
- nutrients
- hormones
- heat
- protective substances
- clotting factors.

Blood is composed of a clear, straw-coloured, watery fluid called *plasma* in which several different types of blood cell are suspended. Plasma normally constitutes 55% of the volume of blood and the cell fraction 45%. Blood cells and plasma can be separated by centrifugation (spinning) or by gravity when blood is allowed to stand (Fig. 4.1A). The cells are heavier than plasma and sink to the bottom of any sample.

Blood makes up about 7% of body weight (about 5.6 litres in a 70 kg man). This proportion is less in women and considerably greater in children, gradually decreasing until the adult level is reached.

Blood in the blood vessels is always in motion because of the pumping action of the heart. The continual flow maintains a fairly constant environment for body cells. Blood volume and the concentration of its many constituents are kept within narrow limits by homeostatic mechanisms. Heat produced from metabolically active organs, such as working skeletal muscles and the liver, is distributed around the body by the bloodstream, contributing to maintenance of core body temperature.

The first part of the chapter describes normal blood physiology, and the later sections are concerned with some disorders of the blood. Effects of ageing on white blood cell function are described in Chapter 15.

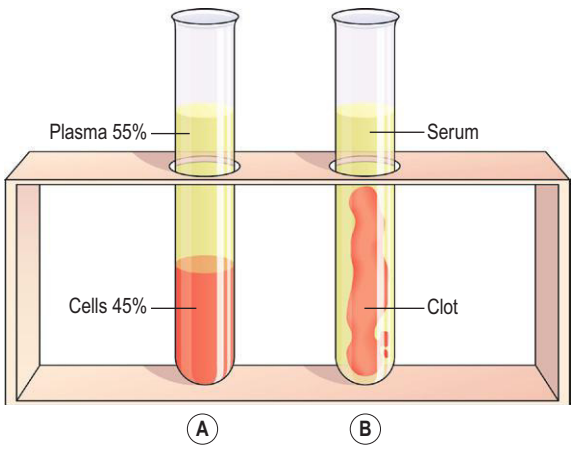


Figure 4.1 A. The proportions of blood cells and plasma in whole blood separated by gravity. **B.** A blood clot in serum.

Plasma

Learning outcomes

After studying this section, you should be able to:

- list the constituents of plasma
- describe their functions

The constituents of plasma are water (90–92%) and dissolved and suspended substances, including:

- plasma proteins
- inorganic salts
- nutrients, principally from digested foods
- waste materials
- hormones
- gases.

Plasma proteins

Plasma proteins, which make up about 7% of plasma, are normally retained within the blood, because they are too big to escape through the capillary pores into the tissues. They are largely responsible for creating the osmotic pressure of blood (p. 86), which keeps plasma fluid within the circulation. If plasma protein levels fall, because of either reduced production or loss from the blood vessels, osmotic pressure is also reduced, and fluid moves into the tissues (oedema) and body cavities.

Plasma viscosity (thickness) is due to plasma proteins, mainly albumin and fibrinogen. Plasma proteins, with the exception of immunoglobulins, are formed in the liver.

Albumins. These are the most abundant plasma proteins (about 60% of total) and their main function is to maintain normal plasma osmotic pressure. Albumins also act as carrier molecules for free fatty acids, some drugs and steroid hormones.

Globulins. Their main functions are:

- as *antibodies* (immunoglobulins), which are complex proteins produced by lymphocytes that play an important part in immunity. They bind to, and neutralise, foreign materials (antigens) such as micro-organisms (see also p. 381).
- transportation of some hormones and mineral salts, e.g. thyroglobulin, carries the hormone thyroxine and transferrin carries the mineral iron
- inhibition of some proteolytic enzymes, e.g. α_2 macroglobulin inhibits trypsin activity.

Clotting factors. These are responsible for coagulation of blood (p. 71). *Serum* is plasma from which clotting factors have been removed (Fig. 4.1B). The most abundant clotting factor is *fibrinogen.*

Electrolytes

These have a range of functions, including muscle contraction (e.g. Ca^{2+}), transmission of nerve impulses (e.g. Ca^{2+} and Na^{+}), and maintenance of acid–base balance (e.g. phosphate, PO_4^{3-}). The pH of blood is maintained between 7.35 and 7.45 (slightly alkaline) by an ongoing buffering system (p. 25).

Nutrients

The products of digestion, e.g. glucose, amino acids, fatty acids and glycerol, are absorbed from the alimentary tract. Together with mineral salts and vitamins they are used by body cells for energy, heat, repair and replacement, and for the synthesis of other blood components and body secretions.

Waste products

Urea, creatinine and uric acid are the waste products of protein metabolism. They are formed in the liver and carried in blood to the kidneys for excretion. Carbon dioxide from tissue metabolism is transported to the lungs for excretion.

Hormones (see Ch. 9)

These are chemical messengers synthesised by endocrine glands. Hormones pass directly from the endocrine cells into the blood, which transports them to their target tissues and organs elsewhere in the body, where they influence cellular activity.

Gases

Oxygen, carbon dioxide and nitrogen are transported round the body dissolved in plasma. Oxygen and carbon dioxide are also transported in combination with haemoglobin in red blood cells (p. 65). Most oxygen is carried in combination with haemoglobin and most carbon dioxide as bicarbonate ions dissolved in plasma (p. 260). Atmospheric nitrogen enters the body in the same way as other gases and is present in plasma but it has no physiological function.

Cellular content of blood 4.1

Learning outcomes

After studying this section, you should be able to:

- discuss the structure, function and formation of red blood cells, including the systems used in medicine to classify the different types
- discuss the functions and formation of the different types of white blood cell
- outline the role of platelets in blood clotting.

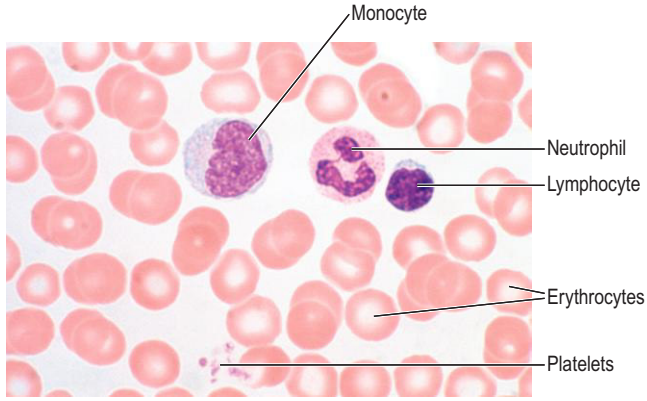


Figure 4.2 A blood smear, showing erythrocytes, a monocyte, a neutrophil, a lymphocyte and a platelet.

There are three types of blood cell (Fig. 4.2).

- erythrocytes (red cells)
- platelets (thrombocytes)
- leukocytes (white cells).

Blood cells are synthesised mainly in red bone marrow. Some lymphocytes, additionally, are produced in lymphoid tissue. In the bone marrow, all blood cells originate from *pluripotent* (i.e. capable of developing into one of a number of cell types) *stem cells* and go through several developmental stages before entering the blood. Different types of blood cell follow separate lines of development. The process of blood cell formation is called *haemopoiesis* (Fig. 4.3).

For the first few years of life, red marrow occupies the entire bone capacity and, over the next 20 years, is gradually replaced by fatty yellow marrow that has no haemopoietic function. In adults, haemopoiesis in the skeleton is confined to flat bones, irregular bones and the ends (*epiphyses*) of long bones, the main sites being the sternum, ribs, pelvis and skull.

Erythrocytes (red blood cells) 4.2

Red blood cells are by far the most abundant type of blood cell; 99% of all blood cells are erythrocytes (Fig. 4.2). They are biconcave discs with no nucleus, and their diameter is about 7 µm (Fig. 4.4). Their main function is in gas transport, mainly of oxygen, but they also carry some carbon dioxide. Their characteristic shape is suited to their purpose; the biconcavity increases their surface area for gas exchange, and the thinness of the central portion allows fast entry and exit of gases. The cells are flexible so they can squeeze through narrow capillaries, and contain no intracellular organelles, leaving more room for haemoglobin, the large pigmented protein responsible for gas transport.

Measurements of red cell numbers, volume and haemoglobin content are routine and useful assessments

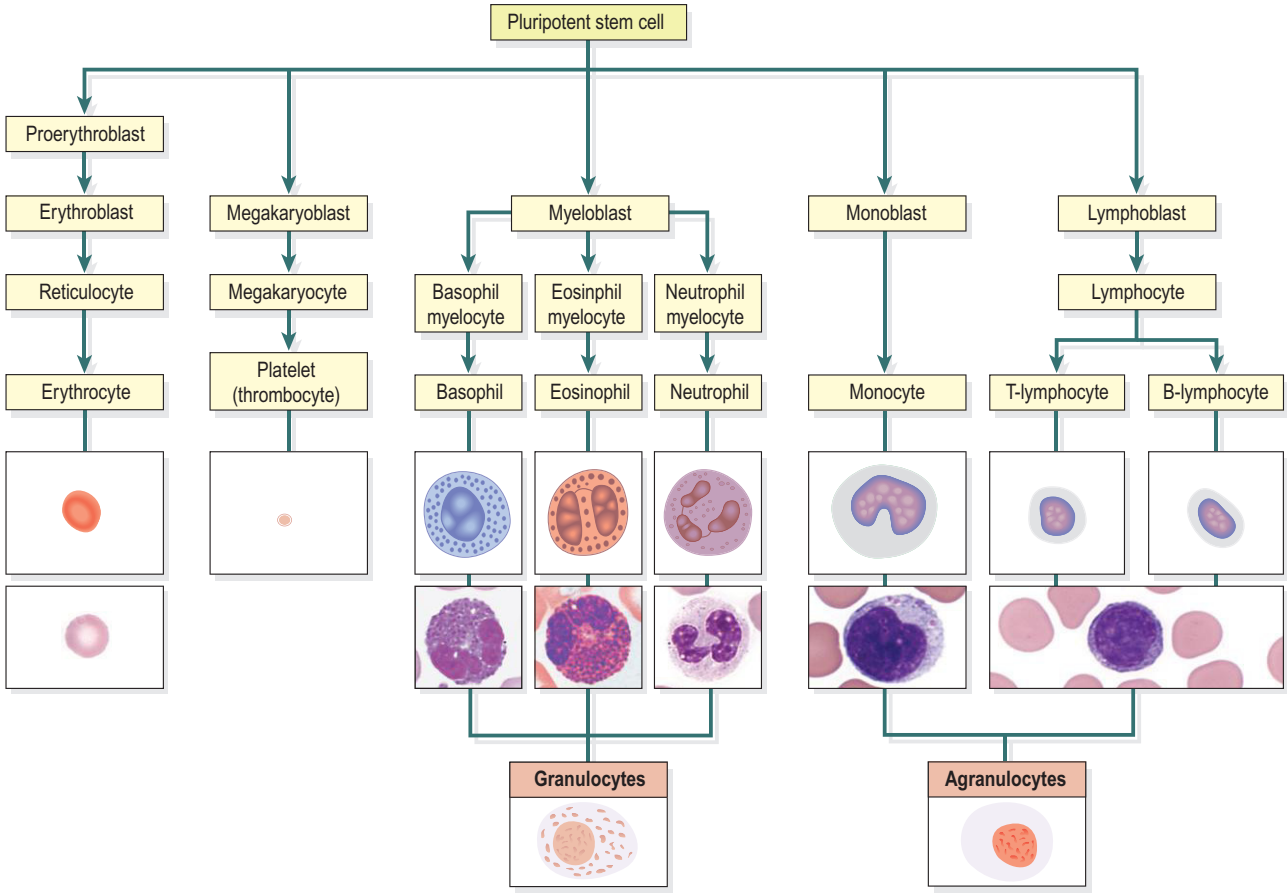


Figure 4.3 Haemopoiesis: stages in the development of blood cells.

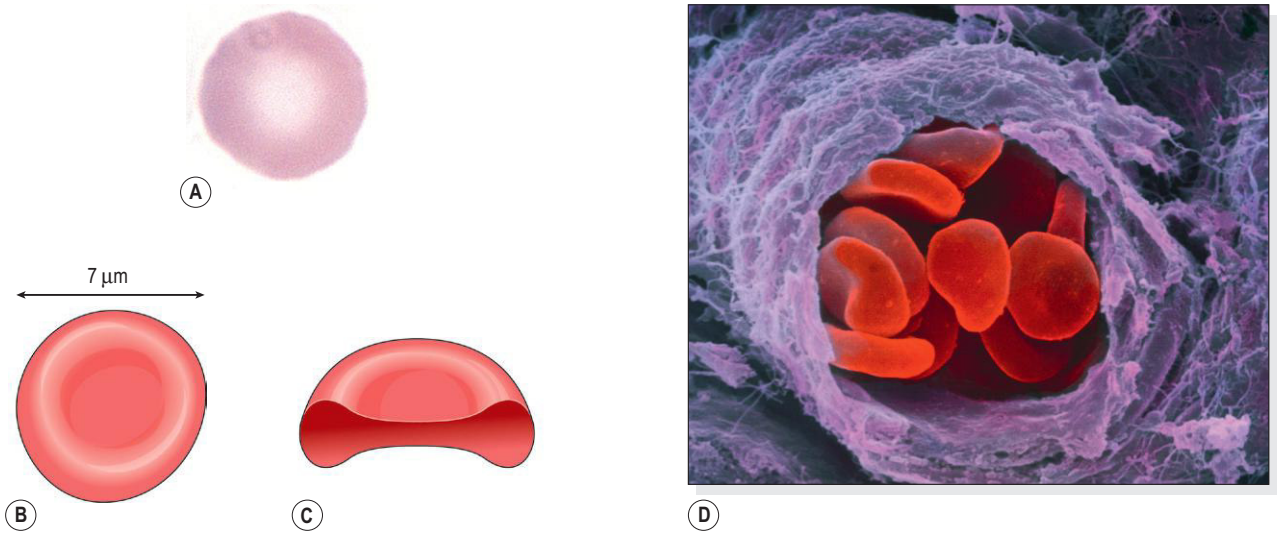


Figure 4.4 The red blood cell. A. Under the light microscope. **B.** Drawn from the front. **C.** Drawn in section. **D.** Coloured scanning electron micrograph of a group of red blood cells travelling along an arteriole.

Table 4.1 Erythrocytes – normal values

Measure	Normal values
Erythrocyte count – number of erythrocytes per litre, or cubic millilitre, (mm^3) of blood	Male: 4.5×10^{12}/L to 6.5×10^{12}/L (4.5–6.5 million/mm^3) Female: 3.8×10^{12}/L to 5.8×10^{12}/L (3.8–5.8 million/mm^3)
Packed cell volume (PCV, haematocrit) – the volume of red cells in 1 L or mm^3 of blood	0.40–0.55 L/L
Mean cell volume (MCV) – the volume of an average cell, measured in femtolitres (1 fL = 10^{-15} litre)	80–96 fL
Haemoglobin – the weight of haemoglobin in whole blood, measured in grams/100 mL blood	Male: 13–18 g/100 mL Female: 11.5–16.5 g/100 mL
Mean cell haemoglobin (MCH) – the average amount of haemoglobin per cell, measured in picograms (1 pg = 10^{-12} gram)	27–32 pg/cell
Mean cell haemoglobin concentration (MCHC) – the weight of haemoglobin in 100 mL of red cells	30–35 g/100 mL of red cells

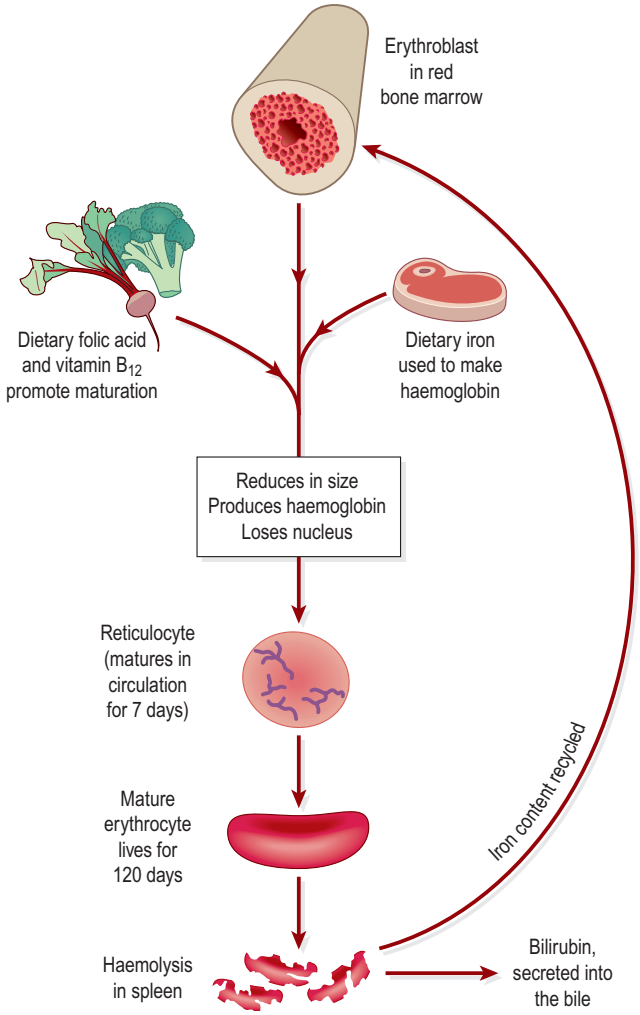


Figure 4.5 Life cycle of the erythrocyte.

made in clinical practice (Table 4.1). The symbols in brackets are the abbreviations commonly used in laboratory reports.

Life span and function of erythrocytes

Because they have no nucleus, erythrocytes cannot divide and so need to be continually replaced by new cells from the red bone marrow, which is present in the ends of long bones and in flat and irregular bones. They pass through several stages of development before entering the blood. Their life span in the circulation is about 120 days. There are approximately 30 trillion (10^{14}) red blood cells in the average human body, about 25% of the body's total cell count, and around 1%, mainly older cells, are cleared and destroyed daily.

The process of development of red blood cells from stem cells takes about 7 days and is called *erythropoiesis* (Fig. 4.3). The immature cells are released into the bloodstream as reticulocytes, and mature into erythrocytes over a day or two within the circulation. During this time, they lose their nucleus and therefore become incapable of division (Fig. 4.5).

Both vitamin B_{12} and folic acid are required for red blood cell synthesis. They are absorbed in the intestines, although vitamin B_{12} must be bound to intrinsic factor (p. 300) to allow absorption to take place. Both vitamins are present in dairy products, meat and green vegetables. The liver usually contains substantial stores of vitamin B_{12}, several years' worth, but signs of folic acid deficiency appear within a few months. The life cycle of the erythrocyte is shown in Figure 4.5.

Haemoglobin

Haemoglobin is a large, complex molecule containing a globular protein (globin) and a pigmented iron-containing complex called haem. Each haemoglobin molecule contains four globin chains and four haem units, each with one atom of iron (Fig. 4.6). As each atom of iron can combine with an oxygen molecule, this means that a single haemoglobin molecule can carry up to four molecules of oxygen. An average red blood cell carries about 280 million haemoglobin molecules, giving each cell a

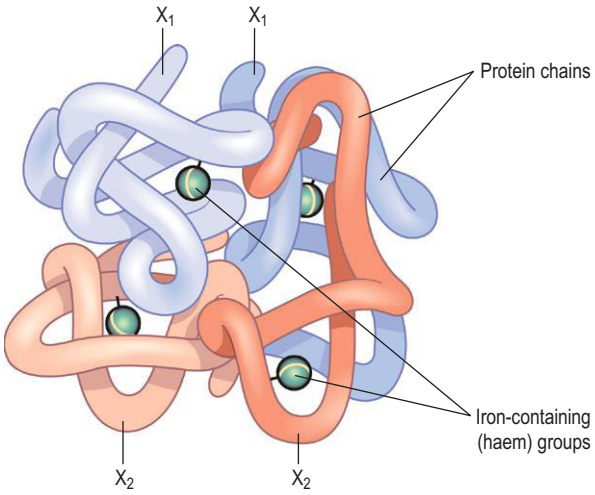


Figure 4.6 The haemoglobin molecule.

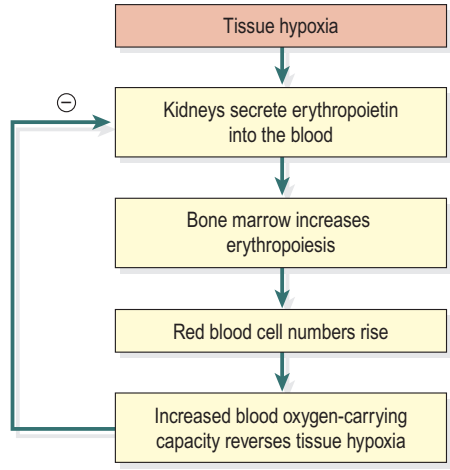


Figure 4.7 Control of erythropoiesis: the role of erythropoietin.

theoretical oxygen-carrying capacity of over a billion oxygen molecules!

Iron is carried in the bloodstream bound to its transport protein, *transferrin*, and stored in the liver. Normal red cell production requires a steady supply of iron. Absorption of iron from the alimentary canal is very slow, even if the diet is rich in iron, meaning that iron deficiency can readily occur if losses exceed intake.

Oxygen transport

When all four oxygen-binding sites on a haemoglobin molecule are full, it is described as *saturated*. Haemoglobin binds reversibly to oxygen to form oxyhaemoglobin, according to the equation:

$$\underset{(Hb)}{\text{Haemoglobin}} + \underset{(O_2)}{\text{oxygen}} \leftrightarrow \underset{(HbO)}{\text{oxyhaemoglobin}}$$

As the oxygen content of blood increases, its colour changes too. Blood rich in oxygen (usually arterial blood) is bright red because of the high levels of oxyhaemoglobin it contains, compared with blood with lower oxygen levels (usually venous blood), which is dark bluish in colour because it is not saturated.

The association of oxygen with haemoglobin is a loose one, so that oxyhaemoglobin releases its oxygen readily, especially under certain conditions.

Low pH Metabolically active tissues, e.g. exercising muscle, release acid waste products, and so the local pH falls. Under these conditions, oxyhaemoglobin readily breaks down, giving up additional oxygen for tissue use.

Low oxygen levels (hypoxia) Where oxygen levels are low, oxyhaemoglobin breaks down, releasing oxygen. In the tissues, which constantly consume oxygen, oxygen levels are always low. This encourages oxyhaemoglobin to release its oxygen to the cells. In addition, the lower the tissue oxygen level, the more oxygen is released, meaning that as tissue oxygen demand rises, so does the supply to match it. On the other hand, when oxygen levels are high, as they are in the lungs, oxyhaemoglobin formation is favoured.

Temperature Actively metabolising tissues, which have higher than normal oxygen needs, are warmer than less active ones, which drive the equation above to the left, increasing oxygen release. This ensures that very active tissues receive a higher oxygen supply than less active ones. In the lungs, where the alveoli are exposed to inspired air, the temperature is lower, favouring oxyhaemoglobin formation.

Control of erythropoiesis

Red cell numbers remain fairly constant, because the bone marrow produces erythrocytes at the rate at which they are destroyed. This is due to a homeostatic negative feedback mechanism. The hormone that regulates red blood cell production is *erythropoietin*, produced mainly by the kidney.

The primary stimulus to increased erythropoiesis is *hypoxia*, i.e. deficient oxygen supply to body cells.

Hypoxia can result from anaemia, low blood volume, poor blood flow, reduced oxygen content of inspired air (as at altitude) or lung disease. Each of these leads to erythropoietin production in an attempt to restore oxygen supplies to the tissues.

Erythropoietin stimulates an increase in the production of proerythroblasts and the release of more reticulocytes into the blood. It also speeds up reticulocyte maturation. These changes increase the oxygen-carrying capacity of the blood and reverse tissue hypoxia, the original stimulus. When the tissue hypoxia is overcome, erythropoietin production declines (Fig. 4.7). When erythropoietin levels are low, red cell formation does not take place even in the presence of hypoxia, and anaemia (the

inability of the blood to carry adequate oxygen for body needs) develops.

Destruction of erythrocytes

The life span of erythrocytes (Fig. 4.5) is about 120 days and their breakdown, or *haemolysis*, is carried out by *phagocytic reticuloendothelial cells*. These cells are found in many tissues but the main sites of haemolysis are the spleen, bone marrow and liver. As erythrocytes age, their cell membranes become more fragile and so more susceptible to haemolysis. Iron released by haemolysis is retained in the body and reused in the bone marrow to form new haemoglobin molecules. *Biliverdin* is formed from the haem part of the haemoglobin. It is almost completely reduced to the yellow pigment *bilirubin*, before being bound to plasma globulin and transported to the liver (Fig. 4.5, see also Fig. 12.37, p. 311). In the liver it is changed from a fat-soluble to a water-soluble form to be excreted as a constituent of bile.

Blood groups 4.3

Early attempts to transfuse blood from one person to another or from animals to humans were only rarely successful, the recipient of the blood usually becoming very ill or dying. It is now known that the surface of red blood cells carries a range of different proteins (called antigens) that can stimulate an immune response if transferred from one individual (the donor) into the bloodstream of an incompatible individual. These antigens, which are inherited, determine the individual's *blood group*. In addition, individuals can make antibodies to these antigens, but not to their own type of antigen, since if they did the antigens and antibodies would react, causing a potentially fatal *transfusion reaction*.

If individuals are transfused with blood of the same group, i.e. possessing the same antigens on the surface of the cells, their immune system will not recognise them as foreign and will not reject them. However, if they are given blood from an individual of a different blood type, i.e. with a different type of antigen on the red cells, their immune system will generate antibodies to the foreign antigens and destroy the transfused cells. This is the basis of the transfusion reaction; the two blood types, the donor and the recipient, are *incompatible*.

There are many different collections of red cell surface antigens, but the most important are the ABO and the Rhesus systems.

The ABO system

About 55% of the population has either A-type antigens (blood group A), B-type antigens (blood group B) or both (blood group AB) on their red cell surface. The remaining 45% have neither A nor B type antigens (blood group O). The corresponding antibodies are called anti-A and anti-B. Blood group A individuals cannot make anti-A (and therefore do not have these antibodies in their plasma), since otherwise a reaction to their own cells would occur; they can, however, make anti-B. Blood group B individuals, for the same reasons, can make only anti-A. Blood group AB make neither, and blood group O make both anti-A and anti-B (Fig. 4.8).

Because blood group AB people make neither anti-A nor anti-B antibodies, they are sometimes known as *universal recipients*: transfusion of either type A or type B blood into these individuals is likely to be safe, since there are no antibodies to react with them. Conversely, group O people have neither A nor B antigens on their red cell membranes, and their blood may be safely transfused into A, B, AB or O types; group O is sometimes known as the *universal donor*. The terms *universal donor* and *universal recipient* are misleading, however, since they imply that the ABO system is the only one that needs to be considered. In practice, although the ABO systems may be compatible, other antigen systems on donor/recipient cells may be incompatible, and cause a transfusion reaction (p. 76). For this reason, prior to transfusion, cross-matching is still required to ensure that there is no reaction between donor and recipient bloods. Inheritance of ABO blood groups is described in Chapter 17 (p. 444).

The Rhesus system 4.4

The red blood cell membrane antigen important here is the Rhesus (Rh) antigen, or Rhesus factor. About 85% of people have this antigen; they are Rhesus positive (Rh^+) and do not therefore make anti-Rhesus antibodies. The remaining 15% have no Rhesus antigen (they are Rhesus negative, or Rh^-). Rh^- individuals are capable of making anti-Rhesus antibodies, but are stimulated to do so only in certain circumstances, e.g. in pregnancy (p. 75), or as the result of an incompatible blood transfusion.

Leukocytes (white blood cells) 4.5

These cells have an important function in defence and immunity. They detect foreign or abnormal (antigenic) material and destroy it, through a range of defence mechanisms described below and in Chapter 15. Leukocytes are the largest blood cells but they account for only about 1% of the blood volume. They contain nuclei and some have granules in their cytoplasm (Table 4.2 and Fig. 4.2). There are two main types:

- *granulocytes* (polymorphonuclear leukocytes) – neutrophils, eosinophils and basophils
- *agranulocytes* – monocytes and lymphocytes.

Rising white cell numbers in the bloodstream usually indicate a physiological problem, e.g. infection, trauma or malignancy.

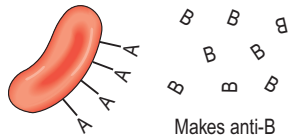
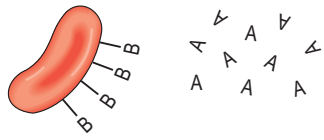
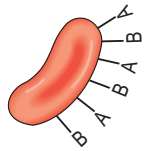
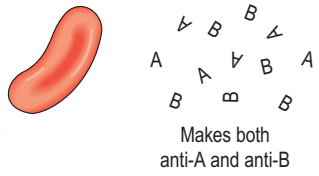
Blood group	Antigen + antibody(ies) present	As donor, is	As recipient, is
A	 Antigen A; Makes anti-B	Compatible with: A and AB Incompatible with: B and O, because both make anti-A antibodies that will react with A antigens	Compatible with: A and O Incompatible with: B and AB, because type A makes anti-B antibodies that will react with B antigens
B	 Antigen B; Makes anti-A	Compatible with: B and AB Incompatible with: A and O, because both make anti-B antibodies that will react with B antigens	Compatible with: B and O Incompatible with: A and AB, because type B makes anti-A antibodies that will react with A antigens
AB	 Antigens A and B; Makes neither anti-A nor anti-B	Compatible with: AB only Incompatible with: A, B and O, because all three make antibodies that will react with AB antigens	Compatible with all groups **UNIVERSAL RECIPIENT** AB makes no antibodies and therefore will not react with any type of donated blood
O	 Neither A nor B antigen; Makes both anti-A and anti-B	Compatible with all groups **UNIVERSAL DONOR** O red cells have no antigens, and will therefore not stimulate anti-A or anti-B antibodies	Compatible with: O only Incompatible with: A, AB and B, because type O makes anti-A and anti-B antibodies

Figure 4.8 The ABO system of blood grouping: antigens, antibodies and compatibility.

Table 4.2 Normal leukocyte counts in adult blood

	Number × 10^9/L	Percentage of total
Granulocytes		
Neutrophils	2.5 to 7.5	40 to 75
Eosinophils	0.04 to 0.44	1 to 6
Basophils	0.015 to 0.1	< 1
Agranulocytes		
Monocytes	0.2 to 0.8	2 to 10
Lymphocytes	1.5 to 3.5	20 to 50
Total	5 to 9	100

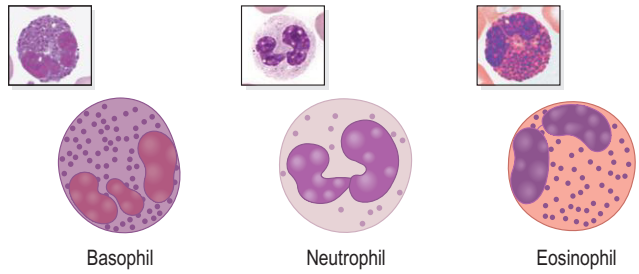


Figure 4.9 The granulocytes (granular leukocytes).

Granulocytes (polymorphonuclear leukocytes)

During their formation, *granulopoiesis*, they follow a common line of development through *myeloblast* to *myelocyte* before differentiating into the three types (Figs 4.3 and 4.9). All granulocytes have multilobed nuclei in their cytoplasm. Their names represent the dyes they take up when stained in the laboratory. Eosinophils take up the red acid dye, eosin; basophils take up alkaline methylene blue; and neutrophils are purple because they take up both dyes.

Neutrophils

These small, fast and active scavengers protect the body against bacterial invasion, and remove dead cells and debris from damaged tissues. They are attracted in large numbers to any area of infection by chemicals called *chemotaxins*, released by damaged cells. Neutrophils are highly mobile, and squeeze through the capillary walls in the affected area by *diapedesis* (Fig. 4.10). Their numbers rise very quickly in an area of damaged or infected tissue. Once there, they engulf and kill bacteria by *phagocytosis*

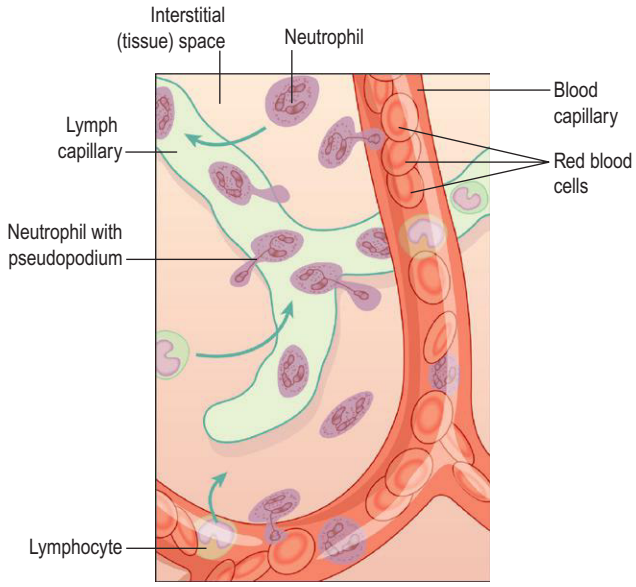


Figure 4.10 Diapedesis of leukocytes.

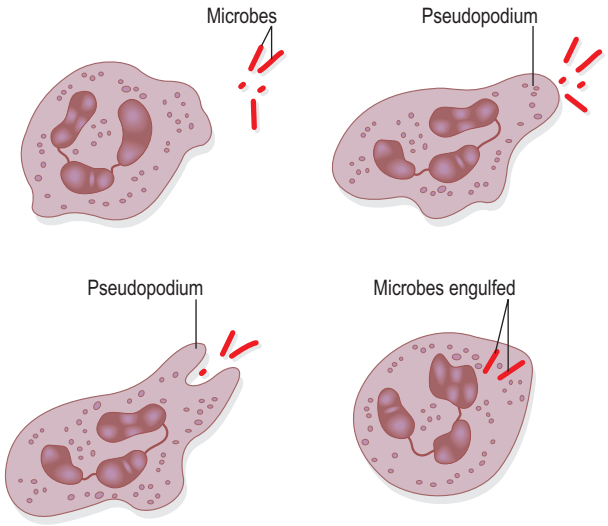


Figure 4.11 Phagocytic action of neutrophils.

(Fig. 4.11 and Fig. 15.1). Their nuclei are characteristically complex, with up to six lobes (Fig. 4.2), and their granules are *lysosomes* containing enzymes to digest engulfed material. Neutrophils live on average 6–9 hours in the bloodstream. Pus that may form in an infected area consists of dead tissue cells, dead and live microbes, and phagocytes killed by microbes.

Eosinophils

Eosinophils, although capable of phagocytosis, are less active in this than neutrophils; their specialised role appears to be in the elimination of parasites, such as worms, which are too big to be phagocytosed. They are equipped with certain toxic chemicals, stored in their granules, which they release when the eosinophil binds to an infecting organism.

Local accumulation of eosinophils may occur in allergic inflammation, such as the asthmatic airway and skin allergies. There, they promote tissue inflammation by releasing their array of toxic chemicals, but they may also dampen down the inflammatory process through the release of other chemicals, such as *histaminase*, an enzyme that breaks down histamine (p. 378).

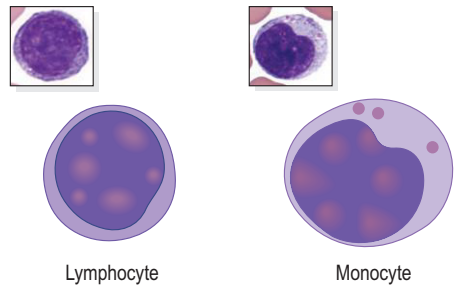


Figure 4.12 The agranulocytes.

Basophils

Basophils, which are closely associated with allergic reactions, contain cytoplasmic granules packed with heparin (an anticoagulant), histamine (an inflammatory agent) and other substances that promote inflammation. Usually the stimulus that causes basophils to release the contents of their granules is an *allergen* (an antigen that causes allergy) of some type. This binds to antibody-type receptors on the basophil membrane. A cell type very similar to basophils, except that it is found in the tissues, not in the circulation, is the *mast cell*. Mast cells release their granule contents within seconds of binding an allergen, which accounts for the rapid onset of allergic symptoms following exposure to, for example, pollen in hay fever (p. 385).

Agranulocytes

The *monocytes* and *lymphocytes* make up 25 to 50% of the total leukocyte count (Figs 4.3 and 4.12). They have a large nucleus and no cytoplasmic granules.

Monocytes

These are the largest of the white blood cells (Fig. 4.2). Some circulate in the blood and are actively motile and phagocytic while others migrate into the tissues where they develop into *macrophages*. Both types of cell produce *interleukin* 1, which:

- acts on the hypothalamus, causing the rise in body temperature associated with microbial infections
- stimulates the production of some globulins by the liver
- enhances the production of activated T-lymphocytes.

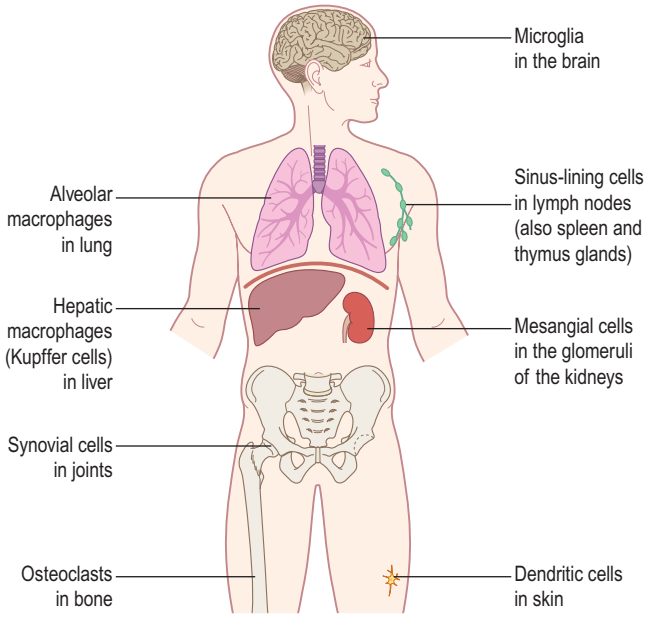


Figure 4.13 The reticuloendothelial system.

Macrophages have important functions in inflammation (p. 376) and immunity (Ch. 15).

The monocyte–macrophage system. This is sometimes called the *reticuloendothelial system*, and consists of the body's complement of monocytes and macrophages. Some macrophages are mobile, whereas others are fixed, providing effective defence at key body locations.

The main collections of fixed macrophages are shown in Figure 4.13.

Macrophages have a diverse range of protective functions. They are actively phagocytic (their name means 'big eaters') and are much more powerful and longer-lived than the smaller neutophils. They synthesise and release an array of biologically active chemicals, called *cytokines*, including interleukin 1 mentioned earlier. They also have a central role linking the non-specific and specific (immune) systems of body defence (Ch. 15), and produce factors important in inflammation and repair. They can 'wall off' indigestible pockets of material, isolating them from surrounding normal tissue. In the lungs, for example, resistant bacteria such as tuberculosis bacilli and inhaled inorganic dusts can be sealed off in such capsules.

Lymphocytes

Lymphocytes are smaller than monocytes and have large nuclei. Some circulate in the blood but most are found in tissues, including lymphatic tissue such as lymph nodes and the spleen. Lymphocytes develop from pluripotent stem cells in red bone marrow and from precursors in lymphoid tissue.

Although all lymphocytes originate from only one type of stem cell, the final steps in their development lead to the production of two distinct types of lymphocyte – *T-lymphocytes* and *B-lymphocytes*. The specific functions of these two cell types are discussed in Chapter 15.

Platelets (thrombocytes) 4.6

These are very small discs, 2–4 µm in diameter, derived from the cytoplasm of megakaryocytes in red bone marrow (Figs 4.2 and 4.3). Although they have no nucleus, their cytoplasm is packed with granules containing a variety of substances that promote blood clotting, which causes *haemostasis* (cessation of bleeding).

The normal blood platelet count is between 200×10^9/L and 350×10^9/L (200 000–350 000/mm^3). The mechanisms that regulate platelet numbers are not fully understood, but the hormone *thrombopoeitin* from the liver stimulates platelet production.

The life span of platelets is between 8 and 11 days and those not used in haemostasis are destroyed by macrophages, mainly in the spleen. About a third of platelets are stored within the spleen rather than in the circulation; this is an emergency store that can be released as required to control excessive bleeding.

Haemostasis

When a blood vessel is damaged, loss of blood is stopped and healing occurs in a series of overlapping processes, in which platelets play a vital part. The more badly damaged the vessel wall is, the faster coagulation begins, sometimes as quickly as 15 seconds after injury.

1. Vasoconstriction. When platelets come into contact with a damaged blood vessel, their surface becomes sticky and they adhere to the damaged wall. They then release *serotonin* (5-hydroxytryptamine), which constricts (narrows) the vessel, reducing or stopping blood flow through it. Other chemicals that cause vasoconstriction, e.g. thromboxanes, are released by the damaged vessel itself.

2. Platelet plug formation. The adherent platelets clump to each other and release other substances, including *adenosine diphosphate* (ADP), which attract more platelets to the site. Passing platelets stick to those already at the damaged vessel and they too release their chemicals. This is a positive feedback system by which many platelets rapidly arrive at the site of vascular damage and quickly form a temporary seal – the platelet plug. Platelet plug formation is usually complete within 6 minutes of injury.

3. Coagulation (blood clotting). This is a complex process that also involves a positive feedback system and only a few stages are included here. The factors involved are listed in Table 4.3. Their numbers represent the order in which they were discovered and not the order of participation in the clotting process. These clotting factors

Table 4.3 Blood clotting factors

I	Fibrinogen
II	Prothrombin
III	Tissue factor (thromboplastin)
IV	Calcium (Ca^{2+})
V	Labile factor, proaccelerin, Ac-globulin
VII	Stable factor, proconvertin
VIII	Antihaemophilic globulin (AHG), antihaemophilic factor A
IX	Christmas factor, plasma thromboplastin component (PTA), antihaemophilic factor B
X	Stuart Prower factor
XI	Plasma thromboplastin antecedent (PTA), antihaemophilic factor C
XII	Hageman factor
XIII	Fibrin stabilising factor

(There is no factor VI)
Vitamin K is essential for synthesis of factors II, VII, IX and X.

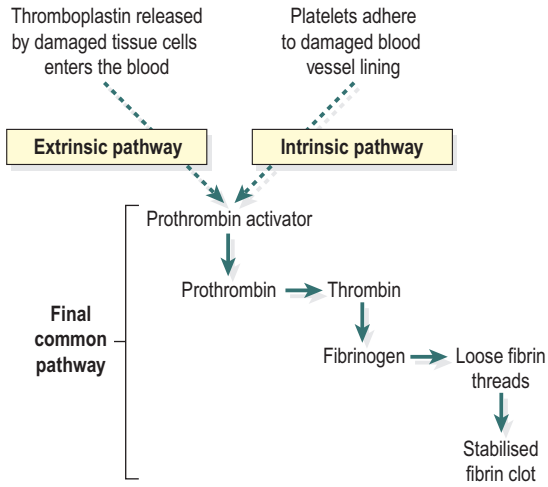


Figure 4.14 Stages of blood clotting (coagulation).

activate each other in a specific order, eventually resulting in the formation of *prothrombin activator*, which is the first step in the *final common pathway*. Prothrombin activates the enzyme *thrombin*, which converts inactive *fibrinogen* to insoluble threads of *fibrin* (Fig. 4.14). As clotting proceeds, the platelet plug is progressively stabilised by increasing amounts of fibrin laid down in a three-dimensional meshwork within it. The maturing blood clot traps blood cells and other plasma proteins including *plasminogen* (which will eventually destroy the clot), and is much stronger than the rapidly formed platelet plug.

The final common pathway can be initiated by two processes which often occur together: the extrinsic and intrinsic pathways (Fig. 4.14). The *extrinsic pathway* is activated rapidly (within seconds) following tissue damage. Damaged tissue releases a complex of chemicals called *thromboplastin* or tissue factor, which initiates coagulation. The *intrinsic pathway* is slower (3–6 minutes) and is

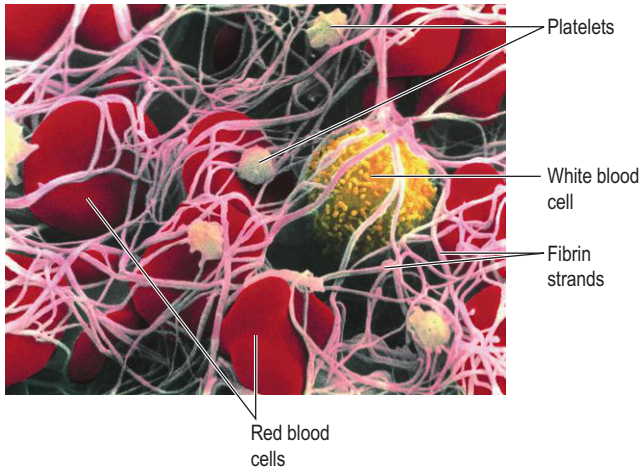


Figure 4.15 Scanning electron micrograph of a blood clot, showing the fibrin meshwork (pink strands), red blood cells, platelets and a white blood cell.

triggered when blood comes into contact with damaged blood vessel lining (endothelium).

After a time the clot shrinks (*retracts*) because the platelets contract, squeezing out serum, a clear sticky fluid that consists of plasma from which clotting factors have been removed. Clot shrinkage pulls the edges of the damaged vessel together, reducing blood loss and closing off the hole in the vessel wall.

Figure 4.15 shows a scanning electron micrograph of a blood clot. The fibrin strands (pink) have trapped red blood cells, platelets and a white blood cell.

4. Fibrinolysis. After the clot has formed, the process of removing it and healing the damaged blood vessel begins. The breakdown of the clot, or *fibrinolysis*, is the first stage. Plasminogen, trapped within the clot as it forms, is converted to the enzyme *plasmin* by activators released from the damaged endothelial cells. Plasmin breaks down fibrin to soluble products that are treated as waste material and removed by phagocytosis. As the clot is removed, the healing process restores the integrity of the blood vessel wall.

Activators
↓
Plasminogen → Plasmin
↓
Fibrin → Breakdown products

Control of coagulation

The process of blood clotting relies heavily on several self-perpetuating processes – that is, once started, a positive feedback mechanism promotes their continuation. For example, thrombin is a powerful stimulator of its own production. The body therefore possesses several mechanisms to control and limit the coagulation cascade;

otherwise once started the clotting process would spread throughout the circulatory system, instead of being limited to the local area where it is needed. The main controls are:

- the perfect smoothness of normal blood vessel lining prevents platelet adhesion in healthy, undamaged blood vessels
- activated clotting factors remain active for only a short time because they are inhibited by natural anticoagulants such as heparin and antithrombin III, which interrupt the clotting cascade.

Erythrocyte disorders

Learning outcomes

After studying this section, you should be able to:

- define the term anaemia
- compare and contrast the causes and effects of iron deficiency, megaloblastic, aplastic, hypoplastic and haemolytic anaemias
- explain why polycythaemia occurs.

Anaemias

Anaemia is the inability of the blood to carry enough oxygen to meet body needs. Usually this is because there are low levels of haemoglobin in the blood, but sometimes it is due to production of faulty haemoglobin.

Anaemia is classified depending on the cause:

- production of insufficient or defective erythrocytes.

If the number of red blood cells being released is too low or the red blood cells are defective in some way, anaemia may result. Important causes include iron deficiency, vitamin B_{12}/folic acid deficiency and bone marrow failure.

- blood loss or excessive erythrocyte breakdown (haemolysis).

If erythrocytes are lost from the circulation, either through loss of blood in haemorrhage or by accelerated haemolysis, anaemia can result.

Anaemia can cause abnormal changes in red cell size or colour, detectable microscopically. Characteristic changes are listed in Table 4.4. Anaemia may be associated with a normal red cell count and no abnormalities of erythrocyte structure (normochromic normocytic anaemia). For example, following sudden haemorrhage, the red cells in the bloodstream are normal in shape and colour, but their numbers are fewer.

Signs and symptoms of anaemia relate to the inability of the blood to supply body cells with enough oxygen, and may represent adaptive measures. Examples include:

- tachycardia; the heart rate increases to improve blood supply and speed up circulation
- palpitations (an awareness of the heartbeat), or angina pectoris (p. 127); these are caused by the increased effort of the overworked heart muscle
- breathlessness on exertion; when oxygen requirements increase, respiratory rate and effort rise in an effort to meet the greater demand.

Table 4.4 Terms used to describe red blood cell characteristics

Term	Definition
Normochromic	Cell colour normal
Normocytic	Cells normal sized
Microcytic	Cells smaller than normal
Macrocytic	Cells bigger than normal
Hypochromic	Cells paler than normal
Haemolytic	Rate of cell destruction raised
Megaloblastic	Cells large and immature

Iron deficiency anaemia

This is the most common form of anaemia in many parts of the world. Dietary iron comes mainly from red meat and highly coloured vegetables. Daily iron requirement in men is about 1–2 mg. Women need 3 mg daily because of blood loss during menstruation and to meet the needs of the growing fetus during pregnancy. Children require more than adults to meet their growth requirements.

In iron deficiency anaemia, the red blood cell count is often normal, but the cells are small, pale, of variable size and contain less haemoglobin than normal.

The amount of haemoglobin in each cell is regarded as below normal when the mean cell haemoglobin (MCH) is less than 27 pg/cell (Table 4.1). The anaemia is regarded as severe when the haemoglobin level is below 9 g/dL blood.

Iron deficiency anaemia can result from deficient intake, unusually high iron requirements, or poor absorption from the alimentary tract.

Deficient intake

Because of the relative inefficiency of iron absorption, deficiency occurs frequently, even in individuals whose requirements are normal. It generally develops slowly over a prolonged period of time, and symptoms only appear once the anaemia is well established. The risk of deficiency increases if the daily diet is restricted in some way, as in poorly planned vegetarian diets, or in weight-reducing diets where the range of foods eaten is small. Babies dependent on milk may also suffer mild iron deficiency anaemia if weaning on to a mixed diet is delayed much past the first year, since the liver carries only a few months' store and milk is a poor source of iron. Other at-risk groups include older adults and the alcohol-dependent, whose diet can be poor.

High requirements

In pregnancy iron requirements are increased both for fetal growth and to support the additional load on the mother's cardiovascular system. Iron requirements also rise when there is chronic blood loss, the causes of which include peptic ulcers (p. 323), heavy menstrual bleeding (menorrhagia), haemorrhoids, regular aspirin ingestion or carcinoma of the GI tract (pp. 324, 329).

Malabsorption

Iron absorption is usually increased following haemorrhage, but may be reduced in abnormalities of the stomach, duodenum or jejunum. Because iron absorption is dependent on an acid environment in the stomach, an increase in gastric pH may reduce it; this may follow excessive use of antacids, removal of part of the stomach, or in pernicious anaemia (see below), where the acid-releasing (parietal) cells of the stomach are destroyed. Loss of surface area for absorption in the intestine, e.g. after surgical removal, can also cause deficiency.

Vitamin B_{12}/folic acid deficiency anaemias

Deficiency of vitamin B_{12} and/or folic acid impairs erythrocyte maturation (Fig. 4.5) and abnormally large erythrocytes (*megaloblasts*) are found in the blood. During normal erythropoiesis (Fig. 4.3) several cell divisions occur and the daughter cells at each stage are smaller than the parent cell because there is not much time for cell enlargement between divisions. When deficiency of vitamin B_{12} and/or folic acid occurs, the rate of DNA and RNA synthesis is reduced, delaying cell division. The cells therefore grow larger than normal between divisions. Circulating cells are immature, larger than normal and some are nucleated (mean cell volume (MCV) > 94 fL). The haemoglobin content of each cell is normal or raised. The cells are fragile and their life span is reduced to between 40 and 50 days. Depressed production and early lysis cause anaemia.

Vitamin B_{12} deficiency anaemia

Pernicious anaemia

This is the most common form of vitamin B_{12} deficiency anaemia. It is commonest in females over 50. It is an autoimmune disease in which autoantibodies destroy intrinsic factor (IF) and parietal cells in the stomach (p. 299).

Dietary deficiency of vitamin B_{12}

Vitamin B_{12} is widely available in animal-derived foodstuffs, including dairy products, meat and eggs, so deficiency is rare except in strict vegans, who eat no animal products at all. The liver has extensive stores of the vitamin, so deficiency can take several years to appear.

Other causes of vitamin B_{12} deficiency

These include the following.

- *Gastrectomy* (removal of all or part or the stomach) – this leaves fewer cells available to produce IF.
- *Chronic gastritis, malignant disease and ionising radiation* – these damage the gastric mucosa including the parietal cells that produce IF.
- *Malabsorption* – if the terminal ileum is removed or inflamed, e.g. in Crohn's disease, the vitamin cannot be absorbed.

Complications of vitamin B_{12} deficiency anaemia

These may appear before the signs of anaemia. Because vitamin B_{12} is used in myelin production, deficiency leads to irreversible neurological damage, commonly in the spinal cord (p. 187). Mucosal abnormalities, such as glossitis (inflammation of the tongue) are also common, although they are reversible.

Folic acid deficiency anaemia

Deficiency of folic acid causes a form of megaloblastic anaemia identical to that seen in vitamin B_{12} deficiency, but not associated with neurological damage. It may be due to:

- dietary deficiency, e.g. in infants if there is delay in establishing a mixed diet, in alcoholism, in anorexia and in pregnancy
- malabsorption from the jejunum caused by, e.g., coeliac disease, tropical sprue or anticonvulsant drugs
- interference with folate metabolism by, e.g., cytotoxic and anticonvulsant drugs.

Aplastic anaemia

Aplastic (hypoplastic) anaemia results from bone marrow failure. Erythrocyte numbers are reduced. Since the bone marrow also produces leukocytes and platelets, *leukopenia* (low white cell count) and *thrombocytopenia* (low platelet count) are also likely. When all three cell types are low, the condition is called *pancytopenia*, and is accompanied by anaemia, diminished immunity and a tendency to bleed. The condition is occasionally (15% of cases) inherited. Usually no cause is identified, but the known causes include:

- drugs, e.g. cytotoxic therapy and, rarely, as an adverse reaction to anti-inflammatory and anticonvulsant drugs and some antibiotics
- ionising radiation
- some chemicals, e.g. benzene and its derivatives
- viral disease, including hepatitis.

The presenting symptoms are usually bleeding and bruising.

Haemolytic anaemias

These occur when circulating red cells are destroyed or are removed prematurely from the blood because the cells are abnormal or the spleen is overactive. Most haemolysis takes place in the liver or spleen and the normal erythrocyte life span of about 120 days can be considerably shortened. If the condition is relatively mild, red cell numbers may remain stable because the red bone marrow production of erythrocytes increases to compensate, so there may be ongoing haemolysis without anaemia. However, if the bone marrow cannot compensate, red blood cell numbers will fall and anaemia results.

Even in the absence of symptoms of anaemia (pallor, tiredness, dyspnoea, etc.), haemolytic anaemias can cause additional symptoms such as jaundice or splenomegaly.

Congenital haemolytic anaemias

In these diseases, genetic abnormality leads to the synthesis of abnormal haemoglobin and increased red cell membrane fragility, reducing their oxygen-carrying capacity and life span. The most common forms are sickle cell anaemia and thalassaemia.

Sickle cell anaemia

The abnormal haemoglobin molecules become misshapen when deoxygenated, making the erythrocytes sickle shaped (Fig. 4.16). If the cells contain a high proportion of abnormal Hb, sickling is permanent. The life span of cells is reduced by early haemolysis, which causes anaemia. Sickle cells do not move smoothly through the circulation. They obstruct blood flow, leading to intravascular clotting, tissue ischaemia and infarction. Acute episodes (sickle crises), caused by blockage of small vessels, cause acute pain in the affected area, often the hands and feet. Longer term problems arising from poor perfusion and anaemia include cardiac disease, kidney failure, retinopathy, poor tissue healing and slow growth in children. Obstruction of blood flow to the brain greatly increases the risk of stroke and seizures, and both mother and child are at significant risk of complications in pregnancy.

Black people are more affected than others. Some affected individuals have a degree of immunity to malaria because the life span of the sickled cells is less than the time needed for the malaria parasite to mature inside the cells.

Complications. Pregnancy, infection and dehydration predispose to the development of 'sickle crises' due to intravascular clotting and ischaemia, causing severe pain in long bones, chest or the abdomen. Excessive haemolysis results in high levels of circulating bilirubin. This in turn frequently leads to gallstones (*cholelithiasis*) and inflammation of the gall bladder (*cholecystitis*) (p. 335).

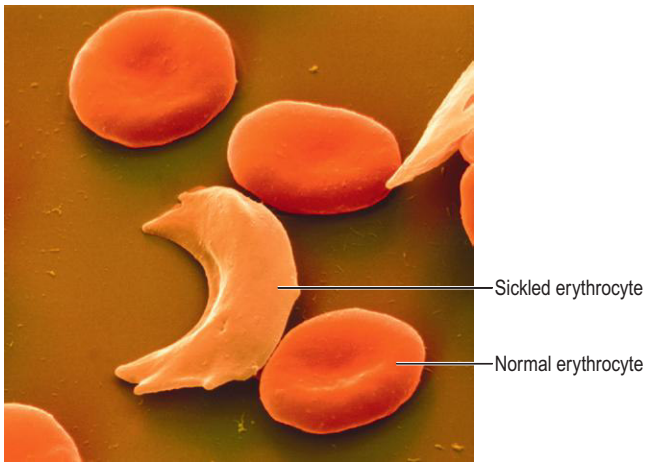


Figure 4.16 Scanning electron micrograph showing three normal and one sickled erythrocyte.

Thalassaemia

This inherited condition, commonest in Mediterranean countries, causes abnormal haemoglobin production, which in turn reduces erythropoiesis and stimulates haemolysis. The resultant anaemia may present in a range of forms, from mild and asymptomatic to profound and life-threatening. Symptoms in moderate to severe thalassaemia include bone marrow expansion and splenomegaly, as production of red blood cells increases to correct the anaemia. In the most severe form of the disease, regular blood transfusions are required, which can lead to iron overload.

Haemolytic disease of the newborn

In this disorder, the mother's immune system makes antibodies to the baby's red blood cells, causing destruction of fetal erythrocytes. The antigen system involved is usually (but not always) the Rhesus (Rh) antigen.

A Rh^- mother carries no Rh antigen on her red blood cells, but she has the capacity to produce anti-Rh antibodies. If she conceives a child fathered by a Rh^+ man, and the baby inherits the Rh antigen from him, the baby may also be Rh^+, i.e. different from the mother. During pregnancy, the placenta protects the baby from the mother's immune system, but at delivery a few fetal red blood cells may enter the maternal circulation. Because they carry an antigen (the Rh antigen) foreign to the mother, her immune system will be stimulated to produce neutralising antibodies to it. The red cells of second and subsequent Rh^+ babies are attacked by these maternal antibodies, which can cross the placenta and enter the fetal circulation (Fig. 4.17). In the most severe cases, the baby dies in the womb from profound anaemia. In less serious circumstances, the baby is born with some degree of anaemia, which is corrected with blood transfusions.

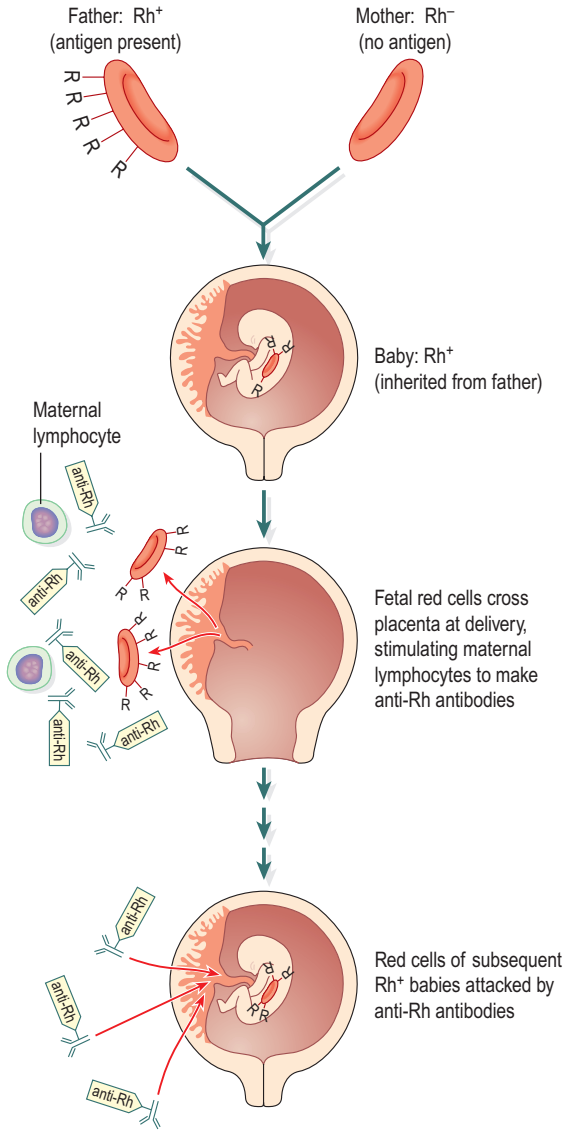


Figure 4.17 The immunity of haemolytic disease of the newborn.

The disease is much less common than it used to be, because it was discovered that if a Rh^- mother is given an injection of anti-Rh antibodies within 72 hours of the delivery of a Rh^+ baby, her immune system does not make its own anti-Rh antibodies to the fetal red cells. Subsequent pregnancies are therefore not affected. The anti-Rh antibodies given to the mother bind to, and neutralise, any fetal red cells present in her circulation before her immune system becomes sensitised to them.

Acquired haemolytic anaemias

In this context, 'acquired' means haemolytic anaemia in which no familial or racial factors have been identified. There are several causes.

Chemical agents

These substances cause early or excessive haemolysis, for example:

- some drugs, especially when taken long term in large doses, e.g. sulphonamides
- chemicals encountered in the general or work environment, e.g. lead, arsenic compounds
- toxins produced by microbes, e.g. *Streptococcus pyogenes, Clostridium perfringens*.

Autoimmunity

In autoimmunity, individuals make antibodies to their own red cell antigens, causing haemolysis. It may be acute or chronic and primary or secondary to other diseases, e.g. carcinoma, viral infection or other autoimmune diseases.

Blood transfusion reactions

Individuals do not normally produce antibodies to their own red blood cell antigens; if they did, the antigens and antibodies would react, causing clumping and lysis of the erythrocytes (see Fig. 4.8). However, if individuals receive a transfusion of blood carrying antigens different from their own, their immune system will recognise them as foreign, make antibodies to them and destroy them (transfusion reaction). This adverse reaction between the blood of incompatible recipients and donors leads to haemolysis within the cardiovascular system. The breakdown products of haemolysis lodge in and block the filtering mechanism of the nephron, impairing kidney function. Other principal signs of a transfusion reaction include fever, chills, lumbar pain and shock.

Polycythaemia

This means an abnormally large number of erythrocytes in the blood. This increases blood viscosity, slows blood flow and increases the risk of intravascular clotting, ischaemia and infarction.

Relative increase in erythrocyte count

This occurs when the erythrocyte count is normal but the blood volume is reduced by fluid loss, e.g. excessive serum exudate from extensive burns.

True increase in erythrocyte count

Physiological. Prolonged hypoxia stimulates erythropoiesis and the number of reticulocytes released into the normal volume of blood is increased. This occurs naturally in people living at high altitudes where the oxygen tension in the air is low and the partial pressure of oxygen in the alveoli of the lungs is correspondingly low. Each cell carries less oxygen so more cells are needed to meet the body's oxygen needs. Other causes of hypoxia, such

as heart or lung disease or heavy smoking can also cause polycythaemia.

Pathological. Some cancers increase red blood cell production, although the reason is not always known.

Leukocyte disorders

Learning outcomes

After studying this section, you should be able to:

- define the terms leukopenia and leukocytosis
- review the physiological importance of abnormally increased and decreased leukocyte numbers in the blood
- discuss the main forms of leukaemia, including the causes, signs and symptoms of the disease.

Leukopenia

In this condition, the total blood leukocyte count is less than 4×10^9/L (4000/mm^3).

Granulocytopenia (neutropenia)

This is a general term used to indicate an abnormal reduction in the numbers of circulating granulocytes (polymorphonuclear leukocytes), commonly called neutropenia because 40–75% of granulocytes are neutrophils. A reduction in the number of circulating granulocytes occurs when production does not keep pace with the normal removal of cells or when the life span of the cells is reduced. Extreme shortage or the absence of granulocytes is called *agranulocytosis*. A temporary reduction occurs in response to inflammation but the numbers are usually quickly restored. Inadequate granulopoiesis may be caused by:

- drugs, e.g. cytotoxic drugs, phenothiazines, some sulphonamides and antibiotics
- irradiation damage to granulocyte precursors in the bone marrow, e.g. radiotherapy
- diseases of red bone marrow, e.g. leukaemias, some anaemias
- severe microbial infections.

In conditions where the spleen is enlarged, excessive numbers of granulocytes are trapped, reducing the number in circulation. Neutropenia predisposes to severe infections that can lead to septicaemia and death. Septicaemia is the presence of significant numbers of active pathogens in the blood.

Leukocytosis

An increase in the number of circulating leukocytes occurs as a normal protective reaction in a variety of pathological conditions, especially infections. When the infection subsides the leukocyte count returns to normal.

Pathological leukocytosis exists when a blood leukocyte count of more than 11×10^9/L (11 000/mm^3) is sustained and is not consistent with the normal protective function. One or more of the different types of cell is involved.

Leukaemia

Leukaemia is a malignant proliferation of white blood cell precursors by the bone marrow. It results in the uncontrolled increase in the production of leukocytes and/or their precursors. As the tumour cells enter the blood the total leukocyte count is usually raised but in some cases it may be normal or even low. The proliferation of immature leukaemic blast cells crowds out other blood cells formed in bone marrow, causing anaemia, thrombocytopenia and leukopenia (pancytopenia). Because the leukocytes are immature when released, immunity is reduced and the risk of infection high.

Causes of leukaemia

Some causes of leukaemia are known but many cases cannot be accounted for. Some people may have a genetic predisposition that is triggered by environmental factors, including viral infection. Other known causes include:

Ionising radiation. Radiation such as that produced by X-rays and radioactive isotopes causes malignant changes in the precursors of white blood cells. The DNA of the cells may be damaged and some cells die while others reproduce at an abnormally rapid rate. Leukaemia may develop at any time after irradiation, even 20 or more years later.

Chemicals. Some chemicals encountered in the general or work environment alter the DNA of the white blood cell precursors in the bone marrow. These include benzene and its derivatives, asbestos, cytotoxic drugs, chloramphenicol.

Genetic factors. Identical twins of leukaemia sufferers have a much higher risk than normal of developing the disease, suggesting involvement of genetic factors.

Types of leukaemia

Leukaemias are usually classified according to the type of cell involved, the maturity of the cells and the rate at which the disease develops (see Fig. 4.3).

Acute leukaemias

These types usually have a sudden onset and affect the poorly differentiated and immature 'blast' cells (Fig. 4.3). They are aggressive tumours that reach a climax within a few weeks or months. The rapid progress

of bone marrow invasion causes rapid bone marrow failure and culminates in anaemia, haemorrhage and susceptibility to infection. The mucous membranes of the mouth and upper gastrointestinal tract are most commonly affected.

Leukocytosis is usually present in acute leukaemia. The bone marrow is packed with large numbers of immature and abnormal cells.

Acute myeloblastic leukaemia (AML). Involves proliferation of myeloblasts (Fig. 4.3), and is most common in adults between the ages of 25 and 60, the risk gradually increasing with age. The disease can often be cured, or long-term remission achieved.

Acute lymphoblastic leukaemia (ALL). Seen mainly in children, who have a better prognosis than adults, with up to 70% achieving cure. The cell responsible here is a primitive B-lymphocyte.

Chronic leukaemias

These conditions are less aggressive than the acute forms and the leukocytes are more differentiated, i.e. at the 'cyte' stage (Fig. 4.3).

Leukocytosis is a feature of chronic leukaemia, with crowding of the bone marrow with immature and abnormal leukocytes, although this varies depending upon the form of the disease.

Chronic myeloid leukaemia (CML). Occurs at all ages and, although its onset is gradual, in most patients it eventually transforms into a rapidly progressive stage similar to AML and proves fatal although it sometimes progresses to ALL and its better prognosis. Death usually occurs within 5 years.

Chronic lymphocytic leukaemia (CLL). Involves proliferation of B-lymphocytes, and is usually less aggressive than CML. It is most often seen in the elderly; disease progression is usually slow, and survival times can be as long as 25 years.

Haemorrhagic diseases

Learning outcomes

After studying this section, you should be able to:

- indicate the main causes and effects of thrombocytopenia
- outline how vitamin K deficiency relates to clotting disorders
- explain the term disseminated intravascular coagulation, including its principal causes
- describe the physiological deficiencies present in the haemophilias.

Thrombocytopenia

This is defined as a blood platelet count below 150×10^9/L ($150\,000/mm^3$) but spontaneous capillary bleeding does not usually occur unless the count falls below 30×10^9/L ($30\,000/mm^3$). It may be due to a reduced rate of platelet production or increased rate of destruction.

Reduced platelet production

This is usually due to bone marrow deficiencies, and therefore production of erythrocytes and leukocytes is also reduced, giving rise to pancytopenia. It is often due to:

- platelets being crowded out of the bone marrow in bone marrow diseases, e.g. leukaemias, pernicious anaemia, malignant tumours
- ionising radiation, e.g. X-rays or radioactive isotopes, which damage the rapidly dividing precursor cells in the bone marrow
- drugs that can damage bone marrow, e.g. cytotoxic drugs, chloramphenicol, chlorpromazine, sulphonamides.

Increased platelet destruction

A reduced platelet count occurs when production of new platelets does not keep pace with destruction of damaged and worn out ones. This occurs in disseminated intravascular coagulation (see below) and autoimmune thrombocytopenic purpura.

Autoimmune thrombocytopenic purpura. This condition, which usually affects children and young adults, may be triggered by a viral infection such as measles. Antiplatelet antibodies are formed that coat platelets, leading to platelet destruction and their removal from the circulation. A significant feature of this disease is the presence of purpura, which are haemorrhages into the skin ranging in size from pinpoints to large blotches. The severity of the disease varies from mild bleeding into the skin to severe haemorrhage. When the platelet count is very low there may be severe bruising, haematuria, gastrointestinal or intracranial haemorrhages.

Vitamin K deficiency

Vitamin K is required by the liver for the synthesis of many clotting factors and therefore deficiency predisposes to abnormal clotting.

Haemorrhagic disease of the newborn

Spontaneous haemorrhage from the umbilical cord and intestinal mucosa occurs in babies when the stored vitamin K obtained from the mother before birth has been used up and the intestinal bacteria needed for its synthesis in the infant's bowel are not yet established. This is most likely to occur when the baby is premature.

Deficiency in adults

Vitamin K is fat soluble and bile salts are required in the colon for its absorption. Deficiency may occur when there is liver disease, prolonged obstruction to the biliary tract or in any other disease where fat absorption is impaired, e.g. coeliac disease (p. 331). Dietary deficiency is rare because a sufficient supply of vitamin K is usually synthesised in the intestine by bacterial action. However, it may occur during treatment with drugs that sterilise the bowel.

Disseminated intravascular coagulation (DIC)

In DIC, the coagulation system is activated within blood vessels, leading to formation of intravascular clots and deposition of fibrin in the tissues. Because of this consumption of clotting factors and platelets, there is a consequent tendency to haemorrhage. DIC is a common complication of a number of other disorders, including:

- infection, such as septicaemia, when endotoxins are released by Gram-negative bacteria
- severe trauma
- premature separation of placenta when amniotic fluid enters maternal blood
- acute pancreatitis when digestive enzymes are released into the blood
- advanced cancer
- transfusion of very large volumes of blood.

Congenital disorders

The haemophilias

The haemophilias are a group of inherited clotting disorders, carried by genes present on the X-chromosome (i.e. inheritance is sex linked, p. 444). The faulty genes code for abnormal clotting factors (factor VIII and Christmas factor), and if inherited by a male child always leads to expression of the disease. Women inheriting one copy are carriers, but, provided their second X chromosome bears a copy of the normal gene, their blood clotting is normal. It is possible, but unusual, for a woman to inherit two copies of the abnormal gene and have haemophilia.

Those who have haemophilia experience repeated episodes of severe and prolonged bleeding at any site, even in the absence of trauma. Recurrent bleeding into joints is common, causing severe pain and, in the long term, cartilage is damaged. The disease ranges in severity from mild forms, where the defective factor has partial activity, to extreme forms where bleeding can take days or weeks to control.

The two main forms of haemophilia differ only in the clotting factor involved; the clinical picture in both is identical:

- haemophilia A. In this disease, factor VIII is abnormal and is less biologically active than normal
- haemophilia B (Christmas disease). This is less common and factor IX is deficient, resulting in deficiency of thromboplastin (clotting factor III).

von Willebrand disease

In this disease, a deficiency in von Willebrand factor causes low levels of factor VIII. As its inheritance is not sex linked, haemorrhages due to impaired clotting occur equally in males and females.

For a range of self-assessment exercises on the topics in this chapter, visit Evolve online resources: https://evolve.elsevier.com/Waugh/anatomy/