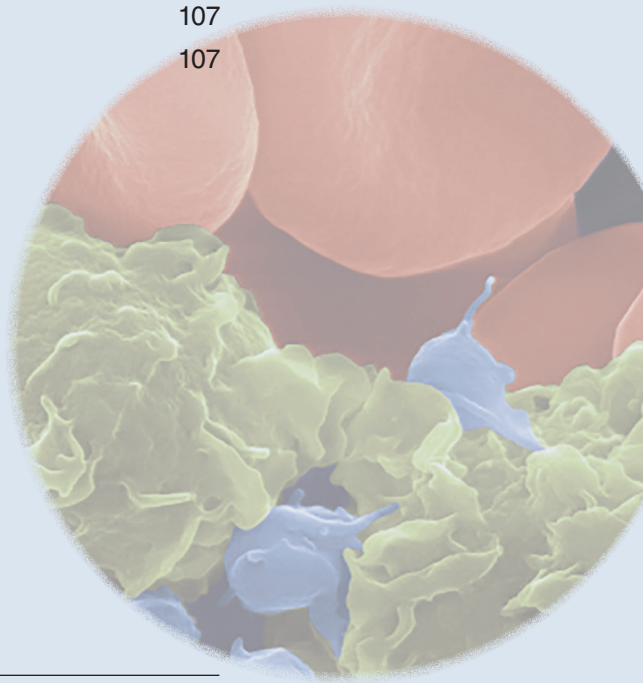


CHAPTER 8

The white cells, part 1: granulocytes, monocytes and their benign disorders

Key topics

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The white blood cells (leucocytes) may be divided into two broad groups: the **phagocytes** and the **lymphocytes**. Phagocytes comprise cells of the **innate** immune system, which can act very quickly after an infection, whereas lymphocytes mediate the **adaptive immune response**, which can develop immunological memory, for example after vaccination. Certain lymphocyte subtypes such as natural killer (NK) cells lack memory capacity and are also considered part of the innate immune system.

Phagocytes can themselves be subdivided into granulocytes (which include neutrophils, eosinophils and basophils) and monocytes. Their normal development and function, and benign disorders of white blood cells, are dealt with in this chapter (Table 8.1; Fig. 8.1). Lymphocytes are considered in Chapter 9.

The function of phagocytes and lymphocytes in protecting the body against infection is closely connected with two soluble protein systems of the body: immunoglobulins and **complement**. These proteins, which may also be involved in blood cell destruction in a number of diseases, are discussed together with the lymphocytes in Chapter 9.

Granulocytes

Neutrophil (polymorph)

This cell has a characteristic dense nucleus consisting of between two and five lobes, and a pale cytoplasm with an irregular outline containing many fine pink–blue (azurophilic) or

Table 8.1 White cells: normal blood counts.

Adults	Blood count	Children	Blood count
Total leucocytes	$4.0–11.0 \times 10^9$/L*		*Total leucocytes*
Neutrophils	$1.8–7.5 \times 10^9$/L*	Neonates	$10.0–25.0 \times 10^9$/L
Eosinophils	$0.04–0.4 \times 10^9$/L	1 year	$6.0–18.0 \times 10^9$/L
Monocytes	$0.2–0.8 \times 10^9$/L	4–7 years	$6.0–15.0 \times 10^9$/L
Basophils	$0.01–0.1 \times 10^9$/L	8–12 years	$4.5–13.5 \times 10^9$/L
Lymphocytes	$1.5–3.5 \times 10^9$/L		

* Normal subjects of African and Middle Eastern descent may have lower counts. In normal pregnancy the upper limits are total leucocytes 14.5×10^9/L, neutrophils 11×10^9/L. Minor variations in the 'normal' range may be present from laboratory to laboratory.

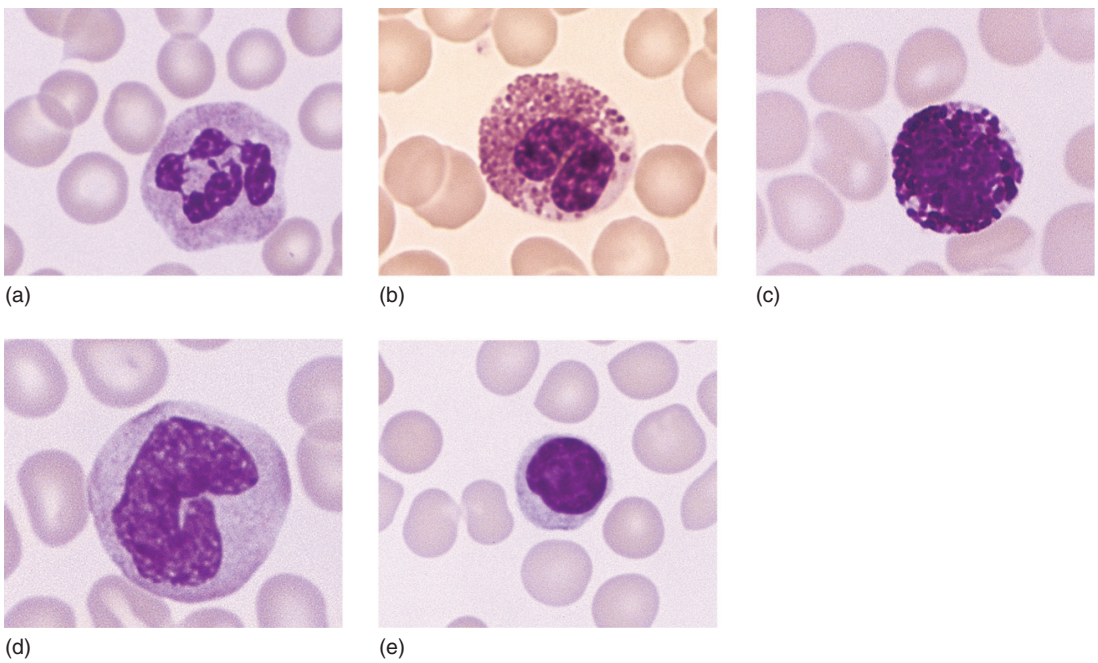


Figure 8.1 White blood cells (leucocytes): **(a)** neutrophil (polymorph); **(b)** eosinophil; **(c)** basophil; **(d)** monocyte; **(e)** lymphocyte.

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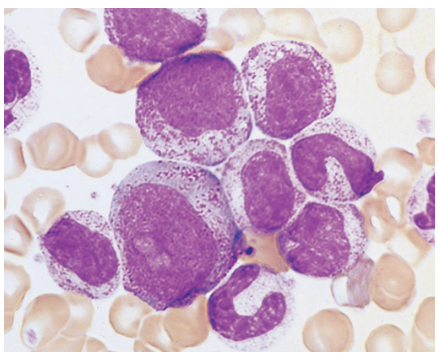
grey–blue granules (Fig. 8.1a). The granules are divided into primary, which appear at the promyelocyte stage, and secondary (specific), which appear at the myelocyte stage and predominate in the mature neutrophil (see Fig. 8.7). Both types of granule are lysosomal in origin: the primary contains myeloperoxidase and other acid hydrolases; the secondary contains lactoferrin, lysozyme and other enzymes. The lifespan of neutrophils in the blood is only 6–10 hours.

Neutrophil precursors

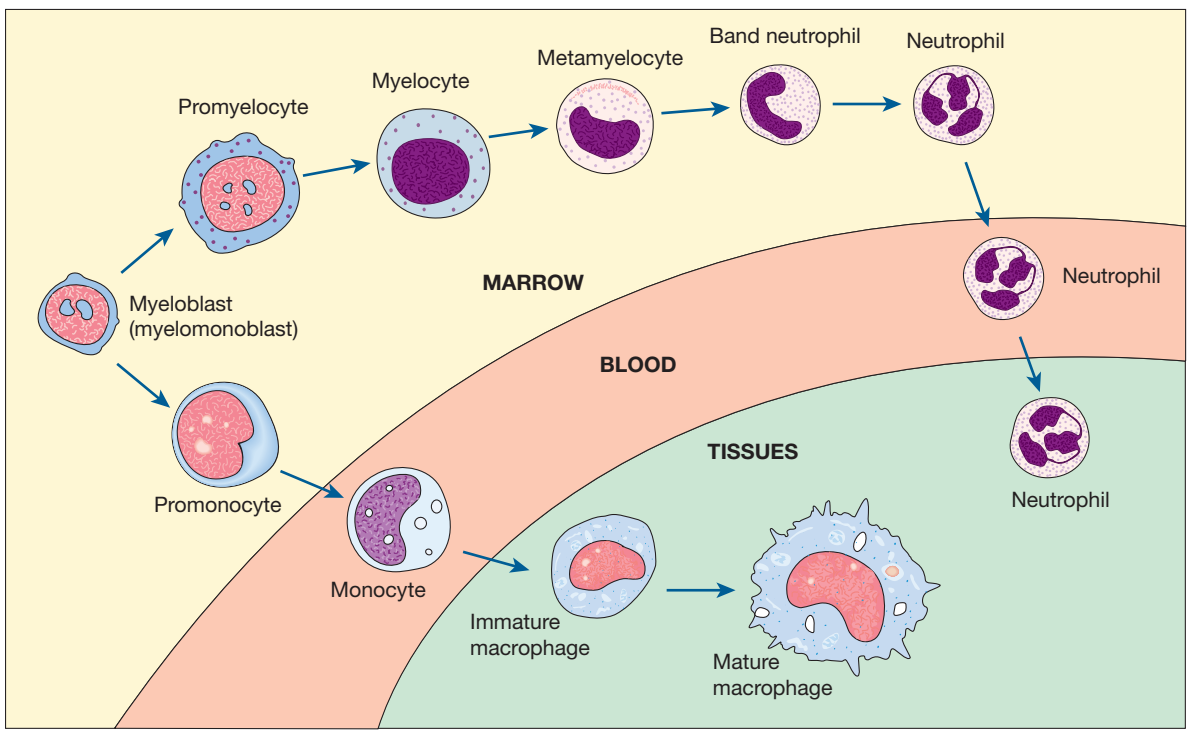
These do not normally appear in normal peripheral blood but are present in the marrow (Fig. 8.2). The earliest recognizable precursor is the **myeloblast**, a cell of variable size which has a large nucleus with fine chromatin and usually two to five nucleoli (Fig. 8.2b). The cytoplasm is basophilic and no granules are present. The normal bone marrow contains up to 5% of myeloblasts.

Myeloblasts give rise to promyelocytes, which are slightly larger cells which retain nucleoli but have developed primary granules in the cytoplasm (Fig. 8.2a). These cells then give rise to myelocytes, which have specific or secondary granules. The nuclear chromatin is now more condensed and nucleoli are not visible. Separate myelocytes of the neutrophil, eosinophil and basophil series can be identified. The myelocytes give rise to **metamyelocytes**, non-dividing cells, which have an indented or horseshoe-shaped nucleus and a cytoplasm filled with primary and secondary granules.

Neutrophil forms between the metamyelocyte and fully mature neutrophil are termed '**band**', 'stab' or 'juvenile'. These cells may occur in normal peripheral blood. They do not contain the clear, fine filamentous distinction between nuclear lobes that is seen in mature neutrophils.



(a)



(b)

Figure 8.2 **(a)** Granulopoiesis. A promyelocyte, myelocytes, and metamyelocytes. Source: A.V. Hoffbrand *et al*. (2019) *Color Atlas of Clinical Hematology: Molecular and Cellular Basis of Disease*, 5th edn. Reproduced by permission of John Wiley & Sons. **(b)** The formation of the neutrophil and monocyte phagocytes. Eosinophils and basophils are also formed in the marrow in a process similar to that for neutrophils.

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Monocytes

These are usually larger than other peripheral blood leucocytes and possess a large central oval or indented nucleus with clumped chromatin (Fig. 8.1d). The abundant cytoplasm stains blue and contains many fine vacuoles, giving a ground-glass appearance. Cytoplasmic granules are also often present. The monocyte precursors in the marrow (monoblasts and promonocytes) are difficult to distinguish from myeloblasts and monocytes.

Eosinophils

These cells are similar to neutrophils, except that the cytoplasmic granules are coarser and more deeply red staining and there are rarely more than three nuclear lobes (Fig. 8.1b). Eosinophil myelocytes can be recognized, but earlier stages are indistinguishable from neutrophil precursors. The blood transit time for eosinophils is longer than for neutrophils. They enter inflammatory exudates and have a special role in allergic responses, defence against parasites and removal of fibrin formed during inflammation. Thus they play a role in local immunity and tissue repair.

Basophils

These are only occasionally seen in normal peripheral blood. They have many dark cytoplasmic granules which overlie the nucleus and contain heparin and histamine (Fig. 8.1c). In the tissues they become mast cells. They have immunoglobulin E (IgE) attachment sites and their degranulation is associated with histamine release.

Granulopoiesis

Granulocytes and monocytes are formed in the bone marrow from a common precursor cell (see Fig. 1.2). In the granulopoietic series progenitor cells, myeloblasts, promyelocytes and myelocytes form a proliferative or mitotic pool of cells, while the metamyelocytes, band and segmented granulocytes make up a post-mitotic maturation compartment (Fig. 8.3).

Large numbers of band and segmented neutrophils (10–15 times more than in the blood) are held in the normal marrow as a 'reserve pool'. **The bone marrow normally contains more myeloid cells than erythroid cells in the ratio of 2:1 to 12:1, the largest proportion being neutrophils and metamyelocytes**. Following their release from the marrow, granulocytes spend only 6–10 hours in the circulation before entering tissues, where they perform their phagocytic function. They spend on average 4–5 days in the tissues before they are destroyed during defensive action or as the result of senescence. In the bloodstream there are two pools usually of about equal size: the circulating pool (included in the blood count) and a marginating pool (not included in the blood count).

Control of granulopoiesis: myeloid growth factors

The granulocyte series arises from bone marrow progenitor cells, which are increasingly specialized. Many growth factors are involved in this maturation process including interleukin-1 (IL-1), IL-3, IL-5 (for eosinophils), IL-6, IL-11, granulocyte–macrophage colony-stimulating factor (GM-CSF), granulocyte CSF (G-CSF) and monocyte CSF (M-CSF) (see Fig. 1.6). The growth factors stimulate proliferation and differentiation and also affect the function of the mature cells on which they act (e.g. phagocytosis, superoxide generation and cytotoxicity in the case of neutrophils; see Fig. 1.5). They also inhibit apoptosis.

Increased granulocyte and monocyte production in response to an infection is induced by increased production of growth factors from stromal cells and T lymphocytes, stimulated by endotoxin, and cytokines such as IL-1 or tumour necrosis factor (TNF) (Fig. 8.4).

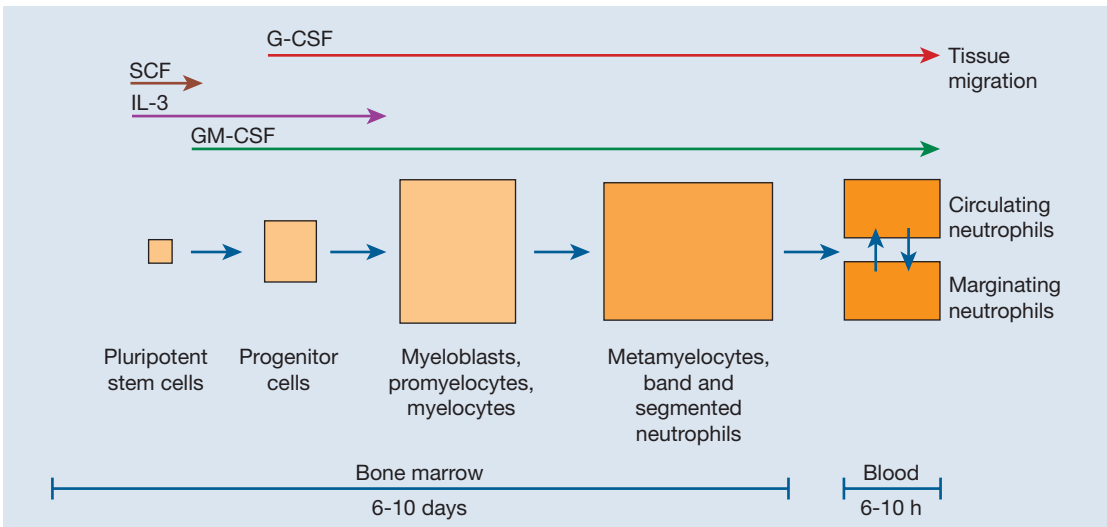


Figure 8.3 Neutrophil kinetics. CSF, colony-stimulating factor; G, granulocyte; IL, interleukin; M, monocyte; SCF, stem cell factor.

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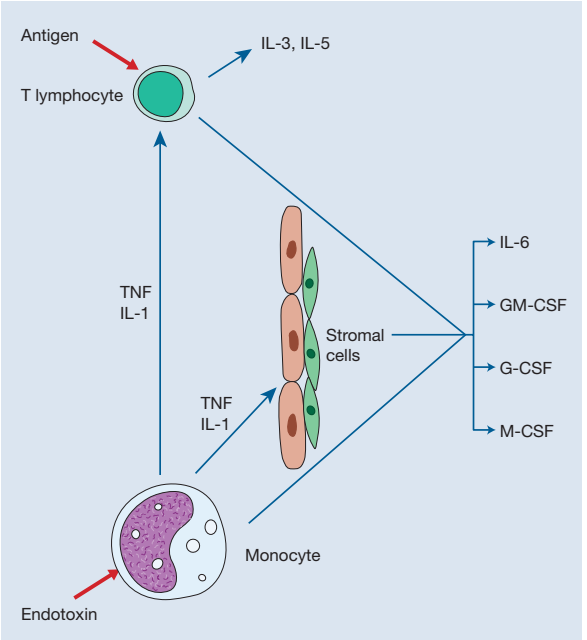


Figure 8.4 Regulation of haemopoiesis; pathways of stimulation of leucopoiesis by endotoxin, for example from infection. It is likely that endothelial and fibroblast cells release basal quantities of granulocyte–macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) in the normal resting state and that this is enhanced substantially by tumour necrosis factor (TNF) and interleukin-1 (IL-1).

Clinical applications of G-CSF

Clinical administration of G-CSF intravenously or subcutaneously produces a rise in neutrophils. Short-acting G-CSF is given daily. Filgrastim was the original recombinant G-CSF, but numerous bioequivalent forms are now used. A longer-acting PEGylated G-CSF, pegfilgrastim, can be given once in 7–14 days. Indications are:

- **Post-chemotherapy, radiotherapy or stem cell transplantation (SCT)** In these situations, G-CSF accelerates granulocytic recovery and shortens the period of neutropenia (Fig. 8.5). This may translate into a reduction of length of time in hospital, antibiotic usage and frequency of infection, but periods of extreme neutropenia after intensive chemotherapy cannot be prevented. The injections may also allow repeated courses of chemotherapy, e.g. for lymphoma, to be given on schedule rather than being delayed because of prolonged neutropenia, particularly a problem in older patients.
- **Myelodysplastic syndromes and aplastic anaemia** G-CSF has been given alone or in conjunction with erythropoiesis-stimulating agents in an attempt to improve bone marrow function and the neutrophil count.
- **Severe benign neutropenia** Both congenital and acquired neutropenia, including cyclical and drug-induced neutropenia, often respond well to G-CSF.
- **Peripheral blood stem cell mobilization** G-CSF is used to increase the number of circulating multipotent progenitors from donors or the patient, improving the harvest of sufficient peripheral blood stem cells for allogeneic or autologous transplantation.

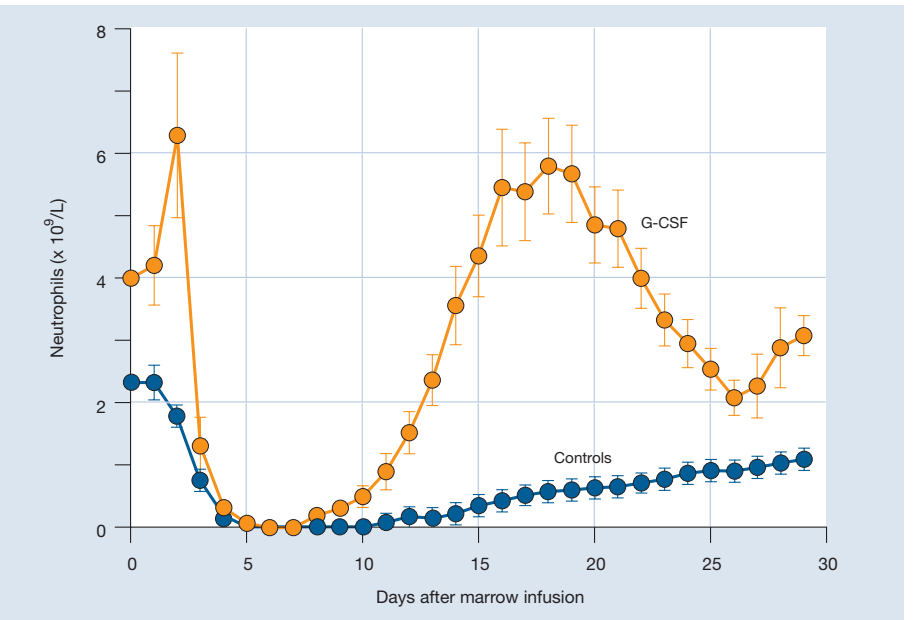


Figure 8.5 Typical effect of granulocyte colony-stimulating factor (G-CSF) on recovery of neutrophils following autologous bone marrow transplantation.

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Monocytes

Monocytes spend only a short time in the marrow and, after circulating for 20–40 hours, leave the blood to enter the tissues, where they mature and carry out their principal functions. Their extravascular lifespan after their transformation to **macrophages (histiocytes)** may be as long as several months or even years. In tissues the macrophages become self-replicating without replenishment from the blood. They assume specific functions in different tissues (e.g. skin, gut, liver; Fig. 8.6). One particularly important lineage is that of **dendritic cells**, which are involved in antigen presentation to T cells (see Chapter 9). GM-CSF and M-CSF are involved in their production and activation.

Disorders of neutrophil and monocyte function

The normal function of neutrophils and monocytes may be divided into three phases. Defects resulting in clinical syndromes can occur in each of these phases.

Chemotaxis (cell mobilization and migration)

The phagocyte is attracted to bacteria or the site of inflammation by chemotactic substances released from damaged tissues, by complement components and by the interaction of leucocyte adhesion molecules with ligands on the damaged tissues. The leucocyte adhesion molecules also mediate recruitment and interaction with other immune cells. They are also variously expressed on endothelial cells and platelets (see Chapter 1).

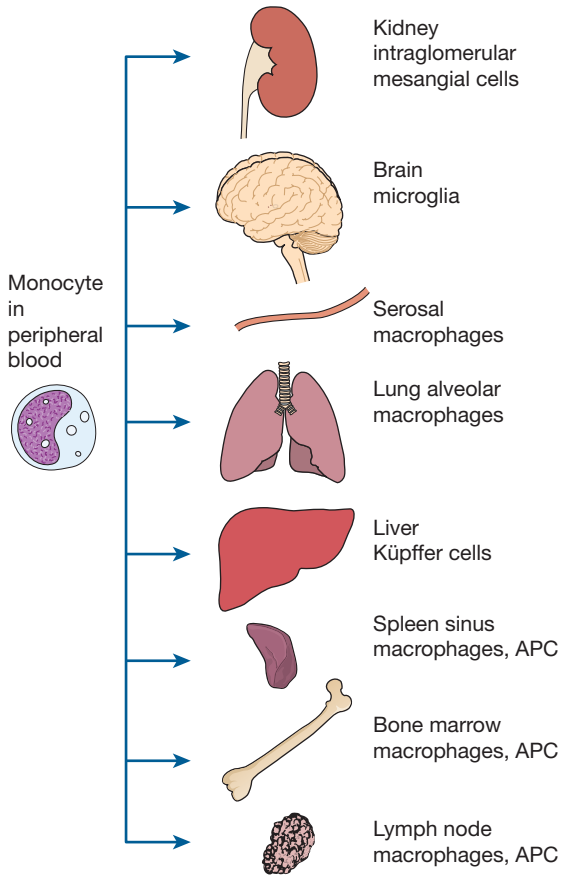


Figure 8.6 Reticuloendothelial system: distribution of macrophages.

Phagocytosis

The foreign material (e.g. bacteria, fungi) or dead or damaged cells of the host are phagocytosed (Fig. 8.7). Recognition of a foreign particle is aided by opsonization with immunoglobulin or complement, because both neutrophils and monocytes have Fc and C3b receptors (see Chapter 9).

Macrophages have a central role in antigen presentation: processing and presenting foreign antigens on human leucocyte antigen (HLA) molecules to the immune system. They also secrete a large number of growth factors and chemokines, which regulate inflammation and immune responses.

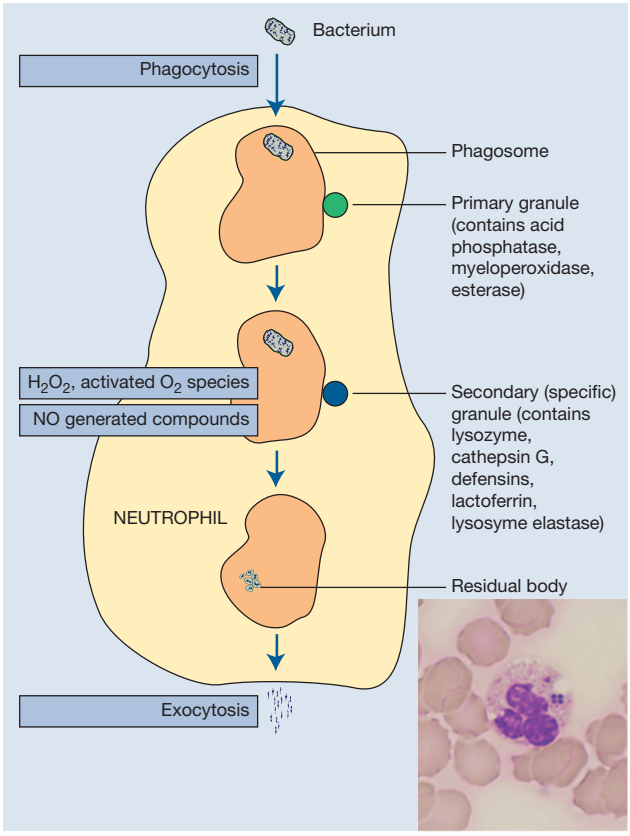


Figure 8.7 Phagocytosis and bacterial destruction. On entering the neutrophil, the bacterium is surrounded by an invaginated surface membrane and fuses with a primary lysosome to form a phagosome. Enzymes from the lysosome attack the bacterium. Secondary granules also fuse with the phagosomes, and new enzymes from these granules including lactoferrin attack the organism. Various types of activated oxygen, generated by glucose metabolism, also help to kill bacteria. Undigested residual bacterial products are excreted by exocytosis. Inset: Neutrophil ingesting meningococci. Source (inset): A.V. Hoffbrand *et al*. (2019) *Color Atlas of Clinical Hematology: Molecular and Cellular Basis of Disease*, 5th edn. Reproduced by permission of John Wiley & Sons.

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Chemokines are chemotactic cytokines which may be produced constitutively and control lymphocyte traffic under physiological conditions; inflammatory chemokines are induced or up-regulated by inflammatory stimuli. They bind to and activate cells via chemokine receptors and play an important part in recruiting appropriate cells to the sites of inflammation.

Killing and digestion

These occur by **oxygen-dependent** and **oxygen-independent** pathways. In the oxygen-dependent reactions, superoxide (O_2^-), hydrogen peroxide (H_2O_2) and other activated oxygen (O_2) species, are generated from O_2 and reduced nicotinamide adenine dinucleotide phosphate (NADPH). In neutrophils, H_2O_2 reacts with myeloperoxidase and intracellular halide to kill bacteria; activated oxygen may also be involved. Nitric oxide (NO), generated through NO synthase from L-arginine, is an oxygen-independent mechanism by which phagocytes also kill microbes.

The other non-oxidative microbicidal mechanisms involve microbicidal proteins. These may act alone (e.g. cathepsin G) or in conjunction with H_2O_2 (e.g. lysozyme, elastase). They may also act with a fall in pH within phagocytic vacuoles into which lysosomal enzymes are released. Lactoferrin, an iron-binding protein, is bacteriostatic by depriving bacteria of iron and generating free radicals (Fig. 8.7).

Defects of phagocytic cell function

Chemotaxis

These defects occur in rare congenital abnormalities (e.g. 'lazy leucocyte' syndrome) and in more common acquired abnormalities, either of the environment, e.g. corticosteroid therapy, or of the leucocytes themselves, e.g. in acute or chronic myeloid leukaemia, myelodysplasia and the myeloproliferative syndromes.

Phagocytosis

These defects usually arise because of a lack of opsonization, which may be caused by congenital or acquired causes of hypogammaglobulinaemia or lack of complement components.

Killing

This abnormality is clearly illustrated by the rare X-linked or autosomal recessive chronic granulomatous disease that results from abnormal leucocyte oxidative metabolism. There is an abnormality affecting different elements of the respiratory burst oxidase or its activating mechanism. The patients have recurring infections, usually bacterial but sometimes fungal, which present in infancy or early childhood.

Other rare congenital abnormalities may result in defects of bacterial killing (e.g. myeloperoxidase deficiency and the Chédiak–Higashi syndrome; see below). Acute or chronic myeloid leukaemia and myelodysplastic syndromes may also be associated with defective killing of ingested microorganisms.

Benign disorders

A number of hereditary conditions may give rise to changes in granulocyte morphology (Fig. 8.8).

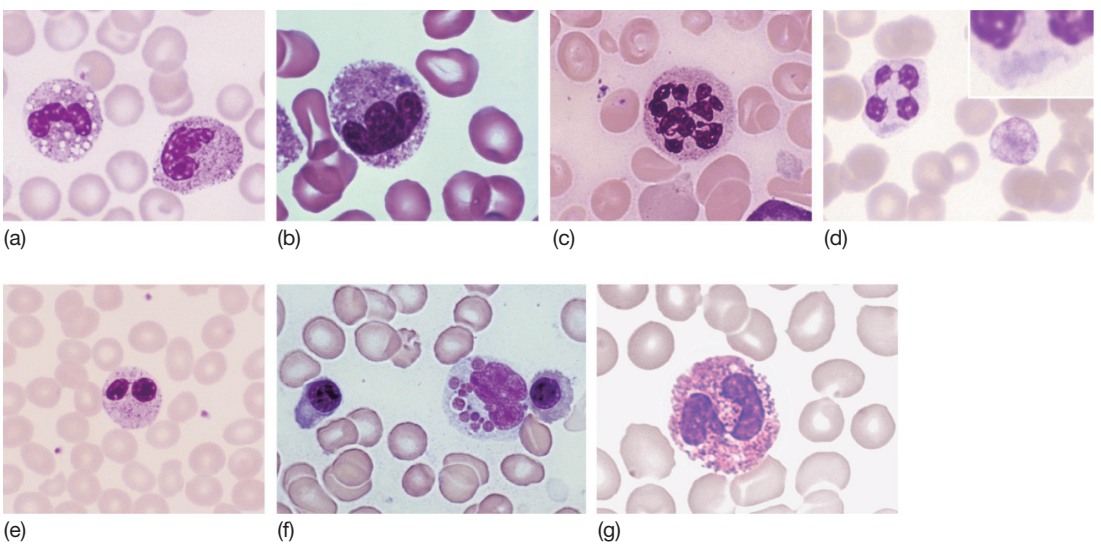


Figure 8.8 Abnormal white blood cells. **(a)** Neutrophil leucocytosis: toxic changes shown by the presence of red–purple granules in the band form neutrophils. **(b)** Neutrophil leucocytosis: a Döhle body can be seen in the cytoplasm of the neutrophil. **(c)** Megaloblastic anaemia: hypersegmented oversized neutrophil in peripheral blood. **(d)** May–Hegglin anomaly: the neutrophils contain basophilic inclusions 2–5 mm in diameter; there is an associated mild thrombocytopenia with giant platelets. **(e)** Pelger–Huët anomaly: coarse clumping of the chromatin in pince nez configuration. **(f)** Chédiak–Higashi syndrome: bizarre giant granules in the cytoplasm of a monocyte. **(g)** Alder anomaly: coarse violet granules in the cytoplasm of a neutrophil.

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Pelger–Huët anomaly

In this uncommon symptomless condition, bilobed neutrophils are found in the peripheral blood. Occasional unsegmented neutrophils are also seen. Inheritance is autosomal dominant, usually due to mutations in the gene encoding the lamin B receptor (LBR), which is important for cholesterol synthesis. It is most common in Northern Europeans. In myelodysplastic syndromes, cells resembling Pelger–Huët neutrophils are often seen on a blood film; these are called **pseudo-Pelger–Huët cells** because they lack the LBR mutations characteristic of the inherited condition.

May–Hegglin anomaly

In this rare condition the neutrophils contain basophilic inclusions of RNA (resembling Döhle bodies) in the cytoplasm. There is an associated mild thrombocytopenia with giant platelets. Inheritance is autosomal dominant and usually due to mutations in the *MYH9* gene, which encodes a myosin heavy chain.

Other rare disorders

In contrast to these two benign anomalies, other rare congenital leucocyte disorders may be associated with severe disease. The Chédiak–Higashi syndrome is inherited in an autosomal recessive manner, and there are giant granules in the neutrophils, eosinophils, monocytes and lymphocytes, accompanied by neutropenia, thrombocytopenia and marked hepatosplenomegaly. It is due to mutations in the *CHS1 (LYST)* gene, which encodes a lysosomal trafficking regulator. Abnormal leucocyte granulation or vacuolation is also seen in patients with rare mucopolysaccharide disorders (e.g. Hurler's syndrome).

Common morphological abnormalities

Figure 8.8 also shows some of the more common abnormalities of neutrophil morphology that can be seen in peripheral blood. Hypersegmented forms occur in megaloblastic anaemia, Döhle bodies and toxic changes in infection. A 'drumstick' (Barr body) appears on the nucleus of a proportion of the neutrophils in normal females and is caused by the presence of two X chromosomes (not illustrated).

Causes of neutrophil leucocytosis

An increase in circulating neutrophils to levels greater than 7.5×10^9/L is one of the most frequently observed blood count changes. The causes of neutrophil leucocytosis are given in Table 8.2. Neutrophil leucocytosis is sometimes accompanied by fever as a result of the release of leucocyte pyrogens. Other characteristic features of reactive neutrophilia may include (a) a 'shift to the left' in the peripheral blood differential white cell count, an increase in the number of band forms and the occasional presence of more primitive cells such as metamyelocytes and myelocytes; and (b) the presence of cytoplasmic toxic granulation and Döhle bodies (Fig. 8.8a, b).

Table 8.2 Causes of neutrophil leucocytosis.

Bacterial infections (especially pyogenic bacterial, localized or generalized)
Inflammation and tissue necrosis (e.g. myositis, vasculitis, cardiac infarct, trauma)
Metabolic disorders (e.g. uraemia, eclampsia, acidosis, gout)
Pregnancy
Neoplasms of all types (e.g. carcinoma, lymphoma, melanoma)
Acute haemorrhage or haemolysis
Drugs (e.g. corticosteroid therapy, which inhibits margination; lithium, tetracycline)
Chronic myeloid leukaemia, myeloproliferative neoplasms (polycythaemia vera, myelofibrosis, essential thrombocythaemia)
Treatment with G-CSF (granulocyte colony-stimulating factor)
Rare inherited disorders
Asplenia

The leukaemoid reaction

The leukaemoid reaction is a reactive and excessive leucocytosis usually characterized by the presence of immature cells (e.g. myeloblasts, promyelocytes and myelocytes) in the peripheral blood. Associated disorders include severe or chronic infections, severe haemolysis or metastatic cancer. Leukaemoid reactions are often particularly marked in children.

Leucoerythroblastic reaction

This is characterized by the presence of erythroblast and granulocyte precursors in the blood (Fig. 8.9). It is due to metastatic infiltration of the marrow or certain benign or neoplastic blood disorders (Table 8.3).

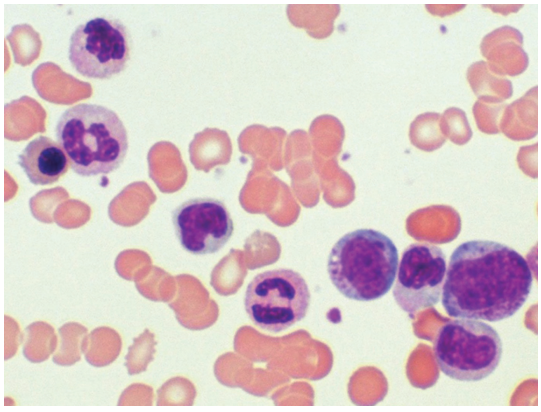


Figure 8.9 Leucoerythroblastic blood film. This shows an erythroblast, promyelocyte, myelocyte and metamyelocytes in a patient with metastatic breast carcinoma in the bone marrow.

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Table 8.3 Causes of leucoerythroblastic blood film.

Metastatic neoplasm in the marrow
Primary myelofibrosis
Acute and chronic myeloid leukaemias
Myeloma, lymphoma
Miliary tuberculosis
Severe megaloblastic anaemia
Severe haemolysis
Osteopetrosis
Secondary marrow fibrosis, e.g. due to rheumatological syndromes

Neutropenia

The lower limit of the normal neutrophil count is 1.8×10^9/L, except in people of African and Middle Eastern descent where values around 1.5×10^9/L are normal. This has been called 'benign ethnic neutropenia'. Lower normal values are also found from 2–3 weeks after birth for the first few months of life (Table 31.1). When the absolute neutrophil level falls below 0.5×10^9/L, the patient is likely to have recurrent infections, and when the count falls to less than 0.2×10^9/L the risks are very serious, particularly if there is also a functional defect. Neutropenia may be selective (Table 8.4) or part of a general pancytopenia (see Chapter 22). It may also be acute or chronic (lasting >3 months).

Benign ethnic neutropenia

Up to 98% of people of West African origin carry a polymorphism in the Duffy antigen chemokine receptor (*DARC*) gene which leads to loss of DARC expression on red cells. This has been selected during evolution because the malaria parasite *Plasmodium vivax* uses DARC as a receptor to enter the red cell. DARC is a chemokine receptor and the loss of its expression on white cells is associated with a lowering of the median neutrophil count by around 0.5×10^9/L. A similar effect is seen in some populations in the Middle East. The reduction in the neutrophil count may result from increased neutrophil margination, which can also occur in other ethnic groups, but there are no significant clinical consequences.

Congenital neutropenia

Severe congenital neutropenia (previously called Kostmann syndrome) usually presents in the first year of life with life-threatening infections. Most cases are dominantly inherited, caused by mutations of the gene *ELANE2*, coding for neutrophil elastase. Other types are autosomal recessive, and mutations of more than 10 genes have been described. In some cases the neutropenia occurs as part of other syndromes with non-haematological manifestations, e.g. Wiskott–Aldrich, Shwachman–Diamond (p. 275) or Chédiak–Higashi (p. 103). G-CSF produces a clinical response in most patients. Some of the forms predispose to myelodysplastic syndromes or acute myeloid leukaemia.

Table 8.4 Causes of neutropenia.

Selective neutropenia
Congenital
Acquired
Drug-induced
Anti-inflammatory drugs (aminopyrene, gold, levamisole, penicillamine)
Antibacterial drugs (cephalosporins, co-trimoxazole, meropenem)
Metronidazole, penicillins, sulfasalazine, tobramycin, vancomycin
Anticonvulsants (carbamazepine, valproate)
Antithyroids (carbimazole, methimazole)
Hypoglycaemics (tolbutamide)
Phenothiazines (chlorpromazine, thioridazine)
Psychotropics and antidepressants (clozapine, olanzapine, imipramine)
Miscellaneous (deferiprone, furosemide, mepacrine, rituximab, ticlopidine)
Benign (racial or familial)
Cyclical
Idiopathic and clonal neutropenia of uncertain significance (see Chapter 16)
Autoimmune
Associated with chronic autoimmune diseases, e.g. systemic lupus erythematosus, Sjogren's syndrome
Rheumatoid arthritis (Felty syndrome)
Hypersensitivity and anaphylaxis
Large granular lymphocytic leukaemia (see p. 227)
Infections
Viral (e.g. hepatitis, influenza, HIV)
Fulminant bacterial infection (e.g. typhoid, military tuberculosis)
Part of general pancytopenia (see Table 22.1)

HIV, human immunodeficiency virus.

Drug-induced neutropenia

A large number of drugs have been implicated (Table 8.4), which may induce neutropenia either by direct toxicity or immune-mediated damage, the drug acting as a hapten. For many drugs the mechanism remains obscure.

Cyclical neutropenia

This is a rare syndrome with 2–4-week periodicity. Severe but temporary neutropenia occurs. Monocytes tend to rise as the neutrophils fall. Germline mutation of *ELANE2*, the gene for neutrophil elastase, underlies some cases.

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Idiopathic and clonal neutropenia of uncertain significance

In these conditions there is neutropenia without morphological features in the blood or marrow cells of myelodysplastic syndromes or another haematological neoplasm. They are defined and discussed under the general descriptions of idiopathic and clonal cytopenias in Chapter 16.

In the idiopathic form (benign chronic neutropenia) no clonal genetic mutations are detected. This is the most common type of chronic neutropenia in both children and adults. It is more common in females and thought to be brought about in some cases by immune cells causing inhibition of myelopoiesis in the bone marrow. If an immune aetiology can be confirmed, e.g. by detection of antineutrophil antibodies, a definite diagnosis of autoimmune neutropenia is made (see below). In the clonal form, clonal genetic mutations are found in the blood and bone marrow cells similar to those found in clonal haemopoiesis of indeterminate prognosis (CHIP; see p. 203).

Autoimmune neutropenia

In some cases of chronic neutropenia an autoimmune mechanism can be demonstrated. The antibody may be directed against one of the neutrophil-specific antigens. The detection of neutrophil antibodies requires difficult laboratory procedures and test characteristics (sensitivity and specificity) are poor, so the tests are not performed routinely.

Clinical features

Severe neutropenia is particularly associated with infections of the mouth and throat. Painful and often intractable ulceration may occur at these sites (Fig. 8.10), on the skin or at the anus. Septicaemia rapidly supervenes. Organisms carried as commensals by normal individuals, such as *Staphylococcus epidermidis* or Gram-negative organisms in the bowel, may become pathogens. Other features of infections associated with severe neutropenia are described in Chapter 12.



Figure 8.10 Ulceration of the tongue in severe neutropenia.

Diagnosis

Bone marrow examination is useful in determining the severity of damage in granulopoiesis (i.e. whether there is reduction in early precursors or whether there is reduction only of circulating and marrow neutrophils, with late precursors remaining in the marrow). Marrow aspiration and trephine biopsy may also provide evidence of leukaemia, myelodysplasia or other infiltration.

Management

The treatment of patients with acute severe neutropenia is described on p. 150. In many patients with drug-induced neutropenia, spontaneous recovery occurs within 1–2 weeks after stopping the drug. Patients with chronic neutropenia have recurrent infections which are mainly bacterial in origin, although fungal and viral infections (especially herpes) also occur. **Early recognition and vigorous treatment with antibiotics, antifungal or antiviral agents, as appropriate, are essential**. Prophylactic antifungal agents, e.g. fluconazole, are often given and antibacterial agents, e.g. ciprofloxacin, may reduce the risk, but resistance is of concern (see Chapter 12). G-CSF or its PEGylated form is effective at raising the neutrophil count in a variety of benign chronic neutropenic states. Corticosteroid therapy or splenectomy has been associated with good results in some patients with autoimmune neutropenia. Corticosteroids impair neutrophil function and should not be used indiscriminately in patients with neutropenia. Rituximab (anti-CD20) may also be effective, although it may itself be a cause of neutropenia. Haemopoietic stem cell transplantation may be indicated if clonal evolution to myelodysplasia occurs.

Causes of monocytosis, eosinophil and basophil leucocytosis

Monocytosis

A rise in blood monocyte count above 0.8×10^9/L is infrequent. The conditions causing monocytosis are listed in Table 8.5.

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