Haematology is the medical specialty concerned with the study, diagnosis, treatment and prevention of diseases related to blood and is the subject of the first part of this book. This chapter discusses blood cells, their production (haematopoiesis), bone marrow and the spleen.

Blood is the fluid contained within the heart, arteries, capillaries and veins of the circulatory system. It delivers oxygen and nutrients to organs and tissues and carries carbon dioxide and metabolic ‘waste’ products to excretory organs such as the kidneys, liver and lungs.

Blood consists of several components:
- Plasma
- Cells (red cells, white cells, platelets)
- Electrolytes (e.g., Na⁺, K⁺, Ca²⁺)
- Proteins (including hormones and immunoglobulins)
- Lipids
- Glucose

The cellular components of blood are synthesized in the bone marrow in a process called ‘haematopoiesis’.

This section discusses mature blood cells found in the bloodstream.

Red blood cells
Red blood cells (‘erythrocytes’) are derived from the erythroid blast-forming unit (BFU-E) progenitor cell. Red cells lack a nucleus and have a biconcave discoid shape. Their primary role is the transportation of oxygen (from lung to tissue) and carbon dioxide (from tissue to lung). They contain haemoglobin, a specialized molecule that avidly binds these gases under conditions of high partial pressure and releases them under conditions of low partial pressure, thus allowing bulk transport of O₂ and CO₂ to proceed in the appropriate direction. Red blood cells are discussed in further detail in Chapter 2.

Platelets
Like red cells, platelets lack nuclei. Platelets (thrombocytes) are derived from megakaryocytes, which derive from the colony-forming unit megakaryocyte (CFU-Meg) progenitor cell. They play a pivotal role in haemostasis (Chapter 6).

White blood cells
White blood cells (leucocytes) are large unpigmented cells with primarily immune roles. They are also found in the bloodstream, along with red blood cells and platelets. Leucocytes are further classified into granulocytes, monocytes/macrophages and lymphocytes. Each group fulfils different immunological roles, participating in immune defences against infection.

Granulocytes
‘Granulocytes’ is the collective term for white blood cells with granules in their cytoplasm. The term encompasses neutrophils, eosinophils and basophils. The specific chemical content of the granules (and thus the cells’ function role) varies according to subtype. Note that some clinicians misleadingly use the term ‘granulocytes’ for neutrophils, which can cause confusion.

Neutrophils
Neutrophils (aka ‘polymorphs’) have multilobed nuclei. Neutrophils (diameter 12–14 μm) comprise ~60% of the bloodstream white cell population. They leave the bone marrow, where they are synthesized, and circulate in the bloodstream for ≤10 hours before entering tissues.

Neutrophils are an essential component of the innate immune system, due to their ability to phagocytose (en-gulf) microorganisms and kill them by releasing cytotoxic molecules from their granules. Once they arrive at the site of an infection or inflammation, they also recruit further immune cells with chemotactic mediators (see Chapter 9: Neutrophils). Neutrophils therefore represent a key component of the first-line defence against bacterial infections.

Eosinophils
Eosinophils (diameter 12–17 μm) have bilobed nuclei. They stain strongly with acidic dyes and comprise ~1%–6% of the bloodstream white cell population. Like other granulocytes, eosinophils release specific cytotoxic and messenger molecules. These are released directly into the extracellular space by degranulation. Note how eosinophils differ in this respect from neutrophils, which phagocytose pathogens before releasing cytotoxic molecules. Eosinophils migrate into areas of inflammation or
infection, particularly infection with multicellular parasites, e.g., helminths (worms). They are also important in both innate (see Chapter 9: Eosinophils) and adaptive immunity and allergic responses.

**Basophils**
Basophils (diameter 14–16 μm) have bilobed nuclei and granular cytoplasm, like eosinophils, but stain strongly with basic dyes. Basophils represent ≤1% of the bloodstream’s white cell population. In concert with eosinophils and mast cells, they contribute strongly to innate and adaptive immunity. Physiological histamine is derived in part from basophilic granules.

**Monocytes/macrophages**
Monocytes and macrophages are larger than granulocytes (diameter ≤25 μm). They have a large eccentrically placed reniform (kidney-shaped) nucleus. In the bloodstream, they are called monocytes and account for ~2%–10% of the white cell population. They circulate for 1–3 days, then leave the circulation and enter the tissues, where they differentiate further, developing into macrophages.

Macrophages comprise the reticuloendothelial system and are found in tissues throughout the body. They phagocytose cellular debris and pathogens and produce various cytokines. They also process and present antigens to lymphocytes as part of the adaptive immune response (see Chapter 10: MHC processing).

**Lymphocytes**
These white blood cells are small and have a relatively large, round nucleus relative to their nongranular, basophilic cytoplasm volume. They all originate from the lymphoid lineage.

**B lymphocytes**
These cells are small lymphocytes (diameter 6–9 μm) expressing the B cell receptor. They secrete immunoglobulins (antibodies). A large proportion of B lymphocytes reside in lymph node germinal centres, where they are known as memory B cells. Some B lymphocytes also mature further into plasma cells.

Plasma cells are larger than B lymphocytes and have a strongly basophilic cytoplasm and an eccentric round nucleus. They are mainly seen in the bone marrow, but a few may be seen circulating in the peripheral blood.

**T lymphocytes**
These cells are small lymphocytes (diameter 6–9 μm) expressing the T cell receptor. T cells are subclassified by type of surface glycoproteins they express, indicated by the CD prefix. Cytotoxic T cells (CD8 +ve) mediate destruction of cells infected by intracellular organisms, while T helper cells (CD4 +ve) release cytokines to regulate and assist in the adaptive immune response (Chapter 10).

**Natural killer cells**
These large granular lymphocytes are also cytotoxic lymphocytes, like T cells, but natural killer (NK) cells are larger. Their behaviour differs from that of T cells in that they do not require major histocompatibility complex (MHC) or antibody-bound antigen complexes to recognize and destroy foreign or infected cells. They are thus prominent in the innate immune response (Chapter 9).

**HAEMATOPOIESIS**
Haematopoiesis is the formation and development of blood cells. The haematopoietic system is composed of the bone marrow, spleen, liver, lymph nodes and thymus.

**Pluripotent haemopoietic stem cells**
All blood cells originally derive from a population of pluripotent, CD34 +ve haemopoietic stem cells, residing in haematopoietic tissues. These stem cells may either:
- Remain as pluripotent stem cells, dividing to form identical daughter cells, maintaining the haemopoietic population
- Differentiate into specific progenitor cells, which ultimately develop into specific cellular components of blood

After initially differentiating into either a myeloid or lymphoid progenitor cell, further developmental changes follow. As cells progress down their respective development pathways, they sequentially acquire characteristic receptors and functions, ultimately forming a mature blood cell (Fig. 1.1) with characteristics specific to the cell type.

**Progenitor cells**
The pluripotent stem cells can differentiate into one of the two multipotent progenitors:
- Myeloid lineage progenitor cell
- Lymphoid lineage progenitor cell
Myeloid lineage multipotent progenitor cell

The CFU generating myeloid cells (CFU-GEMM) multipotent stem cell subsequently further differentiates into either:

- Red cell progenitor (BFU-E)
- Platelet progenitor (CFU-Meg)
- Eosinophil progenitor (CFU-Eos)
- Basophil progenitor (CFU-Baso)
- Neutrophil/monocyte progenitor (CFU-GM)

These cells are all derived from the myeloid lineage.

HINTS AND TIPS

COLONY-FORMING UNITS (CFU)

CFU describes a progenitor cell committed to the development of a particular blood cell. For example, CFU-Baso is a progenitor cell that ultimately develops into a basophil.
Lymphoid lineage multipotent progenitor cell
The common lymphoid progenitor may further differentiate into one of the following:
- Pre-B cell (B cell precursor)
- Pre-T cell (T cell precursor)
- NK cell precursor
These cells are all derived from the lymphoid lineage.

Sites of haematopoiesis
The location of haematopoiesis differs according to developmental stage (Fig. 1.2). Table 1.1 lists the various haematopoiesis locations in health.

In certain pathological situations, the bone marrow becomes unable to maintain a sufficient rate of haematopoiesis. If this scenario persists chronically, the liver and spleen may resume haematopoietic capability. This is known as extramedullary haematopoiesis. Two classic examples where this is seen are thalassaemia major (see Chapter 3: Thalassaemia) and primary myelofibrosis (see Chapter 5: Primary myelofibrosis).

Regulation of haemopoiesis
The presence of growth factors promotes cell division. Growth factors are glycoproteins produced in the bone

![Fig. 1.2 Sites of haemopoiesis. (See also Table 1.1).]
Bone marrow, liver and kidneys. They bind to surface receptors on haemopoietic cells and can trigger replication, differentiation or functional activation, depending on the particular growth factor and the physiological context. In the absence of protective growth factor stimulation, cells undergo apoptosis (regulated cell death of old or dysfunctional cells). Specific growth factors and their respective responsive cells are indicated in Table 1.2. Note that some growth factors are used clinically.

**CLINICAL NOTES**

**CLINICAL USE OF GROWTH FACTORS**

Recombinant growth factors may be used clinically to increase the synthesis of a specific blood cell and compensate for a cytopenia. As an example, erythropoietin is used to increase red cell synthesis in the context of insufficient endogenous erythropoietin (such as in chronic end-stage renal disease). G-CSF stimulates the CFU-GM progenitors to differentiate into mature neutrophils. It is used when neutrophil count is dangerously low, for example following chemotherapy. Eltrombopag and romiplostim stimulate platelet synthesis via stimulation of the thrombopoietin receptor on megakaryocytes. They are used to increase platelet counts in immune thrombocytopenic purpura (ITP).

**Table 1.2 Growth factors**

<table>
<thead>
<tr>
<th>Growth factor</th>
<th>Source</th>
<th>Cellular target</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythropoietin</td>
<td>Kidneys</td>
<td>BFU-E and CFU-E</td>
<td>Stimulates the BFU-E and CFU-E to progress down the differentiation pathway of red cell precursors, ultimately forming mature red cells</td>
</tr>
<tr>
<td>Thrombopoietin</td>
<td>Liver</td>
<td>CFU-Meg, megakaryocytes</td>
<td>Enhancement of basal production rate of megakaryocytes (from CFU-Meg) and platelets (from megakaryocytes)</td>
</tr>
<tr>
<td>G-CSF</td>
<td>Endothelial cell, macrophages, lymphocytes</td>
<td>CFU-G</td>
<td>Differentiation into mature neutrophils</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>Macrophages, T cells and mast cells</td>
<td>CFU-GM</td>
<td>Granulocyte and monocyte precursor growth and differentiation</td>
</tr>
<tr>
<td>Interleukin 2</td>
<td>Activated T cells, NK cells, macrophage</td>
<td>Pre-T cell</td>
<td>T cell growth and differentiation</td>
</tr>
<tr>
<td>Interleukin 3</td>
<td>T cells, thymic epithelium</td>
<td>CFU-GEMM</td>
<td>Haematopoiesis</td>
</tr>
<tr>
<td>Interleukin 5</td>
<td>T cells, mast cells, eosinophil</td>
<td>CFU-Eos</td>
<td>Eosinophil growth and differentiation</td>
</tr>
<tr>
<td>Interleukin 6</td>
<td>T cells, macrophages, some B cells</td>
<td>Activated B cells, plasma cells, T cells, macrophages</td>
<td>Inflammatory cytokine that induces acute-phase response</td>
</tr>
</tbody>
</table>

*BFU-E, Erythroid burst-forming unit; CFU, colony-forming unit; CFU-Eos, CFU eosinophil progenitor; CFU-G, CFU neutrophil precursor; CFU-GEMM, CFU generating myeloid cells; CFU-GM, CFU granulocyte-macrophage precursor (the neutrophil/monocyte precursor); G-CSF, granulocyte-colony stimulating factor; GM-CSF, granulocyte-macrophage colony stimulating factor; NK, natural killer.*

**Bone marrow**

Bone marrow is the major haematopoietic organ in adults, producing ~500 billion cells daily and accounting for ~5% of body weight. It is divided into red marrow and yellow marrow. Red marrow is red due to haematopoiesis and yellow marrow is yellow due to fat. In situations where the existing red marrow is unable to perform haematopoiesis at a rate sufficient for normal physiological function, yellow marrow retains the ability to resume haematopoiesis, in which case it becomes red marrow.

**Structure**

Bone marrow tissue lies within central cavities of bones, supported by a matrix of bony trabeculae. Red marrow provides an optimal microenvironment for haematopoietic stem cell growth and development. It has two main components: haematopoietic parenchyma (developing blood cells) and supporting stromal tissue.

**Stroma**

In red marrow, stroma consists of vascular sinusoids and specialized fibroblasts. Vascular sinusoids consist of blood-filled spaces, fed by arterioles and interconnected by multiple fenestrated capillaries. Sinusoids ultimately drain (radially) into a large central vein from whence they enter the venous circulation. The fenestrations allow passage...
of matured blood cells out of the marrow and into the bloodstream by this route. Specialized fibroblasts (adventitial reticular cells) secrete reticulin (a subtype of collagen) fibres, which form a supportive mechanical framework for the haematopoietic tissue.

**Haemopoietic tissue**

Also known as ‘haematopoietic islands’ or ‘haematopoietic cords’, the synthetic tissue of red marrow contains stem cells, progenitors, precursors and mature bloods cells. This haematopoietic tissue fills the area between the vascular sinusoids. Anatomical compartmentalization occurs according to the type of blood cell being synthesized, e.g., red cell synthesis occurring in erythroblastic islands, megakaryopoiesis occurring in zones adjacent to the sinusoids, etc.

**Haematopoietic cord macrophages**

Macrophages, full of iron-rich stores of ferritin and haemosiderin, are centrally located within each cluster of haematopoietic synthesis. They have three main functions:

1. Provision of an iron supply for developing erythroblasts (for haemoglobin synthesis)
2. Phagocytosis of the cellular debris associated with haematopoiesis
3. Contributing to the cellular regulation of haematopoiesis

**Lymphocyte differentiation**

Bone marrow synthesizes lymphocytes and is thus termed a ‘primary’ lymphoid organ.

**B cell differentiation**

B cell development is dependent on bone marrow stroma. As B cell precursors develop, they migrate towards the central axis of the marrow cavity and become less reliant on stromal support. Any developing B cells that demonstrate binding to self-antigens are destroyed at this stage. The surviving B cells enter the circulation, travelling to the spleen/lymph nodes for final maturation.

**T cell differentiation**

T lymphocyte precursors leave the bone marrow earlier in their development. They enter the circulation and travel to the thymus for maturation.

**Natural killer cell differentiation**

NK cells undergo initial development in the bone marrow, but ultimately deploy to secondary lymphoid tissue (tonsils, lymph nodes and spleen) for further maturation.

---

**THE SPLEEN**

The spleen is the largest secondary lymphoid organ. In some ways, it may be thought of as a very large and sophisticated lymph node. The spleen is responsible for the following physiological roles:

- Removal of particulate matter from the bloodstream (e.g., opsonized bacteria, antibody-coated cells)
- Destruction of elderly and poorly deformable erythrocytes
- Initiation of the immune response to blood-borne antigens
- A storage zone for platelets (~1/3 of the platelet population is found in the spleen)
- Fetal haematopoiesis

**Embryology**

The spleen originates as a mesodermal proliferation from the primitive gut during the fifth week of fetal development.

**Anatomy**

The spleen is an intraperitoneal organ, measuring between 6 cm and 13 cm when healthy. It is wrapped in a dense fibro-elastic capsule that protrudes conspicuously into the organ, subdividing it. Blood supply to the spleen is via the splenic artery, which enters at the hilus. Venous drainage via the splenic vein also leaves via the hilus, ultimately entering the portal vein via the superior mesenteric vein. It is connected to the body wall by the lienorenal ligament and to the stomach by the gastrolienal ligament. It is anatomically related to:

- Stomach, tail of pancreas, left colic flexure (anteriorly)
- Left kidney (medially)
- Diaphragm, ribs 9–11 (posteriorly)

There are two types of functional tissue: red pulp and white pulp. These are separated by the marginal zone.

**Red pulp**

Red pulp is a 3D meshwork of splenic cords (connective tissue) and numerous blood-filled sinusoids. Blood cells are extravasated into splenic cord filtration beds where lattice-like networks of connective tissue and macrophages perform the mechanical filtration function of the spleen, removing antigens, microorganisms, senescent blood cells and blood-borne particulate matter. Once through the filtration bed, cells return to the circulation via the sinusoids, which drain into the venous system.

**White pulp**

White pulp consists of B cell follicles and peri-arteriolar lymphoid sheaths (PALS), which protrude into the red pulp. PALS are dense areas of lymphatic tissue, mainly consisting of T cells, wrapped around splenic arterioles. The B cell follicles are continuous with the PALS.
Marginal zone
This region (histologically considered white pulp) delineates red pulp and white pulp. Some resident macrophages and marginal zone B cells are permanent features. Other B cells and T cells are only present temporarily, in transit between the circulation and their splenic domains (follicles or PALS respectively). This makes the marginal zone an optimal site for antigen processing and presentation and lymphocyte/dendritic cell interaction.

Disorders of the spleen

Splenomegaly
Enlargement of the spleen (splenomegaly) may arise in many different disorders, as illustrated in Table 1.3. Clinically palpable splenomegaly must be accurately assessed with appropriate imaging.

<table>
<thead>
<tr>
<th>System/mechanism</th>
<th>Specific causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection: bacterial</td>
<td>Tuberculosis, Salmonella, Brucella, Syphilis, Infective endocarditis</td>
</tr>
<tr>
<td>Infection: viral</td>
<td>Epstein–Barr virus, Hepatitis, Cytomegalovirus, HIV</td>
</tr>
<tr>
<td>Infection: parasitic</td>
<td>Malaria, Toxoplasmosis, Schistosomiasis, Visceral leishmaniasis, Trypanosomiasis</td>
</tr>
<tr>
<td>Inflammation/immune</td>
<td>Sarcoidosis, Rheumatoid arthritis, Systemic lupus erythematosis</td>
</tr>
<tr>
<td>Haematological malignancy (Chapter 5)</td>
<td>Lymphomas, Leukaemias, Myeloproliferative disorders (especially primary myelofibrosis)</td>
</tr>
<tr>
<td>Nonmalignant haematological causes</td>
<td>Haemoglobinopathies, Haemolytic anaemia</td>
</tr>
<tr>
<td>Congestive (portal hypertension)</td>
<td>Liver cirrhosis, Right ventricular failure, Thrombosis of portal, hepatic or splenic veins</td>
</tr>
<tr>
<td>Trauma</td>
<td>Splenic intracapsular haematoma</td>
</tr>
<tr>
<td>Infiltrative</td>
<td>Lipid deposition disorders (e.g., Gaucher disease), Niemann–Pick disease, Amyloidosis, Glycogen storage disorders</td>
</tr>
</tbody>
</table>

Hypersplenism
Irrespective of the underlying cause of a splenomegaly, the enlarged spleen filters out more cells, resulting in excessive clearance of cells from the bloodstream. This reduces circulating numbers and results in cytopenias, resulting in the release of immature blood cells into the bloodstream from functionally normal bone marrow. This phenomenon is called hypersplenism and should be identified, because the effective treatment of the underlying cause of the splenomegaly can improve blood cell counts without resorting to a splenectomy.

Splenic infarction
Splenic infarction is the ischaemic death of splenic tissue due to occlusion of the arterial supply. It may affect part (partial infarction) or all (complete infarction) of the spleen. Emboli (secondary to atrial fibrillation) are the most common cause, but locally formed thrombi within the splenic artery or its major branches (associated with sickle-cell disease and myeloproliferative disorders) can also be responsible.

Rupture of the spleen
The spleen may rupture secondary to abdominal trauma, certain infections (e.g., Epstein–Barr virus; see Clinical notes) or disorders of haematopoiesis, e.g., primary myelofibrosis.

CLINICAL NOTES

EPSTEIN-BARR VIRUS
EBV infection (aka glandular fever or infectious mononucleosis) can cause splenomegaly for ≤8 weeks postinfection. Although it commonly causes mild/moderate splenomegaly, it is rarely serious. To prevent splenic rupture, patients with acute EBV infection are advised to avoid contact sports for at least 8 weeks.

Table 1.3 Causes of splenomegaly

<table>
<thead>
<tr>
<th>System/mechanism</th>
<th>Specific causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection: bacterial</td>
<td>Tuberculosis, Salmonella, Brucella, Syphilis, Infective endocarditis</td>
</tr>
<tr>
<td>Infection: viral</td>
<td>Epstein–Barr virus, Hepatitis, Cytomegalovirus, HIV</td>
</tr>
<tr>
<td>Infection: parasitic</td>
<td>Malaria, Toxoplasmosis, Schistosomiasis, Visceral leishmaniasis, Trypanosomiasis</td>
</tr>
<tr>
<td>Inflammation/immune</td>
<td>Sarcoidosis, Rheumatoid arthritis, Systemic lupus erythematosis</td>
</tr>
<tr>
<td>Haematological malignancy (Chapter 5)</td>
<td>Lymphomas, Leukaemias, Myeloproliferative disorders (especially primary myelofibrosis)</td>
</tr>
<tr>
<td>Nonmalignant haematological causes</td>
<td>Haemoglobinopathies, Haemolytic anaemia</td>
</tr>
<tr>
<td>Congestive (portal hypertension)</td>
<td>Liver cirrhosis, Right ventricular failure, Thrombosis of portal, hepatic or splenic veins</td>
</tr>
<tr>
<td>Trauma</td>
<td>Splenic intracapsular haematoma</td>
</tr>
<tr>
<td>Infiltrative</td>
<td>Lipid deposition disorders (e.g., Gaucher disease), Niemann–Pick disease, Amyloidosis, Glycogen storage disorders</td>
</tr>
</tbody>
</table>

a Most common causes for splenomegaly in the UK
**Principles of haematology**

**Splenectomy**
Indications for splenectomy (surgical removal of the spleen) include:
- Severe splenic trauma causing uncontrollable bleeding
- Splenic lymphoma
- Immune cytopenias (autoimmune haemolytic anaemia, immune thrombocytopenia)
- Nonimmune haemolysis when secondary to splenic RBC destruction (Thalassaemia major, hereditary spherocytosis)
- Splenic cysts (only rarely)

Autosplenectomy refers to the hyposplenism that develops when the spleen is rendered nonfunctional by disease. Splenic artery thrombosis is an illustrative example. Sickle cell disease is one of the most common causes in infancy, due to cumulative localized small-vessel thrombosis. Coeliac disease is another well-known cause of autosplenectomy, although the exact mechanism is unclear.

**Congenital abnormalities**
Congenital asplenia (absent spleen) is rare and usually associated with other congenital abnormalities. Conversely, ~10% of people have accessory spleens (additional small areas of splenic tissue).

**Management of the hyposplenic patient**
Regardless of the cause of their hyposplenism, asplenic and hyposplenic patients are at an increased risk of infection, particularly infection by encapsulated bacteria (e.g., *Neisseria meningitides*, *Streptococcus pneumoniae*, *Haemophilus influenzae*). This is primarily because the spleen, being the largest lymphoid organ, is the major site for immunoglobulin synthesis, including IgM. IgM is necessary for opsonization of encapsulated organisms. Macrophages lining the meshwork of the red pulp also ingest and remove unopsonized bacteria. In the absence of a spleen, both these functions are lost. The clinical consequence is a patient with lifelong susceptibility to overwhelming postsplenectomy infections (OPSI).

To reduce the chance of OPSI, several interventions are required in asplenic/hyposplenic patients:

1. Vaccinations (courses to be completed >2 weeks prior to splenectomy or initiated >2 weeks post splenectomy). The first three vaccines must be protein conjugate vaccines, which are more effective than plain polysaccharide vaccines:
   - Pneumococcal vaccine (with boosters every 5–10 years afterwards)
   - *Haemophilus influenzae* vaccination course
   - Meningococcal vaccines
   - Influenza vaccination (repeated annually lifelong)

2. Lifelong prophylactic daily oral antibiotics: Penicillin V (clarithromycin if penicillin-allergic). Many patients unfortunately stop taking their daily antibiotics after a few years, only to die of overwhelming sepsis.

3. Clear advice regarding the need for urgent medical review if patients develop symptoms of infection, e.g., sore throat/fever/productive cough/lethargy/diarrhoea/vomiting, etc.

It is of paramount importance that patients repeat the above vaccinations as required for the rest of their lives, as well as continuing to take their daily prophylactic antibiotics.

**LYMPHADENOPATHY**
Enlarged lymph nodes (lymphadenopathy) are normal when occurring in response to infection or inflammation. However, in the absence of these factors, lymphadenopathy may be an important indicator of neoplastic disease. An illustration showing the main groups of lymph nodes is given in Fig. 1.3. Acute, localized tender/painful lymphadenopathy is generally a helpful indicator of infection in the area drained by the enlarged nodes. Insidious, painless, non-tender generalized (involving >1 anatomical region) node enlargement is more likely to be due to malignancy (see Chapter 5: Lymphadenopathy red flags) but may be due to a nonmalignant pathology. Examples are detailed in Table 1.4.
Fig. 1.3 Lymph node locations. Solid circles represent palpable lymph node(s), unfilled circles represent impalpable or internal lymph nodes. Note that the popliteal lymph nodes are palpable in the popliteal fossa on the posterior surface of the leg.
Blood consists primarily of different cell types suspended in fluid plasma. Blood delivers oxygen and nutrients to cells of the body and removes carbon dioxide and waste products. There are several types of blood cells, each with characteristic structure and functions: erythrocytes, platelets, lymphocytes, granulocytes and monocytes. Blood cells are synthesized via a process of development known as haematopoiesis. Different development pathways for different cell types all originate from haemopoietic stem cells. Haematopoiesis occurs in different tissues according to developmental stage. This takes place in the bone marrow in adults. The spleen plays several important immunological roles as well as filtering particulate matter and removing aged red cells from the bloodstream. Lymph node enlargement (lymphadenopathy) may occur in response to infection or malignancy.

---

### Table 1.4 Causes of generalized lymphadenopathy

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Examples</th>
<th>Mechanism</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection:</td>
<td></td>
<td>Connective tissue disease</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>viral</td>
<td>Epstein-Barr virus</td>
<td></td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td></td>
<td>Cytomegalovirus</td>
<td></td>
<td>Churg-Strauss syndrome</td>
</tr>
<tr>
<td></td>
<td>Herpes Simplex 1 and 2</td>
<td></td>
<td>Dermatomyositis</td>
</tr>
<tr>
<td></td>
<td>Rubella</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Measles</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hepatitis B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection:</td>
<td></td>
<td>Drugs</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>protozoal</td>
<td>Toxoplasmosis</td>
<td>Isoniazid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leishmaniasis</td>
<td>Aspirin</td>
<td></td>
</tr>
<tr>
<td>Infection:</td>
<td></td>
<td>Penicillins</td>
<td></td>
</tr>
<tr>
<td>bacterial</td>
<td>Borreliosis (Lyme disease)</td>
<td>Tetracyclines</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leptospirosis (Weil syndrome)</td>
<td>Sulphonamides</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tularaemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Brucellosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection:</td>
<td></td>
<td>Neoplasia</td>
<td>Leukaemias</td>
</tr>
<tr>
<td>fungal</td>
<td>Histoplasmosis</td>
<td></td>
<td>Lymphomas</td>
</tr>
<tr>
<td></td>
<td>Cryptococcosis</td>
<td></td>
<td>Nonhaematological metastatic malignancy</td>
</tr>
<tr>
<td></td>
<td>Coccidioidomycosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td>Miscellaneous</td>
<td>Sarcoïdosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Amyloidosis</td>
</tr>
</tbody>
</table>