CHAPTER 15

Resistance and immunity

ANIMATIONS

From the months spent in the womb to the end of life, every individual is under constant attack from an enormous range of potentially harmful invaders. These threats include such diverse entities as bacteria, viruses, cancer cells, parasites and foreign (non-self) cells, e.g. in tissue transplant. The body has therefore developed a wide selection of protective measures, which can be divided into two categories.

Non-specific defence mechanisms. These protect against any of an enormous range of possible dangers.

Specific defence mechanisms. These are grouped together under the term immunity. Resistance is directed against only one specific invader. In addition, *immunological memory* develops, which confers long-term immunity to specific infections. An *antigen* is anything that stimulates an immune response.

The later sections of the chapter describe the effects of ageing on the immune system, and consider some disorders of lymphatic system function.

Non-specific defence mechanisms

Learning outcomes

After studying this section, you should be able to:

- identify the body's main non-specific defence cells
- describe the functions and features of the inflammatory response
- explain the process of phagocytosis
- list the main antimicrobial substances of the body.

These are the first lines of general defence; they prevent entry and minimise further passage of microbes and other foreign material into the body.

There are five main non-specific defence mechanisms:

- defence at body surfaces
- phagocytosis
- natural antimicrobial substances
- the inflammatory response
- immunological surveillance.

Defence at body surfaces

Healthy, intact skin and mucous membranes provide an efficient physical barrier protecting the body's exposed surfaces. Few pathogens can establish themselves on healthy skin. Sebum and sweat secreted onto the skin surface contain antibacterial and antifungal substances.

Epithelial membranes lining body cavities and passageways exposed to the external environment (e.g. the respiratory, genitourinary and digestive tracts) are more delicate, but are also well defended. Epithelia produce antibacterial secretions, often acidic, containing antibodies and enzymes, as well as sticky mucus for trapping passing microbes.

Hairs in the nose act as a coarse filter, and the sweeping action of cilia in the respiratory tract (Fig. 10.12) moves mucus and inhaled foreign materials towards the throat. Then it is coughed up (*expectorated*) or swallowed.

The one-way flow of urine from the bladder minimises the risk of infection ascending through the urethra into the bladder. In the female, the acidity of vaginal secretions discourages microbial growth.

Phagocytosis 15.1

The process of phagocytosis (cell eating) is shown in Figure 4.11, page 69. Phagocytic defence cells such as macrophages and neutrophils are the body's first line of cellular defence. They actively migrate (chemotaxis, p. 68) to sites of inflammation and infection, because neutrophils themselves and invading microbes release chemicals that attract them (chemoattractants). Phagocytes attack and engulf their targets (Fig. 15.1). They indiscriminately digest and destroy foreign cells, antigenic material and damaged body cells and debris. They may also release chemicals toxic to invading microbes into the interstitial fluid. Macrophages have an important role as a link between the non-specific and specific defence mechanisms. After ingestion and digestion of an antigen, they act as *antigen-presenting cells*, displaying their antigen on their own cell surface to stimulate T-lymphocytes and activate the immune response (p. 379).

The body's population of fixed and roaming macrophages (the *monocyte-macrophage system*) is also discussed in Chapter 4.

Natural antimicrobial substances

Hydrochloric acid. This is present in high concentrations in gastric juice, and kills the majority of ingested microbes.

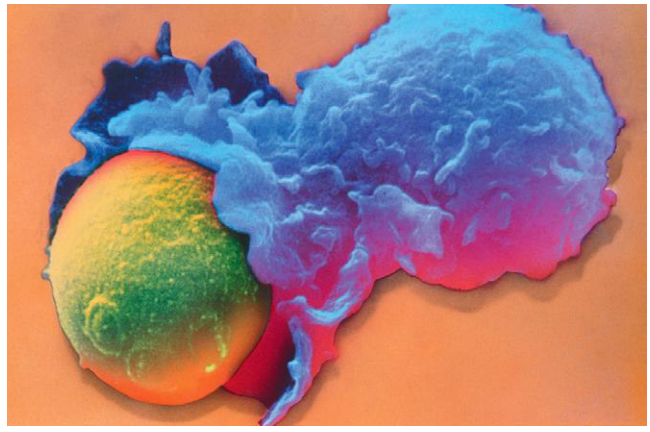

Figure 15.1 White blood cell (blue) phagocytosing a yeast cell (yellow).

Lysozyme. This antibacterial enzyme is present in granulocytes, tears, and other body secretions, but not in sweat, urine or cerebrospinal fluid. It destroys bacterial cell walls but does not affect viruses or other pathogens.

Antibodies. These protective proteins are found coating membranes and in body fluids, and inactivate bacteria (p. 381).

Saliva. This is secreted into the mouth and washes away food debris that may otherwise encourage bacterial growth. It contains antibodies, lysozyme and buffers to neutralise bacterial acids that promote dental decay.

Interferons. These chemicals are produced by T-lymphocytes, macrophages and body cells that have been invaded by viruses. They prevent viral replication within infected cells, and the spread of viruses to healthy cells.

Complement 15.2. Complement is a system of about 20 proteins found in the blood and tissues. It is activated by the presence of immune complexes (an antigen and antibody bound together) and by foreign sugars on bacterial cell walls. Complement:

- binds to, and damages, bacterial cell walls, destroying the microbe
- binds to bacterial cell walls, stimulating phagocytosis by neutrophils and macrophages
- attracts phagocytic cells such as neutrophils into an area of infection, i.e. stimulates chemotaxis.

The inflammatory response 15.3

This is the physiological response to tissue damage and is accompanied by a characteristic series of local changes (Fig. 15.2). Its purpose is protective: to isolate, inactivate and remove both the causative agent and damaged tissue, so that healing can take place. The cardinal signs of inflammation are *redness*, *heat*, *swelling* and *pain*.

Inflammatory conditions are recognised by their Latin suffix '-itis'; for example, appendicitis is inflammation of the appendix and laryngitis is inflammation of the larynx.

Causes of inflammation

Any form of tissue damage stimulates the inflammatory response, even in the absence of infection. The wide range of causative agents includes extremes of temperature, trauma, corrosive chemicals including extremes of pH, abrasion and infection by pathogens.

Acute inflammation

Acute inflammation is typically of short duration, e.g. days to a few weeks, and may range from mild to very severe, depending on the extent of the tissue damage. Most aspects of the inflammatory response are hugely beneficial, promoting removal of the harmful agent and setting the scene for healing to follow.

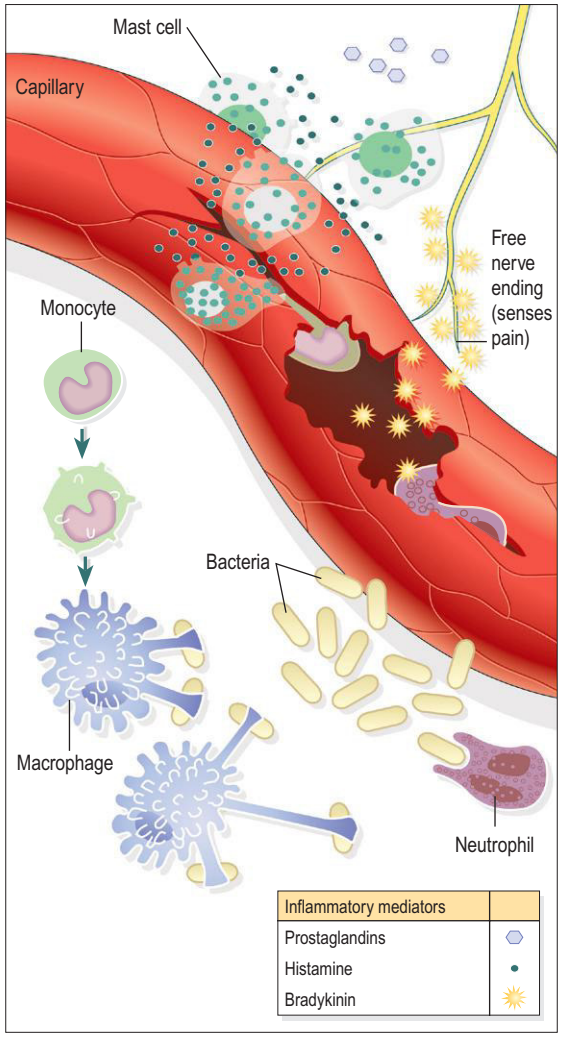

Figure 15.2 The inflammatory response.

The acute inflammatory response is described here for convenience as a collection of separate events: increased blood flow, accumulation of tissue fluid, migration of leukocytes, increased core temperature, pain and suppuration. In reality, these events significantly overlap and develop together.

Some of the most important substances released in inflammation are summarised in Table 15.1.

Increased blood flow

Following injury, both the arterioles supplying the damaged area and the local capillaries dilate, increasing blood flow to the site.

This is caused mainly by the local release of a number of chemical mediators from damaged cells, e.g. histamine and serotonin. Increased blood flow to the area of tissue damage provides more oxygen and nutrients for the increased cellular activity that accompanies

Table 15.1 Summary of the principal substances released in inflammation

Substance	Made by	Trigger for release	Main pro-inflammatory actions
Histamine	Mast cells (in most tissues), basophils (blood); stored in cytoplasmic granules	Binding of antibody to mast cells and basophils	Vasodilation, itching, ↑ vascular permeability, degranulation, smooth muscle contraction (e.g. bronchoconstriction)
Serotonin (5-HT)	Platelets Mast cells and basophils (stored in granules) Also in CNS (acts as neurotransmitter)	When platelets are activated, and when mast cells/basophils degranulate	Vasoconstriction, ↑ vascular permeability
Prostaglandins (PGs)	Nearly all cells; not stored, but made from cell membranes as required	Many different stimuli, e.g. drugs, toxins, other inflammatory mediators, hormones, trauma	Diverse, sometimes opposing, e.g. fever, pain, vasodilation or vasoconstriction, ↑ vascular permeability
Heparin	Liver, mast cells, basophils (stored in cytoplasmic granules)	Released when cells degranulate	Anticoagulant (prevents blood clotting), which maintains blood supply (nutrients, O_2) to injured tissue and washes away microbes and wastes
Bradykinin	Tissues and blood	When blood clots, in trauma and inflammation	Pain Vasodilation

inflammation. Increased blood flow causes the increased temperature and reddening of an inflamed area, and contributes to the swelling (oedema) associated with inflammation.

Increased tissue fluid formation

One of the cardinal signs of inflammation is swelling of the tissues involved, which is caused by fluid leaving local blood vessels and entering the interstitial spaces.

This is partly due to increased capillary permeability caused by inflammatory mediators such as histamine, serotonin and prostaglandins, and partly due to elevated pressure inside the vessels because of increased blood flow. Most of the excess tissue fluid drains away in the lymphatic vessels, taking damaged tissue, dead and dying cells and toxins with it.

Plasma proteins, normally retained within the bloodstream, also escape into the tissues through the leaky capillary walls; this increases the osmotic pressure of the tissue fluid and draws more fluid out of the blood. These proteins include antibodies, which combat infection, and *fibrinogen*, a clotting protein. Fibrinogen in the tissues is converted by *thromboplastin* to fibrin, which forms an insoluble mesh within the interstitial space, walling off the inflamed area and helping to limit the spread of any infection. Some pathogens, e.g. *Streptococcus pyogenes*, which causes throat and skin infections, release toxins that break down this fibrin network and promote spread of infection into adjacent, healthy tissue.

Sometimes tissue oedema can be harmful. For instance, swelling around respiratory passages can obstruct breathing, and significant swelling often causes pain. On the other hand, the swelling around a painful, inflamed joint cushions it and limits movement, which encourages healing.

Migration of leukocytes

Loss of fluid from the blood thickens it, slowing flow and allowing the normally fast-flowing white blood cells to make contact with, and adhere to, the vessel wall. In the acute stages, the most important leukocyte is the neutrophil, which adheres to the blood vessel lining, squeezes between the endothelial cells and enters the tissues (diapedesis, see Fig. 4.10, p. 69), where its main function is in phagocytosis of antigens. Phagocyte activity is promoted by the raised temperatures (local and systemic) associated with inflammation.

After about 24 hours, macrophages become the predominant cell type at the inflamed site, and they persist in the tissues if the situation is not resolved, leading to chronic inflammation. Macrophages are larger and longer lived than neutrophils. They phagocytose dead/dying tissue, microbes and other antigenic material, and dead/dying neutrophils. Some microbes resist digestion and provide a possible source of future infection, e.g. *Mycobacterium tuberculosis* (p. 268).

Chemotaxis. This is the chemical attraction of leukocytes, including neutrophils and macrophages, to an area of inflammation.

It may be that chemoattractants act to retain passing leukocytes in the inflamed area, rather than actively attracting them from distant areas of the body. Chemoattractants include microbial toxins, chemicals released from leukocytes, prostaglandins from damaged cells and complement proteins.

Increased temperature

The increased temperature of inflamed tissues has the twin benefits of inhibiting the growth and division of microbes, whilst promoting the activity of phagocytes.

The inflammatory response may be accompanied by a rise in body temperature (fever, *pyrexia*), especially if there is bacterial infection. Body temperature rises when an endogenous pyrogen (interleukin 1) is released from macrophages and granulocytes in response to microbial toxins or immune complexes. Interleukin 1 is a chemical mediator that resets the temperature thermostat in the hypothalamus at a higher level, causing pyrexia and other symptoms that may also accompany systemic inflammation, e.g. fatigue and loss of appetite. Pyrexia increases the metabolic rate of cells in the inflamed area and, consequently, there is an increased need for oxygen and nutrients.

Pain

This occurs when local swelling compresses sensory nerve endings. It is exacerbated by chemical mediators of the inflammatory process, e.g. bradykinin and prostaglandins which potentiate the sensitivity of the sensory nerve endings to painful stimuli. Although pain is an unpleasant experience, it may indirectly promote healing, because it encourages protection of the damaged site.

Suppuration (pus formation)

Pus consists of dead phagocytes, dead cells, fibrin, inflammatory exudate and living and dead microbes. A localised collection of pus in the tissues is called an *abscess* (Fig. 14.10). The most common pyogenic (pus-forming) bacteria are *Staphylococcus aureus* and *Streptococcus pyogenes*.

Outcomes of acute inflammation

Resolution. This occurs when the cause has been successfully overcome. Damaged cells and residual fibrin are removed, being replaced with new healthy tissue, and repair is complete, with or without scar formation.

Development of chronic inflammation. Acute inflammation may become chronic if resolution is not complete, e.g. if live microbes remain at the site, as in some deep-seated abscesses, wound infections and bone infections.

Chronic inflammation

The processes involved are very similar to those of acute inflammation but, because the process is of longer duration, considerably more tissue damage is likely. The inflammatory cells are mainly lymphocytes instead of neutrophils, and fibroblasts are activated, leading to the laying down of collagen, and *fibrosis*. If the body defences are unable to clear the infection, they may try to wall it off instead, forming nodules called *granulomas*, within which are collections of defensive cells. Tuberculosis is an example of an infection that frequently becomes chronic, leading to granuloma formation. The causative bacterium, *Mycobacterium tuberculosis*, is resistant to body defences and so pockets of organisms (Ghon foci, p. 269) are sealed up in granulomas within the lungs.

Chronic inflammation may either be a complication of acute inflammation (see above) or follow chronic exposure to an irritant. Fibrosis (scar formation) is discussed in Chapter 14.

Immunological surveillance

A population of lymphocytes, called natural killer (NK) cells, constantly patrol the body searching for abnormal cells. Cells that have been infected with a virus, or mutated cells that might become malignant, frequently display unusual markers on their cell membranes, which are recognised by NK cells. Having detected an abnormal cell, the NK cell immediately kills it. Although NK cells are lymphocytes, they are much less selective about their targets than the other two types discussed in this chapter (T- and B-cells).

Immunity

Learning outcomes

After studying this section, you should be able to:

- discuss the roles of the different types of T-lymphocyte in providing cell-mediated immunity
- describe the process of antibody-mediated immunity
- distinguish between artificially and naturally acquired immunity, giving examples of each
- distinguish between active and passive immunity, giving examples of each.

The body's first line of defence is its collection of non-specific defences, including phagocytes such as macrophages. If these are overwhelmed, activation of the powerful immune system follows. Immunity possesses three key attributes not seen with non-specific defences: specificity, memory and tolerance.

Specificity. Unlike mechanisms such as the inflammatory response and the phagocytic action of macrophages,

which are triggered by a wide range of threats, an immune response is directed against one antigen and no others.

Memory. Again, unlike general defence mechanisms, an immune response against a particular antigen will usually generate immunological memory of that antigen. This means that the immune response on subsequent exposures to the same antigen is generally faster and more powerful.

Tolerance. The cells of the immune system are aggressive and potentially extremely destructive. Control of their activity is essential for protection of healthy body tissues. As immune cells travel around the body, they check the marker proteins that cells show on their cell membranes. Healthy body cells display the expected 'self' markers and are ignored by the patrolling immune cells. However, non-self cells, such as cancer cells, foreign (transplanted) cells or pathogens, possess different patterns of markers, which immediately activate the immune cell and usually lead to the destruction of the non-self cell.

Lymphocytes

Lymphocytes make up 20–30% of circulating white blood cells but at any one time most of them are found in lymphatic and other tissues rather than in the bloodstream. They include natural killer cells (p. 379) involved in immunological surveillance, T-cells (the majority) and B-cells. T- and B-cells are responsible for immunity (specific defence) and are produced in the bone marrow and some lymphatic tissues, although T-cells migrate to the thymus gland for final maturation.

For each of the millions of possible antigens that might be encountered in life, there is a corresponding T- and B-cell programmed to respond to it. There are, therefore, vast numbers of different T- and B-cells in the body, each capable of responding to only one antigen (antigen specificity).

T-cells

The hormone thymosin, produced by the thymus gland, is responsible for promoting T-cell maturation, which leads to the formation of fully specialised (differentiated), mature, functional T-cells. It is important to recognise that a mature T-cell has been programmed to recognise only one type of antigen, and during its subsequent travels through the body will react to no other antigen, however dangerous it might be. Thus, a T-cell manufactured to recognise the chickenpox virus will not react to a measles virus, a cancer cell, or a tuberculosis bacterium.

T-cells provide *cell-mediated immunity*, discussed below.

B-cells

These are both produced and matured in the bone marrow. They produce antibodies (immunoglobulins), proteins designed to bind to, and destroy, an antigen. As with T-cells, each B-cell targets one specific antigen; the antibody released reacts with one type of antigen and no other. B-cells provide *antibody-mediated immunity*, discussed below.

Cell-mediated immunity  15.4

T-cells that have matured in the thymus gland are released into the circulation. When they encounter their antigen for the first time, they become sensitised to it. If the antigen has come from outside the body, it needs to be 'presented' to the T-cell on the surface of an antigen-presenting cell. There are different types of antigen-presenting cell, including macrophages. Macrophages are part of the non-specific defences, because they engulf and digest antigens indiscriminately, but they are a crucial 'link' cell between initial non-specific defences and the immune system. After digesting the antigen they transport the most antigenic fragment to their own cell membrane and display it on their surface (Fig. 15.3). They display (*present*) this antigen to the T-cell that has been processed to target that particular antigen, activating the T-cell.

If the antigen is an abnormal body cell, such as a cancer cell, it too will be displaying foreign (non-self) material on its cell membrane that will stimulate the T-cell. Whichever way the antigen is presented to the T-cell, it stimulates it to divide and proliferate (*clonal expansion*) (Fig. 15.3). Four main types of specialised T-cell are produced, each of which is still directed against the original antigen, but which will tackle it in different ways.

Cytotoxic T-cells

These directly inactivate any cells carrying antigens. They attach themselves to the target cell and release powerful toxins, which are very effective because the two cells are so close together. The main role of cytotoxic T-cells is in destruction of abnormal body cells, e.g. infected cells and cancer cells.

Helper T-cells

These are essential not only for cell-mediated immunity, but also antibody-mediated immunity. Their central role in immunity is emphasised in situations where they are destroyed, as by the human immunodeficiency virus (HIV). When helper T-cell numbers fall significantly, the whole immune system is compromised. T-helpers are the commonest of the T-cells; their main functions include:

- production of chemicals called *cytokines*, e.g. interleukins and interferons, which support and promote cytotoxic T-cells and macrophages
- cooperating with B-cells to produce antibodies; although B-cell are responsible for antibody

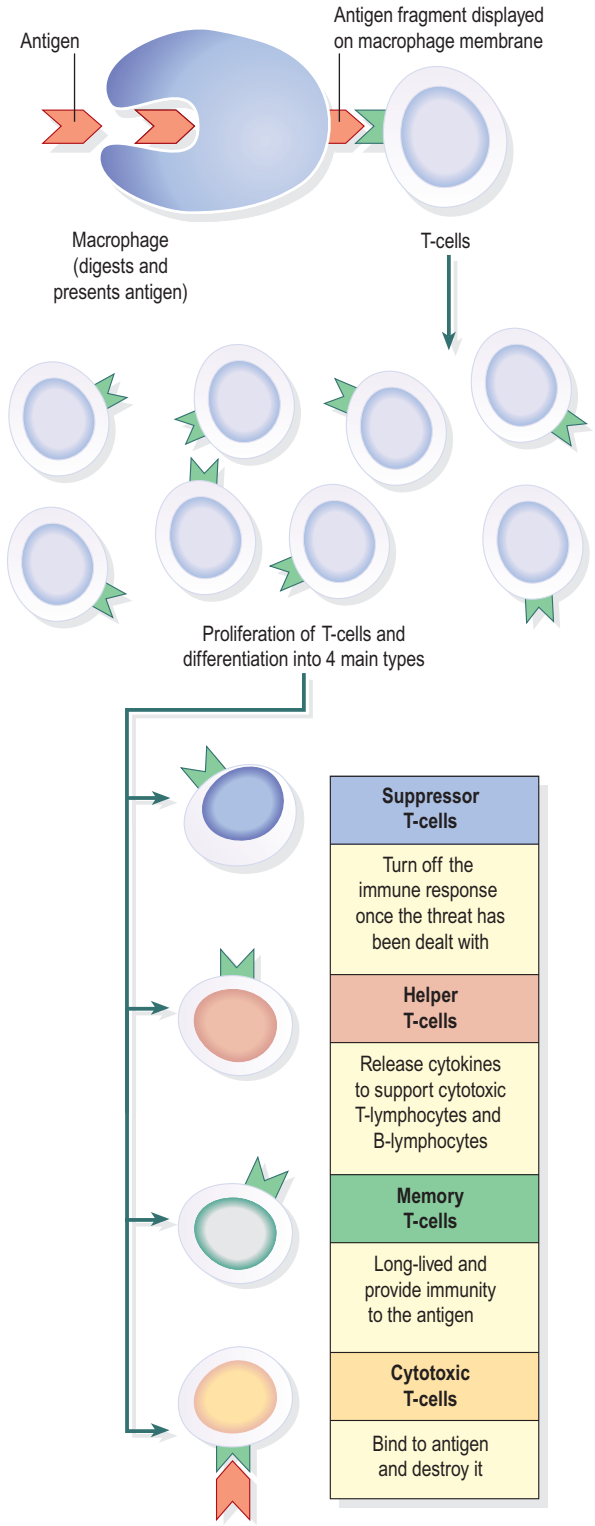

Figure 15.3 Clonal expansion of T-cells.

manufacture, they require to be stimulated by a helper T-cell first.

Suppressor T-cells

These cells act as 'brakes', turning off activated T- and B-cells. This limits the powerful and potentially damaging effects of the immune response. Suppressor T-cells are also thought to help prevent the development of auto-immunity (p. 385) and to protect the fetus in pregnancy.

Memory T-cells

These long-lived cells survive after the threat has been neutralised, and provide *cell-mediated immunity* by responding rapidly to another encounter with the same antigen.

Antibody-mediated (humoral) immunity 15.5

B-cells are much less mobile than T-cells, and spend much of their time in lymphoid tissue, e.g. the spleen and lymph nodes. B-cells, unlike T-cells, recognise and bind antigen particles without having to be presented with them by an antigen-presenting cell. Once its antigen has been detected and bound, and with the help of an activated helper T-cell, the B-cell enlarges and begins to divide (clonal expansion, Fig. 15.4). It produces two functionally distinct types of cell, plasma cells and memory B-cells.

Plasma cells

These secrete massive quantities of antibodies (immunoglobulins, Ig) into the blood. Antibodies are carried throughout the tissues. Plasma cells live no longer than a day and produce millions of molecules of only one type of antibody, which targets the specific antigen that originally bound to the B-cell. Antibodies:

- bind to antigens, labelling them as targets for other defence cells such as cytotoxic T-cells and macrophages
- bind to bacterial toxins, neutralising them
- activate complement (p. 377).

There are five main types of antibody, summarised in Table 15.2. 15.6

Memory B-cells

Like memory T-cells, these cells remain in the body long after the initial episode has been dealt with, and rapidly respond to another encounter with the same antigen by stimulating the production of antibody-secreting plasma cells. The interdependence of the two parts of the immune system is summarised in Figure 15.5.

The fact that the body does not normally develop immunity to its own cells is due to the fine balance that exists between the immune reaction and its suppression. *Autoimmune diseases* (p. 385) are due to the disturbance of this balance.

Acquired immunity

The immune response to an antigen following the first exposure (primary immunisation) is called the *primary*

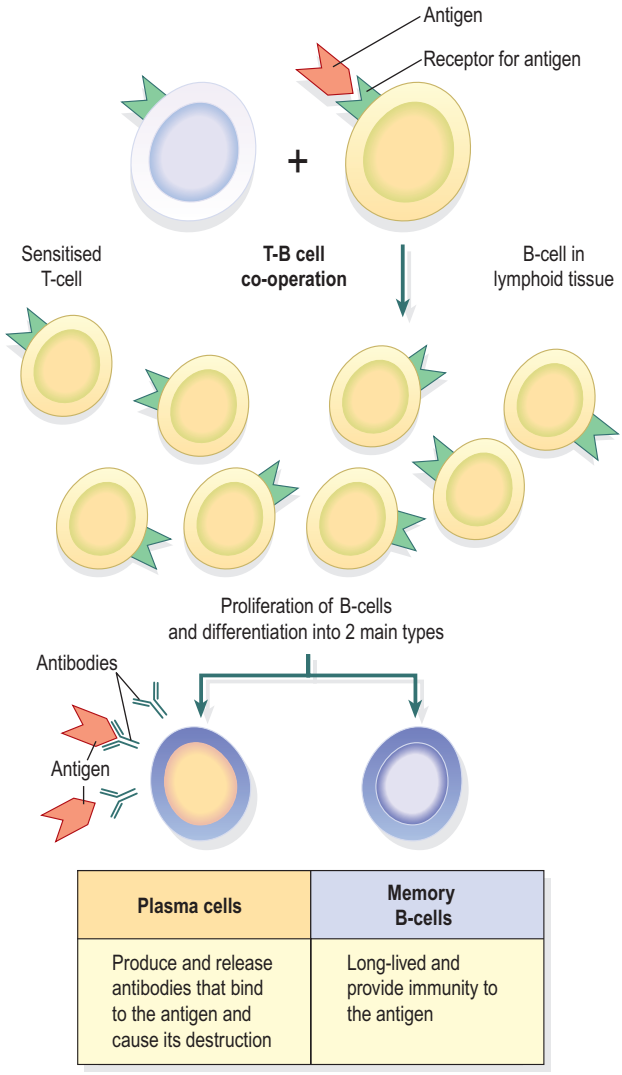

Figure 15.4 Clonal expansion of B-cells.

response. Second and subsequent exposures give rise to a *secondary response* (Fig. 15.6).

The primary response. Exposure of the immune system to an antigen for the first time leads to a slow and delayed rise in antibody levels, peaking 1–2 weeks after infection. This delayed response reflects the time required to activate the T-cell system, which then stimulates B-cell division. Antibody levels start to fall once the infection is cleared, but if the immune system has responded well, it will have generated a population of long-lived memory B-cells, making the individual immune to future infection.

The secondary response. On subsequent exposures to the same antigen, the immune response is much faster and 10–15 times more powerful, because the memory B-cells generated after the first infection rapidly divide and antibody production begins almost immediately.

Table 15.2 The five types of antibody

Type of antibody	Function
IgA	Found in body secretions like breast milk and saliva, and prevent antigens crossing epithelial membranes and invading deeper tissues
IgD	This is made by B-cells and displayed on their surfaces. Antigens bind here to activate B-cells
IgE	Found on cell membranes of, e.g., basophils and mast cells, and if it binds its antigen, activates the inflammatory response. This antibody is often found in excess in allergy
IgG	This is the largest and most common antibody type. It attacks many different pathogens, and crosses the placenta to protect the fetus
IgM	Produced in large quantities in the primary response and is a potent activator of complement

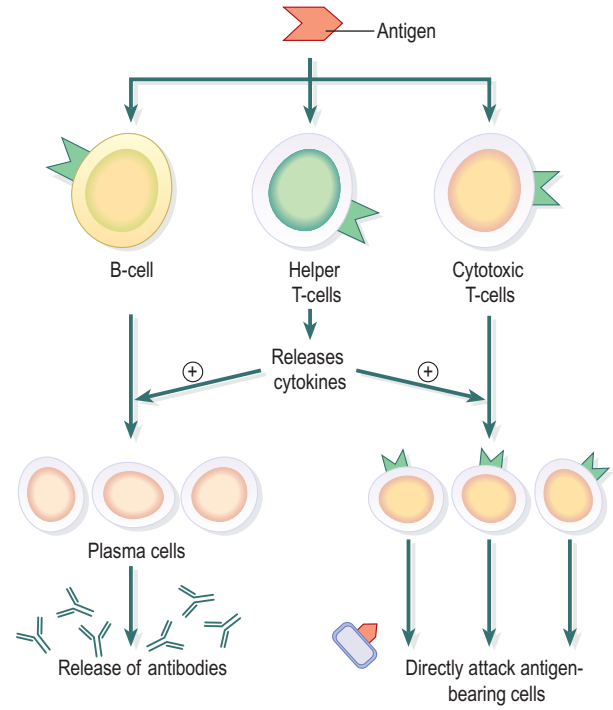

Figure 15.5 Interdependence of the T- and B-cell systems in the immune response.

Immunity may be acquired *naturally* or *artificially* and both forms may be active or passive (Fig. 15.7). Active immunity means that the individual has responded to an antigen and produced his own antibodies, lymphocytes are activated and the memory cells formed provide long-lasting resistance. In passive immunity the individual is given antibodies produced by someone else. The

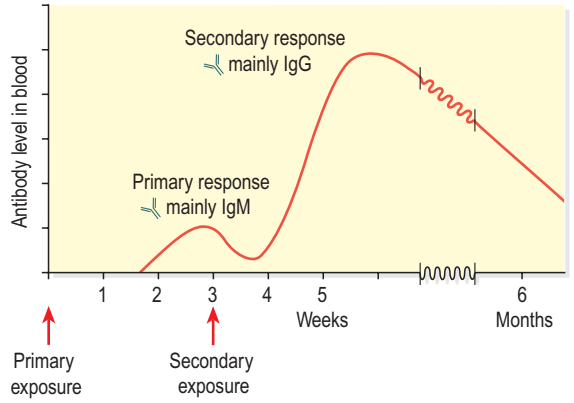

Figure 15.6 The antibody responses to antigen exposure.

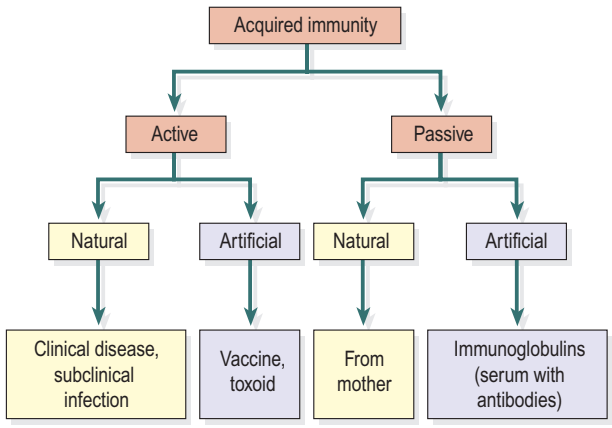

Figure 15.7 Summary of the types of acquired immunity.

antibodies break down with time, so passive immunity is relatively brief.

Active naturally acquired immunity

The body may be stimulated to produce its own antibodies by:

- *Having the disease*. During the course of the illness, B-cells develop into plasma cells that produce antibodies in sufficient quantities to overcome the infection. After recovery, the memory B-cells produced confer immunity to future infection by the same antigen.
- *Having a subclinical infection*. Sometimes the infection is not sufficiently severe to cause clinical disease but stimulates sufficient memory B-cells to establish immunity, e.g. hepatitis A, p. 333. In other cases, subclinical infection may be too mild to stimulate an adequate response for immunity to develop.

Active artificially acquired immunity

This type of immunity develops in response to the administration of dead or live artificially weakened pathogens (vaccines) or deactivated toxins (toxoids). The vaccines and toxoids retain the antigenic properties that stimulate the development of immunity but they cannot cause the disease. Many infectious diseases can be prevented by artificial immunisation. Examples are shown in Box 15.1.

Box 15.1 Diseases preventable by vaccination

- Anthrax
- Cholera
- Diphtheria
- Hepatitis B
- Measles
- Mumps
- Poliomyelitis
- Rubella
- Smallpox
- Tetanus
- Tuberculosis
- Typhoid
- Whooping cough

Active immunisation against some infectious disorders gives lifelong immunity, e.g. diphtheria, whooping cough or mumps. In other infections the immunity may last for a number of years or for only a few weeks before revaccination is necessary. Apparent loss of immunity may be due to infection with a different strain of the same pathogen, which has different antigenic properties but causes the same clinical illness, e.g. viruses that cause the common cold and influenza. In older or poorly nourished individuals, lymphocyte production, especially B-cells, is reduced and the primary and secondary response may be inadequate.

Passive naturally acquired immunity

This type of immunity is acquired before birth by the passage of maternal antibodies across the placenta to the fetus, and to the baby in breast milk. The variety of different antibodies provided depends on the mother's active immunity. The baby's lymphocytes are not stimulated and this form of immunity is short lived.

Passive artificially acquired immunity

In this type, ready-made antibodies, in human or animal serum, are injected into the recipient. The source of the antibodies may be an individual who has recovered from the infection, or animals, commonly horses, that have been artificially actively immunised. Specific immunoglobulins (antiserum) may be administered *prophylactically* to prevent the development of disease in people who have been exposed to the infection, e.g. rabies, or *therapeutically* after the disease has developed.

Summary of the immune response to a bacterial infection

Figure 15.8 shows the main events that make up the body's integrated response to infection. Initially, non-specific defence cells (neutrophils, natural killer cells and macrophages) accumulate at the site of infection, and attempt to limit bacterial expansion. If the threat is strong

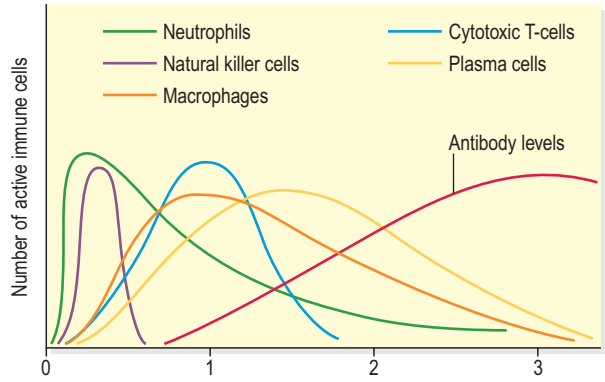

Figure 15.8 Summary of the defensive response to bacterial infection.

enough and many macrophages are involved, arriving T-cells are activated, producing populations of cytotoxic and helper T-cells, which in turn activate B-cells. As B-cells proliferate and differentiate into plasma cells, antibody levels progressively rise.

Ageing and immunity

Learning outcomes

After studying this section, you should be able to:

- describe the effects of ageing on the immunity.

Immunity declines with advancing age, increasing the risk of infection in older adults and lengthening recovery times. The thymus gland progressively shrinks from its maximum size at puberty and may be only a quarter of that by age 50. This is linked to decreased T-cell responsiveness, and as the B-cell response is dependent upon T-cell function, antibody levels also fall with age. Levels of autoantibodies and incidence of autoimmunity increase in later life, and reduced function of natural killer cells is associated with increasing incidence of most types of cancer.

Abnormal immune function

Learning outcomes

After studying this section, you should be able to:

- describe, with examples, the four types of allergic response
- describe the basis of autoimmune disease
- discuss the specific examples of autoimmune disease
- discuss the cause and effects of acquired immune deficiency syndrome (AIDS).

Hypersensitivity (allergy) 15.7

Allergy is an inappropriate, powerful immune response to an antigen (allergen) that is usually harmless. Examples include house dust, animal dander and grass pollen. It is therefore usually the immune response that causes the damage to the body, not the allergen itself. Upon initial exposure to the allergen the individual becomes sensitised to it, and on second and subsequent exposures the immune system mounts a response entirely out of proportion to the perceived threat. It should be noted that these responses are exaggerated versions of normal immune function (secondary response, Fig. 15.6). Sometimes symptoms are mild, although annoying, e.g. the running nose and streaming eyes of hay fever. Occasionally the reaction can be extreme, overwhelming body systems and causing death, e.g. anaphylactic shock, see below.

There are four mechanisms of hypersensitivity, which are classified according to the parts of the immune system that are involved. They are summarised in Figure 15.9.

Type I, anaphylactic hypersensitivity

This occurs in individuals with very high levels of immunoglobulin E (IgE). When exposed to an allergen, e.g. house dust, these high levels of antibody activate mast cells and basophils (p. 69), which degranulate. The most important substance released is histamine, which constricts some smooth muscle, e.g. airway smooth muscle, causes vasodilation and increases vascular permeability (leading to exudation of fluid and proteins into the tissues). Examples of type I reactions include the serious situation of anaphylaxis. There is profound bronchoconstriction and shock (p. 118) due to extensive vasodilation. The condition can lead to death.

Type II, cytotoxic hypersensitivity

When an antibody reacts with an antigen on a cell surface, that cell is marked for destruction by the body's defence cells. This is the usual procedure in the elimination of, for example, bacteria, but if the antibodies are directed against self-antigens the result is destruction of the body's own tissues (autoimmune disease). Type II mechanisms cause other conditions, e.g. haemolytic disease of the newborn (p. 75) and transfusion reactions (p. 76).

Type III, immune-complex-mediated hypersensitivity

Antibody–antigen complexes (immune complexes) are usually cleared efficiently from the blood by phagocytosis. If they are not, for example when there is phagocyte failure or an excessive production of immune complexes (e.g. in chronic infections), they can be deposited in tissues, e.g. kidneys, skin, joints and the eye, where they set up an inflammatory reaction. The kidney is a common site of deposition because it receives a large proportion of the cardiac output and filters the blood. Immune complexes collecting here lodge in and block the glomeruli (p. 350), impairing kidney function (glomerulonephritis). Penicillin allergy is also a type III reaction; antibodies bind to penicillin (the antigen), and the symptoms are the result of deposition of immune complexes in tissues – rashes, joint pains and sometimes haematuria.

Type IV, delayed type hypersensitivity

Unlike types I–III, type IV hypersensitivity does not involve antibodies, but is an overreaction of T-cells to an antigen. When an antigen is detected by memory T-cells, it provokes clonal expansion of the T-cell (Fig. 15.3), and large numbers of cytotoxic T-cells are released to eliminate the antigen. Usually this system is controlled and the T-cell response is appropriate. If not, the actively aggressive cytotoxic T-cells damage normal tissues.

An example of this is contact dermatitis (p. 371). Graft and transplant rejection is also caused by T-cells; an incompatible skin graft, for instance, will become necrotic and slough off in the days following application of the graft.

Autoimmune disease

Normally, an immune response is mounted only against foreign (non-self) antigens, but occasionally the body fails to recognise its own tissues and attacks itself. The resulting autoimmune disorders, examples of type II hypersensitivity, include a number of relatively common conditions (Table 15.3).

Immunodeficiency

When the immune system is compromised, there is a tendency to recurrent infections, often by microbes not normally pathogenic in humans (*opportunistic infections*). Immunodeficiency is classified as *primary* (usually occurring in infancy and genetically mediated) or *secondary*, that is, acquired in later life as the result of another

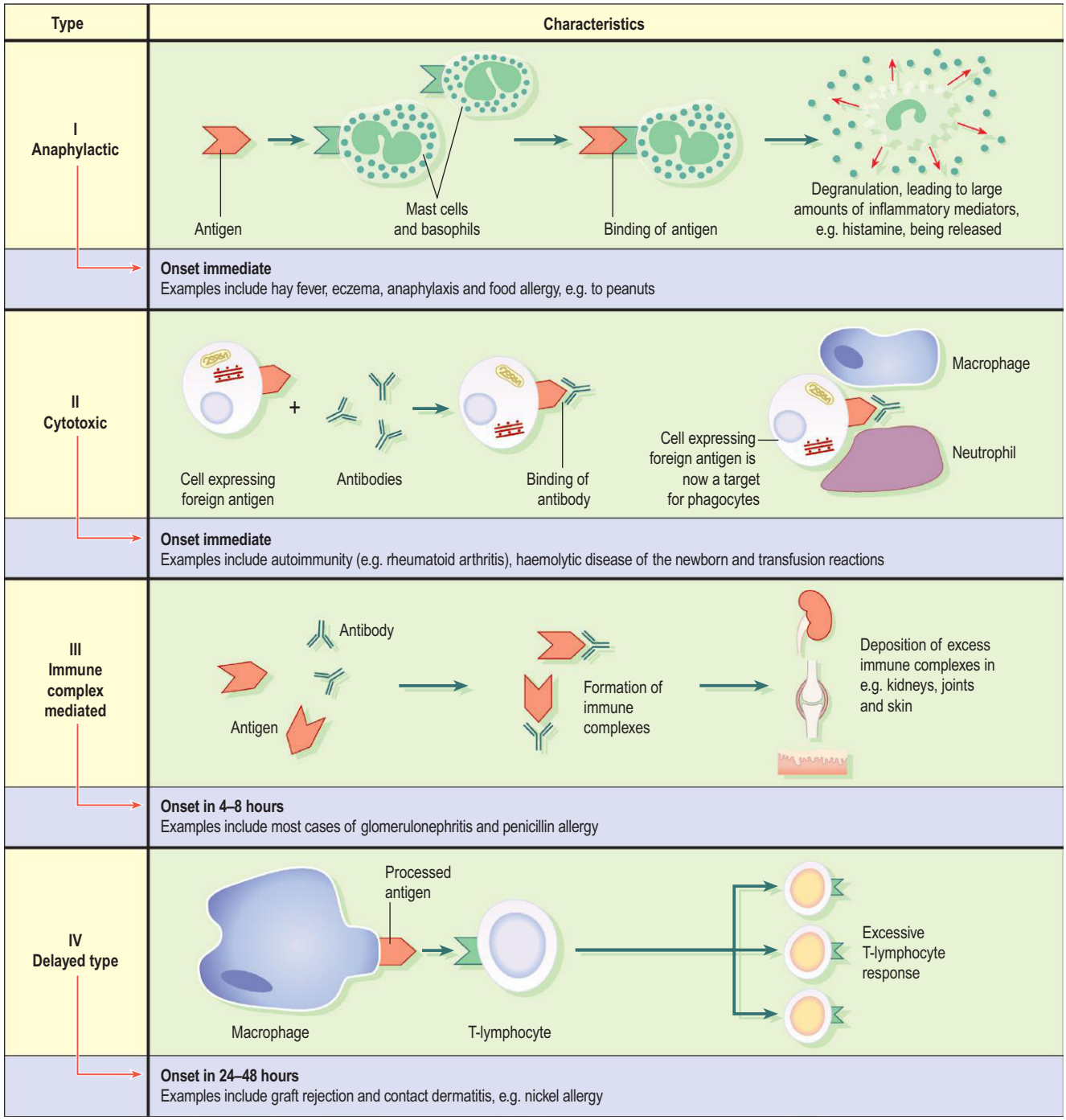

Figure 15.9 The four types of hypersensitivity.

disease, e.g. protein deficiency, acute infection, chronic renal failure, bone marrow diseases, following splenectomy or acquired immune deficiency syndrome (AIDS).

Acquired immune deficiency syndrome (AIDS)

This condition is caused by the human immunodeficiency virus (HIV), an RNA retrovirus which produces the enzyme *reverse transcriptase* inside the cells of the infected person (host cells). This enzyme transforms viral RNA to DNA and this new DNA, called the provirus, is incorporated into the host cell DNA. The host cell then produces new copies of the virus that infect other host cells. When infected host cells divide, copies of the provirus are integrated into the DNA of daughter cells, spreading the disease within the body.

HIV has an affinity for cells that have a protein receptor called CD_4 in their membrane, including T-cells, monocytes, macrophages, some B-cells and, possibly,

Table 15.3 Common autoimmune disorders

Condition	Autoantibodies made against:
Rheumatoid arthritis (p. 432)	Synovial membrane of joints
Hashimoto's disease (p. 232)	Thyroglobulin
Graves' disease (p. 231)	TSH receptors on thyroid cells
Myasthenia gravis (p. 435)	Acetylcholine receptors of skeletal muscle
Glomerulonephritis (p. 350)	Glomerular membrane
Type 1 diabetes (p. 236)	Beta cells of the pancreas

cells in the gastrointestinal tract and neuroglial cells in the brain. CD_4 helper T-cells (Fig. 15.3) are the main cells involved. HIV establishes itself within the body's CD_4 cell populations and gradually destroys them, while at the same time it is protected from other body defence mechanisms. Because CD_4 cells are central to the body's immune system, both antibody-mediated and cell-mediated immunity are progressively eroded with the consequent development of widespread opportunistic infections, often by microbes of relatively low pathogenicity.

HIV has been isolated from semen, cervical secretions, lymphocytes, plasma, cerebrospinal fluid, tears, saliva, urine and breast milk. The secretions known to be especially infectious are semen, cervical secretions, blood and blood products.

Infection is spread by:

- sexual intercourse, vaginal and anal
- contaminated needles used:
  - during treatment of patients
  - when drug users share needles
- an infected mother to her child:
  - across the placenta before birth (vertical transmission)
  - during childbirth
  - in breast milk.

Stages of HIV infection. A few weeks after initial infection there may be an acute influenza-like illness with no specific features, followed by a period of 2 or more years without symptoms.

Chronic HIV infection may cause persistent generalised lymphadenopathy (PGL). Some patients may then develop AIDS-related complex (ARC) and experience chronic low-grade fever, diarrhoea, weight loss, anaemia and leukopenia.

AIDS is the most advanced stage of HIV infection, associated with a low CD_4 count and the presence of one or more characteristic infections, tumours or presentations:

- pneumonia, commonly caused by *Pneumocystis jirovecii* (formerly *Pneumocystis carinii*), but many other microbes may be involved
- persistent nausea, diarrhoea and weight loss due to recurrent infections of the alimentary tract by a wide variety of microbes
- meningitis, encephalitis and brain abscesses may be recurrent, either caused by opportunistic microbes or possibly by HIV
- neurological function may deteriorate, characterised by forgetfulness, loss of concentration, confusion, apathy, dementia, limb weakness, ataxia and incontinence (p. 356)
- skin conditions, often extensive, may occur, e.g. eczema, psoriasis, cellulitis, impetigo, warts, shingles and cold sores (see Ch. 14)
- generalised lymphadenopathy (p. 140)
- development of malignant tumours is not uncommon, because of the progressive failure of immunological surveillance as the virus destroys the T-cell population. Typical cancers include:
  - lymphoma (p. 141)
  - Kaposi's sarcoma, consisting of tumours under the skin and in internal organs (p. 373).

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