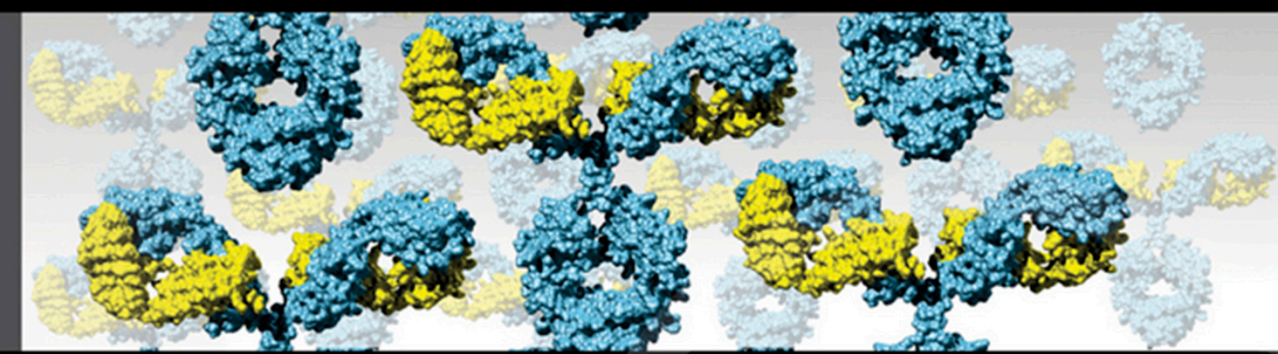
IMMUNOLOGY

Lecture Notes



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7th Edition

WILEY Blackwell

Immunology

Lecture Notes

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Preface to the seventh edition

The first edition of *Lecture Notes: Immunology* that was published in 1987 was conceived and written by Professor Gordon Reeves to provide an introduction to immunology and show its relevance to students of medicine and biology in a straightforward and comprehensible way, avoiding unnecessary detail and jargon. These principles have been maintained in successive editions, whilst updating the text to take account of advances that clarify understanding of the immune system and the application of this knowledge to medicine. These criteria have also been applied in formulating this seventh edition of *Lecture Notes: Immunology*.

This is the first edition of *Lecture Notes: Immunology* to be published with full colour illustrations. We have taken advantage of this by including photographs of important clinical features of a number of immunopathological conditions. We have also incorporated high quality molecular graphic images of key molecules of the immune system (antibodies, T-cell receptors and HLA proteins); we are especially grateful to our colleague, Dr Paddy Tighe (University of Nottingham) for producing these molecular images.

New features of this seventh edition have been introduced to help maximize the reader's acquisition of knowledge and understanding from the text. Clinical Case Scenarios have been introduced throughout to give clinical contextualisation of important immunological principles and to illustrate the scientific basis of clinical understanding and reasoning. The introductory chapter has been substantially revised and the sections on clinically relevant immunological methods in Chapters 4 and 5 have been completely updated. The content has been revised throughout to incorporate important new knowledge and concepts that aid basic understanding of the immune system and immunopathology. More detail has been added to many of the answers to the self-assessment questions so that readers can more fully appreciate why their own answers are right (or wrong!). We hope that all of these new features will make the reading of this book both more informative and more enjoyable.

Ian Todd
Gavin Spickett
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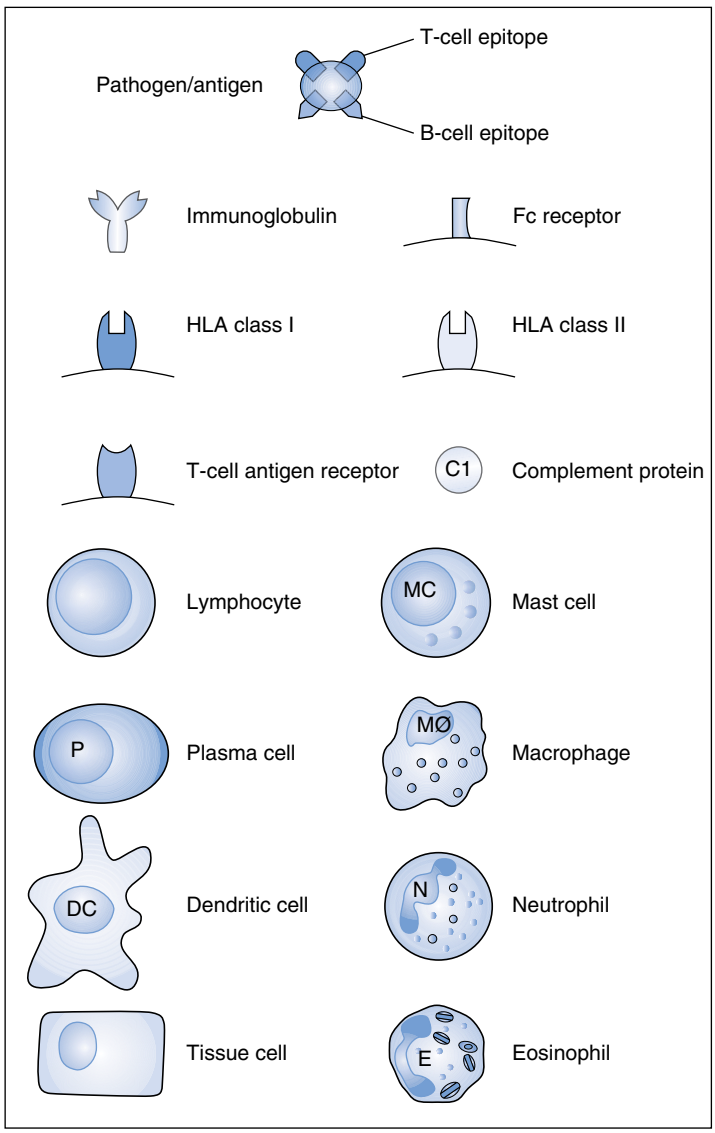
From the preface to the first edition

The undergraduate student meeting immunology during a busy medical or biological sciences curriculum or the qualified doctor attempting to get to grips with the subject for specialist training is often daunted by what appears to be an opaque wall of mystifying jargon surrounding a mass of intricate information. The aim of *Lecture Notes on Immunology* is to provide a concise statement covering the basic facts and concepts that are essential for a first understanding of the subject and its relevance to medicine and allied disciplines. Nomenclature has been simplified and appropriately defined and the major principles introduced in a biological setting. Figures and tables are used to summarize or highlight important information, and key words are emphasized in the text in bold type.

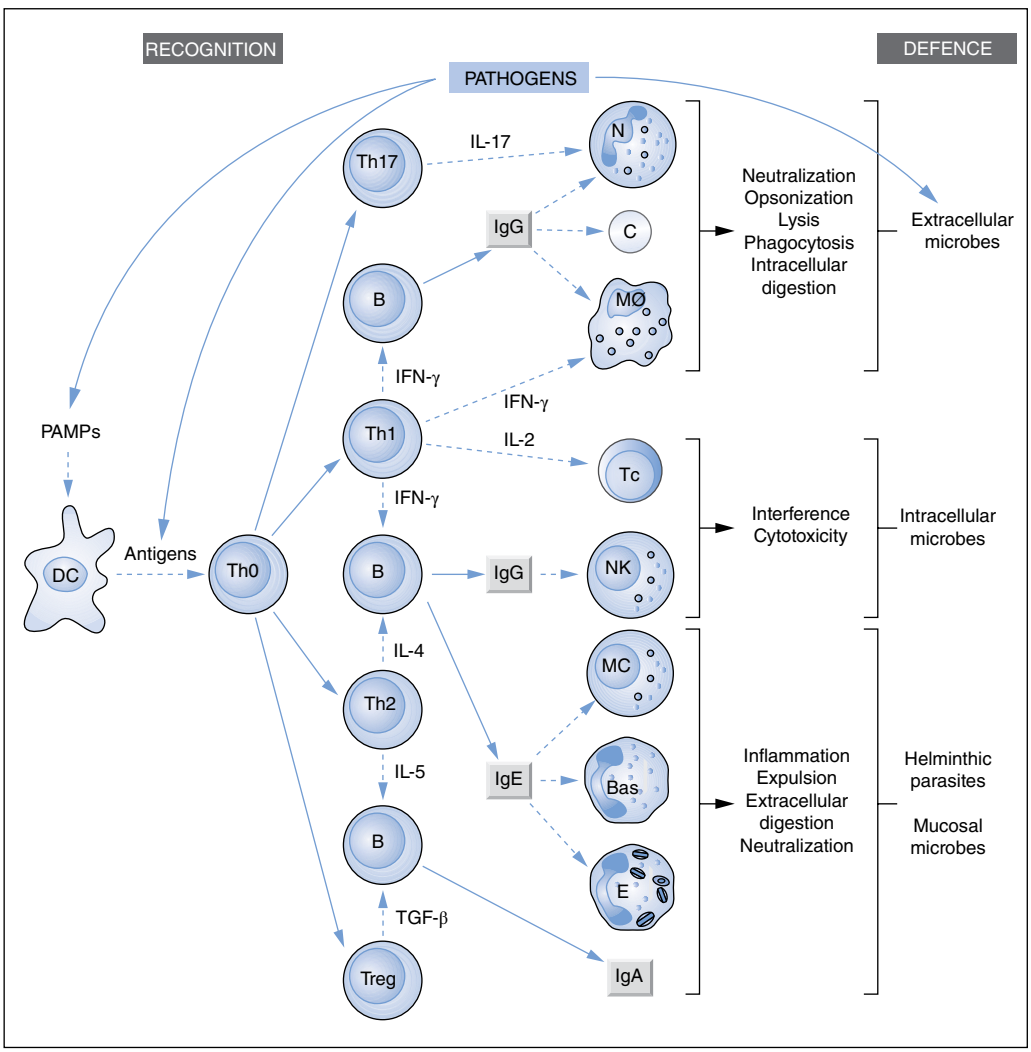
This text is based on the teaching modules developed in the Nottingham Medical School which have been designed to provide sufficient grounding to enable students to comprehend and utilize developments in immunology in their practice of medicine. Students often feel more comfortable with the detail when they have glimpsed the whole and for this reason the initial chapter outlines the salient features of immunity. These are also summarized in an 'overview of the immune system' presented as the frontispiece. Many of these thoughts have been stimulated by the, often penetrating, questions of first-year students as well as the more clinically informed enquiries of medical graduates and I hope that this text will assist the questioning process.

Gordon Reeves

Key to symbols used in this edition



Overview of the immune system



The left side concerns the **RECOGNITION** of pathogens, with their molecular components acting as pathogen-associated molecular patterns (PAMPs) to induce innate immunity, and as antigens that generate adaptive immunity. In particular, dendritic cells that are activated by PAMPs play a pivotal role as antigen presenting cells that stimulate naive helper T cells (Th0). The dendritic cells, and other tissue cells, also deliver 'polarizing signals' (which are themselves determined by the nature of the pathogens): these steer the differentiation of the T cells into particular subsets (Th1, Th2, Th17, Treg) that produce different cytokines, e.g. interferon-γ (IFN-γ), interleukin-4 (IL-4), interleukin-17 (IL-17) and transforming growth factor-β (TGF-β), respectively. These T cells then regulate the activity of

Continued

particular effector cells of the immune system as well as promoting B cells to switch to the production of particular classes of antibodies (IgG, IgE or IgA). The T cell-derived cytokines thus play key roles in determining 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 right side shows how particular combinations of immune effector cells and molecules generate the type of **DEFENCE** appropriate to each category of pathogen. Thus, macrophages and neutrophil phagocytes working with complement proteins and antibodies (particularly IgG) generate the effector functions appropriate for the phagocytosis and digestion, or lysis, of extracellular microbes (e.g. many bacteria); natural killer cells (with or without IgG antibodies) and cytotoxic T cells kill infected cells (e.g. virus-infected cells); mast cells, basophils and eosinophils, together with IgE antibodies, promote the expulsion or digestion of mucosal parasites, and IgA antibodies are also abundant at mucosal surfaces.

Each component of this overview is described in Chapter 1 and the more detailed chapters that follow.

Part 1

Immunity and the Immune System

1

The nature of immunity

Key objectives

This chapter will enable you to:

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

Immunology is a relatively new science. It is a branch of biomedical science that covers the study of all aspects of immunity and the immune system in organisms. Immunity is a state of resistance to infection, and the immune system is composed of those constituents of the body (i.e. molecules, cells, tissues and organs) that contribute to generating this resistance. Immunology deals with the physiological functioning of the immune system in states of both health and disease. It incorporates malfunctions of the immune system, as well as the physical, chemical and physiological characteristics of the components of the immune system. These components can be studies individually (in isolation), in terms of their mutual interactions, and within the body as a whole. Its origin is usually attributed to events in the eighteenth century – firstly, to Lady Mary Wortley Montagu, the wife of the British ambassador in Constantinople (now known as Istanbul), who observed the positive effects of variolation on the native population in 1712. Variolation is the deliberate infection with smallpox, where dried smallpox scabs were blown into the nose of an individual who then contracted a mild form of the disease. 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.

Subsequently, 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.

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. Jenner was subsequently able to inoculate the boy 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. These are restored and now contain the Jenner Museum and a Conference Centre.[1]

Immunology: Lecture Notes, Seventh Edition. Ian Todd, Gavin Spickett and Lucy Fairclough.

Table 1.1 Examples of types of pathogens and the diseases they cause.

Type of pathogen	Example pathogens	Diseases
Virus	Variola Human immunodeficiency virus	Smallpox Acquired immune deficiency syndrome
Bacteria	*Staphylococcus aureus* or *Streptococcus pneumoniae*	Community-acquired pneumonia
Fungi	*Candida albicans*	Thrush
Parasite	*Plasmodium malariae*	Malaria
Prion	Creutzfeldt–Jakob disease (CJD) prion	CJD

Although this vaccination was successful, it took almost two centuries (1796–1980) before the World Health Organization (WHO) was able to announce that smallpox was eradicated in 1980.

Interestingly, Jenner knew nothing of infectious agents that cause disease. Numerous scientific breakthroughs occurred, but it was not until Robert Koch first demonstrated, in 1876, that bacterial infectious agents (pathogens) cause disease. Any organism with the potential to cause disease is called a pathogen. There are five broad categories of pathogens, namely, viruses, bacteria, fungi, other relatively large and eukaryotic organisms (termed parasites) and prions (Table 1.1).

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. Clearly, the two important biological events are **recognition** of the target pathogen and effective **defence** against it. A major consideration is how many recognition specificities are required and how many kinds of defence, that is, methods of pathogen destruction, are necessary.

There exists an enormous variety of infectious pathogens, including many types of bacteria, viruses, fungi, parasites and prions, 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 1.2 and 1.3, respectively. These components vary in terms of whether their main role is recognition or defence, although most 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 1.2). **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 1.2).

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

Table 1.2 Cells of the immune system.

Cell type	Developmental lineage	Morphological definition	Type of immunity
Neutrophils	Myeloid	PMN leucocytes or granulocytes	Innate
Eosinophils	Myeloid	PMN leucocytes or granulocytes	Innate
Basophils	Myeloid	PMN leucocytes or granulocytes	Innate
Mast cells	Myeloid	PMN 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

PMN, polymorphonuclear.

Table 1.3 Secreted mediators of immunity.

Antimicrobial

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)

Regulatory/inflammatory

Cytokines (e.g. interleukins, interferons, tumour necrosis factors)

Chemokines (and other chemoattractants)

Eicosanoids (e.g. prostaglandins, leukotrienes)

Histamine

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.

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 Chapter 2, and the development, activation and functions of lymphocytes are described in Chapters 3 and 4; immunoglobulins are considered in Chapter 5.

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 she/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, for example, 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 Figure 1.1. This compares the speed and magnitude of the human response to an antigen that the subjects had not previously encountered (bacteriophage φX174). 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 titre[2] 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

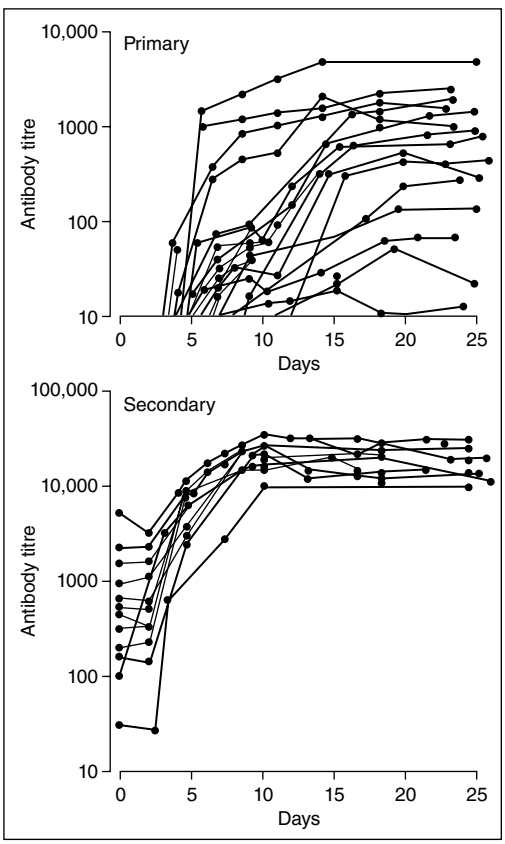


Figure 1.1 Primary and secondary antibody responses following intravenous injection of bacteriophage ϕX174 used as a test antigen in humans (Data kindly provided by Drs Peacock and Verrier Jones).

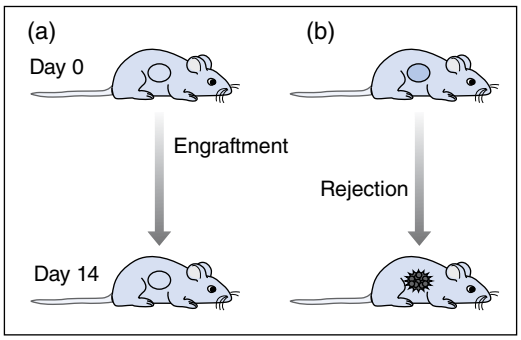


Figure 1.2 Discrimination between self and non-self illustrated by skin grafting in a rodent. (a) The graft was of 'self' type. (b) The graft was from an unrelated animal.

response, and it is for this reason that prior exposure, for example, 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 Figure 1.2. 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 been accepted (Fig. 1.2a) or whether they have been rejected (Fig. 1.2b). 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. 1.3; Clinical Case Scenario 1.1). The skin itself constitutes an effective barrier to infection

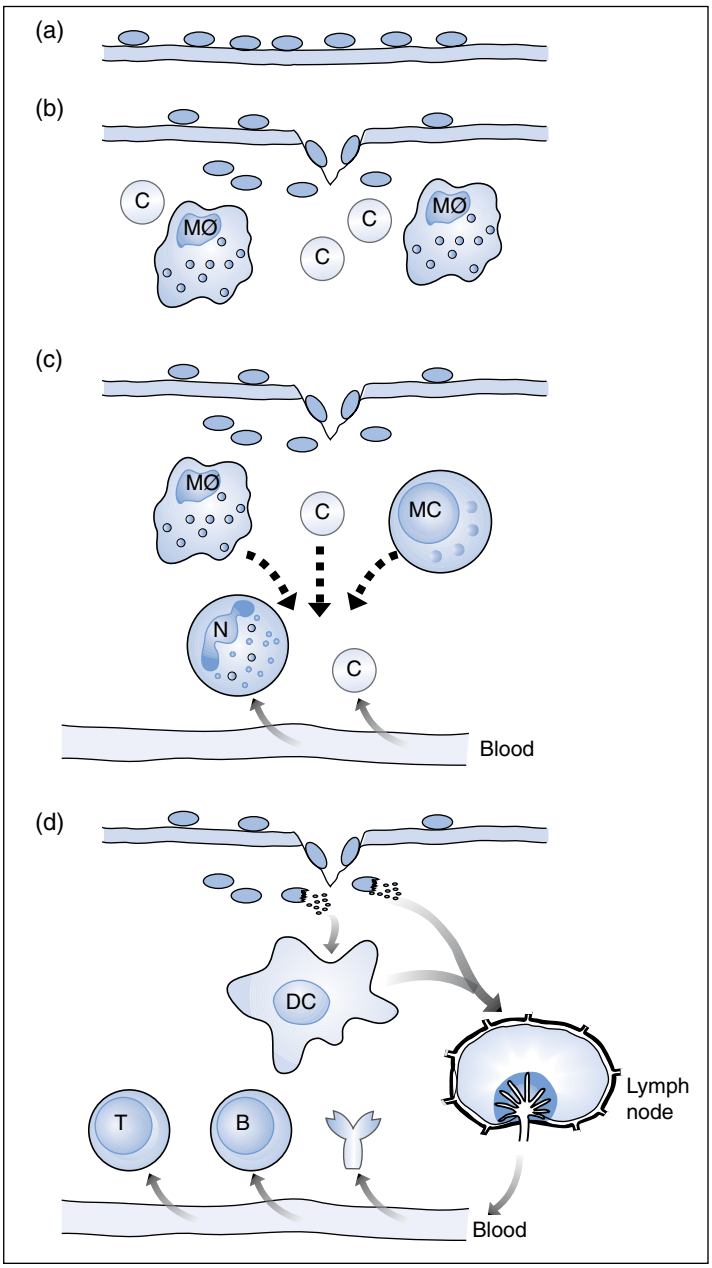


Figure 1.3 Stages of an immune response to bacterial skin infection. (a) Bacteria are unable to penetrate the intact keratinized epithelial barrier. (b) Bacterial entry (e.g. via a cut) stimulates an immediate local innate response by tissue macrophages and complement proteins. (c) An early induced inflammatory 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.

because most microbes cannot penetrate the hard, keratinized surface of the epidermis (Fig. 1.3a), 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. 1.3b). 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**

CLINICAL CASE SCENARIO 1.1 'Just a scratch'

Darren, a fit and healthy 27-year-old, attended a walk-in clinic, concerned about a swelling on his left calf. Six days earlier, he had taken part in a cross-country race and had grazed his calf on some brambles. Although the skin had been broken and the wound bled, he had thought nothing more of it at the time and completed the race. However, he was now worried that the lesion might be infected.

When the doctor examined the affected area on Darren's calf, she noted that it was swollen and red; Darren told her that the area felt warm and slightly painful when touched. The swelling was circular, with a diameter of about 6 cm and a diffuse edge. There was a small amount of pus in the centre of the wound. Darren's temperature was normal and there were no systemic signs of infection (e.g. fever, chills, malaise).

The doctor concluded that this was an uncomplicated case of cellulitis (inflammation of the skin and subcutaneous tissues associated with acute infection) in a healthy young adult and that the site of inflammation on the calf was associated with a normal, acute immune response to localized infection. She considered that the infection was most probably streptococcal or possibly staphylococcal (but unlikely to be methicillin-resistant *Staphylococcus aureus* (MRSA)). The doctor prescribed an oral course of high-dose flucloxacillin antibiotic that inhibits bacterial cell wall synthesis and is effective against both streptococci and staphylococci. She advised Darren to complete the course of antibiotics.

Within a week, the swelling, redness and tenderness resolved and Darren experienced no further problems.

(For further information relevant to this case, see Chapter 10, p. 118.)

(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 in the 'Innate and Adaptive Immunity' section. 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 **vasodilation** and increase in **vascular permeability**; **adhesion** of inflammatory cells to the blood vessel wall; their chemical attraction, that is, **chemotaxis**; **immobilization** of cells at the site of infection; and **activation** of the relevant cells and molecules to liberate their lytic products (Fig. 1.4). 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. 1.3c).

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. 1.5). 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 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. 1.3d). The activated T and B cells return to the blood circulation whence they enter the inflamed, infected tissues,

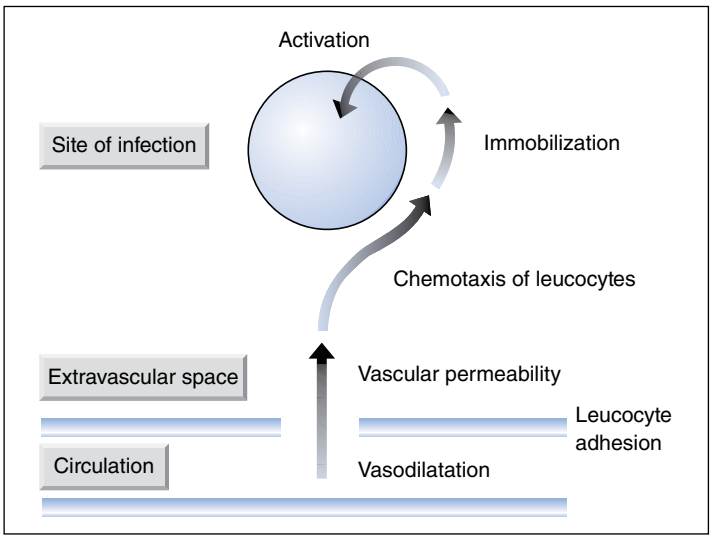


Figure 1.4 Amplifying events involved in the local recruitment of inflammatory cells and molecules from the circulation into an extravascular site of infection.

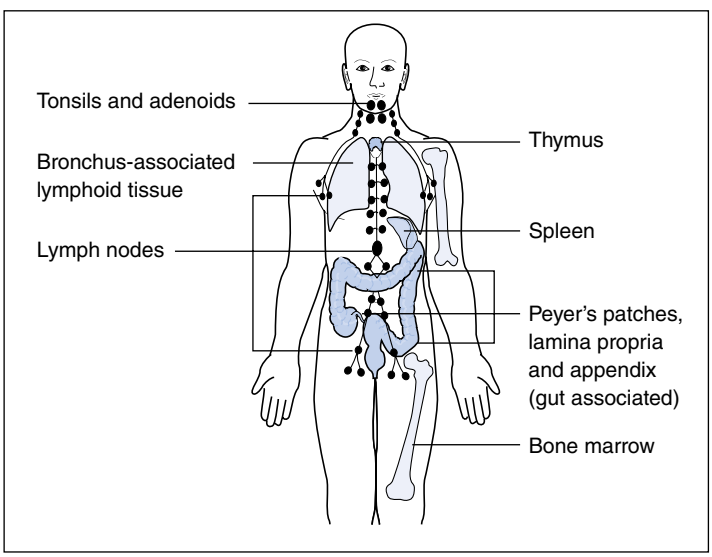


Figure 1.5 The lymphoid system in humans, showing the distribution of primary and secondary lymphoid organs and tissues.

together with antibodies secreted by terminally differentiated B cells called **plasma cells**, in a similar manner to the earlier influx of other leucocytes and complement proteins (Fig. 1.3d). 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 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. 1.6a). 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

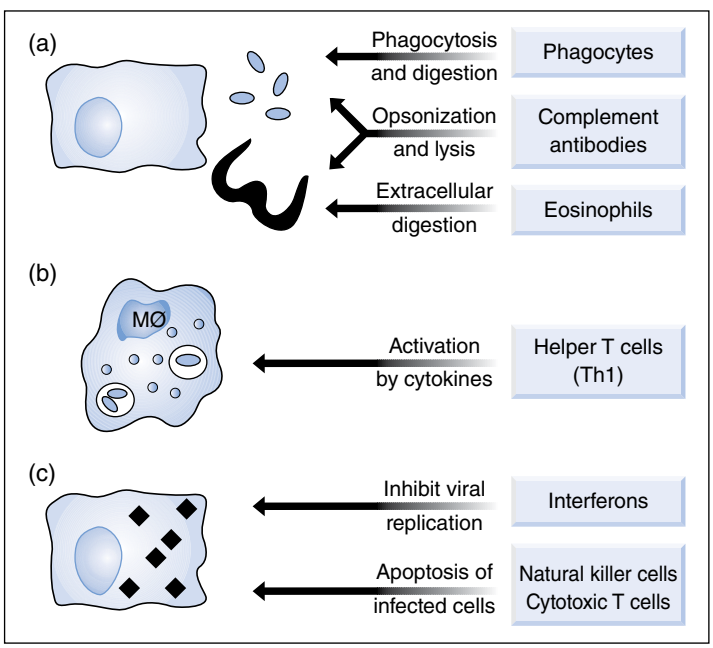


Figure 1.6 Immunological defence strategies. (a) Extracellular pathogens (e.g. bacteria and parasitic worms) are directly exposed to antibodies, complement, phagocytes (macrophages and neutrophils) and eosinophils. (b) Microbes that are resistant to digestion (e.g. mycobacteria) can survive intracellularly 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.

cytokines derived from **helper T lymphocytes** (**Th cells**) in order to overcome the microbes' resistance to digestion (Fig. 1.6b). 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. 1.6c).

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 integrated innate and adaptive defensive response that is generated. The activities of the immune components that generate rapid innate responses (e.g. macrophages, granulocytes, NK 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 'polarizing 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, that is, 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 and 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. When the reaction is excessive or inappropriate, major tissue damage can ensue and this is referred to as **hypersensitivity**. When the driving force for the response is from a non-infectious agent (i.e. innocuous), this leads to **allergy**. However, when the source is from self-components (i.e. self-tissue), this leads to the development of **autoimmunity**. 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.