IMMUNOLOGY

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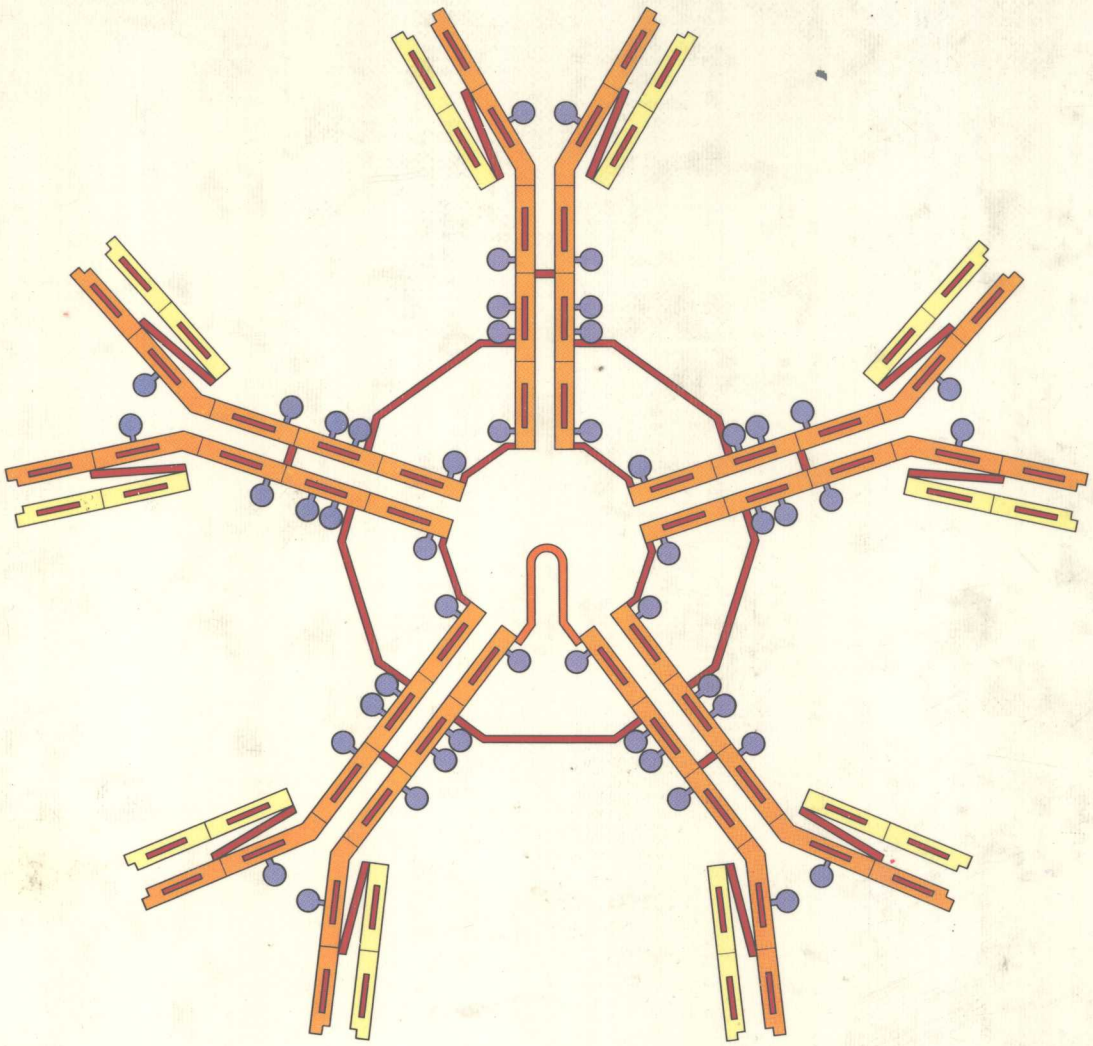

IMMUNOLOGY

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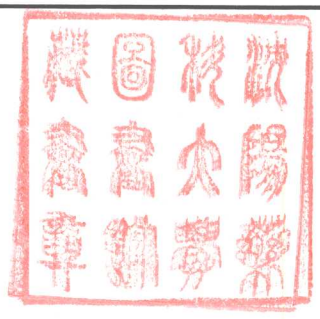

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Preface

We believe this to be a remarkably unusual book. We have attempted to present the subject primarily with appealing visual images, many of which are the distillation of much complicated scientific research. These illustrations are complemented specifically by individual captions, and more generally by a concise narrative text which links these images into an evolving conceptual thread. The book covers basic immunology and the fundamental principles relating to clinical immunology. The subject is covered in some depth and much attention is given to the underlying experimental studies. We hope that anyone interested in immunology, be they undergraduate, postgraduate or clinician, will find this an attractive but nonetheless thorough account, which they will find difficult to put down once they have opened it.

We would like to acknowledge the many immunologists and molecular biologists whose research findings have been included to explain particular immunological reactions, and to develop ideas on the function of the immune system. We greatly admire their work, and hope we will be forgiven for not mentioning all these scientists individually. In some cases, we have selected particular items, or simplified experiments to make points more readily understood. Readers who wish to grapple with the fine details of the experiments and hypotheses may locate the original papers by reference to review articles included as further reading at the end of each chapter.

IMR
JB
DKM

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Dr. John Horton, Reader in Immunology, Department of Zoology, University of Durham, Durham. (*Evolution of Immunity*)

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Dr. Peter Lydyard, Honorary Senior Lecturer and Research Associate, Department of Immunology, The Middlesex Hospital Medical School, London. (*Cells Involved in the Immune Response; The Lymphoid System; Development of the Immune Response*)

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Professor Michael Steward, Professor of Immunology, Department of Medical Microbiology, London School of Hygiene and Tropical Medicine, London (*Antigen-Antibody Reactions; Immunological Tests*)

Dr. Janice Taverne, Research Associate, Department of Immunology, The Middlesex Hospital Medical School, London (*Immunity to Protozoa and Worms*)

Dr. Roger Taylor, Reader in Immunology, Department of Pathology, University of Bristol, Bristol. (*Regulation of the Immune Response*)

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1 Adaptive and Innate Immunity

Our environment contains a large variety of infectious microbial agents – viruses, bacteria, fungi and parasites. Any of these can cause pathological damage and if they multiply unchecked will eventually kill their host. It is evident that the great majority of infections in normal individuals are of limited duration and leave very little permanent damage. This is due to the individual's immune system which combats infectious agents.

The immune system is divided into two functional divisions, namely the innate immune system and the adaptive immune system. Innate immunity acts as a first line of defence against infectious agents and most potential pathogens are checked before they establish an overt infection. If these first defences are breached the adaptive immune system is called upon. The adaptive system produces a specific reaction to each infectious agent which normally eradicates that agent. Furthermore, the adaptive immune system remembers that particular infectious agent and can prevent it causing disease later (Fig. 1.1). For example, diseases such as measles and diphtheria produce a life-long immunity following an infection.

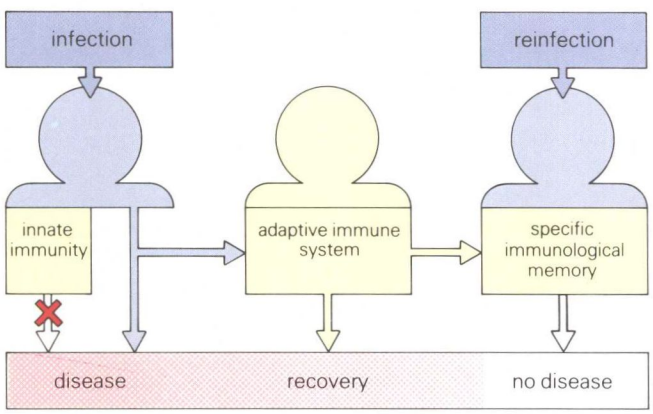


Fig. 1.1 Adaptive and innate immunity. When an infectious agent enters the body it first encounters elements of the innate immune system. These may be sufficient to prevent disease but if not, a disease will result and the adaptive immune system is activated. The adaptive immune system produces recovery from the disease and a specific immunological memory is established so that following reinfection with the same agent no disease results; the individual has acquired immunity to the infectious agent.

The innate and adaptive immune systems consist of a variety of molecules and cells distributed throughout the body whose functions are described below (Fig. 1.2). The most important cells are the leucocytes or white blood cells which are described fully in 'Cells Involved in the Immune Response'. The leucocytes fall into two broad categories: 1) phagocytes, including neutrophil polymorphs, monocytes and macrophages, which form part of the innate immune system; 2) lymphocytes, which mediate adaptive immunity. Cells of the immune system (lymphoid cells) are organized into organs as described in 'The Lymphoid System'.

	Innate Immune System	Adaptive Immune System
	resistance not improved by repeated infection	resistance improved by repeated infection
soluble factors	lysozyme, complement, acute phase proteins eg. CRP, interferon	antibody
cells	phagocytes natural killer (NK) cells	T lymphocytes

Fig. 1.2 The major elements of the innate and adaptive immune systems. There is considerable interaction between the two systems. Immunity due to soluble factors is sometimes referred to as humoral immunity.

THE INNATE IMMUNE SYSTEM

The exterior of the body presents an effective barrier to most organisms; in particular, most infectious agents cannot penetrate intact skin (Fig. 1.3).

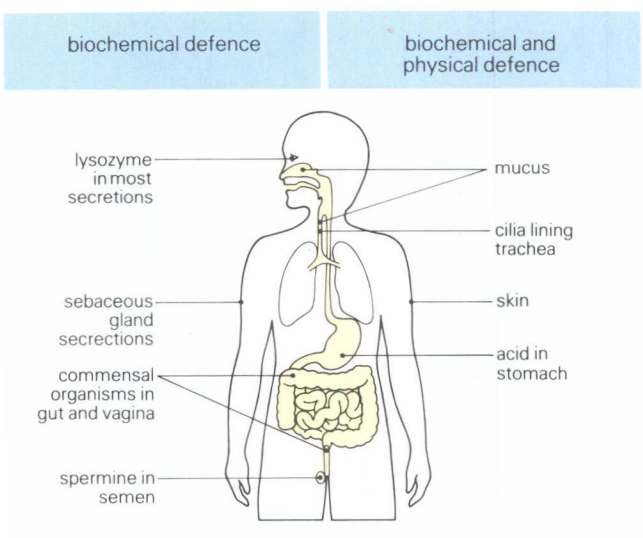


Fig. 1.3 Exterior defenses. Most of the infectious agents which an individual encounters do no penetrate the body's surfaces, but are prevented from entering by a variety of biochemical and physical barriers. The body tolerates a number of commensal organisms which compete effectively with many potential pathogens.

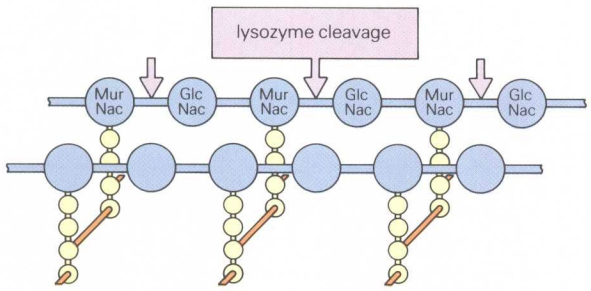


Fig. 1.4 Action of lysozyme on the cell wall of *S. aureus*. In the structure of *S. aureus* cell wall proteoglycan the backbone of N-acetylglucosamine (GlcNac) alternates with N-acetylmuramic acid (MurNac) crosslinked by amino acid side chains (yellow) and bridges of 5-glycine residues (orange). Lysozyme splits the molecule at the places indicated.

The importance of this barrier is made abundantly clear when an individual suffers serious burns. In this case prevention of infection via the damaged skin is a major concern. Most infections enter the body via the epithelial surface of the nasopharynx, gut, lungs and genito-urinary tract. A variety of physical and biochemical defences protect these areas from most infections. For example, lysozyme is an enzyme distributed widely in different secretions which is capable of splitting a bond found in the cell walls of many bacteria (Fig. 1.4).

Phagocytes

If an organism penetrates an epithelial surface it encounters phagocytic cells of the reticuloendothelial system. These cells are of several different types but they are all derived from bone marrow stem cells. Their function is to engulf particles, including infectious agents, internalize them and destroy them. For this purpose they are strategically placed where they will encounter such particles; for example, the Kupffer cells of the liver line the sinusoids along which blood flows while the synovial A cells line the synovial cavity (Fig. 1.5). The blood phagocytes include the neutrophil polymorph and the blood monocyte (Fig. 1.6). Both of these cells can migrate out of the blood vessels into the tissues in response to a suitable stimulus but they differ in that the polymorph is a short-lived cell while the monocyte develops into a tissue macrophage.

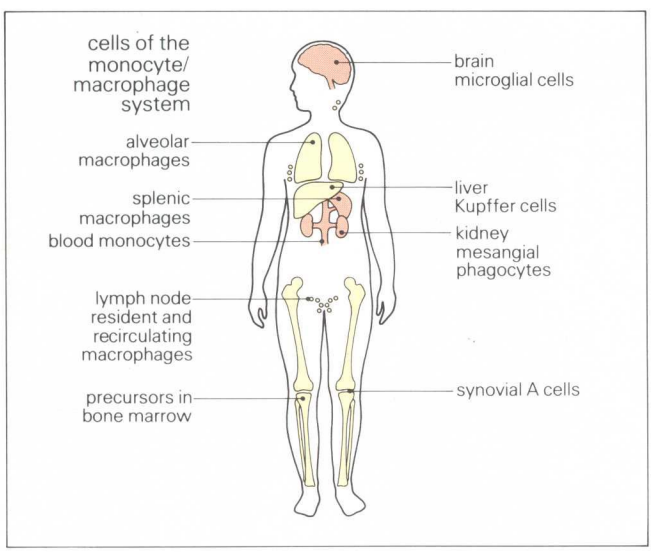


Fig. 1.5 Phagocytes of the reticuloendothelial system. Many organs contain phagocytic cells. Cells of the monocyte/macrophage series (listed left) are derived from blood monocytes which are manufactured in the bone marrow. Monocytes pass out of the blood vessel and become macrophages in the tissues. The other phagocytes listed are also derived from bone marrow stem cells.

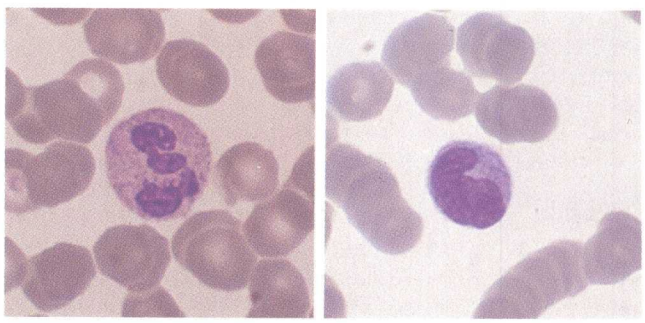


Fig. 1.6 Phagocytes. Apart from the fixed cells of the reticuloendothelial system there are polymorphonuclear neutrophils (left) and blood monocytes (right), both derived from bone marrow stem cells. Courtesy of Dr. P. M. Lydyard.

NK Cells and Soluble Factors

Natural killer (NK) cells are leucocytes capable of recognizing cell surface changes on virally-infected cells. The NK cells bind to these target cells and can kill them. The NK cells are activated by interferons which are themselves components of the innate immune system (Fig. 1.7). Interferons are produced by virally-infected cells and sometimes also by lymphocytes. Apart from their action on NK cells, interferons induce a state of viral resistance in uninfected tissue cells. Interferons are produced very early in infection and are the first line of resistance against many viruses.

The serum concentration of a number of proteins increases rapidly during infection. These are referred to as acute phase proteins. The concentrations of these acute phase proteins can increase from 2 to 100-fold by comparison with their normal levels and they remain elevated throughout the infection. An example of this is C-reactive protein, so-called because of its ability to bind the C protein of pneumococci. C-reactive protein bound to bacteria promotes the binding of complement which facilitates their uptake by phagocytes; this process of protein coating to enhance phagocytosis is known as opsonization (Fig. 1.8). Complement is a group of about twenty serum proteins, rather like the blood clotting system, which interact with each other and with other components of the innate and adaptive immune systems. The complement system is spontaneously activated by the surface of a number of microorganisms by the so-called alternative complement pathway. Following activation some complement components can cause opsonization of the microorganisms for phagocytes while others attract phagocytes to the site of infection.

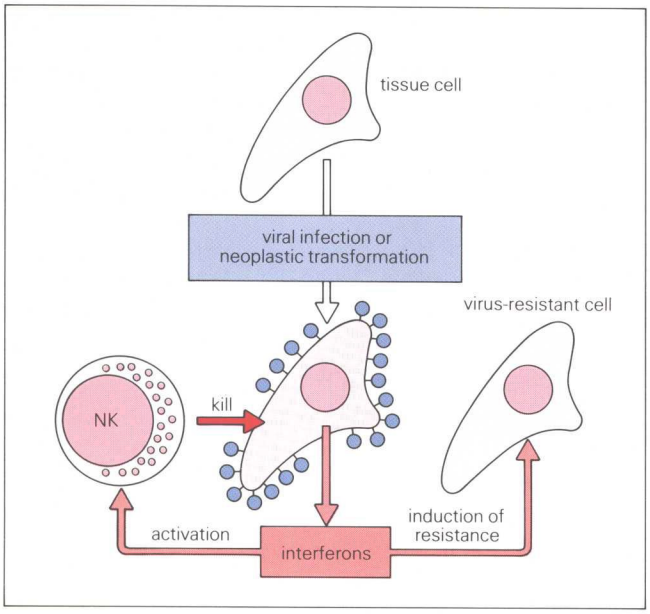


Fig. 1.7 Interferon and NK cells. When a cell becomes infected by virus, or transforms into a cancerous cell its surface molecules are altered. These alterations can sometimes be recognized by natural killer (NK) cells which engage the cell and kill it. Virally-infected cells produce interferons which can signal to neighbouring tissue cells and put them into a state capable of resisting viral replication, so preventing virus spread. Additionally, interferons can activate NK cells and enhance their cytotoxic action.

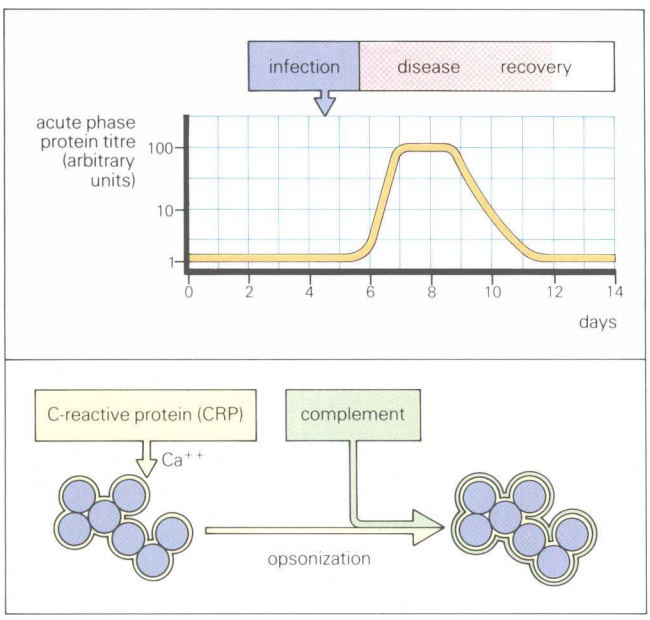


Fig. 1.8 Acute phase proteins. Acute phase proteins (here exemplified by C-reactive protein) are serum proteins which increase rapidly in concentration (up to 100 fold) following infection (graph). They are important in the innate immunity to infection. C-reactive protein (CRP) recognizes and binds, in a Ca^{++} dependent fashion, to molecular groups found on a wide variety of bacteria and fungi. In particular it binds the phosphorylcholine moiety of pneumococci. The CRP acts as an opsonin and also activates complement with all the associated sequelae.

A further group of complement components causes direct lysis of the cell membranes of bacteria by the 'lytic pathway' (Fig. 1.9). Although the various molecules of the innate immune system have been described separately, *in vivo* they act in concert. For example, the destruction of bacterial cell walls by lysozyme facilitates an attack on the cell membrane by the lytic pathway complement components. As will become evident later the complement system performs a number of functions in addition to its action in opsonization and lysis of microorganisms. These can be summarized as the control of inflammation.

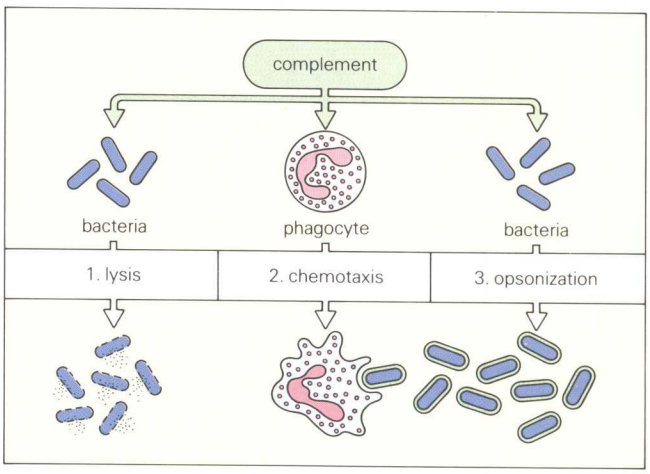


Fig. 1.9 Complement functions. The complement system has an intrinsic ability to lyse the cell membranes of many bacterial species (1). Complement products released in this reaction attract phagocytes to the site of the reaction – chemotaxis (2). Once they arrive at the site of reaction other complement components coating the bacterial surface allow the phagocyte to recognize the bacteria and facilitate bacterial phagocytosis — opsonization (3). These are all functions of the innate immune system, although the reactions can also be triggered by the adaptive immune system.

INFLAMMATION

Inflammation is the body's reaction to an injury such as an invasion by an infectious agent. In just the same way as it is necessary to increase the blood supply to active muscles during exercise to provide glucose and oxygen so it is also necessary to direct elements of the immune system into sites of infection. Three major things occur during this response namely:

1. An increased blood supply to the infected area,
2. Increased capillary permeability caused by retraction of the endothelial cells. This permits larger molecules to traverse the endothelium than would ordinarily be capable of doing so and thus allows the soluble mediators of immunity to reach the site of infection,
3. Leucocytes, particularly neutrophil polymorphs and to a lesser extent macrophages, migrate out of the capillaries and into the surrounding tissue. Once in the tissue they migrate towards the site of infection by a process known as chemotaxis. These three events manifest themselves as inflammation.

Chemotaxis

Chemotaxis is the process by which phagocytes are attracted to sites of inflammation (Fig. 1.10). It can be demonstrated *in vitro* that phagocytes will actively migrate up a concentration gradient of certain (chemotactic) molecules. Particularly active is C5a, a fragment of one of the complement components. When purified C5a is applied to the base of an ulcer *in vivo* neutrophil polymorphs can be seen sticking to the endothelium of the nearby capillaries shortly afterwards. Initially this occurs on the side of the capillary nearest the point of application but as the C5a diffuses further the neutrophils stick to all sides of the endothelium before traversing the endothelium, crossing the basement membrane and migrating up the gradient of the chemotactic molecule. Adherence and diapedesis of leucocytes is illustrated in figures 1.11 and 1.12. Both neutrophil polymorphs and macrophages are attracted by C5a but neutrophils are the predominant cell in sites of acute inflammation reflecting their numerical preponderance in the blood.

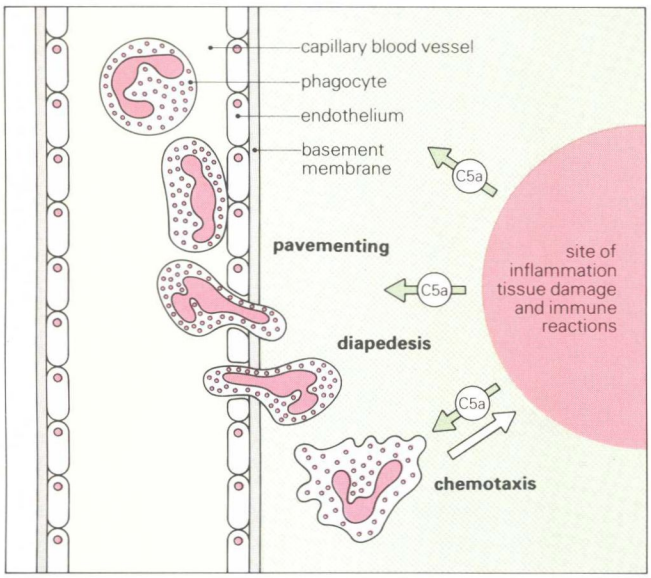


Fig. 1.10 Chemotaxis. At a site of inflammation tissue damage and complement activation by the infectious agent cause the release of chemotactic peptides (eg. C5a, a fragment of one of the complement components, which is one of the most important chemotactic peptides). These peptides diffuse to the adjoining capillaries causing passing phagocytes to adhere to the endothelium (pavementing). The phagocytes insert pseudopods between the endothelial cells and dissolve the basement membrane (diapedesis). They then pass out of the blood vessel and move up the concentration gradient of the chemotactic peptides towards the site of inflammation.

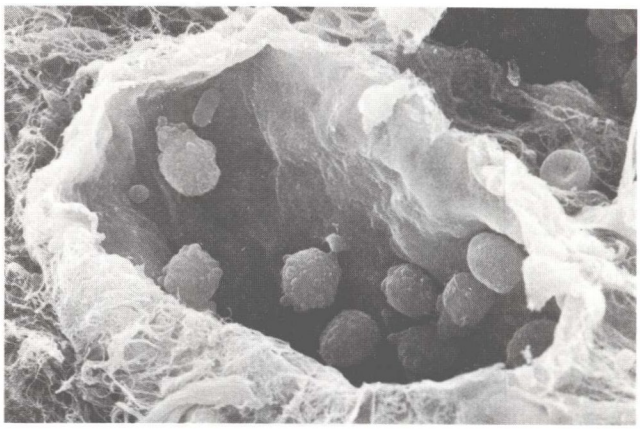


Fig. 1.12 Scanning electron micrograph showing leucocytes adhering to the wall of a venule in inflamed tissue. ×16,000. Courtesy of Professor M. J. Karnovsky.

Phagocytosis

Once they have arrived at a site of inflammation the phagocytes have to recognize the infectious agent. They have receptors on their surface which allow them to attach non-specifically to a variety of microorganisms, but the attachment is greatly enhanced if the microorganism has been opsonized by the C3b component of complement. Complement activation at the site of infection causes C3b to be deposited on the infectious agent and since both neutrophils and macrophages have receptors which specifically bind to C3b this allows the phagocytes to recognize their targets (Fig. 1.13). The importance of complement opsonization can be seen in those very rare patients who are genetically deficient in complement component C3. These patients suffer from recurrent bacterial infections and septicaemia.

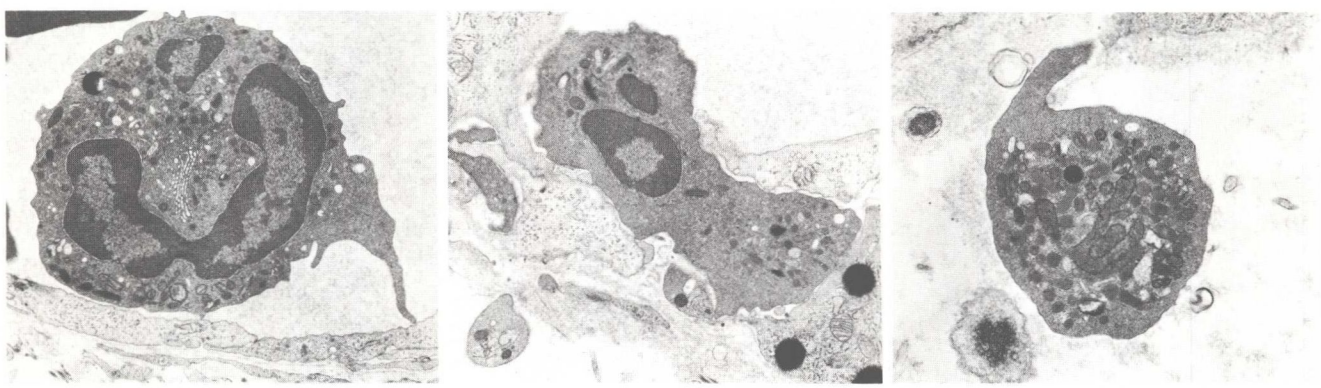


Fig. 1.11 Electron micrographs showing the three phases of diapedesis. The first micrograph shows a leucocyte adhering to the capillary endothelium (left) before it penetrates the endothelium (middle). The third micrograph illustrates a leucocyte which has traversed the endothelium (right). X 4000. Courtesy of Dr. I. Jovis.

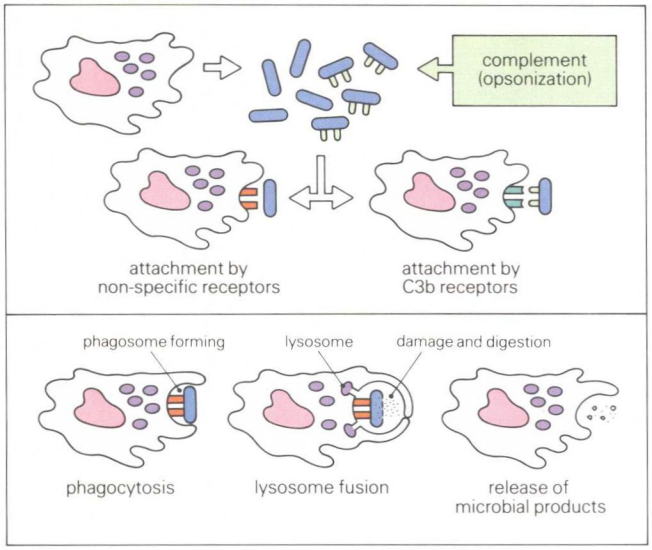


Fig. 1.13 Phagocytosis. Phagocytes arrive at a site of inflammation by chemotaxis. They may then attach to microorganisms via their non-specific cell surface receptors, or if the organism is opsonized with a fragment of the third complement component (C3b) through activation of the complement system, attachment will be through the cell surface receptors for C3b. If the membrane now becomes activated by the attached infectious agent, it is taken into a phagosome by pseudopods which extend around it. Once inside, lysosomes fuse with the phagosome forming a phagolysosome and the infectious agent is killed by a battery of microbicidal mechanisms. Undigested microbial products may be released to the outside.

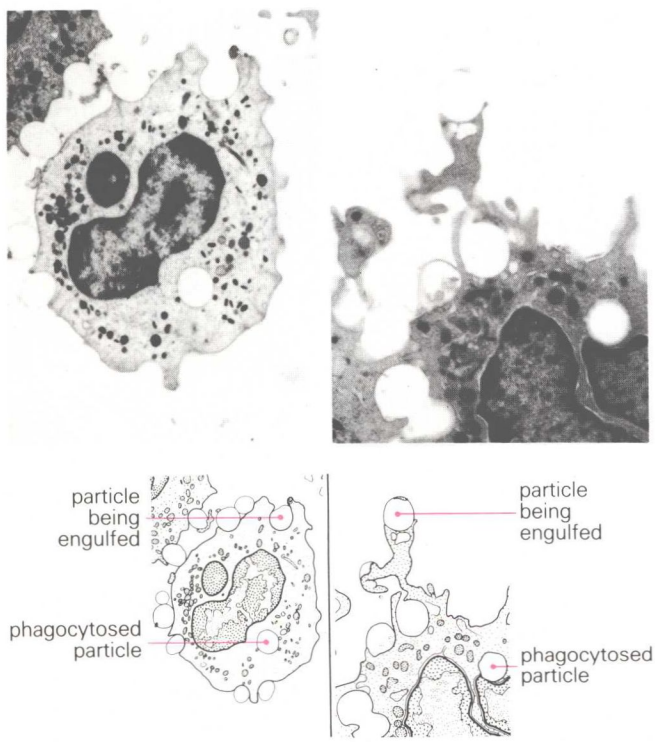


Fig. 1.14 Electron micrographic study of phagocytosis. These two micrographs show human phagocytes engulfing latex particles. ×3000 (left), ×4500 (right). Courtesy of Professor C. H. W. Horne.

After attachment the phagocytes proceed to engulf the microorganism by extending pseudopods around it. These fuse and the microorganism is internalized in a phagosome (Fig. 1.14). Lysosomes fuse with the phagosome and destroy the trapped microorganism. The mechanisms involved are described more fully in 'Immunity to Viruses, Bacteria and Fungi' and 'Immunity to Protozoa and Worms'.

ANTIBODY — A FLEXIBLE ADAPTOR

Problems arise when the phagocytes are unable to recognize the infectious agent either because they lack a suitable receptor for it or because the microorganism does not activate complement and so cannot become attached to the phagocyte via the C3b receptor. Ideally, what is needed is a flexible adaptor that can attach at one end to the microorganism and at the other to the phagocyte. In answer to this requirement molecules known as antibodies have evolved and these are fully described in 'Antibody Structure and Function'. Antibodies are a class of molecules produced by B lymphocytes of the adaptive immune system which act as flexible adaptors between the infectious agents and phagocytes (Fig. 1.15).

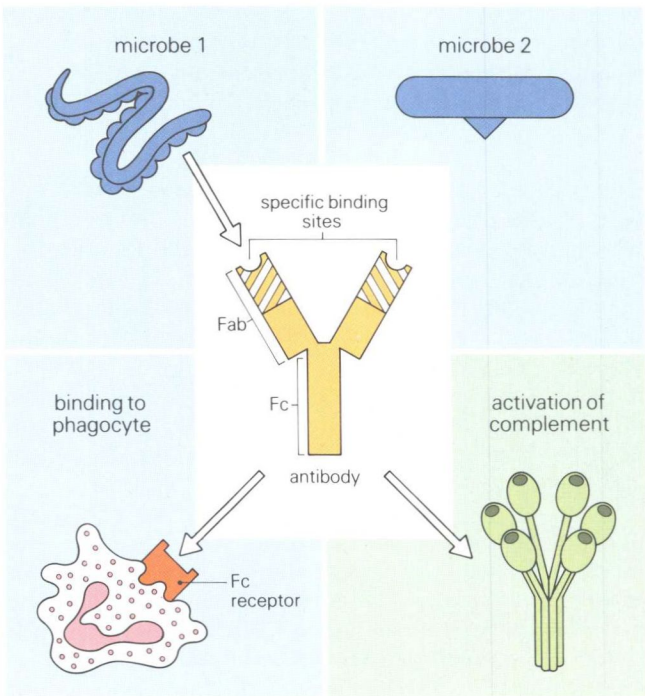


Fig. 1.15 Antibody — a flexible adaptor. When a microorganism lacks the inherent ability to activate complement or phagocytes, the body provides a class of flexible adaptor molecules with a series of different shapes which can attach to the surface of different microbes. These flexible adaptor molecules are, of course, antibodies and the body can make several million different antibodies able to recognize a wide variety of infectious agents. Thus the antibody illustrated binds microbe 1, but not microbe 2, by its 'antigen binding portion' (Fab) while the 'Fc portion' (which may activate complement) binds to Fc receptors on host tissue cells, particularly phagocytes.

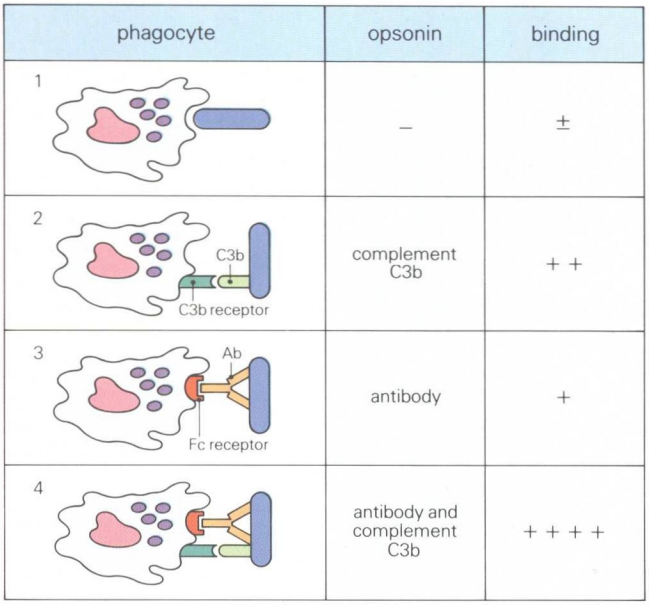


Fig. 1.16 Opsonization. Phagocytes have some intrinsic ability to bind directly to bacteria and other microorganisms (1), but this is much enhanced if the bacteria have activated complement (C3b) so that they can bind the bacteria via their C3b receptor (2). Opsonization of organisms which do not activate complement well, if at all, is performed by antibody (Ab) which acts as a bridge to attach the microbe to the Fc receptor on the phagocyte (3). If both antibody *and* C3b opsonize, binding is greatly enhanced (4).

Any particular antibody molecule can only bind to one type of infectious agent, the other end of the molecule binds to the phagocyte via a receptor, the Fc receptor. Macrophages, neutrophils and all other cells of the reticuloendothelial system have Fc receptors. Since antibodies also cause the activation of complement by the so-called 'classical pathway' infectious agents will often have both antibody and C3b bound to their surface. In this case the phagocyte will recognize the agent via both its Fc receptors and its C3b receptors so that attachment and phagocytosis are greatly enhanced (Fig. 1.16).

It should be evident that antibodies are effectively bifunctional molecules. One part, which is extremely variable between different antibodies, is responsible for binding to the many different infectious agents the body may encounter while the second, constant portion binds to the Fc receptors of cells and also activates complement. In fact, antibodies act as adaptors not just for phagocytes but also for other cells and different antibodies can act as adaptors for different cell types.

ANTIGEN

Antibody molecules do not bind to the whole of an infectious agent. Each antibody molecule binds to one of many molecules on the microorganism's surface. Molecules to which antibodies bind are called antigens (*antibody generators*). Different antibodies will bind to different antigens since each antibody is specific for a particular antigen. Indeed, a particular antigen specifically induces the production of the antibodies which can bind to it. The way in which a sufficient diversity of antibody molecules are generated able to recognize different antigens, is explained in the 'Generation of Antibody Diversity'. Each antibody binds to a particular part of the antigen called an antigenic determinant or epitope. Note that the terms antigenic determinant and epitope are synonymous. A particular antigen can have several different epitopes or may have several identical epitopes (Fig. 1.17). In reality, the antibodies are specific for the epitopes rather than for the whole antigen molecule but since each antigen has its own particular set of epitopes which are not usually shared with other antigens the collection of antibodies in an antiserum are effectively specific for the antigen. The characteristics of antigen-antibody combination are discussed in 'Antigen-Antibody Reactions'.

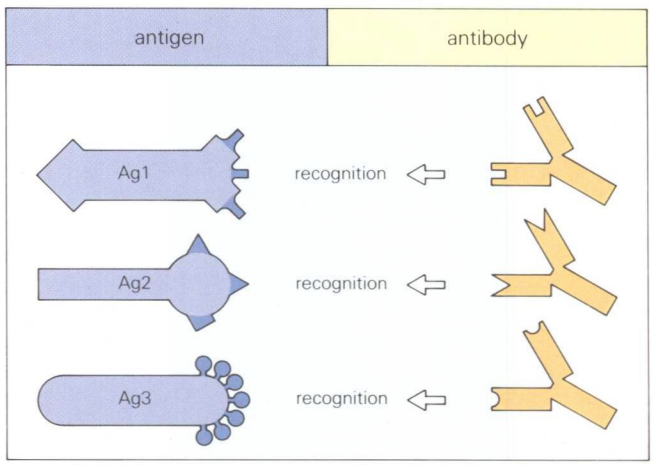


Fig. 1.17 Antigens. Foreign molecules which generate antibodies are called antigens. Antigen molecules each have a set of antigenic determinants also called epitopes. The epitopes on one antigen (Ag1) are usually different from those on another (Ag2). Some antigens (Ag3) have repeated epitopes. Epitopes are molecular shapes recognized by the antibodies and cells of the adaptive immune system. Each cell recognizes one epitope rather than the whole antigen. Even simple microorganisms have many different antigens.

ADAPTIVE IMMUNITY AND CLONAL SELECTION

The specificity of the adaptive immune system is based on the specificity of the antibodies and lymphocytes. It is found that each lymphocyte is only capable of recognizing one particular antigen. Since the immune system as a whole can specifically recognize many thousands of antigens this means that the lymphocytes recognizing any particular antigen are a very small proportion of the total. How then is an adequate response to an infectious agent generated? The answer is by clonal selection. Antigen binds to the small number of cells which can recognize it and induces them to proliferate so that they now constitute sufficient cells to mount an adequate immune response, that is the antigen selects the specific clones of antigen-binding cells (Fig. 1.18).

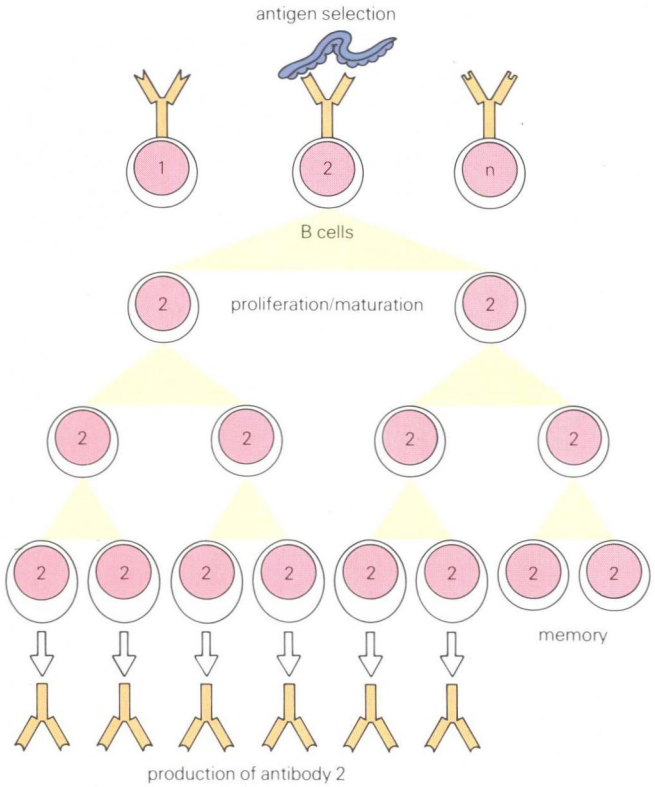


Fig. 1.18 Clonal selection. Each antibody-producing cell (B cell) is programmed to make just one antibody, which is placed on its surface as an antigen receptor. Each B cell has a different antigen binding specificity (1-n). Antigen binds to only those B cells with the appropriate surface receptor. These cells are stimulated to proliferate and mature into antibody-producing cells and the longer-lived, memory cells, all with the same antigen binding specificity (2).

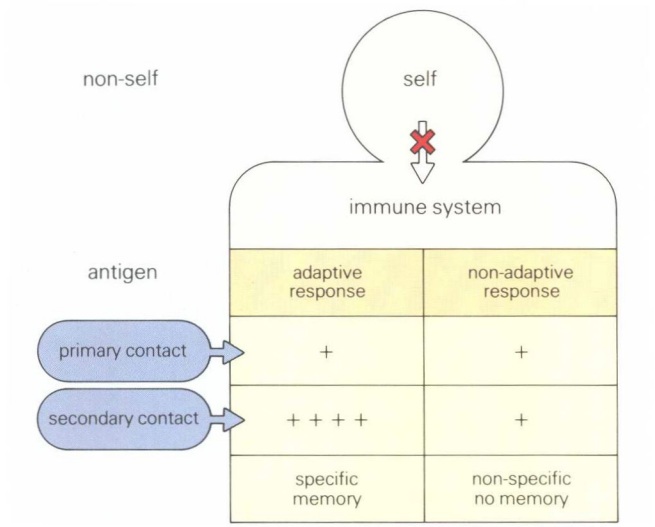


Fig. 1.19 Summary of self/non-self discrimination. The immune system discriminates self from non-self, and reacts against non-self molecules (antigens). Following a primary contact with antigen, there are weak adaptive, and non-adaptive responses, but if the same antigen persists or is encountered a second time there is a much enhanced specific response to that antigen. The characteristics of an adaptive immune response are specificity and memory.

This process occurs both for the B lymphocytes, which proliferate and mature into antibody-producing cells and for the T lymphocytes, which are involved in the recognition and destruction of virally-infected cells.

This raises the question of exactly what the immune system is capable of recognizing. Broadly speaking, the immune system regards all molecules not belonging to the individual as 'non-self' and reacts against them, and it recognizes many of the individual's own molecules as 'self' but does not react against them. The failure to react to a potentially antigenic molecule is referred to as tolerance (see 'Immunological Tolerance'). The critical importance of self/non-self discrimination is outlined in figure 1.19 in the context of the adaptive and non-adaptive immune response. The body must both tolerate its own tissues and react effectively against all infective agents if disease is to be avoided.

INTEGRATED DEFENCE MECHANISMS

It will be appreciated that the innate and adaptive immune systems do not act in isolation. Antibodies produced by lymphocytes help phagocytes to recognize their targets. Following clonal activation by antigen, T lymphocytes produce lymphokines which stimulate phagocytes to destroy infectious agents more effectively. The macrophages in turn help the lymphocytes by transporting antigen from the periphery to lymph nodes and other lymphoid organs where it is presented to lymphocytes in a form they can recognize (Fig. 1.20).

The immune system is not the only system which protects the body from injury; the clotting, fibrinolytic and kinin systems are also involved in mediating inflammation and in the resolution of tissue damage. These systems interact to maintain the integrity of the vascular system and to limit the spread of tissue damage whether it is caused by physical damage or infectious agents.

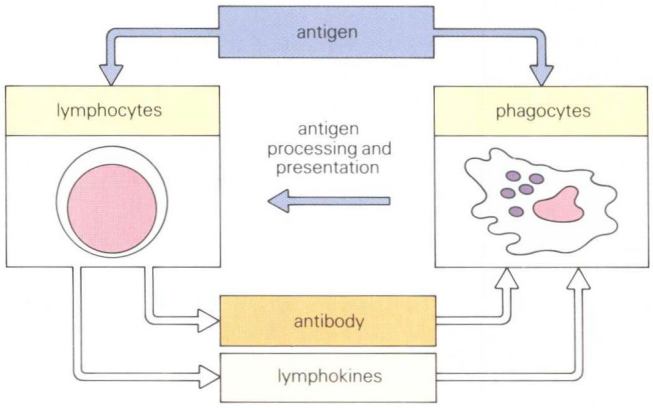


Fig. 1.20 Interaction between lymphocytes and phagocytes. The adaptive and non-adaptive areas of the immune system interact at all levels. Lymphocytes are responsible for specific recognition: they produce antibody and lymphokines, soluble molecules which help the phagocytes combat the infection. Antigen processed by phagocytes and other cells which cannot themselves specifically recognize antigen, present the antigen to lymphocytes which can recognize it.

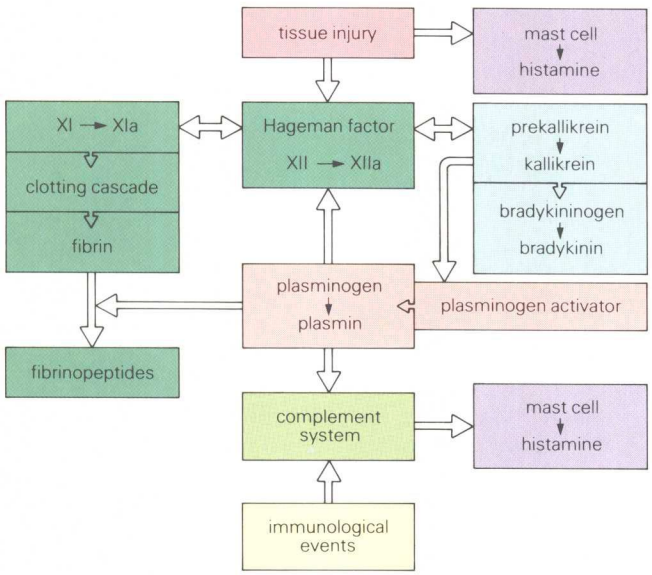
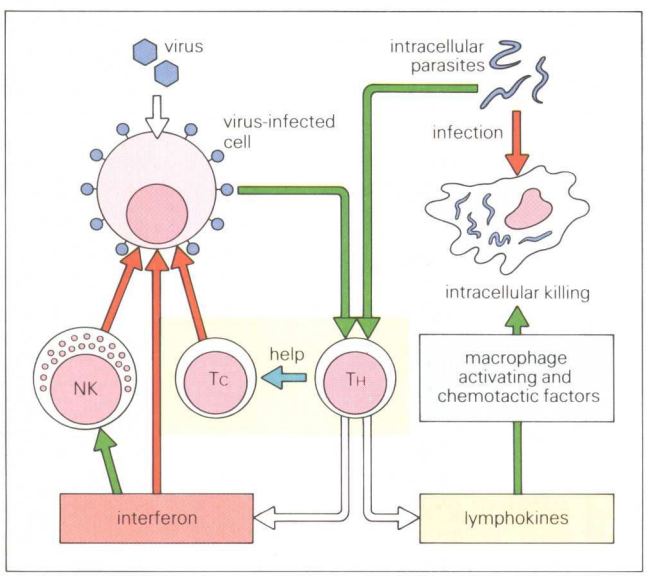


Fig. 1.21 The plasma enzyme systems in inflammation. This diagram summarizes the four plasma enzyme systems which interact in the control of inflammation. These are the clotting system (turquoise), the kinin system (light blue), the fibrinolytic system (pink) and the complement system (green). When tissue injury occurs enzymes are released and surfaces are exposed which activate Hageman factor XII and trigger mast cells to release histamine. Activated Hageman factor (XIIa) activates, and is reciprocally activated by, factor XIa and kallikrein. The kinin system produces bradykinin which induces pain, increased vascular permeability and vasodilation. Kallikrein activates the fibrinolytic system to produce plasmin which can activate Hageman factor and complement components and splits fibrin to produce chemotactic fibrinopeptides. Immunological events (for example, the combination of antibody with antigen) interact with these systems and modulate inflammation via the complement system. Different components (for example, C3a and C5a) trigger mast cells to release histamine producing vasodilation, increased capillary permeability and chemokinesis. (Other factors act as spasmogens, cause endothelial cell retraction, and are chemotactic for phagocytes.)



Immunological events can interact with this integrated system of damage control via the complement system (Fig. 1.21). Complement components released from sites of inflammation act directly on the local vasculature and the fragments C3a and C5a can also activate mast cells. These cells are widely distributed throughout the body and contain mediators which cause vasodilation and increased vascular permeability. The immune system can

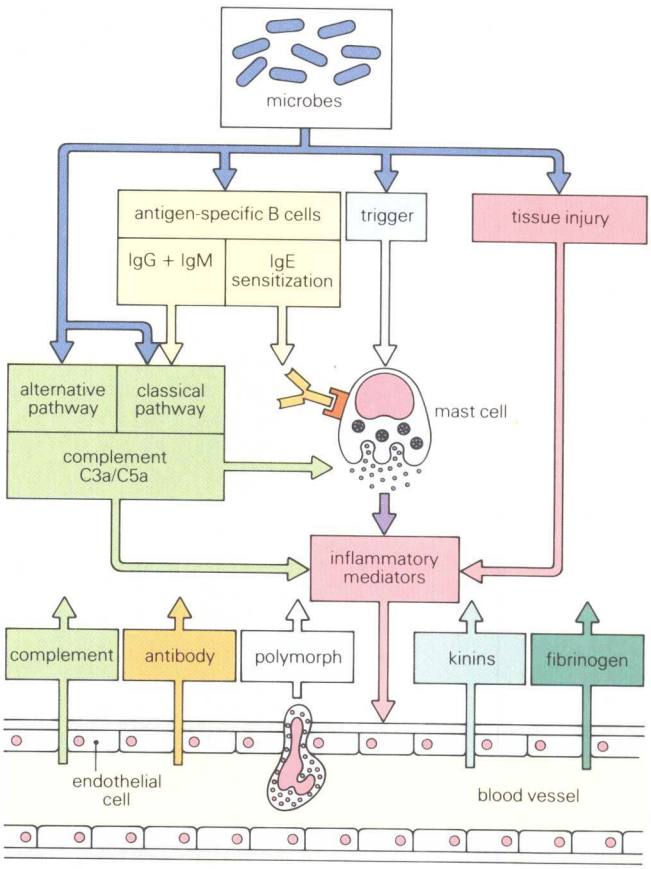


Fig. 1.22 Immune system in acute inflammation. The adaptive immune system modulates inflammatory processes via the complement system. Antigen from microbes stimulates antigen-specific B cells to produce antibody; some (IgE) binds to mast cells while others (IgG and IgM) activate complement. Complement can also be activated directly by microbes via an alternative pathway. When triggered by microbial antigens the sensitized mast cell releases mediators. In association with complement (which also activates mast cells via C3a and C5a) the mediators induce local inflammation facilitating the arrival of phagocytes and more plasma enzyme system molecules.

Fig. 1.23 Innate and acquired mechanisms of killing intracellular organisms. Viruses and intracellular parasites stimulate T cells of the adaptive immune system (yellow). T-helper cells (T_H) cooperate in the maturation of T-cytotoxic cells (T_C) and release lymphokines, including interferon. T_C cells and NK cells can kill virally-infected cells. Interferons (also produced by the infected cell) stimulate NK cells and inhibit viral replication directly. Other lymphokines attract macrophages to the site of infection and enable them to kill intracellular organisms which would otherwise persist.

also interact directly with mast cells via a type of antibody (IgE) which binds to Fc receptors on the mast cell (Fig. 1.22). The inflammatory reaction effects the arrival of molecules and cells to the site of infection where they activate the macrophages to destroy their intracellular parasites (Fig. 1.23).

VACCINATION

Specificity and memory, two of the key elements of the adaptive immune response are exploited in vaccination since the adaptive immune system mounts a much stronger response on second encounter with antigen. The principle is to alter a microorganism or its toxins in such a way that they become innocuous without losing antigenicity. Take for example, vaccination against diphtheria. The diphtheria bacterium produces a toxin which is cytotoxic for muscle cells. The toxin can be chemically modified by formalin treatment so that it retains its antigenic epitopes but loses its toxicity; the resulting toxoid is used as a vaccine (Fig. 1.24). Other infectious agents such as polio can be attenuated so that they retain their antigens but lose their pathogenicity.

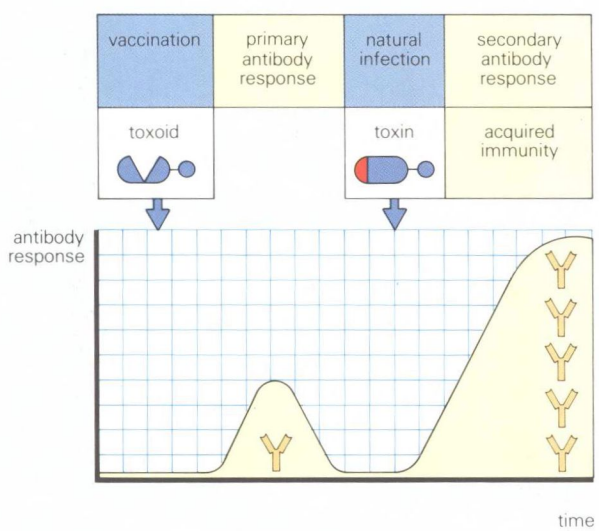


Fig. 1.24 Principle of vaccination. The principle of vaccination is illustrated by immunization with diphtheria toxoid. Diphtheria toxoid retains some of the epitopes of the diphtheria bacillus toxin so that a primary antibody response to these epitopes is produced following vaccination with toxoid. In a natural infection the toxin restimulates B memory cells which produce the faster and more intense secondary antibody response to the epitope so neutralizing the toxin.

IMMUNOPATHOLOGY

Up to this point the immune system has been presented as an unimpeachable asset. It is certainly true that deficiencies in any part of the immune system leave the individual exposed to a greater risk of infection, although other parts

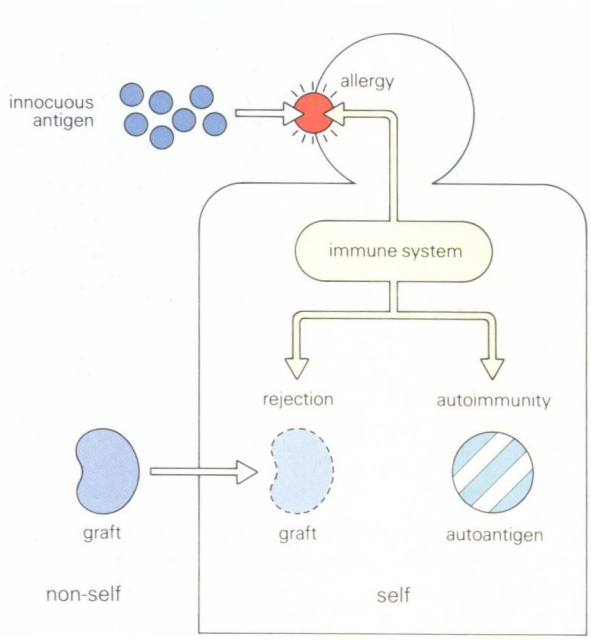


Fig. 1.25 Undesirable consequences of immunity. Tissue damage may occur through the operation of immune mechanisms, either because the immune response is excessive or the antigen is persistent. Thus, in allergic patients, some innocuous antigen, such as pollen provokes an immune reaction out of proportion to any damage it might do; we speak of hypersensitivity reactions. The immune system recognizes foreign tissue grafts like any other antigen and rejects them. Sometimes the self/non-self recognition system breaks down and the body's own components are recognized as non-self (autoantigens) in which case autoimmune diseases can ensue.

of the system often partly compensate for such deficiencies. Clearly strong evolutionary pressures from infectious agents have led to the development of the system in its present form.

Nevertheless, there are occasions when the immune system is itself a cause of disease or other undesirable consequences (Fig. 1.25).

It has been stated that the immune system is established on a principle of self/non-self recognition. In some cases tolerance of self antigens breaks down and autoimmune disease may develop (see 'Autoimmunity and Autoimmune Disease'). In other cases innocuous antigens such as pollen are recognized and the immune system mounts an inappropriate response to them giving rise to symptoms of allergy. This is referred to as hypersensitivity and is discussed in 'Hypersensitivity Types 1, 2, 3, and 4'. Hypersensitivity reactions can also occur during infections. In some infections the amount of tissue damage produced by the immune reactions to a resistant microorganism may be comparable to that produced by the infection itself. It is often not possible to say where an advantageous reaction to an infection ends and hypersensitivity begins, particularly since the fundamental mechanisms underlying both are the same. In spite of these drawbacks it must always be remembered that overwhelming selective pressures have led to the development of the immune system as we see it today.

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