KEY KNOWLEDGE

This chapter is designed to enable students to:

- understand the significance of immunity as a multipronged defence against disease
- recognise innate immunity and adaptive immunity as major subdivisions of the immune system
- understand the operation of innate immunity
- understand the operation of adaptive immunity
- become familiar with the cells of the immune system and their modes of operation.

FIGURE 7.1 A false-coloured scanning electron micrograph showing a white blood cell, known as a dendritic cell (grey) starting to engulf a yeast spore (yellow). Note the extensions (pseudopodia) of the dendritic cell that are spreading around the yeast cell at the start of the process of phagocytosis. The actions of phagocytic cells are just one of the many immune mechanisms that defend against infection. In this chapter, we will explore the two arms of the immune system, namely innate immunity and adaptive immunity.
Inflammation of the gut

Julie, a normally busy young woman, is aware that she is suffering fatigue and is losing weight. Julie tells her friends that her gut is increasingly ‘playing up from time to time’ and she is having stomach cramps. However, Julie thinks that her problem is due to something in her diet that is upsetting her gut. She knows that her fatigue is due to the fact that her sleep is frequently interrupted by her need to go to the toilet when her gut is ‘playing up’ and she has severe diarrhoea.

On one of her frequent visits to the toilet, Julie realises from stains on the toilet paper that blood is present in her faeces. Alarmed that this as a possible sign of bowel cancer, Julie goes to her local doctor, who takes her medical history and arranges for her to have a blood test to check for anaemia, and to have a test for the presence of blood in her faecal samples.

Based on the positive test results, Julie is referred to a specialist. She undergoes a procedure called colonoscopy. In this procedure, a colonoscope, a long flexible tube fitted with a small camera and light, is inserted into the gut via the anus for the purpose of examining the internal lining of the colon (see figure 7.2). The colon is part of the large intestine between the caecum and the rectum. This instrument can detect polyps (small growths), colon cancer, ulcers, and areas of inflammation and bleeding.

The results of the colonoscopy show that Julie is suffering from a condition called ulcerative colitis (UC) in which the lining of her colon is inflamed and has many small ulcers (see figure 7.3). Fortunately, Julie’s condition is now successfully controlled by medication, including an anti-diarrhoea drug and prescription steroids to control the inflammation of the lining of her colon. For some sufferers of UC, surgical intervention may be required.

UC is a chronic inflammatory disease of the colon. In UC, the lining of the colon becomes inflamed and develops ulcers that produce pus and mucus. The combination of inflammation and ulceration causes abdominal discomfort and diarrhoea. Periods of active UC flare up from time to time and tend to be interspersed with periods of remission.
Let’s now look at immunity and then explore the two major subdivisions of the immune system, namely innate immunity and adaptive immunity, which defend us against infectious diseases.

**Immunity: defence against infection**

**Immunity** is resistance to infectious disease. The term ‘immunity’ is derived from the Greek *immunitas* = exemption from duty. However, in a biological sense, immunity means ‘exemption from disease’.

The cells and tissues involved in resistance to infection are part of the body’s immune system. The human immune system is the collection of organs, tissues, cells and molecules that protects us from various damaging agents around us, including pathogens, toxins and other foreign molecules. The essence of immune defence is the ability of the immune system to distinguish between the body’s own cells and molecules, and the foreign cells and molecules that carry distinctive ‘non-self’ antigens.

The mildest form of UC is a condition in which a person passes faeces, with or without blood, less than four times daily. The most severe form is fulminant UC, a very serious condition in which a person passes faeces more than ten times daily, has continuous rectal bleeding that requires blood transfusions, has abdominal swelling and tenderness, and shows system-wide toxic effects.

What is the cause of UC? The normal response of the innate immune system to infection involves acute (short-term) inflammation that isolates and eliminates invading pathogens. However, after the pathogens have been eliminated, this acute inflammatory response must be turned off. If this does not happen, healthy tissue becomes damaged by the active molecules released by immune cells.

UC arises when the body’s immune system malfunctions by failing to ‘turn off’ an acute inflammatory response. In UC, the immune system sets up an inflammatory response, perhaps mistakenly in response to harmless material in the colon, and it is not switched off, so that the inflammation persists and becomes chronic (of long duration). (This of course begs the question: What causes the failure to switch off the acute inflammatory process?)

Estimates of the number of people in Australia affected by ulcerative colitis at any given time range between 16,000 and 33,000 people.

‘Fulminant’ means occurring with rapidity and severity, and comes from the Latin *fulminare* = ‘to strike with lightning.’

The remarkable efficiency of the immune system in distinguishing between ‘self’ and ‘non-self’ markers is unfortunately demonstrated when the immune system of the recipient of a transplanted organ recognises the transplant as carrying non-self markers and attacks it, causing its rejection (refer back to chapter 6, pages 263–270).
Cells of the immune system

All the immune cells that provide us with defence against infection are various kinds of white blood cells that are found in lymph, blood, lymphoid organs and tissues. White blood cells are greatly outnumbered in the blood by the oxygen-carrying red blood cells. White blood cells are present in normal blood at concentrations in the range of 4000 to 10,000 cells per microlitre. Contrast this with red blood cells, which are present at concentrations ranging from 4.2 to 5.4 million cells per microlitre for adult females and 4.7 to 6.1 million cells per microlitre for adult males.

The different kinds of white blood cells can be distinguished by features such as the shapes and sizes of their nuclei and the presence (or absence) of prominent granules in their cytoplasm. Figure 7.4 shows some examples of different kinds of white blood cells. See if you can identify one or more kinds of white blood cells based on the descriptions in the figure caption. Later in this chapter, you will meet these various cells and learn about their particular roles in innate immunity and in adaptive immunity.

**FIGURE 7.4** Photomicrographs of human blood smears (400×) stained with Wright’s stain and showing one or more white blood cells against a background of smaller pale red blood cells. Can you identify the neutrophil that has a distinctive multi-lobed nucleus? What about a basophil with its large number of densely stained cytoplasmic granules? What about a lymphocyte — either a B cell or a T cell — that is a smaller white blood cell with a relatively large round nucleus typically surrounded by a thin ring of cytoplasm? What about an eosinophil with its bilobed nucleus and many granules? Can you identify a monocyte — a larger cell with a kidney-shaped or notched nucleus? (Check bottom of page 282 for answers.)
All the cells of the immune system are white blood cells derived from multipotent stem cells in the bone marrow (see figure 7.5). One subgroup of immune cells are the lymphocytes, which include B cells and T cells found in large numbers in lymph nodes. Other immune cells, such as neutrophils, circulate in the bloodstream; others, for example macrophages and dendrites, are located close to points where pathogens can gain entry to the body, such as in the mucous membranes of the throat, airways and gut.

**FIGURE 7.5** Diagram showing the production of immune cells from multipotent stem cells in the bone marrow. All these cells, except for B cells and T cells, contribute to innate immunity. NK cell = natural killer cell. The B cells and T cells are the key players in adaptive immunity.

**ODD FACT**
About three litres of lymph are collected by lymphatic vessels each day and drain into the blood circulatory system.

**Role of lymphatic system in immunity**

The lymphatic system consists of a network of thin-walled lymphatic vessels containing lymph that reaches all tissues of the body and interconnects the lymphoid organs. These organs include bone marrow, thymus, spleen, and lymph nodes and they are composed of lymphoid tissue — so called because they contain large numbers of lymphocytes. The distribution of lymphoid tissue throughout the body, in particular in the hundreds of lymph nodes, enables foreign antigens to be rapidly detected (see figure 7.6).

The lymphatic system plays important roles in immunity:

- The bone marrow and the thymus are called **primary lymphoid organs** because they are the sites where mature lymphocytes (B cells and T cells) develop from precursor cells.
- The lymph nodes and spleen are composed of **secondary lymphoid organs**. These organs are the sites where mature B cells and T cells are activated by meeting their complementary antigens and developing into effector cells. **Lymph nodes are where adaptive immune responses occur.**
The various organs of the lymphatic system are listed here.

**Bone marrow:**
- forms the soft tissue in the hollow centre of long bones
- is the source of pluripotent stem cells, from which all the cells of the immune system (and other blood cells, such as red blood cells and platelets) originate
- is the site of development of B cells.

**Thymus:**
- is located just behind the sternum (breastbone) of the rib cage
- shrinks with age, from about 70 grams in infants to about 3 grams in elderly people
- is the site where T cells develop after being released from the bone marrow.

**Spleen:**
- is a flattened organ lying in the upper-left sector of the abdomen
- filters the blood passing through it, clearing the blood of bacteria and viruses as well as worn-out red blood cells

Cells in figure 7.4 on page 280: (a) Upper right: neutrophil; lower left: lymphocyte, probably a T cell or a B cell. (b) basophil (c) eosinophil (d) monocyte (at left) and lymphocyte, probably a T cell or a B cell (at right).
• contains T cells and B cells that detect and respond to infectious agents in the blood
• contains other immune cells, including macrophages and dendritic cells.

**Lymph nodes:**
• are small bean-shaped structures located along lymphatic vessels
• are present in high numbers in strategic locations within the body — in the armpits, groin, neck and abdomen
• are located along blood vessels and lymphatic vessels, which enable B cells and T cells to enter and exit the lymph nodes. Most enter the lymph nodes via incoming arteries, but about 10 per cent enter via the incoming lymphatic vessel
• are the sites where any ‘new’ foreign antigen meets and activates B cells and T cells and where immune responses occur
• swell when infections occur, because the numbers of B and T cells in the lymph nodes increase — this produces the so-called ‘swollen glands’
• consist of an internal structure comprising an outer cortex, an inner cortex and a central medulla (see figure 7.7):
  - The outer cortex contains follicles with large numbers of B cells that divide and diversify; antigen-presenting cells, such as dendritic cells, are also found here.
  - The inner cortex mainly contains T cells and other immune cells such as dendritic cells.
  - The medulla contains B cells, including special antibody-producing B cells called plasma cells.
• trap cancer cells or bacteria travelling in lymph vessels — for this reason, people who have a cancer surgically removed, such as a breast cancer, typically will also have the lymph nodes draining the affected organ removed (see figure 7.8).

**ODD FACT**
It is estimated that up to 99 per cent of bacteria that enter a lymph node are removed at this point.

*FIGURE 7.7* Diagram showing the LS through a lymph node. Immune cells and foreign particles enter the lymph node either from the incoming lymphatic vessel or the incoming artery. Immune cells leave the lymph node in the outgoing lymphatic vessel. Lymph nodes contain clusters of B cells in the follicles of the outer cortex and clusters of T cells in the inner cortex.
Subdivisions of the immune system

Immunity has two major subdivisions (see figure 7.9) whose combined operations protect the body from infectious diseases:

1. **innate immunity**, also known as non-specific or natural immunity
2. **adaptive immunity**, also known as specific or acquired immunity.

Different immune cells and active molecules, in particular soluble proteins, are involved in these two kinds of immunity.

The innate immune system is the body’s pre-existing defence against invasions by pathogens and it comes into operation within minutes of an infection. In contrast, the adaptive immune system comes into operation only after the innate immune defences are evaded or overwhelmed, and this takes days to develop fully.

**FIGURE 7.8** Diagram showing lymphatic drainage of the female breast. Note the numerous lymph nodes that are present along the lymphatic vessels.

**FIGURE 7.9** The immune system provides the body’s defence against various pathogens. The immune defence system has two major subdivisions: (i) innate or non-specific immunity and (ii) adaptive or specific immunity.
Both subdivisions of immunity protect against infection within the body through the actions of:

1. **Immune cells that directly attack invading pathogens.** Direct attack by immune cells against pathogens form the cellular (or cell-mediated) immune responses. (Later in this chapter we will meet some of these cells — the natural killer (NK) cells of innate immunity and cytotoxic T cells of adaptive immunity.)

2. **Soluble molecules in the blood, lymph and interstitial fluid that disable pathogens.** The actions of these molecules form the humoral immune responses. (Later in this chapter we will meet some of these soluble molecules, such as the complement proteins of innate immunity and the antibodies of adaptive immunity.)

Table 7.1 summarises differences between innate immunity and adaptive immunity. Check out this table.

**TABLE 7.1** Summary of differences between innate (non-specific) immunity and adaptive (specific) immunity.

<table>
<thead>
<tr>
<th></th>
<th><strong>Innate immunity</strong></th>
<th><strong>Adaptive immunity</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>also known as non-specific and natural immunity</strong></td>
<td>present in animals, plants, fungi and invertebrates</td>
<td>present only in jawed vertebrates*</td>
</tr>
<tr>
<td><strong>response is not antigen specific</strong></td>
<td>produces non-specific (generic) responses against classes of pathogens, not against specific pathogens</td>
<td>response is antigen specific</td>
</tr>
<tr>
<td><strong>immune responses occur mainly at sites of infection</strong></td>
<td>only reacts against microbes</td>
<td>produces specific responses, with tailor-made antibodies against each particular microbe</td>
</tr>
<tr>
<td><strong>present from birth</strong></td>
<td>activity is always present so that maximum response is rapid and immediate</td>
<td>immune responses occur mainly in secondary lymphoid organs, such as lymph nodes</td>
</tr>
<tr>
<td><strong>defence provided is not long-lasting</strong></td>
<td>no ‘memory’ of prior infections, so that an identical response occurs with every infection</td>
<td>reacts against both microbes and foreign molecules such as toxins</td>
</tr>
<tr>
<td><strong>Major responses are:</strong></td>
<td>1. Cellular attack on bacteria and virus-infected cells</td>
<td>develops only after infection or after immunisation</td>
</tr>
<tr>
<td></td>
<td>2. Attack by soluble proteins These two responses (1 &amp; 2) combine to produce inflammation</td>
<td>normally inactive or silent so that maximum response is slower — within days or weeks</td>
</tr>
</tbody>
</table>

*Among the vertebrates, only lampreys and hagfish do not have adaptive immunity; these are jawless vertebrates.

Note that innate immunity provides a number of fixed or non-specific defences against groups of pathogens. ‘Non-specific’ means that innate immunity identifies and responds to a limited number of features of pathogens. In
contrast, adaptive immunity provides defences that are specifically tailored for attack against each particular pathogen. As its name suggests, the adaptive immunity recognises an unlimited number of antigens.

Note also that innate immunity retains no memory of pathogens that infect the body and, as a result, if the same kind of pathogen invades again, the innate immune responses are the same as for the first infection. In contrast, the adaptive immunity retains a ‘memory’ of past infections and, as a result, if the same pathogen invades again, the adaptive immune system produces a quicker and stronger response.

Immunity operates through three lines of defence against pathogens:
1. The **first line of defence** consists of physical and chemical barriers to prevent pathogens from gaining entry to the body.
2. The **second line of defence** consists of the actions of immune cells and soluble proteins mounting a rapid but non-specific attack against pathogens that gain entry to the body.
3. The **third line of defence** consists of the actions of immune cells and antibodies tailored specifically to attack each invading pathogen.

The first and second lines of defence involve operations of the innate immune system.

The third line of defence comes into operation only if the second line of defence fails. This line of defence involves the operations of the adaptive immune system.

The two subdivisions of the immune system do **not** operate in isolation, although the timing of their responses differs. The first to come into operation are the innate immune responses and, only after they have failed, do adaptive immune responses begin. Communication between cells of the two immune subdivisions ensures that immune responses are highly coordinated. Cells of the adaptive immune system are alerted, by innate immune cells, to the antigens present on particular pathogens that have overwhelmed the innate immune system.

In the following section, we will explore the innate immune system. Then we will examine the adaptive immune system (see page 308).

### KEY IDEAS

- The immune system comprises various organs, cells, and molecules that act to protect the body from infectious microbes.
- Immunity depends on the ability to distinguish between ‘self’ and ‘non-self’ markers (antigens) on cells.
- All the cells of the immune system originate as stem cells in the bone marrow.
- Primary lymphoid organs are sites where immune cells are produced and mature.
- Secondary lymphoid organs are the sites where immune cells are activated by meeting antigens and where immune responses occur.
- The immune system has two major subdivisions: innate (non-specific) immunity and adaptive (specific) immunity.
- Immunity provides three lines of defence against infectious disease.
- The first and second lines of defence involve operations of the innate immune system.
- The third line of defence involves operations of the adaptive immune system.
- Innate and adaptive immunity both operate through cellular responses and the actions of soluble proteins (humoral responses).
The innate immune system

Your innate immunity, also known as non-specific immunity and natural immunity, provides immediate protection against pathogens through two lines of defence:

- The first and external line of defence is achieved by physical and chemical barriers that prevent entry of pathogens to the body. This first line of defence involves the immediate strategy: ‘Keep pathogens out’.
- The second line of defence is initiated if pathogens overcome the first line of defence and gain entry to the body. The second line of defence involves the strategy: ‘Identify and eliminate pathogens’.

First line of defence: keep them out!

The best protection against infection is preventing pathogens from crossing the body surfaces. This is achieved by the epithelial tissues of the body and their secretions, which are the major components of the first line of defence.

Epithelial tissues include (i) the external layers of the skin, and (ii) the internal linings or mucous membranes of the cavities of the airways, the gut and the urogenital tract. These epithelial tissues form a physical barrier to the entry of microbes because their cells are densely packed, leaving no intercellular space between them. In addition, secretions of various epithelial cells contain anti-microbial agents that produce a chemical barrier against pathogens (see figure 7.10).

The major barriers that prevent entry of pathogens are the intact skin, mucous membranes and their secretions:

- **Intact skin:** The intact skin constitutes an important physical and chemical barrier to microbial infection. The epidermis of the skin is composed of many layers of cells (keratinocytes) with the outermost layer consisting of flattened dead cells. The constant shedding of these dead surface cells is an effective barrier against entry of pathogens (see figure 7.11). Sebaceous glands in the skin produce a secretion called sebum, which provides a protective and anti-microbial film on the skin. Sweat secreted onto the skin contains an anti-microbial protein called dermcidin, which acts against a wide range of pathogens.
**Mucous membranes:** The inner spaces of the airways, the gut, and the urogenital tract are lined by mucous membranes consisting of epithelial cells. Adjacent cells have tight junctions between them that prevent the entry of microbes.

Special cells in the mucous membranes of the gut, the genital tract and the airways secrete a thick gelatinous fluid called **mucus** that can trap particulate matter, including pathogens. In the airways, the mucous membranes include many cells with **cilia** on their outer surfaces. Cilia are fine hair-like outfoldings of the plasma membrane (see figure 7.12a). Regular beating of the cilia moves mucus from deep in the airways to the back of the throat (see figure 7.12b). Some mucus is swallowed, and the acid secretions of the stomach destroy any bacteria. Other mucus is expelled from the back of the throat when people cough or blow their noses.

Some mucous membranes are washed constantly or regularly by secretions. Examples include the surfaces of the mouth and throat, which are washed by the constant flow of saliva, and the surfaces of the bladder and the urethra, which are regularly washed by urine that is sterile and slightly acidic. This surface-washing prevents pathogens from becoming established.
Another barrier to the entry of pathogens is microbiological:

- **Presence of normal flora:** The term ‘normal flora’ refers to the non-pathogenic bacteria that are the normal residents in particular regions of the body, including the gut, the mouth and throat, and the genital tract. The presence of these harmless bacteria inhibits the growth of pathogenic microbes. For example, the normal flora of the vagina is *Lactobacillus acidophilus*. These bacteria produce lactic acid, which prevents the establishment of pathogenic microbes.
KEY IDEAS

- The first line of defence is part of the innate immune system.
- The first line of defence consists of physical and chemical barriers that prevent entry of pathogens to the body.
- Epithelial tissues and their secretions are the major physical and chemical barriers of the first line of defence.
- Secretions that contribute to preventing entry include mucus, tears, saliva and urine.
- The so-called ‘normal flora’ that are the non-pathogenic bacterial residents of regions of the body act as a microbiological barrier to pathogenic bacteria.

QUICK CHECK

4. Give an example of:
   a. an epithelial tissue
   b. a mucous membrane.

5. Where would you expect to find a ciliated mucous membrane?

6. Briefly outline how mucus defends against entry of pathogens to the body.

7. How does the ‘normal flora’ of the body contribute to the first line of defence?

Second line of defence: identify and eliminate!

Jason falls and grazes his knees so that the epidermis of his skin is eroded and the dermis is exposed (see figure 7.13). He brushes the dirt away from the injured area and sees that it is bleeding. His first line of defence against pathogens has been breached. Pathogenic bacteria in the soil have gained access to the internal environment of his body and this infection places Jason at risk of disease. However, when the first line of defence has been crossed, the second line of defence of the innate immune system comes into operation.

FIGURE 7.13 The breaks in the skin created by the grazes enable bacteria to enter the tissues. The second line of defence of the innate immune system comes into action immediately and involves the operation of immune cells, including macrophages and neutrophils, and humoral factors, including soluble proteins.
The second line of defence involves the actions of immune cells and soluble proteins that produce inflammation, the major defensive response of innate immunity to infection (see figure 7.14).

The immune cells involved in innate immunity include:
- phagocytic cells, which identify and destroy extracellular pathogens
- natural killer cells (NK cells), which identify and destroy cells infected with pathogens.

The various soluble proteins involved in innate immunity include:
- complement proteins in the bloodstream
- interferons secreted by many immune cells.

The inflammatory response is a localised protective response to infection that results from the action of immune cells and soluble proteins.

First, let’s meet the cells of the innate immune system.

Cells of the innate immune system

Different kinds of cells take part in the innate immune responses of the body to pathogens. Check out table 7.2, which summarises the functions of various cells involved in innate immunity. The cells of most interest to us are two phagocytic cells (neutrophils and macrophages), natural killer cells (NK cells) and mast cells. Phagocytic refers to various kinds of cells that can use the process of phagocytosis.

In the following section, we will explore how cells of the innate immune system eliminate pathogens.

The phagocytes and the natural killer (NK) cells of our innate immune systems can eliminate pathogens. The cell type and the mechanism used depend on whether the pathogen is extracellular or intracellular.
- Extracellular pathogens, such as bacteria in tissue fluid or blood, can be directly attacked by phagocytic cells, and their attack strategy is termed phagocytosis.
- Once pathogens have gained entry to body cells, they cannot be directly attacked by innate immune cells. Instead, infected body cells (along with their intracellular pathogens) are eliminated by immune cells called natural killer (NK) cells, using a strategy called degranulation.

Each of these processes is described below.

Phagocytosis: attacking extracellular pathogens

Among the ‘big guns’ of the innate immune system is the group of innate immune cells known as phagocytes (phago- = eating; kyto- = cell). These cell types eliminate pathogens and cell debris by engulfing them in the process of phagocytosis. Phagocytic cells, such as macrophages and neutrophils, are like the ‘vacuum cleaners’ of the immune system.

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Phagocytes were first introduced in chapter 5, page 208.
### TABLE 7.2 Various cell types involved in the innate immune responses to pathogens. Of these cell types, the most important include (1) neutrophils and macrophages, which are the major cells involved in the phagocytic attack against pathogens, and (2) natural killer (NK) cells, which eliminate virus-infected cells and cancer cells. (Data on frequencies taken from STEMCELL™ technologies, document #23629)

<table>
<thead>
<tr>
<th>Cell type (a) in blood</th>
<th>Stylised image</th>
<th>Description &amp; characteristics</th>
<th>Major role in innate immunity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>monocytes 2–12% of circulating white blood cells</strong></td>
<td><img src="image1" alt="Stylised image" /></td>
<td>circulating white blood cells (2–12%); can leave bloodstream and move into tissues where they differentiate into macrophages</td>
<td>precursors of macrophages</td>
</tr>
<tr>
<td><strong>neutrophils ‘first into the fray’ 30–80% of circulating white blood cells</strong></td>
<td><img src="image2" alt="Stylised image" /></td>
<td>most abundant circulating white blood cells (30–80%) with distinctive multi-lobed nuclei; short-lived; one of the major cells involved in phagocytosis, which kills engulfed microbes by toxic chemicals; first cells to arrive at infection site in response to chemotactic signals from other cells</td>
<td>identify and mount phagocytic attack on microbes</td>
</tr>
<tr>
<td><strong>eosinophils up to 7% of circulating white blood cells</strong></td>
<td><img src="image3" alt="Stylised image" /></td>
<td>circulating white blood cells; bilobed nucleus; phagocytic; release toxic chemicals from granules; major defence against parasites that are too large to be attacked by phagocytosis, e.g. parasitic worms</td>
<td>defence against larger parasites; attack uses toxic chemicals released from cytoplasmic granules</td>
</tr>
<tr>
<td><strong>basophils up to 2% of circulating white blood cells</strong></td>
<td><img src="image4" alt="Stylised image" /></td>
<td>rare circulating white blood cells; phagocytic; contain cytoplasmic granules that are rich in histamine and heparin</td>
<td>release of histamine and other molecules as part of inflammatory response; play a role in allergic reactions</td>
</tr>
<tr>
<td><strong>natural killer (NK) cells ‘the assassins’ 1–6% of circulating white blood cells</strong></td>
<td><img src="image5" alt="Stylised image" /></td>
<td>NK cells contain granules filled with potent chemicals; recognise and attack cells lacking ‘self’ markers; degranulation releases proteases and also perforin proteins, which insert holes in plasma membrane of foreign cells; induce programmed cell death (apoptosis)</td>
<td>elimination of virus-infected cells and cancer cells by degranulation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(b) in tissues</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>macrophages ‘the vacuum cleaners’</strong></td>
<td><img src="image6" alt="Stylised image" /></td>
<td>develop from monocytes that migrate into tissues; phagocytic; present in almost every tissue of body; eliminate microbes and cell debris; initiate acute inflammatory responses by secretion of various cytokines (also play a role as antigen-presenting cells)</td>
<td>identify and eliminate pathogens by phagocytosis; also remove dead cells and cell debris</td>
</tr>
<tr>
<td><strong>dendritic cells ‘sentinels on patrol’ in tissues</strong></td>
<td><img src="image7" alt="Stylised image" /></td>
<td>phagocytic cells, resident in tissues; characteristic star-shaped cell; present in skin epidermis, and on surface of linings of airways and gut; migrate via lymphatic vessels to lymph glands where they act as antigen-presenting cells</td>
<td>mobile cells that identify pathogens and secrete antiviral cytokines</td>
</tr>
<tr>
<td><strong>mast cells ‘border guards’</strong></td>
<td><img src="image8" alt="Stylised image" /></td>
<td>contain granules rich in histamine and heparin; found in tissues close to the external environment; involved in early recognition of pathogens; release chemical signals that attract other immune cells to infection site; involved in acute inflammatory response</td>
<td>release of histamine and other active molecules during acute inflammation; play role in allergies</td>
</tr>
</tbody>
</table>
The major phagocytic cells of the innate immune system are:
- neutrophils, which circulate in the bloodstream but can migrate into sites of infection in tissues
- macrophages (see figure 7.15), which are present in most tissues but are most concentrated in tissues close to epithelial layers. This is an ideal location for macrophages because this is close to potential entry points for pathogens to the body.

The stages in phagocytosis are:
1. The pathogen is identified by a pattern recognition receptor on the surface of the macrophage and is engulfed by outfoldings of the plasma membrane of the macrophage (also refer back to figure 7.1).
2. The pathogen is completely enclosed in a vesicle called a phagosome.
3. Lysosomes fuse with the phagosome (forming a phagolysosome) and release toxic chemicals that attack the pathogen. Toxic chemicals include oxygen radicals and nitric oxides that damage macromolecules, lysozymes that attack the cell walls of Gram-positive bacteria, and proteases and other digestive enzymes.
4. The pathogen undergoes digestion from this combined chemical attack. (See marginal note.)
5. Indigestible material is discharged from the phagocytic cell by a process of exocytosis.
In order to defend against pathogens, cells of the innate immune system must first identify pathogens as ‘foreign’ or non-self before they can eliminate them. Phagocytic cells of the innate immune system, such as macrophages and neutrophils, have many receptors called pattern recognition receptors (PRRs). Some PRRs are located on the surfaces of these immune cells, while other are present in their cytoplasm. PRRs enable cells of the innate immune system to identify pathogens by recognising and binding to non-specific molecular patterns found on groups of pathogens (see figure 7.17). This level of identification is a bit like being able to identify dogs and cats at the generic level, as, for example: 'That’s a cat!' or 'No, it's a dog!'
Contrast this with the level of pathogen identification that occurs with the adaptive immune system. We will see later in this chapter (see page 315) that the cells of the adaptive immune system can identify every different pathogen and antigen. This is a bit like being able to identify every dog and every cat by breed, colour, age, and every other distinguishing features, as, for example: ‘That’s a three-legged eight-year-old black Labrador named Lulu.’

Examples of molecular patterns that are recognised by PRRs and their level of identification are as follows:

- lipopolysaccharide (LPS) of cell walls of Gram-negative bacteria: ‘That’s a bacterium.’
- lipoteichoic acids on cell walls of Gram-positive bacteria: ‘That’s another bacterium.’
- flagellin protein present in bacteria with flagella: ‘Yet another bacterium.’
- the glycoproteins of enveloped viruses: ‘That’s a virus.’

**Degranulation: eliminating intracellular pathogens**

Degranulation is the release of anti-microbial and toxic molecules from membrane-bound granules stored in the cytoplasm of some innate immune cells. The release of granules into target cells is the main weapon used by natural killer (NK) cells to eliminate infected body cells. NK cells are like the assassins of the innate immune system (see figure 7.18). In particular, NK cells recognise missing or abnormal HLA markers on virus-infected cells and cancer cells and eliminate these cells by degranulation.

**FIGURE 7.18** False-coloured scanning electron microscope image of a natural killer (NK) cell (blue) attacking a cancer cell (pink). (Image courtesy of Dr Donna Stolz and Mr Marc Rubin of the Center for Biologic Imaging at the University of Pittsburgh.)
Elimination of targets by NK cells: Figure 7.19a shows a transmission EM image of an NK cell that contains several large granules (see lower left).

The granules in NK cells contain active protease enzymes, known as **granzymes**, and a pore-forming protein called **perforin** (see figure 7.19b). The combined action of these proteins destroys the target cell. Perforin molecules form a ring structure that punches a hole in the plasma membrane of the target cells, enabling entry of the proteases into the target cell. Once inside the cytoplasm of an infected target cell, the proteases induce apoptosis (refer back to chapter 5, page 209). Elimination of an infected cell or a cancer cell by degranulation of an NK cell is completed within hours.

**Killing virus-infected cells by apoptosis, rather than by lysis, is important.** Why? Lysis of a virus-infected cell simply explodes the cell, releasing the virus particles into the extracellular fluid so that the virus particles can infect other cells. In contrast, apoptosis destroys both the cell and any viruses it contains in a systematic manner, preventing the further spread of the virus.

**How do NK cells identify abnormal body cells?**

Body cells infected with viruses and cancer cells are part of a person’s body. How do natural killer (NK) cells recognise these infected and abnormal cells as targets for elimination?

NK cells identify targets for elimination even though the targets are body cells. The decision: ‘*kill or don’t kill*’ by an NK cell is believed to be determined by receptors on the plasma membrane of the NK cell: one receptor is for ‘kill’ and another is an inhibitory receptor that blocks the kill signal.

All body cells carry ligands that can bind to ‘kill’ receptors on NK cells. This binding activates the ‘kill’ receptors that signal an NK cell to eliminate any cell bound to it. However, this kill signal is inhibited by normal HLA markers on healthy body cells. The activation of the inhibitory receptors sends a signal that

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**ODD FACT**

As well as NK cells, other innate immune cells also release granules by exocytosis to kill target cells. These immune cells include neutrophils with granules containing cell-killing reactive oxygen species, and eosinophils with granules containing a protein (PRG2) that kills parasitic helminth worms.
blocks the kill signal. As a result, an NK cell does not identify healthy body cells as targets for elimination (see figure 7.20a).

Virus infections of body cells suppress the expression of class I HLA markers. Likewise, cancer cells produce abnormal HLA markers. These missing or abnormal HLA markers make these cells susceptible to being killed by NK cells because they cannot inhibit the ‘kill’ signal. An abnormal cell with missing HLA markers is like a flashing red light that signals to an NK cell: ‘Stop, degranulate and eliminate me.’

When contact is made with an infected cell that is missing or has abnormal HLA markers, the NK receptor for the inhibition of the ‘kill’ signal is not activated (see figure 7.20b). As a result, the NK cell responds to the ‘active kill’ signal and degranulates, spilling the lethal contents of its granules onto the target cell.

![Diagram of NK cell interaction with normal and abnormal cells](Image)

**Figure 7.20** Natural killer (NK) cells identify and destroy abnormal body cells such as virus-infected cells and cancer cells, but not normal body cells. (a) The NK cell does not attack a normal body cell because its inhibitory receptor is activated when it binds to a HLA self marker on this cell. (b) The NK cell attacks an abnormal body cell because the inhibitory receptor is not activated.

### Key Ideas

- The second line of defence of the innate immune system comes into immediate operation if pathogens overcome the barriers of the first line of defence.
- The second line of defence involves the operation of innate immune cells and humoral factors.
- The main cells involved in the cellular responses of innate immunity are macrophages, neutrophils and natural killer (NK) cells.
- Macrophages and neutrophils directly attack and eliminate extracellular pathogens through the process of phagocytosis.
- Pattern recognition receptors on phagocytic cells identify pathogens for elimination.
- Natural killer (NK) cells attack pathogens indirectly by identifying and eliminating pathogen-infected body cells and cancer cells through the process of degranulation.
**QUICK CHECK**

8 Give an example of the following that are part of innate immunity:
   a the most common circulating white blood cell
   b the ‘assassins’
   c a phagocytic cell
   d a cell that eliminates intracellular pathogens
   e a non-specific feature of a bacterial cell that could be recognised by a PRR.

9 Identify two methods by which innate immune cells eliminate pathogens.

10 What different outcome results from the lysis of a virus-infected cell as compared to the apoptosis of a virus-infected cell?

11 Identify the following as true or false:
   a The level of identification of pathogens by the cells of innate immunity is more specific than that of cells of adaptive immunity.
   b Neutrophils are the first cells to arrive at a site of infection.
   c Natural killer (NK) cells eliminate pathogens by degranulation.
   d Macrophages are tissue-based cells of the innate immune system that eliminate pathogens by phagocytosis.
   e Macrophages eliminate infected body cells by phagocytosis.
   f Pattern recognition receptors enable innate immune cells to identify a toxin in the bloodstream.

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**Humoral innate immunity**

In the section above, we explored various cell-mediated responses to infection, namely phagocytosis and degranulation. The other important part of the innate immune system is the humoral component, which involves the action of soluble proteins and their derivatives.

The second line of defence against pathogens involves humoral responses to pathogens. These responses involve the actions of soluble active molecules. Key soluble molecules involved in innate immunity include proteins known as complement and interferons.

**Complement proteins**

Dissolved in the plasma of your blood are proteins that form what is called complement. In total, the complement system comprises a large group of protease proteins (more than 25). The 11 major complement proteins are denoted C1 through C9, D and B, with the most abundant being C3. These plasma proteins are called ‘complement’ because they complement or add to the function of immune cells.

The complement proteins circulating in the bloodstream are inactive enzymes. **Complement proteins are activated when they make direct contact with molecules on the surface of a pathogen.**

The activation of the first complement protein starts a sequence of reactions that take place on the surface of a pathogen (but not on a healthy human body cell). The first protein in the series enzymatically alters the next protein in the series. The product of the first reaction then activates the next enzyme in the series, which, in turn, activates the next protein, and so on. The activation of a complement protein occurs when the protein is cut (cleaved) into two fragments — a larger activated protein and a smaller peptide fragment. This sequence of reactions starts a cascade that can neither be stopped nor reversed.
Figure 7.21 shows the complement cascade that begins when molecules of protein C3b bind to the surface of a pathogen. Review this diagram and note, for example, that the C3 protein is cleaved into two products, C3a and C3b, and that the C3b protein then catalyses the next step in the sequence.

The complement cascade produces some larger active protein fragments (such as C3b and C5b) that remain on the surface of the pathogen, and also smaller active peptide fragments (such as C3a and C5a) that diffuse away from the surface of the pathogen.

Various activated complement proteins formed by the cascade contribute to innate immune defence in the following ways:
1. by opsonising pathogens, making them more susceptible to phagocytosis
2. by recruiting immune cells involved in an inflammatory response
3. by destroying bacterial pathogens by lysis.
Opsono- (ancient Greek) = to cater or to buy food.

Each of these actions of activated complement proteins is outlined below.

1. **Opsonisation**: Some complement proteins, particularly protein C3b, smother the surface of a pathogen and form a complex with the surface antigens on the pathogen. This process is termed *opsonisation*. Opsonisation makes pathogens more susceptible to elimination by phagocytosis because phagocytes, such as macrophages, have receptors for complement proteins on their plasma membranes and these bind to the opsonised microbes (see figure 7.22).

![Figure 7.22](image)

**FIGURE 7.22** Complement proteins (C3b) opsonise a pathogen by coating its surface. The presence of complement receptors (CR) on the macrophage enables it to bind to the pathogen and begin to eliminate the pathogen by phagocytosis. Could you draw the next image in this series?

2. **Chemotaxis**: Chemotaxis refers to the movement of cells in response to a chemical stimulus. Small complement peptides, such as C3a and C5a, that diffuse from the pathogen surface act as chemical signals attracting immune cells involved in the inflammatory response to the site of the infection.

3. **Lysis of pathogens**: Some complement proteins are involved in the direct ‘explosive’ killing of extracellular pathogens. This occurs when a membrane-attack complex (MAC) forms on the plasma membrane of the pathogen. The formation of a MAC starts with the C5b protein on the surface of the pathogen that binds to one molecule each of proteins C6, C7 and C8, and then binds to several C9 molecules (see figure 7.23). The MAC inserts into the plasma membrane of the pathogen and produces a pore that allows fluid to enter, causing the pathogen cell to swell and burst — explosive death by osmotic shock!

![Figure 7.23](image)

**FIGURE 7.23** A membrane-attack complex (MAC) is formed by a combination of several complement proteins. When the MAC is completed (see RH image), a hole is created in the plasma membrane of the pathogen. This hole allows for an inflow of fluid into the pathogen, creating an osmotic shock and causing the pathogen cell to burst (lyse).
Interferons are a subgroup within the larger group of signalling molecules called cytokines. Refer back to chapter 5, page 184.

**Interferons: antiviral agents**

**Interferons (INFs)** are important in the innate immunity response to virus infections. The name of these proteins reflects the fact that they ‘interfere’ with viral replication. Because viral infections can occur quickly, interferons are critical in the body’s initial responses.

Once a body cell is infected with viruses, the cell secretes interferons. That cell is doomed, but the interferons that it secretes into its surroundings act as warning signals to nearby cells so that they can prepare in advance for a possible virus infection.

Interferons bind to receptors on neighbouring cells, producing signals that:

1. induce transcription of a number of specific genes that encode production of inactive forms of antiviral enzymes inhibiting protein synthesis and destroying RNA. These enzymes are activated only if a virus succeeds in infecting the cell and, if activated, they block the synthesis of viral proteins
2. make the plasma membrane less fluid, making its fusion with viral particles more difficult and so reducing the chance of viral infection in these cells
3. cause virus-infected cells to undergo apoptosis
4. activate immune cells, such as natural killer (NK) cells, that eliminate virus-infected cells by apoptosis

Figure 7.24 shows the various responses produced by interferon signals.

Different viruses infect different tissues. The further a virus must travel to reach its target cell, the more likely it will be destroyed before it gets there. Interferons are particularly important if a virus gains entry to the body close to its target cell. This is the case with cold and influenza viruses that infect cells in the nose and throat. Because infection occurs quickly, the body sometimes does not have the time to develop antibodies against these viruses and relies on interferons for its defence. If a person develops a cold or flu, interferons have failed to prevent the infection and the infection has developed into a disease that must be eliminated by the adaptive immune system.
KEY IDEAS

- Complement consists of a large group of inactive protease proteins in the bloodstream.
- Activation of complement proteins involves a cascade of reactions that occurs on the surface of pathogens.
- Activated complement proteins contribute to the elimination of bacterial pathogens by opsonisation and by formation of membrane-attack complexes (MACs).
- Interferons secreted by a virus-infected cell signal nearby cells to make various advance preparations to reduce the chance of a virus infection.
- Interferons signal virus-infected cells to undergo apoptosis.

QUICK CHECK

12 Identify the following as true or false:
   a. Soluble proteins form the humoral component of innate immunity.
   b. Complement proteins are involved in the elimination of intracellular pathogens.
   c. Activation of complement C3 involves its cleavage into two fragments, C3a and C3b.
   d. Interferon released by a virus-infected cell can signal nearby cells to produce antiviral proteins.

13 A bacterial cell is ‘opsonised’. Briefly explain what has happened to this bacterial cell.

14 How many different complement proteins are involved in the formation of a membrane-attack complex (MAC)?

15 Identify the following statements as true or false:
   a. Interferons cure virus-infected cells.
   b. A signal from interferons that is received by a virus-infected cell results in the death of that cell by apoptosis.
   c. Opsonisation of a bacterial cell prevents it from being eliminated by phagocytosis.
   d. Complement refers to a collection of various immune cells that circulate in the bloodstream.

The inflammatory response

We have now met the cells and the soluble proteins that are involved in responses to infection by the innate immune system. Now let’s examine inflammation, the major and rapid response of the innate immune system to an invading pathogen.

Inflammation is an early response of the human body to infection, such as the entry of bacteria via an open cut into a region of a finger (see figure 7.25). Inflammation is normally a short-term (acute) immune response that is localised around the site of entry of a pathogen so that the local area involved becomes red, swollen, hot and often painful. An acute inflammatory response is rapid in onset, appearing within minutes or hours of the onset of an infection.

Inflammation is an important protective response of the innate immune system to eliminate an infectious pathogen. (Note that inflammation may also occur when cells are damaged by agents other than pathogens, as, for example, thermal burns to the skin, corrosive chemical spills, frostbite and sunburn.)
When bacteria enter the body via a cut in the skin, the inflammatory response:
- localises and prevents the spread of the pathogen
- eliminates the pathogen and also removes any tissue debris
- repairs the damaged tissue (healing) and restores the normal (non-inflammatory) state.

Let’s look at what happens when a person cuts her finger on a piece of glass, and bacteria on the glass gains entry to body tissues. The person’s immune system rapidly initiates an inflammatory response. The first stage of the acute inflammatory response is the vascular stage, which involves changes to the blood vessels; the second stage is the cellular stage, which involves actions of various immune cells; the third stage is the resolution stage, which switches off the inflammatory response.

1. **The vascular stage of inflammation**

1.1 *Dilation of blood vessels*: The trigger for the dilation of blood vessels is the release of chemicals, including histamine and prostaglandins, from cells damaged by the cut. The arteriole and venule of the local capillary bed dilate so that the blood flow to the damaged area increases (see figure 7.26). This vasodilation produces the redness typical of acute inflammation, and the increased blood flow produces heat.

1.2 *Increased permeability of local capillaries*: The capillaries in the area around the cut become more “leaky” so that protein-rich fluid (exudate) escapes from the capillaries into the infected region. The exudate causes the swelling (edema) that is typical of inflammation. The swelling causes pressure on the surrounding tissue, which stimulates pain receptors and contributes to the pain that is characteristic of inflammation. Clotting agents in the exudate assist in clot formation, which isolates the infection.

**FIGURE 7.25** When the skin is cut with a piece of glass or a knife, the entry of pathogenic bacteria into surrounding tissues can result. Acute inflammation is a rapid response of the body’s innate immune system to this invasion.

**FIGURE 7.26** Diagram showing (a) normal situation and (b) the dilation of the blood vessels in a region of localised acute inflammation, which increases the blood flow in the region. What is the trigger for this increase in diameter of the blood vessels? Note also the net out flow of fluid (exudate) from the blood into the surrounding extracellular matrix, which causes localised swelling.
2. The cellular stage of inflammation

2.1 *Escape of immune cells from capillaries*: The expansion of the capillary bed enables neutrophils to squeeze between the endothelial cells that line the capillaries (see figure 7.27).

2.2 *Migration of neutrophils to infection site*: Neutrophils are the first immune cells to arrive at the infection site, attracted by cytokines released by damaged cells. Other immune cells, including macrophages from nearby tissues, follow. These cells release signals, such as histamine and more cytokines, that attract more phagocytic cells to the infection site.

![Diagram showing a neutrophil squeezing between the endothelial cells that line capillaries and the post-capillary venules. The neutrophils escape into the interstitial fluid and migrate to the infection site.]

2.3 *Phagocyte attack on bacteria*: Both neutrophils and macrophages attack bacterial *pathogens* by engulfing them in a process called phagocytosis (refer back to page 291). Phagocytic cells also remove cell debris from the infection site by a similar process. Pus consists mainly of dead phagocytic cells and other immune cells, and also contains living cells and cell debris. Figure 7.28a summarises the events in acute inflammation, and figure 7.28b shows the effects in real life.

The resolution stage: returning to normal

While the infection is present, pro-inflammatory cytokines are released to maintain the inflammatory response. This response continues until the pathogen has been eliminated. However, once the infection is under control and tissue repair underway, it is important that the normal state is restored. This is termed the resolution stage.

Resolution is a complex process that includes a reversal of all the processes that produced the acute inflammation, as, for example, the reversal of capillary dilation and cessation of release of pro-inflammatory cytokines. Resolution involves the release of many active molecules or mediators, including anti-inflammatory cytokines, the appropriately named lipids resolvins and protectins.

If normality is not established, a situation of *chronic inflammation* is created, which is damaging to the body and is the cause of several diseases. This is the ‘dark side’ of inflammation, occurring when the immune system does not shut off in the absence of infection but continues to produce active immune cells and pro-inflammatory molecules.

Long-term chronic inflammation is seen in several diseases, as, for example, ulcerative colitis (UC) (refer back to page 278), and rheumatoid arthritis (RA), which is an autoimmune disease where chronic inflammation of the tissues around the joints occurs, causing swelling, pain and stiffness.
FIGURE 7.28 Acute inflammation. (a) Diagram summarising the events of acute inflammation. (b) Acute inflammation in real life. This may look nasty, but this image shows the innate immune system producing an acute inflammation that has contained the infection. Note the classic signs of inflammation — redness, swelling, and you can almost feel the pain. What is the major component of the pus?
**KEY IDEAS**

- The three stages of an inflammatory response are the vascular stage, the cellular stage and the resolution stage.
- The signs of inflammation are redness, swelling, heat and pain.
- The vascular stage of inflammation involves changes in the capillaries supplying the site of infection.
- Actions by cells in the cellular stage of inflammation include various cell movements, as well as phagocytic activity at the infection site.
- If the inflammatory response is not turned ‘off’ when an infection is contained, a damaging situation of chronic inflammation can arise.

**QUICK CHECK**

16 What is pus?
17 Briefly explain why the area around an infection becomes swollen.
18 Identify two key changes in capillary vessels that occur during the vascular stage of inflammation.
19 Identify the following statements as true or false:
   a. The main response of the innate immune system to invading pathogens is acute inflammation.
   b. The stages in an inflammatory response in order are: cellular stage, resolution stage and vascular stage.
   c. Resolution of an inflammatory response requires the production of more pro-inflammatory molecules.
   d. Cytokines released by cells at the infection site attract more immune cells to the site.
   e. The redness around an area of inflammation is the result of dilation of the associated capillaries.
20 Give an example of a human disease that is believed to be the result of chronic inflammation.

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**The common cold**

Kylie is standing in a crowded train and a man near her sneezes but fails to cover his mouth. Invisible airborne particles carrying pathogens rush past her face. As she breathes in, several pathogens enter her nasal passages and move down the airways towards her lungs, while other pathogens adhere to the skin of her face. Among these unwelcome entries to her nasal passages are some rhinoviruses.

Her innate immune system immediately comes into action to eliminate the pathogens in her throat and lungs. At first, she shows no signs of infection. Some days later, Kylie is feeling unwell (see figure 7.29a) and is showing the first symptoms of the common cold — a sore throat and a runny nose (see figure 7.29b). Her innate immune system has been overcome by the viral infection in the epithelial cells of her upper airways. Now her adaptive immunity must come into action to deal with the virus. Kylie’s adaptive immune responses require several days to become fully effective and, during this period, the virus continues to replicate; she continues to show symptoms and feels ill. After this period, her adaptive immune responses progressively eliminate the rhinovirus, a process taking seven to ten days.

**Time course of an infectious disease**

Let’s look at what might happen when a person is infected by viruses or bacteria. Figure 7.30 shows the time course of an infection that overcomes the innate immune defences, develops into a disease and is then resolved.
FIGURE 7.29 (a) On average, adults have two to three colds each year, while children have even more. Greater than 200 different viral infections can develop into the common cold disease, the most common being rhinovirus, which is transmitted as an aerosol (airborne) or by direct contact. (b) Early symptoms of the common cold.

FIGURE 7.30 Diagram showing the changing levels of an invading pathogen. If the innate immune responses fail to contain the pathogen, the pathogen’s numbers increase and reach a level when the adaptive immune responses are called into action. Several days are needed for these adaptive defences to become fully effective and the pathogen continues to replicate. After this time, adaptive immune responses eliminate the pathogen.
Initially, the innate immune defences respond to the infection (period shown in red). However, if the viruses reach a certain level, the innate immune defences are overcome. Then the adaptive immune defences are called into action. The responses of adaptive immunity typically take days to develop (period shown in yellow) and the pathogens continue to increase in number. (This is the period during which Kylie felt ill and miserable.) However, after several more days, the adaptive immune responses are fully developed and they progressively eliminate the pathogen (period shown in blue).

The situation described above, in which the pathogen is progressively eliminated by adaptive immune defences, is the most common outcome. If, however, the adaptive immune defences are overcome, the infection may become long-lasting or chronic. In other cases, the infection can develop into a life-threatening situation requiring emergency intervention, such as can occur with *Staphylococcus pyogenes* toxic shock syndrome (refer back to Matthew’s story on pages 240–241, in chapter 6).

Let’s now look in more detail at adaptive immunity, the third line of defence that protects us against both pathogens and toxins.

### Adaptive immunity

Adaptive immunity is also called the *acquired immunity* because we acquire or develop this form of immunity through contact with the various pathogens we meet during our lifetimes. This is in contrast to our innate immune system — we are born with that. The adaptive immune responses are initiated after innate immunity has failed to check an infection, but adaptive immune responses are slower to come into full operation.

Three distinguishing features of adaptive immunity are:

- specificity
- self-tolerance
- memory.

One of these features is shared with innate immunity. Which is it? **Specificity:** Adaptive immunity is specific because its responses are tailor-made to recognise each antigen involved with an infection. When an infection occurs, only the specific adaptive immune cells that can recognise the pathogen are selected for action and proliferate. This process corresponds to the yellow sector in figure 7.30 above and involves clonal selection and clonal expansion (see page 319).

**Tolerance:** Adaptive immunity is self-tolerant and immune cells will not normally respond to the antigens on healthy body cells (self antigens). If self-tolerance breaks down, one of the so-called autoimmune diseases can result (see chapter 8, page 351).

**Memory:** As well as defending against an established infection, adaptive immunity has the ability to remember previous antigens to which it has responded. This is termed immunological memory and it enables more rapid responses in the case of future infections by the same pathogen. Most of the cells involved in the adaptive immune response to infection are removed by apoptosis after a particular pathogen has been eliminated. However, a small number of so-called memory cells remain (refer back to figure 7.30 and see the purple arrow).

Memory cells are already primed to produce a more rapid and stronger adaptive immune response when a pathogen re-infests. The pathogen is often eliminated before any symptoms appear. Refer to figure 7.31, which shows the antibody levels produced during the body’s first and second responses to surface antigens on an infectious pathogen. The action of memory B cells can be seen in the faster and greater production of antibodies on the second exposure to an antigen as compared to the initial exposure.
Components of adaptive immunity

The key components of adaptive immunity include:

- special white blood cells (lymphocytes) — T cells and B cells
- special antigen-binding proteins — antibodies, also known as immunoglobulins
- lymph nodes — secondary lymphoid organs where B cells and T cells meet foreign antigens and are activated, and where adaptive immune responses occur.

Adaptive immunity operates in two different ways (see figure 7.32):

1. **Humoral immunity** involves the actions of antibodies that identify and bind to extracellular pathogens, to toxins and to other extracellular foreign antigens. Antibodies are products of special B cells termed plasma cells.
2. **Cell-mediated immunity** involves various actions of T cells. Cytotoxic T cells eliminate body cells that are infected by pathogens or have abnormal or missing self markers. Note that cell-mediated responses do not directly attack pathogens. Instead, they remove infected cells and, by this means, eliminate intracellular pathogens.

Let’s look first at the antibodies that are the antigen-binding proteins of the humoral component of adaptive immunity. Then we will examine the cells of adaptive immunity.

**Antibodies: weapons against extracellular antigens**

Antibodies, also known as immunoglobulins, directly identify and bind to extracellular foreign antigens, either neutralising them or tagging them for destruction. Many antibodies are free molecules in solution in the blood or lymph, or in secondary lymphoid organs. Other antibodies are present as surface receptors on B cells (see figure 7.33) Each type of antibody has a unique antigen-binding site so that it can recognise and bind to just one specific antigen. The major antibodies involved in these immune responses are immunoglobulin G (IgG) and immunoglobulin M (IgM).
FIGURE 7.32 Diagram showing the two components of adaptive immunity. The cell-mediated component (shown at left) is delivered by helper T cells and cytotoxic T cells, and the humoral component (shown at right) is delivered by antibodies that are the product of special B cells, called plasma cells. ‘Raw’ refers to antigens as they exist without any processing. ‘Presented’ refers to antigens displayed on the surface of a cell that presents them to T cells.
The antigens that are targeted by antibodies may be on the surface of extracellular pathogens, or they may be free-floating foreign molecules, such as toxins in the blood, lymph or extracellular fluid. Antigens can even be part of a molecule, such as a small peptide fragment from a protein molecule.

Antibodies do not directly destroy pathogens but defend against infectious pathogens and toxins as follows:

1. Antibodies bind to surface antigens on pathogens and form a coating that neutralises pathogens by blocking their receptors so that the pathogens cannot attach to healthy body cells and infect them.

   Likewise, antibodies bind to bacterial toxins, animal toxins and venoms. The antibodies bind to and neutralise the harmful effects of the toxin or venom. For example, a person bitten by a venomous snake is given antivenom by intravenous injection. Antivenom is a solution of specific antibodies that combine with the venom molecules, preventing them from binding to cell-surface receptors — this renders the venom harmless.

2. By binding to surface antigens on pathogens, antibodies tag pathogens for destruction. The elimination is carried out either by complement proteins or by phagocytic cells such as macrophages.

   For example:
   - Complement proteins activated by antibodies on the surface of pathogens destroy the pathogens by lysis as a result of forming MACs.
   - Antibodies coating the surface of pathogens opsonise them, making them more susceptible to elimination by phagocytic cells (see figure 7.34).

**FIGURE 7.33** Diagram showing a B cell with its surface receptors, each receptor composed of a Y-shaped antibody (immunoglobulin) molecule. Each receptor has two antigen-binding sites, one at the end of each arm of the Y. Activated B cells also secrete the same antibodies into extracellular fluids where they can bind directly to soluble antigens or they can bind to surface antigens on an extracellular pathogen.

Refer back to page 298 to check on how activated complement proteins assist in the elimination of pathogens.

**FIGURE 7.34** A coating of antibodies bound to the surface antigens of an extracellular pathogen tags the pathogen for destruction by a phagocyte, such as a macrophage. Surface antigens of the pathogen are shown as red triangles, and the matching antibodies produced by B cells are shown as blue Y shapes.

**Structure of antibodies**

Antibodies, also known as immunoglobulins, are antigen-binding proteins produced by B cells. All antibody molecules have the same basic structure consisting of two identical heavy polypeptide chains and two identical light polypeptide chains. This means that antibodies are proteins with a quaternary structure (refer back to chapter 2, page 53).
In terms of their amino acid sequences, both the heavy chain and the light chain have two distinct regions: (1) a constant region that does not vary, and (2) a variable region that differs between antibodies.

Examine figure 7.35. An antibody forms a Y-shaped structure. The variable regions are located at the end of each arm of the Y and these regions are the antigen-binding sites, where the antibody binds to its specific antigen. (This region is denoted by the symbol \text{Fab} = \text{fragment antigen binding}.) The shape of the antigen-binding site determines whether an antibody and antigen can bind. The remainder of the antibody forms its constant region (shown in purple for the H chain and in yellow for the L chain, and denoted \text{Fc}). Complement proteins can bind to the constant region of an antibody.

![Diagram showing the basic structure of an antibody molecule — two identical heavy (H) chains and two identical light (L) chains. Both the H chains and the L chains have a variable region (shown in black and about 110 amino acids long) where the antigen specific to that antibody can bind. The amino acid sequences in the variable regions of each chain differ between antibodies that can bind to different antigens.](image)

Figure 7.36 shows a ribbon model of immunoglobulin G, the main antibody in the blood. A hinge at the region of the disulfide bond gives flexibility to the antibody molecule, enabling it to maintain the best fit with its antigen.

**Classes of antibodies**

The five classes of antibody (immunoglobulin) differ in the particular kind of heavy chain in their structure and differ in their specific functions. Table 7.3 identifies these five classes of antibody and lists some of their characteristics.

Note that:

- IgG is the main antibody in the blood and provides the key antibody-based defence against pathogens.
- IgM is the first antibody to appear in an infection and provides defence until sufficient IgG is formed.
- IgA attaches to the surfaces of the mucous membranes of airways, gut and urogenital tract.
- IgE stimulates the release of histamine and other chemicals that cause allergies.
FIGURE 7.36 Ribbon model of an antibody, immunoglobulin G (IgG). This 3D representation shows the protein backbone of this antibody. The two heavy chains of this antibody are colour-coded in orange and yellow, and the two light chains are in red and blue. (Image courtesy of Dr Song Tan, Penn State University.)

TABLE 7.3 Different classes of antibodies and some of their features. The identity of the heavy chain determines the class to which an antibody belongs. Every antibody molecule has either two lambda chains or two kappa chains in its structure. Which class of antibody gives passive adaptive immunity to a newborn baby until its own immune system becomes operational?

<table>
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<tr>
<th>Feature</th>
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<th>IgA</th>
<th>IgM</th>
<th>IgD</th>
<th>IgE</th>
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<tr>
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<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Able to cross placenta</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Found in saliva, tears, sweat and on mucous membranes</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Present in breast milk</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Present on surface of B cells</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Active against viruses</td>
<td>yes</td>
<td>yes</td>
<td>some</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Active against some bacteria</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Activate complement</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Attach to surfaces of mast cells (involved in allergic reactions)</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>yes</td>
</tr>
</tbody>
</table>
Figure 7.37 is a diagram showing the different classes of antibodies. These classes differ in their heavy chains and some differ in the number of units in the functional antibody: 1, 2 or 5.

**Figure 7.37** The five classes of antibodies. Three classes, IgG, IgE and IgD, consist of single units, while IgA and IgM consist of 2 and 5 units respectively. Can you suggest why IgG is able to cross the placenta, but not IgA?

Antigen-binding sites for different antigens are unique

Cells of adaptive immunity are able to produce a remarkable diversity of antibodies that can respond to billions of different antigens. The antigen-binding sites on one antibody molecule have a unique shape that recognises just one particular antigen (see figure 7.38a). Binding can only occur between an antibody and an antigen that includes a shape that is complementary to (fits into) the shape of the antigen-binding site of an antibody — a bit like a key and a lock. Different antibodies have differently shaped antigen-binding sites.

**Figure 7.38** (a) Diagram showing a stylised antigen bound to an antibody. Note that the antigen includes a shape that can fit the antigen-binding site of the antibody. (b) Diagram showing stylised antibodies with differently shaped antigen-binding sites. The shape of the site determines the antigen that can be bound to the antibody.
Given that we are capable of producing an enormous number of different antibodies in terms of their antigen-binding sites, how is this achieved? Check out the next section.

Diversity of antibodies

We cannot possibly know all the antigens that we might meet during our lives, yet our adaptive immune system has the remarkable ability of responding to every possibility. This is achieved because our B cells can produce approximately ten billion different kinds of antibody (immunoglobulin), with each different antibody able to recognise and bind to one specific antigen.

Each of these billions of different antibodies has a different amino acid sequence in the variable regions of both its heavy and its light chains. These differences produce the extraordinarily large number of different shapes of antigen-binding sites on antibody molecules. The human genome comprises an estimated 21 000 different genes. Clearly, each different antibody cannot be the product of one different gene. How can the human genome encode billions of different amino acid sequences in these different antibodies?

The mystery was not solved until 1976 when the Japanese scientist Susumu Tonegawa (1939–) discovered how this incredible multitude of different antibodies was created. Tonegawa showed that the variable regions of each antibody are encoded by combinations of several genes randomly picked from a few larger pools of genes.

For example, the variable region of the heavy chain of a human antibody is encoded by three genes (V, J and D) that are randomly picked, one from each of a pool of 51 V genes, 6 J genes and 27 D genes. This is a bit like picking one ball at random from each of three barrels (see figure 7.39). This process generates a possible $51 \times 6 \times 27 = 8262$ different genetic combinations to encode variable regions of the heavy chains of an antibody.

So, just three genes picked at random from a total of 84 genes creates more than 8000 different genetic combinations that encode the variable regions of the heavy chains. This process of gene shuffling is termed V(D)J recombination and it takes place in B cells while they are in the bone marrow.

A similar process involving two genes (V and J) occurs for variable regions of the light chains of antibody molecules. About 320 different gene combinations are possible for the light chain of an antibody molecule. Combining the possibilities for both the heavy and the light chains produces...
B cells) generates the diversity seen (similar to that occurring with beta). Random gene rearrangement of two protein chains (alpha and beta) in T cell surface receptors consist of two protein chains (alpha and beta). Random gene rearrangement (similar to that occurring with B cells) generates the diversity seen in T cell receptors.

In 1987, Susumu Tonegawa was awarded the Nobel Prize in Medicine or Physiology for his discovery of ‘the genetic principle for generation of antibody diversity’.

KEY IDEAS

- Adaptive or acquired immunity forms the third line of defence against infection.
- Adaptive immunity has a humoral component and a cell-mediated component.
- Humoral adaptive immunity targets extracellular antigens and is achieved through the action of antibodies.
- Cell-mediated immunity attacks infected or abnormal cells and is brought about by T cells.
- Antibodies, also known as immunoglobulins, are a diverse group of antigen-binding proteins consisting of two identical heavy chains and two identical light chains.
- Antibodies are the products of B cells.
- Antibodies can only bind to those antigens that include a shape that is complementary to the shape of the antigen-binding sites of the antibodies.
- Antibody diversity is produced by processes including V(D)J recombination and somatic mutation of B cell genes.

QUICK CHECK

21 Identify the following statements as true or false:
   a At birth, a baby has no adaptive immune defences.
   b Antibodies are antigen-binding proteins produced by B cells.
   c Cell-mediated adaptive immunity is produced by T cells.
   d An antibody can bind only to an antigen that includes a shape that is complementary to the antigen-binding sites of the antibody.
   e Adaptive immunity, unlike innate immunity, has a ‘memory’.
   f Innate immune responses occur after adaptive immune responses have been overcome.
   g Antibodies are released in advance of possible invasions by infectious pathogens.
   h V(D)J recombination of antibody genes occurs in B cells when they are in the bone marrow.

22 Give an example of:
   a A class of antibody that can cross the placenta
   b A class of antibody that is found on the surface of mucous membranes
   c A type of immune cell that eliminates infected body cells
   d A randomly picked gene that contributes to the diversity of the heavy chains of an antibody.

8262 \times 320 = 2.6 \text{ million different variations.} More antibody diversity is produced because of somatic mutations in the genes concerned. In addition, variations in how the genes are joined create even more diversity.

Through these gene re-arrangements, the B cell population in the bone marrow has the capability of producing billions of antibodies with different antigen-binding sites. This antibody diversity can be expressed both in the soluble antibodies secreted by B cells into extracellular fluids, as well as in the antibodies that form the surface receptors on B cells. It would, of course, be wasteful to produce all these antibodies since most would never be needed and others would only be needed at particular times. As we will see (page 319), the adaptive immune system has a neat solution and, when a specific antibody is required, only the B cells that produce that particular antibody become active and multiply.
Cells of adaptive immunity

The main cells of the adaptive immune system are members of the class of white blood cells known as lymphocytes. The lymphocytes that play the key roles in adaptive immunity are T cells and B cells. Lymphocytes are small cells (about 7 to 10 µm in diameter, similar in size to red blood cells). They are found in the blood and the lymph, and are highly concentrated in secondary lymphoid organs such as lymph nodes. Figure 7.40 shows a scanning electron microscope (SEM) of whole blood that includes two lymphocytes. (Refer back to figure 7.4 on page 280 to see light microscope images of lymphocytes in blood smears.) The contrast between these images shows the power of SEM in providing vivid 3D images.

Using conventional staining, B cells cannot be visually differentiated from T cells. However, they can be distinguished by the different cell-surface markers they carry, including their specific receptors. Each B cell has a large number of identical B cell receptors, while each T cell has multiple identical copies of T cell receptors.

B cells and T cells: different roles in adaptive immunity

The roles of these cells in adaptive immunity differ:

- T cells deliver the cell-mediated immune defences that include the direct elimination of pathogen-infected cells and other abnormal cells, such as cancer cells.
- B cells deliver the humoral immune defences by secreting antibodies that bind to surface antigens on pathogens and label them for elimination; antibodies also bind to soluble toxins.

Figure 7.41 shows a dense population of lymphocytes, mainly B cells, in the cortex of a lymph node.
A remarkable diversity of surface receptors is present in the large populations of B cells and T cells in the lymph nodes. This diversity exists even though the majority of antigens that these cells can recognise may never gain entry to the body. The body is armed in advance against invasion by every possible harmful antigen, but the numbers of B and T cells in the populations that can respond to one specific antigen are very small. However, when an infection occurs, the numbers of the specific T cells and B cells that can respond to the infection are greatly increased.

Table 7.4 shows a summary of the different roles of T and B cell lines of adaptive immunity. Also refer back to figure 7.32 on page 310. Note that:

- **B cells** recognise extracellular pathogens and label them for destruction with antibodies, while T cells recognise and eliminate intracellular pathogens.
- **B cells** respond to ‘raw’ antigens, while **T cells** respond to antigens that are ‘presented’ to them by other cells.

### TABLE 7.4 Summary of the two cell lines of adaptive immunity. From each cell line, mature functional immune cells develop that, when activated by exposure to their specific antigens, deliver their immune responses.

<table>
<thead>
<tr>
<th>Cell line</th>
<th>Features</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T cells</strong> 'helpers and hunters'</td>
<td>mature in thymus, then migrate to lymph nodes; each T cell has many surface receptors that recognise one specific antigen; activated by exposure to antigens presented to them on the surface of other cells; differentiate into various types of T cells, including helper T cells and cytotoxic T cells</td>
<td>Activated cytotoxic T cells eliminate infected and abnormal cells. Activated helper T cells send signals that stimulate B cells to secrete specific antibodies. Memory cells retain a ‘memory’ of antigens met previously.</td>
</tr>
<tr>
<td><strong>B cells</strong> 'antibody factories'</td>
<td>mature in bone marrow, then migrate to lymph nodes as naïve B cells; each B cell has many receptors that recognise just one kind of antigen; activated by direct exposure to raw antigens; develop into plasma cells that produce antibodies that defend against the specific antigen that activated the B cell</td>
<td>Activated B cells produce antibodies against extracellular antigens, either free-floating or on the surface of pathogens. Memory cells retain a ‘memory’ of antigens met previously.</td>
</tr>
</tbody>
</table>
B cells and T cells must pass a test

T cells and B cells develop in the primary lymphoid organs — T cells in the thymus and B cells in the bone marrow.

Each single B cell and T cell carries many copies of one surface receptor that can recognise and bind to just one specific antigen. When B cells and T cells are in the primary lymphoid organs, they are put through a test. What test? Cells are tested by being exposed to self-antigens. Any cells that do not recognise self-antigens fail the test and are eliminated by apoptosis. Cells that fail to respond to non-self-antigens are also eliminated. Testing ensures that the surviving T cells and B cells are self-tolerant and will not attack the body’s own healthy cells carrying self-antigens, but will attack foreign antigens.

Cells that pass the test graduate as naïve T cells and B cells. These cells migrate to secondary lymphoid organs, such as the lymph nodes. This is where the naïve B and T cells are activated by exposure to their complementary antigens and undergo cycles of cell division and differentiate into effector cells. Lymph nodes are the location where the various adaptive immune responses to pathogens take place.

In a sample of normal blood, lymphocytes (T cells, B cells of adaptive immunity, and the NK cells of innate immunity) constitute from 14 to 47 per cent of the total white blood cells. The majority (about 80%) of the circulating lymphocytes are T cells, with B cells making up a smaller proportion (5 to 15%).

Let’s now look at how B cells operate.

B cells: antibody factories

The critical role of B cells in adaptive immunity is to produce antibodies that are specific to foreign antigens and toxins. These antibodies defend only against extracellular antigens, such as antigens on the surface of a pathogen in the blood, or soluble antigens, such as toxins or venoms, in extracellular body fluids. After an infection starts, about one week is required before the specific antibodies needed to counter the infection are present in sufficient amounts. While this is happening, a person can feel quite ill. During this period, the B cells with receptors that match the antigen concerned go through cycles of cell division and differentiate into special antibody-secreting cells, called plasma cells.

Within the population of B cells in the lymph nodes, only a few cells have one particular receptor. This small number of B cells with receptors specific to one particular antigen is not adequate to counter a specific bacterial infection. So, if a new pathogen gains entry to the body and multiplies rapidly, how can a few B cells produce enough antibodies to defend against the new pathogen? The answer is: ‘By clonal selection and clonal expansion.’

Clonal selection and clonal expansion of B cells

Consider a ‘new’ antigen that gains entry to the body, such as an antigen on the surface of a microbe. When this antigen reaches the lymph nodes, it comes into contact with many naïve B cells that do not recognise it. Eventually, however, the antigen meets a B cell that can recognise and bind to it. In effect, this antigen has ‘selected’ the specific B cell that can eliminate it (and the pathogen on which it is present). This is clonal selection.

The binding of the antigen to its ‘selected’ B cell activates the B cell and initiates cycles of cell division. The daughter cells from each division also replicate, and so do their daughter cells, and so on. The result is the production of a large clone of B cells, all having identical antigen-binding receptors — this is called clonal expansion. Most of these cells differentiate into short-lived plasma cells that secrete soluble antibodies against the specific antigen (see figure 7.42). B cells can produce antibody molecules at an estimated rate of up to 200 per second.

ODD FACT

After being ‘selected’, the B cell repeatedly divides, doubling in number every six hours. Within a week, a clone of about 20,000 B cells has been built up.
This explanation as to how the ‘right’ antibodies are produced just when they are needed is termed the clonal selection theory. This theory provides an explanation for the specificity of adaptive immunity, that is, how the antibodies produced at a given time are those that specifically defend against the invading pathogen.

The clonal selection theory was first proposed in 1955 by an Australian, Sir Frank Macfarlane Burnet (see box at the end of this section). Evidence in support of Burnet’s clonal selection theory came from later research findings of Sir Gustav Nossal (1931–) who demonstrated that each B cell carries multiple copies of just one kind of cell-surface receptor. Can you suggest why this finding gave support to Macfarlane Burnet’s theory?

Figure 7.43 shows a transmission electron micrograph of an activated B cell or plasma cell. These cells are very active in protein synthesis — remember that antibodies are composed of polypeptide chains. Because of this, cell organelles such as the rough endoplasmic reticulum are very prominent features of activated B cells. Newly synthesised antibodies are not retained within plasma cells but are transported out of these cells as free-floating molecules in the bloodstream and lymph. For this reason, another organelle expected to be prominent in plasma cells is the Golgi complex.

In the next sections, we will explore the T cells of adaptive immunity.
An Australian Nobel Laureate: Sir Frank Macfarlane Burnet

Sir Macfarlane Burnet became interested in how the body defences act against infection by microorganisms and extended his research to include the immune system. He realised that the essential basis of the body’s defence was its ability to identify foreign material as being different from its own constituents. He proposed a radical new theory, the ‘clonal selection theory’ (see page 319). Sir Macfarlane Burnet received many awards for his work. He received numerous honorary degrees, fellowships and prizes, leading to the ultimate achievement of the Nobel Prize for Medicine in 1960. The citation for his Nobel Prize is shown in figure 7.45. The Nobel Prize was shared with Sir Peter Medawar (1915–1987) of University College, London. Sir Macfarlane Burnet was one of the twentieth century’s great scientists.

The highest awards for achievement in science are the Nobel Prizes, set up under the will of Alfred Nobel, a Swedish chemist and engineer who died in 1896. The distinguished Australian scientist Frank M. Burnet, later Sir Macfarlane Burnet (see figure 7.44), received a Nobel Prize. He was born in the country town of Traralgon in Victoria and, after graduating in medicine from the University of Melbourne, chose to carry out research on viruses, particularly animal viruses. After working in England, Dr Macfarlane Burnet returned to the Walter and Eliza Hall Institute of Medical Research (refer to chapter 8, The Walter and Eliza Hall Institute of Medical Research) where he later became Director from 1944 to 1965. He experimented on influenza viruses by growing them in fertilised hens’ eggs.

Although their main research was on the influenza virus, Sir Macfarlane Burnet and his co-workers also did important work on other viruses including poliomyelitis, herpes, Murray Valley encephalitis, myxomatosis and smallpox-like viruses. They also worked on organisms half-way between viruses and bacteria, the rickettsias. The causative agent of Q-fever, Coxiella burnetii, is named after Burnet.

KEY IDEAS

- Primary lymphoid organs are where B cells and T cells of the immune system are tested for their ability to tolerate self antigens but react to foreign antigens.
- Cells passing the test are selected as naïve cells and released to migrate to lymph nodes.
T cells: helpers and killers

T cells make up the majority (about 80% of circulating blood lymphocytes and are critical in the processes of cell-mediated adaptive immunity.) Precursor T cells are produced in the bone marrow and migrate to the thymus where they mature into naïve T cells. Naïve T cells are activated to effector T cells in the lymph nodes by exposure to their matching antigens. T cell receptors consist of two polypeptide chains (alpha and beta), and each receptor has a single antigen-binding site (see figure 7.46).

Any one T cell carries thousands of T cell receptors, all with identical antigen-binding sites. However, the genes that encode T cell receptors are produced by a process of random gene shuffling (such as occurs for the polypeptide chains of antibodies (refer back to page 315)). As a result, the receptors present in a population of T cells are extremely diverse and can recognise a great variety of antigens. It is important to note that T cells can only recognise their matching antigens when they are linked to an MHC self marker on the surface of another cell.

The key role of T cells is in cell-mediated immunity. Once a pathogen gains entry to a cell, it is ‘hidden’ from any defence by antibodies. **Only T cells are able to take action against intracellular pathogens.**

Several kinds of T cells exist, including **cytotoxic T cells** and **helper T cells.** These two kinds of T cell look the same but can be distinguished because they have different cell-surface markers — cytotoxic T cells have CD8 markers on their surfaces and are sometimes called CD8⁺ T cells. Helper T cells have CD4 markers and are sometimes called CD4⁺ T cells.

The HLA self markers (also known as MHC markers) are outlined in chapter 6, page 263. HLA/ MHC class I markers are on all nucleated cells, while HLA/MHC class II markers are restricted to a few immune cells only, including dendritic cells. In this section, the term MHC will be used.
Cytotoxic T cells: the killers

The major role of cytotoxic T cells (Tc cells) is to monitor body cells for the presence, on their surface, of foreign antigens that have been generated within the body cell by intracellular pathogens. Such antigens include viral proteins produced during the multiplication of a virus within a cell and bacterial compounds resulting from metabolic activity of the bacteria within a cell. Infected body cells advertise their infected state on their surfaces by displaying pathogen antigens that are linked to MHC class I molecules.

The monitoring of body cells by Tc cells requires that contact be established between the T cell and the cell to be monitored. If any cells are identified as being infected, cytotoxic T cells set about destroying them. By destroying infected cells, Tc cells stop infections from spreading to nearby body cells.

Cytotoxic T cells recognise the foreign antigens that are linked to MHC class I molecules on the surface of an infected body cell. Figure 7.47 shows a diagram of a cytotoxic T cell making contact with an infected body cell. Note the foreign antigen (shown in red) that is linked to an MHC class I marker (shown in green). The T cell receptor (TCR) (shown in grey) recognises this MHC-linked antigen as a signal that this body cell is infected.

![Diagram of a cytotoxic T cell making contact with an infected body cell](image)

This binding of the antigen to the T cell receptor activates these cytotoxic T cells. These activated cells undergo cycles of cell division and form effector cytotoxic T cells. These cell divisions brings about a several thousand-fold increase in the number of effector cytotoxic T cells that can recognise the particular antigen. Although this clonal expansion may take a week to occur, the adaptive immune system is now well equipped to destroy infected cells.

How do cytotoxic T cells kill?

Effector cytotoxic T cells attack infected body cells by releasing perforin, a protein that inserts into the plasma membranes of target cells and creates pores. Cytotoxic T cells release destructive granules, called granzyme B, that enter the infected cell via the pore and initiate cell death by apoptosis (see figure 7.48). The cytotoxic T cells are then free to attack other infected cells that display the same foreign antigen.

Figure 7.49 shows a fluorescence image of a Tc cell that has recognised and will destroy a pathogen-infected cell.

As well as recognising viral and bacterial antigens, Tc cells can also recognise abnormal proteins such as those resulting from DNA mutations in cancer cells. Through this recognition, cytotoxic T cells can target and eliminate cancer cells.
The other major effector cells in adaptive immunity are the **helper T cells**. To appreciate the role of helper T cells in adaptive immunity, we first need to meet dendritic cells in their role as antigen-presenting cells (APCs).

**KEY IDEAS**

- T cells deliver the cell-mediated components of adaptive immunity.
- Each T cell carries multiple copies of one specific T cell receptor that can recognise just one antigen.
- T cells include cytotoxic T cells and helper T cells.
- T cells can only recognise antigens when they are located on the surface of another cell and are linked to MHC molecules.
- Cytotoxic T cells attack pathogen-infected cells (and also cancer cells) using chemical compounds, resulting in the death of the target cell by apoptosis.
Antigen-presenting cells

In 2011, the Nobel Prize in Medicine or Physiology was awarded to Ralph Steinman (1943–2011) ‘for his discovery of the dendritic cell and its role in adaptive immunity’. (Sadly, Steinman, who discovered dendritic cells in 1973, died before receiving news of this award.) Dendritic cells are cells of the innate immune system, but they also play an important role in activating naïve T cells of the adaptive immune system, both cytotoxic T cells that kill infected body cells, and helper T cells that direct the activities of other immune cells.

Cells that can move antigens to their surface and display these antigens to other immune cells are called antigen-presenting cells (APCs). The principal cells involved in antigen presentation to other immune cells are dendritic cells. Figure 7.50 shows a dendritic cell interacting with a lymphocyte. Macrophages can also engage in antigen presentation.

Let’s look at the process of antigen presentation by APCs, such as dendritic cells.

FIGURE 7.50 Image of a dendritic cell (at right) interacting with a lymphocyte. Dendritic cells are the major cell type that presents antigens to cells of the adaptive immune system. (Image courtesy of Olivier Schwartz and Institut Pasteur.)
**Dendritic cells: major antigen-presenting cells**

- **From where do dendritic cells obtain the antigens they present?**
  Pathogens can enter the human body by ingestion, injection and by inhaling. Typically, these pathogens are met close to the entry point by phagocytic cells that engulf and eliminate them. In particular, dendritic cells are active in this role because they are located on and in epithelial tissues of the skin and the linings of the airways and the gut — all potential points of entry of pathogens to the body. Dendritic cells capture these pathogens from the external environment, and they are the source of the antigens that are presented by dendritic cells.

- **How do dendritic cells obtain these antigens?**
  Dendritic cells engulf pathogens by phagocytosis and degrade them. However, **dendritic cells retain, in their cytoplasm, some peptide fragments from degraded pathogen proteins**. These peptide fragments are the antigens that will be presented.

- **How are the antigens presented?**
  Dendritic cells link these foreign antigens to MHC class II molecules in their cytoplasm and then transfer them to their cell surfaces, putting them ‘on display’.

- **Where does antigen presentation take place?**
  Dendritic cells transport these antigens to the nearest lymph nodes and present them to naïve helper T cells that carry receptors that recognise and then bind to the displayed antigens (see figure 7.51). Figure 7.51 shows how a foreign antigen from a degraded microbe is processed by a dendritic cell for presentation to a naïve helper T cell. Note that the foreign antigen is linked to an MHC class II molecule on the surface of the dendritic cell. By presenting antigens to T cells, APCs such as dendritic cells initiate specific immune responses.

![Figure 7.51](image)

**FIGURE 7.51** (a) A dendritic cell engulfs a microbe by phagocytosis — this microbe will be degraded. (b) Some peptide fragments from degraded microbial proteins are retained by the dendritic cell. These foreign antigens are linked to MHC II molecules and shifted to the surface of the dendritic cell where they are ‘on display’. (c) In the lymph nodes, dendritic cells display the foreign antigen on their surfaces to naïve helper T cells. Any helper T cell with a matching receptor can bind to the antigen. The antigen T cell receptor binding activates helper T cells to undergo cycles of cell division and differentiate into effector helper T cells.
Helper T cells

Helper T cells are regarded as the most important cells in adaptive immunity because they are involved in all adaptive immune responses. The importance of helper T cells in defense against infectious microbes can be seen in people with untreated AIDS. The helper T cell population of such people is progressively lost, and they become susceptible to infections by microbes that are normally harmless (see chapter 8, page 360).

As shown in figure 7.51 immediately above, antigens are presented by dendritic cells to naïve helper T cells. Binding of the antigen to T cell receptors starts a cascade of intracellular signalling that activates the T cells.

Activated helper T cells proliferate, and the effector helper T cells stimulate immune responses in the secondary lymphoid organs where adaptive immune cells are concentrated.

Activated effector helper T cells secrete various cytokines, including interleukin 2, that:

- helps activate cytotoxic T cells to seek and destroy cells infected by pathogens carrying that antigen
- helps activate B cells into becoming antibody-producing plasma cells that will produce and release antibodies to defend against pathogens carrying that antigen
- helps activate macrophages to remove antibody-coated pathogens by phagocytosis.

It may be seen that effector helper T cells simulate the activities of both the cell-mediated arm of adaptive immunity and the humoral arm of adaptive immunity.

Figure 7.52 is a diagram summarising the central role of effector helper T cells in adaptive immunity. Note that the dendritic cell initiates helper T cell activity through its antigen presentation role.

**FIGURE 7.52** Diagram showing the central role of helper T cells in adaptive immunity. Note that cytokines secreted by effector helper T cells (T\(_H\) cells) activate both cytotoxic T cells (T\(_C\) cells) that kill infected body cells and B cells that are involved in producing antibodies that target extracellular pathogens and toxins.

We have explored the remarkable immune defences of the human body, both the innate immune system and the adaptive immune system. The following box outlines some of the strategies that have evolved in pathogens in order to avoid these defence mechanisms.
PATHOGENS STRIKE BACK!

Some pathogens can avoid elimination by the body’s innate immune system. Pathogens that can succeed in doing this are more dangerous (virulent) than other pathogens. An infection by a highly virulent pathogen is more likely to develop into disease than an infection by a less virulent pathogen. Among the various strategies seen in bacteria that protect them from attacks by the body immune system are the following:

- **Evading recognition as ‘non-self’**
  Some bacterial pathogens cover their outer surfaces with molecules that are naturally produced by the human cells. The presence of these molecules means that these pathogens are mistakenly identified by innate immune cells as ‘self’ and so do not come under immune attack. Bacteria that conceal their ‘non-self’ identity include *Treponema pallidum*, the cause of syphilis, a sexually transmitted disease (see figure 7.53). These bacteria bind a glycoprotein that is found in human connective tissue to their surfaces. This coating of fibronectin conceals the foreign antigens of the bacteria so that they are identified by the body’s immune cells as self.

![FIGURE 7.53 Model of Treponema pallidum, the causative agent of syphilis. Refer back to chapter 6, page 238, and identify the shape of this bacterium. How does it avoid immune attack?](image)

- **Avoiding phagocytosis**
  The extracellular capsule of some bacterial species (refer back to chapter 6, page 243) contains molecules that enable these bacteria to avoid engulfment by phagocytic cells (see figure 7.54). *Streptococcus pyogenes* is one such bacterial species that avoids phagocytosis because of the presence of a polysaccharide capsule surrounding each bacterial cell. Another bacterial species that has a polysaccharide capsule that confers resistance to phagocytosis is *Klebsiella pneumoniae*, the cause of one form of pneumonia.

(continued)
Some bacteria produce exoenzymes, which attack the immune cells of the body. Exoenzymes are enzymes that are released to the external environment of the cell that produces them. Among the exoenzymes produced by pathogenic bacteria of the genera *Streptococcus* and *Staphylococcus* are leukocidins (leuko- = white; -cide = to kill), which destroy white blood cells of the body. These white blood cells include the phagocytic cells of the body’s second line of defence and the lymphocytes of the body’s third line of defence. Leukocidins break down the lysosomes in the white blood cells, and the chemical contents they release cause the death of these cells and damage other cells in the region. As would be expected, *Streptococcus* and *Staphylococcus* bacteria cause serious and life-threatening diseases, including streptococcal toxic shock syndrome.

### Key Ideas

- Dendritic cells are the major cells that present antigens to naïve helper T cells.
- Antigens in the external environment that gain entry to the body are captured by dendritic cells, prepared for presentation and transported to lymph nodes.
- Naïve helper T cells are activated by binding to matching antigens on the surface of dendritic cells.
- Naïve helper T cells can only recognise presented antigens that are linked to MHC class II molecules.
- Effector helper T cells play a central role in adaptive immunity by stimulating the actions of both antibody-secreting B cells and cytotoxic T cells.
QUICK CHECK

29 Briefly explain the term ‘antigen presentation’.

30 Identify the following statements as true or false:
   a Antigen presentation by dendritic cells occurs in lymph nodes.
   b Dendritic cells acquire antigens by phagocytosis.
   c The target cells for antigen presentation are antibody-producing B cells.
   d The loss of helper T cells would be expected to create a life-threatening situation.
   e The antigens presented by dendritic cells are peptide fragments of degraded pathogen proteins.

BIOLOGIST AT WORK

Dr Marie-Liesse Asselin-Labat — medical researcher and laboratory head

I grew up in France and, while I was finishing high school, I met a medical researcher who had studied pharmacy. At the time I didn’t think I wanted to study medicine or science, but her work sounded very interesting so I decided to do the same.

My pharmacy degree gave me the chance to interact with hospitals and the pharmaceutical industry, which I really enjoyed. It also made me realise that basic research was key to the development of better treatments for patients, so I went on to do my PhD in Paris studying the molecular mechanisms involved in the response of leukaemic cells to blood cell hormones.

Although my husband and I were both born in France, we were eager to live and work in an English-speaking country. Around the same time, my research interest changed — I wanted to concentrate more on understanding the events responsible for the development of cancers in the context of the whole organ. So I applied to do my postdoctoral studies in the Stem Cells and Cancer Division at the Walter and Eliza Hall Institute of Medical Research, working on breast cancer.

There isn’t really a ‘normal’ day for me. As a laboratory head, I have a lot of different responsibilities. Of course I still do experiments in the lab, but I also supervise a small team of scientists. I split my week between desk work, such as writing grant applications and reading scientific papers, and working in the lab. My daily interaction with the younger students is inspiring for me — being able to help develop their passion for science is a real pleasure.

When I first started at the institute I worked on breast cancer. I was part of the team that first discovered breast stem cells and then went on to discover a possible cellular link between female hormones and the development of breast cancer. I was honoured to receive the inaugural Lawrence Creative Prize from the Centenary Institute in 2011 for my work.

I now focus my research on lung cancer — I want to apply the theories we developed about breast cancer to other diseases. Lung cancer still has very poor outcomes for people with the disease, and I am determined to keep working on problems that affect people. It is very important to me to try to understand how diseases such as breast and lung cancer develop.

But I am more than just a scientist — I have three young boys, aged eight, six and three. While I was on maternity leave I used the time to think about what I wanted to do next. I was determined to further develop my career as a scientist. I was fortunate to have support from the institute to facilitate my return to work. It is not always easy, but in the right environment you really can balance a full-time job with having a family.
1 Pyogenic, or pus-forming, bacteria have polysaccharide capsules, which means that these pathogens cannot be directly recognised by the pattern recognition receptors on phagocytic cells, such as macrophages. Examples of these bacteria include Streptococcus pyogenes (see figure 7.56) and S. pneumoniae.

**Streptococcus pyogenes**

Exotoxins:
- SPE A, B and C
- M protein (in fimbriae)
- Lipoteichoic acid (LTA)

Invasins:
- Streptolysins
- Streptokinases
- Proteases

M protein (in fimbriae)

Lipoteichoic acid (LTA)

Protein F and Sfb

**FIGURE 7.56**

a If these pyogenic bacteria gain entry to the extracellular fluids of the body, could they be eliminated by the immediate cell-based innate immune defences? Briefly explain.
b Which component of the innate immune defence could mount a defence against these bacteria?
c If this defence is successful, how would the bacteria be eliminated?

2 Assume that the innate immune defences are overwhelmed, and the adaptive immune system must come into action against these extracellular pyogenic bacteria.

a Could these bacteria be recognised and eliminated by cytotoxic T cells? Explain.
b Briefly identify the components of the adaptive immune defences that could recognise and eliminate these bacteria.

3 An inherited condition known as Bruton’s X-linked agammaglobulinemia is characterised by the absence of immunoglobulin in the blood serum. This is one of several kinds of immunodeficiency diseases and is characterised by the failure of an affected child, typically male, to produce antibodies.

a Identify the probable primary defect in Bruton’s agammaglobulinemia.
b Would you expect a male infant with this condition to be susceptible to infection by pyogenic bacteria?

4 Examine figure 7.57, which shows the course of events in an infection by hepatitis A virus (HAV).

**FIGURE 7.57** Order of events during hepatitis A (HAV) infection. Note that viremia refers to the presence of the virus in the blood.

a What story is told by this graph?
b Could a person with a HAV infection, but who shows no symptoms, transmit the virus to other people?
c What is meant by the label Anti-HAV IgM?
d Which antibody is the first to appear in response to an infection?
e Which antibody appears later, but is more persistent?
Consider two food handlers who could be the source of an outbreak of HAV among clients in their café.
f Could the identification of the HAV antibody levels of each food handler indicate whether or not that person was the likely cause of the HAV outbreak that occurred four weeks previously? Explain your decision.
Chapter review

Key words
acquired immunity  adaptive immunity  antibodies  antigen-binding sites  antigen-presenting cells (APCs)  bone marrow  chronic inflammation  cilia  clonal expansion  clonal selection  clonal selection theory  clone  colonoscopy  complement  cytotoxic T cells  degranulation  epithelial tissues  exoenzymes  extracellular  first line of defence  granzyme  helper T cells  immunity  immunoglobulins  immunological memory  inflammation  innate immunity  interferons (INFs)  intracellular  leukocidins  lymph nodes  lymphocytes  lysis  macrophages  membrane-attack complex (MAC)  memory cells  molecular pattern  mucous membranes  mucus  naïve  natural immunity  neutrophils  non-specific immunity  opsonisation  pattern recognition receptor (PRR)  perforin  phagocytes  phagocytic  phagocytosis  phagosome  primary lymphoid organs  sebum  second line of defence  secondary lymphoid organs  somatic mutations  spleen  third line of defence  thymus  ulcerative colitis (UC)  V(D)J recombination

Questions
1 Making connections ➔ Use at least eight chapter key words to construct a concept map. You may choose to add additional words.
2 Interpreting graphical data ➔ Examine the following graph showing the time course of three events that form part of one particular defensive response of the immune system.

![Graph image](image_url)

FIGURE 7.58

a Briefly outline the various events depicted in this graph.
b What immune response is shown in this graph?
c On what evidence did you make your decision?

3 Demonstrating understanding ➔ A pathogen has crossed the mucous membrane of the airways and an immune cell can only identify this pathogen as follows: ‘This is a bacterium; it’s not a virus.’
   a Is this an example of a specific or a generic identification?
   b To which line of defence does this immune cell belong — first, second or third?
   c What is a possible identity of this immune cell?
   d Identify a cellular response to this pathogen that might then be expected to occur. Another immune cell recognises this pathogen as a particular species of Gram-negative bacteria, as follows: ‘This is *Vibrio cholera*.’
   e To which line of defence does this immune cell belong — first, second or third?
   f Identify a humoral response to this pathogen that might be expected to occur.
   g What kind of immune cell can produce this response?

4 Developing valid biological explanations ➔ Suggest a possible explanation in biological terms for the following observations:
   a Babies born with an inherited defect in the protein perforin that makes this protein non-functional are at risk of death from viral infection or tumours early in their lives.
   b A history of recurrent virus infections in a patient suggests a defect in the immune defences carried out by T cells.
c Photomicrographs of blood smears taken from healthy people are expected to show a majority of red blood cells.

d A white blood cell in a photomicrograph of a blood smear taken from a healthy person is more likely to be a neutrophil than a basophil.

e A person feeling unwell often has swollen glands.

f A person who suffers and recovers from an infectious disease such as measles has lifelong immunity to that disease.

g Pus may appear during the process of the healing of a skin wound.

h At birth, a baby has some level of adaptive immunity.

5 **Demonstrating knowledge and understanding**

Read the following statement taken from a research paper:

*One should be aware that dissecting innate and acquired host defence mechanisms is an artificial approach. In real life the two components of the host response are complementary and synergistic.* (Source of quotation: van Krevel, R. *Innate Immunity to Mycobacterium tuberculosis,* Clin. Microbiol. Rev. April 2002 vol. 15 no. 2 294–309).

a What key point about immunity is being made in this statement by the authors of this paper?

b Identify an example of complementary action between cells of innate immunity and cells of adaptive immunity.

6 **Demonstrating knowledge and understanding**

Consider each of the following immune responses and identify each as part of either innate immunity or adaptive immunity or both:

- inflammatory response to infection
- activation of the complement cascade to opsonise bacteria
- movement of mucus from airways by action of cilia
- recognition and elimination of a virus-infected cell
- presentation of antigens to naïve immune cells
- physical barrier to infectious agents
- secretion of cytokines.

7 **Recognising differences and similarities**

Identify one key difference and one similarity between the members of the following pairs:

- primary lymphoid organ and secondary lymphoid organ
- innate immunity and adaptive immunity
- a cell-mediated immune response and a humoral immune response
- a B cell and a T cell
- degranulation and phagocytosis
- immunoglobulin G (IgG) and immunoglobulin M (IgM).

8 **Interpreting graphical data**

Carefully examine figure 7.59, noting the units on each axis.

![Graph showing antibody concentrations over time](image)

- a What story is told in this graph?
- b What is an antigen? An antibody?
- c Briefly describe what is happening in the period from day 0 to day 5 after a person is exposed to antigen A.
- d In this period, why is there a delay in the appearance of antibodies to antigen A?
- e At day 28, the person is exposed to two antigens — a new antigen B and the previously met antigen A.
- f What two differences are apparent in the response to antigen A on the second exposure as compared to the first exposure?
- g Explain this difference.
- h True or false: The re-exposure to the antigen results in the maximum production of nearly a thousand times more antibodies.
- i Why was the response to antigen B after day 28 not the same as the response to antigen A over the same period?

9 **Communicating understanding**

A person’s innate immune system successfully defended against a viral infection and the person does not develop the viral disease. Identify how natural killer cells contribute to this successful defence.

10 **Demonstrating knowledge and understanding**

Examine figure 7.60.

- a Complete this diagram by labelling the structures numbered 1, 2, and 3.
- b What is the major antigen-presenting cell?
- c What is an alternative name for a helper T cell: CD4* cell or CD8* cell?
d Compete the following sentences by choosing from the alternatives supplied:
   i Binding of a receptor on a helper T cell
to a presented antigen (kills/activates/opsonises) the T cell.
   ii Another cell that can act as an antigen-presenting cell is a (mast cell/macrophage/neutrophil).
   iii For presentation, antigens must be linked to (an MHC molecule/a complement protein/any antibody).

**FIGURE 7.60**

11 Demonstrating understanding
d Rejection of a transplanted organ may behyperacute, occurring in the first 24 hours after transplantation. This is caused by pre-existing antibodies in the recipient that bind to antigens on the transplant and results in the activation of the complement system and migration of neutrophils to the transplant site. (Hyperacute rejection can be prevented by pre-screening for these anti-graft antibodies.)
   Is hyperacute rejection an immune response of the innate immune system or the adaptive immune system? Explain your choice.

b A second form of rejection is termed acute rejection and it usually begins after the first week of transplantation. This is caused by a mismatch of HLA antigens and involves the action of T cells. (Acute rejection is minimised by the use of immunosuppressive therapy following transplantation.)
   i Is acute rejection an immune response of the innate immune system or the adaptive immune system? Explain your choice.
   ii Explain why the acute rejection does not appear until after the first week of transplantation.

12 Discussion question Infectious diseases are currently the world’s largest killers of children and young adults, accounting for more than 13 million deaths a year — one in two deaths in developing countries. (Source: H Kuhse et al. *Bioethics: An anthology*. Wiley, 2015). The World Health Organization (WHO) has identified tuberculosis (TB) as a top infectious disease killer worldwide, with 9.6 million people falling ill with TB and 1.5 million dying from the disease in 2014. Of these deaths, over 95% were in low- and middle-income countries.
   A new concern is the emergence of a rare form of TB labelled extensively drug-resistant tuberculosis (XDR-TB). XDR-TB is resistant to the first-line drugs used effectively in the standard treatment of TB and is also resistant to at least one of the second-line drugs used to treat multidrug-resistant TB (MDR-TB). Awareness of this threat of XDR-TB was raised in 2006, following an outbreak in South Africa in which 52 of 53 patients with XDR-TB in a rural hospital died.
   Several issues are raised by the emergence of drug-resistant infectious diseases, such as XDR-TB, which is spread via airborne particles from coughing, sneezing, shouting or singing by people with the disease. These issues raise the following questions:
   a What infection controls are appropriate given individual human rights?
   b Should infection control in a community at risk rely on voluntary cooperation of infected people or should restrictions on their mixing with the general population be considered?
   c Might any such restrictions act as disincentives for infected people to seek treatment?
   In 2006, a person who was diagnosed with XDR-TB refused to remain in hospital and discharged herself. Five days later, this person was traced and forcibly hospitalised.
   d Discuss whether you consider this limitation of the patient’s human rights by health authorities to be appropriate in the interests of public health.