

Part 1

Immunity and the Immune System

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Chapter 1

The nature of immunity

Key objectives

This chapter will enable you to:

- 1 Outline the general purpose and properties of the immune system in terms of recognition and defence.
- 2 Distinguish the features of innate and adaptive immunity, and the components of the immune system involved in each.
- 3 Give an overview of the processes that generate an immune response appropriate for defence of the body against the pathogen that instigated the response.

Infectious diseases, frequently compounded by malnutrition, are still a major cause of illness and death throughout the world. In developed countries, however, the situation has changed dramatically. In Britain, eighteenth century Bills of Mortality listed cholera, diphtheria, smallpox, tetanus and typhoid as major causes of death, whereas today the annual mortality statistics emphasize the importance of cardiovascular disease and cancer. The balance has shifted so much that a series of deaths from a particular infectious disease is likely to precipitate the setting up of a committee of inquiry. These changes have been brought about by the introduction of successful immunization programmes in conjunction with chemotherapy and various public health measures. The key role of the immune system in defence against pathogens of

many kinds has recently received dramatic emphasis with the rapid spread of the acquired immunodeficiency syndrome (AIDS). Allergic hypersensitivity and autoimmunity are also disturbances of immunity that cause many other kinds of disease, e.g. asthma and glomerulonephritis. Manipulation of the immune system has become of increasing importance in the treatment of disease and in organ transplantation.

This all began with the centuries-old knowledge that an individual who had recovered from a life-threatening infection, e.g. plague, could subsequently nurse another affected individual without fear of contracting the disease again. He or she had become **immune**. The term **immunity** was originally used to indicate exemption from taxes, and this meaning still exists in the term 'diplomatic immunity'.

The sequence of events that led to the global eradication of smallpox in 1980 spans more than two centuries and demonstrates vividly the way in which the immune response can be modified to render a previously life-threatening pathogen ineffective in causing disease.

Variolation and vaccination

It is estimated that over 50 million people died of smallpox in eighteenth century Europe. In 1712, a duke's daughter from Nottinghamshire, Lady Mary Pierrepont, eloped with a diplomat, Edward

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Chapter 1 The nature of immunity

Wortley-Montagu, and later travelled with him when he became British Ambassador to Turkey. She wrote from Constantinople in 1717 concerning the local habit of preventing smallpox by inoculating material obtained from smallpox crusts. She introduced it into England with royal patronage following initial experiments on condemned criminals and orphaned children. However, this procedure was not without risk of causing smallpox (variola) itself and the high morbidity and mortality associated with it made others look for less dangerous and more effective ways of controlling the disease.

Edward Jenner – a Gloucestershire family doctor – made the important observation that dairymaids, who frequently contracted cowpox (an infection of the hands acquired during milking), were remarkably resistant to smallpox and did not develop the disfigured pock-marked faces of those who had had smallpox infection. Hence the rhyme:

'Where are you going to, my pretty maid?'

'I'm going a-milking, sir', she said.

'What is your fortune, my pretty maid?'

'My face is my fortune, sir', she said.

Edward Jenner had suffered painfully from variolation performed when he was 8 years old. The increasing spread of smallpox throughout the population led him to develop the alternative technique of vaccination. This was first performed in 1796 when he inoculated material obtained from cowpox pustules into the arm of a healthy boy. He was subsequently able to inoculate him with smallpox more than 20 times without any untoward effect. This courageous experiment aroused much criticism, but Jenner offered his new preventive treatment to all who sought it and performed many of his vaccinations in a thatched hut – which became known as the Temple of Vaccinia – in the grounds of his house at Berkeley. Recently, these buildings have been restored and contain a Jenner Museum and Conference Centre¹.

¹Further information can be obtained from the Custodian, The Chantry, Church Lane, High Street, Berkeley, Gloucestershire GL13 9BH, UK.

Many other forms of immunization have followed from this work, and one of the current goals of the World Health Organization's Tropical Disease Programme is to identify immunological ways of controlling and, hopefully, eliminating other major infections, e.g. malaria (against which vector control has largely failed and chemotherapy is becoming less effective).

Several other kinds of immunological manipulation have proved to be of therapeutic benefit, e.g. the administration of specific antibody in the prevention of rhesus haemolytic disease of the newborn. The advent of monoclonal antibodies of many different specificities offers promise for targeting therapeutic agents to tissues and tumours as well as having many diagnostic applications. Experimental work has shown that the administration of antigen or antibody can be used to turn off specific immune responses – a situation known as immunological tolerance or enhancement. This is of particular relevance to clinical transplantation and the treatment of many immunological and metabolic disorders.

Recognition and defence components

Before considering the complexity of the immune system as it exists, it is useful to consider some of the general design requirements of an immune system in order for it to protect the host organism and display the characteristic features already described. Clearly, the two important biological events are **recognition** of the target pathogen and effective **defence** against it. Using a military analogy, the former is equivalent to reconnaissance and the latter might include artillery support invoked by those in the front line. A major consideration is how many recognition specificities are required and how many kinds of defence, i.e. methods of pathogen destruction, are necessary. The next question to be decided is whether the units that recognize and the units that defend should be combined together, or whether a division of labour is preferable in which recognition units and defence units operate as separate entities. These possibilities are illustrated in Figs 1.1

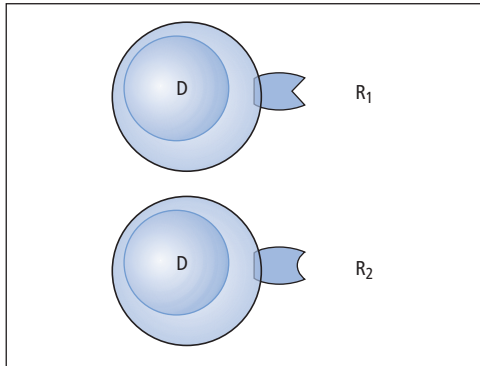


Figure 1.1 Combined recognition (R) and defence (D) units to deal with a pathogenic invader: R and D units with single recognition specificities (exemplified by cytotoxic T cells).

and 1.2, and examples are given in the captions of components of the immune response that use these different strategies.

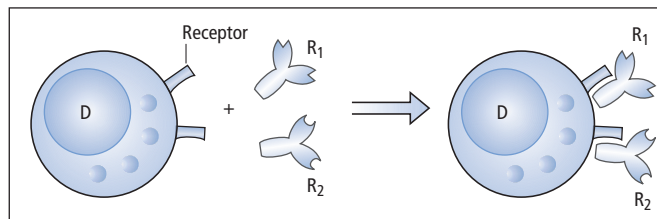
There exists an enormous variety of infectious pathogens, including many types of viruses, bacteria, fungi, protozoa and multicellular parasites, each with its own mechanisms of transmission, infection and reproduction. This means that no single recognition or defensive strategy is effective against all pathogens and therefore a wide variety of cellular and secreted components are present within the body that collectively constitute the immune system. Examples of the main cells and molecules of the immune system are given in Tables 1.1 and 1.2, respectively. These components vary in terms of whether their main role is recognition or defence, although many possess a combination of these properties.

Innate and adaptive immunity

The cellular components that mediate recognition and defence can be categorized by various criteria, including their developmental lineage from stem cells in the bone marrow (**myeloid** or **lymphoid**), and their morphology as mature blood leucocytes (Table 1.1). **Polymorphonuclear leucocytes** (PMNs) are distinguished from **mononuclear cells** by their lobulated nuclei and they largely coincide with the **granulocytes** defined by distinctive cytoplasmic granules. The immune system's cellular components can also be considered as mediators of either **innate** or **adaptive immunity** (Table 1.1).

The recognition properties associated with innate immunity may have evolved to recognize chemical structures that are characteristic of infectious pathogens and differ from constituents of host organisms. These include various microbial lipids, carbohydrates, proteins and even nucleic acids that are collectively termed **pathogen-associated molecular patterns (PAMPs)**. They are bound by secreted proteins (e.g. mannose-binding lectin and C-reactive protein) and by cell surface and cytoplasmic proteins (e.g. macrophage mannose receptor and Toll-like receptors) called **pattern recognition molecules** that are inflexible in their specificities and identical between cells; these are considered in detail in Chapter 2. Innate immunity is rapidly activated in the early stages of an infection and its defensive properties can limit the proliferation and spread of a pathogen within the body. However, it is only moderately efficient in clearing infection, and its capabilities remain the same on repeated exposure to the same microbe.

Figure 1.2 Separate recognition (R) and defence (D) units to deal with a pathogenic invader: R units can have different specificities (R₁, R₂, etc.), and interact with different D units (e.g. IgG binding to Fc receptors on neutrophils and IgE binding to Fc receptors on mast cells).



Chapter 1 The nature of immunity

Table 1.1 Cells of the immune system.

| Cell type | Developmental lineage | Morphological definition | Type of immunity |
|-------------------------|-----------------------|--|------------------|
| Neutrophils | Myeloid | Polymorphonuclear leucocytes or granulocytes | Innate |
| Eosinophils | Myeloid | Polymorphonuclear leucocytes or granulocytes | Innate |
| Basophils | Myeloid | Polymorphonuclear leucocytes or granulocytes | Innate |
| Mast cells | Myeloid | Polymorphonuclear leucocytes or granulocytes | Innate |
| Monocytes/macrophages | Myeloid | Mononuclear leucocytes | Innate |
| Dendritic cells | Myeloid | Mononuclear leucocytes | Innate |
| Natural killer cells | Lymphoid | Mononuclear leucocytes | Innate |
| Cytotoxic T lymphocytes | Lymphoid | Mononuclear leucocytes | Adaptive |
| Helper T lymphocytes | Lymphoid | Mononuclear leucocytes | Adaptive |
| B lymphocytes | Lymphoid | Mononuclear leucocytes | Adaptive |

Table 1.2 Secreted mediators of immunity.

| |
|---|
| <i>Antimicrobial</i> |
| Antibodies/immunoglobulins (IgM, IgG, IgA, IgE, IgD) |
| Pentraxins (e.g. C-reactive protein) |
| Collectins (e.g. mannan-binding lectin) |
| Complement proteins |
| Defensins |
| Lytic enzymes |
| Interferons |
| Cytotoxins (perforins, granzymes) |
| <i>Regulatory/inflammatory</i> |
| Cytokines (e.g. interleukins, interferons, tumour necrosis factors) |
| Chemokines (and other chemoattractants) |
| Eicosanoids (e.g. prostaglandins, leucotrienes) |
| Histamine |

The resolution of an infection usually requires an additional adaptive immune response by **T lymphocytes** and **B lymphocytes** (often referred to simply as T cells and B cells). Each lymphocyte specifically recognizes an individual **antigen** (usually a protein, but also other types of

chemical for B lymphocytes), and there are mechanisms for enhancing the specificity of recognition. Thus, the antigen receptor expressed by a particular lymphocyte is different from that of virtually all other lymphocytes in the body. In addition, the B lymphocytes produce and secrete a soluble form of their antigen receptors called **antibodies** or **immunoglobulins**. An adaptive immune response takes longer to activate than innate immunity but generates more effective defence which improves upon repeated exposure to the same microbe. The details of antigen recognition are considered in Chapters 2, and the development, activation and functions of lymphocytes are described in Chapter 3 and 4; immunoglobulins are considered in Chapter 5.

Cardinal features of adaptive immune responses

It is the cardinal features of adaptive immunity mediated by lymphocytes that Edward Jenner recognized in immunity to smallpox and utilized in the development of vaccination. Furthermore,

an individual who is immune to smallpox will not be protected against diphtheria unless he has also met the *Corynebacterium diphtheriae* on a previous occasion. This illustrates the **specificity** of the adaptive immune response. Lymphocytes can detect remarkably small chemical differences between antigens, e.g. subtly differing strains of influenza virus, minor substitutions of a benzene ring or the difference between dextro and laevo isomers. Were it not for the fact that cowpox and smallpox viruses share important antigens, the experiments of Jenner would have been a dismal failure (although he would not have attempted them without the evidence of the milkmaids).

Another feature of adaptive immune responses is the **memory** that develops from previous experiences of foreign material – a characteristic that enables immunization to be of clinical value. This altered reactivity may last for the entire lifespan of the individual. The ability of an organism to respond more rapidly and to a greater degree when confronted with the same antigen on a second occasion is illustrated in Fig. 1.3. This compares the speed and magnitude of the human response to an antigen that the subjects had not previously encountered (bacteriophage ϕ X174). In the first or **primary** response there is a delay of at least 10 days before the antibody level in the circulation reaches its maximum and this level shows considerable variation between individuals, rarely exceeding a titre² of 1000. In the **secondary** response, all individuals respond maximally within 10 days and in all cases the levels attained are of a titre of 10,000 or more. The outcome of an acute infection is often a close race between the activities of the replicating pathogen and the adaptive immune response, and it is for this reason that prior exposure, e.g. to a vaccine, can give the host a considerable advantage.

A third important feature of adaptive immune responses is **self-discrimination**, which is illustrated in Fig. 1.4. If split-skin grafts are placed on the flanks of rodents, it is possible to observe within 2 weeks whether they have healed well and

²The titre is the reciprocal of the weakest dilution of serum at which antibody can still be detected.

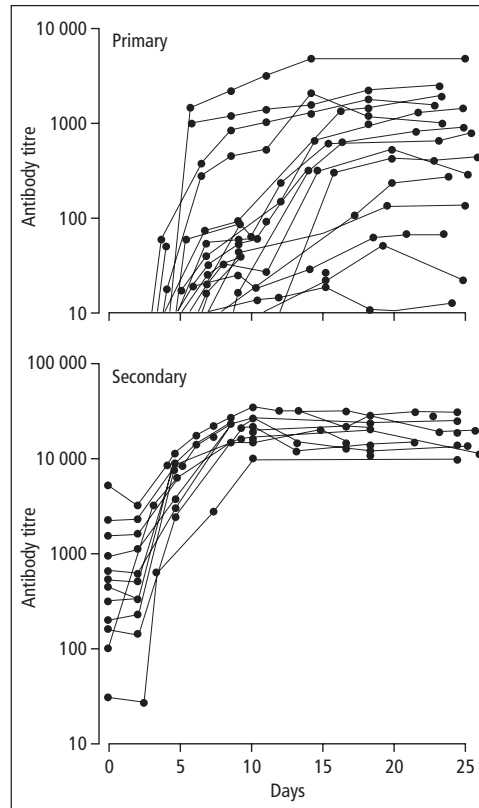


Figure 1.3 Primary and secondary antibody responses following intravenous injection of bacteriophage ϕ X174 used as a test antigen in humans. (Data kindly provided by Drs Peacock and Verrier Jones.)

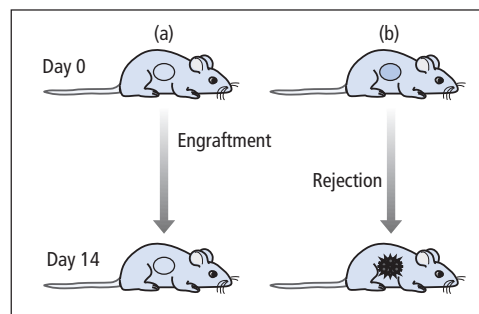


Figure 1.4 Discrimination between self and non-self illustrated by skin grafting in a rodent. (a) The graft was of 'self' type; (b) the graft was from an unrelated animal.

Chapter 1 The nature of immunity

been accepted (Fig. 1.4a) or whether they have been rejected (Fig. 1.4b). In this experiment, the successful graft was obtained from another animal of identical genetic composition (i.e. another member of the same inbred strain). The rejected graft came from an unrelated member of the same species. These chemical differences are relatively minor and demonstrate not only the recognition ability of lymphocytes, but also the efficient way in which they fail to react against tissue of 'self' origin. Previously, it was thought that components of the immune system failed to recognize self at all, but it is now clear that self-recognition does occur in a controlled and regulated manner such that – except in the special circumstance of autoimmune disease – tissue damage does not take place.

Stages of an immune response

The different properties of innate and adaptive immunity mean that they are complementary, and they cooperate with each other in order to give the best possible defence. This can be exemplified by considering the stages of a generalized response to a bacterial skin infection (Fig. 1.5). The skin itself constitutes an effective barrier to infection because most microbes cannot penetrate the hard, keratinized surface of the epidermis (Fig. 1.5a), but if this is breached (e.g. by a cut), then microbes may infiltrate and start to replicate in the softer underlying dermal tissues. If this is a primary response to infection (because it is the first time this particular microbe has infected the body), then there will be no immunological memory to generate an early adaptive response, but components of the innate immune system that are resident in the infected tissues can be rapidly activated, including **complement proteins** in the tissue fluid and **macrophages** (Fig. 1.5b). The activation of a range of complement proteins triggered by interactions with bacterial surface molecules may result in bacterial **lysis** by the **membrane attack complex** of complement and/or **opsonization** (i.e. coating) of the bacteria by complement proteins that help to adhere the bacteria to the macrophages, which express **complement receptors** as well as the

pattern recognition molecules mentioned above. Macrophages are **phagocytes** that can engulf microbes and bring about their **digestion**.

The activation of complement proteins and macrophages not only results in microbial destruction directly, but also induces amplifying events (i.e. **inflammation**). In addition, tissue resident **mast cells**, which are a major source of inflammatory mediators, are activated by complement-derived peptides. These amplifying events can be divided into several categories: local **vasodilatation** and increase in **vascular permeability; adhesion** of inflammatory cells to the blood vessel wall; their chemical attraction, i.e. **chemotaxis; immobilization** of cells at the site of infection and **activation** of the relevant cells and molecules to liberate their lytic products (Fig. 1.6). In the present example, the inflammatory mediators induce the influx of leucocytes (particularly **neutrophils** that, like macrophages, are phagocytes) and plasma containing further supplies of complement proteins (Fig. 1.5c).

While the innate response is being established during the first few hours and days of the infection, the processes are being set in train to generate the adaptive response. This involves the transport of microbial components (i.e. antigens) from the site of infection to neighbouring lymphoid tissues, which is where the majority of lymphocytes reside transiently during their circulation around the body. Lymphocytes develop in **primary lymphoid organs**, consisting of **bone marrow** and **thymus**, in the adult. Lymphocytes circulate through **lymph nodes**, the white pulp of the **spleen** and **mucosa-associated lymphoid tissue**: these locations are referred to as **secondary lymphoid organs** (Fig. 1.7). The total weight of these various lymphoid components can exceed that of the liver. It is at these sites that large numbers (i.e. hundreds of millions) of the different varieties of lymphocyte come into intimate contact with each other and with specialized **antigen-presenting cells** so as to provide an optimal environment for the activation of the small proportion of the body's lymphocytes that specifically recognize the antigens of a

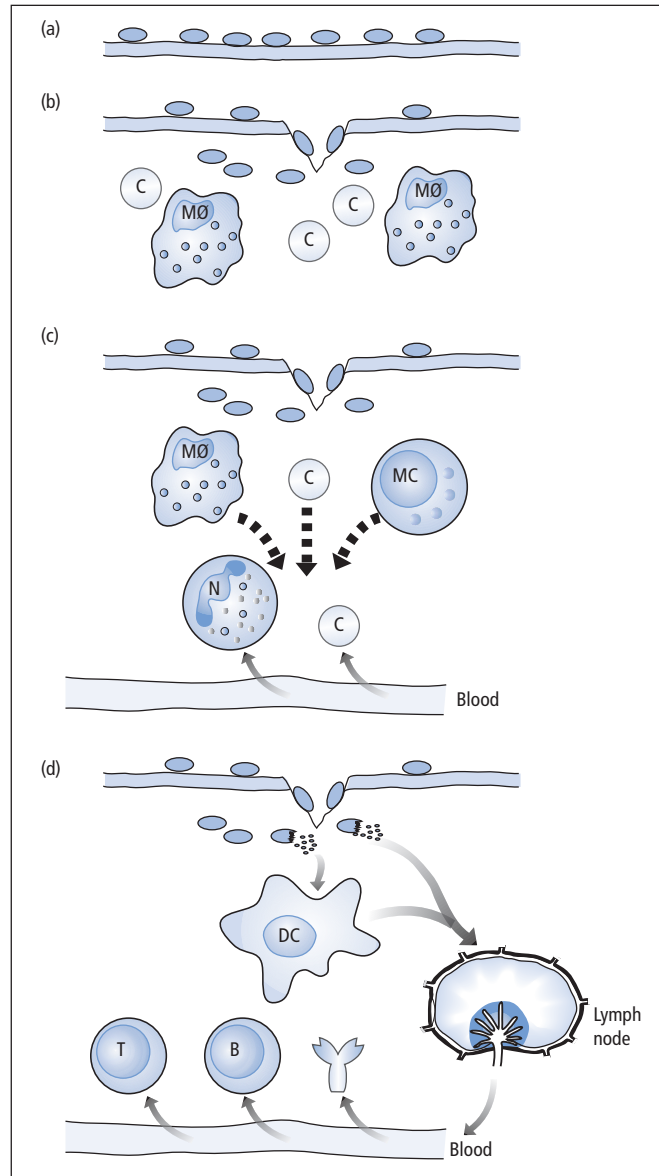


Figure 1.5 Stages of an immune response to bacterial skin infection. (a) Bacteria are unable to penetrate the intact keratinized epithelial barrier; (b) bacterial entry (e.g. via a cut) stimulates an immediate local innate response by tissue macrophages and complement proteins; (c) an early induced inflammatory response is stimulated by inflammatory mediators produced by macrophages, complement proteins and mast cells, leading to infiltration by neutrophils from the blood and plasma containing more complement; (d) bacterial antigens are carried in the lymph, and associated with dendritic cells (DC), to draining lymph nodes where specific T and B lymphocytes are activated. These lymphocytes, and antibodies produced by the B cells, return to the infected tissues via the blood circulation.

particular microbe. This is why antigens are carried to lymphoid tissues to induce lymphocyte activation rather than these interactions occurring initially within the site of infection. For example, tissue fluid that drains from infected tissues into the lymphatic system may carry microbial antigens to draining lymph nodes where they can be recognized by specific B cells. In addition, microbial

antigens are captured and processed by antigen-presenting cells, called **dendritic cells**, which are present in most tissues. The dendritic cells then migrate to the draining lymph nodes where they present the antigens to T cells (Fig. 1.5d). The activated T and B cells return to the blood circulation whence they enter the inflamed, infected tissues, together with antibodies secreted by terminally

Chapter 1 The nature of immunity

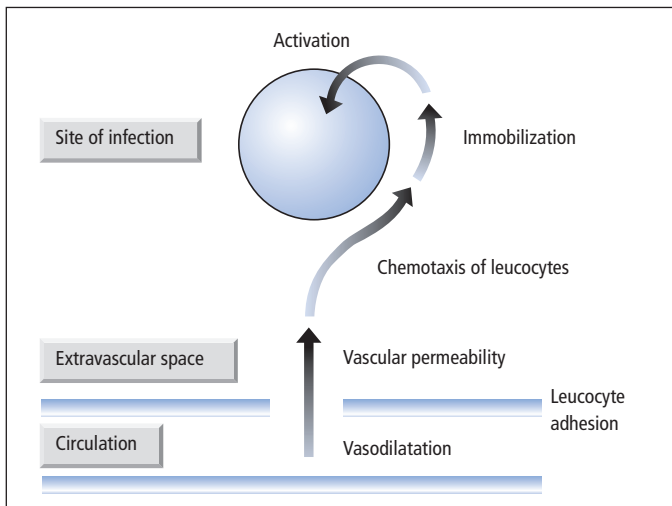


Figure 1.6 Amplifying events involved in the local recruitment of inflammatory cells and molecules from the circulation into an extravascular site of infection.

differentiated B cells called **plasma cells**, in a similar manner to the earlier influx of other leucocytes and complement proteins (Fig. 1.5d). The efficiency of bacterial elimination will then be enhanced by antibodies that opsonize the bacteria, thereby augmenting complement activation and phagocytosis, and regulatory proteins called **cytokines** produced by the T cells that increase the antimicrobial activity of the phagocytes.

Some of the T and B cells activated by antigens of the infecting microbe revert to a resting state

and constitute the body's population of **memory lymphocytes** specific for that microbe. A subsequent infection with the same, or a closely related (i.e. antigenically similar), microbe would induce a faster and bigger secondary response by these lymphocytes, as described earlier in this chapter.

Immunological defence strategies

The nature of the defensive strategy that the immune system employs in order to eliminate a

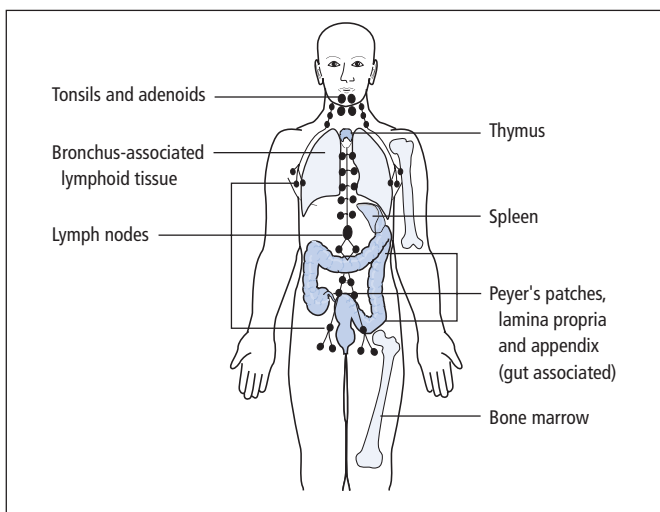
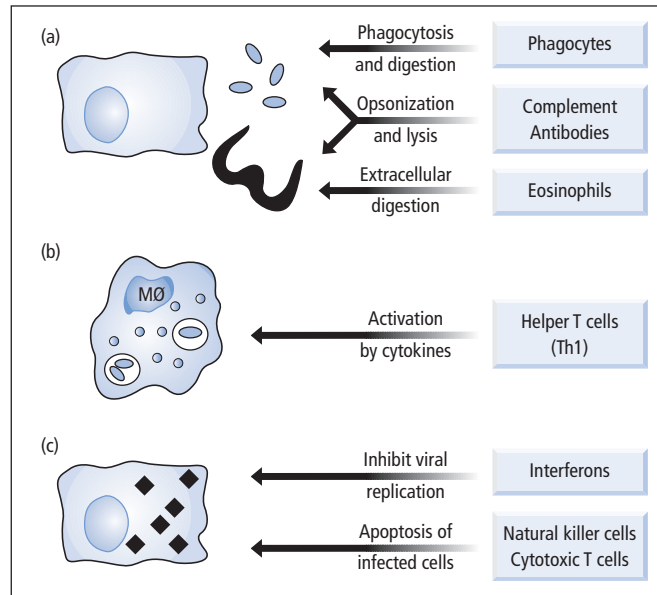


Figure 1.7 The lymphoid system in humans, showing the distribution of primary and secondary lymphoid organs and tissues.

Figure 1.8 Immunological defence strategies. (a) Extracellular pathogens (e.g. bacteria and parasitic worms) are directly exposed to antibodies, complement, phagocytes (macrophages and neutrophils) and eosinophils; (b) microbes that are resistant to digestion (e.g. mycobacteria) can survive intracellularly in macrophage vesicles, but Th1-derived cytokines (e.g. γ -interferon) can enhance the digestive activity of the macrophages; (c) intracellular pathogens, like viruses that generate cytosolic antigens, are targeted by interferons that block their replication, and killer cells (NK and Tc cells) that induce apoptosis of the infected cells.



microbe is determined not only by the biological nature of the microbe, but also by the tissue compartment in which the infection is concentrated. In particular, it is critical whether the microbe remains **extracellular** (i.e. in fluids or at the surfaces of cells of the tissues it infects), or enters the cytoplasm of cells to become **intracellular**. Extracellular pathogens (including many types of bacteria and parasitic worms), which do not cross the plasma membrane of cells, are vulnerable to opsonization by antibodies and complement proteins; bacteria can then be phagocytosed by macrophages and neutrophils, and parasitic worms are attacked by eosinophils (Fig. 1.8a). Antibodies and complement proteins are considered in Chapters 5 and 6, respectively, phagocytes in Chapter 7 and eosinophils in Chapter 8. However, some phagocytosed microbes are resistant to intracellular digestion and can survive and replicate in cytoplasmic vesicles of macrophages where they are no longer exposed to antibodies and complement: mycobacteria that cause tuberculosis and leprosy are important examples of this. The macrophages must then be stimulated into a heightened state of activation by cytokines derived from **helper T lymphocytes (Th cells)** in order

to overcome the microbes' resistance to digestion (Fig. 1.8b). Some microbes deliberately invade cells; this applies to all viruses, which hijack the metabolic machinery of the cells they parasitize in order to replicate. In order to combat intracellular viruses, **interferons** induce an **antiviral state** in cells, which inhibits viral replication. In addition, **natural killer (NK) cells** and **cytotoxic T lymphocytes (Tc cells)**, which are described in Chapter 9, deliberately kill infected cells, thus inhibiting viral replication (Fig. 1.8c).

An overview

The frontispiece gives a schematic overview of the cells and secreted mediators of immunity that have been introduced in this chapter and that are discussed in more detail in the following chapters. This shows how these components of the immune system interact and cooperate to generate the various defensive options that are effective against different categories of infective agents.

Pathogens are the source of the PAMPs and antigens necessary for the generation of innate and adaptive immunity, respectively, and these pathogens then become the target of the

Chapter 1 The nature of immunity

integrated innate and adaptive defensive response that is generated. The activities of the immune components that generate rapid innate responses (e.g. macrophages, granulocytes, natural killer cells and complement proteins) are greatly enhanced by the addition of the adaptive response by T and B lymphocytes. Dendritic cells are a pivotal link between innate and adaptive immunity; they are activated by microbial PAMPs that interact with their pattern recognition molecules, together with 'danger signals' released by stressed and damaged cells (e.g. 'DAMPs' discussed in Chapter 2). This activation of dendritic cells enables them to efficiently activate T cells by presenting antigens.

The dendritic cells and other cell types also provide 'polarising signals' that promote naive helper T cell (Th0 cell) differentiation into various T-cell subsets that are characterized by the production and secretion of different regulatory proteins called **cytokines** that stimulate different cellular activities. The frontispiece shows these main functional subsets (Th1, Th2, Th17 and T_{reg}), some of the key cytokines they produce and the cell types on which they act; this is discussed in detail in Chapter 4. Furthermore, although all B cells are initially programmed to produce classes of immunoglobulins called IgM and IgD, the different T-cell subsets promote immunoglobulin class switching in B cells to produce other classes of antibodies (IgG, IgE or IgA) that have different functional properties; this is discussed in detail in Chapter 5.

The frontispiece summarizes the particular combinations of immune effector cells and secreted mediators that are orchestrated by T-cell-derived cytokines and B-cell-derived antibodies to generate the combinations of defensive and inflammatory activities appropriate for the

nature of the infections generated by particular pathogens. Overall, the purpose of the polarizing signals is to ensure that the qualitative nature of the immune response generated is appropriate to the nature of the pathogen whose PAMPs and antigens triggered the response.

The abundance of means by which recognition and defence can be achieved is necessary to meet the enormous task that confronts the immune system, i.e. the constant threat to the survival of the host from a universe of pathogenic organisms ranging from the smallest viruses, through bacteria, protozoa and fungi, to metazoan parasites with their often complex life cycles. The remarkable ability of successful pathogens to evolve mechanisms by which they can evade the immune response adds a further dimension, which is considered in detail in Chapter 10.

Immunopathology

The outcome for the host is often 'survival at a price' and damage to host tissues by the immune system is a common finding during the course of most infectious diseases – a situation referred to as **hypersensitivity** or **allergy**. Furthermore, the development of **autoimmunity** (i.e. immune recognition of self components) is not uncommon during infection and the chronicity of these reactions may be related to the difficulties involved in eliminating certain pathogens from host cells. Some pathogens are also able to initiate various forms of **lymphoproliferative disease** and can cause **immunodeficiency**. **Immunopathology** is composed of these various deviations from the ideal, many examples of which are found in human disease. These are described in Part 2.

Key points

- 1** Immunity provides protection against pathogenic organisms, and the functions of the immune system are recognition of these foreign pathogens and defence of the body against them.
- 2** A wide variety of cells and secreted molecules necessarily constitute the immune system in order to deal with the vast array of pathogenic organisms that can infect the body.
- 3** Innate and adaptive immunity constitute the two main arms of the immune system which differ in their recognition and activation properties. Adaptive immunity improves upon repeated exposure to the same antigens.
- 4** Lymphocytes are responsible for the specificity, memory and self-discrimination of adaptive immune responses, as exemplified in vaccination.
- 5** The early innate response to infection stimulates an inflammatory response and initiates the processes that result in the adaptive lymphocyte response.
- 6** Defence is mediated by a range of innate and adaptive cells and molecules that stimulate inflammation and cause digestion or lysis of foreign pathogens or infected cells. Different defence mechanisms are required to deal with extracellular pathogens, and with intracellular pathogens either in macrophage vesicles or in the cytosol.
- 7** Polarizing signals generated in response to the stimulation of the immune system by a particular pathogen promote the type of immune response appropriate to that pathogen.
- 8** Different subsets of T cells (e.g. Th1, Th2, Th17) stimulate the production of different classes of antibodies and the activation of different immune effector cells and molecules, thereby generating qualitatively different immune responses that are required for the eradication of different pathogens.
- 9** Activation of the immune system can also lead to damage to host tissues and some pathogens can induce abnormal proliferation of the lymphoid system or cause it to become deficient. These together constitute the various forms of immunopathology.