Type	Disease	Pathogen	General classification*	Route of infection
Bacteria	Trachoma	*Chlamydia trachomatis*	Chlamydias	Oral/respiratory/ocular mucosa
	Bacillary dysentery	*Shigella flexneri*	Gram-negative bacilli	Oral
	Food poisoning	*Salmonella enteritidis, S. typhimurium*	Gram-negative bacilli	Oral
	Plague	*Yersinia pestis*	Gram-negative bacilli	Infected flea bite, respiratory
	Tularemia	*Pasteurella tulaensis*	Gram-negative bacilli	Handling infected animals
	Typhoid fever	*Salmonella typhi*	Gram-negative bacilli	Oral
	Gonorrhea	*Neisseria gonorrhoeae*	Gram-negative cocci	Sexually transmitted
	Meningococcal meningitis	*Neisseria meningitidis*	Gram-negative cocci	Oral/respiratory
	Meningitis, pneumonia	*Haemophilus influenzae*	Gram-negative coccobacilli	Oral/respiratory
	Legionnaire's disease	*Legionella pneumophila*	Gram-negative coccobacilli	Inhalation of contaminated aerosol
	Whooping cough	*Bordetella pertussis*	Gram-negative coccobacilli	Oral/respiratory
	Cholera	*Vibrio cholerae*	Gram-negative vibrios	Oral
	Anthrax	*Bacillus anthracis*	Gram-positive bacilli	Oral/respiratory by contact with spores
	Diphtheria	*Corynebacterium diphtheriae*	Gram-positive bacilli	Oral/respiratory
	Tetanus	*Clostridium tetani*	Gram-positive bacilli (anaerobic)	Infected wound
	Boils, wound infections	*Staphylococcus aureus*	Gram-positive cocci	Wounds; oral/respiratory
	Pneumonia, scarlet fever	*Streptococcus pneumoniae*	Gram-positive cocci	Oral/respiratory
	Tonsilitis	*Streptococcus pyogenes*	Gram-positive cocci	Oral/respiratory
	Leprosy	*Mycobacterium leprae*	Mycobacteria	Infected respiratory droplets
	Tuberculosis	*Mycobacterium tuberculosis*	Mycobacteria	Oral/respiratory
	Respiratory disease	*Mycoplasma pneumoniae*	Mycoplasmas	Oral/respiratory
	Typhus	*Rickettsia prowazeckii*	Rickettsias	Bite of infected tick
	Lyme disease	*Borrelia burgdorferi*	Spirochetes	Bite of infected deer tick
	Syphilis	*Treponema pallidum*	Spirochetes	Sexual transmission
Fungi	Aspergillosis	*Aspergillus* species	Ascomycetes	Opportunistic pathogen, inhalation of spores
	Athlete's foot	*Tinea pedis*	Ascomycetes	Physical contact
	Candidiasis, thrush	*Candida albicans*	Ascomycetes (yeasts)	Opportunistic pathogen, resident flora
	Pneumonia	Pneumocystis carinii	Ascomycetes	Opportunistic pathogen, resident lung flora
Protozoan parasites	Leishmaniasis	*Leishmania major*	Protozoa	Bite of an infected sand fly
	Malaria	*Plasmodium falciparum*	Protozoa	Bite of an infected mosquito
	Toxoplasmosis	*Toxoplasma gondii*	Protozoa	Oral, from infected material
	Trypanosomiasis	*Trypanosoma brucei*	Protozoa	Bite of an infected tsetse fly
Helminth parasites (worms)	Common roundworm	*Ascaris lumbricoides*	Nematodes (roundworms)	Oral, from infected material
	Schistosomiasis	*Schistosoma mansoni*	Trematodes	Through skin by bathing in infected water

Figure 8.2 ***(opposite page and above)*** **Diverse microorganisms cause human disease.** Pathogenic organisms are of four main types—viruses, bacteria, fungi, and parasites, which are mostly protozoa or worms. Some important pathogens in each category are listed along with the diseases they cause. *The classifications given are intended as a guide only and are not taxonomically consistent; families are given in the case of the viruses; general groupings often used in medical bacteriology for the bacteria; and higher taxonomic divisions for the fungi and parasites.

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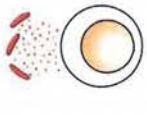
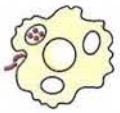
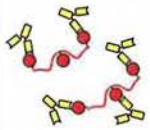
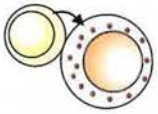
	Direct mechanisms of tissue damage by pathogens			Indirect mechanisms of tissue damage by pathogens		
	Exotoxin release	Endotoxin release	Direct cytopathic effect	Immune complexes	Anti-host antibody	Cell-mediated immunity
Pathogenic mechanism						
Infectious agent	*Vibrio cholerae*	*Yersinia pestis*	Influenza virus	*Treponema pallidum*	*Streptococcus pyogenes*	*Mycobacterium tuberculosis*
Disease	Cholera	Plague	Influenza	Kidney damage in secondary syphilis	Rheumatic fever	Tuberculosis

Figure 8.3 Pathogens damage tissues in different ways. Pathogens can directly kill cells and damage tissues in three ways. Exotoxins released by microorganisms act at the surfaces of host cells, usually via a cell-surface receptor (first column). When phagocytes degrade certain microorganisms, endotoxins are released that induce the phagocytes to secrete cytokines, causing local or systemic symptoms (second column). Cells infected by pathogens are usually killed or damaged in the process (third column). Tissue damage can also be caused in an indirect fashion. Antibodies produced by B cells in response to pathogens can form large antigen:antibody complexes that damage blood vessels and kidneys (fourth column). Antibodies against a pathogen can react with a human cell, causing it to be treated by the immune system as though it were a foreign invader (fifth column). In clearing pathogens from an infected site, inflammatory cells of the immune system damage tissue and leave debris (sixth column). A representative example of a pathogen and the disease it causes is given under each type of damage.

they exploit the human body, and in the type of damage they cause. Upon infection, tissue damage and disease symptoms can be caused directly by the pathogen, or indirectly as a consequence of the response of the host's immune system to the pathogen (Figure 8.3). For purposes of host defense, a distinction can be made between pathogens that replicate in the spaces between human cells to produce extracellular infections and pathogens that replicate inside human cells to produce intracellular infections. Both extracellular and intracellular spaces can be further subdivided (Figure 8.4). These different sites of replication affect the types of immune mechanism that can be used to eliminate the pathogen. Extracellular forms of pathogens are accessible to soluble molecules of the immune system, whereas intracellular forms are not. Those intracellular pathogens that live in the nucleus or cytosol

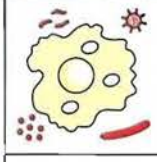
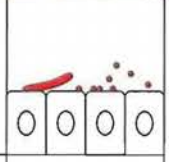
	Extracellular		Intracellular	
	Interstitial spaces, blood, lymph	Epithelial surfaces	Cytoplasmic	Vesicular
Site of infection				
Organisms	Viruses Bacteria Protozoa Fungi Worms	*Neisseria gonorrhoeae* *Candida albicans* Worms	Viruses *Chlamydia* species Protozoa	Mycobacteria Trypanosomes *Cryptococcus neoformans*
Protective immunity	Antibodies Complement Phagocytosis	IgA antibodies Antimicrobial peptides	Cytotoxic T cells NK cells	Activated macrophages

Figure 8.4 Pathogens exploit different compartments of the body that are defended in different ways. Virtually all pathogens have an extracellular stage in their life cycle. For the other compartments, a representative example of each type of pathogen that exploits the compartment is given. For some pathogens, all stages of their life cycle are extracellular, whereas others exploit intracellular sites as places to grow and replicate. Different components of the immune system contribute to protective immunity against different types of microorganism in different locations. NK cells, natural killer cells.

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are attacked by killing the infected cell, which interferes with the pathogen's life cycle and exposes pathogens that are released from the killed cells to the soluble molecules of the immune system. Those pathogens that live in intracellular vesicles, in contrast, can be attacked by activating the infected cell to intensify its antimicrobial activity. However, virtually all pathogens, whether viruses, bacteria, fungi or parasites, are present at some time in the extracellular spaces and can be attacked by antibodies.

Most pathogens infect only a few related host species and for this reason humans are only infrequently infected through transmission from another vertebrate species, such as the domesticated animals with which humans are often in contact, or wild animals that are hunted, butchered, and eaten. The vast majority of human infections result from transmission of the pathogen either directly or indirectly from another person who is already infected. Transmission can be directly from one person to another, or, as in the case of many parasites, it requires an intermediate passage through a distantly related organism, for example an insect or mollusc, that is necessary for completing the pathogen's life cycle.

The ability of different pathogens to persist outside the body varies considerably and determines the ease with which a particular disease is spread. The bacterial disease anthrax is spread by spores that are resistant to heat and desiccation and can, therefore, be passed over long distances from one person to another. It is these properties that make anthrax a 'hot topic' in discussions of germ warfare. In contrast, the human immunodeficiency virus (HIV) is very sensitive to changes in its environment and can be passed between individuals only by intimate contact and the exchange of infected body fluids and cells.

Experiments involving deliberate infection show that a large initial dose of pathogenic microorganisms is usually necessary to cause disease. To establish an infection a microorganism must colonize a tissue in sufficient numbers to overwhelm the cells and molecules of innate immunity that are rapidly recruited to the site of invasion. Even in these circumstances the effects will be minor unless the infection can spread within the body. Extracellular pathogens usually spread to other tissues by carriage in lymph or blood, which leads to the initiation of an adaptive immune response in secondary lymphoid tissue. Intracellular infections spread from one cell to its neighbors within a tissue, or by the release of infectious microorganisms that can be spread over greater distances in the extracellular fluids, again leading to the activation of adaptive immunity (Figure 8.5).

Recovery from an infectious disease involves clearance of infectious organisms from the body and repair of the damage caused by both infection and

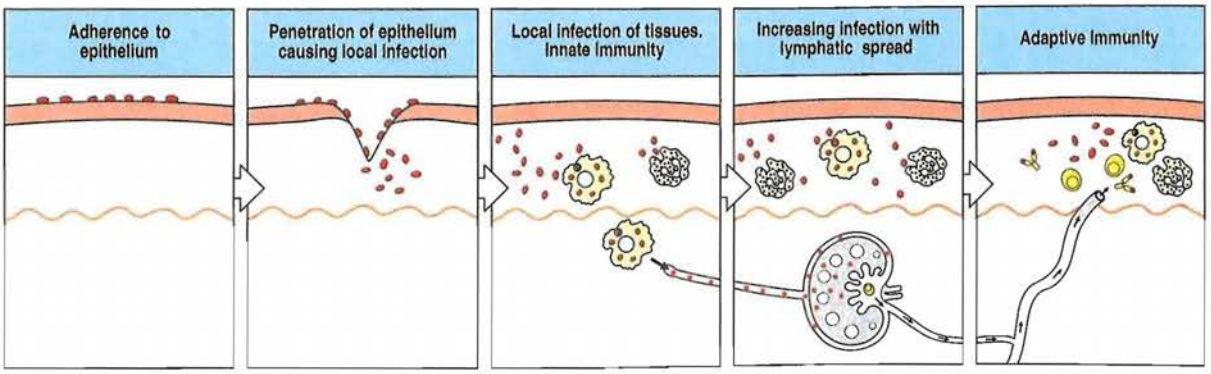


Figure 8.5 Stages in infection and host defense. To enter the body through the skin, a pathogen must first adhere to it (first panel). A wound allows the pathogen to penetrate the connective tissue underlying the protective epithelium (second panel). The pathogen replicates while the defenses of innate immunity develop a state of inflammation at the infected site (third panel). Pathogens are carried to the draining lymph node, where they are trapped and stimulate antigen-specific T and B cells to mount an adaptive immune response (fourth panel). After lymphocyte division and differentiation, antibodies and effector T cells arrive at the infected site and work with the cells and molecules of innate immunity to clear the pathogen (last panel).

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the immune response. A cure is not always possible. Infection can overwhelm the immune system with death as the consequence, as was once common for smallpox infections. In intermediate situations the infection persists but its pathological effects are controlled by the adaptive immune response, as usually occurs on infection with herpes viruses.

8-2 Surface epithelia present a formidable barrier to infection

The surface of the human body is protected by a continuous covering of epithelial cells, which forms a barrier between the internal milieu of the body's organs and tissues and the external world containing pathogens. These epithelia comprise the skin and the mucosal epithelial linings of the respiratory, gastrointestinal, and urogenital tracts (Figure 8.6). Infections occur only

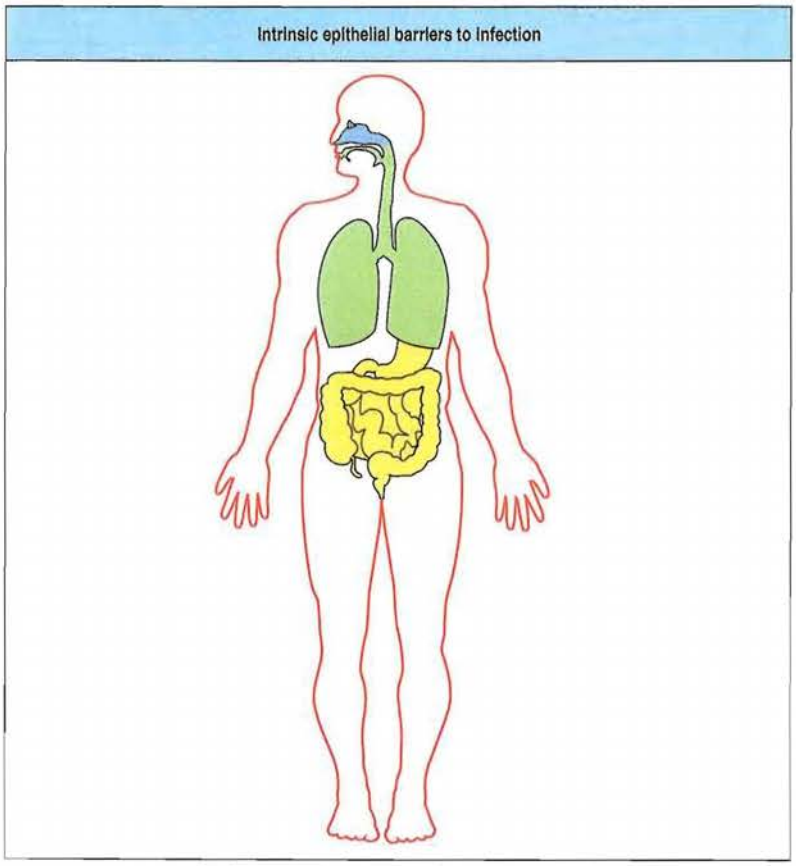


Figure 8.6 Many barriers prevent bacteria from crossing epithelia and colonizing tissues. Surface epithelia provide mechanical, chemical, and microbiological barriers to infection.

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when these barriers are breached or when pathogens colonize the surfaces or interiors of the epithelial cells themselves. The skin principally provides a physical barrier, whereas the mucosal tissues permit various forms of communication between the body and its environment, including interactions with other members of the human species. Because the skin provides almost all of the outer covering of the body, it is much more frequently breached by wounds or burns than the mucosa and it is thus more susceptible to the passive entry of pathogens. In contrast, the relatively protected mucosa are more susceptible to pathogens that actively exploit the communication functions of these tissues to gain entry to the body.

Surface epithelia are more than just a physical barrier to infection: they are also loaded with chemical weapons that inhibit the attachment and growth of microorganisms. Lysozyme in tears and saliva degrades bacterial cell walls, while the acid and hydrolytic enzymes secreted by the lining of the stomach create an environment unfriendly to bacterial growth (see Figure 8.6). All epithelial surfaces secrete antimicrobial peptides called defensins. These comprise the α defensins, which include neutrophil peptides and the cryptdins made by Paneth cells of the small intestine, and the β defensins, which are secreted by epithelial cells of the epidermis, respiratory tract, and gastrointestinal tract. Defensins kill bacteria, fungi, and enveloped viruses by perturbing their membranes. To prevent defensins from disrupting human cells they are synthesized as part of longer, inactive polypeptides and function poorly under physiological conditions of ionic strength, needing the lower ionic concentrations of sweat, tears, or the lumen of the gut to become active.

Most epithelia are also coated with a flora of nonpathogenic microorganisms that compete with pathogens for nutrients and for attachment sites on epithelial cells (see Figure 8.6). More than 500 microbial species live in the healthy human gut; they are called commensal species, meaning that they 'eat at the same table'. As well as inhibiting colonization by pathogens they enhance human nutrition by further processing digested food and making some vitamins. *Escherichia coli*, a major bacterial component of the normal gut flora, secretes antibacterial proteins called colicins, that prevent the colonization of the gut by other bacteria. When a patient takes a course of antibiotic drugs the nonpathogenic flora is killed together with the pathogens that caused the disease. After such treatment the body is recolonized by microorganisms; in this situation other pathogenic organisms can establish themselves, causing further disease (Figure 8.7).

8-3 Complement activation by the alternative pathway tags microorganisms for destruction

As soon as a pathogen penetrates an epithelial barrier and starts living in the tissues the defense mechanisms of innate immunity are brought into play. One of the first components of innate immunity to be activated is complement. Complement proteins are ubiquitous in blood and lymph, making complement activation a molecular defense mechanism that can be used immediately an infection begins. We saw in Chapter 7 how complement activated through the classical and alternative pathways works together with antibodies to opsonize pathogens so that they can be phagocytosed more easily. Complement activation through the **alternative pathway** occurs at the very beginning of a primary infection, long before any pathogen-specific antibody is made.

The first step in the alternative pathway involves the spontaneous hydrolysis and activation of complement component C3, a process that occurs continually at low rate in blood, lymph, and extracellular fluids. The rate increases in

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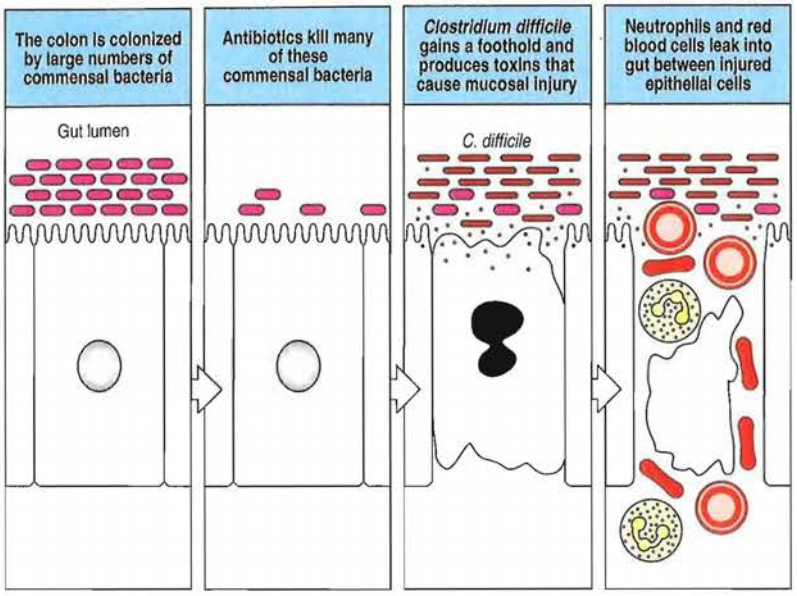


Figure 8.7 Antibiotic treatments disrupt the natural ecology of the colon. When antibiotics are taken orally to counter a bacterial infection, beneficial populations of commensal bacteria in the colon are also decimated. This provides an opportunity for pathogenic strains of bacteria to populate the colon and cause further disease. The pathogen shown here is *Clostridium difficile*; it produces a toxin that can cause severe bloody diarrhea in patients treated with antibiotics.

the vicinity of certain pathogens. The product of spontaneous C3 hydrolysis, iC3, binds to **factor B** in the blood or extracellular fluid, making factor B susceptible to cleavage by **factor D**. This reaction produces iC3Bb, a soluble form of C3 convertase that then cleaves C3 into C3a and C3b. Although most of the C3b fragments produced are either hydrolyzed by water or become attached to serum proteins, some covalently bond to the pathogen's surface (Figure 8.8). When factor B binds to these C3b fragments and is cleaved by factor D, the complex of C3bBb is formed on the pathogen's surface. This complex is the **C3 convertase of the alternative pathway** (Figure 8.9).

Once some C3 convertase molecules have been assembled, they cleave more C3 and fix more C3b at the pathogen's surface, leading to the assembly of yet more convertase. This process is one of progressive amplification that, from the initial deposition of a few molecules, can rapidly coat the pathogen with C3b. When C3b fragments are bound at high density to a pathogen's surface they form effective ligands for the complement receptors (CR1, for example)

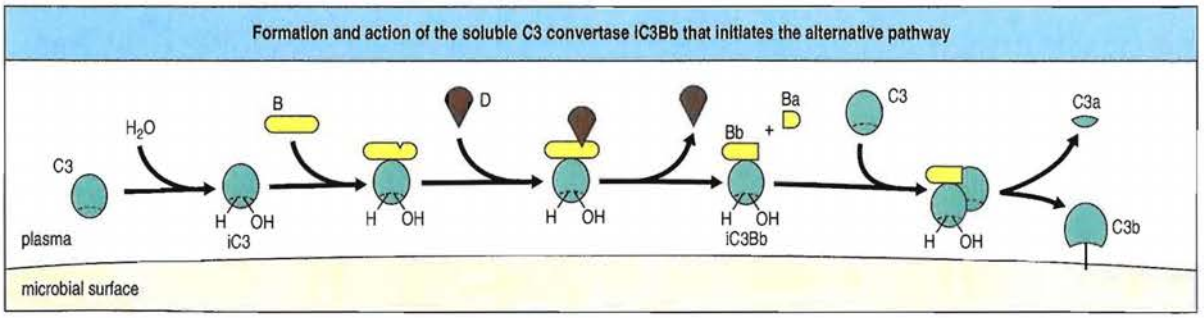


Figure 8.8 Formation and action of the soluble C3 convertase that initiates the alternative pathway of complement activation. In the plasma close to a microbial surface the thioester bond of C3 spontaneously hydrolyzes at low frequency. This activates the C3 which then binds factor B. Cleavage of B by factor D produces a soluble C3 convertase, called iC3Bb, which then activates C3 molecules by cleavage into C3b and C3a. Some of the C3b fragments become covalently attached to the microbial surface.

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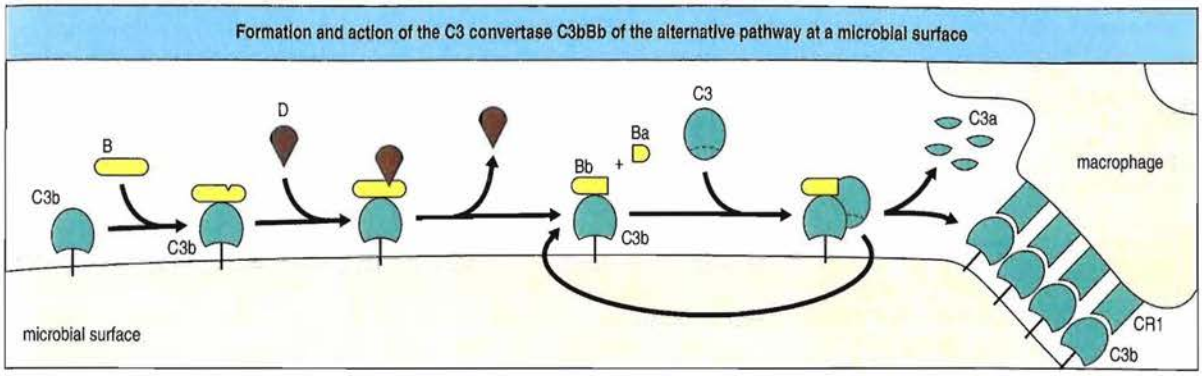


Figure 8.9 Formation and action of the C3 convertase, C3bBb, of the alternative pathway at a microbial surface. Through the action of the soluble C3 convertase, iC3Bb, C3b fragments are bound to the microbial surface (see Figure 8.8). These bind factor B which is then cleaved by factor D to produce C3bBb, the surface-bound convertase of the alternative pathway. This enzyme cleaves C3 to produce further C3b fragments bound to the microbe and small soluble C3a fragments. The C3b fragments can be used either to make more C3 convertase, which amplifies the activation of C3, or to engage the CR1 receptors of a macrophage or neutrophil and promote phagocytosis of the microbe. The small, soluble C3a fragments attract phagocytes to sites of complement fixation.

of macrophages resident in the infected tissue, as described in Section 7-21, p. 212. The covalently coupled C3b fragments thereby target the pathogen for destruction by phagocytosis (see Figure 8.9).

The sequence of complement-activating reactions can also be continued by binding of C3b to existing C3bBb complexes at the pathogen's surface to form the alternative C5 convertase, $C3b_2Bb$, the counterpart of the C5 convertase of the classical pathway C4b2a3b (see Section 7-23, p. 215, and Figure 7.44, p. 216). This enzyme activates C5 and the terminal components of complement (C6–C9), forming pores in the microbial membrane that are sufficient to lyse certain pathogens, notably the *Neisseria* bacteria that cause meningitis and gonorrhea. The activation of C5 also releases C5a, a small soluble peptide that facilitates pathogen destruction by the recruitment of neutrophils into the site of infection. C5a is the most potent of the anaphylatoxins (see Section 7-24, p. 216).

The actions of several proteins that control complement activation ensure that C3b fragments are densely deposited on microbial surfaces but not on the surfaces of human cells. The plasma protein **properdin** (**factor P**) binds to the C3 convertase C3bBb on microbial surfaces and protects it from inhibition by factor H, a plasma protein that dampens down complement reactions. In contrast, initiation of the alternative pathway on the surface of human cells is stopped at an early stage by the human cell-surface proteins CR1, decay-accelerating factor (DAF), and membrane co-factor protein (MCP), as well as by the plasma protein factor H. As described in Section 7-23, p. 215, these control proteins all act to destroy C3 convertase activity by binding to C3b and displacing Bb, and/or by rendering C3b susceptible to cleavage by factor I (Figure 8.10).

Because complement activation limits bacterial infections, some bacteria have evolved mechanisms to evade the actions of complement. Bacteria with an abundance of sialic acid on their surface, such as *Streptococcus pyogenes* and *Staphylococcus aureus*, mimic human cells. Consequently, when C3b becomes bound to their surface it is readily inactivated by factor H. Because antibodies coat the bacterial surface and mask the sialic acids before complement is bound, these bacteria are only resistant to the effect of complement when no specific antibacterial antibody is present.

The combined effects of the reactions that promote and regulate C3 activation is to deposit C3b on the surface of human cells. This mechanism provides a simple and effective way of distinguishing self from nonself, and for guiding mechanisms of death and destruction towards invading pathogens and away from human cells.

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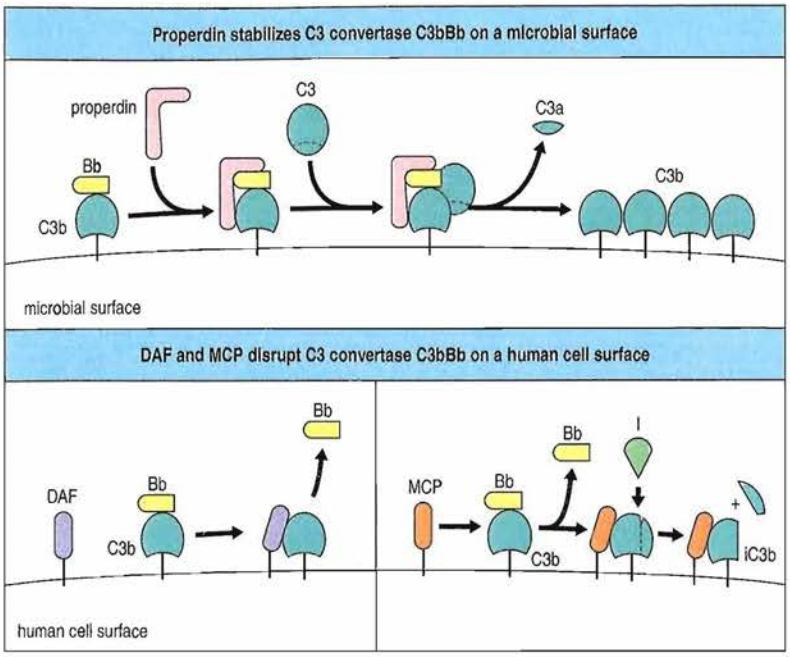


Figure 8.10 Control proteins stabilize the C3 convertase of the alternative pathway on microbial surfaces and destabilize it on human cell surfaces. The soluble protein properdin (factor P) binds to C3bBb and extends its lifetime on the microbial surface. When C3bBb is formed on a human cell surface it is rapidly disrupted by the action of one of two membrane proteins: decay-accelerating factor (DAF) or membrane cofactor protein (MCP). In combination, these regulatory proteins ensure that much complement is fixed to pathogen surfaces and little is fixed to human cell surfaces.

8-4 Several classes of plasma protein limit the spread of infection

In addition to complement, several other types of plasma protein impede the invasion and colonization of human tissues by microorganisms. Damage to blood vessels activates the coagulation system, a cascade of plasma enzymes that forms blood clots, which immobilize microorganisms and prevent them from entering the blood and lymph, as well as reducing the loss of blood and fluid. Platelets are a major component of blood clots and during clot formation they release a variety of highly active substances from their storage granules. These include prostaglandins, hydrolytic enzymes, growth factors, and other mediators that stimulate various cell types to contribute to antimicrobial defense, wound healing, and inflammation. Further mediators, including the vasoactive peptide bradykinin, are produced by the kinin system, a second enzymatic cascade of plasma proteins that is triggered by tissue damage. By causing vasodilation, bradykinin increases the supply of the soluble and cellular materials of innate immunity to the infected site.

Many pathogens use proteases to damage human tissues and human defenses, thereby facilitating invasion and dissemination. In some instances the proteins are made by the pathogen, in others the pathogen hijacks a human protease, for example plasmin, for its own purposes. To counter these mechanisms, human secretions and plasma contain protease inhibitors. Several of the microbicidal peptides of innate immunity are specific inhibitors of microbial proteases. These include the cryptdins secreted by Paneth cells in the gut and the serpins that inactivate serine proteases and regulate the clotting cascade (Figure 8.11, top panel). Most of these inhibitors act by binding irreversibly to the active site of the protease and are specific for a narrow spectrum of proteases.

About 10% of serum proteins are protease inhibitors. Among these are the α_2-macroglobulins, glycoproteins of 180 kDa that circulate as monomers,

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dimers, and trimers and are able to inhibit a broad range of proteases. α_2-Macroglobulins have structural similarities with complement component C3, including the presence of internal thioester bonds. The α_2-macroglobulin molecule lures a protease with a bait region that it is allowed to cleave. This activates the α_2-macroglobulin, producing two effects: first, the thioester is used to covalently bind the protease to the α_2-macroglobulin; second, the α_2-macroglobulin undergoes a conformational change by which it envelops the protease and prevents it attacking other substrates (Figure 8.11, bottom panel). The resulting complexes of protease and α_2-macroglobulin are rapidly cleared from the circulation by a receptor present on hepatocytes, fibroblasts, and macrophages.

8-5 Phagocytosis by macrophages provides a first line of cellular defense against invading microorganisms

When a pathogen invades a human tissue the first effector cells of the immune system it encounters are the resident macrophages. **Macrophages** are the mature forms of circulating monocytes that have left the blood and taken up residence in the tissues. They are prevalent in the connective tissues, the linings of the gastrointestinal and respiratory tracts, the alveoli of the lungs, and in the liver, where they are known as **Kupffer cells**. Macrophages are long-lived phagocytic cells that participate in both innate and adaptive immunity.

Although macrophages phagocytose bacteria and other microorganisms in a nonspecific fashion, the process is made more efficient by the participation of receptors on the macrophage surface that bind to specific ligands on the microbial surface. Deposition of C3b fragments on the surface of a pathogen, through activation of the alternative pathway of complement, provides ligands for the CR1 complement receptor of macrophages. When C3b is degraded by factor I to iC3b it then becomes a ligand for the macrophage's CR3 and CR4 receptors. The combination of opsonization by complement and phagocytosis by macrophages allows pathogens to be recognized and destroyed from the very beginning of an infection (see Section 7-21, p. 212).

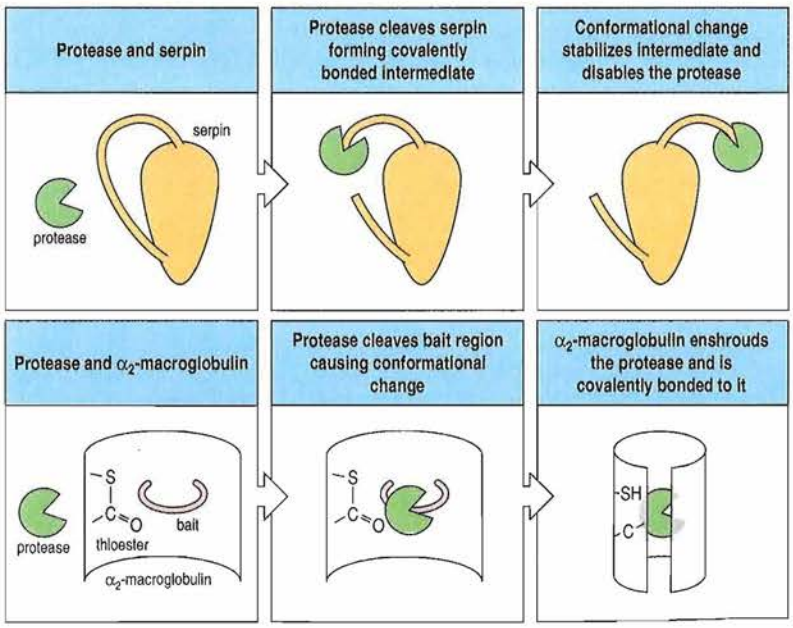


Figure 8.11 Serpins and α_2-macroglobulin inhibit potentially damaging proteases. Microbial invasion and colonization of human tissues is dependent on the actions of microbial proteases. In response, human plasma is loaded with protease inhibitors. One type of protease inhibitor, as exemplified by the serpins, permanently inactivates the protease by covalently binding into its active site (upper panels). The α_2-macroglobulins take a different approach: they first trap the protease with a 'bait' region and when the protease cleaves the bait the α_2-macroglobulin binds it covalently through activation of its thioester group and enshrouds the protease so that it cannot access other protein substrates, even though it is still active.

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Phagocytosis of pathogens by macrophages is also aided by receptors of innate immunity that bind directly to components of the microbial surface that are characteristic of pathogens but absent from human cells. The CR3 and CR4 complement receptors recognize several microbial cell-surface molecules, including bacterial lipopolysaccharide (LPS), the lipophosphoglycan of *Leishmania*, the filamentous hemagglutinin of *Bordetella*, and cell-surface structures on yeasts such as *Candida* and *Histoplasma*. Several other phagocytic receptors are carbohydrate-binding proteins—lectins—that bind to particular combinations or configuration of sugars that are not a feature of human cells. The mannose receptor is a calcium-dependent (C-type) lectin that binds to certain bacteria and viruses, including HIV. The scavenger receptors are a heterogenous group of receptors with a preference for molecules rich in sialic acid (Figure 8.12).

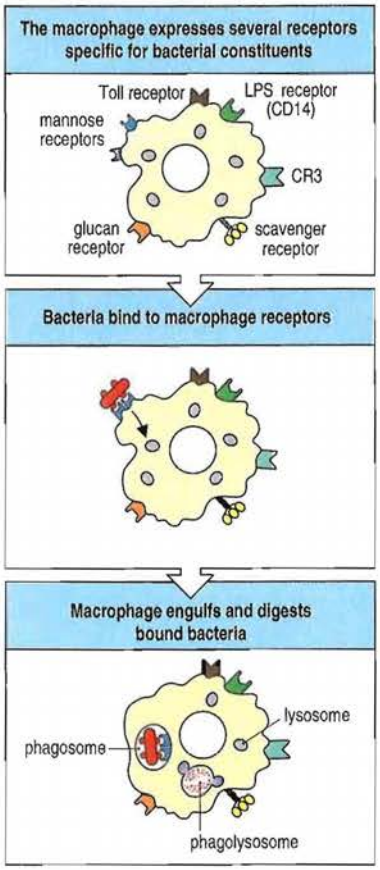


Figure 8.12 Macrophages have several types of surface receptor that bind to constituents of microbial surfaces and promote phagocytosis. Many of the receptors are lectins that bind carbohydrates that are characteristic of microorganisms.

8-6 Receptors that detect microbial products signal macrophage activation

In addition to receptors that facilitate the phagocytosis of microorganisms, macrophages also have receptors or sensors for pathogen components that signal the macrophage to make and secrete cytokines that recruit other cells to defend the infected tissue. In this category are the Toll-like receptors (TLR), which in humans comprise a family of 10 receptors with specificities for different microbial products (Figure 8.13). The best studied of these receptors is TLR-4, for which one ligand is LPS, the major cell-surface component of Gram-negative bacteria and the endotoxin that is most commonly responsible for **septic shock,** the most severe outcome of **sepsis**, or infection of the bloodstream. TLR-4 does not bind LPS directly. When LPS is released from bacterial surfaces, as will occur on phagocytosis, it is bound by the LPS receptor CD14 on the macrophage surface. Alternatively, LPS picked up in the plasma by the soluble LPS-binding protein is delivered to CD14 at the macrophage surface. The TLR-4 dimer and another protein called MD-2 then associate with the complex of CD14 and LPS to generate intracellular signals via the cytoplasmic signaling domain of TLR-4. Among the cytokines released by the macrophage in response to these signals is TNF-α, which is the cytokine directly responsible for causing septic shock.

Septic shock causes the death of more than 100,000 people in the United States each year, with Gram-negative bacteria being the most common cause. The role of TLR-4 in combating infections with Gram-negative bacteria is shown by a recently discovered association of a TLR-4 variant with septic shock. This variant has glycine at position 299 in the amino-acid sequence instead of the asparagine found in the common form of TLR-4, and is overrepresented in patients with septic shock. Indeed, the only person known to be homozygous for this TLR-4 allotype died in adolescence of infection of the kidneys caused by the commensal bacterium *E. coli*.

The TLR-4 receptor also responds to chemically or structurally related ligands present on other pathogens. Other members of the TLR family sense different microbial products from the TLR-4 ligands; in each case, they are constituents of common groups of pathogens and are not found in human cells. Double-stranded RNA, sensed by TLR-3, is an intermediate nucleic acid present in many viral infections, while the unmethylated CpG nucleotide motifs detected by TLR-9 are abundant in bacterial genomes but rare in the human genome. Some of the TLRs form homodimers exclusively, whereas others form heterodimers. Such combinations of different chains potentially increase the diversity of receptor specificities. The only Toll-like receptor that is known to bind directly to the product it detects is TLR-5, which binds to bacterial flagellin. For the other members of the family, including TLR-4, it is uncertain whether direct contact is made with a microbial product.

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Recognition of microbial products through Toll-like receptors			
Receptor	**Ligands**	**Microorganisms recognized**	**Cell carrying receptor**
TLR-4 homodimer	Lipopolysaccharide	Gram-negative bacteria	Macrophage
TLR-9 homodimer	DNA with unmethylated CpG motifs	Bacteria	
TLR-3 homodimer	Double-stranded DNA	Viral RNAs	
TLR-5 homodimer	Flagellin	Gram-negative bacteria	Intestinal epithelium
TLR-7 homodimer	Imidazoquinolines (antiviral drugs)		
TLR-2 (TLR-1,-6) heterodimers	Peptidoglycan, lipoarabinomannan, porins, bacterial lipoprotein, bacterial lipopeptide, yeast mannan, glycophosphatidyl-inositol anchors	Gram-positive bacteria Mycobacteria *Neisseria* Yeast Trypanosomes	Macrophage

Figure 8.13 Toll-like receptors recognize microbial constituents. Each of the known Toll-like receptors (TLRs) appears to recognize one or more microbial molecular patterns, but TLR-5 is the only case so far in which a direct interaction with a microbial product, the bacterial protein flagellin, has been demonstrated. TLR-9 is an intracellular receptor. Toll is the name of a receptor in the fruit fly *Drosophila melanogaster* with which the signaling domains of the human Toll-like receptors have structural similarity. Like many of the names given to genes and proteins by fruit fly geneticists Toll is a whimsical name and, in this case, derived from German slang.

The Toll-like receptors all trigger a common pathway of intracellular signaling, which is also shared by the IL-1 receptor and its relatives. It involves an adaptor protein called MyD88 and the interleukin-1 receptor associated kinase (IRAK) complex. Their actions lead to the translocation of the transcription factor nuclear factor κB (NFκB) from the cytoplasm to the nucleus, where it directs the transcription of genes for inflammatory cytokines (Figure 8.14). Patients deficient in IRAK function have impaired signaling through all the Toll-like receptors as well as through receptors for IL-1 and IL-18. These children suffer from recurrent infections with pyogenic bacteria and have generally poor inflammatory responses. However, they do not show any increased susceptibility to other types of pathogen, such as viruses, showing that signaling through Toll-like receptors is not necessary for providing passable protection against many common infections.

8-7 Activation of resident macrophages induces inflammation at sites of infection

On sensing the presence of pathogens through Toll-like and other receptors, macrophages are stimulated to secrete a battery of cytokines and other substances that recruit effector cells, prominently neutrophils, into the infected area. The infiltrating cells cause a state of **inflammation** to develop within the tissue. Inflammation describes the local accumulation of fluid accompanied

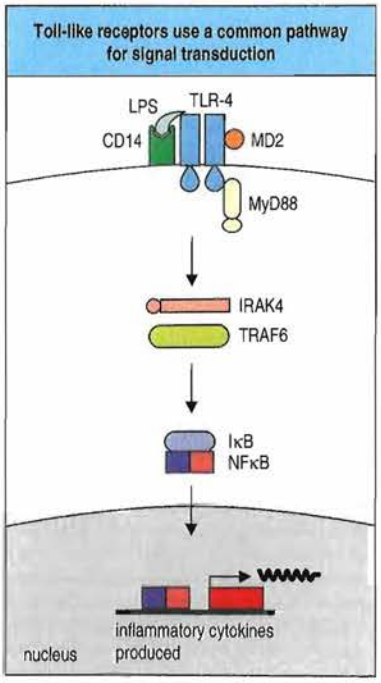


Figure 8.14 Toll receptors use a common pathway of signal transduction. This pathway is also used by IL-1 and IL-18. Common components of the pathway are the adaptor molecule MyD88, the interleukin-1 receptor-associated kinase 4 (IRAK4), the TNF-receptor-associated kinase 6 (TRAF6), the inhibitor of NFκB (IκB) and NFκB. MD2 is a soluble protein that associates with the extracellular domains of TLR-4, but not other TLR family members, and confers sensitivity to LPS. In the absence of a signal, NFκB is bound by IκB, which prevents it from entering the nucleus. In the presence of a signal, kinase activation causes IκB to be phosphorylated, which induces the release of NFκB and its passage to the nucleus where it activates genes encoding inflammatory cytokines.

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by swelling, reddening, and pain. These effects stem from changes induced in the local blood capillaries that lead to an increase in their diameter (a process called dilation), reduction in the rate of blood flow, and increased permeability of the blood vessel wall. The increased supply of blood to the region causes the local redness and heat associated with inflammation. The increased permeability of blood vessels allows the movement of fluid, plasma proteins, and white blood cells from the blood capillaries into the adjoining connective tissues, causing the swelling and pain.

Translocation of NFκB to the macrophage nucleus (see Figure 8.14), initiates transcription of various cytokine genes. Prominent cytokines produced by activated macrophages are **IL-1**, **IL-6**, **CXCL8**, **IL-12**, and **tumor necrosis factor-α** (**TNF-α**). These proinflammatory cytokines have powerful effects that can be localized in the infected tissue or be manifest systemically throughout the body; they also contribute to both the innate and the adaptive immune response (Figure 8.15).

CXCL8, also called IL-8, is one of a large family of around 40 chemoattractant cytokines, or **chemokines** (Figure 8.16). Some chemokines, including CXCL8, attract leukocytes into sites of tissue damage or infection. Others direct the traffic of leukocytes during their development or their recirculation through the tissues of the body. Chemokines are small, structurally similar proteins of

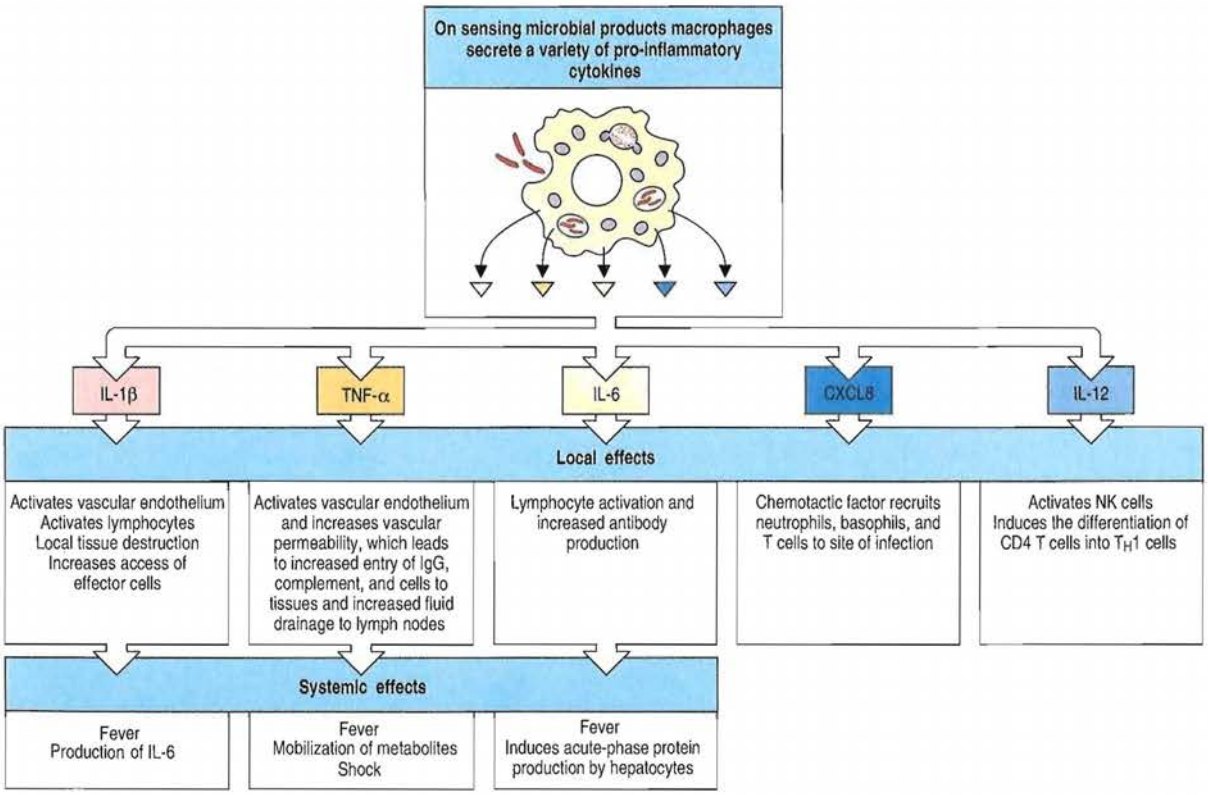


Figure 8.15 Important cytokines secreted by macrophages in response to bacterial products include IL-1, TNF-α, Il-6, CXCL8, and IL-12. TNF-α is an inducer of a local inflammatory response that helps to contain infections. It also has systemic effects, many of which are harmful. The chemokine CXCL8 is also involved in the local inflammatory response, helping to attract neutrophils to the site of infection. IL-1, IL-6, and TNF-α have a critical role in inducing the acute-phase response in the liver and induce fever, which favors effective host defense in various ways. IL-12 activates natural killer (NK) cells and favors the differentiation of CD4 T cells into the T_H1 subset in adaptive immunity.

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around 60–140 amino acids. Two major subfamilies are defined on the basis of pairs of cysteine residues, which are either adjacent (CC) or separated by another amino acid (CXC). Cells are attracted from the blood into infected tissue by following a concentration gradient of chemokine produced by cells

Class	Chemokine	Produced by	Receptors	Cells attracted	Major effects
CXC	CXCL8 (IL-8)	Monocytes Macrophages Fibroblasts Keratinocytes Endothelial cells	CXCR1 CXCR2	Neutrophils Naive T cells	Mobilizes, activates and degranulates neutrophils Angiogenesis
	CXCL7 (PBP, β-TG NAP-2)	Platelets	CXCR2	Neutrophils	Activates neutrophils Clot resorption Angiogenesis
	CXCL1 (GROα) CXCL2 (GROβ) CXCL3 (GROγ)	Monocytes Fibroblasts Endothelium	CXCR2	Neutrophils Naive T cells Fibroblasts	Activates neutrophils Fibroplasia Angiogenesis
	CXCL10 (IP-10)	Keratinocytes Monocytes T cells Fibroblasts Endothelium	CXCR3	Resting T cells NK cells Monocytes	Immunostimulant Antiangiogenic Promotes T_H1 immunity
	CXCL12 (SDF-1)	Stromal cells	CXCR4	Naive T cells Progenitor ($CD34^+$) B cells	B-cell development Lymphocyte homing Competes with HIV-1
	CXCL13 (BLC)	Stromal cells	CXCR5	B cells	Lymphocyte homing
CC	CCL3 (MIP-1α)	Monocytes T cells Mast cells Fibroblasts	CCR1, 3, 5	Monocytes NK and T cells Basophils Dendritic cells	Competes with HIV-1 Antiviral defense Promotes T_H1 immunity
	CCL4 (MIP-1β)	Monocytes Macrophages Neutrophils Endothelium	CCR1, 3, 5	Monocytes NK and T cells Dendritic cells	Competes with HIV-1
	CCL2 (MCP-1)	Monocytes Macrophages Fibroblasts Keratinocytes	CCR2B	Monocytes NK and T cells Basophils Dendritic cells	Activates macrophages Basophil histamine release Promotes T_H2 immunity
	CCL5 (RANTES)	T cells Endothelium Platelets	CCR1, 3, 5	Monocytes NK and T cells Basophils Eosinophils Dendritic cells	Degranulates basophils Activates T cells Chronic inflammation
	CCL11 (Eotaxin)	Endothelium Monocytes Epithelium T cells	CCR3	Eosinophils Monocytes T cells	Role in allergy
	CCL18 (DC-CK)	Dendritic cells	?	Naive T cells	Role in activating naive T cells
C	XCL1 (Lymphotactin)	CD8>CD4 T cells	?	Thymocytes Dendritic cells NK cells	Lymphocyte trafficking and development
CXXXC (CX_3C)	CX3CL1 (Fractalkine)	Monocytes Endothelium Microglial cells	CX_3CR1	Monocytes T cells	Leukocyte–endothelial adhesion Brain inflammation

Figure 8.16 Properties of selected chemokines. Chemokines fall mainly into two related but distinct groups. The CC chemokines, which in humans are all encoded in one region of chromosome 4, have two adjacent cysteine residues, whereas the CXC chemokines, which are found in a cluster on chromosome 17, have an amino-acid residue between the equivalent two cysteines. A C chemokine with only one cysteine at this location, and fractalkine, a CX_3C chemokine, are encoded elsewhere in the genome. Each chemokine interacts with one or more receptors, and affects one or more types of cell.

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within the infected site. Chemokines interact with their target cells by binding to specific cell-surface receptors, which in humans comprise a family of 16 seven-span transmembrane proteins that signal through associated GTP-binding proteins (Figure 8.17).

The principal function of CXCL8, a CXC chemokine (see Figure 8.16), is to recruit neutrophils from the blood into infected areas. CXCL8, for example, is bound by chemokine receptors CXCR1 and CXCR2. Interaction with a chemokine has two distinct effects on the targeted leukocyte: first, the cell's adhesive properties are altered so that it can leave the blood and enter tissue; second, its movement is guided towards the center of infection along a gradient of the chemokine, present both in solution and attached to the extracellular matrix and endothelial cell surfaces. Chemokines have structural and functional similarity to the defensins: some chemokines have antimicrobial activity while some defensins have chemoattractant properties and bind to chemokine receptors.

The cytokine IL-12 serves to activate natural killer (NK) cells, lymphocytes of the innate immune response that enter infected sites soon after infection. Cytokines IL-1 and TNF-α facilitate entry of neutrophils, NK cells, and other effectors into infected areas by inducing changes in the endothelial cells of the local blood vessels. Other effector molecules released by macrophages are plasminogen activator, phospholipase, and other enzymes, prostaglandins, oxygen radicals, peroxides, nitric oxide, leukotrienes, and platelet-activating factor (PAF), which all contribute to inflammation and tissue damage. In the course of complement activation, the soluble complement fragments C3a and C5a recruit neutrophils from the blood into infected tissues and stimulate mast cells to degranulate, releasing the inflammatory molecules histamine and TNF-α, among others. Molecules involved in the induction of inflammation are known generally as **inflammatory mediators**. The combined effect of all this activity is to produce a local state of inflammation with its characteristic symptoms.

In response to TNF-α, vascular endothelial cells make platelet-activating factor, which triggers blood clotting and blockage of the local blood vessels. This restricts the leakage of plasma from the blood and prevents pathogens from entering the blood and disseminating infection throughout the body. However, in those instances in which infection does spread to the blood, and endotoxins such as LPS provoke widespread production of TNF-α, the actions that contain local infection so effectively can become catastrophic (Figure 8.18). A systemic bacterial infection of the blood induces macrophages in the liver, spleen, and other sites to release TNF-α, which causes dilation of blood vessels and massive leakage of fluid into tissues throughout the body, leading to a profound state of shock (septic shock). One symptom is widespread blood clotting in capillaries—disseminated intravascular coagulation—which exhausts the supply of clotting proteins. More critically, septic shock frequently leads to failure of vital organs such as the kidneys, liver, heart, and lungs, which are soon compromised by the lack of a normal blood supply. Consequently, there is a high mortality rate for patients suffering septic shock.

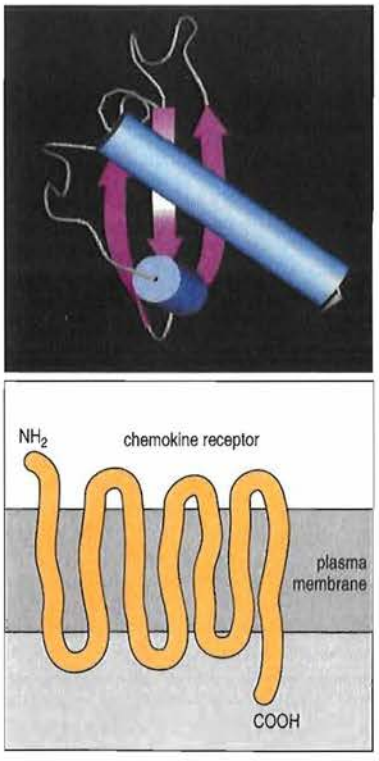


Figure 8.17 Chemokines bind to chemokine receptors that are G-protein-coupled receptors. The structure of the chemokine CXCL8 is shown in the upper panel. The receptors for the chemokines are members of the family of seven-span receptors, which also includes the photoreceptor protein rhodopsin and many other receptors. They have seven transmembrane helices, as depicted in the schematic in the lower panel, and all the family interact with G proteins.

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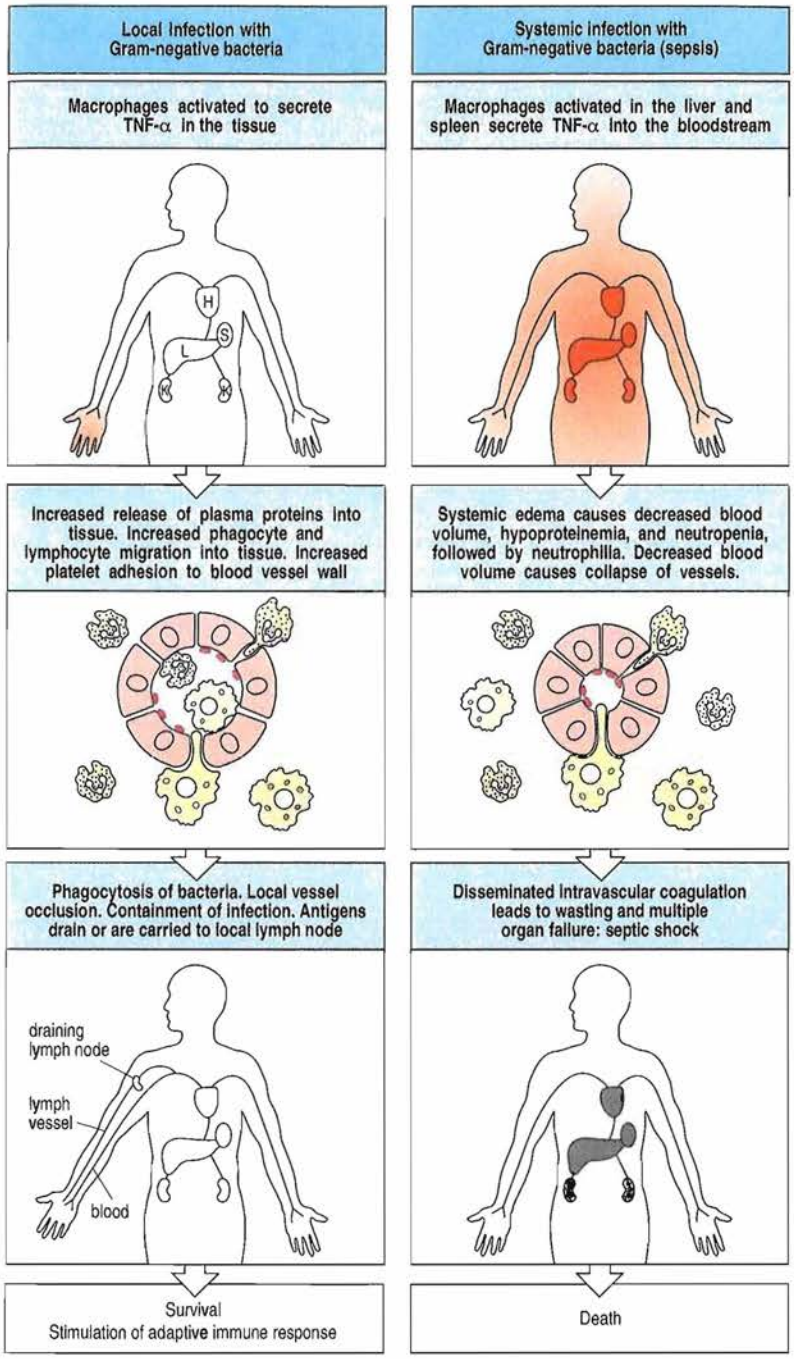


Figure 8.18 TNF-α released by macrophages induces protection at the local level but can lead to catastrophe when released systemically. The panels on the left describe the causes and consequences of the release of TNF-α within a local area of infection. In contrast, the panels on the right describe the causes and consequences of the release of TNF-α throughout the body. The initial effects of TNF-α are on the endothelium of blood vessels, especially venules. It causes increased blood flow, vascular permeability, and endothelial adhesiveness for white blood cells and platelets. These events cause the blood in the venules to clot, preventing the spread of infection and directing extracellular fluid to the lymphatics and lymph nodes, where the adaptive immune response is activated. When an infection develops in the blood, the systemic release of TNF-α and the effect it has on the venules in all tissues simultaneously induce a state of shock that can lead to organ failure and death. H, heart; K, kidney; L, liver; S, spleen.

8-8 Neutrophils are dedicated phagocytes that are summoned to sites of infection

By engulfing and killing microorganisms, phagocytic cells are the principal means by which the immune system destroys invading pathogens. The two kinds of phagocyte that serve this purpose—the macrophage and the neutrophil—have distinct and complementary properties. Macrophages are

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long-lived, they reside in the tissues, work from the very beginning of infection, raise the alarm, and have functions other than phagocytosis. **Neutrophils**, on the other hand, are short-lived dedicated killers that circulate in the blood awaiting a call from a macrophage to enter infected tissue.

Neutrophils are a type of granulocyte, having numerous granules in the cytoplasm, and are also known as **polymorphonuclear leukocytes** because of the variable and irregular shapes of their nuclei (see Figure 1.9, p. 10). Neutrophils were historically called microphages because of their smaller size compared with macrophages. What they lack in size they more than make up for in number: they are the most abundant white blood cells, a healthy adult having some 50 billion in circulation at any time. This abundance combined with the short life span of the circulating neutrophil—less than two days—means that around 60% of the hematopoietic activity of the bone marrow is devoted to neutrophil production. Mature neutrophils are kept in the bone marrow for about five days before being released into the circulation; this constitutes a large reserve of neutrophils that can be called on at times of infection.

Neutrophils are excluded from healthy tissue, but at infected sites the release of inflammatory mediators attracts neutrophils to leave the blood and enter the infected area in large numbers, where they soon become the dominant phagocytic cell. Every day, some 3×10^9 neutrophils enter the tissues of the mouth and throat, the most contaminated sites in the body. The arrival of neutrophils is the first of a series of reactions, called the **inflammatory response**, by which cells and molecules of innate immunity are recruited into sites of wounding or infection. Although neutrophils are specialized for working under the anaerobic conditions that prevail in damaged tissues, they still die within a few hours after entry. In doing so, they form the creamy **pus** that characteristically develops at infected wounds and other sites of infection. This is why extracellular bacteria such as *S. aureus*, which are responsible for the superficial infections and abscesses that neutrophils tackle in large numbers, are known as pus-forming or **pyogenic** bacteria.

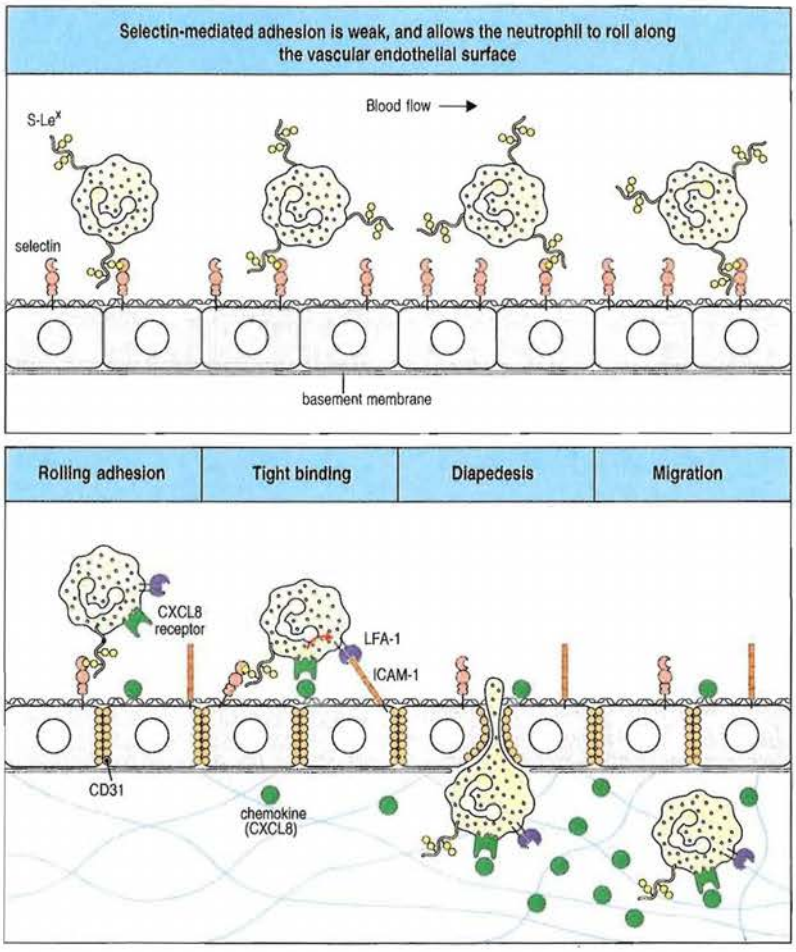
8-9 The homing of neutrophils to infected tissues is induced by inflammatory mediators

During infection, inflammatory mediators cause changes in the adhesion molecules expressed by the vascular endothelium of blood capillaries in and around the infected site. The vascular endothelium is then said to be activated. Inflammatory mediators also induce the expression of complementary adhesion molecules on circulating neutrophils. These changes enable neutrophils in the blood to bind to activated vascular endothelium within an infected site and to squeeze between endothelial cells and enter the infected tissue. The release of inflammatory mediators by the increasing numbers of neutrophils steadily increases the inflammation within the infected tissue.

Neutrophils have receptors for inflammatory mediators on their surfaces: examples are receptors for C5a, cleaved from C5 during complement activation, and for the CXCL8 secreted by activated macrophages. In addition, neutrophils have a receptor for chemoattractants that are specifically produced by bacterial infections. This receptor is specific for peptides containing N-formylmethionine, a component of bacterial but not of human proteins. Binding of ligands to surface receptors induces the changes in neutrophil adhesion molecules.

The process by which neutrophils migrate out of blood capillaries and into tissues is called **extravasation** and it occurs in four steps. The first is the interaction between circulating leukocytes and blood vessel walls that slows down

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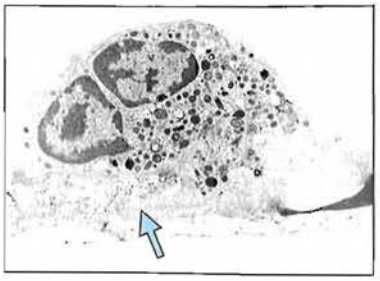


Figure 8.19 Neutrophils are directed to sites of infection through interactions between adhesion molecules. Inflammatory mediators and cytokines produced as the result of infection induce the expression of selectin on vascular endothelium, which enables it to bind leukocytes. The top panel shows the rolling interaction of a neutrophil with vascular endothelium due to transient interactions between selectin on the endothelium and sialyl-Lewis^x (s-Le^x) on the leukocyte. The bottom panel shows the conversion of rolling adhesion into tight binding and subsequent migration of the leukocyte into the infected tissue. The four stages of extravasation are shown. Rolling adhesion is converted into tight binding by interactions between integrins on the leukocyte (LFA-1 is shown here) and adhesion moleules on the endothelium (ICAM-1). Expression of these adhesion molecules is also induced by cytokines. A strong interaction is induced by the presence of chemoattractant cytokines (the chemokine CXCL8 is shown here) that have their source at the site of infection. They are held on proteoglycans of the extracellular matrix and cell surface to form a gradient along which the leukocyte can travel. Under the guidance of these chemokines, the neutrophil squeezes between the endothelial cells and penetrates the connective tissue (diapedesis). It then migrates to the center of infection along the CXCL8 gradient. The electron micrograph shows a neutrophil that has just started to migrate between adjacent endothelial cells but has yet to break through the basement membrane, which is at the bottom of the photograph. The blue arrow points to the pseudopod that the neutrophil is inserting between the endothelial cells. The dark mass in the bottom right-hand corner is an erythrocyte that has become trapped under the neutrophil. Photograph (× 5500) courtesy of I. Bird and J. Spragg.

the leukocytes. This interaction is mediated by selectins, adhesion molecules that bind to particular types of carbohydrate (see Figure 6.4, p. 149). In healthy tissue, vascular endothelial cells contain granules, known as **Weibel–Palade bodies**, which contain **P-selectin**. On exposure to inflammatory mediators, including leukotriene LTB_4, C5a, and histamine, the P-selectin in the Weibel–Palade bodies is transported to the cell surface. A second selectin, **E-selectin**, is also expressed on the endothelial cell surface a few hours after exposure to LPS or TNF-α. The two selectins bind to the sialyl-Lewis^x carbohydrates of cell-surface glycoproteins on the leukocyte. These reversible interactions allow the neutrophils to adhere to the blood vessel walls and to 'roll' slowly along them by forming new adhesive interactions at the front of the cell while breaking them at the back (Figure 8.19, top panel).

The second step in extravasation depends on interactions between the integrins LFA-1 and CR3 on the neutrophil and adhesion molecules on the endothelium, for example ICAM-1, whose expression is also induced by TNF-α. Under normal conditions, LFA-1 and CR3 interact only weakly with endothelial adhesion molecules, but exposure to the CXCL8 coming from cells in the inflamed tissues, induces conformational changes in the LFA-1 and CR3 on a rolling leukocyte that strengthen their adhesion. As a result, the neutrophil holds tightly to the endothelium and stops rolling (see Figure 8.19, bottom panels).

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In the third step, the neutrophil crosses the blood vessel wall. LFA-1 and CR3 contribute to this movement, as does adhesion involving the immunoglobulin superfamily protein CD31, which is expressed by both neutrophils and endothelial cells at their junctions with one another. The leukocyte squeezes between neighboring endothelial cells, a maneuver known as **diapedesis**, and reaches the basement membrane, a part of the extracellular matrix. It then crosses the basement membrane by secreting proteases that break down the membrane. The fourth and final step in extravasation is movement of the neutrophil toward the center of infection in the tissue. This migration is accomplished on the gradient of CXCL8, which originates within the infected site (see Figure 8.19).

At various stages in their maturation, activation, and performance of effector function, all types of white blood cell leave the blood and home to particular tissues. All these migrations involve mechanisms analogous to those controlling the entry of neutrophils into infected tissue. Cytokines and chemokines induce changes in adhesion molecules on white blood cells and vascular endothelium that determine where and when extravasation occurs.

8-10 Neutrophils are potent killers of pathogens and are themselves programmed to die

Neutrophils phagocytose microorganisms by mechanisms similar to those used by macrophages. Neutrophils express both Fc receptors and complement receptors that facilitate the phagocytosis of pathogens opsonized with complement in the innate response, and with antibody and complement once specific antibody is available (Figure 8.20). The range of particulate material that neutrophils engulf is greater than that tackled by macrophages, as is the diversity of the microbicidal substances stored in their three types of granules. Because mature neutrophils are programmed to die young, they devote more of their resources to the storage and delivery of antimicrobial weaponry than the longer-living macrophage.

Almost immediately after a pathogen is engulfed by a neutrophil, a battery of degradative enzymes and other toxic substances is brought to bear upon it. Phagosomes containing recently captured microorganisms are fused with the preformed neutrophil granules (which are modified lysosomes). These contain hydrolytic degradative enzymes, NADPH-dependent oxidases, and antimicrobial peptides such as the α-defensins (Figure 8.21). In the resulting

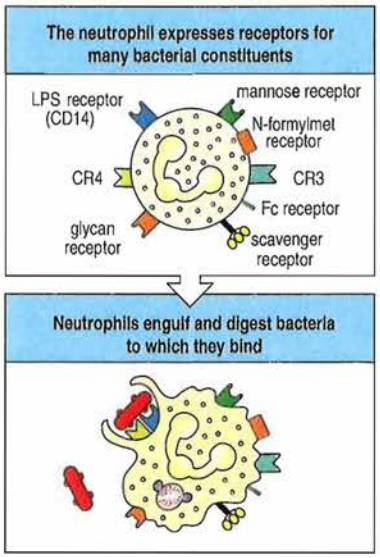


Figure 8.20 Bacteria binding to neutrophil receptors induce phagocytosis and microbial killing. The figure illustrates this type of mechanism for two such receptors, CD14 and CR4, which are specific for bacterial lipopolysaccharide (LPS). Bacteria binding to these receptors stimulate the phagocytosis and degradation of the bacterium.

Class of mechanism	Specific products
Acidification	pH=~3.5 – 4.0, bacteriostatic or bactericidal
Toxic oxygen-derived products	Superoxide (O_2^-), hydrogen peroxide (H_2O_2), singlet oxygen ($^1O_2^*$), hydroxyl radical (OH^*), hypohalite (OCl)
Toxic nitrogen oxides	Nitric oxide (NO)
Antimicrobial peptides	Defensins and cationic proteins
Enzymes	NAPDH-dependent oxidases: generate toxic oxygen derivatives Lysozyme: dissolves cell walls of some Gram-positive bacteria Acid hydrolases: further digest bacteria
Competitors	Lactoferrin (binds Fe) and vitamin B_{12}-binding protein

Figure 8.21 Bactericidal agents produced or released by phagocytic cells on the ingestion of microorganisms. Most of these agents are present in both macrophages and neutrophils. Some of them are toxic; others, such as lactoferrin, work by binding essential nutrients and preventing their uptake by bacteria.

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phagolysosome, the NADPH-dependent oxidases generate toxic oxygen radicals and hydrogen peroxide, the latter being quickly converted into hypochlorous acid. Activated phagocytes also produce nitric oxide (NO), generated from arginine and oxygen by the inducible enzyme nitric oxide synthase (iNOS). NO reacts with oxygen radicals within the phagolysosome to produce highly toxic peroxynitrite.

This general oxidative attack on ingested microorganisms is accompanied by a transient increase in oxygen consumption called the **respiratory burst**. The combination of toxic oxygen metabolites, proteases, phospholipases, lysozyme, and antimicrobial peptides is able to kill both Gram-positive and Gram-negative bacteria, fungi, and even some of the enveloped viruses. The mature neutrophil cannot replenish its granule contents, so once they are used up the neutrophil dies by apoptosis and is ultimately phagocytosed by a macrophage. The dependence of the body's defenses upon neutrophils is seen from the miserable effects of their absence. Patients with neutrophil deficiencies suffer recurrent infections, often by the bacteria and fungi that form part of the normal flora of healthy people.

The toxic oxygen species produced by activated neutrophils can diffuse out of the cell and damage host cells. To limit the damage, the respiratory burst is also accompanied by the synthesis of enzymes that inactivate these potent small molecules: superoxide dismutase converts superoxide to hydrogen peroxide, and catalase degrades hydrogen peroxide to water and oxygen.

In some circumstances the contents of phagocyte lysosomes and granules are released to the outside of the cell. This enables neutrophils to attack antibody-coated pathogens that are too big for them to ingest, such as parasitic worms. The phagocyte adapts to this situation by secreting the contents of its granules onto the surface of the worm at the region of contact. This secretory reaction can also be provoked by contact with host cells, and phagocyte activation can thus cause extensive tissue damage during the course of an infection.

8-11 Inflammatory cytokines raise body temperature and activate hepatocytes to make the acute-phase response

A systemic effect of the inflammatory cytokines IL-1, IL-6, and TNF-α is to cause the rise in body temperature called **fever**. The cytokines act on temperature-control sites in the hypothalamus, and on muscle and fat cells, altering energy mobilization to generate heat (Figure 8.22). In this context,

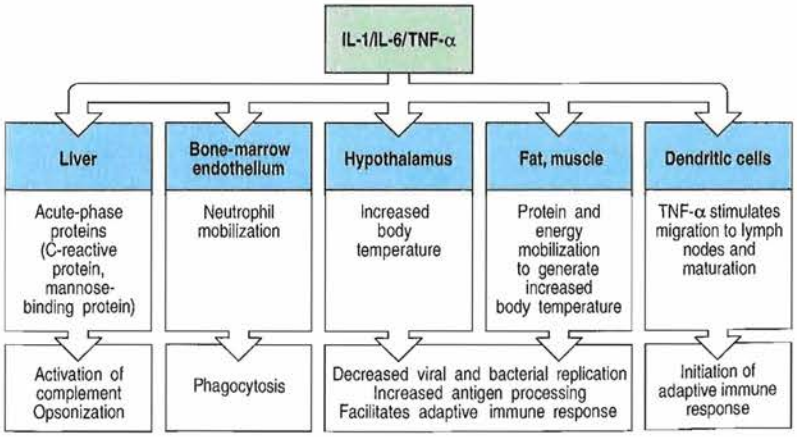


Figure 8.22 The macrophage-produced cytokines TNF-α, IL-1, and IL-6 have a spectrum of biological activity that helps to coordinate the body's response to infection.

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such molecules are called 'endogenous pyrogens' to distinguish them from the 'exogenous' products of pathogens that also raise the body's temperature. On balance, a raised body temperature helps the immune system fight infection, because most bacterial and viral pathogens grow better at temperatures lower than that of the human body, and adaptive immunity becomes more potent at higher temperatures. At elevated temperatures, bacterial and viral replication is decreased, whereas processing of antigen is enhanced. In addition, human cells become more resistant to the deleterious effects of TNF-α when experiencing fever.

A further systemic effect of TNF-α, IL-1, and IL-6 is to change the spectrum of soluble plasma proteins secreted by hepatocytes in the liver, thus producing the **acute-phase response**. Those proteins whose synthesis and secretion is increased during the acute-phase response are called **acute-phase proteins** (Figure 8.23). Two of the acute-phase proteins—C-reactive protein and mannose-binding lectin—enhance the fixation of complement at pathogen surfaces. **C-reactive protein** is a pentamer of identical subunits and a member of the **pentraxin** family of proteins. C-reactive protein binds to the phosphorylcholine component of lipopolysaccharides in bacterial and fungal cell walls, but not to the phosphorylcholine present in the phospholipids of human cell membranes. In binding to bacteria, C-reactive protein acts as an opsonin, which can then bind C1q, initiating the classical pathway of complement fixation in the absence of specific antibody. The interaction of C-reactive protein with C1q involves the stalks of the C1q molecule, whereas the interaction of antibodies with C1q involves the globular heads (see Figure 7.31, p. 208). Despite these differences in the initial binding mechanism, the same sequence of complement reactions occurs when either C-reactive protein or antibody interacts with a pathogen.

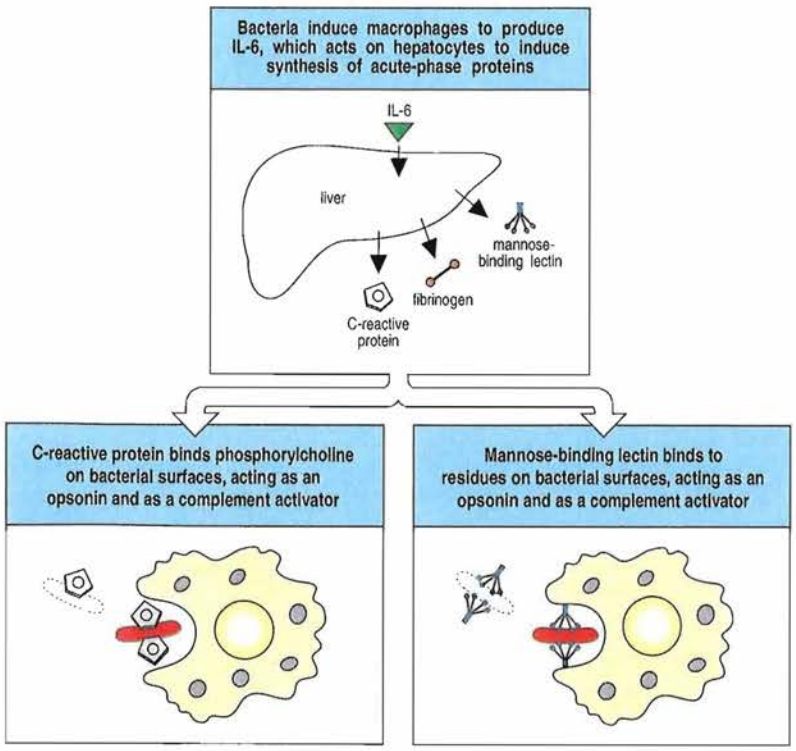


Figure 8.23 The acute-phase response increases the supply of the recognition molecules of innate immunity. Acute-phase proteins are produced by liver cells in response to the cytokines released by phagocytes in the presence of bacteria. In humans they include C-reactive protein, fibrinogen, and mannose-binding lectin. Both C-reactive protein and mannose-binding lectin bind to structural features of bacterial cell surfaces that are not found on human cells. On binding to bacteria, they act as opsonins and also activate complement, facilitating phagocytosis and also direct lysis (dashed lines) of the bacteria.

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Step in pathway	Protein serving function in pathway			Relationship
	Alternative	Lectin	Classical	
Initiation	D	MBL-associated serine protease	C1s	Serine proteases
Covalent binding to cell surface	C3b	C4b		Homologous
C3/C5 convertase	Bb	C2a		Homologous
Control of activation	CR1 H	CR1 C4bp		Identical Homologous
Opsonization	C3b			Identical
Initiation of membrane-attack complex formation	C5b			Identical
Local inflammation	C5a, C3a			Identical

Figure 8.24 There are close structural relationships between components of the alternative, lectin-mediated, and classical pathways of complement activation. Although there are many different complement components they are built from a small number of structural modules. C3, C4, and C5 form one set of related components; C6–C9 form another. A third family comprises the serine proteases, which include factor D of the alternative pathway, C1r and C1s of the classical pathway, and the serine protease associated with the mannose-binding lectin (MBL). Factor B of the alternative pathway and C2 of the classical pathway are highly homologous. The major divergence between the three pathways is in their initiation. The antibodies that initiate the classical pathway, the MBL that initiates the lectin pathway, and the spontaneous hydrolysis of C3 that initiates the alternative pathway are distinct molecular mechanisms.

The second acute-phase protein that activates the complement system is **mannose-binding lectin** (**MBL**). It binds to mannose-containing carbohydrates of bacteria and yeast and is a calcium-dependent lectin. In its overall structure and domain organization, the MBL molecule is similar to C1q, although there are no obvious similarities in their amino-acid sequences. MBL resembles a bunch of flowers in which the carbohydrate-recognition domains form the flowers. Each flower contains three binding sites and each MBL molecule has five or six flowers, giving MBL either 15 or 18 potential sites for attachment to a pathogen's surface. Even relatively weak individual interactions with a carbohydrate structure can be developed into high-avidity interactions through the use of multipoint attachments. Although some carbohydrates on human cells contain mannose, they do not bind MBL because their geometry does not permit multipoint attachment to MBL.

Like C1q, MBL activates a proteolytic enzyme complex (MBL-associated serine protease or MASP) that cleaves C4 and C2 and thus initiates complement activation. This pathway is known as the lectin pathway of complement activation. MBL also serves as an opsonin that facilitates the uptake of bacteria by monocytes in the blood. These cells do not express the macrophage mannose receptor but have receptors that can bind to MBL molecules coating a bacterial surface. MBL is a member of a protein family called the **collectins**; the family also includes the pulmonary surfactant proteins A and D (SP-A and SP-D), which work in the lungs to opsonize pathogens such as *Pneumocystis carinii*.

In the absence of infection, C-reactive protein and MBL are present at low levels in plasma; their levels increase during the acute-phase response. Both proteins bind to structures that are commonly found on pathogens but not on human cells, and initiate complement activation and fixation by a pathway that is almost identical to the classical pathway used by antibodies. Such comparisons reveal how the antibodies of the adaptive immune response have a role analogous to that of C-reactive protein and MBL in innate immunity and serve to expand the range of pathogen-recognition molecules. Furthermore, nearly all of the complement components used in the classical and lectin pathways are structurally and functionally related to components of the alternative pathway, which was probably the first sequence of complement reactions to evolve (Figure 8.24).

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Alleles encoding nonfunctional variants of MBL are present at frequencies greater than 10% in human populations. Consequently, deficiency of MBL is common and causes increased susceptibility to infection. Individuals who carry two variant alleles are more likely to develop severe meningitis caused by *Neisseria meningitidis*, a bacterium that is carried as a harmless commensal by about 1% of the population. Similar susceptibility is observed in people who are deficient for a terminal complement component, showing that complement-mediated killing of the bacteria is the mechanism by which healthy carriers keep their *N. meningitidis* in order.

8-12 Type I interferons inhibit viral replication and activate host defenses

When a human cell becomes infected with a virus it responds by making cytokines called **type I interferons** or simply **interferon**. These comprise a quite different family of proteins from the gamma interferon (IFN-γ) that is secreted by inflammatory effector lymphocytes (NK cells, CD8 T cells, and CD4 $T_H1$cells; see Sections 8-13 and 8-19), and which is called type II interferon. The immediate effects of type I interferon are to interfere with viral replication by the infected cell, and to signal neighboring uninfected cells that they too should prepare for a viral infection. Further effects of type I interferon are to alert cells of the immune system that infection is about, and to make virus-infected cells more vulnerable to attack by killer lymphocytes. As almost all types of human cell are susceptible to viral infections, virtually all cells are equipped to make type I interferon and its cell-surface receptor. The receptor is always present on cell surfaces, ready to bind interferon newly made in response to infection. Although type I interferon is barely detectable in the blood of healthy people, upon infection it becomes abundant.

There are many different forms, or isotypes, of type I interferon. Humans have a single form of **interferon-β** (**IFN-β**), multiple forms of **interferon-α** (**IFN-α**) and several additional isotypes: IFN-δ, -κ, -λ, -τ and -ω. The isotypes have a similar structure, bind to the same cell-surface receptor, and are specified by linked genes on human chromosome 9.

The induction of type I interferon synthesis is triggered by intracellular events that follow viral infection or ligand binding to a cell-surface receptor, for example double-stranded RNA binding to TLR-3. Double-stranded RNA, a type of nucleic acid not found in healthy human cells, is a component of some viral genomes, and an intermediary nucleic acid in viral life cycles. Infection or ligand binding is the trigger that leads to the phosphorylation of a cytoplasmic protein called interferon-response factor 3 (IRF3), which dimerizes and enters the nucleus to initiate transcription of the IFN-β gene, which is also dependent on the transcription factors NFκB and AP-1. Once IFN-β is secreted it acts in an autocrine fashion, binding to receptors on the same cell that made it, or in paracrine fashion, by binding to receptors on uninfected cells nearby (Figure 8.25).

When interferon binds to its receptor, the Jak1 and Tyk2 kinases associated with the receptor initiate intracellular reactions that change the expression of a variety of human genes, a process called the **interferon response** (Figure 8.26). Among the cellular proteins induced by interferon are some that interfere directly with viral genome replication. An example is the enzyme oligoadenylate synthetase, which polymerizes ATP by 2′–5′ linkages rather than the 3′–5′ linkages normally present in human nucleic acids. These unusual oligomers activate an endoribonuclease that degrades viral RNA. Also activated by IFN-α and IFN-β is a serine/threonine protein kinase (PI kinase) that phosphorylates the protein synthesis initiation factor eIF-2, thereby preventing viral protein synthesis and the production of new infectious virions.

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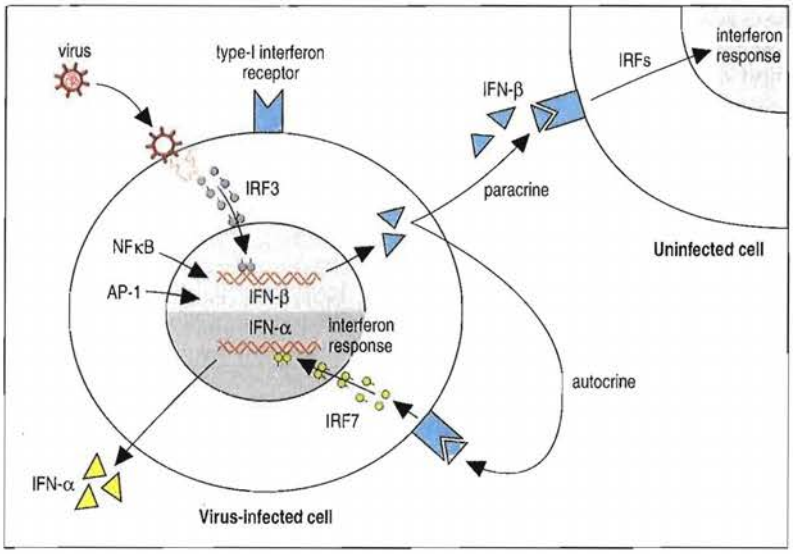


Figure 8.25 Virus-infected cells are stimulated to produce type I interferons. The cell on the left is infected with a virus that triggers signals that lead to the phosphorylation, dimerization and passage to the nucleus of the transcription factor interferon-response factor 3 (IRF3). Transcription factors NFκB and AP-1 are also mobilized and coordinate with IRF3 to turn on transcription of the interferon (IFN)-β gene. These events are depicted in the upper half of the cell. Secreted IFN-β binds to the interferon receptor on the infected cell surface, acting in autocrine fashion to mobilize other interferon-response factors and change patterns of gene expression to give the interferon response. These events are depicted in the lower half of the cell, being exemplified by IRF7 turning on transcription of the IFN-α gene, which it does without the need for AP-1 or NFκB. Secreted IFN-β will also bind to the interferon receptor expressed by nearby cells that are not infected by the virus, acting in paracrine fashion to induce the interferon response that helps these cells to resist infection.

Several of the interferon-induced proteins are transcription factors similar to IRF3, the only one of the group that is made constitutively. The other interferon-response factors are instrumental in turning on the transcription of many different genes, including those for interferons other than IFN-β. Interferon-response factor 7 (IRF7) initiates the transcription of IFN-α, which does not require the participation of NFκB and AP-1. In this manner, a positive feedback loop develops, in which a small amount of interferon serves to increase both the size and range of future production.

As well as interfering with viral replication, interferon also induces cellular changes that make the infected cell more likely to be attacked by killer lymphocytes. NK cells are lymphocytes of innate immunity that provide defense against viral infections by secreting cytokines and killing infected cells. When IFN-α or IFN-β bind to the interferon receptors on circulating NK cells these become activated and drawn into infected tissues, where they attack virus-infected cells. Interferon also causes changes in the cell-surface molecules of infected cells that make them more visible to cytotoxic CD8 T cells of the adaptive immune response (see Figure 8.26): it increases the transcription of MHC class I genes and the TAP peptide transporter proteins (see Section 3-9, p. 78), which together increase the overall abundance of MHC class I molecules at the infected cell's surface. Interferon also favors production of the LMP2 and LMP7 proteasome subunits, which by replacing other forms of

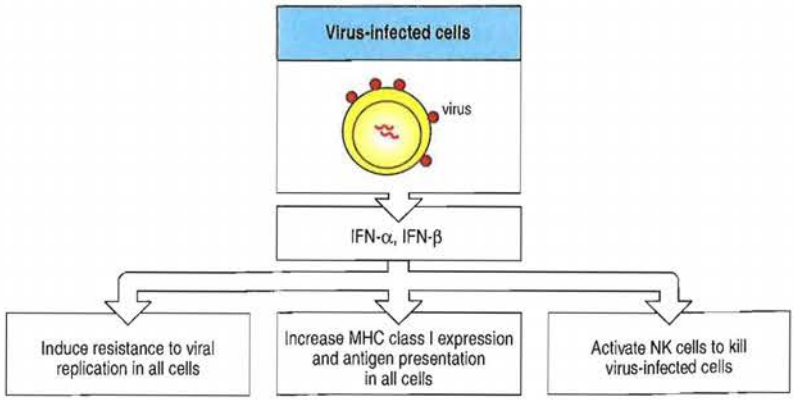


Figure 8.26 Major functions of the type I interferons. The interferons-α and -β (IFN-α and IFN-β) have three major functions. First, they induce resistance to viral replication by activating cellular genes that destroy viral mRNA and inhibit the translation of viral proteins. Second, they induce MHC class I expression in most cells of the body, thus increasing the level of antigen presentation to CD8 cytotoxic T cells by infected cells, and the resistance of uninfected cells to NK cells. Third, they activate NK cells to kill virus-infected cells.

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proteasome subunit skew intracellular protein degradation towards the production of peptides that bind to MHC class I molecules (see Section 3-9, p. 78). All these interferon-regulated genes are located in the MHC.

Because of its power to boost the immune response, type I interferon has been explored as a treatment for human disease. It has been found to ameliorate several conditions: infections with hepatitis B or C virus; the degenerative autoimmune disease multiple sclerosis, which affects the central nervous system; and certain leukemias and lymphomas.

Although almost all human cells can secrete type I interferon, specialized cells called **interferon-producing cells** (**IPCs**) or **natural interferon-producing cells** (**NIPCs**) secrete up to 1000-fold more interferon than other cells. These lymphocyte-like cells are present in the blood, making up less than 1% of the total leukocytes, and are distinguished by cytoplasm resembling that of a plasma cell, another cell type engaged in the massive production of secreted protein (Figure 8.27). During an infection, interferon-producing cells congregate in the T-cell areas of draining lymph nodes, after having entered from the blood at high endothelial venules. The interferon-producing cell serves as a mobile and abundant source of interferon, making it available throughout the body. As well as responding to viral infections, interferon-producing cells have TLR-9 receptors for bacterial DNA, which enables them to secrete interferon in the presence of bacteria. The interferon response is, therefore, not limited to viral infections.

The interferon-producing cell resembles the dendritic cell in ways that seem important but are not yet fully understood. Because high concentrations of type I interferon can drive the maturation of dendritic cells, a function of the interferon-producing cells present in the T-cell areas of lymph nodes draining an infected site might be to complete the maturation of dendritic cells arriving at the node in the draining lymph. On the other hand, when interferon-producing cells are cultured with microbial products and inflammatory cytokines (but not type I interferon) they differentiate into cells resembling dendritic cells. The capacity, professional or otherwise, of these **plasmacytoid dendritic cells** (**PDC**) to present antigens to T cells remains to be determined, although they do have much of the necessary molecular equipment.

8-13 NK cells provide an early defense against intracellular infections

In Chapter 6 we saw how cytotoxic CD8 T cells kill virus-infected cells on recognition of virus-derived peptides presented by MHC class I molecules. The circulating lymphocyte population contains a second type of cytotoxic lymphocyte known as the **natural killer cell** (**NK cell**). This cell has many similarities in effector mechanisms to the cytotoxic T lymphocyte. What most clearly distinguishes NK cells from T cells is that the former do not rearrange or express their T-cell receptor genes; neither do NK cells rearrange or express immunoglobulin genes. NK cells represent a third type of lymphocyte that is distinct from B cells and T cells and active in innate immunity.

NK cells are large lymphocytes that circulate in the blood, but unlike circulating B cells and T cells they have a well developed cytoplasm containing cytotoxic granules. When first discovered, NK cells were called 'large granular lymphocytes;' they provide innate immunity against intracellular infections and migrate from the blood into infected tissues in response to inflammatory cytokines. Patients who lack NK cells suffer from persistent viral infections, particularly of herpes viruses, which they cannot clear without help from antiviral drugs, despite making a normal adaptive immune response. These

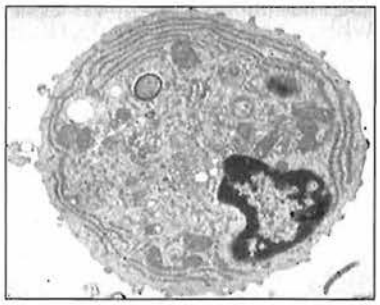


Figure 8.27 Type-I-interferon-producing cell from human peripheral blood. Note the extensive rough endoplasmic reticulum that is similar in appearance to that of a plasma cell and is due to the massive synthesis and secretion of interferon by these cells. Image courtesy of Dr Yong-Jun Liu.

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rare individuals demonstrate the importance of NK cells in managing virus infections and show how the response of NK cells complements that of cytotoxic T cells. NK cells have two types of effector function—cell killing and the secretion of cytokines—that are used in different ways depending on the pathogen.

When NK cells are freshly isolated from blood they can kill certain types of target cell. This base level of cytotoxicity is increased 20–100-fold on exposure to the IFN-α and IFN-β produced in response to viral infection. Type I interferons also induce the proliferation of NK cells. NK cells are also activated by IL-12, which especially targets NK cells, and by TNF-α, both of which are produced by macrophages early in many infections. The actions of these four cytokines produce a wave of activated NK cells during the early part of a virus infection that can either terminate the infection or contain it during the time required to develop cytotoxic CD8 T cells (Figure 8.28).

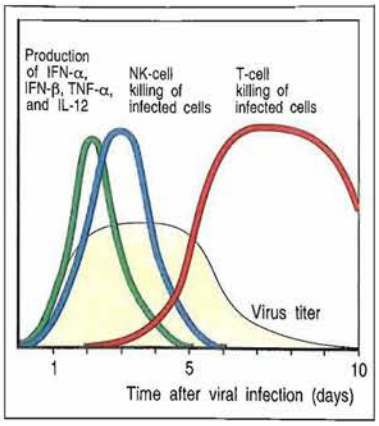


Figure 8.28 NK cells provide an early response to virus infection. The kinetics of the immune response to an experimental virus infection of mice are shown. As a result of infection, a burst of cytokines is secreted, including IFN-α, IFN-β, TNF-α, and IL-12 (green curve). These induce the proliferation and activation of NK cells (blue curve), which are seen as a wave emerging after cytokine production. NK cells control virus replication and the spread of infection while effector CD8 T cells (red curve) are developing. The level of virus (the virus titer) is given by the curve described by the yellow shading.

Stimulation of NK cells with IFN-α and IFN-β favors the development of cytotoxic effector function, whereas stimulation with IL-12 favors the production of cytokines. The principal cytokine released by NK cells is IFN-γ, which activates macrophages (see Section 6-14, p. 169). Macrophage secretion of IL-12 and NK-cell secretion of IFN-γ create a system of positive feedback that increases the activation of both types of cell within an infected tissue. Interactions between NK cells and dendritic cells can also lead to mutual activation or to killing of dendritic cells, events that influence if and when dendritic cells will migrate to secondary lymphoid tissue and initiate the adaptive immune response. In the early stage of an infection, NK cells are the major producers of IFN-γ, which then activates macrophages to secrete cytokines that initiate the T-cell response. When effector T cells are formed and enter the infected site, they become the major source of IFN-γ and of cell-mediated cytotoxicity. With the arrival of effector T cells, NK-cell functions are turned off by IL-10, an inhibitory cytokine made by cytotoxic T cells.

8-14 NK-cell receptors differ in the ligands they bind and the signals they generate

NK cells circulate in the blood in a partially activated state, poised to enter infected tissue when macrophages sound the alarm. Keeping NK cells in this state of readiness for infection, and curbing their potential to attack healthy tissue, is an extensive array of cell-surface receptors, of which some deliver activating signals and others inhibitory signals. The NK-cell receptors fall into two broad structural types: in one the ligand-binding site is an immunoglobulin-like domain and the other has a lectin-like ligand-binding domain similar to the carbohydrate-recognition domain of the mannose-binding lectin. Although it is convenient to call the latter group the **NK-cell lectin-like receptors**, many actually bind protein ligands rather than carbohydrates. The main families of NK-cell receptors are shown in Figure 8.29. Although some receptors are expressed by all NK cells, for example the lectin-like receptor NKG2D, most are expressed by subpopulations of NK cells. Consequently, individual NK cells express different combinations of receptors, imparting heterogeneity to a person's NK-cell population and providing a repertoire of responses to pathogens. Among other cell types involved in the innate immune response, such as macrophages, dendritic cells, and neutrophils, individual cells also express different combinations of receptors.

Ligands for NK-cell receptors are usually cell-surface proteins whose expression is altered in response to infection or other trauma. Many of them are MHC class I or MHC class I-like molecules. The activating lectin-like receptor NKG2D binds to MIC-A and MIC-B, which are class-I-like heavy chains that

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NK-cell receptors					
Inhibitory			Activating		
Receptor	Structural type	Ligand	Receptor	Structural type	Ligand
KIR2DL	Ig	HLA-C	KIR2DS	Ig	HLA-C
KIR3DL	Ig	HLA-B,C	KIR3DS	Ig	HLA-B?
LILRB1,2	Ig	HLA class I	LILRA3	Ig	?
CD94:NKG2A	Lectin	HLA-E	CD94:NKG2C/E	Lectin	HLA-E
LAIR-1	Ig	?	LAIR-2	Ig	?
			NKG2D	Lectin	MIC-A,B and others
			NKp30	Ig	?
			NKp44	Ig	?
			NKp46	Ig	?
			CD16	Ig	Fc

Figure 8.29 NK cells express diverse inhibitory and activating receptors. This diagram shows only some of the receptors and organizes them according to signaling potential, structural type (immunoglobulin-like (Ig) and lectin-like), and ligands, where known. In the nomenclature for the killer-cell immunoglobulin-like receptors (KIRs), 2DL and 3DL correspond to receptors having long cytoplasmic tails and two or three immunoglobulin-like domains respectively; 3DS corresponds to a receptor having a short cytoplasmic tail and three immunoglobulin-like domains. Whereas all KIRs and leukocyte-associated immunoglobulin-like receptors (LAIRs) are expressed by NK cells, only a minority of the leukocyte immunoglobulin-like receptors (LILRs) are expressed by NK cells. NKp30, NKp44, and NKp46 are collectively called the natural cytotoxicity receptors; they are important for the killing of tumor cells and are the only receptors uniquely expressed by NK cells.

do not associate with β_2-microglobulin and are encoded by genes in the HLA region. MIC-A and MIC-B are examples of stress-induced proteins. The only tissue in which they are made constitutively is intestinal epithelium, and there the amount is small. When any epithelial cell becomes infected, damaged, or cancerous, however, expression of MIC-A and MIC-B is induced, and for intestinal epithelium it increases. Once expressing MIC-A and MIC-B, epithelial cells become targets for NK-cell attack mediated through the NKG2D receptor. Through the agency of small proteins called adaptor molecules, which associate with the cytoplasmic tail of NKG2D, kinases are activated and lead to the release of cytotoxic granules and cytokines. Other ligands for the NKG2D receptor are a different type of class I-like molecule, encoded by a family of genes on human chromosome 6 away from the HLA region.

Other lectin-like NK-cell receptors are heterodimers formed from CD94 paired with either NKG2A or NKG2C. Both the CD94:NKG2A and CD94:NKG2C receptors recognize composite ligands composed of a peptide derived from the leader sequence of an HLA-A, -B, or -C allotype bound to the oligomorphic class I molecule HLA-E. As HLA-E is so finicky in the peptides it binds, the presence and abundance of HLA-E on the cell surface is completely dependent on the amounts of other HLA class I heavy chains being made by the cell. Although the CD94:NKG2A and CD94:NKG2C receptors have similar ligand-binding specificity, they differ radically in signaling function. Whereas NKG2C associates with an adaptor molecule and delivers activating signals, NKG2A has a cytoplasmic tail that recruits phosphatases to deliver inhibitory signals. These two receptors are rarely expressed by the same NK cell; CD94:NKG2A is more frequently expressed than CD94:NKG2C and serves to prevent NK cells from attacking healthy human cells expressing a normal complement of HLA class I molecules.

The **killer-cell immunoglobulin-like receptors** (**KIR**) are a family of activating and inhibitory NK-cell receptors that use either two or three immunoglobulin domains to bind to polymorphic determinants of HLA-A,

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-B, or -C ligands. Of these ligand–receptor interactions, those between HLA-C and inhibitory KIR are best understood. Three-dimensional structures of the complex of HLA-C and KIR show that KIR interacts with the same face of the MHC class I molecule as the T-cell receptor, the face formed by the two α helices and the bound peptide (Figure 8.30). The difference is that KIR covers less of the face than the T-cell receptor, just that part containing the carboxy-terminal parts of the bound peptide and the α_1 helix, and the amino-terminal part of the α_2 helix. The presence of asparagine or lysine residues at position 80 in the HLA-C α_1 helix defines two groups of HLA-C allotypes that bind to different KIRs. Whereas all allotypes of HLA-C are KIR ligands, it is not so for HLA-A and -B, pointing to HLA-C being particularly specialized towards control of the NK-cell response.

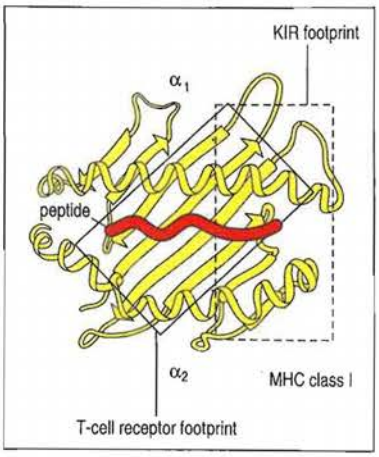


Figure 8.30 KIRs interact with the same face of the MHC class I molecule as the T-cell receptor. The ribbon diagram (yellow) is of the α_1 and α_2 domains of an MHC class I molecule and shows the bound peptide (red). The T-cell receptor interacts with that part of the face formed by the two α helices and the peptide, as outlined by the gray-shaded rectangle. A KIR interacts with the right-hand half of the same face as the T-cell receptor, as outlined by the dashed line.

Inhibitory KIRs with specificity for HLA-A, -B, and -C are used to protect healthy cells from NK-cell attack, in a manner analogous to CD94:NKG2A. Other members of the KIR family are activating receptors, some of which have a similar HLA-C specificity to the inhibitory receptors. Although likely, it has yet to be demonstrated that activating KIRs serve to activate NK cells against infection. Conversely, the **natural cytotoxicity receptors** (**NCR**), a distinct group of activating NK-cell receptors of the immunoglobulin superfamily, are known to mediate NK-cell killing of tumor cells, but their ligands remain poorly defined.

Although many NK-cell receptors have been identified, the ways in which they work together to recognize virus-infected cells are poorly understood, and are likely to depend on the type of virus and the type of cell infected. Many viruses interfere with MHC class I expression in the cells they infect, a tactic that prevents cytotoxic CD8 T cells from killing the infected cells. The reduced level of MHC class I can then make the infected cells vulnerable to killing by NK cells, which on interaction with the infected cells will not be inhibited through engagement of their inhibitory MHC class I receptors. For some viruses, such as human cytomegalovirus, the situation could be further complicated by viral proteins that mimic MHC class I molecules and interfere with NK-cell attack by ligation of the NK cells' inhibitory receptors.

8-15 Three genetic complexes contribute to NK-cell recognition of 'missing-self'

The families of genes encoding lectin-like NK-cell receptors cluster together in a region of chromosome 12 called the natural killer complex (NKC; Figure 8.31). Similarly, the KIR genes are found in a region of chromosome 14 called the leukocyte receptor complex (LRC), which also contains genes for other receptors of the immunoglobulin superfamily. Next to the KIR genes in the LRC is the family of leukocyte immunoglobulin-like receptor (LILR) genes, which include two that are present on NK cells and have a broad specificity for HLA class I molecules (see Figure 8.29). Receptors determined by NKC and LRC genes interact with class I and class I-like ligands that are the products of genes in the HLA complex.

As we saw in Chapter 3, some HLA class I genes in humans are highly polymorphic while others are present as only one or a very few alleles in the population. A similar division can be made for the NK-cell receptors. As a group, the human lectin-like receptors are less polymorphic than the immunoglobulin-like receptors. Most conserved is NKG2D, but it binds to diverse ligands, of which MIC-A is highly polymorphic.

KIRs are the most diverse of the NK-cell receptors—so diverse that unrelated people rarely (< 1%) have exactly the same set of KIR alleles. Three factors combine to create this diversity. First, individuals possess different numbers

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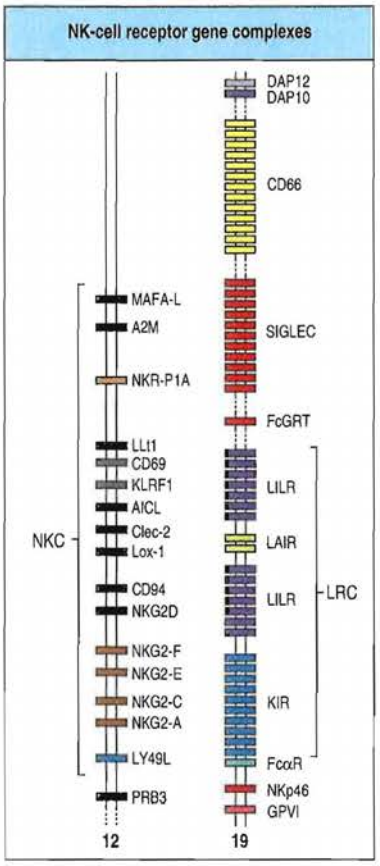


Figure 8.31 Many NK-cell receptors are encoded by genes in one of two genetic complexes. The natural-killer complex (NKC) on human chromosome 12 encodes lectin-like NK-cell receptors, whereas the leukocyte receptor complex (LRC) on chromosome 19 encodes NK-cell receptors that are members of the immunoglobulin superfamily. The LRC comprises the killer-cell immunoglobulin-like receptor (KIR), the leukocyte immunoglobulin-like receptor (LILR), and the leukocyte-associated immunoglobulin-like receptor (LAIR) gene families. Flanking the LRC are genes encoding other immunoglobulin-like molecules of the immune system, including the NKp46 receptor of NK cells, and the DAP10 and DAP12 signaling adaptor molecules that transduce signals from activating NK-cell receptors. Figure based on data courtesy of John Trowsdale.

of KIR genes (ranging from 7 to 15); second, KIR haplotypes have different numbers of genes encoding activating and inhibitory receptors; third, the individual KIR genes are polymorphic. Some people have genotypes containing only genes specifying inhibitory KIRs, whereas others have an equivalent number of genes encoding activating and inhibitory KIRs. Differences in KIR type are beginning to be correlated with clinical parameters in infectious disease, autoimmune disease, and transplantation.

Only one of the KIR genes, KIR2DL4, is expressed by all human NK cells. The others are expressed on subpopulations of NK cells, with an almost random distribution in the number and combination of KIR genes expressed by any given cell. Once the pattern of KIR expression is set during NK-cell development it remains stable. Variation in KIR expression makes a prominent contribution to the NK-cell repertoire, and clones of NK cells can be defined on the basis of the combination of expressed KIR genes. The one requirement placed on NK-cell receptors is that they inhibit the NK cell from killing when confronted with healthy cells expressing self-HLA class I molecules (Figure 8.32). Because the ligands for KIRs are polymorphic MHC class I molecules, which KIRs can serve as inhibitory receptors for a person's MHC class I molecules depends on that person's HLA class I type. However, this restriction

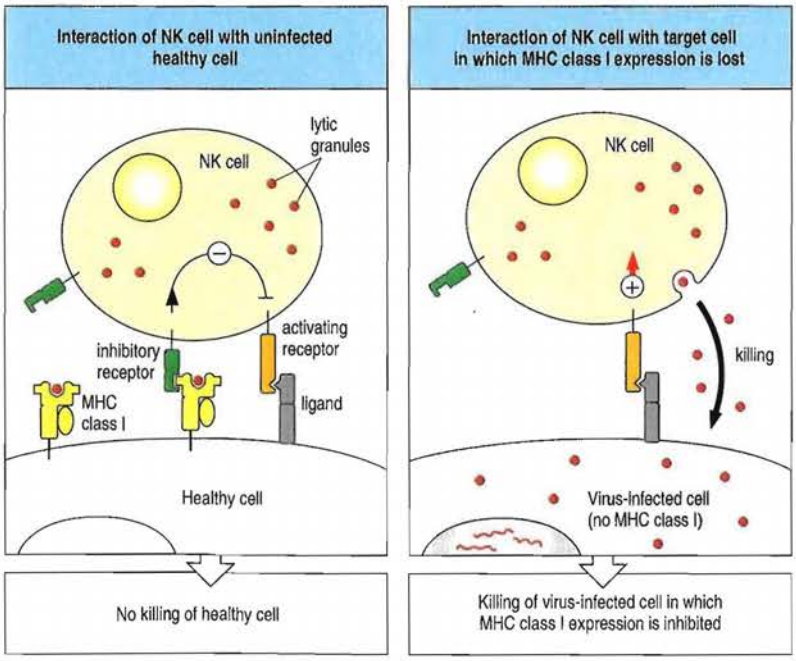


Figure 8.32 Possible mechanism by which NK cells distinguish uninfected cells from infected cells. NK cells have activating and inhibitory receptors that interact with ligands on the surfaces of human cells. The nature of the activating receptors and their ligands is uncertain. The inhibitory receptors interact with MHC class I molecules, which are present on virtually all healthy cells. On interaction with a healthy cell the inhibitory signals dominate and inhibit NK-cell cytotoxicity (left panel). Infection of a cell with an intracellular parasite might change the expression or conformation of MHC class I molecules such that the interaction of the cell with the receptors on the NK cell generates a stimulatory signal that causes the NK cell to kill the infected cell (right panel).

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does not prevent NK cells expressing inhibitory KIRs for which there is no self-HLA class I ligand. In such cases, either another KIR or CD94:NKG2A or an LILR provides the necessary inhibitory receptor for self-HLA class I. By expressing at least one inhibitory receptor that binds to a self-HLA class I allotype, each NK cell is tolerant of the healthy cells of its own body (autologous cells) and does not attack them.

Although tolerant of healthy autologous cells, NK cells need not be tolerant of healthy allogeneic cells—cells from another individual. In culture, NK cells from one person will mount an attack on cells from another person that lack one, or more, of the HLA class I ligands that would engage their inhibitory receptors (Figure 8.33). In this situation there is a subpopulation of NK cells that cannot be inhibited by the HLA class I molecules on the target cell and it is these NK cells that kill the targets. Certain HLA-C-controlled alloreactions can be beneficial in eradicating residual leukemic cells and preventing relapse following allogeneic hematopoietic-cell transplantation to treat acute myelogenous leukemia. Whereas T-cell alloreactions are generated by the active recognition of a foreign MHC molecule, NK-cell alloreactions are caused by the absence of a self-MHC class I determinant. Alloreactive NK cells are, therefore, said to see 'missing-self'.

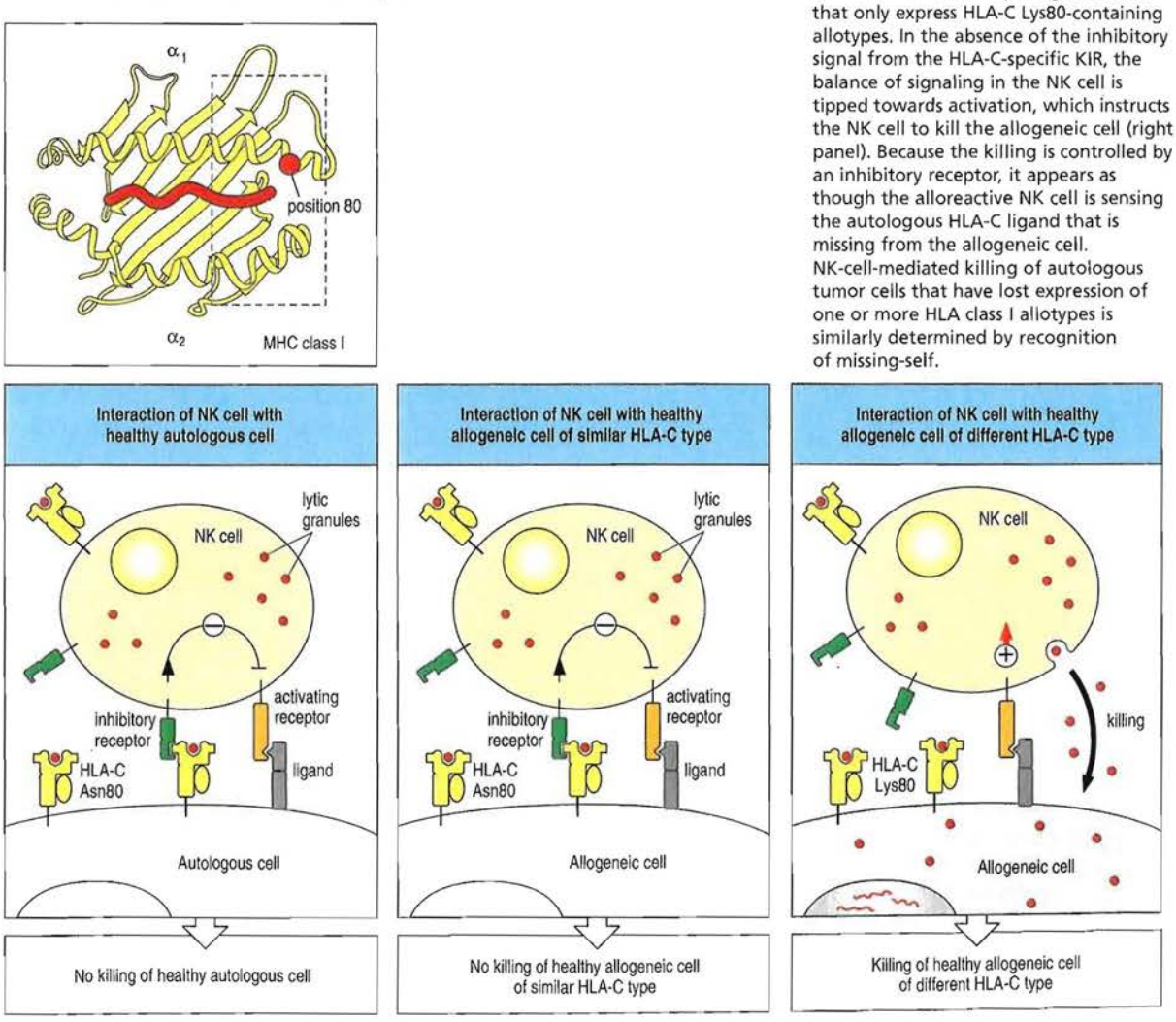


Figure 8.33 NK cells mediate alloreactions determined by HLA class I type. In humans the dominant NK-cell alloreactions are due to an amino-acid substitution at position 80 in HLA-C. This position is in the carboxy-terminal half of the helix of the α_1 domain (ribbon diagram at top left) and can be either asparagine (Asn) or lysine (Lys). HLA-C-mediated alloreactions arise from subpopulations of NK cells that are dependent on inhibitory HLA-C-specific KIRs for their tolerance to healthy autologous cells. The lower left panel shows such an NK cell, which is kept in check by interaction between its inhibitory KIR, which is specific for HLA-C Asn80, and an HLA-C Asn-80-containing allotype on the interacting cell. This NK cell will also be inhibited by healthy allogeneic cells that express HLA-C Asn80-containing allotypes (center panel), but will not be inhibited by allogeneic cells that only express HLA-C Lys80-containing allotypes. In the absence of the inhibitory signal from the HLA-C-specific KIR, the balance of signaling in the NK cell is tipped towards activation, which instructs the NK cell to kill the allogeneic cell (right panel). Because the killing is controlled by an inhibitory receptor, it appears as though the alloreactive NK cell is sensing the autologous HLA-C ligand that is missing from the allogeneic cell. NK-cell-mediated killing of autologous tumor cells that have lost expression of one or more HLA class I allotypes is similarly determined by recognition of missing-self.

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8-16 Minority subpopulations of B and T cells contribute to innate immunity

During B- and T-cell development, minority subpopulations are produced that can be distinguished on the basis of nonconventional cell-surface phenotype and a restricted repertoire of B- or T-cell receptors. Within these minority subpopulations, each lymphocyte clone is much larger than is usual in the majority subpopulation, so these minority subpopulations can respond to a primary infection without first undergoing a lengthy period of clonal expansion and differentiation. Two of these subpopulations have been introduced already: B-1 cells (see Section 4-6, p. 108) and γ:δ T cells (see Section 3-4, p. 71).

The B-1 lineage of B cells arises early in embryonic development and uses a limited set of V regions to produce surface IgM that is characterized by a rather general affinity for polysaccharide antigens (Figure 8.34). B-1 cells respond rapidly to antigen, producing detectable levels of antibody within 48 hours of infection. These responses are independent of cognate T-cell help, do not involve isotype switching or somatic hypermutation, and do not produce immunological memory. B-1 cells are characteristically found in the peritoneal cavity and do not depend on the bone marrow for renewal.

γ:δ T cells have less diverse T-cell receptors than α:β T cells and do not recognize peptide antigens presented by MHC molecules. About 4% of the T cells in human blood are γ:δ T cells with a restricted set of receptors encoded by $V_{\gamma 2}V_{\delta 2}$ gene segments (in an alternative nomenclature $V_{\gamma 2}$ is $V_{\gamma 9}$). These cells respond quickly to infections by releasing inflammatory cytokines and killing infected cells. In a variety of infectious diseases the abundance of $V_{\gamma 2}V_{\delta 2}$ T cells in the blood increases substantially, to become as much as 60% of all T cells. The MIC-A molecule appears to be a ligand for $V_{\gamma 2}V_{\delta 2}$ T-cell receptors, but the situation is complicated by the presence of the NKG2D receptor on these cells because it too binds MIC-A (Figure 8.35).

Other ligands for $V_{\gamma 2}V_{\delta 2}$ T-cell receptors are neither proteins nor peptides, but small organic phosphates and alkylamines. Such compounds are produced during infection as a consequence of microbial metabolism and breakdown, but can also be formed by human digestion and metabolism. In habitual tea drinkers, breakdown of the unusual amino acid theatin present in tea yields ethylamine, which stimulates γ:δ T cells. The absence of MHC restriction for γ:δ T cells, and the wide-ranging size and structure of the antigens they recognize, has led to the view that γ:δ T-cell receptors behave more like antibodies than like α:β T-cell receptors in the antigens they bind.

A minority subpopulation of α:β T cells also has a restricted T-cell receptor repertoire. These cells are called NK T cells because they express NKR-PIA, one of the lectin-like NK-cell receptors. The T-cell receptors of NK T cells comprise an α chain consisting of $V_{\alpha 24}$ and $J_{\alpha 15}$ segments associated with a $V_{\beta 11}$-containing β chain. Unlike the majority of α:β T cells, NK T cells are not restricted to binding peptide antigens presented by polymorphic MHC class I molecules, but bind lipid antigens presented by CD1D, a β_2-microglobulin-associated class I molecule that is distinguished by its hydrophobic antigen-binding site. In the thymus, positive selection of NK T cells is accomplished by

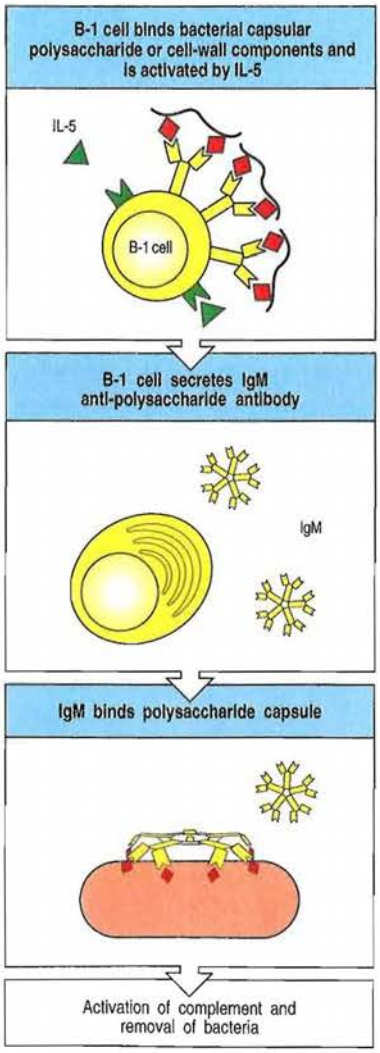


Figure 8.34 B-1 cells provide a quick response to carbohydrate antigens such as bacterial polysaccharides. Almost all the antibody made by B-1 cells is of the IgM isotype and its principal effector function is the activation of complement. Although the B-1 cell response is stimulated by IL-5 made by T cells, it does not depend on cognate interactions with T cells.

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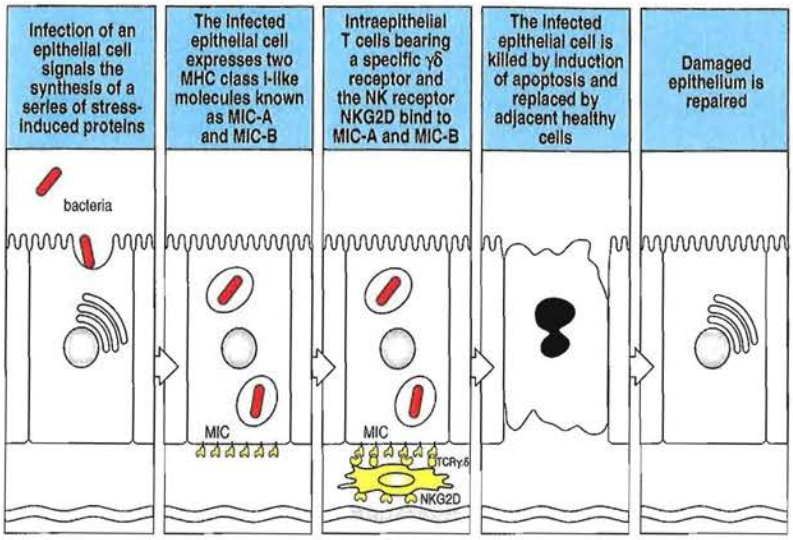


Figure 8.35 T cells of the mucosal immune system bearing γ:δ T-cell receptors and the activating NKG2D receptor recognize and kill injured enterocytes. Infection or other injury to enterocytes, the epithelial cells lining the lumen of the gut, stimulates a stress response, which causes expression on the cell surface of the MHC class-like molecules, MIC-A and MIC-B. Many intraepithelial T cells bear a γ:δ T-cell receptor that is specific for MIC-A and MIC-B; they also bear the MIC-A- and MIC-B-specific NK-cell receptor NKG2D. For NK cells, NKG2D is an activating receptor, but on these γ:δ T cells it acts as a co-receptor for the γ:δ receptor. When a stressed enterocyte express MIC-A and MIC-B the γ:δ T cells induce it to die by apoptosis. The dying enterocyte is removed from the epithelium, allowing the local tissue injury to be repaired.

complexes of self lipids and CD1D expressed by cortical thymocytes. Outside the thymus, CD1D is expressed by intestinal epithelium, where it presents lipids derived from pathogens infecting the gut. NK T cells have the machinery to kill infected cells and to release large quantities of IL-4 and IFN-γ within an hour or two of having their T-cell receptors engaged by complexes of CD1D and lipid antigens. The cytokines released by NK T cells contribute to the activation of NK cells, macrophages, and dendritic cells in the early phase of the immune response. Although their receptors recognize an MHC class I molecule, NK T cells do not express CD8: they express either CD4 or no co-receptor at all.

CD1D is one of five isoforms of CD1, the others being CD1A, B, C, and E. They specialize in the presentation of lipid antigens and are encoded by a family of genes on human chromosome 1. Microorganisms usually have lipids that are chemically and structurally distinct from those of human cells and they, like microbial cell-surface carbohydrates, offer good targets for antigen receptors of the human immune system. By binding to the hydrophobic alkyl and acyl chains of lipids, CD1 presents the hydrophilic head groups or sugars for interaction with T-cell receptors.

The CD1A, B, and C isoforms present lipid antigens to diverse, conventional CD8 and CD4 α:β T cells. These isoforms are not expressed in intestinal epithelium, but in dendritic cells and activated monocytes, where they cycle between the cell surface and intracellular endosomal and lysosomal vesicles. The three isoforms are distinguished by the types of lipid they bind and the endosomal compartments to which they traffic in search of lipid antigens. Unlike conventional MHC class I molecules, CD1 molecules can associate with the invariant chain in the course of their travels. An example of a lipid antigen presented by CD1 is the mycolic acid of mycobacteria (Figure 8.36). Although CD1E protein is made and is present inside cells its role in antigen presentation is not known.

Summary

Innate immunity provides a variety of defenses against infection that work immediately a pathogen is first confronted or very soon after. These fixed defenses are always available and do not improve with repeated exposure to the same pathogen. The skin and other epithelia form physical barriers that

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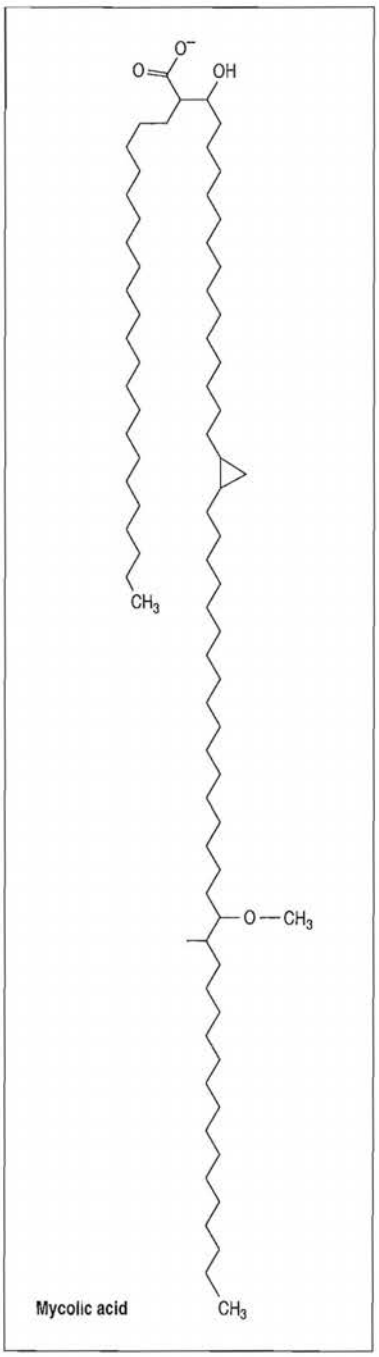


Figure 8.36 Mycolic acid. This molecule is present in the cell walls of mycobacteria and is a ligand for the α:β receptor of NK T cells. Its physical and chemical properties are very different from the peptides recognized by other α:β T cells.

prevent entry to the body's tissue. Reactive ions, peptides, and other small molecules are chemical weapons that directly kill microorganisms. Inhibiting a pathogen's progress in colonizing tissues and spreading infection are the protease inhibitors, clotting cascade, and kinin reactions. A host of plasma proteins and cell-surface molecules provide systems for identifying microbiological invaders and distinguishing them from self. Complement provides a general means to tag almost any component at a microbial surface; more specific receptors bind common chemical aspects of microbial macromolecules that are not a part of the human body. As well as helping resident macrophages to phagocytose pathogens, these interactions induce the macrophages to pour out inflammatory cytokines that summon other effector cells of innate immunity—neutrophils, NK cells, γ:δ T cells, and NK T cells—to the site of infection. Interaction between these cells, and with resident macrophages and dendritic cells, produces mutual activation and cytokine secretion that heightens the state of inflammation in the infected tissue. Bacterial infections are frequently overcome by the phagocytic powers and potent poisons of abundant neutrophils. In viral infections, the production of type I interferons by infected cells and interferon-producing cells will often set the stage for NK cells to terminate infection. Only when the defenses of innate immunity are failing to contain an infection is the decision made to mobilize reinforcements from adaptive immunity.

Adaptive immune responses to infection

Through the activation of phagocytes, the production of cytokines, and the creation of a state of inflammation, innate immunity sets the scene for the development of the adaptive immune response. In this part of the chapter we shall consider the adaptive immune response to pathogens to which an individual has never been previously exposed. Such infections stimulate a **primary immune response**, involving the coordinated activation of naive T cells and B cells and the production of effector cells and molecules, including antibodies specific against the pathogen. These effectors help to clear the pathogen from the body and prevent reinfection in the short term, while the pathogen is still infecting others in the population. Usually, an adaptive immune response also leads to long-lasting immunity against the pathogen, which we shall consider in the last part of this chapter. Adaptive responses build on a foundation of effector mechanisms that are all part of innate immunity. Indeed, the inflammation produced by the innate immune response provides the essential environment for starting the adaptive immune response. The adaptive response refines and amplifies these effector mechanisms, providing the extra dimension of antigen specificity. In this part of the chapter we shall see how the component parts of adaptive immunity, which have been discussed in Chapters 2–7, work together in clearing infections.

8-17 Adaptive immune responses start with T-cell activation in secondary lymphoid tissues

The innate immune response develops locally at the site of infection through the action of plasma proteins, the stimulation of macrophages, the recruitment of effector cells, and the establishment of a state of inflammation. Movement of antigens, cytokines, and other inflammatory mediators away

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from the site of infection has an impact on more distant sites, particularly nearby lymphoid tissues, and can even have systemic effects. When the innate immune response fails to terminate infection in a timely fashion, molecular and cellular communications between the infected tissue and its most accessible secondary lymphoid tissue initiate an adaptive immune response. This involves an extensive process in which pathogen-specific lymphocyte clones are selected, expanded, and differentiated. All this takes place within the secondary lymphoid tissue over the course of several days and leads to the generation of several types of effector lymphocytes. The effector CD4 T_H1 and cytolytic CD8 T cells then migrate to the infected tissue to function, while CD4 T_H2 cells and plasma cells perform their functions in the lymphoid tissues.

Although all adaptive immune responses have much in common, there are also important differences that depend on the tissue infected and the secondary lymphoid tissue that it alerts. Infections of the skin and connective tissues drain through the lymphatics to lymph nodes, infections of the blood are pumped into the spleen, and infections of mucosal surfaces are dealt with by Peyer's patches and other lymphoid aggregations that lie immediately beneath the mucosal epithelium. In this part of the chapter we shall use the lymph node and Peyer's patches to exemplify the events that proceed in secondary lymphoid tissues.

The start of the adaptive immune response is marked by the migration in the lymph of antigen-laden or infected dendritic cells from the infected tissue to the draining lymph node. Dendritic cells have many properties of macrophages and throughout the innate immune response they have been stimulated or infected by the pathogen, taking up antigens and reacting to the cytokines made by other immune-system cells. Eventually, the sum of intracellular signals emanating from these stimuli cause a switch to be thrown and the dendritic cell migrates in the lymph and enters the lymph node in response to chemokines made by stromal cells in the node. With this journey, the dendritic cell matures, changing the focus of its activity from antigen uptake to antigen presentation and stimulation of naive T cells. The dendritic cell thus becomes a professional antigen-presenting cell (see Section 6-5, p. 151).

On entering lymph nodes in the lymph, dendritic cells are attracted by chemokines produced by the high endothelial venules in the T-cell areas, where the dendritic cells take up residence. As naive T cells enter the node from a high endothelial venule they are drawn toward the dendritic cells in the T-cell areas by the chemokine CCL18 (also called DC-CK) (see Figure 8.16), which is made by dendritic cells and specifically attracts naive T cells. The T cells scan the dendritic cell surface to find peptide:MHC complexes that bind to their antigen receptors. The small number of T cells that are specific for the antigens in the node are activated on engagement of their T-cell receptors; proliferation and differentiation begin and eventually lead to large clones of antigen-specific effector T cells.

Pathogens and their antigens are also carried passively in the lymph from infected tissue to the draining lymph node. There they are taken up by the macrophages resident in the node, processed, and presented to naive T cells. Lymph-node macrophages are ferociously efficient at removing pathogens from afferent lymph. In an experiment in which 3 billion streptococci were perfused through a single lymph node in a small volume of fluid (5 ml), over 99% of the organisms were removed. Lymph nodes are equally efficient in removing antigen-specific T cells from the blood. Within two days of an antigen being presented in a lymph node, all the antigen-specific T cells in the circulation were trapped there (Figure 8.37).

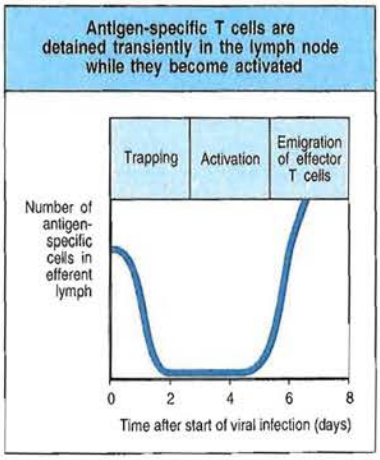


Figure 8.37 Antigen-specific T cells become trapped in lymph nodes. This graph charts the presence of virus-specific T cells in efferent lymph during the course of an experimental virus infection. Before infection, virus-specific T cells recirculate between blood, lymph nodes, and lymphatics. On infection, antigen-specific T cells are trapped, and collect in the lymph nodes draining the infected tissue. After 2 days they can no longer be detected in the efferent lymph. For 2–4 days from the start of the infection, the T cells remain in the lymph node, where they divide and differentiate into effector T cells. At that time, effector T cells leave in the efferent lymph to travel to the infected tissue. Because of clonal expansion, the number of antigen-specific T cells in the efferent lymph after day 4 becomes much larger than the numbers detected before infection.

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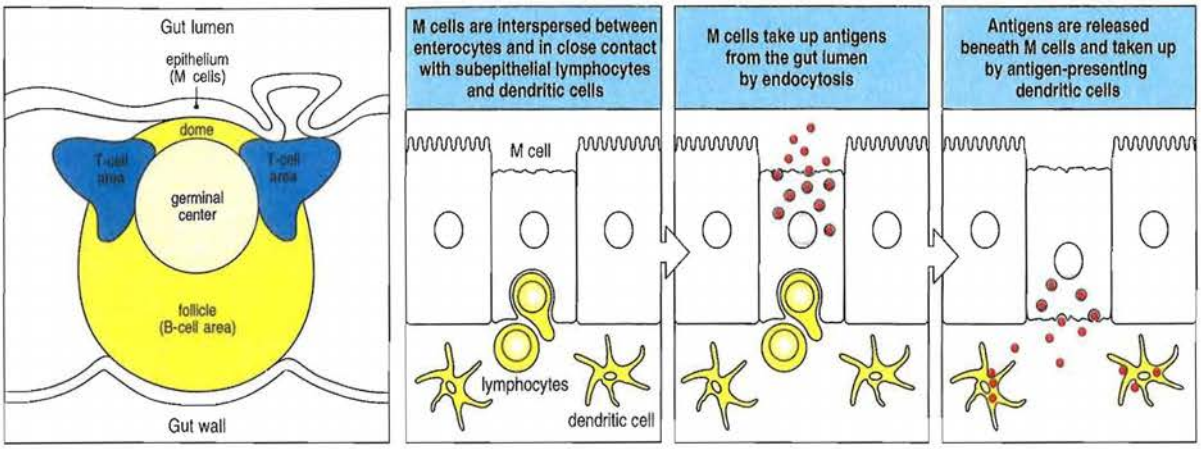


Figure 8.38 In the gut M cells deliver antigen to Peyer's patches. A typical region of gut-associated lymphoid tissue is shown in the schematic on the left. These areas are organized similarly to the lymph node and the white pulp of the spleen, with distinctive B- and T-cell zones, lymphoid follicles, and germinal centers. The other three panels show how the M cells of the gut epithelial wall deliver pathogens from the luminal side of the gut mucosa to the lymphoid tissue within the gut wall. The cell membrane at the base of these cells is folded around lymphocytes and dendritic cells within the Peyer's patches. M cells take up antigens from the lumen of the gut by endocytosis and the antigens are transported through the cells by transcytosis and delivered directly to antigen-presenting cells and lymphocytes of the mucosal immune system.

Dendritic cells that do not enter a node but are carried on by the lymph to the blood, take up residence in the T-cell areas of the spleen, where they initiate an adaptive immune response. Similarly, pathogens that fail to be removed from the lymph by lymph-node macrophages and pass into the blood will usually be taken out of circulation by macrophages in the spleen.

8-18 Microfold cells in the gut deliver antigens to Peyer's patches

Compared to the skin, the internal mucosal surfaces of the body are more vulnerable to infection, and most infections are caused by pathogens that have crossed a mucosal barrier. Mucosal surfaces are protected by lymphocytes and mucosa-associated lymphoid tissues (MALT) (see Chapter 1) that are dedicated to the purpose. The characteristics of mucosal defense are well illustrated by the small intestine, an organ devoted to the digestion and uptake of food, which is also home to some 14 million commensal microorganisms. Both food and commensal organisms represent an abundance of foreign antigens. They do not, however, stimulate an immune response except in situations where the gut epithelium has become inflamed due to damage, infection, or cancer.

Peyer's patches are the secondary lymphoid organs of the small intestine. They form domed follicles within the gut wall and are organized into B- and T-cell areas (Figure 8.38). Within the mucosal epithelium and above the dome of a Peyer's patch are specialized M cells that take up antigens and pathogens from the lumen of the gut and deliver them to the Peyer's patch by transcytosis. Unlike enterocytes, the predominant cell of the gut epithelium, these cells do not have microvilli but microfolds, hence their name of **microfold cells** or **M cells**. M cells also differ from enterocytes by not having the protection of a thick glycocalyx and a secreted mucus. M cells are, therefore, sites where pathogens find it easier to breach the intestinal wall, a lure that delivers them directly to a secondary lymphoid organ (see Figure 8.38).

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Pathogens and antigens arriving at the basal side of the M cells encounter dendritic cells and macrophages that process and present their antigens. These will be scanned by circulating naive T cells that enter Peyer's patches from the blood and return to it via the lymphatics draining the intestines. Naive T cells that recognize specific antigens presented by the dendritic cells and macrophages in a Peyer's patch will be trapped there to proliferate and differentiate.

8-19 Primary CD4 T-cell responses are influenced by the cytokines made by cells of innate immunity

Effector CD4 T cells are of two types: T_H1, which promote a response dominated by inflammatory effector cells; and T_H2, which promote an antibody-mediated response. The decision as to which way a naive CD4 T cell will differentiate occurs when the T cell is first being stimulated by a professional antigen-presenting cell and is largely determined by the cytokine environment created by the ongoing innate immune response. When mutual interaction between dendritic cells, macrophages, and NK cells has favored production of IL-12 and IFN-γ, differentiation to T_H1 cells is favored. Thus, an innate response favoring inflammatory effector cells causes the adaptive immune response to continue with the strategy (Figure 8.39). By contrast, differentiation to T_H2 cells is favored when IL-4 dominates the cytokine environment produced by the innate response.

The direction of CD4 T-cell differentiation is also influenced by the abundance and density of the peptide:MHC complexes at the surface of professional antigen-presenting cells and their affinity for T-cell receptors. Peptides that are abundantly presented, or have strong affinity for T-cell receptors, tend to stimulate T_H1 responses, whereas peptides that are in low abundance, or have weak affinity for T-cell receptors, tend to stimulate T_H2 responses. Allergic responses, in which minute amounts of antigen preferentially stimulate T_H2 cells and IgE production, are of the latter type.

There is an inherent tendency for CD4 T cells to become polarized towards either a T_H1 or T_H2 response, because the cytokines produced by one type of effector CD4 T cell inhibit the differentiation and/or the function of the other type. The IL-10 produced by T_H2 cells prevents the development of a T_H1 response through a general inhibition of antigen processing and presentation by dendritic cells and macrophages. Thus, IL-12 is never produced, which in turn prevents activation of NK cells, differentiation of T_H1 cells, and IFN-γ production. The lack of IFN-γ further inhibits macrophages and their ability to act as professional antigen-presenting cells. Conversely, the IFN-γ produced by T_H1 cells prevents the activation of T_H2 cells (Figure 8.40). However, although highly polarized responses do occur, as in the two forms of leprosy (see Section 6-9, p. 159), the majority of immune responses involve contributions from both T_H1 and T_H2 CD4 cells.

CD8 T cells, which secrete cytokines as well as killing cells, can be influenced to make cytokines favoring either a T_H1 or T_H2 CD4 T-cell response. The unhelpful CD4 T_H2 response in lepromatous leprosy is thought to arise from the presence of CD8 T cells secreting IL-10 and transforming growth factor

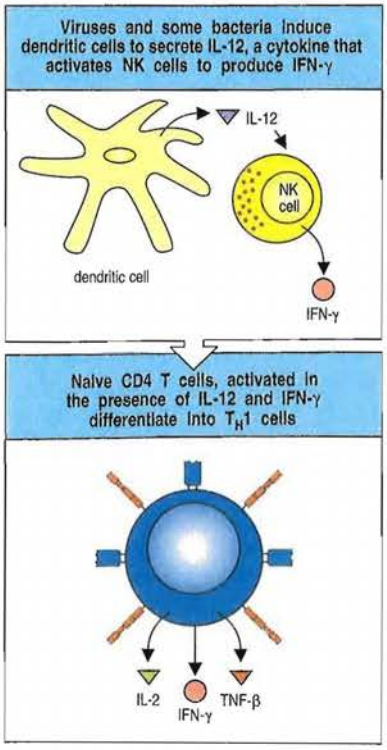


Figure 8.39 Cytokines elicited by the pathogen affect the differentiation of CD4 T cells. The innate immune response to different types of pathogen involves the secretion of cytokines that influence the course of the adaptive immune response. In response to viruses and intracellular bacteria, macrophages and dendritic cells produce IL-12. This cytokine stimulates NK cells to produce IFN-γ, which drives proliferating CD4 T cells to become of the T_H1 type.

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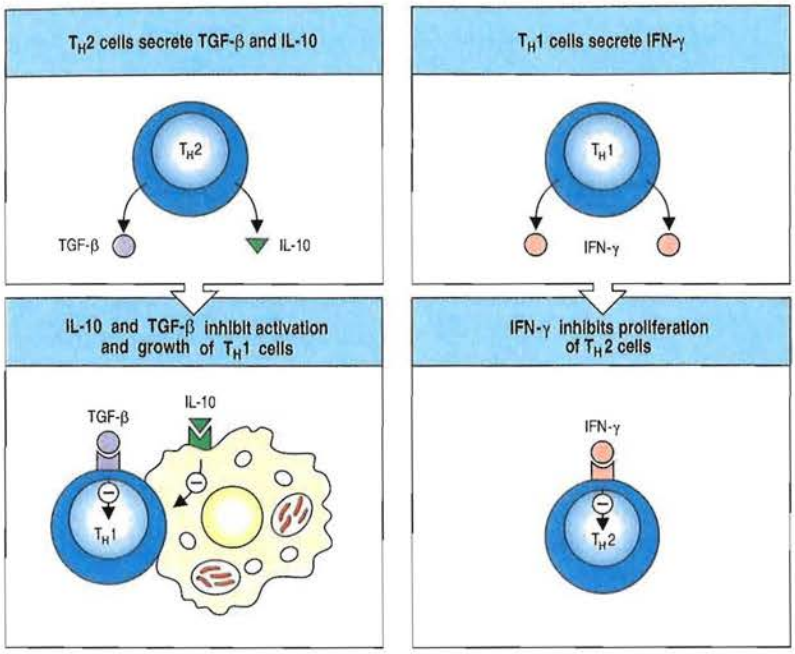


Figure 8.40 Each type of CD4 T cell produces cytokines that inhibit the other type of CD4 T cell. T_H2 cells make IL-10 and TGF-β (top left panel). IL-10 prevents macrophages from activating T_H1 cells, perhaps by preventing the synthesis of IL-12 by the macrophage. TGF-β acts directly on T_H1 cells to inhibit their growth (bottom left panel). T_H1 cells make IFN-γ (top right panel), which blocks the growth of T_H2 cells (bottom right panel).

(TGF)-β, which suppress the T_H1 response. In the less severe tuberculoid form of the disease, the cytotoxic T cells secrete IFN-γ, which helps polarize the CD4T cells to the more helpful T_H1 response that activates infected macrophages to kill the mycobacteria they contain.

8-20 Effector T cells are guided to sites of infection by newly expressed cell adhesion molecules

The activation of naive T cells and their differentiation into effector T cells takes 4–5 days. In the process, their complement of cell-surface adhesion molecules changes, enabling them to leave the secondary lymphoid tissue and travel to the site of infection. The expression of L-selectin, which enables naive T cells to enter lymph nodes, is lost, and the expression of other adhesion molecules is increased. A crucial change is the increased expression on effector T cells of the integrin VLA-4, which binds to VCAM-1 adhesion molecules induced on vascular endothelium by inflammatory cytokines (Figure 8.41).

The differential expression of adhesion molecules directs effector T cells to distinct anatomical sites. T cells activated in Peyer's patches by antigens from the gut leave in the lymph that drains the intestines, and after passing through mesenteric lymph nodes they ultimately reach the thoracic duct and

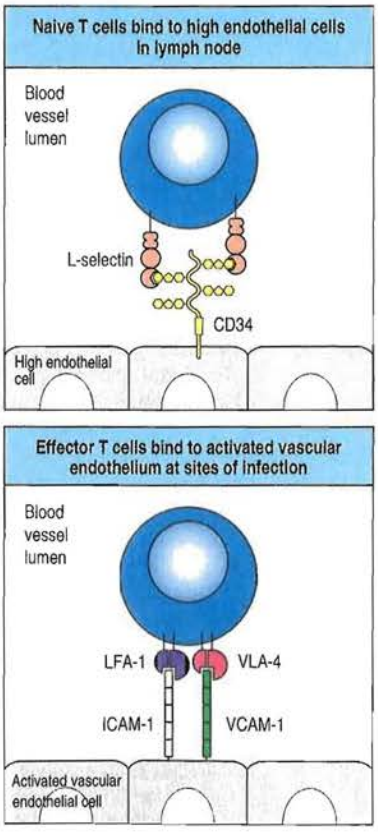


Figure 8.41 Changes in the adhesion molecules expressed by effector T cells enable them to leave the blood and enter infected tissues. As shown in the upper panel, naive T cells express L-selectin, which binds to the sulfated carbohydrates of vascular addressins (such as CD34) on high endothelial vessels in lymph nodes. As shown in the lower panel, effector T cells no longer express L-selectin but express VLA-4 and increased amounts of LFA-1. These adhesion molecules bind to VCAM-1 and ICAM-1 respectively, whose expression is induced on vascular endothelium at sites of inflammation. This change enables effector T cells to home to infected tissues.

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are drained into the blood. The effector T cells circulate in the blood and re-enter the mucosal tissue by recognizing the mucosal addressin **MAdCAM-1**, which is present on the endothelial cells of small blood vessels lining the walls of the gut and other mucosal surfaces. Within the lamina propria of the gut wall, effector T cells form small groups and aggregates as well as being scattered singly. With this pattern of lymphocyte traffic (Figure 8.42) an immune response initiated in one or a few Peyer's patches brings effector T cells to all mucosal tissues to prevent the spread of infection.

When effector T cells recognize specific antigen in the infected tissue they produce cytokines, such as TNF-α, which induce the expression of E-selectin, VCAM-1, ICAM-1, and the chemokine CCL5 (see Figure 8.16). These feed back onto the effector T cells to activate their adhesion molecules. The increased binding of endothelial VCAM-1 and ICAM-1 to T-cell VLA-4 and LFA-1 recruits more effector T cells into the inflamed tissue. The TNF-α and IFN-γ secreted by effector T cells work synergistically to enhance inflammation by changing the shape of vascular endothelial cells in ways that increase blood flow, vascular permeability, and supply of leukocytes and plasma to the infected tissue.

8-21 Antibody responses develop in lymphoid tissues under the direction of T_H2 cells

Whereas effector CD8 T cells and T_H1 cells work mainly at sites of infection, effector T_H2 cells activate B cells within the secondary lymphoid tissues, from whence secreted antibodies then travel in blood or lymph or across epithelia to the sites of infection. Early in an infection, pathogen-derived antigens are presented by the dendritic cells and macrophages in the draining lymph

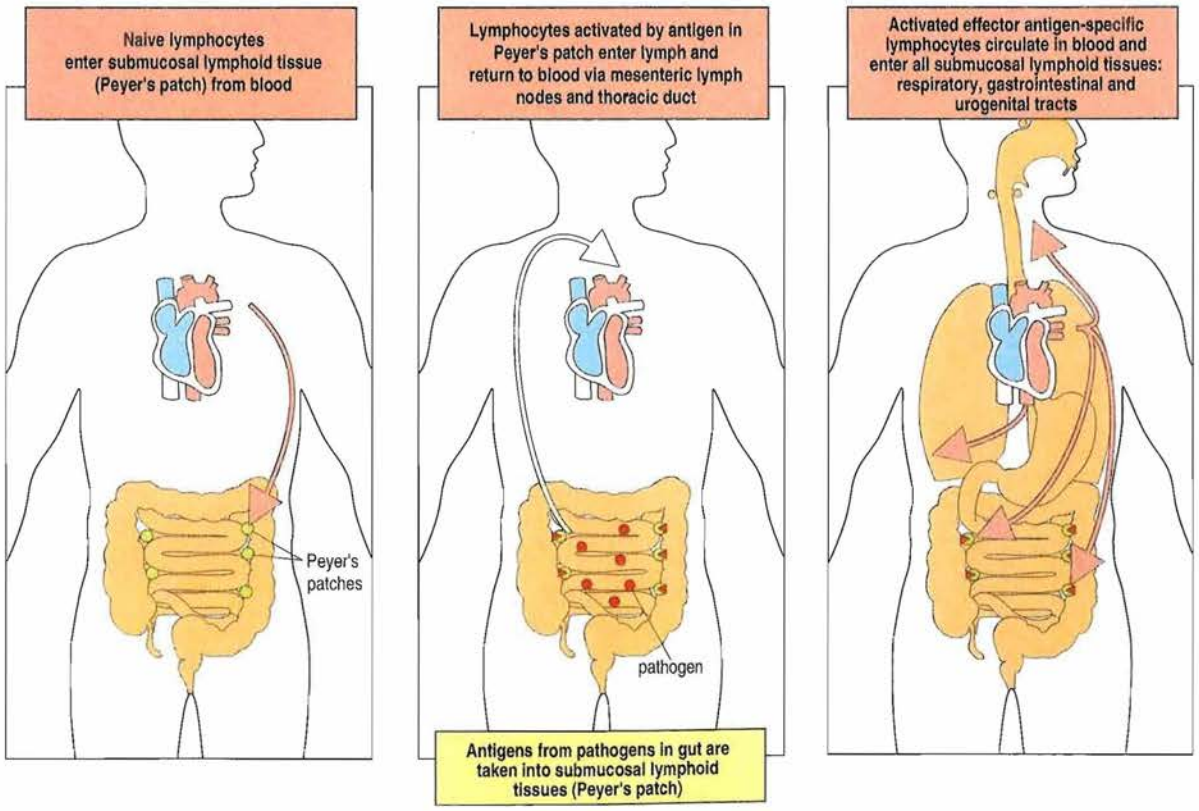


Figure 8.42 Anatomy of mucosal immune responses. Naive lymphocytes enter the submucosal lymphoid tissues, such as a Peyer's patch, from the blood (left panel). Antigens (red triangles) derived from an infection of pathogenic organisms in the gut (red circles) are taken up into the Peyer's patch where they stimulate antigen-specific lymphocytes. The activated lymphocytes then leave the Peyer's patch in the draining lymph and return to the blood via the mesenteric lymph nodes and the thoracic duct (center panel). The activated lymphocytes circulate in the blood and enter all the submucosal lymphoid tissues, not just the ones in which the immune response originated (right panel). In this way all the mucosal tissues are defended against spread of the infection.

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node. Clones of antigen-specific T cells are expanded within the T-cell areas of the node and some differentiate into effector T_H2 cells. Naive B cells also recirculate through the blood and lymph, entering lymph nodes by the same mechanisms used by naive T cells. B cells enter lymph nodes in the T-cell areas, where they bind and endocytose specific antigen by capturing it with their cell-surface immunoglobulin. The endocytosed antigen is then processed by the B cells and presented on MHC class II molecules to the effector T_H2 cells, which in response secrete the cytokines necessary for B-cell proliferation and differentiation.

After encounter with antigen, some 5 days are required for effector T_H2 cells to be produced from naive T cells. At about this time, antigen-specific B cells in contact with T_H2 cells begin to proliferate in the T-cell area to form a primary focus. Some of the B cells activated in these primary foci migrate to the medullary cords of the node, where they become short-lived plasma cells that produce a first wave of pathogen-specific antibody (Figure 8.43, top row). The corresponding B cells in the spleen move to those parts of the red pulp directly adjoining the T-cell zones of the white pulp. In these sites, B-cell numbers increase exponentially for 2–3 days; the cells undergo six or seven cell divisions before their progeny differentiate into antibody-producing plasma cells. Most of these plasma cells die by apoptosis after 2–3 days. Other

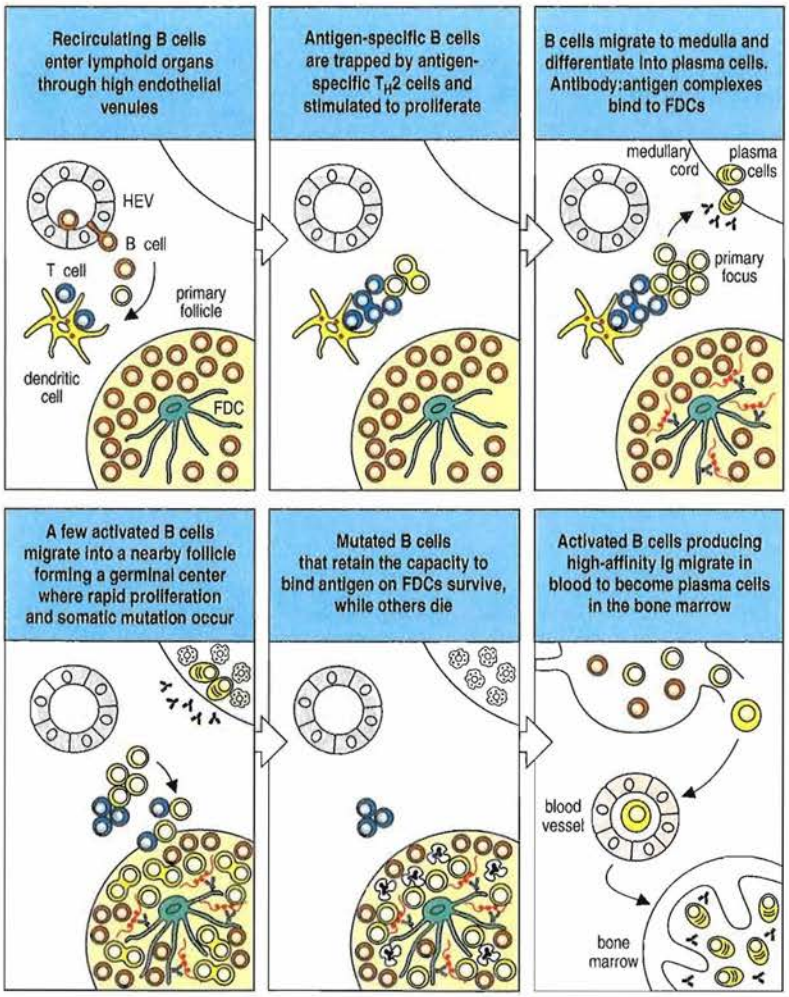


Figure 8.43 Secondary lymphoid tissues provide an environment in which antigen-specific B cells can interact with helper T_H2 cells specific for the same antigen. Top row: Naive B cells leave the blood at high endothelial venules (HEV) and meet effector T_H2 cells specific for the same antigen in the T-cell areas of the lymphoid tissues (a lymph node is illustrated here). B cells that engage with their cognate T_H2 cells become activated and proliferate. Some of the activated B cells move to the medullary chords of the lymph node, where they divide further and differentiate into plasma cells that over a few days secrete antibodies of the first wave. Bottom row: Other activated B cells migrate with their effector T_H2 cells to primary lymphoid follicles, where they are stimulated both by the cytokines released by the T_H2 cells and by the antigen:antibody complexes bound to the surface of follicular dendritic cells (FDC). The resultant B-cell proliferation forms a germinal center, the site of somatic hypermutation and selection of B cells expressing mutant immunoglobulins with higher affinity for antigen. The surviving B cells move to the medullary cords of the lymph node or migrate to the bone marrow, where they become plasma cells secreting a second wave of antibodies with higher overall affinity than those in the first wave.

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activated B cells migrate to the follicles, where they proliferate further, forming a germinal center in which the B cells undergo somatic hypermutation (see Figure 8.43, bottom row).

The antibodies produced by the first wave of plasma cells form immune complexes with antigen and activate complement. Some of the immune complexes bind to follicular dendritic cells in the lymphoid follicles (see Figure 8.43). The variant antibodies produced by the mutated B cells are tested against the antigen in the immune complexes collected on the follicular dendritic cells. B cells having the highest-affinity antigen receptors compete most effectively for antigen and will be selected to survive, to be helped by CD4 T cells, and to become plasma cells (see Figure 7.12, p. 190). They secrete a second wave of antibody with a higher overall affinity for antigen than the antibody of the first wave.

8-22 Antibody secretion by plasma cells occurs at sites distinct from those at which B cells are activated by T_H2 cells

As we saw in the previous section, the first B cells to differentiate into plasma cells migrate to the medullary cords in lymph nodes or to the red pulp of the spleen. The other activated B cells enter the lymphoid follicles and form a germinal center. About 10% of the activated B cells in germinal centers leave as immature plasma cells called **plasmablasts**, and migrate to distant sites, where they differentiate into plasma cells that live, on average, for about a month. The remaining 90% die in the germinal center, having failed to capture antigen and cognate T-cell help (see Figure 7.12, p. 190).

Plasmablasts originating in the follicles of Peyer's patches and mesenteric lymph nodes migrate by the same route as the effector T cells that originate at those sites. They travel in draining lymph to the blood, in which they circulate, and then leave the blood through the walls of small blood vessels to enter the lamina propria of the gut and other epithelia. Plasmablasts originating in peripheral lymph nodes migrate to the medullary cords or the bone marrow, and those originating in the spleen migrate to the bone marrow (Figure 8.44). In immune responses that successfully terminate an acute infection, germinal centers are present for only 3–4 weeks after the supply of antigen is turned off. After this time, small amounts of antigen are retained on follicular dendritic cells and these continue to stimulate the proliferation of B cells in follicles. These B cells are likely to be the precursors of pathogen-specific plasma cells that can be found in the mucosa and bone marrow over periods of months to years. They are thus the source of the antibodies that provide protective immunity.

The primary adaptive immune response terminates most infections that elude the innate immune response. However, within the population suffering from an infectious disease, some individuals succumb to its effects before the

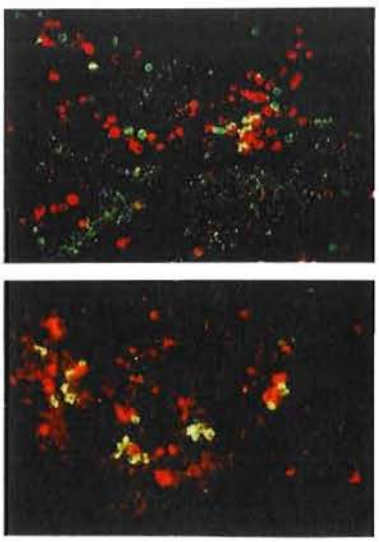


Figure 8.44 Plasma cells are dispersed in medullary cords of lymph nodes and in bone marrow. In these sites they secrete antibody directly into the blood for distribution to the rest of the body. In the upper micrograph, plasma cells in lymph node medullary cords are stained green (with fluorescein anti-IgA) if they are secreting IgA, and red (with rhodamine anti-IgG) if they are secreting IgG. The lymphatic sinuses are outlined by granular staining selective for IgA. In the lower micrograph, plasma cells in the bone marrow are revealed with light-chain specific antibodies (fluorescein anti-λ and rhodamine anti-κ stain). Plasma cells secreting immunoglobulins containing λ light chains are stained yellow-green; those secreting immunoglobulins containing κ light chains stain red. Photographs courtesy of P. Brandtzaeg.

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	Cytotoxic CD8 T cell	T_H1 cell	T_H1/T_H2 cell
Typical pathogens	Vaccinia virus Influenza virus Rabies virus *Listeria*	*Mycobacterium tuberculosis* *Mycobacterium leprae* *Leishmania donovani* *Pneumocystis carinii*	*Clostridium tetani* *Staphylococcus aureus* *Streptococcus pneumoniae* Polio virus *Pneumocystis carinii*
Location	Cytosol	Macrophage vesicles	Extracellular fluid
Antigen recognition	Peptide:MHC class I on infected cell	Peptide:MHC class II on infected macrophage	Peptide:MHC class II on antigen-specific B cell
Effector action	Killing of infected cell	Activation of infected macrophages	Activation of specific B cell to make antibody

Figure 8.45 The role of the three kinds of effector T cell in the response to typical pathogens.

immune system can gain the upper hand. Those at greatest risk are the young, the old, the malnourished, and those already suffering from other diseases. Some infections can never be cleared, because certain pathogens successfully evade or subvert the immune response so that they can persist in the body for life. In this latter category are the protozoan parasites *Leishmania* and *Toxoplasma*, and the herpes viruses, including Epstein–Barr virus, herpes simplex virus, and cytomegalovirus. Depending on the way in which a pathogen exploits the human body, the type of immune response that eliminates or contains it is different (Figure 8.45).

Summary

Most infections are highly localized and can be cleared by the innate immune response. Only if infection spreads to secondary lymphoid tissues, or its antigens are carried there by dendritic cells, is an adaptive immune response made, and its initiation is dependent on the inflammatory cytokines produced by the cells of innate immunity. In the secondary lymphoid tissues the presentation of pathogen-derived antigens to naive circulating T cells causes pathogen-specific T cells to divide and differentiate into effector T cells within the lymphoid tissue. The relative production of T_H1 and T_H2 effector CD4 T cells and of CD8 T cells depends on the nature of the infection and the mix of inflammatory cytokines produced at the site of infection. Effector T_H1 cells and CD8 T cells leave the lymphoid tissues and travel in the lymph and blood to the infected tissues. Once there, T_H1 cells activate the destruction of extracellular pathogens by macrophages, while CD8 T cells kill infected human cells. Effector T_H2 cells remain mainly in the lymphoid tissues, where they help to activate pathogen-specific B cells and drive isotype switching and affinity maturation of their immunoglobulins. There are differences in the delivery of antigen and in lymphocyte traffic for infections arising at mucosal surfaces compared to skin infections.

Immunological memory and the secondary immune response

As well as clearance of the infection, a successful primary adaptive immune response also establishes a state of long-term **protective immunity**. A second or subsequent encounter with the same pathogen will provoke a faster, stronger, **secondary immune response**. This is produced by circulating antibody and by clones of long-lived B and T cells that have been formed during the primary response. In a person with protective immunity, the infection is

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usually cleared before it produces any symptoms. The purpose of vaccination is to produce a state of protective immunity against a particular pathogen before the pathogen itself is encountered.

8-23 Immunological memory after infection is long lived

In the period immediately after recovery from an infection, a person will usually encounter the pathogen again as it is passed around family, friends, colleagues, and other members of the community. Such reinfections are terminated quickly by the effector cells and antibodies built up during the first infection. Specific antibodies present in blood and extracellular fluids as a result of a primary immune response are one of the first immune defenses encountered by a pathogen on a subsequent infection. Their rapid action prevents the infection from becoming established. As a result of the reinfection, new supplies of antibody and effector cells will be made. In the absence of further infection the levels of antibody and effector T cells gradually decline, eventually reaching very low levels that are no longer effective. However, the B- and T-cell populations retain a 'memory' of the infection that enables a rapid and powerful secondary adaptive immune response to be made should reinfection occur, even many years after the primary infection. Memory is sustained by populations of pathogen-specific memory B and T cells that persist over long periods of time and can be reactivated when confronted with the pathogen. Memory B and T cells are activated more quickly and in greater numbers than naive lymphocytes were in the primary response. As a consequence, the infection is cleared quickly by the secondary response, with few or no symptoms of disease (Figure 8.46).

This phenomenon of **immunological memory** is classically illustrated by epidemiological studies of the inhabitants of one of the Faroe Islands in the North Atlantic Ocean, who were severely affected by a measles epidemic that infected the entire population. Many years later, when measles virus was again introduced to the island, only those members of the population born after the original epidemic developed disease. All those who had survived the first measles epidemic retained a protective immunity that prevented their second measles infection from becoming established and causing disease.

8-24 Pathogen-specific memory B cells are more abundant and make better antibodies than naive B cells

During a primary infection, proliferation of antigen-specific B cells produces plasma cells to confront the ongoing infection and **memory B cells** to deal with future infections. A few weeks after a primary infection has been cleared, the number of memory B cells reaches a maximum, which is sustained for

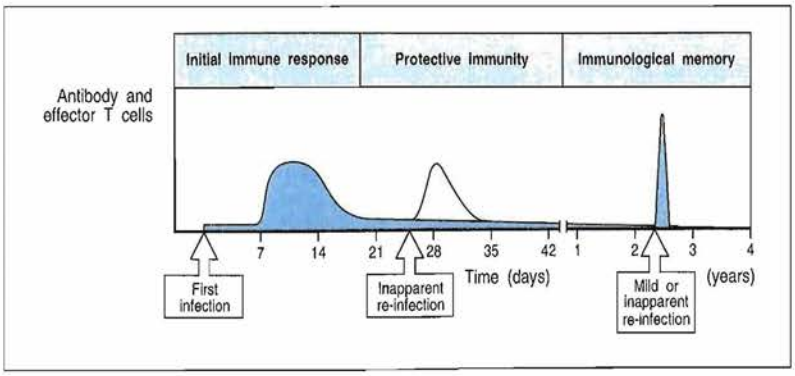


Figure 8.46 Protective immunity consists of preformed antibodies and existing effector T cells, and of immunological memory. The abundance of pathogen-specific antibodies and effector T cells is tracked here through the course of a person's successive exposures to a pathogen. During first infection the level rises, reaching a plateau as the immune system gains control. After clearance the levels decline, but for a time are sufficient to quickly terminate any reinfection. After an extended period without exposure to the pathogen, levels decline to the point where protective immunity is mediated by memory B and T cells, which respond rapidly to infection by producing new supplies of antibody and effector T cells.

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life. On secondary infection, 10–100 times more pathogen-specific B cells respond than did naive B cells in the primary response. Not only is the number of pathogen-specific B cells greater in the secondary response, the overall affinity of the antibodies they make is increased. Memory B cells are also distinguished from naive B cells by their ability to make antibodies of isotypes other than IgM. The population of memory B cells generated by the primary response includes cells that have switched to IgG, IgA, and IgE, so these isotypes emerge at the very beginning of a secondary response.

Both the amount of antibody and its average affinity continue to increase upon successive infections with, or vaccinations against, a pathogen (Figure 8.47). Increase in affinity is much greater for IgG than for IgM, because the IgG derives from isotype-switched B cells that have undergone somatic hypermutation and affinity maturation in germinal centers (see Section 7-4, p. 188). IgM, in contrast, is produced chiefly from B cells that differentiate early in the immune response and retain unchanged the antigen-binding sites of the naive B-cell receptors. The progressive increase in the affinity of antibody in the blood is therefore due to the replacement of IgM with IgG and IgA having mutated antigen-binding sites of higher affinity (see Section 7-4, p. 188).

The higher affinity of their antigen receptors makes memory B cells more efficient than naive B cells in binding and internalizing antigen for processing and presentation to helper T cells. Memory B cells also express high levels of MHC class II molecules on their surface compared with naive B cells, which also makes their presentation of antigen more efficient. These factors enable the secondary response to be more sensitive to the presence of antigen. Smaller pathogen populations are sufficient to trigger a B-cell response, which will therefore occur at a time earlier during an infection than was the case for the primary response.

By the generation and maintenance of populations of antigen-specific memory B cells, the immune system makes a heavy investment in protection against re-exposure to infections already experienced and survived. For these, a strong memory B-cell response can be recalled years after infection. There is an obvious advantage to this strategy. Infections are passed from person to person within human populations, often over extended periods, and the likelihood of repeated exposure to the same pathogen remains high. Antibodies produced in the primary response remain in the blood and lymph for some time after the infection has cleared. They are important contributors to a secondary response because they can bind to pathogens immediately the pathogen enters the body. The strength of B-cell memory is such that even with organisms that produce high mortality on first infection, for example the smallpox virus, the mortality on secondary exposure is very low.

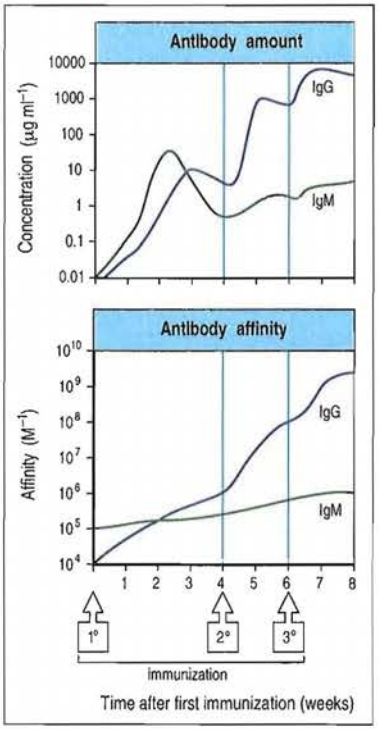


Figure 8.47 The amount and affinity of antibody increase after successive immunizations with the same antigen. The upper panel shows the increase in the amount of antibody present in blood serum over a course of three immunizations with the same antigen. The relative amounts of the IgM (green) and IgG (blue) isotypes are shown. The lower panel shows the changes in average antibody affinity that occur. Note that the vertical axis of each graph has a logarithmic scale.

8-25 T-cell memory is maintained by T cells that have different cell-surface markers from naive T cells

Memory T cells have been harder to study than memory B cells, because T cells do not undergo isotype switching and somatic hypermutation, processes that indelibly mark memory B cells as different from effector cells of the primary response. In the absence of cell-surface markers that absolutely distinguish memory T cells from effector T cells, the distinction is made using several cell-surface proteins that are expressed at distinguishable levels or in different forms on the surface of naive cells and memory cells (Figure 8.48). Of these changes, those affecting the tyrosine phosphatase CD45 are particularly important, both for T-cell function and for distinguishing naive and memory T cells. Isoforms of CD45 having differently sized extracellular domains are produced by alternative patterns of mRNA splicing. Naive T cells predominantly express the CD45RA isoform, which has a larger extracellular domain associated with

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Cell-surface molecule	Other names	Relative expression on cells of indicated subset		Comments
		Naive	Memory	
LFA-3	CD58	1	>8	Ligand for CD2, involved in adhesion and signaling
CD2	T11	1	3	Mediates T-cell adhesion and activation
LFA-1	CD11a/CD18	1	3	Mediates leukocyte adhesion and signaling
α_4 integrin	VLA4	1	4	Involved in T-cell homing to tissues
CD44	Ly24 Pgp-1	1	2	Lymphocyte homing to tissues
CD45RO		1	30	Lowest molecular weight isoform of CD45
CD45RA		10	1	High molecular weight isoform of CD45
L-selectin		High	Most high, some low	Lymph node homing receptor
CD3		1.0	1.0	Part of T-cell receptor complex

Figure 8.48 Naive and memory T cells differ in their surface phenotype. Many of the cell-surface molecules that distinguish memory T cells from naive T cells are also shared with effector T cells. The changes serve to increase the adhesion of the T cell to antigen-presenting cells and to endothelial cells and also to increase the sensitivity of the memory T cell to antigen stimulation.

weaker signals in response to specific antigen; memory T cells predominantly express the CD45RO isoform which has a smaller extracellular domain associated with stronger signals in response to antigen (Figure 8.49).

Direct functional evidence for a memory T cell with distinctive properties comes largely from the study of CD8 cytotoxic T cells. Memory CD8 T cells differ from effector cytotoxic CD8 T cells in that they need an induction period

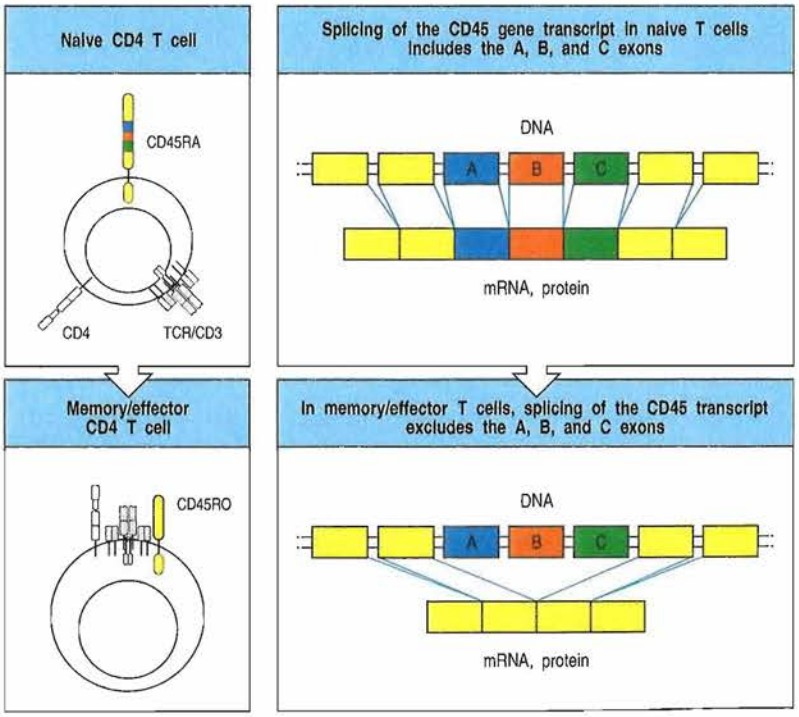


Figure 8.49 Memory CD4 T cells express an altered CD45 isoform with modified interactions with the T-cell receptor and co-receptors. CD45 is a transmembrane tyrosine phosphatase involved in T-cell activation. Through differential splicing of CD45 mRNA, the isoform of CD45 expressed by naive CD4 T cells, called CD45RA, is larger than the isoform expressed by memory CD4 T cells, called CD45RO. The absence of the sequences encoded by exons A, B, and C in CD45RO enables it to associate with both the T-cell receptor and the CD4 co-receptor and improve the efficiency of signal transduction.

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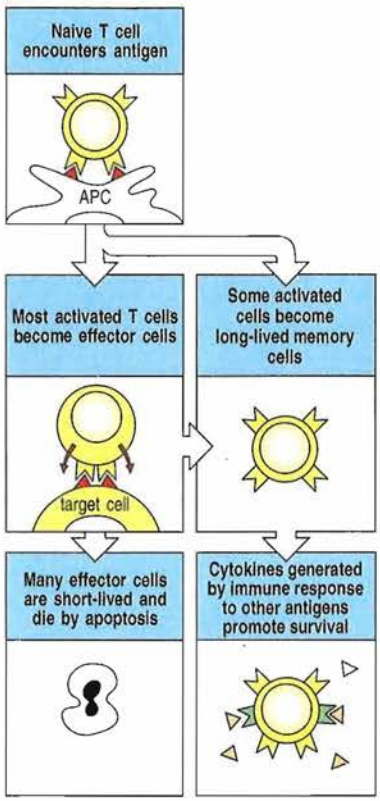


Figure 8.50 Encounter with antigen generates effector T cells and long-lived memory T cells. Most of the effector T cells generated from antigen-stimulated naive T cells are relatively short lived, dying either from antigen overload or from lack of antigenic stimulus or necessary cytokines. Some, however, become long-lived memory T cells. In order to persist, the memory cells need periodic stimulation with cytokines; these are generated in the course of immune responses to antigens different from the antigens specific for the memory cells themselves.

of 1–2 days before they have the capacity to lyse target cells. Effector CD8 T cells, on the other hand, can program a target cell for lysis in a matter of minutes. Memory CD8 T cells are also unlike naive CD8 T cells because their induction period is shorter than that for naive T cells and no cell division is involved. Although memory CD8 T cells can be stimulated without help from CD4 T cells, the quality and quantity of the resulting response is improved by the participation of CD4 T cells.

The evidence for memory CD4 T cells is less direct, principally because helper function (for example, the stimulation of antibody production by B cells) requires several days after antigen stimulation to become measurable, a period comparable to that needed for the presumed induction. By contrast, the cytolytic function of CD8 T cells can be determined within a few hours after completion of the induction period. What has been defined is a subset of CD4 T cells in immunized animals that have the characteristic cell-surface marker molecules of effector cells but different activation requirements. Unlike effector CD4 T cells, these presumed memory T cells can be stimulated to secrete effector cytokines only by antigen presented by a professional antigen-presenting cell.

A healthy adult human has 10^{12} peripheral α:β T cells, of which half are naive T cells and half are memory T cells. From sequence analysis of T-cell receptors it is estimated that the naive T cells have 2.5×10^7 antigen specificities and the memory T cells have only 1.5×10^5 antigen specificities. The acquisition of T-cell memory for a pathogen means that, on average, 100-fold more T cells will respond to a secondary infection with a pathogen than responded to the primary infection.

8-26 Maintenance of immunological memory does not require stimulation with antigen

A general property of lymphocytes is their requirement for regular stimulation in order to survive. If such survival signals are not received, then lymphocytes die through apoptosis. For naive circulating T cells, survival signals are generated through interactions of the T-cell receptor with complexes of MHC and self-peptides on the surface of healthy cells. These interactions are similar to those that caused positive selection of the lymphocytes during development in the thymus.

Memory CD8 T cells do not receive their survival signals from receptor-mediated interactions with peptide:MHC complexes but through antigen-independent stimulation involving the cytokine IL-15, which is induced as part of the interferon response. The cellular receptor for IL-15 has two of its polypeptides in common with the IL-2 receptor, and the two cytokines have complementary properties: IL-15 causes memory cells to proliferate, whereas IL-2 inhibits their proliferation. It seems that memory CD8 T-cell populations are maintained in the absence of secondary infection with specific pathogen, and this is achieved by continuing cell division and turnover, which is stimulated by cytokines produced as a general result of any immune activity (Figure 8.50). By this process, which is also implicated in

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sustaining the memory B-cell population, the maintenance of immunological memory does not require the presence of specific antigen or its persistence in the body following resolution of infection.

Although the overall size of the memory CD8 T-cell population remains stable, the number of memory cells that represent memory to a particular pathogen changes with time and history of infection. To accommodate the memory T cells acquired upon infection with a current virus, some of the memory T cells corresponding to previous infections with other viruses will be lost. Such losses can be recouped on subsequent reinfections. Although recent or recurrent infections will be better represented in the memory-cell population, this does not unduly compromise the memory response to other infections: elderly humans can make effective secondary responses to pathogens which were only encountered in childhood.

8-27 The second and subsequent responses to a pathogen are mediated solely by memory lymphocytes and not by naive lymphocytes

The secondary adaptive immune response to a pathogen involves the reactivation of clones of B and T cells that were first activated and expanded during the primary response. Activation of naive lymphocytes with specificity for the pathogen does not occur in a secondary immune response. This is because the cells and molecules made during the primary response prevent the activation of naive lymphocytes. This phenomenon is put to practical use in prevention of the **hemolytic anemia of the newborn** caused by antibodies specific for the rhesus (Rh) antigen on erythrocytes. If a Rh^- mother carrying a Rh^+ child is infused with anti-Rh IgG antibody before she begins to make an immune response to her child's red cells, the response will be inhibited. Fetal red cells that enter the maternal circulation bind the anti-Rh IgG antibodies. When these red cells subsequently bind to the surface immunoglobulin of naive maternal B cells that are Rh specific, a cross-linking of B-cell receptors and Fc receptors occurs. This cross-linking delivers an inhibitory signal to the naive B cell. In contrast, when the same antigen:antibody complexes interact with the antigen receptors and the Fc receptors on the surface of memory B cells, an activating signal is delivered (Figure 8.51).

Such a mechanism, whereby the primary response to a pathogen or antigen prevents the further activation of naive cells during a secondary response, is believed to underlie the phenonemon of **original antigenic sin.** This implicitly puritanical term was coined on the basis of observations that the first influenza strain encountered by a person constrained the types of antibody

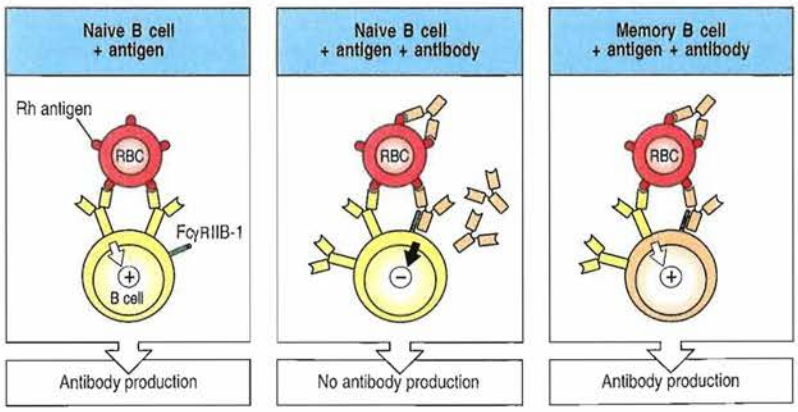


Figure 8.51 IgG antibody suppresses the activation of naive B cells by cross-linking the B-cell receptor to the receptor FcγRIIB-1 on the B-cell surface. Antigen binding to the B-cell antigen receptor delivers an activating signal (left panel) via the B-cell receptor; simultaneous signaling via the antigen receptor and FcγRIIB-1 delivers a negative signal to naive B cells (middle panel). Such cross-linking does not affect memory B cells (right panel). In this example the antigen is the Rh^+ alloantigen of erythrocytes. In pregnancy a fetus that is Rh^+ can stimulate an Rh^- mother to make Rh^--specific antibody. This response can be inhibited by prior infusion of some anti-Rh IgG antibody.

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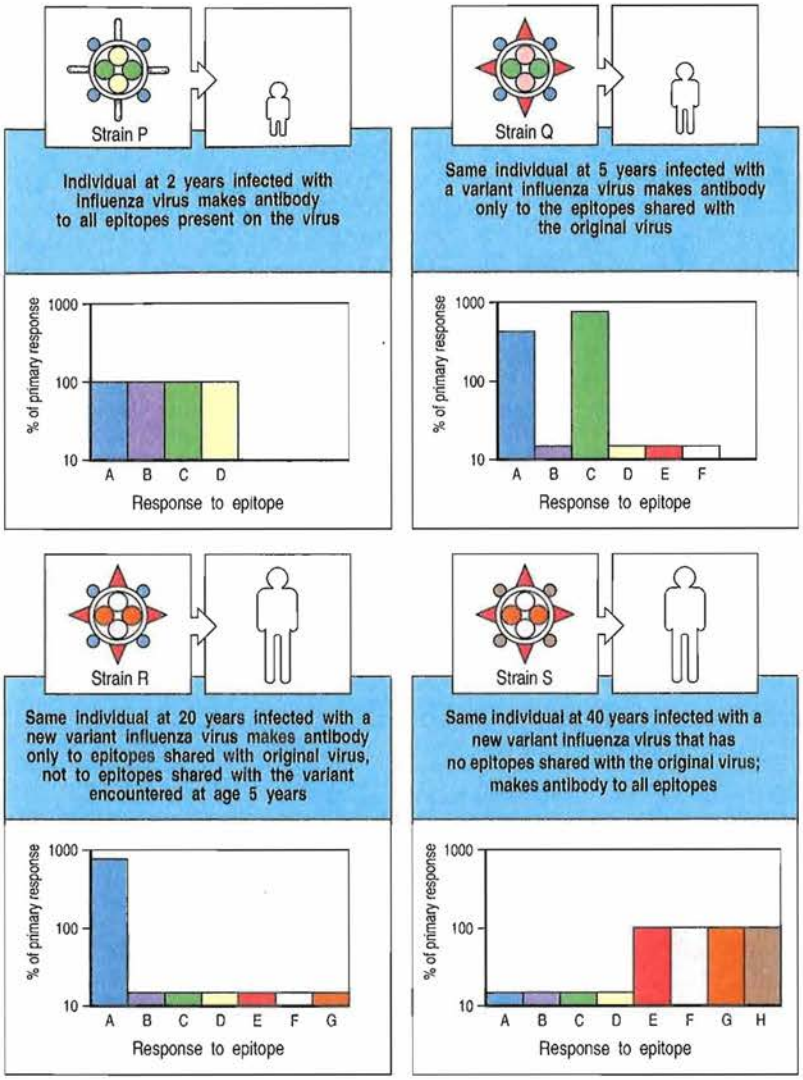


Figure 8.52 Highly mutable viruses such as influenza can escape from the protective immunity of the human host without eliciting new immunity to the changes in the virus. A child 2 years old is infected with influenza virus strain P and responds by making antibodies against all the viral epitopes: A, B, C, and D (top left panels). At 5 years old the child is infected with the Q strain of the virus, which shares epitopes A and C with strain P but has new epitopes E, and F. The child's immune system uses only memory B cells resulting from the earlier infection with strain P in defense against strain Q and so the response is restricted to antibodies against epitopes A and C (top right panels). At 20 years old, the same individual is infected with a third strain of influenza, R, which has epitope A in common with strain P, epitopes E and F in common with strain Q, and a new epitope, G. Even 18 years after the first influenza infection, the antibody response concentrates solely on epitope A, which is shared with strain P (bottom left panels). Only when the person is infected with influenza strain S, which lacks epitopes A, B, C, and D, can a primary response be made to epitopes E, F, G, and H of strain S (bottom right panels). Strain S is seen as a novel virus to the person's immune system and as a consequence the person will likely suffer a full blown influenza as a result of this infection.

made in response to future infections with different strains. During a second infection only those epitopes that are common to the infecting strain and the original strain stimulate antibody production. This dependence on the memory cells that developed during the first infection is seen even when subsequent infections involve influenza strains with highly immunogenic epitopes that are different from those on the original strain. The strategy of the immune system is to use only B cells that are rapidly and easily mobilized. This allows the highly mutable influenza virus to increasingly escape from the protective immunity of a host while the host's immune system is paralyzed and prevented from responding to the changes in the virus. As a result, protective immunity to influenza is not retained for life, and the virus successfully infects millions of human beings every year. The imprint made by original antigenic sin is broken only on infection with a strain of influenza that lacks all the B-cell epitopes of the strain to which a person was first exposed (Figure 8.52).

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Summary

In the course of the primary immune response, effector T cells and antibodies accumulate. Once an infection has been cleared, these cells and molecules will prevent reinfection by the same pathogen in the short term. In the long term, persistent clones of memory B and T cells expanded during the primary response afford protective immunity if the same antigen is encountered. When that happens they mount a secondary response that is both stronger and more rapid than the primary response. Antibodies produced in the secondary response are of higher affinity and of isotypes other than IgM. Activation of naive lymphocytes is suppressed and only memory lymphocytes are reactivated. In a secondary immune response, the immune system, therefore, devotes all its resources to producing high-affinity antibodies and specific T cells that rapidly clear the invading pathogen before the infection can become established. The maintenance of memory cells does not appear to require the persistence of the original antigen; instead, survival signals for memory lymphocytes are provided by cytokines such as IL-15.

Summary to Chapter 8

The human body has three types of defense, all of which must be overcome if a pathogen is to establish an infection and then exploit its human host for the remainder of that person's life. The first defense is made up of the protective epithelial surfaces of the body, which successfully prevent most pathogens from ever gaining entry to the rich resources of the body's interior. Any pathogen that succeeds in penetrating an epithelial surface is immediately faced by the recognition molecules and effector cells of innate immunity. Some of these elements of immunity have been refined over hundreds of millions of years to respond to the distinguishing features of bacteria and other groups of pathogens. Viruses pose a different challenge, because they are made by human cells and, unlike bacteria, do not have chemically distinctive surface macromolecules that nonspecifically distinguish them from human cells. However, NK cells have receptor systems that can sense subtle changes in the surface of infected cells and, by killing the cells, eliminate or contain viral infections.

Most infections are efficiently cleared by the innate immune response and lead to neither disease nor incapacitation. In the minority of infections that escape innate immunity and spread from their point of entry, the pathogen then faces the combined forces of innate and adaptive immunity. The week or so required for the primary adaptive immune response to develop is the time during which the body is most vulnerable and during which infections can progress to the point of causing disease, damage, and even death. This delay, during which the pathogens have the upper hand and can be transmitted to other people, is largely responsible for the devastation caused by epidemic infections. Most infections, however, never reach that stage, but are successfully terminated by the adaptable and specific recognition systems of adaptive immunity. A successful recovery from infectious disease and the consequent development of immunological memory provide the body with enhanced defenses that will repel future attack from the causal agent (Figure 8.53). Once a state of immunity has been established, a subsequent encounter with the pathogen provokes a stronger and more rapid attack that clears the pathogen from the body before the infection can take hold.

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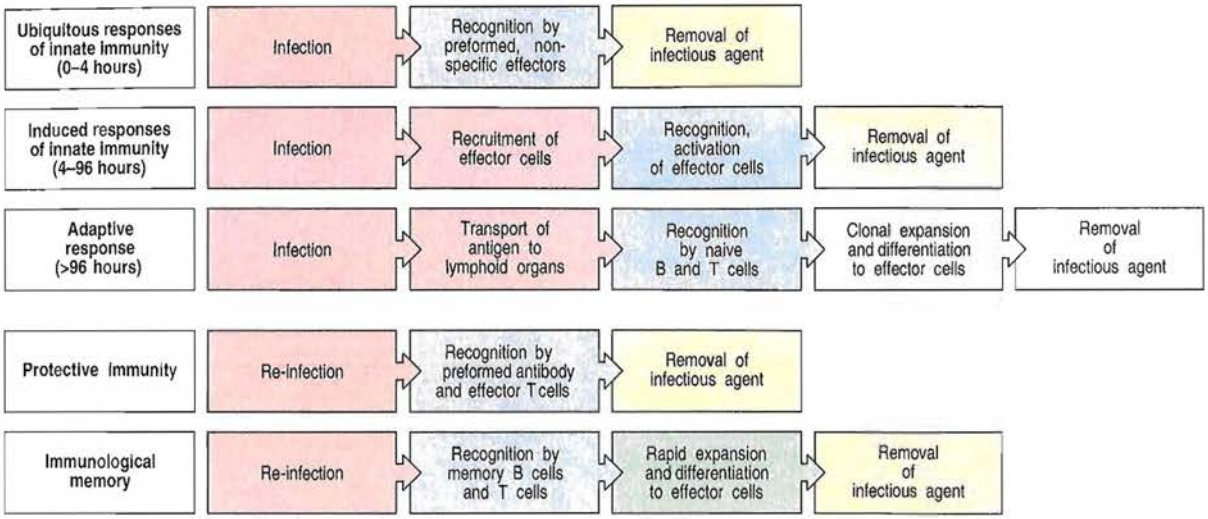


Figure 8.53 The immune response to an initial infection. The innate immune response can be divided into mechanisms that start immediately on infection, for example complement activation and macrophage phagocytosis, and those induced within a few hours by inflammatory cytokines. The effector functions of adaptive immunity begin to work only after 4 or more days. In the period after the termination of an infection, the effector cells and molecules made in the primary response continue to provide protective immunity but gradually decline. In the long term, immunological memory enables the strength of the secondary response to far surpass the primary response.

Questions

Question 8–1

Describe (a) three direct and (b) three indirect mechanisms through which pathogens cause damage to their hosts. (c) Give an example of an infectious agent and the disease it causes through each mechanism. (Refer to Figure 8.3.)

Question 8–2

When an infection establishes itself at a particular anatomical site the microenvironment influences which immune response will be induced and used to eradicate the pathogen.

A. Name the specific extracellular and intracellular locations where infections can be established, indicating which are extracellular and which are intracellular.

B. Viruses can be found both outside and inside cells. Describe the immune mechanisms used to eradicate them in each case.

C. Which intracellular site is colonized by trypanosomes? What immune mechanism is used against them when in this location?

D. Which class of antibodies would be most likely to act against pathogens that colonize epithelial surfaces? Give an example of such a pathogen. (Refer to Figure 8.4.)

Question 8–3

Surface epithelia lining the skin and respiratory, urogenital and gastrointestinal tracts provide protective barriers for the body against the external environment where pathogens are encountered.

A. Describe the three main ways in which epithelia act as barriers to infection, giving details of the various mechanisms employed.

B. How can antibiotics upset the barrier function of intestinal epithelia? Give a specific example. (Refer to Figures 8.6 and 8.7)

Question 8–4

A. What are the main (i) similarities and (ii) differences in the general properties and roles of macrophages and neutrophils?

B. How do they both destroy extracellular pathogens? Give details of the process. (Refer to Figures 8.20 and 8.21.)

Question 8–5

Describe in chronological order the four steps involved in the extravasation of neutrophils to infected tissue sites during an innate immune response. Use the following terms in your description: rolling adhesion, tight binding, diapedesis, migration, inflammatory mediators, integrins,

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adhesion molecules, chemokines, Weibel–Palade bodies, P-selectin, E-selectin, sialyl-Lewis^x and basement membrane protease. (Refer to Figure 8.19.)

Question 8–6

A. Using the table below match the local and systemic effects in Column A with the appropriate cytokine in Column B. Note that more than one answer in Column B may be used.

B. Which of these cytokines are produced by macrophages? Which cells produce the other(s)? (Refer to Figures 8.15, 8.22, 8.25, and 8.27.)

Column A	Column B
a. Activation of blood vessel endothelium	1. IL-1
b. Lymphocyte activation	2. IL-6
c. Fever	3. CXCL8
d. Induction of IL-6 synthesis	4. IL-12
e. Increase in vascular permeability	5. TNF-α
f. Localized tissue destruction	6. Type I interferons
g. Production of acute-phase proteins by hepatocytes	
h. Induction of resistance to viral replication	
i. Increase in levels of MHC class I molecules on cell surfaces	
j. Activation of NK cells	
k. Biased differentiation of naive T cells into T_H1 cells	
l. Enhanced antibody production	
m. Leukocyte chemotaxis	
n. Activation of binding by β_2 integrins (LFA-1, CR3)	
o. Septic shock	
p. Mobilization of metabolites	

Question 8–7

A. What induces type I interferon production?

B. Do normal cells produce this inducer? Why, or why not?

C. Identify three effects of type I interferons during viral infection. (Refer to Figures 8.25 and 8.26.)

Question 8–8

Natural killer cells (NK cells) carry so-called activating and inhibitory receptors on their surface.

A. What property of NK cells do these receptors activate and inhibit, respectively? Explain your answer.

B. How are NK cells thought to use these receptors to recognize and eliminate virus-infected cells?

C. Why are the actions of NK cells considered nonspecific and categorized as innate immunity?

D. Why do the NK cells of the recipient of an organ transplant sometimes attack the transplanted tissue? (Refer to Figures 8.29, 8.32, and 8.33.)

Question 8–9

A. Explain briefly how immunological memory operates in (i) the short term and (ii) the long term.

B. Why is a secondary immune response, which may occur many years after the first exposure to the pathogen, initiated much more rapidly than a primary immune response?

Question 8–10

List some of the differences in cell-surface molecules between naive T cells and memory T cells, and explain how these differences help memory T cells to mount a strong secondary immune response. (Refer to Figures 8.48 and 8.49.)

Question 8–11

During inflammation, host tissue may be damaged owing to the release of toxic oxygen derivatives produced by activated macrophages and neutrophils. Explain how host mechanisms are induced to limit these damaging bystander effects.

Question 8–12

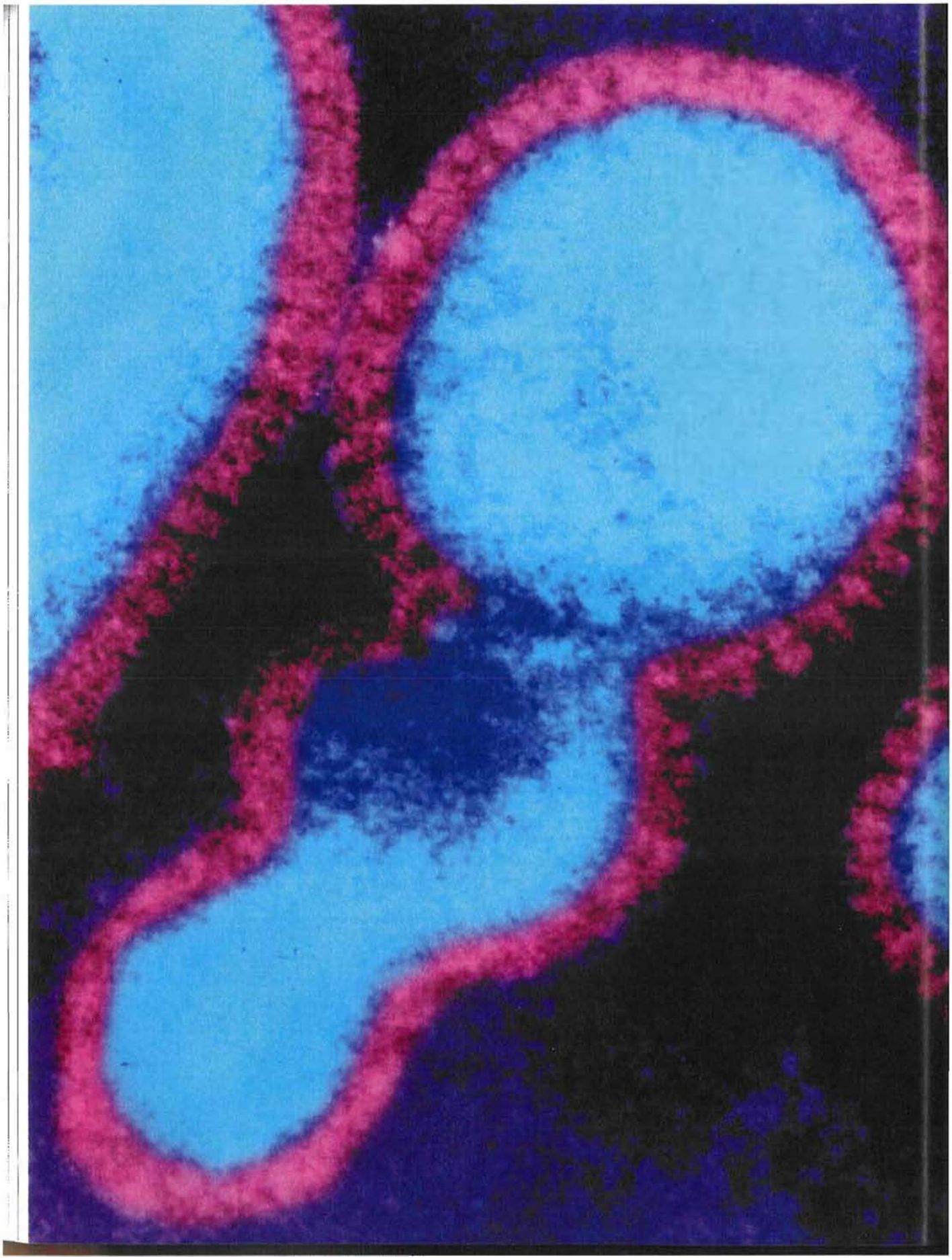
Explain specifically how the systemic release of TNF-α by macrophages causes (a) septic shock, (b) disseminated intravascular coagulation, (c) organ failure, and (d) hemorrhaging during infection with blood-borne pathogens. (Refer to Figure 8.18.)

Question 8–13

A. In the context of antibody production, explain how the phenomenon of 'original antigenic sin' is exploited clinically to prevent hemolytic anemia of the newborn.

B. Which receptors must be cross-linked for this to occur? (Refer to Figure 8.51.)

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Chapter 9

Failures of the Body's Defenses



In Chapter 8 we saw how most pathogens that threaten the human body are prevented from establishing infection, and that those infections that do occur are usually terminated by the actions of innate and adaptive immunity. In this situation there is strong pressure on pathogens to evolve ways of escaping or subverting the immune response. Microorganisms with such advantages can compete more successfully with other potential pathogens to exploit the resources of the human body. The first part of this chapter describes examples of the different types of mechanism they use.

The body's defenses against infection can also fail because of inherited deficiencies of the immune system. Some of these are described in the second part of the chapter. Within the human population there are mutant alleles for many of the genes encoding components of the immune system. These mutant genes cause immunodeficiency diseases, which vary in severity depending on which gene is defective. Correlation of the molecular defects in immunodeficiency diseases with the types of infection to which patients become vulnerable reveals the effectiveness of the various arms of the immune response against different kinds of pathogen.

In the third part of the chapter we explore one particular host–pathogen relationship that combines themes from the first two parts of the chapter. This concerns the human immunodeficiency virus (HIV), which is extraordinarily effective at both escaping and subverting the immune response. During the course of an infection, which can last for decades, HIV gradually but inexorably wears down the immune system to the point where it no longer works. The long-term consequence of HIV infection is that patients become severely immunodeficient and develop the fatal disease known as acquired immune deficiency syndrome (AIDS).

Evasion and subversion of the immune system by pathogens

The immune response to any pathogen involves complex molecular and cellular interactions between the pathogen and its host, and any stage in this interaction could be targeted by a pathogen and used for its own benefit. The systematic study of pathogen genomes reveals that most, if not all, pathogens have means of escaping or subverting immune defenses, and that some of them have many genes devoted to this purpose.

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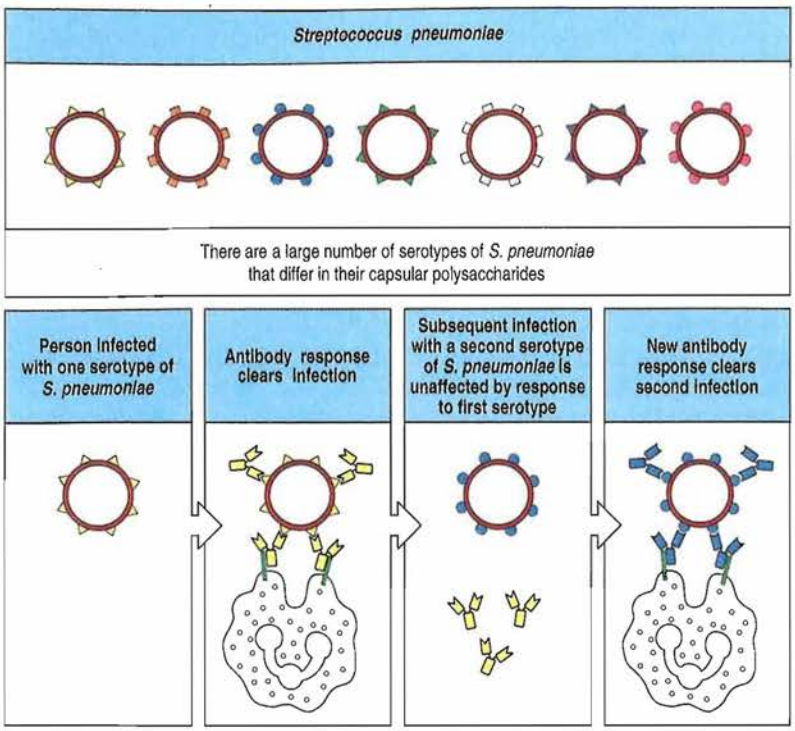


Figure 9.1 Protective immunity towards *Streptococcus pneumoniae* is serotype-specific. Different strains, or serotypes, of *S. pneumoniae* have antigenically different capsular polysaccharides, as shown in the upper panel. Antibodies against capsular polysaccharides opsonize the pathogen and enable it to be phagocytosed. A person infected with one serotype of *S. pneumoniae* clears the infection with type-specific antibody, as shown in the lower panels. These antibodies, however, have no protective effect when the same person is infected with a different type of *S. pneumoniae*. The second infection can be cleared only by a new primary response.

9-1 Genetic variation within some species of pathogen prevents effective long-term immunity

Antibodies directed against macromolecules on the surfaces of pathogens are the most important source of long-term protective immunity to many infectious diseases. Some species of pathogen evade such protection by existing as numerous different strains, which differ in the antigenic macromolecules on their outer surfaces. One such is the bacterium *Streptococcus pneumoniae*, which causes pneumonia. Different genetic strains of *S. pneumoniae* differ in the structure of the capsular polysaccharides and compete with each other to infect humans. These strains, of which at least 90 are known, are called **serotypes** because antibody-based serological assays are used to define the differences between them. After resolution of infection with a particular serotype, or type, of *S. pneumoniae*, a person will have made antibodies that prevent reinfection with that type but which will not prevent primary infection with another type (Figure 9.1). *S. pneumoniae* is a common cause of bacterial pneumonia because its genetic variation prevents individuals from developing an effective immunological memory against all strains. Genetic variation in *S. pneumoniae* has evolved as a result of selection by the immune response of its human hosts.

9-2 Mutation and recombination allow influenza virus to escape from immunity

Some viruses also display genetic variation, influenza virus being a well-studied example. This virus infects epithelia of the respiratory tract and passes easily from one person to another in the aerosols generated by coughs and sneezes. Protective immunity to influenza is provided principally by antibodies that bind to the hemagglutinin and neuraminidase glycoproteins of the

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viral envelope. These antibodies are made during the primary immune response to the virus. The course of a primary infection is short (1–2 weeks) and the virus is cleared from the system by a combination of cell-mediated immunity and antibody. The pattern of infection of influenza virus characteristically causes **epidemics**, in which the virus spreads rapidly through the population and then quickly subsides. Long-term survival of the influenza virus is ensured by the generation of new viral strains that evade the protective immunity generated during past epidemics.

Influenza is an RNA virus with a genome consisting of eight RNA molecules. RNA replication is relatively error-prone and generates many point mutations on which selection can act. New viral strains that lack the hemagglutinin or neuraminidase epitopes that induced protective immunity in the previous epidemic regularly emerge and cause an influenza epidemic every other winter or so. An individual's protective immunity against influenza is determined by the strain of virus to which they were first exposed—the phenomenon of 'original antigenic sin' (see Section 8-27, p. 273). The history of exposure to particular strains of the virus differs within the population, largely according to age, and so there are subpopulations of people with differing degrees of immunity to the current strain of influenza. The people to suffer most at any particular time will be those whose protective immunity has been lost because of the new mutations present in the current strain. This type of evolution of influenza, which causes relatively mild and limited disease epidemics, is called **antigenic drift** (Figure 9.2, left panels).

In contrast, every 10–50 years an influenza virus emerges that is structurally quite different from its predecessors and is able to infect almost everyone. Besides spreading more widely to cause a **pandemic** (a worldwide epidemic), such viruses cause more severe disease and a greater number of deaths than do the viruses that result from antigenic drift. The influenza strains that cause pandemics are recombinant viruses that have some of their RNA genome derived from an avian influenza virus and the remainder from a human influenza virus. In these recombinant strains, the hemagglutinin and/or the neuraminidase are encoded by RNA molecules of avian origin and are antigenically very different from those against which people have protective immunity. New pandemic strains often arise in parts of south-east Asia where farmers live in close proximity to their livestock such as pigs, chickens, and ducks. One theory is that the recombinant viruses arise in pigs that have become simultaneously infected with both avian and human viruses. If such a recombinant jumps back into the human population it has a tremendous competitive advantage, and in sweeping through the human population will rapidly replace other viral strains. Recombinant influenza viruses can similarly sweep through bird populations and are greatly feared by poultry farmers. This mode of evolution is called **antigenic shift** (see Figure 9.2, right panels).

9-3 Trypanosomes use gene rearrangement to change their surface antigens

Mutation and recombination are not the only means by which pathogens can change the face they present to the immune system. Certain protozoans regularly change their surface antigens by a process of gene rearrangement, the most striking example being the African trypanosomes (for example, *Trypanosoma brucei*), which cause sleeping sickness. The trypanosome life cycle involves both mammalian and insect hosts. Insect bites transmit trypanosomes to humans, in whom the parasites replicate in the extracellular spaces. The trypanosome's surface is formed of a glycoprotein, of which there are numerous variants, each encoded by a different gene. The trypanosome

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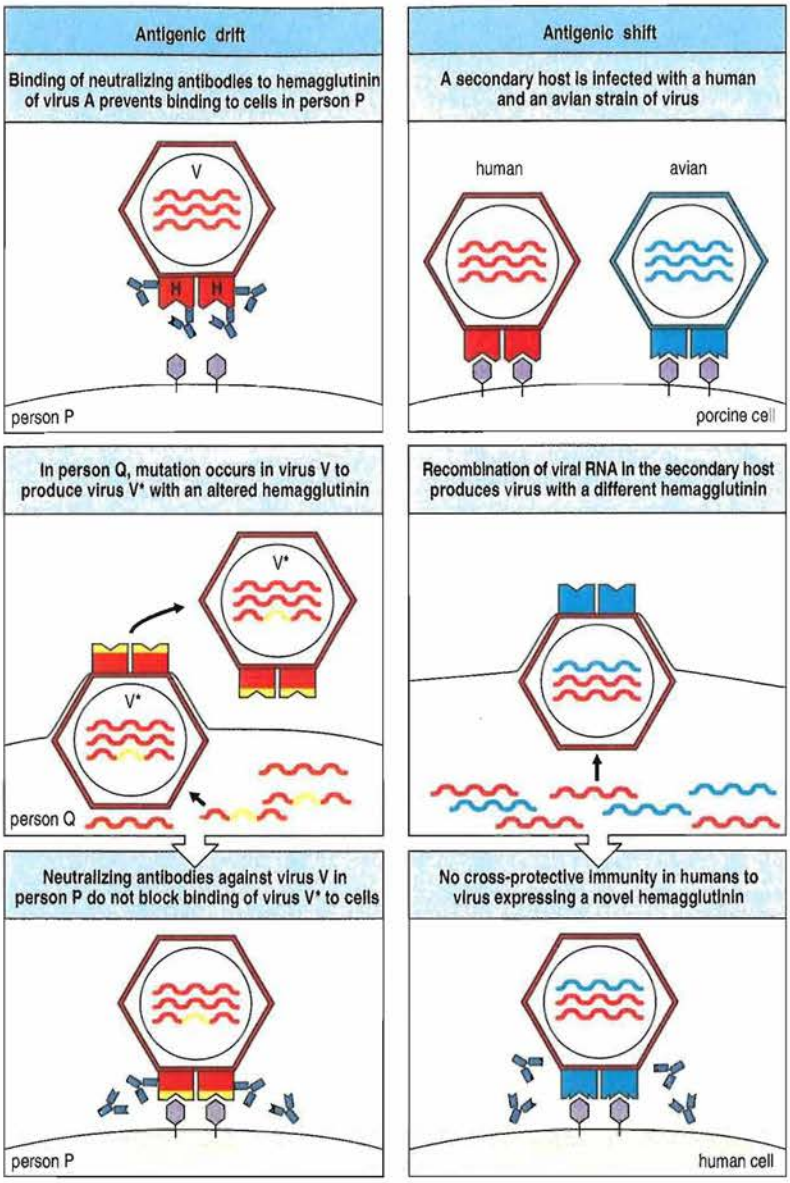


Figure 9.2 Variation in influenza virus due to mutation and recombination allows repeated infections. The left panels show the process of antigenic drift in the influenza virus. Only the viral hemagglutinin (H) is shown for simplicity. A person P infected with influenza strain V produces neutralizing antibodies against the viral hemagglutinin. When person P is further challenged with strain A, these antibodies bind to the hemagglutinin and prevent the virus from infecting cells (top panel). Person P is thus immune to strain V. Influenza virus mutates frequently, as depicted in the center panel where point mutation (yellow) in the hemagglutinin gene of strain V produces strain V* in which the hemagglutinin epitopes recognized by the preexisting protective antibodies are eliminated. This shift allows strain V* of influenza virus to infect cells of person P without obstruction from the antibodies previously made against strain V (bottom panel). For P to clear infection with strain V* requires a primary immune response to this strain with development of specific neutralizing antibodies. The right panels show the process of antigenic shift. A human influenza virus (red) and an avian influenza virus (blue) simultaneously infect a cell within the secondary host, a pig (top panel), and their RNA segments become reassorted to produce a recombinant virus (center panel). The recombinant virus expresses hemagglutinin of avian origin that is antigenically very different from that in the original human virus. The recombinant virus readily infects humans because antibodies protective against the original hemagglutinin cannot bind to the new hemagglutinin (bottom panel). For simplicity, only three of the eight RNA molecules are drawn.

genome contains more than 1000 genes encoding these **variable surface glycoproteins** (**VSG**s). At any time, an individual trypanosome produces only one form of VSG. This is because rearrangement of a VSG gene into a unique site in the genome—the expression site—is required for its expression. Rearrangement occurs by a process of gene conversion (Figure 9.3). The vast majority of the rapidly replicating trypanosomes that emerge after initial infection will express the same dominant form of VSG. A very small minority will, however, have changed the expressed VSG gene, and now express other forms. The host makes an antibody response to the dominant form of VSG, but not to the minority forms. Antibody-mediated clearance of trypanosomes expressing the dominant VSG facilitates the growth of those expressing the minority forms, of which one will come to dominate the trypanosome popu-

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lation. In time, the numbers of trypanosomes expressing the new dominant form are sufficient to stimulate antibody production, whereupon they too are cleared and yet other variants selected.

This mechanism of immune evasion causes trypanosome infections to produce a dramatic cycling in the number of parasites within an infected person (see Figure 9.3, bottom panel). The chronic cycle of antibody production and antigen clearance leads to a heavy deposition of immune complexes and inflammation. Neurological damage occurs and eventually leads to coma, the so-called sleeping sickness. Trypanosome infections are a major health problem for humans and cattle in large parts of Africa. Indeed it is largely because of trypanosomes that wild populations of big game animals still survive in Africa and have not been replaced by domestic cattle. Malaria, another disease caused by a protozoan parasite that escapes immunity by varying its surface antigens, is also a major cause of human mortality in equatorial Africa.

Trypanosomes change their coats by gene rearrangements similar to the gene conversions used by chicken B lymphocytes to produce their primary repertoire of immunoglobulins (see Section 4-1, p. 100). Similar strategies of antigenic variation are also used by several species of bacteria whose ability to escape from the human immune response makes them successful pathogens and major public-health problems. *Salmonella typhimurium*, a common cause of food poisoning, can alternate expression of two antigenically distinct flagellins, proteins of the bacterial flagella. This occurs by reversible inversion of part of the promoter of one of the flagellin genes, which inactivates that gene and allows the expression of the second gene. *Neisseria gonorrhoeae*, the cause of the widespread sexually transmitted disease gonorrhea, has several variable antigens, the most impressive being the pilin protein, a component of the adhesive pili on the bacterial surface. Like the VSGs of African trypanosomes, pilin is encoded by a family of variant genes, only one of which is expressed at a time. Different versions of the pilin gene introduced into the expression site provide a minority population of variant bacteria. When the host's immune response places pressure on the dominant type, another is ready to take its place.

9-4 Herpes viruses persist in human hosts by hiding from the immune response

To terminate an established viral infection, infected cells must be killed by cytotoxic CD8 T cells. For this to occur, some of the peptides presented by MHC class I molecules at the surface of infected cells must be of viral origin, a condition easily fulfilled by rapidly replicating viruses such as influenza. Consequently, influenza infections are efficiently cleared by the immune system by a combination of cytotoxic T cells and antibodies, the latter neutralizing extracellular virus particles. In contrast, some other viruses are difficult to clear because they enter a quiescent state within human cells, one in which they neither replicate nor generate enough virus-derived peptides to signal their presence to cytotoxic T cells. Development of this dormant state, which is called **latency** and does not cause disease, is a favored strategy of the herpes viruses. Later on, when the initial immune response has subsided, the virus will reactivate, causing an episode of disease.

Herpes simplex virus, the cause of cold sores, first infects epithelial cells and then spreads to sensory neurons serving the area of infection. The immune response clears virus from the epithelium, but the virus persists in a latent state in the sensory neurons. Various stresses can reactivate the virus, including sunlight, bacterial infection, or hormonal changes. After reactivation, the virus travels down the axons of the sensory neurons and reinfects

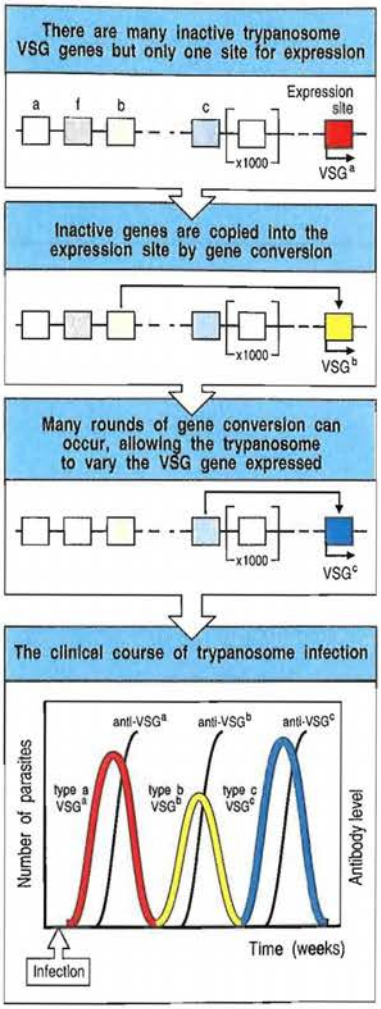


Figure 9.3 Antigenic variation by African trypanosomes allows them to escape from adaptive immunity. In the top panel, the VSG^a gene (shown in red) is in the expression site and the VSG^b gene (yellow) and VSG^c gene (blue) are inactive. In the second panel, gene conversion has replaced VSG^a with VSG^b at the expression site; in the third panel, VSG^c has replaced VSG^b at the expression site. The bottom panel shows how the patient's antibody response (thin black lines) to the VSG proteins selects for low-frequency variants and causes a cycle in which parasite populations (red, yellow, and blue lines) alternate between boom and bust over a number of weeks.

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the epithelial tissue (Figure 9.4). Viral replication in epithelial cells and production of viral peptides restimulates CD8 T cells, which kill the infected cells, creating a new sore. This cycle can be repeated many times throughout life. Neurons are a favored site for latent viruses to lurk because they express very small numbers of MHC class I molecules, further reducing the potential for presentation of viral peptides to CD8 T cells.

The herpes virus varicella-zoster (also called herpes zoster) remains latent in one or a few ganglia, chiefly dorsal root ganglia, after the acute infection of epithelium—chickenpox—is over. Stress or immunosuppression can reactivate the virus, which moves down the nerve and infects the skin. Reinfection causes the reappearance of the classic varicella rash of blisters, which cover the area of skin served by the infected ganglia. The disease caused by reactivation of varicella-zoster is commonly known as shingles. In contrast to herpes simplex virus, reactivation of varicella-zoster usually occurs only once in a lifetime.

A third herpes virus that causes a persistent infection is the Epstein–Barr virus (EBV), to which most humans are exposed. First exposure in childhood produces a mild cold-like disease, whereas adolescents or adults encountering EBV for the first time develop infectious mononucleosis (also known as glandular fever), an acute infection of B lymphocytes. EBV infects B cells by binding to the CR2 component of the B-cell co-receptor complex (see Figure 7.3, p. 184). Most of the infected B cells proliferate and produce virus, leading in turn to the stimulation and proliferation of EBV-specific T cells. The result is an unusually large number of mononuclear white blood cells (lymphocytes, mostly T cells), which gives the disease its name. After some time, the acute infection is brought under control by CD8 cytotoxic T cells, which kill the virus-infected B cells. The virus persists in the body, however, because a minority of B cells become latently infected. This involves shutting off the synthesis of most viral proteins except EBNA-1, which maintains the viral genome in these cells. Latently infected cells do not present a target for attack by CD8 cytotoxic cells because the proteasome is unable to degrade EBNA-1 into peptides that can be bound and presented by MHC class I molecules.

After recovery from the initial exposure to EBV it is unusual for reactivation of the virus to lead to disease. It seems likely that CD8 T cells quickly control episodes of viral reactivation. In immunosuppressed patients, however, reactivation of the virus can cause a disseminated EBV infection, and infected B cells can also undergo malignant transformation, causing B-cell lymphoproliferative disease.

9-5 Certain pathogens sabotage or subvert immune defense mechanisms

Pathogens also exploit the immune-system cells that are ranged against them. For example, *Mycobacterium tuberculosis* commandeers the macrophage's pathway of phagocytosis for its own purposes. On being phagocytosed, *M. tuberculosis* prevents fusion of the phagosome with the lysosome, thus protecting itself from the bactericidal actions of the lysosomal contents. It then survives and flourishes within the cell's vesicular system. *Listeria monocytogenes*, in contrast, escapes from the phagosome into the macrophage's cytosol, where it grows and replicates. However, the intracytosolic way of life elicits cytotoxic CD8 T-cell responses against *L. monocytogenes*, which eventually terminate the infection.

The protozoan parasite *Toxoplasma gondii*, the cause of **toxoplasmosis**, creates its own specialized environment within the cells that it infects. It

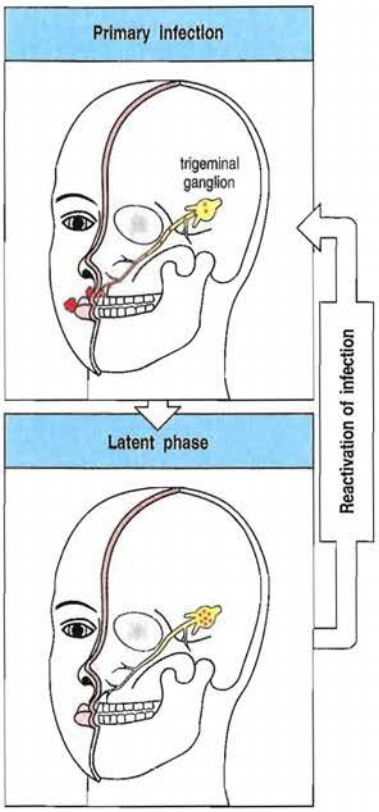


Figure 9.4 Persistence and reactivation of herpes simplex virus infection. The initial infection around the lips is cleared by the immune response and the resulting tissue damage is manifest as cold sores (upper panel). The virus (small red dots) has meanwhile entered sensory neurons, for example those in the trigeminal ganglion whose axons innervate the lips, where it persists in a latent state (lower panel). Various types of stress can cause the virus to leave the neurons and reinfect the epithelium, once again reactivating the immune response and causing cold sores. People infected with herpes simplex viruses periodically get cold sores as a result of this process. During its active phase the virus can be passed from one person to another.

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surrounds itself with a membrane-bounded vesicle that does not fuse with other cellular vesicles or cell membranes. Such isolation prevents the binding of *T. gondii*-derived peptides to MHC molecules and their presentation to T cells. The spirochete *Treponema pallidum*, the cause of syphilis, evades specific antibody by coating itself with human proteins. This is also a strategy pursued by the schistosome, a parasitic helminth.

Of the four groups of pathogens (see Figure 1.2, p. 3), viruses have evolved the greatest variety of mechanisms for subverting or escaping immune defenses. This is because their replication and life cycle depend completely on the metabolic and biosynthetic processes of human cells. Viral self-defense strategies include: capture of cellular genes encoding cytokines or cytokine receptors, which when expressed by the virus can divert the immune response; synthesis of proteins that inhibit complement fixation; and synthesis of proteins that inhibit antigen processing and presentation by MHC class I molecules. Examples of defensive mechanisms used by herpes viruses and pox viruses are shown in Figure 9.5.

Viral strategy	Specific mechanism	Result	Virus examples
Inhibition of humoral immunity	Virally encoded Fc receptor	Blocks effector functions of antibodies bound to infected cells	Herpes simplex Cytomegalovirus
	Virally encoded complement receptor	Blocks complement-mediated effector pathways	Herpes simplex
	Virally encoded complement control protein	Inhibits complement activation of infected cell	Vaccinia
Inhibition of inflammatory response	Virally encoded cytokine homolog, e.g., β-chemokine receptor	Sensitizes infected cells to effects of β-chemokine; advantage to virus unknown	Cytomegalovirus
	Virally encoded soluble cytokine receptor, e.g., IL-1 receptor homolog, TNF receptor homolog, interferon-γ receptor homolog	Blocks effects of cytokines by inhibiting their interaction with host receptors	Vaccinia Rabbit myxoma virus
	Viral inhibition of adhesion molecule expression, e.g., LFA-3 ICAM-1	Blocks adhesion of lymphocytes to infected cells	Epstein–Barr virus
	Protection from NFκB activation by short sequences that mimic TLRs	Blocks inflammatory responses elicited by IL-1 or bacterial pathogens	Vaccinia
Blocking of antigen processing and presentation	Inhibition of MHC class I expression	Impairs recognition of infected cells by cytotoxic T cells	Herpes simplex Cytomegalovirus
	Inhibition of peptide transport by TAP	Blocks peptide association with MHC class I	Herpes simplex
Immunosuppression of host	Virally encoded cytokine homolog of IL-10	Inhibits T_H1 lymphocytes Reduces interferon-γ production	Epstein–Barr virus

Figure 9.5 Mechanisms used by herpes and pox viruses to subvert the immune response.

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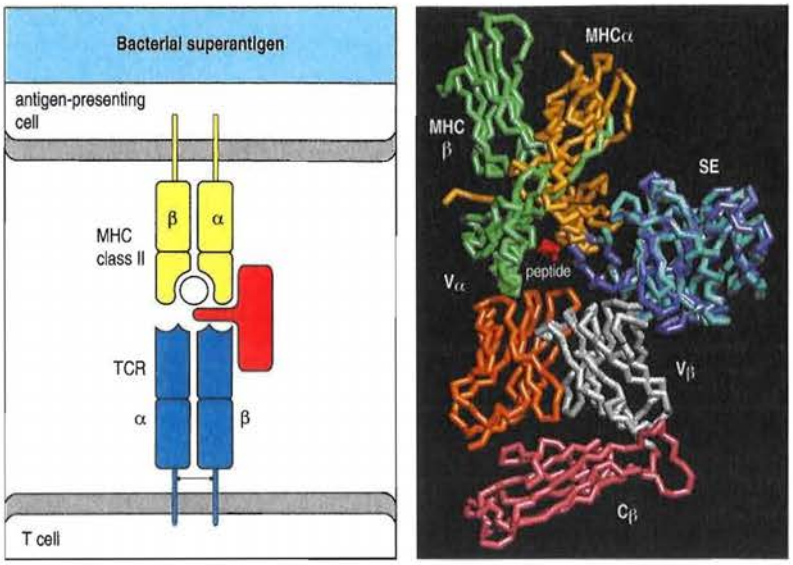


Figure 9.6 Bacterial superantigens bridge α:β T-cell receptors and MHC class II molecules in the absence of a specific peptide. In the diagram of the interaction (left panel) the superantigen is red. The molecular model (right panel) shows the interactions of the superantigen staphyloccal enterotoxin (SE) with an MHC class II molecule and an α:β T-cell receptor. Although the MHC class II molecule has a bound peptide it is usually not one for which the T-cell receptor is specific.

9-6 Bacterial superantigens stimulate a massive but ineffective T-cell response

Some pathogens induce a general suppression of a person's immune response. For example, staphylococci produce toxins such as the **staphylococcal enterotoxins** and **toxic shock syndrome toxin-1**, which can bind simultaneously to MHC class II molecules and T-cell receptors in the absence of a specific peptide antigen (Figure 9.6). By forming a bridge between a CD4 T cell's receptors and the MHC class II molecules of an antigen-presenting cell these toxins mimic specific antigen and cause the T cell to divide and differentiate into effector T cells. Because the toxins bind to sites shared by many different T-cell receptors they stimulate an excessive polyclonal response that can involve 2–20% of the total number of circulating CD4 T cells. Because of this property these toxins are called **superantigens**. The consequence of superantigen stimulation is a massive production and release of cytokines, particularly IL-1, IL-2, and TNF-α, which causes systemic shock (see Figure 8.18, p. 243). At the same time, a useful adaptive immune response is suppressed. After proliferation, T cells that have bound superantigens undergo apoptosis in the absence of any further specific stimulation, removing many antigen-specific T-cell clones from the peripheral circulation.

9-7 Immune responses can contribute to disease

Since the immune response is a powerful and destructive force, some of the disease symptoms, or **pathology**, in most infections are due to the immune response. For some infectious diseases all pathology is due to the immune response, an example being the wheezy bronchiolitis caused by T_H2 cells responding to infection with **respiratory syncytial virus** (**RSV**). This virus accounts for a large proportion of hospital admissions for infants in the developed countries—some 90,000 admissions and 4500 deaths each year in the United States alone. A failed attempt at developing a vaccine against RSV revealed that infants vaccinated with a killed virus preparation suffered worse disease on subsequent infection with RSV than did unvaccinated infants. This unfortunate outcome was because the vaccine failed to induce neutralizing antibodies but successfully activated virus-specific T_H2 cells. On subsequent infection with RSV, the secondary response of the T_H2 cells produced IL-3, IL-4, and IL-5 in quantities that exacerbated the disease-causing aspects of the

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immune response—the induction of bronchospasm, increased secretion of mucus and recruitment of tissue-damaging eosinophils into the tissues of the respiratory tract.

Tissue damage and disease symptoms can also result from the immune response to parasites, as illustrated by *Schistosoma mansoni*. These blood flukes lay their eggs in the hepatic portal vein. Some eggs reach the intestine and are shed in the feces, thereby enabling the infection to spread to other people. Other eggs lodge in the portal circulation of the liver, where they elicit a powerful immune response that leads to chronic inflammation, hepatic fibrosis, and eventual liver failure. Underlying this progression is an excessive activation of T_H2 cells.

Summary

From the human perspective the ideal immune system would be one that terminates infection before the pathogen damages tissues or saps the body's resources. In contrast, an ideal situation for a pathogen is one in which the immune system does not interfere with growth and replication, while other parts of the body provide food and shelter. To further their cause, pathogens have evolved ways of reducing the effectiveness of the human immune response. Antigenic variation in the pathogen prevents the maturation of the adaptive response and the development of useful immunological memory. Latency, a means of avoiding the immune response, allows viruses to lie low within cells until immunity has waned. More active strategies are for pathogens to interfere with key elements of the immune response, either to inhibit normal immune function or to recruit the response to the pathogen's advantage. Immune responses to pathogens can themselves be a significant cause of pathology.

Inherited immunodeficiency diseases

Inherited defects in genes for components of the immune system cause **immunodeficiency diseases**, which reveal themselves by enhanced susceptibility to infection. Before the advent of antibiotic therapy during the 1940s, most individuals with inherited immune defects died from infection during infancy or early childhood. Because many normal infants also succumbed to infection in that earlier era, death from immunodeficiency did not stand out until the 1950s when the first such disease was described. Since then, many inherited immunodeficiency diseases have been identified and correlated with susceptibility to particular classes of pathogen. Each disease is due to a defect in a particular protein or glycoprotein, and the precise symptoms depend on the role of that component in the immune response (Figure 9.7).

9-8 Most inherited immunodeficiency diseases are caused by recessive gene defects

Before the 1950s, any dominant trait causing a severe immunodeficiency would probably have been eliminated from the population with the death of the child in whom it first occurred. Thus, most of the inherited immunodeficiency syndromes that have been identified are due to recessive mutations in single genes. One of the few dominant immune defects known is a defect in the receptor for interferon-γ (IFN-γ), in which the defective receptor still binds IFN-γ but cannot produce an intracellular signal. Infants with this defect are susceptible to disseminated infection with mycobacteria, including the normally innocuous strain used for vaccination against tuberculosis.

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For recessive defects in autosomal genes, that is genes on chromosomes other than the sex chromosomes, only children who inherit a defective allele from both parents are immunodeficient. The parents are heterozygous for the defect and are usually healthy. Such people are referred to as **carriers**. Recessive defects in genes on the X chromosome are a special case, because women

Name of deficiency syndrome	Specific abnormality	Immune defect	Susceptibility
Severe combined immune deficiency	ADA deficiency	No T or B cells	General
	PNP deficiency	No T or B cells	General
	X-linked *scid*, γ_c chain deficiency	No T cells	General
	Autosomal *scid* DNA repair defect	No T or B cells	General
DiGeorge's syndrome	Thymic aplasia	Variable numbers of T and B cells	General
MHC class I deficiency	TAP mutations	No CD8 T cells	Chronic lung and skin inflammation
MHC class II deficiency	Lack of expression of MHC class II	No CD4 T cells	General
Wiskott–Aldrich syndrome	X-linked; defective WASP gene	Defective anti-polysaccharide antibody and impaired T cell activation responses	Encapsulated extracellular bacteria
X-linked agamma-globulinemia	Loss of Btk tyrosine kinase	No B cells	Extracellular bacteria, viruses
X-linked hyper-IgM syndrome	Defective CD40 ligand	No isotype switching	Extracellular bacteria *Pneumocystis carinii* *Cryptosporidium parvum*
Common variable immunodeficiency	Unknown; MHC-linked	Defective IgA and IgG production	Extracellular bacteria
Selective IgA	Unknown; MHC-linked	No IgA synthesis	Respiratory infections
Phagocyte deficiencies	Many different	Loss of phagocyte function	Extracellular bacteria and fungi
Complement deficiencies	Many different	Loss of specific complement components	Extracellular bacteria especially *Neisseria* spp.
Natural killer (NK) cell defect	Unknown	Loss of NK function	Herpes viruses
X-linked lympho-proliferative syndrome	SH2D1A mutant	Inability to control B cell growth	EBV-driven B cell tumors
Ataxia telangiectasia	Gene with PI 3-kinase homology	T cells reduced	Respiratory infections
Bloom's syndrome	Defective DNA helicase	T cells reduced Reduced antibody levels	Respiratory infections

Figure 9.7 Inherited immunodeficiency syndromes of humans, their gene defects, and their pathogen susceptibilities. ADA, adenosine deaminase; PNP, purine nucleotide phosphorylase; TAP, transporter associated with antigen processing; WASP, Wiskott–Aldrich syndrome protein; EBV, Epstein–Barr virus; NK cell, natural killer cell; PI-3 kinase, phosphoinositol-3 kinase.

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have two copies of the X chromosome whereas men have only one. As there is no other copy of the gene to compensate, inheritance of one defective copy of an X-linked gene by a male child is sufficient to cause disease. A woman who inherits a single defective gene will also have the normal gene and usually will be healthy. Because of this mode of inheritance, X-linked immunodeficiencies are far more common in men than in women and are also more common than immunodeficiencies linked to autosomes.

A wide range of defects in immune system genes exists in the human population. Whereas those listed in Figure 9.7 were discovered in patients with severe disease, other immune system gene defects were found first in seemingly healthy blood donors. Examples of the latter are the lack of certain complement components (see Section 7-19, p. 210) or of one of the MHC class I molecules. Those immune system genes that can be lost with little noticeable effect are usually members of multigene families in which another family member compensates for the defective gene. Modern genetic methods and knowledge of the full set of human genes have facilitated both the identification of genetic defects and their correlation with immunodeficiency and altered immune response.

9-9 Antibody deficiency leads to an inability to clear extracellular bacteria

The first immunodeficiency disease to be described is characterized by antibody deficiency and X-linked inheritance and is named **X-linked agammaglobulinemia (XLA)**. The defect in XLA is in a protein tyrosine kinase, which is called Bruton's tyrosine kinase (Btk) to honor the discoverer of the syndrome. Btk contributes to intracellular signaling from the B-cell receptor and is necessary for the growth and differentiation of pre-B cells (see Section 4-4, p. 106). Btk is normally also expressed in monocytes and T cells, but these cells are not functionally compromised by its absence from XLA patients. Other immunodeficiency diseases affecting antibody production have been described, and almost all are caused by failure of either the development or the activation of B lymphocytes.

Women with one functional and one nonfunctional copy of the *Btk* gene are themselves healthy, but are carriers who pass XLA on to half their male children. In females, one X chromosome is randomly inactivated in each cell. In carriers, those B-cell precursors in which the inactivated X has the defective *Btk* gene develop normally, whereas B-cell precursors in which the inactivated X has the functional *Btk* gene fail to develop. Thus, all circulating B cells in heterozygous females have as their active X chromosome the one having the functional *Btk* gene; consequently, carrier females make entirely normal B-cell responses (Figure 9.8).

Patients who lack antibodies are vulnerable to infection with extracellular pyogenic bacteria that have polysaccharide capsules resistant to phagocytosis. These include *Haemophilus influenzae, Streptococcus pneumoniae, Streptococcus pyogenes,* and *Staphylococcus aureus.* In people who make normal antibody responses, such organisms are cleared by phagocytosis after opsonization by antibody and complement. Antibody-deficient patients are also more susceptible to viral infections, particularly those caused by enteroviruses, which enter the body through the gut and which in normal individuals are neutralized by antibodies.

Genetic defects can also cause deficiency in a particular isotype or class of antibody. The most common kind of inherited deficiency of this type is IgA deficiency, which is experienced by about 1 person in 800. No obvious

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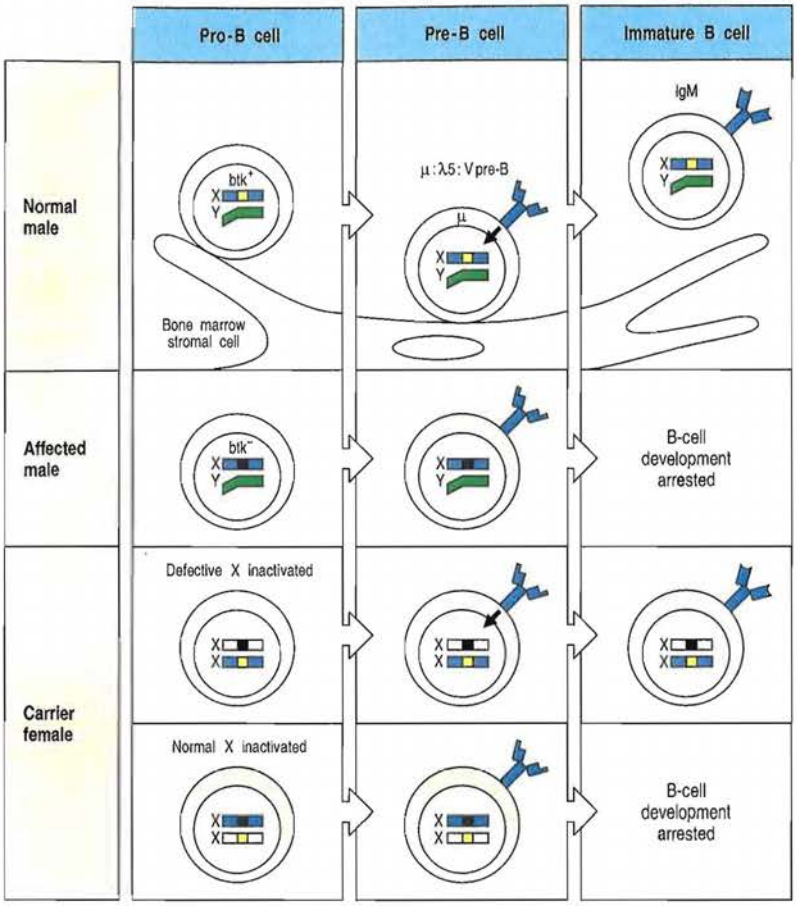


Figure 9.8 In patients with X-linked agammaglobulinemia B cells do not develop beyond the pre-B cell stage. In XLA, Bruton's tyrosine kinase is defective. In patients with this disease B cells become arrested at the pre-B cell stage because intracellular signals cannot be generated by the pre-B cell receptor. Most patients with this disease are males because males have only one copy of the X chromosome. Heterozygous females are carriers of the disease trait although healthy themselves. During development, female cells randomly inactivate one of their X chromosomes. Consequently, half of the developing B cells in a female carrier become arrested at the pre-B cell stage because they inactivate the X chromosome that carries the good copy of the btk gene; the other half develop to become functional B cells because they inactivate the X chromosome that carries the bad copy of the btk gene and use the X chromosome having the good copy.

increased susceptibility to infectious disease is associated with this condition, which might reflect the fact that modern humans tend to eat cooked and processed foods, which greatly reduces the threat posed by pathogens entering the gastrointestinal tract. In contrast, chronic lung disease is more common in people with IgA deficiency, suggesting that the trend towards poorer air quality in the cities, where most people live, makes the role of IgA in the respiratory tract of increasing importance.

Patients who have immunodeficiencies confined to B-cell functions are able to resist many pathogens successfully, and those to which they are susceptible can be treated with antibiotics. However, although pyogenic infections can be cured in this way, the successive rounds of infection and treatment sometimes lead to permanent tissue damage caused by the excessive release of proteases from both the infecting bacteria and the defending phagocytes. These effects are particularly pronounced in the airways, where the bronchi lose their elasticity and become sites of chronic inflammation. This condition, called **bronchiectasis**, can lead to chronic lung disease and eventual death. To prevent such developments, patients with XLA are given monthly injections of gamma globulin, an antibody-containing preparation made from the plasma of healthy blood donors. Such preparations contain antibodies against the range of common pathogens and provide what is called **passive immunity** against those pathogens.

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9-10 Diminished antibody production also results from inherited defects in T-cell help

Diminished antibody production is also a symptom of defective genes for the membrane-associated cytokine CD40 ligand. As discussed in Chapter 7, interaction of CD40 ligand on activated T cells with B-cell CD40 is a crucial part of the T-cell help given to B cells. This stimulates B-cell activation, the development of germinal centers, and isotype switching. CD40 ligand is encoded on the X chromosome and so most patients with a hereditary deficiency in CD40 ligand are males. In the absence of CD40 ligand, virtually no specific antibody is made against T-cell-dependent antigens. IgG, IgA, and IgE levels are extremely low, and IgM levels are abnormally high. Recognition of this latter characteristic led to the condition being named **X-linked hyper-IgM syndrome**. Patients with this immunodeficiency are inherently susceptible to infection with pyogenic bacteria, but these infections can usually be prevented by regular injections of gamma globulin and cleared by antibiotics when they do occur. A further consequence of the disease is the absence of germinal centers in the lymph nodes and other secondary lymphoid tissues (see Figure 7.15, p. 192).

Macrophage activation by T cells also depends on the interaction of CD40 ligand on the T cell with CD40 on the macrophage. The lack of this interaction in patients with X-linked hyper-IgM syndrome impairs the inflammatory response and the mobilization of leukocytes by inflammatory cytokines. Whereas infection normally induces an increase in the number of white cells in the blood (**leukocytosis**), this cannot occur in patients lacking CD40 ligand. On the contrary, their blood can become profoundly deficient in neutrophils. This state, called **neutropenia**, leads to severe sores and blisters in the mouth and throat. These anatomical sites are always infested with bacteria and their health depends on continual surveillance by phagocytes. These symptoms of neutropenia can be cured by the intravenous administration of granulocyte–macrophage colony-stimulating factor (GM-CSF), a cytokine that stimulates the production and release of phagocytes by the bone marrow. In normal individuals, GM-CSF is secreted by macrophages in response to activation by T cells through interactions with CD40 and CD40 ligand.

9-11 Defects in complement components impair antibody responses and cause the accumulation of immune complexes

The effector functions recruited by antibodies to clear pathogens and antigens are all facilitated by complement activation. Consequently, the spectrum of infections associated with complement deficiencies overlaps substantially with that associated with defective antibody production. Defects in the activation of C3, and in C3 itself, are associated with susceptibility to a wide range of pyogenic infections, emphasizing the important role of C3 as an opsonin that promotes the phagocytosis of bacteria by macrophages and neutrophils. In contrast, defects in C5–C9, the terminal complement components that form the membrane-attack complex, have more limited effects, of which susceptibility to *Neisseria* is the best example. The most effective defense against *Neisseria* is complement-mediated lysis of extracellular bacteria, and this requires all the components of the complement pathway (Figure 9.9).

The early components of the classical pathway are necessary for the elimination of immune complexes. As discussed in Section 7-22, p. 214, attachment of complement components to soluble immune complexes allows them to be transported, or ingested and degraded, by cells bearing complement receptors. Immune complexes are mainly transported by erythrocytes,

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Complement protein	Effects of deficiency
C1, C2, C4	Immune-complex disease
C3	Susceptibility to capsulated bacteria
C5–C9	Only effect is susceptibility to *Neisseria*
Factor D, properdin (factor P)	Susceptibility to capsulated bacteria and *Neisseria* but no immune-complex disease
Factor I	Similar effects to deficiency of C3
DAF, CD59	Autoimmune-like conditions including paroxysmal nocturnal hemoglobinuria

Figure 9.9 Diseases caused by deficiencies in the pathways of complement activation.

which capture the complexes with the CR1 complement receptor that binds to C4b or C3b. Deficiencies in complement components C1–C4 impair the formation of C4b and C3b and lead to the accumulation of immune complexes in the blood, lymph, and extracellular fluid and their deposition within tissues. In addition to directly damaging the tissues in which they deposit, immune complexes activate phagocytes, causing inflammation and further tissue damage.

Deficiencies in the proteins that control complement activation can also cause immunodeficiency. People who lack the plasma protein factor I in effect lack C3. Because factor I is absent, the conversion of C3 to C3b is unchecked, and supplies of C3 are rapidly depleted (see Section 7-25, p. 217). Patients who lack properdin (factor P), a plasma protein that enhances the activity of the alternative pathway, have a heightened susceptibility to *Neisseria*, because reduced deposition of C3 prevents formation of the membrane-attack complex and bacterial lysis. In contrast, a deficiency in decay-accelerating factor (DAF) or CD59 causes an autoimmune-like condition. The cells of patients lacking DAF or CD59 are not protected from activating the alternative pathway of complement activation. The resultant complement-mediated lysis of erythrocytes causes paroxysmal nocturnal hemoglobinuria (see Section 7-26, p. 220).

Another disease caused by a deficiency of a complement regulator is **hereditary angioneurotic edema**. In this condition the absence of the C1 inhibitor C1INH leads to uncontrolled activation of the classical pathway (see Section 7-25, p. 217). One consequence is overproduction of the vasoactive C2a fragment, causing the accumulation of fluid in the tissues and epiglottal swelling, which can lead to death by suffocation.

9-12 Defects in phagocytes result in enhanced susceptibility to bacterial infection

Phagocytosis by macrophages and neutrophils is the principal method by which the immune system destroys bacteria and other microorganisms. Any defect that compromises phagocyte activity will, therefore, have a profound effect on the capacity to clear infections (Figure 9.10). One kind of deficiency arises from mutations in the gene encoding CD18, the common β subunit of the leukocyte integrins CR2, CR4, and LFA-1 (see Figure 6.4, p. 149). These cell adhesion molecules are needed for phagocytes to leave the blood and enter sites of infection (see Figure 8.19, p. 245). Phagocytes lacking functional

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integrins are, therefore, unable to migrate to where they are needed. This defect is known as **leukocyte adhesion deficiency**.

Leukocyte adhesion deficiency is associated with persistent infection with extracellular bacteria, which cannot be cleared because of the defective phagocyte function. Children with this defect have recurrent pyogenic infections and problems with wound healing; if they survive long enough, they develop severe inflammation of the gums. Their neutrophils and macrophages cannot migrate into tissues and also, because CR2 and CR4 are complement receptors as well as adhesion molecules, they cannot take up and destroy bacteria opsonized with complement (see Section 7-21, p. 212). Patients deficient in CD18 suffer from infections that respond poorly to antibiotic treatment and which persist despite the generation of normal B-cell and T-cell responses. Neutropenia caused by chemotherapy, malignancy, or aplastic anemia produces a similar susceptibility to severe pyogenic bacterial infections.

Other kinds of defect in phagocytes affect their ability to kill ingested bacteria. In **chronic granulomatous disease**, the antibacterial activity of phagocytes is compromised by their inability to produce the superoxide radical O_2^- (see Section 8-10, p. 246). Mutations affecting any of the four proteins of the NADPH oxidase system can produce this phenotype. Patients with this disease suffer from chronic bacterial infections, often leading to granuloma formation. Deficiencies in the enzymes glucose-6-phosphate dehydrogenase and myeloperoxidase also impair intracellular bacterial killing, leading to a similar but less severe phenotype. A different phenotype characterizes **Chédiak–Higashi syndrome**, in which phagocytosed materials are not delivered to lysosomes because of a defect in the vesicle fusion mechanism. The lack of phagocyte function has effects in many different organs as well as leading to persistent and recurrent bacterial infections. The gene defects that cause this disease are still unknown.

Syndrome	Cellular abnormality	Immune defect	Associated infections and other diseases
Leukocyte adhesion deficiency	Defective CD18 (cell adhesion molecule)	Defective migration of phagocytes into infected tissues	Widespread infections with capsulated bacteria
Chronic granulomatous disease (CGD)	Defective NADPH oxidase. Phagocytes cannot produce O_2^-	Impaired killing of phagocytosed bacteria	Chronic bacterial and fungal infections. Granulomas
Glucose-6-phosphate dehydrogenase (G6PD) deficiency	Deficiency of glucose-6-phosphate dehydrogenase. Defective respiratory burst	Impaired killing of phagocytosed bacteria	Chronic bacterial and fungal infections. Anemia is induced by certain agents
Myeloperoxidase deficiency	Deficiency of myeloperoxidase in neutrophil granules and macrophage lysosomes and impaired production of toxic oxygen species	Impaired killing of phagocytosed bacteria	Chronic bacterial and fungal infections
Chédiak–Higashi syndrome	Defect in vesicle fusion	Impaired phagocytosis due to inability of endosomes to fuse with lysosomes	Recurrent and persistent bacterial infections. Granulomas. Effects on many organs

Figure 9.10 Defects in phagocytic cells cause persistent bacterial infections.

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9-13 Defects in T-cell function result in severe combined immune deficiencies

Whereas B cells contribute only to the antibody response, T cells function in all aspects of adaptive immunity. This means that inherited defects in the mechanisms of T-cell development and T-cell function have a general depressive effect on the immune system's capacity to respond to infection. Patients with T-cell deficiencies tend to be susceptible to persistent or recurrent infections with a broader range of pathogens than patients with B-cell deficiencies. Those patients who make neither T-cell-dependent antibody responses nor cell-mediated immune responses are said to have **severe combined immune deficiency** (**SCID**).

T-cell development and function depend on the action of many proteins and so the SCID phenotype can arise from defects in any one of a number of genes. Because of the inheritance pattern of the X chromosome, X-linked diseases are more easily discovered, and at least two forms of SCID are of this type. The first form of X-linked SCID is due to mutation in a gene on the X chromosome that encodes the common γ chain of several cytokine receptors, including the receptors for IL-2, IL-4, IL-7, IL-9, and IL-15. In each of these receptors the γ chain transduces ligand binding into signals that alter gene expression. This is accomplished through interaction of the γ chain with the Jak3 kinase (see Section 6-12, p. 164). Indeed, as would be predicted, patients defective in the Jak3 kinase have an autosomally inherited immunodeficiency similar in phenotype to that of patients with X-linked SCID. The phenotype of SCID is so severe that affected infants survive only if they are isolated in a pathogen-free environment, or if their immune system is replaced by bone marrow transplantation and the passive administration of antibodies.

Another X-linked deficiency of T-cell function is **Wiskott–Aldrich syndrome** (**WAS**), which involves the impairment of platelets as well as lymphocytes. The relevant gene on the X chromosome encodes a protein called Wiskott–Aldrich syndrome protein (WASP). This protein is involved in the cytoskeletal reorganization needed before T cells can deliver cytokines and signals to the B cells, macrophages, and other target cells with which they routinely interact during the immune response.

SCID due to an absence of T-cell function is also caused by defects in **adenosine deaminase** (**ADA**) or **purine nucleotide phosphorylase** (**PNP**), which are enzymes involved in purine degradation. Although the absence of these enzymes causes an accumulation of nucleotide metabolites in all cells, the effects of this are particularly toxic to developing T cells and, to a lesser extent, to developing B cells. Infants with these immunodeficiencies have an underdeveloped thymus that contains few lymphocytes. ADA and PNP deficiencies are autosomally inherited (Figure 9.11).

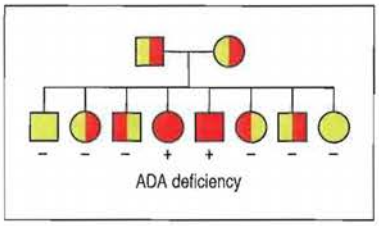


Figure 9.11 Adenosine deaminase (ADA) deficiency is inherited in autosomal fashion. The inheritance of ADA deficiency in a family. Both parents are healthy carriers who have one functional copy of the ADA gene (red) and one defective copy (green). Two of the eight children inherited defective copies of the ADA gene from both parents and have ADA deficiency (+). Males are indicated by squares and females by circles.

Another kind of SCID is caused by the lack of expression of HLA class II molecules. The disease was named **bare lymphocyte syndrome** because the defect was first discovered on B lymphocytes, the major population of peripheral blood cells that expresses HLA class II. In these patients, CD4 T cells fail to develop (see Section 5-7, p. 133), which compromises all aspects of adaptive immunity. Bare lymphocyte syndrome arises from defects in transcriptional regulators essential for the expression of all HLA class II loci. A homozygous defect in any one of four proteins produces the condition. One protein is the class II transactivator (CIITA), the other three are components of RFX, a transcriptional complex that binds to a conserved sequence in the promoter of HLA class II genes called the X box.

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A defect in either of the two genes encoding the TAP peptide transporter impedes the binding of peptides by HLA class I molecules, leading to an unusually low abundance of HLA class I molecules on cell surfaces. This form of immunodeficiency, called **bare lymphocyte syndrome** (**MHC class I**), is less severe than the SCID caused by absence of HLA class II, its principal effect being selective loss of CD8 T cells (see Section 5-7, p. 133) and of cytotoxic T-cell responses to intracellular infections.

Defects in various proteins and enzymes that contribute to the rearrangement of immunoglobulin and T-cell receptor genes also cause autosomally inherited forms of SCID. These include the RAG-1 and RAG-2 proteins and also the DNA-dependent protein kinase (DNA-PK) implicated in the resolution of the hairpins produced during DNA rearrangement.

9-14 Some inherited immunodeficiencies lead to specific disease susceptibilities

Patients who lack either the receptor for IFN-γ or that for IL-12 can suffer persistent and ultimately fatal infections of common intracellular bacteria, such as the ubiquitous, nontuberculous strain of mycobacteria, *Mycobacterium avium*. The IFN-γ made by NK cells during the innate immune response and by CD4 and CD8 T cells during the adaptive immune response is the key cytokine that activates macrophages to kill the bacteria that infect them. The IL-12 secreted by infected macrophages is essential for activating the secretion of IFN-γ by NK cells, CD4 T cells, and CD8 T cells. A consequence of this type of immunodeficiency is that vaccination against tuberculosis with the live vaccine strain of *Mycobacterium bovis*, Calmette-Guèrin, can actually cause disseminated infection and disease.

As we saw in Section 9-4, many healthy people maintain a persistent EBV infection of B cells, which is held in check by EBV-specific T cells. For patients, mostly boys, with a defect in the SH2D1A gene on the X chromosome, a balance is never achieved and childhood EBV infections can become overwhelming and even progress to lymphoma. This immunodeficiency is called **X-linked lymphoproliferative syndrome**. Although the SH2D1A protein is believed to be a regulator of lymphocyte-activating signals, its precise functions and contribution to the control of EBV infection are uncertain.

9-15 Hematopoietic stem cell transplantation is used to correct genetic defects of the immune system

Many immunodeficiencies are due to gene defects that principally affect hematopoietic cells. These conditions can, in principle, be corrected by transplantation of hematopoietic stem cells obtained from the bone marrow or peripheral blood of a healthy donor. Such therapy is not undertaken lightly and the potential benefits from correcting the immunodeficiency must be weighed against the risks associated with the immunosuppressive treatments required for successful transplantation. The benefits of hematopoietic stem cell transplantation are directly correlated with the degree of HLA matching between patient and donor. Matching serves two purposes: first, it reduces the graft-versus-host disease (GVHD) caused by alloreactive T cells in the transplant that attack nonhematopoietic cells of the recipient; second, it ensures effective reconstitution of the adaptive immune system (see Figure 5.11, p. 134). After transplantation, all bone marrow derived cells in the recipient are of donor HLA type, whereas all other cells are of the recipient's HLA type. Positive selection of T cells is exclusively on thymic epithelium of the recipient's HLA type. Thus, the extent to which the mature T cells respond to antigens presented by professional antigen-presenting cells of donor HLA

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type is directly correlated with the number of shared HLA class I and II allotypes (see Section 5-6, p. 132).

Now that the genes responsible for immunodeficiency diseases are being identified, another type of therapeutic strategy is being explored. In **somatic gene therapy**, a functional copy of the defective gene is introduced into stem cells that have been isolated from the patient's bone marrow. The stem cells in which the defect has been corrected are then reinfused into the patient, where they provide a self-renewing source of immunocompetent lymphocytes and other hematopoietic cell types. Although highly attractive in principle, the practical development of gene therapy is at an early and experimental stage.

Summary

The best characterized gene defects affecting the immune system are those that show up in early childhood and confer exceptional vulnerability to common infections. The characterization of immunodeficiency diseases and the gene defects that cause them is almost the only way in humans of determining the relative importance of different cells and molecules in immune defenses, and of testing current models of how the human immune system works. The most severe immunodeficiencies are due to gene defects that cause an absence of all T-cell function and thus, directly or indirectly, impair B-cell function as well. Such deficiencies are known as severe combined immune deficiencies (SCID). The absence of antibodies due to genetic defects in B-cell development or function leads to particular susceptibility to pyogenic bacteria. Deficiencies in the early components of complement pathways cause a failure to opsonize. This results in increased susceptibility to bacterial infection, as do defects in phagocytes.

Acquired immune deficiency syndrome

Acquired immune deficiency syndrome (AIDS) was first described by physicians early in the 1980s. The disease is characterized by a massive reduction in the number of CD4 T cells, accompanied by severe infections of pathogens that rarely trouble healthy people, or by aggressive forms of Kaposi's sarcoma or B-cell lymphoma. All patients diagnosed as having AIDS eventually die from the effects of the disease. In 1983 the virus now known to cause AIDS, the **human immunodeficiency virus (HIV)**, was first isolated. Two types of HIV are now distinguished—HIV-1 and HIV-2. In most countries HIV-1 is the principal cause of AIDS. HIV-2 is less virulent, causing a slower progression to AIDS. It is endemic in West Africa and has spread widely through Asia.

AIDS is a disease new to the medical profession and also to the human species. The earliest evidence for HIV comes from samples from African patients obtained in the late 1950s. It is believed that the viruses first infected humans in Africa by jumping from other primate species—HIV-1 coming from the chimpanzee, HIV-2 from the sooty mangabey. In neither of these species does the endogenous HIV-related virus cause disease.

As commonly occurs when a naive host population is hit with a new infectious agent, the effects of HIV on the human population have been immense and AIDS is now a disease of pandemic proportions. The World Health Organization currently estimates that 42 million people are infected with HIV. Although advances continue to be made in understanding the nature of the disease and its origins, the number of people infected with HIV continues to grow—5 million new infections in 2002—and tens of millions of people will die from AIDS in the years to come (Figure 9.12).

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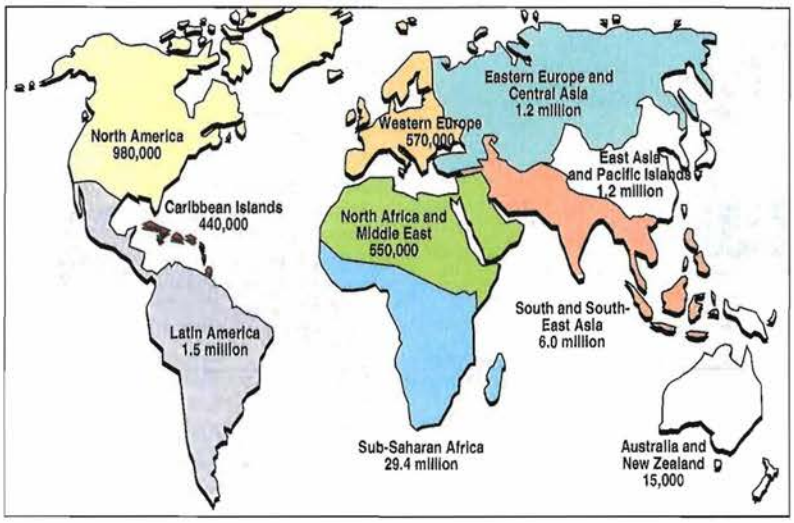


Figure 9.12 Incidence of HIV infection. Numbers of adults and children living with HIV/AIDS at the end of 2002, as estimated by the World Health Organization.

9-16 HIV is a retrovirus that causes slowly progressing disease

HIV is an RNA virus with an RNA nucleoprotein core (the nucleocapsid) surrounded by a lipid envelope derived from the host-cell membrane and containing virally encoded envelope proteins (Figure 9.13). HIV is an example of a retrovirus, so called because these viruses use an RNA genome to direct the synthesis of a DNA intermediate, a situation backwards or 'retro' from that used by most biological entities. One nucleocapsid protein is a protease used to cleave the gp41 and gp120 envelope glycoproteins from a larger precursor polyprotein; other nucleocapsid proteins are the enzymes reverse transcriptase and integrase, which are required for viral replication.

When HIV infects a cell, the RNA genome is first copied into a complementary DNA (cDNA) by reverse transcriptase. The viral integrase then integrates the cDNA into the genome of the host cell to form a **provirus**, a process facilitated by repetitive DNA sequences called long terminal repeats (LTRs) that flank all retroviral genomes. Proviruses use the transcriptional and translational machinery of the host cell to make viral proteins and RNA genomes, which assemble into new infectious virions. The genes and proteins of HIV are illustrated in Figure 9.14. HIV belongs to a group of retroviruses that cause slowly progressing diseases. They are collectively called the **lentiviruses**, a name derived from the latin word *lentus*, meaning slow.

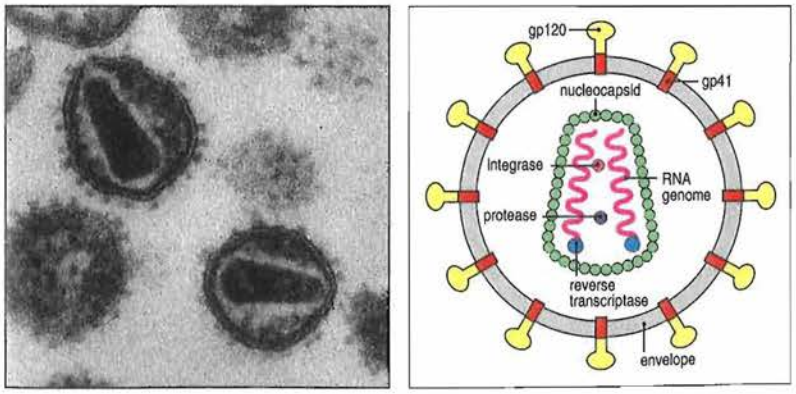
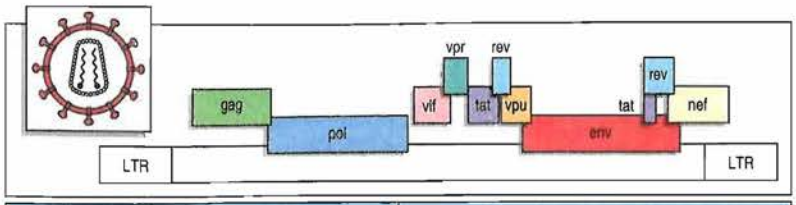


Figure 9.13 The virion of human immunodeficiency virus (HIV). The left panel is an electron micrograph showing three virions. The right panel is a diagram of a single virion. gp120 and gp41 are virally encoded envelope glycoproteins of molecular mass 120 kDa and 41 kDa, respectively. Photograph courtesy of Hans Gelderblom.

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Gene		Gene product/function
gag	Group-specific antigen	Core proteins and matrix proteins
pol	Polymerase	Reverse transcriptase, protease, and integrase enzymes
env	Envelope	Transmembrane glycoproteins. gp120 binds CD4 and CCR5; gp41 is required for virus fusion and internalization
tat	Transactivator	Positive regulator of transcription
rev	Regulator of viral expression	Allows export of unspliced and partially spliced transcripts from nucleus
vif	Viral infectivity	Affects particle infectivity
vpr	Viral protein R	Transport of DNA to nucleus. Augments virion production. Cell cycle arrest
vpu	Viral protein U	Promotes intracellular degradation of CD4 and enhances release of virus from cell membrane
nef	Negative-regulation factor	Augments viral replication *in vivo* and *in vitro*. Downregulates CD4 and MHC class II

Figure 9.14 The genes and proteins of HIV-1. HIV-1 has an RNA genome consisting of nine genes flanked by long terminal repeats (LTRs). The products of the nine genes and their known functions are tabulated. Several of the viral genes are overlapping and are read in different frames. Others encode large polyproteins which after translation are cleaved to produce several proteins having different activities. The gag, pol, and env genes are common to all retroviruses and their protein products are all present in the virion.

In almost all people, HIV produces an infection that cannot be successfully terminated by the immune system and continues for many years. Although the initial acute infection is controlled to the point at which disease is not apparent, the virus persists and replicates in a manner that gradually exhausts the immune system, leading to immunodeficiency and death.

9-17 HIV infects CD4 T cells, macrophages, and dendritic cells

Macrophages, dendritic cells, and CD4 T cells are vulnerable to HIV infection because they express CD4, which the virus uses as a receptor. Chimpanzees, our closest living relative, are resistant to HIV infection because of a small difference in the structure of their CD4 glycoprotein in comparison to ours. The gp120 envelope glycoprotein of HIV binds tightly to human CD4, enabling virions to attach to CD4-expressing human cells. Before entry of the virus into the cell, gp120 must also bind to a co-receptor in the host-cell membrane. Once the co-receptor is bound, the gp41 envelope glycoprotein mediates fusion of the viral envelope with the plasma membrane of the host cell, allowing the viral genome and associated proteins to enter the cytoplasm.

The viral co-receptors are normal human chemokine receptors that are subverted by HIV to further its own propagation at the expense of the human host. There are different variants of HIV, and the cell types that they infect largely depend upon which co-receptor they bind. The HIV variants that spread infection from one person to another bind to the CCR5 co-receptor present on macrophages, dendritic cells, and CD4 T cells. Although they infect several types of human cell these HIV variants are called 'macrophage-tropic' for want of a better term. The HIV variants that infect activated CD4 T cells bind to the CXCR4 co-receptor and are called 'lymphocyte-tropic'. Whereas infection by macrophage-tropic HIV variants requires only modest levels of cell-surface CD4, infection by the lymphocyte-tropic viruses requires the higher levels present on activated CD4 T cells. Macrophages and dendritic

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cells at the site of virus entry are the first cells to be infected. Subsequently, the virus produced by the macrophages starts to infect the CD4 T-cell population. In about 50% of cases, the viral phenotype switches to the lymphocyte-tropic type late in infection. This is followed by a rapid decline in CD4 T-cell count and progression to AIDS. In their mutual interaction with the human population the two types of HIV variant have complementary roles: the lymphocyte-tropic viruses cause the disease, while the macrophage-tropic variants make it a pandemic.

The production of infectious virions from HIV provirus requires the activation of an infected CD4 T cell. Activation induces the synthesis of the transcription factor NFκB, which binds to promoters in the provirus. This directs the infected cell's RNA polymerase to transcribe viral RNAs. At least two of the proteins encoded by the virus serve to promote replication of the viral genome. Among other activities, the **Tat** protein binds to a sequence in the LTR of the viral mRNA, known as the transcriptional activation region (TAR), where it prevents transcription from shutting off and thus increases the transcription of viral RNA. The **Rev** protein controls the supply of viral RNA to the cytoplasm and the extent to which that RNA is spliced. At early times in infection Rev delivers RNA that encodes the proteins necessary for making virions. Later, complete viral genomes are supplied, which assemble with the viral proteins to form complexes that bud through the plasma membrane to give infectious virions (Figure 9.15).

9-18 Most people who become infected with HIV progress in time to develop AIDS

Infection with HIV usually occurs after the transfer of bodily fluids from an infected person to an uninfected recipient. Provirus can be carried in infected CD4 T cells, dendritic cells, and macrophages, whereas virions can be transmitted via blood, semen, vaginal fluid, or mother's milk. Infection is commonly spread by sexual intercourse, intravenous administration of drugs with contaminated needles, breast feeding, or transfusion of human blood or blood components from HIV-infected donors.

Immediately after HIV infection a person can either be asymptomatic or experience a transient 'flu-like' illness. In either case, virus becomes abundant in the peripheral blood, while the number of circulating CD4 T cells markedly declines (Figure 9.16). This acute viremia is almost always accompanied by activation of an HIV-specific immune response, in which anti-HIV antibodies are produced and cytotoxic T cells become activated to kill virus-infected cells. This response reduces the load of virus carried by the infected person and causes a corresponding increase in the number of circulating CD4 T cells. When an infected person first exhibits detectable levels of anti-HIV antibodies in their blood serum, they are said to have undergone **seroconversion**. The amount of virus persisting in the blood after the symptoms of acute viremia have passed is directly correlated with the subsequent course of disease.

The initial phase of infection is followed by an asymptomatic period, also called 'clinical latency'. During this phase, which can last for 2–15 years, there is persistent infection and replication of HIV in CD4 T cells, causing a gradual decrease in T-cell numbers. Eventually, the number of CD4 T cells drops below that required to mount effective immune responses against other infectious agents. That transition marks the end of clinical latency, the beginning of the period of increasing immunodeficiency, and the onset of AIDS. Patients with AIDS become susceptible to a range of opportunistic infections and some cancers, and it is from the effects of these that they die.

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At the beginning of the AIDS epidemic in North America and Europe, viral transmission through infected blood products caused hemophiliacs and other patients dependent on blood products to become infected with HIV. Because hemophiliacs are so dependent on the medical profession, whether they be HIV-infected or not, it was possible to study the progress of their HIV infections in a systematic and rigorous manner. The results, which were

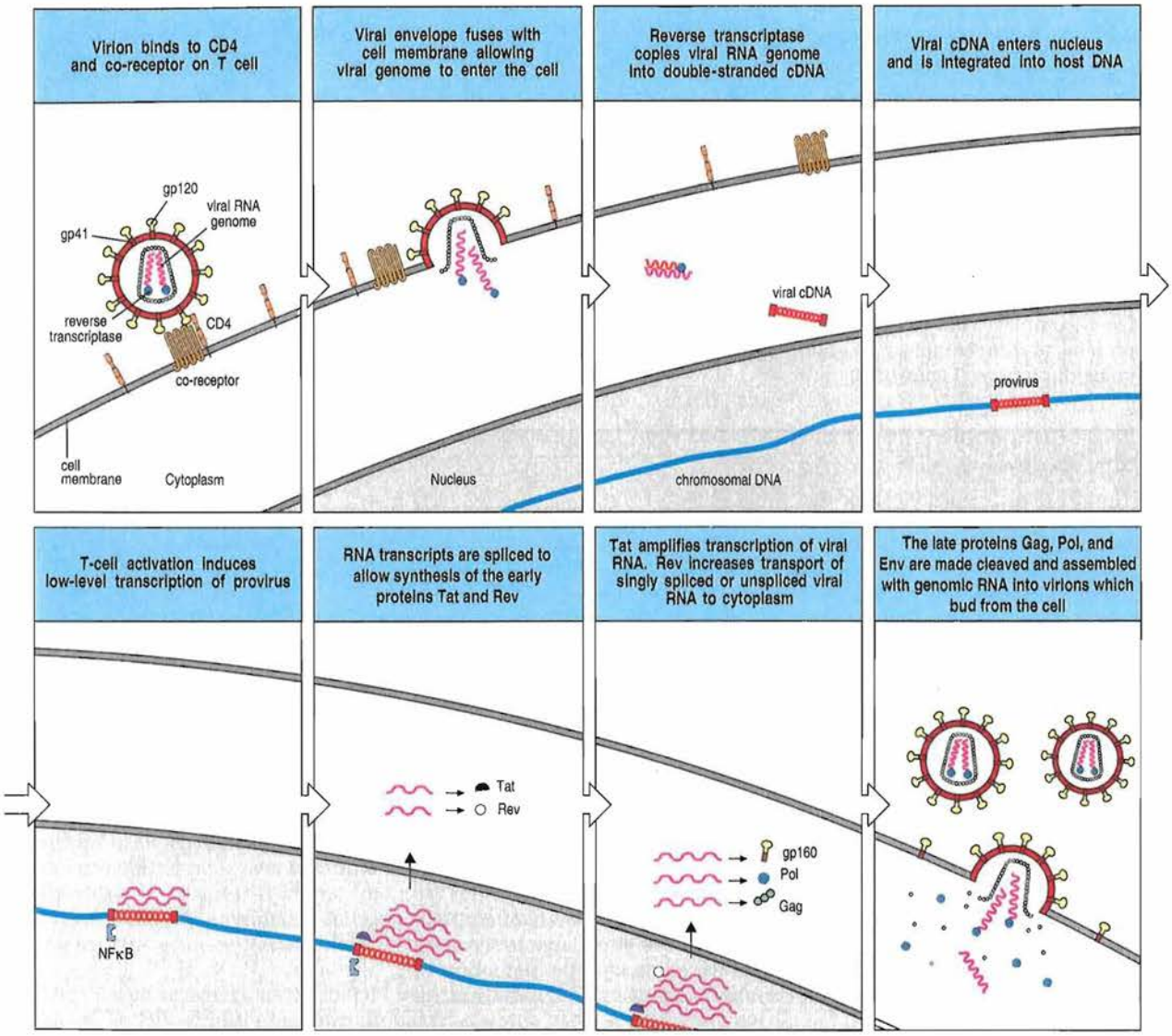


Figure 9.15 The life cycle of HIV in human cells. The virus binds to CD4 on a cell surface by using the envelope protein gp120, which is altered by CD4 binding so that it now also binds a specific chemokine co-receptor on the cell. This binding releases gp41, which then causes fusion of the viral envelope with the plasma membrane and release of the viral core into the cytoplasm. The RNA genome is released and is reverse transcribed into double-stranded cDNA. This migrates to the nucleus in association with the viral integrase, and is integrated into the cell genome, becoming a provirus. Activation of a T cell causes low-level transcription of the provirus that directs the synthesis of the early proteins Tat and Rev, which then expand and change the pattern of provirus transcription to produce mRNA encoding the protein constituents of the virion and RNA molecules corresponding to the HIV genome. Envelope proteins travel to the plasma membrane, whereas other viral proteins and viral genomic RNA assemble into nucleocapsids. New virus particles bud from the cell, acquiring their lipid envelope and envelope glycoproteins in the process.

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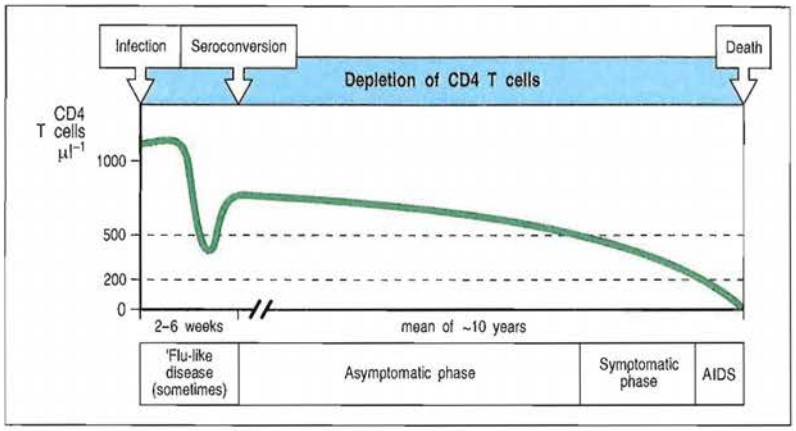


Figure 9.16 After infection with HIV there is a gradual extinction of CD4 T cells. The number of CD4 T cells (green line) refers to those present in peripheral blood. Opportunistic infections and other symptoms become more frequent as the CD4 T-cell count falls, starting at around 500 cells μl^{-1}. The disease then enters the symptomatic phase. When CD4 T-cell counts fall below 200 cells μl^{-1} the patient is said to have AIDS.

obtained during the time before effective treatments were available, demonstrate that most HIV-infected individuals are destined to progress to AIDS in the absence of effective medical intervention (Figure 9.17). Today, HIV infection through contaminated blood products has largely been eliminated in the richer countries by routine screening of individual units of blood for the presence of HIV.

Although the vast majority of infected people gradually progress to AIDS, a small minority do not; they are called 'long-term nonprogressors'. A small percentage seroconvert but their CD4 T-cell counts and other measures of immune competence are maintained. They have exceptionally low levels of circulating virus, and are being studied intensively to determine how they are able to control the infection. Another small group of people remain seronegative and disease-free despite extensive exposure to the virus. Some of this group have specific cytotoxic lymphocytes and T_H1 cells directed against infected cells, which suggests that at some time they have either been infected with the virus or have been exposed to noninfectious HIV antigens. The mechanisms that allow these people to resist AIDS are just beginning to be understood. As described in the next section, some people have a well-defined inherent resistance to AIDS: they are deficient in the viral co-receptor CCR5.

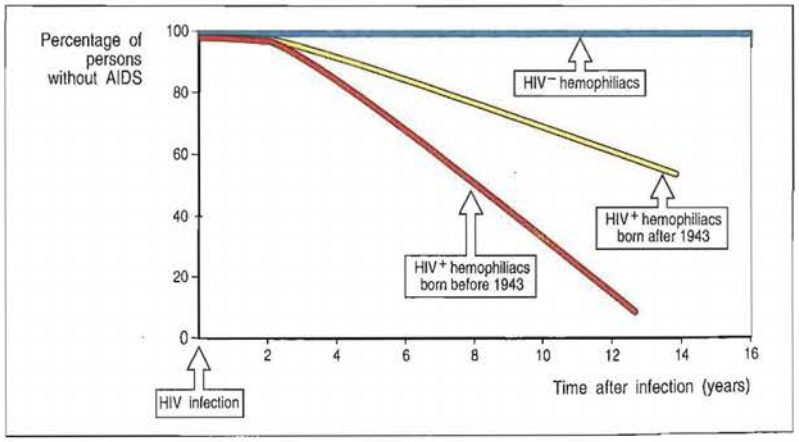


Figure 9.17 Once an HIV infection is established it usually leads to AIDS. Hemophilia is an inherited disease in which components of the blood clotting pathway do not function. Any wound can result in excessive bleeding for these patients and is potentially fatal. Effective treatment for hemophilia is provided by regular blood infusions of clotting factors purified from the blood of healthy donors. In the early 1980s, when the AIDS epidemic was well underway but the cause of the disease was unknown, some seemingly healthy blood donors were actually infected with HIV. The virus from such donations ended up contaminating some batches of clotting factor, with the result that many hemophiliacs became infected with HIV. The graph shows the health of HIV-infected and uninfected hemophiliacs over a period of some 15 years following infection. The development of AIDS is dependent upon HIV infection and is an almost inevitable consequence of infection, as seen from the fact that none of the plots tapers off. The time taken for AIDS to become manifest decreases with the patients' age.

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9-19 Genetic deficiency of the CCR5 co-receptor for HIV confers resistance to infection

Some people who are heavily exposed to HIV never become infected. Likewise, their isolated macrophages and lymphocytes cannot be deliberately infected with macrophage-tropic variants of HIV, the viral strains responsible for the spread of infection. These people are resistant to HIV infection because none of their cells has CCR5, the co-receptor for macrophage-tropic HIV variants, on the cell surface. The genetic basis for this defect is a mutated allele of the CCR5 gene in which a 32-nucleotide deletion from the coding region leads to an altered reading frame, premature termination of translation, and a nonfunctional protein. So far, the mutant allele has been found only in caucasoid populations, in which approximately 10% of the population are heterozygous for the mutant allele and 1% are homozygous. Only people who are homozygous for the mutant allele are resistant to HIV infection. A few individuals who are homozygous for the nonfunctional CCR5 variant have become infected with HIV, apparently as a result of primary infection by lymphocyte-tropic strains of the virus that use the CXCR4 co-receptor.

CCR5 is a normal component of the human immune system, in which it is a receptor for the chemokines CCL3 (MIP-1α), CCL4 (MIP-1β) and CCL5 (RANTES). The fact that almost everyone has a functional CCR5 gene strongly argues that this receptor has made useful contributions to human immunity, survival, and reproduction. On the other hand, for individuals facing exposure to HIV the survival advantage of not having CCR5 clearly outweighs that of having it. In the absence of the HIV pandemic, homozygosity for the CCR5 deletion would be considered a form of immunodeficiency, like the milder immunodeficiencies described in the previous part of this chapter, but in today's world it becomes an important asset of disease resistance. This type of evolutionary process, in which an immune system component that was useful in fighting past wars against pathogens becomes detrimental during a current conflict, has happened throughout human history. A pathogen subverts an immune system component and consequently selects for the survival of those humans who have genetic variants that resist that subversion. What we experience is a never-ending arms race, forever selecting for polymorphism and change in the human immune system.

That the CCR5 deletion mutant was already at high frequency in the caucasoid population before HIV began its colonization of the human species is a strong indication that this mutation enhanced human survival during a previous disease epidemic. One idea is that the mutant was selected and driven to high frequency by the Black Death, the pandemic of plague that ravaged Europe during the Middle Ages, causing up to 30% mortality in some communities. In the current age HIV will probably have its strongest selective effect in sub-Saharan Africa, where some 30 million people are infected with HIV and constitute more than 30% of the population of several countries. As treatment is rarely available for African patients, mortality rates will be high and survival will be greatly enhanced by genetic variants in any immune system component that prevents infection or reduces disease severity.

9-20 HIV escapes the immune response and develops resistance to antiviral drugs by rapid mutation

People infected with HIV make adaptive immune responses that can prevent the overt symptoms of disease for many years. Included in these responses are T_H1 and T_H2 cells, B cells that make neutralizing antibodies, and CD8 cytotoxic T cells that kill virus-infected cells (Figure 9.18). However, the virus is rarely eliminated. One reason the virus keeps ahead of the human immune response is its high rate of mutation during the course of an infection.

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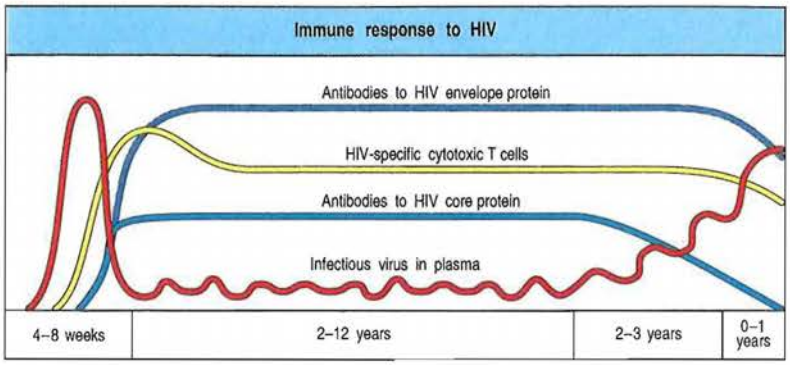


Figure 9.18 The adaptive immune response to HIV limits the effects of infection. During the course of infection, the levels of HIV virions and of components of adaptive immunity in the blood plasma change. Early in infection, while the adaptive immune response is being activated, the virus reaches high levels (red line). With the production of HIV-specific antibodies (blue lines) and HIV-specific cytotoxic T cells (yellow line), the virus is kept at a low level but is not eliminated. When the destruction of CD4 T cells outstrips their rate of renewal, adaptive immunity gradually collapses and virus levels increase again.

HIV and other retroviruses have high mutation rates because their reverse transcriptases lack proofreading mechanisms of the type possessed by cellular DNA polymerases. Consequently, reverse transcriptases are prone to making errors and these nucleotide substitutions soon accumulate to give new variant viral genomes. Even though the infection of a person might start from a single viral species, mutation throughout the infection produces many viral variants, called quasi-species, that coexist within the infected person.

The presence of variant viruses increases the difficulty of terminating the infection by immune mechanisms. Immune attack by neutralizing antibody will select for the survival of viral variants that have lost the epitope recognized by the antibody. Similarly, pressure from virus-specific cytotoxic T cells selects for viruses in which the peptide epitope recognized by the cytotoxic T cell has changed. In some instances the homologous peptide derived from the variant virus interferes with the presentation of the antigenic peptide from the original virus, thereby allowing both viral species to escape the cytotoxic T cell.

The high mutation rate of HIV greatly complicates the task of developing a vaccine against it. It also limits the effectiveness of antiviral drugs. Potential targets for drugs are the viral reverse transcriptase that is essential for the synthesis of provirus, and the viral protease that cleaves viral polyproteins to give viral enzymes and proteins. Inhibitors of reverse transcriptase and protease have been found, and these drugs prevent further infection of healthy cells. Unfortunately, mutation inevitably produces HIV variants with proteins resistant to the action of the drugs. For protease inhibitors, resistance appears within days (Figure 9.19) whereas resistance to the reverse transcriptase inhibitor zidovudine (AZT) takes months to develop. The difference is because zidovudine resistance requires the accumulated effects of three or four independent mutations in the reverse transcriptase, whereas the protease can acquire resistance with just one mutation. One situation in which a relatively short course of drug treatment has long-term benefit is pregnancy. Treating HIV-infected pregnant women with zidovudine can prevent HIV transmission to their children *in utero* and at birth.

Because HIV can so easily escape from the effects of any single drug, several antiviral drugs are now used together in what is called **combination therapy**.

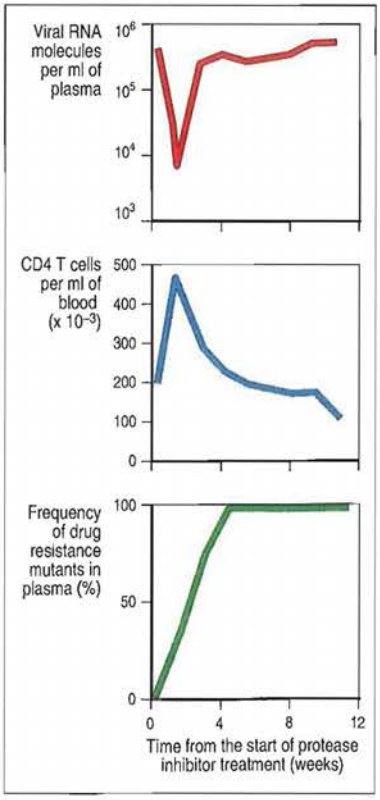


Figure 9.19 HIV can rapidly acquire resistance to protease inhibitor drugs. When a patient is treated with a single protease inhibitor drug the decrease in viral load (top panel) and increase in CD4 T-cell numbers (center panel) is only transient. The drug's benefit is short-lived because it selects for existing minority populations of drug-resistant HIV variants that rapidly expand and then continue the progress to AIDS (bottom panel).

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The ideal is to destroy the entire population of viruses before any one of them has accumulated enough mutations to resist all the drugs. Such combination therapy, also called **highly active anti-retroviral therapy** (**HAART**) is effective at reducing the abundance of virus (the viral load) (Figure 9.20) and retarding disease progression. The drugs do not stop virus production by cells that are already infected, but prevent new infections from forming a provirus and becoming productive. Two weeks after starting combination therapy the amount of virus in the blood has decreased to about 5% of the level before treatment. The rapidity of this decline is because both activated CD4 T cells and free virions have short lifetimes. At this point no CD4 T cells are making virus and the level now present in the blood is due to production by longer-lived HIV-infected cells: macrophages, dendritic cells, and memory CD4 T cells. Continuing treatment further decreases the abundance of virus, but at a slower rate than before. Although the virus eventually becomes undetectable this does not reflect its eradication, as the virus re-emerges in patients who stop taking their medicine.

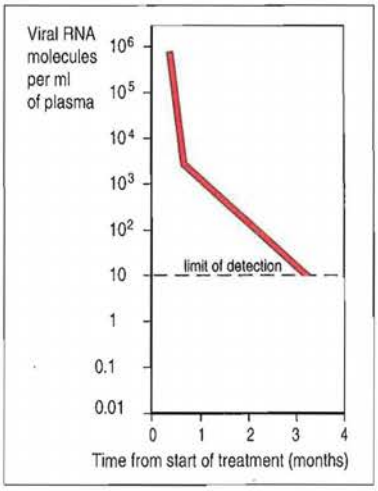


Figure 9.20 Combination drug therapy reduces HIV in the blood to below detectable levels. The abundance of HIV in patients' blood at different times after starting a course of combination drug therapy is shown.

9-21 Clinical latency is a period of active infection and renewal of CD4 T cells

The administration of antiviral drugs to HIV-infected individuals has revealed the active nature of the infection during the period of clinical latency. Within two days of starting a course of drugs the amount of virus in the blood decreases dramatically (see Figure 9.20). At the same time, the number of CD4 T cells increases substantially (Figure 9.21). This shows, first, that virus is being produced and cleared continuously within infected individuals, and second, that in the face of HIV infection the body continues to produce new CD4 T cells, which quickly become infected with HIV. Thus the period of clinical latency, when the overall numbers of CD4 T cells in the blood are gradually declining, is actually a time of immense immune activity. Vast numbers of T cells are produced and die and virions are neutralized, the latter most probably through antibody-mediated opsonization and phagocytosis.

Although measurement of lymphocyte and virion numbers in the blood is used clinically to monitor the progress of HIV infection, the secondary lymphoid

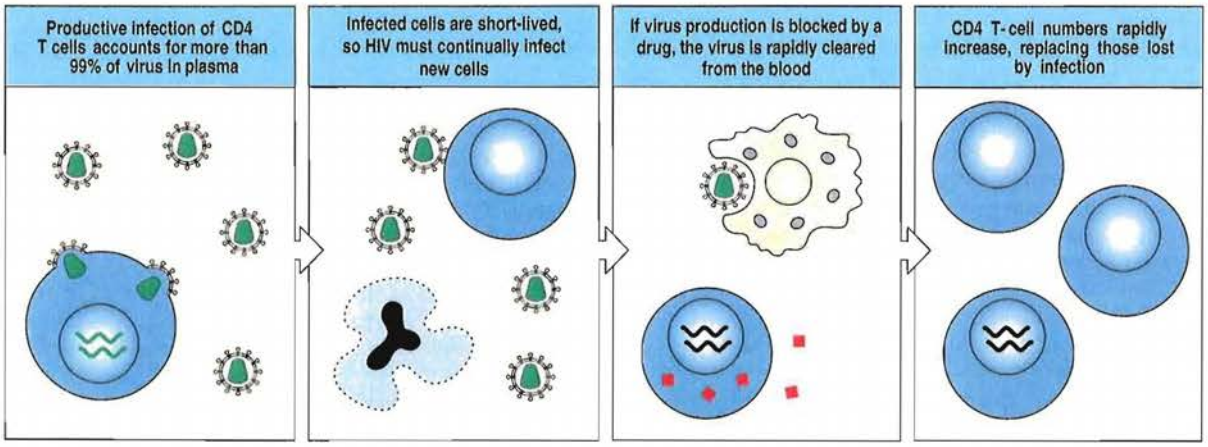


Figure 9.21 Antiviral drugs rapidly clear virus from the blood and increase the number of circulating CD4 T cells. The first and second panels show that maintenance of HIV levels in the blood depends on the continual infection of newly produced CD4 T cells. This is because cells live for only a few days once infected. The third and fourth panels show the effects of administering a drug (red squares) that blocks the viral life cycle. The existing virions in the blood are rapidly cleared by the actions of neutralizing antibody, complement, and phagocytes. Newly produced CD4 T cells are not infected, whereupon they live longer and accumulate in the circulation.

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tissues are the sites where most lymphocytes are found and where CD4 T cells are activated and produce virus. In HIV-infected people these tissues are loaded with virions, many of which are trapped on the surface of follicular dendritic cells.

9-22 HIV infection leads to immunodeficiency and death from opportunistic infections

Within a few days of being infected with HIV, a CD4 T cell dies. Three kinds of mechanism are thought to contribute to the death toll. One is direct killing as a result of the viral infection or virions binding to cell-surface receptors, the second is increased susceptibility of infected cells to apoptosis, and the third is killing by cytotoxic CD8 T cells specific for viral peptides presented by HLA class I molecules on the infected CD4 T cell.

Throughout clinical latency the daily loss of CD4 T cells is for the most part compensated for by the supply of new CD4 T cells. However, with time a steady decline in the CD4 T-cell number is evident, showing how the virus gradually wins this war of attrition. Eventually, the numbers of CD4 T cells become so low that immune responses to all foreign antigens are compromised and HIV-infected people become exceedingly susceptible to other infections. Because CD4 T cells are required for all aspects of adaptive immunity, the vulnerability of patients with AIDS due to late-stage HIV infection resembles that of children with inherited severe combined immune deficiency.

The infections that most frequently affect AIDS patients are due to infectious agents that are already present in or on the body and that are actively kept under control in healthy people. Such agents are called opportunistic pathogens and the infections they cause are known as opportunistic infections (Figure 9.22). There is a rough hierarchy in the times at which particular opportunistic infections occur in AIDS, which is correlated with the order in which the different types of immunity collapse. Cellular immunity due to CD4 T_H1 cells tends to be lost before either antibody responses or cytotoxic CD8 T cells.

The oral and respiratory tracts are soft tissues loaded with organisms and in many AIDS patients they are the site of the first opportunistic infections. For example, *Candida* causes oral thrush and *Mycobacterium tuberculosis* causes tuberculosis. Later, patients can suffer from diseases caused by the reactivation of latent herpes viruses that are no longer under control by CD8 T cells. Such diseases include shingles due to varicella-zoster, B-cell lymphoma due to EBV, and an endothelial tumor called Kaposi's sarcoma, which is caused by the herpes virus HHV8. *Pneumocystis carinii*, a common environmental fungus that is hardly ever a problem to healthy people, frequently causes pneumonia and death in AIDS patients. In the later stages of AIDS, reactivation of cytomegalovirus, a herpes virus with similar effects to those of EBV, can cause B-cell lymphoproliferative disease. Infection with the opportunistic pathogen *Mycobacterium avium* also becomes prominent. The opportunistic infections suffered by individual AIDS patients vary greatly. With the collapse of the immune system, only drugs and other interventions can be used to treat the opportunistic infections. These are rarely completely effective or without

Infections	
Parasites	*Toxoplasma* species *Cryptosporidium* species *Leishmania* species *Microsporidium* species
Bacteria	*Mycobacterium tuberculosis* *Mycobacterium avium intracellulare* *Salmonella* species
Fungi	*Pneumocystis carinii* *Cryptococcus neoformans* *Candida* species *Histoplasma capsulatum* *Coccidioides immitis*
Viruses	Herpes simplex Cytomegalovirus Varicella–zoster
Malignancies	
Kaposi's sarcoma (associated with herpes virus HHV8) Non-Hodgkin's lymphoma, including EBV-positive Burkitt's lymphoma Primary lymphoma of the brain	

Figure 9.22 A variety of opportunistic infections kill patients with AIDS. The most common of the opportunistic infections that kill AIDS patients in developed countries are listed. The malignancies are listed separately but they are also the result of impaired responses to infectious agents.

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their own deleterious effects. Eventually, the accumulated tissue damage resulting from the direct effects of HIV infection, opportunistic infections, and medical intervention causes death.

Summary

A major cause of acquired immunodeficiency in the human population today is the human immunodeficiency virus (HIV). This is a slow-acting retrovirus that remains latent for years after the initial infection. HIV infects CD4 T cells, macrophages, and dendritic cells, which all carry the CD4 glycoprotein on their surface, which is the receptor for the virus. The effects of HIV are due chiefly to a gradual and sustained destruction of CD4 T cells, which leads eventually to a profound T-cell immunodeficiency known as acquired immune deficiency syndrome (AIDS). CD4 T cells proliferate as part of their normal function and are continually being renewed; these properties allow HIV to maintain a long-lasting infection in which individuals remain relatively healthy for years. Patients with AIDS succumb to a range of opportunistic infections and to some otherwise rare, virus-associated cancers. HIV has only begun to infect humans in the past 50 years and the lack of any accommodation between host and pathogen is reflected in the strong correlation between infection and death. Genetic polymorphisms in the human population can also influence susceptibility to HIV infection. Because infection with HIV is usually dependent on the presence of the chemokine receptor CCR5, a viral co-receptor, people who lack this cell-surface protein have considerable resistance to HIV infection.

A feature of HIV infection that encourages its dissemination in the population is that infected individuals can live normal lives for many years without knowing they are infected. This poses problems for social approaches to reducing the frequency of sexual transmission. A second approach is to develop vaccines that provide protective immunity, terminating the initial acute HIV infection. Determination of the most effective aspects of the initial immune response will be crucial to this approach, which is also bedeviled by the mutability of HIV. The third approach is that of designing drugs that interfere with the growth and replication of HIV while not affecting normal functions of human cells. This pharmacological approach is the one that has seen most investment and the results have been mixed. The mutability of the virus, which enables it to escape from individual drugs, is currently perceived as the major problem and its solution is the use of combination drug therapy.

Summary to Chapter 9

In the course of their long relationship with humans, successful pathogens have developed mechanisms that allow them to exploit the human body to the full. Indeed, a pathogen is, by definition, an organism that is habitually able to overcome the body's immune defenses to such an extent that it causes disease. One class of adaptations is those whereby the pathogen changes itself or its behavior to evade the ongoing immune response. This prevents the immune system from adapting to the pathogen and improving the response. In a second type of adaptation, the pathogen is able to impair or prevent the immune response. Pathogens can have more than one such adaptation, and for some pathogens a considerable fraction of their genome is devoted to foiling the immune system. Highly successful pathogens are not necessarily the most virulent. Nonlethal ubiquitous host–pathogen relationships, such as that of humans and the Epstein–Barr virus, have generally evolved over a long period of association. However, even these pathogens can cause life-threatening disease when the immune system is compromised.

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Inherited immunodeficiencies are caused by a defect in one of the genes necessary for the development or function of the immune system. Depending on the gene involved, immunodeficiencies range from manageable susceptibilities to particular pathogens to a general vulnerability created by the complete absence of adaptive immunity. The most severe inherited immunodeficiences are very rare—evidence of the importance of the immune system to human survival.

Immunodeficiency can also be acquired as the result of infection. The human immunodeficiency virus (HIV) infects macrophages, dendritic cells, and CD4 T cells and eventually reduces the number of CD4 T cells to a level at which severe immunodeficiency results—the acquired immune deficiency syndrome (AIDS). This retroviral pathogen has only just begun to exploit the human species, but it already has a variety of effective adaptations acquired during its history in other primate hosts. Most people infected with HIV have no overt symptoms of disease for years, which facilitates the spread of HIV by sexual transmission, and HIV infection has now reached epidemic proportions within the human population. The discovery of natural genetic traits that endow individual humans with resistance to HIV indicates possibilities for accommodation in the longer term.

Questions

Question 9–1

A. Explain what is meant by serotype-specific immunity.

B. How does *Streptococcus pneumoniae* exploit serotype-specific immunity to evade detection? (Refer to Figure 9.1.)

Question 9–2

A. Which antigens are most important in the immune response to the influenza virus?

B. Explain the difference between antigenic drift and antigenic shift in the influenza virus.

C. Which is most likely to lead to a major worldwide pandemic?

D. What is the role of the phenomenon of 'original antigenic sin' in immunity to this virus? (Refer to Figures 9.2 and 8.52, and Section 8-27.)

Question 9–3

During the course of a trypanosome infection, a periodic rise and fall in the number of parasites is seen. Say what feature of trypanosomes is causing this, and explain these observations. (Refer to Figure 9.3.)

Question 9–4

Using Table Q9–4 match the mechanism of evasion and subversion of the immune system in Column 1 with the pathogen in Column 2.

Question 9–5

A. Explain the mechanism by which human immunodeficiency virus (HIV) enters a host cell.

B. Explain the cellular tropism of HIV, discussing the difference between macrophage-tropic and lymphocyte-tropic HIV.

Table Q9–4

a. Variant pilin protein expression	1. *Staphylococcus aureus*
b. Induction of quiescent (latent) state in neurons	2. *Toxoplasma gondii*
c. Reactivation of infected ganglia after stress or immunosuppression	3. *Salmonella typhimurium*
d. Alternate expression of two antigenic forms of flagellin	4. Influenza virus
e. Recombination of RNA genomes of avian and human origins	5. *Mycobacterium tuberculosis*
f. Escape from phagosome and growth and replication in cytosol	6. Varicella-zoster
g. Survival in a membrane-bounded vesicle resistant to fusion with other cellular vesicles	7. *Neisseria gonorrhoeae*
h. Coating its surface with human proteins	8. *Treponema pallidum*
i. Inhibiting fusion of phagosome with lysosome and survival in the host cell's vesicular system	9. *Listeria monocytogenes*
j. Immunosuppression caused by nonspecific proliferation and apoptosis of T cells	10. Herpes simplex virus

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C. Some people seem to be resistant to HIV infection because a primary infection cannot be established in macrophages. What is the reason for this? (Refer to Figure 9.15.)

Question 9–6

A. What does the term seroconversion mean in relation to an HIV infection?

B. What relationship does seroconversion have to the time course of an HIV infection? (Refer to Figures 9.16 and 9.18.)

Question 9–7

A. Deficiencies in antibody production can be due to a variety of underlying genetic defects. Name two immunodeficiency diseases, other than the severe combined immunodeficiences, in which a defect in antibody production is the cause of the disease, and for which the underlying genetic defect is known. For each disease, say how (i) antibody production is affected, and (ii) what the underlying defect is and why it has this effect.

B. What is the main clinical manifestation of immunodeficiency diseases in which antibody production is defective but cell-mediated immune responses are intact? (Refer to Sections 9-9, 9-10, and Figure 9.7.)

Question 9–8

A. Explain why an inherited deficiency in complement components C3 or C4 can result in less efficient clearance of immune complexes from the blood and lymph than normal.

B. What clinical symptoms can this lead to?

C. What is the only known effect of deficiencies in complement components C5–C9? Explain this effect. (Refer to Section 9-11, and Figure 9.9.)

Question 9–9

A. Name three immunodeficiency diseases caused by defects in phagocytes.

B. Which immunodeficiency disease is caused by a defect in the phagocyte NADPH oxidase system, and what is the cellular effect of this defect?

C. What are the main clinical effects of defects in phagocyte function? (Refer to Section 9-12, and Figure 9.10.)

Question 9–10

A. What type of immune deficiency would you see in a child lacking the common γ chain of the receptor for cytokines IL-2, IL-4, and IL-7, among others? Explain your answer.

B. Why would you see the same type of immunodeficiency in a child lacking Jak3 kinase function?

C. What treatment might be possible to remedy this immunodeficiency? (Refer to Section 9-13.)

Question 9–11

Which property of HIV renders the virus difficult to eradicate by the body's immune defenses, and also limits the efficacy of drug therapies?

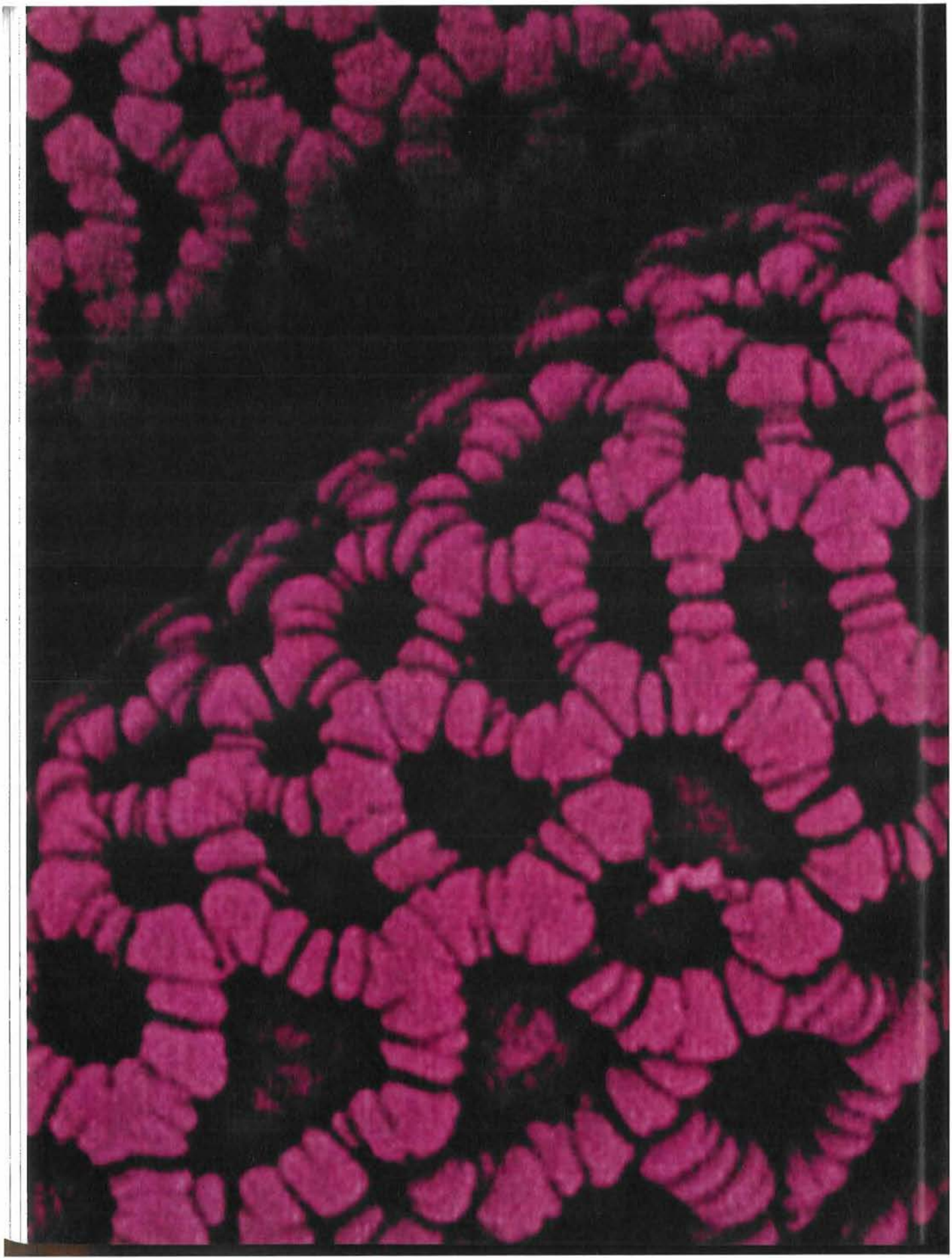
Question 9–12

Explain why a staphylococcal infection might produce a medical emergency.

Question 9–13

What would you predict might happen to the course of the HIV infection in a person who developed toxic-shock syndrome while in the latent phase of HIV? Explain your answer. (Refer to Figure 9.15.)

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Chapter 10

Over-reactions of the Immune System



The protective functions of the immune system depend on recognition events that distinguish molecular components of infectious agents from those of the human body. In this context the immune system is said to recognize a pathogen's molecules as foreign. Besides infectious agents, humans come into daily contact with numerous other molecules that are equally foreign but do not threaten health. Many of these molecules derive from the plants and animals that we eat or are present in the environments where we live, work, and play. For most people for most of the time, contact with these molecules stimulates neither inflammation nor adaptive immunity.

In some circumstances, however, certain kinds of innocuous molecule stimulate an adaptive immune response and the development of immunological memory in predisposed members of the population. On subsequent exposures to the antigen the immune memory produces inflammation and tissue damage that is at best an irritation, and at worst a threat to life. The person feels ill, as though fighting off an infection, when no infection exists. The over-reactions of the immune system to harmless environmental antigens are called either **hypersensitivity reactions** or **allergic reactions**. The environmental antigens that cause these reactions are termed **allergens** and they induce a state of hypersensitivity or **allergy**, the latter word being of Greek derivation and meaning 'altered reactivity.'

Unfortunately, the antigens that provoke these over-reactions are often common in the human environment: in developed countries some 10–40% of the inhabitants are allergic to one or more environmental antigens. Some of the antigens responsible for common hypersensitivities are listed in Figure 10.1.

10-1 Four types of hypersensitivity reaction are caused by different effector mechanisms of adaptive immunity

Hypersensitivity reactions are conventionally grouped into four types according to the effector mechanisms that produce the reaction (Figure 10.2). Some antigens (penicillin, for example) cause different types of hypersensitivity reaction, depending on the circumstances in which they are encountered. **Type I hypersensitivity reactions** result from the binding of antigen to antigen-specific IgE bound to its Fc receptor, principally on mast cells. This interaction causes the degranulation of mast cells and the release of inflammatory mediators. Type I reactions are commonly caused by inhaled particulate antigens, of which plant pollens are good examples. Type I reactions have effects of varying severity, ranging from a runny nose to breathing difficulties and

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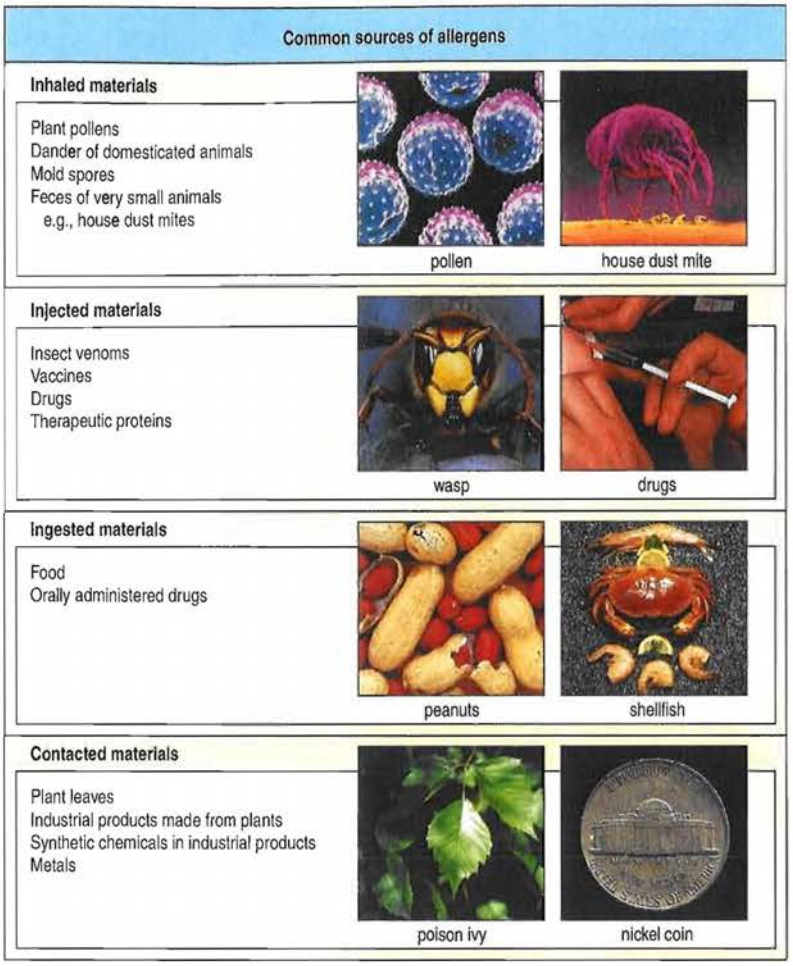


Figure 10.1 Some substances that are a common cause of hypersensitivity reactions.

even death by asphyxiation. Because of their prevalence and diversity, a large part of this chapter will be devoted to the IgE-mediated hypersensitivity reactions.

Type II hypersensitivity reactions are caused by small molecules that bond covalently to cell-surface components of human cells, producing modified structures that are perceived as foreign by the immune system. The B-cell response to these new epitopes produces IgG, which on binding to the modified cells causes their destruction through complement activation and phagocytosis. The antibiotic penicillin is an example of a small reactive molecule that can induce a type II hypersensitivity reaction.

Type III hypersensitivity reactions are due to small soluble immune complexes formed by soluble protein antigens binding to the IgG made against them. Some of these immune complexes become deposited in the walls of small blood vessels or the alveoli of the lungs. The immune complexes activate complement and initiate an inflammatory response that damages the tissue, impairing its physiological function. When antibodies or other proteins derived from nonhuman animal species are given therapeutically to patients, type III hypersensitivity reactions are a potential side-effect.

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The effector molecules initiating type I, II, and III hypersensitivity reactions are all antibodies. In contrast, **type IV hypersensitivity reactions** are caused by the products of antigen-specific effector T cells. Most reactions are caused by CD4 T_H1 cells. For example, the inflammatory reaction around the site of an insect bite or sting is caused by CD4 T_H1 cells that respond to peptide epitopes derived from venom and other insect proteins introduced by the bite. A minority of type IV hypersensitivity reactions are due to cytotoxic CD8 T cells. They arise when small, reactive, lipid-soluble molecules pass through cell membranes and bond covalently to intracellular human proteins. Degradation of these chemically modified proteins yields abnormal peptides that bind to HLA class I molecules and stimulate a cytotoxic T-cell response. For example, the allergic response to poison ivy involves cytotoxic T cells. These recognize peptides derived from intracellular proteins that are modified by chemical reaction with pentadecacatechol, a chemical acquired by touching the plant's leaves.

Type I hypersensitivity reactions

A prerequisite for a type I hypersensitivity reaction is that the person makes IgE antibody when he or she first encounters the antigen. This is how a person becomes **sensitized** to the antigen. IgE differs from other antibody isotypes in being located predominantly in tissues, where it is bound to mast cells by high-affinity surface receptors known as FcεRI. We first look at the effector cells and molecules that produce a type I response, and then consider the characteristic properties of allergens and how sensitization occurs.

10-2 IgE binds irreversibly to Fc receptors on mast cells, basophils, and activated eosinophils

IgE antibody causes allergic reactions because of its exceptionally high affinity for its Fc receptor and the cellular distribution of the receptor. Binding of the IgE constant region to its high-affinity receptor—**FcεRI**—is the tightest of the antibody–Fc receptor interactions ($K_d \approx 10^{10}\ M^{-1}$, see Figure 7.24, p. 200) and can be considered for all practical purposes as irreversible. Also, unlike other isotypes, IgE binds to its receptor in the absence of antigen. FcεRI is expressed constitutively by mast cells and basophils, and by eosinophils after

	Type I	Type II		Type III	Type IV		
Immune reactant	IgE	IgG		IgG	T_H1 cells	T_H2 cells	CTL
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Cell-surface receptor	Soluble antigen	Soluble antigen	Soluble antigen	Cell-associated antigen
Effector mechanism	Mast-cell activation	Complement, FcR⁺ cells (phagocytes, NK cells)	Antibody alters signaling	Complement Phagocytes	Macrophage activation	Eosinophil activation	Cytotoxicity
Example of hypersensitivity reaction	Allergic rhinitis, asthma, systemic anaphylaxis	Some drug allergies (eg penicillin)	Chronic urticaria (antibody to FcαRIα)	Serum sickness, Arthus reaction	Contact dermatitis, tuberculin reaction	Chronic asthma, chronic allergic rhinitis	Contact dermatitis

Figure 10.2 Hypersensitivity reactions fall into four classes on the basis of their mechanism. The types of preexisting immunity causing the reaction are listed along with the types of antigen that provoke the response, the underlying effector mechanism, and the nature of the ailment produced.

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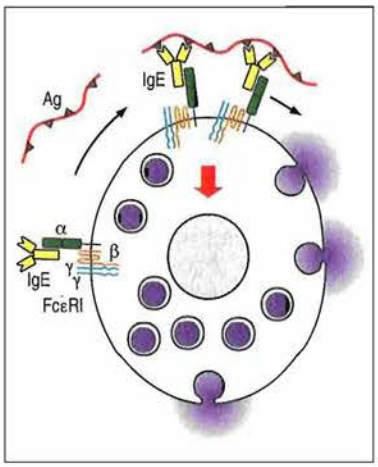


Figure 10.3 Cross-linking of FcεRI on the surface of mast cells by antigen and IgE causes mast-cell activation and degranulation. The high-affinity IgE receptor (FcεRI) on mast cells, basophils, and activated eosinophils is formed from one α chain, one β chain, and two γ chains. The binding site for IgE is formed by the two extracellular immunoglobulin-like domains of the α chain. The β chain and the two disulfide-bonded γ chains are largely intracellular and contribute to signaling. When receptors are cross-linked by antigen binding to IgE on the surface of a mast cell, a signal is transmitted that leads to the release of preformed granules containing histamine and other inflammatory mediators.

they have been activated by cytokines. After a primary IgE response has subsided and the antigen has been cleared by the usual means, all antigen-specific IgE molecules that have not encountered antigen will be bound by their Fc regions to FcεRI on these cells. The stable complexes of IgE and FcεRI effectively provide mast cells, basophils, and eosinophils with antigen-specific receptors. All these cells have granules containing preformed inflammatory mediators. When the antigen is next encountered it will bind to the receptors and activate the cells to release their inflammatory mediators (Figure 10.3). Initial degranulation is followed by induced synthesis of a wider range of mediators.

Two important features distinguish the 'antigen receptors' on mast cells, basophils, and eosinophils from those of B cells and T cells. The first is that the cell's effector function becomes operational immediately after antigen binds to the 'receptor' and does not require a phase of cell proliferation and differentiation. The second is that each cell is not restricted to carrying receptors of a single antigen specificity but can carry a range of IgE representing that present in the circulation. These features combine to quicken and strengthen the response to any antigen to which a person has been sensitized. When any one of those antigens enters a tissue, all the mast cells in the vicinity bearing a sufficient number of molecules of IgE specific for that antigen will be triggered to degranulate immediately.

IgE-mediated activation of mast cells, basophils, and activated eosinophils is thought to provide protection against parasites (see Section 7-13, p. 202), which are prevalent in tropical regions. This type of environment is where the human species originated and where it has lived for most of its existence. In the developing countries of the tropics, parasites are abundant and a one-third of the world's population is infected by one or more parasites.

In contrast, in the developed countries where parasite infections are rare, IgE responses tend to be stimulated by contact with nonthreatening substances in the environment. In North America and Europe, the impact of allergic disease is increasingly being felt in all aspects of human life. Some physicians have called it an 'epidemic of allergy'. Because allergy has directed medical research in this area we know far more about the allergic effects of IgE than we do about its benefits in controlling infection.

10-3 Tissue mast cells orchestrate IgE-mediated allergic reactions through the release of inflammatory mediators

Mast cells are resident in mucosal and epithelial tissues lining the body surfaces and serve to alert the immune system to local trauma and infection. Present in all vascularized tissues except the central nervous system and the retina, their initial response to activation is to release inflammatory molecules that are stored in 50–200 large granules that fill the cytoplasm (Figure 10.4). The name **mast cell** derives from the German word *Mastzellen*, meaning



Figure 10.4 Light micrograph of mast cell stained for the granule protease chymase to show the numerous granules that fill its cytoplasm. The mast cell is in the center of the picture: its nucleus is stained pink and the cytoplasmic granules are stained red. Magnification × 1000. Photograph courtesy of D. Friend.

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'fattened' or 'well-fed cells', which is how they appear under the microscope. Mast-cell granules contain principally histamine, heparin, tumor necrosis factor-α (TNF-α), chondroitin sulfate, neutral proteases, and other degradative enzymes and inflammatory mediators (Figure 10.5). Heparin, an acidic proteoglycan, is largely responsible for the characteristic staining of the mast-cell granules with basic dyes.

On leaving the bone marrow, immature mast cells travel in the blood as agranular cells that enter tissues and settle near small blood vessels. There they mature and form their characteristic granules. This differentiation is mediated by stem-cell factor (SCF), which interacts with CD117 (also called Kit) on the mast-cell surface. The importance of mast cells for IgE-mediated inflammatory reactions is well illustrated by the phenotype of mice lacking functional CD117. These mice have no differentiated mast cells and none of the inflammatory responses normally caused by IgE.

Two kinds of human mast cell are distinguished: a mucosal mast cell, which produces the protease tryptase, and a connective tissue mast cell, which produces chymotryptase. In patients with T-cell immunodeficiencies, only connective tissue mast cells are present, suggesting that the development of mucosal mast cells is dependent on T cells. Mast-cell activation occurs in the presence of any antigen that can cross-link the IgE molecules bound to FcεRI at the cell surface. This can be accomplished by antigens with repetitive epitopes that cross-link IgE molecules of the same specificity, or by antigens possessing two or more different epitopes that cross-link IgE molecules of different specificities. Once a mast cell's receptors have been cross-linked, degranulation occurs within a few seconds, releasing the stored mediators into the immediate extracellular environment (see Figure 10.5).

Prominent among these chemicals is histamine, an amine derivative of the amino acid histidine (Figure 10.6). Histamine exerts a variety of physiological effects through three kinds of histamine receptor—H1, H2, and H3—which

Class of product	Product	Biological effects
Enzyme	Tryptase, chymase, cathepsin G, carboxypeptidase	Remodeling of connective tissue matrix
Toxic mediator	Histamine, heparin	Toxic to parasites Increase vascular permeability Cause smooth muscle contraction
Cytokine	TNF-α (some stored preformed in granules)	Promotes inflammation, stimulates cytokine production by many cell types, activates endothelium
	IL-4, IL-13	Stimulate and amplify T_H2-cell response
	IL-3, IL-5, GM-CSF	Promote eosinophil production and activation
Chemokine	CCL3	Chemotactic for monocytes, macrophages, and neutrophils
Lipid mediator	Leukotrienes C_4, D_4 and E_4	Cause smooth muscle contraction Increase vascular permeability Cause mucus secretion
	Platelet-activating factor	Chemotactic for leukocytes Amplifies production of lipid mediators Activates neutrophils, eosinophils, and platelets

Figure 10.5 Molecules released by mast cells on stimulation by antigen binding to IgE. Proteases, histamine, heparin, and TNF-α (shown in red) are prepackaged in granules and are released immediately the mast cell is stimulated by antigen binding. TNF-α is also synthesized after mast-cell activation. The other molecules are synthesized and released only as a result of mast-cell activation.

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have been defined on different cell types. Acute allergic reactions involve histamine binding to the H1 receptor on nearby smooth muscle cells and on endothelial cells of blood vessels. Stimulation of the H1 receptor on endothelial cells induces vessel permeability and the entry of other cells and molecules into the allergen-containing tissue, causing inflammation. Smooth muscle cells are induced to contract on binding histamine, which constricts airways, for example, and histamine also acts on the epithelial linings of mucosa to induce the increased secretion of mucus. All these actions produce different effects depending upon the tissue exposed to allergen. Sneezing, coughing, wheezing, vomiting, and diarrhea can all be induced in the course of an allergic reaction.

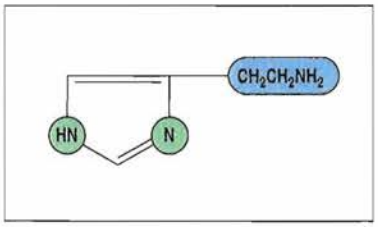


Figure 10.6 The chemical structure of histamine.

Other molecules released from mast-cell granules include mast-cell chymotryptase, tryptase, and other neutral proteases that activate metalloproteases in the extracellular matrix. Collectively, these enzymes break down extracellular matrix proteins. The action of histamine is complemented by that of TNF-α, which is also released from mast-cell granules. TNF-α activates endothelial cells, causing an increased expression of adhesion molecules, thus promoting leukocyte traffic from the blood into the increasingly inflamed tissue (see Figure 8.19, p. 245). Mast cells are unique in their capacity to store TNF-α and release it on demand. At the start of an inflammatory response, mast cells are usually the main source of this cytokine.

Besides the preformed inflammatory mediators in granules, mast cells synthesize and secrete other mediators in response to activation (see Figure 10.5). These include chemokines, cytokines—IL-4 and more TNF-α—prostaglandins, and leukotrienes. The latter are synthesized from fatty acids (Figure 10.7, top panel). All these mediators act locally within the area of tissue surrounding the

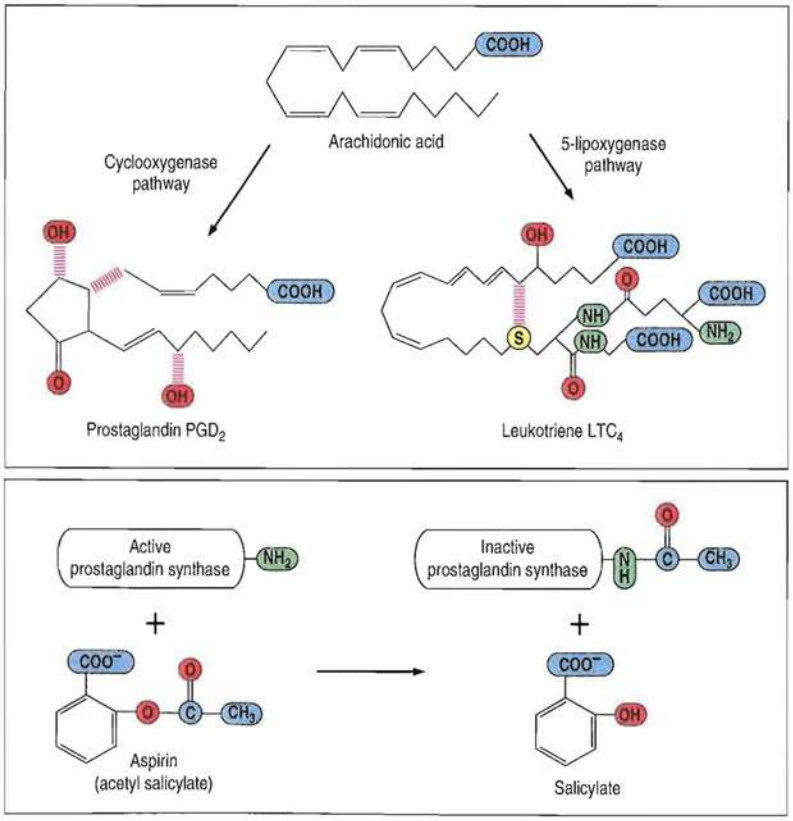


Figure 10.7 Mast cells synthesize prostaglandins and leukotrienes from arachidonic acid by different enzyme pathways. Arachidonic acid, an unsaturated fatty acid, is used as the substrate for the cyclooxygenase pathway to make prostaglandins, and as the substrate for the 5-lipoxygenase pathway to make leukotrienes, as shown in the top panel. Arachidonate is itself made from linolenic acid, one of the essential unsaturated fatty acids that must be provided in the diet because it cannot be made by human cells. Aspirin (acetyl salicylate) prevents the synthesis of prostaglandins by the cyclooxygenase pathway by irreversibly inhibiting the enzyme prostaglandin synthase, as shown in the bottom panel.

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activated mast cells. The leukotrienes have activities similar to those of histamine, but are more than a hundred times more potent on a molecule-for-molecule basis. The two kinds of mediator are therefore complementary. Histamine provides a rapid response while the more potent leukotrienes are being made. In the later stages of allergic reactions, leukotrienes are principally responsible for inflammation, smooth muscle contraction, constriction of airways, and mucus secretion from mucosal epithelium. Mast cells also secrete prostaglandin D_2 (PGD_2), which promotes dilation and increased permeability of blood vessels and also acts as a chemoattractant for neutrophils. Aspirin reduces inflammation by inactivating prostaglandin synthase, the first enzyme in the cyclooxygenase pathway. The inactivation is irreversible because aspirin binds covalently to the active site of the enzyme (see Figure 10.7, bottom panel).

The combined effect of the chemical mediators released by mast cells is to attract circulating leukocytes to the site of mast-cell activation, where they amplify the reaction initiated by antigen and IgE on the mast-cell surface. These effector leukocytes include eosinophils, basophils, neutrophils, and T_H2 lymphocytes. In parasite infections these cells work together either to promote explosive reactions that kill the parasite or expel it from the body (see Section 7-13, p. 202). In allergic reactions the same reactions give only detrimental side-effects—damage to the body's tissues and impairment of their function.

10-4 Eosinophils and basophils are specialized granulocytes that release toxic mediators in IgE-mediated responses

Eosinophils are granulocytes whose granules contain arginine-rich basic proteins. In histological sections these proteins stain heavily with eosin, hence the name eosinophil, meaning 'liking eosin' (Figure 10.8). Normally, only a minority of eosinophils are circulating in the blood. Most are resident in tissues, especially in the connective tissue immediately underlying epithelia of the respiratory, gastrointestinal, and urogenital tracts. As with mast cells, the activation of eosinophils by external stimuli leads to the staged release of toxic molecules and inflammatory mediators. Preformed chemical mediators and proteins present in the granules are released first (Figure 10.9, top panel). The normal function of these highly toxic molecules is to kill invading microorganisms and parasites directly. This is followed by a slower induced synthesis and secretion of prostaglandins, leukotrienes, and cytokines, which amplify the inflammatory response by activation of epithelial cells and leukocytes, including more eosinophils (see Figure 10.9, bottom panel).

The eosinophil response is highly toxic and potentially damaging to the host as well as to parasites. Limiting the damage are various control mechanisms.

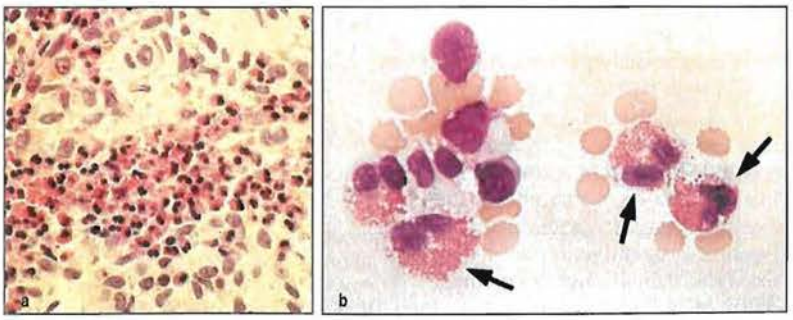


Figure 10.8 Eosinophils have a characteristic staining pattern in histological sections. Panel a shows a light micrograph of a section through a Langerhans' cell histiocytosis in skin that is heavily infiltrated with eosinophils. The eosinophils have bilobed nuclei and stain pink with the stain eosin. Panel b shows a higher-power light micrograph of a blood smear in which partly degranulated eosinophils (arrows) are surrounded by erythrocytes. Panel a courtesy of T. Krausz; panel b courtesy of F. Rosen and R. Geha.

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Class of product	Product	Biological effects
Enzyme	Eosinophil peroxidase	Toxic to targets by catalyzing halogenation Triggers histamine release from mast cells
	Eosinophil collagenase	Remodeling of connective tissue matrix
Toxic protein	Major basic protein	Toxic to parasites and mammalian cells Triggers histamine release from mast cells
	Eosinophil cationic protein	Toxic to parasites Neurotoxin
	Eosinophil-derived neurotoxin	Neurotoxin
Cytokine	IL-3, IL-5, GM-CSF	Amplify eosinophil production by bone marrow Cause eosinophil activation
Chemokine	CXCL8	Promotes influx of leukocytes
Lipid mediator	Leukotrienes C_4, D_4 and E_4	Cause smooth muscle contraction Increase vascular permeability Cause mucus secretion
	Platelet-activating factor	Chemotactic to leukocytes Amplifies production of lipid mediators Activates neutrophils, eosinophils, and platelets

Figure 10.9 Activated eosinophils secrete toxic proteins contained in their granules and also produce cytokines and inflammatory mediators. The enzymes and toxic proteins are contained preformed in the granules and are released immediately on eosinophil activation (shown in red). The cytokines, chemokines, and lipid mediators are synthesized only after activation.

When the body is healthy, the number of eosinophils is kept low by limiting their production in the bone marrow. When infection or antigenic stimulation activates T_H2 cells, the IL-5 and other cytokines released by the T_H2 cells stimulate the bone marrow to increase both the production of eosinophils and their release into the circulation. The migration of eosinophils into tissues is controlled by a group of chemokines (CCL5, CCL7, CCL11, and CCL13) that bind to the receptor CCR3, expressed by eosinophils. Of these chemokines, CCL11, also called eotaxin, is particularly important in the migration of eosinophils and is produced by activated endothelial cells, T cells, and monocytes.

The activity of eosinophils is further controlled by modulation of their sensitivity to external stimuli. This is achieved through the regulated expression of FcεRI. In the resting state, eosinophils do not express FcεRI, do not bind IgE, and cannot therefore be induced to degranulate by antigen. Once an inflammatory response is set in motion, cytokines and chemokines in the inflammatory site induce eosinophils to express FcεRI. The expression of Fcγ receptors and complement receptors on the eosinophil surface also increases, facilitating the binding of eosinophils to pathogen surfaces coated with IgG and complement.

The potential of eosinophils to cause tissue damage is clearly seen in patients who have abnormally high numbers of eosinophils. Certain T-cell lymphomas, for example, constitutively secrete IL-5, which continually expands the eosinophil population. This expansion is detected by a greatly increased number of eosinophils in the blood (**hypereosinophilia**). With so many circulating eosinophils, only a small proportion need to be activated for their effects to be seriously disruptive. Patients with hypereosinophilia can suffer damage to the endocardium of the heart (Figure 10.10) and to nerves, leading to heart failure and neuropathy. Both of these effects are thought to be due to cytotoxic and neurotoxic proteins released from eosinophil granules.

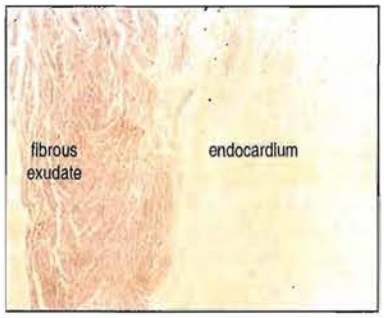


Figure 10.10 The presence of an abnormally large number of circulating eosinophils causes damage to the heart. The photograph shows a section of endocardium from a patient with hypereosinophilic syndrome. The damaged tissue is characterized by an organized fibrous exudate and an endocardium thickened by fibrous tissue. Although the patient has large numbers of circulating eosinophils, these cells are not seen in the injured endocardium, which is thought to be damaged by the contents of granules released by circulating eosinophils. Photograph courtesy of D. Swirsky and T. Krausz.

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In localized allergic reactions, mast-cell degranulation and the activation of T_H2 cells cause the accumulation of activated eosinophils at the site. Their presence is characteristic of chronic allergic inflammation; for example, eosinophils are considered the principal cause of the airway damage that occurs in chronic asthma.

Basophils are granulocytes whose granules stain with basic dyes such as hematoxylin (Figure 10.11). The granules of basophils package a similar, but not identical, set of mediators to those of mast cells. Although basophils resemble mast cells in some ways, they are developmentally more closely related to eosinophils. They share a common stem-cell precursor, as well as requiring similar growth factors, including IL-3, IL-5, and GM-CSF. The production of eosinophils and basophils seems to be reciprocally regulated, so that a combination of TGF-β and IL-3 promotes the maturation of basophils while suppressing that of eosinophils. Basophils are normally present in very low numbers in the circulation and are therefore more difficult to study than other leukocytes. Their functions in defense against parasites seem similar to those of eosinophils. Like eosinophils, basophils are recruited into sites of allergic reactions, where they are activated to degranulate by antigen cross-linking the IgE bound to the FcεRI on the basophil cell surface.

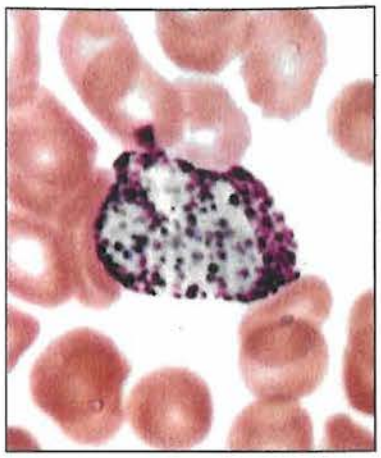


Figure 10.11 Light micrograph of basophil stained with Wright's Giemsa. The basophil in the center is surrounded by erythrocytes in this blood smear. Magnification × 1000. Photograph courtesy D. Friend.

Mast cells, eosinophils, and basophils often act in concert. Mast-cell degranulation initiates the inflammatory response, which then recruits eosinophils and basophils. Eosinophil degranulation releases **major basic protein**, which in turn causes the degranulation of mast cells and basophils. This latter effect is augmented by any of the cytokines—IL-3, IL-5, and GM-CSF—that affect the growth, differentiation, or activation of eosinophils and basophils.

10-5 Mast cells, basophils, and eosinophils can amplify an IgE response started by T_H2 cells

IgE is responsible for most allergic responses (Figure 10.12). The production of IgE is favored when the immune system is challenged with small quantities

IgE-mediated allergic reactions

Syndrome	Common allergens	Route of entry	Response
Systemic anaphylaxis	Drugs Serum Venoms Peanuts	Intravenous (either directly or following rapid absorption)	Edema Increased vascular permeability Tracheal occlusion Circulatory collapse Death
Wheal and flare	Insect bites Allergy testing	Subcutaneous	Local increase in blood flow and vascular permeability
Allergic rhinitis (hay fever)	Pollens (ragweed, timothy, birch) Dust-mite feces	Inhaled	Edema of nasal mucosa Irritation of nasal mucosa
Bronchial asthma	Pollens Dust-mite feces	Inhaled	Bronchial constriction Increased mucus production Airway inflammation
Food allergy	Shellfish Milk Eggs Fish Wheat	Oral	Vomiting Diarrhea Pruritis (itching) Urticaria (hives) Anaphylaxis

Figure 10.12 Allergic reactions mediated by IgE.

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of antigen and when the cytokine IL-4 is present at the time that naive CD4 T cells are presented with antigen. Under these circumstances CD4 T cells tend to make a T_H2 response (see Section 8-19, p. 263), which then produces more IL-4 and additional cytokines that stimulate B cells to switch their immunoglobulin isotype to IgE (see Section 7-5, p. 192). Initial sensitization to an allergen is thus favored by circumstances that promote the production of antigen-specific T_H2 cells and the production of IgE, and disfavored by conditions that produce T_H1 cells. The principal function of IL-4 seems to be to facilitate the IgE response; in mice unable to make this cytokine the main defect is diminished IgE synthesis.

Once started, an IgE response can be amplified through the participation of mast cells, basophils, and activated eosinophils. These cells bind IgE to their FcεRI, which can then be cross-linked by antigen, causing cellular activation. As part of this activation the cells secrete IL-4 and express CD40 ligand. Like T_H2 cells, the activated mast cells, basophils, and eosinophils can drive class switching and IgE production by B cells (Figure 10.13). These cellular interactions can occur at the site of allergic reactions, where B cells are seen to form germinal centers.

10-6 Common allergens are small proteins inhaled in particulate form that stimulate an IgE response

In the previous sections we have considered the effector cells responsible for the symptoms of allergies. Here we turn to the types of antigen to which people become sensitized. Because T cells are stimulated by antigen-derived peptides, the allergens that provoke type I responses are invariably proteins. Much human allergy is caused by a limited number of airborne proteins that are inhaled. Small amounts of the protein enter the body by crossing the mucosa of the respiratory tract and then stimulate T_H2 responses in the local lymphoid tissues. Allergens are only a small proportion of all the proteins that humans inhale, and a central goal of research on allergy is to define what distinguishes proteins that become allergens from those that do not. A definitive answer has yet to be found. Figure 10.14 shows some of the properties that characterize inhaled allergens.

Most allergens are small, soluble proteins that are present in dried-up particles of material derived from plants and animals. Examples are pollen grains, the mixture of dried cat skin and saliva that forms dander, and the dried feces of the house dust mite *Dermatophagoides pteronyssimus*. The light dry particles become airborne and are inhaled by humans. Once inhaled, the particles become caught in the mucus bathing the epithelia of the airways and lungs. They then rehydrate, releasing the antigenic proteins. These antigens are carried to professional antigen-presenting cells within the mucosa. The antigens

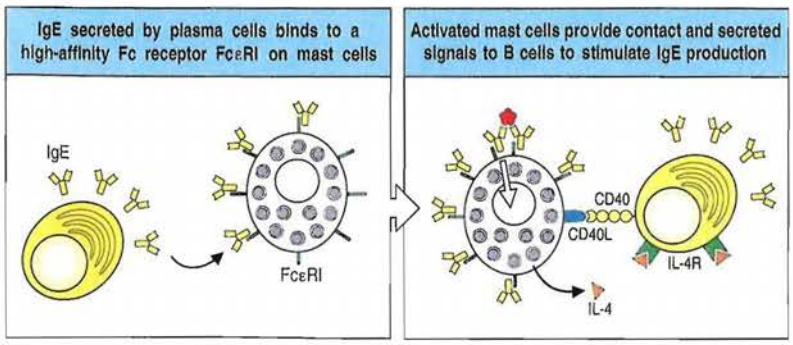


Figure 10.13 Antigen binding to IgE on mast cells leads to amplification of IgE production. IgE secreted by plasma cells binds to the high-affinity IgE receptor on mast cells (illustrated here) and basophils. When the surface-bound IgE is crosslinked by antigen, these cells express CD40 ligand (CD40L) and secrete IL-4, which in turn binds to IL-4 receptors (IL-4R) on the activated B cell, stimulating isotype switching by B cells and the production of more IgE. These interactions can occur *in vivo* at the site of allergen-triggered inflammation, for example in bronchial-associated lymphoid tissue.

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are then processed and presented by these cells to CD4 T cells, stimulating a T_H2 response that leads to the production of IgE and its binding to mast cells (Figure 10.15). Small soluble protein antigens are more efficiently leached out of particles and penetrate the mucosa. A substantial proportion of allergens are proteases, and it is likely that their enzymatic activities facilitate the breakdown of the particle, the release of allergen, and the generation of peptides that stimulate T_H2 cells.

The major allergen responsible for more than 20% of the allergies in the human population of North America is a cysteine protease derived from *D. pteronyssimus*. Advances in the heating and cooling of homes, offices, and other buildings are believed to be responsible for the prevalence of this allergy because they provide an environment that encourages both the growth of *D. pteronyssimus* and the desiccation of its feces. The air currents created by forced-air heating, air conditioners, and vacuum cleaners all help to move the particles into the air, where they will be breathed in by the buildings' human inhabitants.

The cysteine protease of *D. pteronyssimus* is related to the protease papain, which comes from the papaya fruit and is used in cooking as a meat tenderizer. Workers involved in the commercial production of papain become allergic to the enzyme, an example of an occupational immunological disease. Similarly, the protease subtilisin, the 'biological' component of some laundry detergents, causes allergy in laundry workers. Chymopapain, a protease related to papain, is used in medicine to degrade intervertebral disks in patients with sciatica. A rare complication of this procedure affects patients who are sensitized to chymopapain; they experience an acute systemic allergic response to the enzyme, an example of systemic anaphylaxis.

Features of inhaled allergens that may promote the priming of T_H2 cells that drive IgE responses	
Molecular type	Proteins, because only they induce T-cell responses
Function	Allergens are often proteases
Low dose	Favors activation of IL-4-producing CD4 T cells
Low molecular weight	Allergen can diffuse out of particle into mucus
High solubility	Allergen is readily eluted from particle
High stability	Allergen can survive in desiccated particle
Contains peptides that bind host MHC class II	Required for T-cell priming

Figure 10.14 Properties of inhaled allergens.

10-7 Predisposition to allergy has a genetic basis

In the caucasoid populations of Europe and North America, up to 40% of people are more likely than the rest of the population to make IgE responses to common environmental antigens. Allergists call this predisposed state **atopy**. As a group, atopic people have higher levels of soluble IgE and circulating eosinophils than nonatopic people. Family studies indicate a genetic basis for atopy, with an involvement of genes on chromosomes 5 and 11.

The candidate gene on chromosome 11 encodes the β subunit of FcεRI, and the region implicated on chromosome 5 contains a cluster of genes including

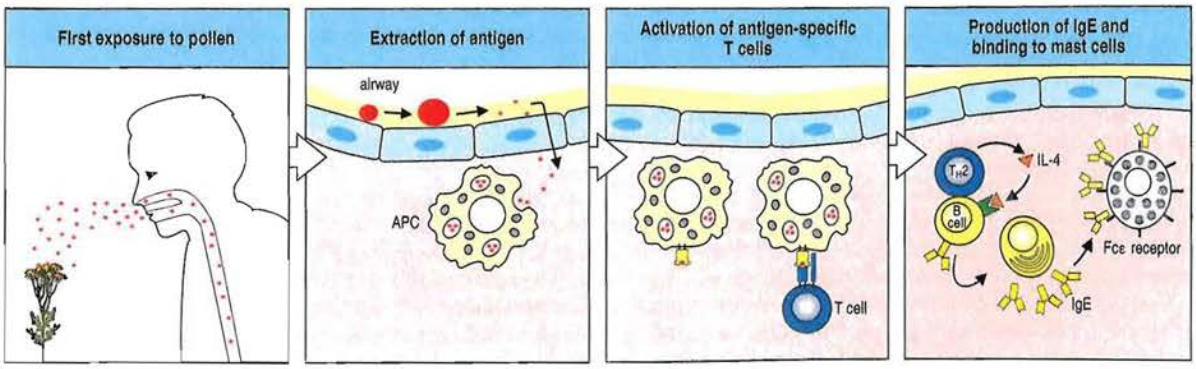


Figure 10.15 Sensitization to an inhaled allergen. Antigens that leach from inhaled pollen are taken up by antigen-presenting cells (APC) in the mucosa of the airways. These activate naive T cells to become T_H2 effector cells, which secrete IL-4. IL-4 binds to the B cell's IL-4 receptor, causing the B cell to switch its immunoglobulin isotype and secrete IgE. The IgE binds to FcεRI on mast cells.

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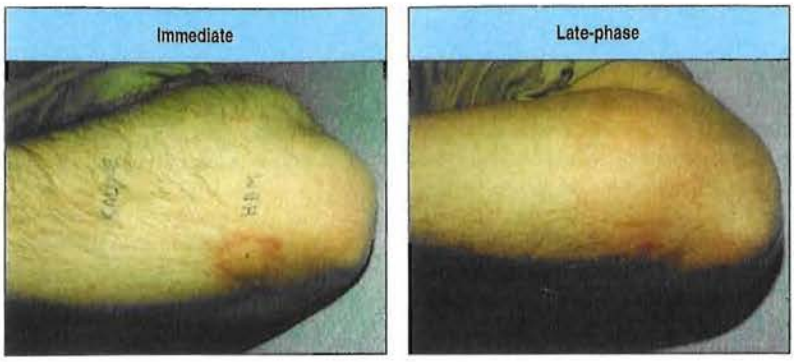


Figure 10.16 Allergic reactions consist of an immediate reaction followed later by a late-phase reaction. The photographs show the immediate reaction (left panel) and the late-phase reaction (right panel) that develop from the injection of house dust mite (HDM) antigen into the epidermis of an allergic individual. In the left panel the site of allergen injection is labeled HDM and the site of the control injection of saline is labeled 'saline'. HDM produces a wheal-and-flare reaction. The wheal is the raised area of skin with the injection site at the center, the flare is the redness (erythema) spreading out from the wheal. In the right panel, the swelling from the HDM injection has spread to involve surrounding tissue. Photographs courtesy of A.B. Kay.

those for IL-3, IL-4, IL-5, IL-9, IL-12, IL-13, and GM-CSF. These cytokines are directly involved in isotype switching, eosinophil survival, and mast-cell proliferation. For example, an inherited sequence difference in the promoter region of the IL-4 gene is correlated with the raised IgE levels seen in atopic people. HLA class II polymorphism also affects the IgE response to certain allergens. An IgE response to several pollen antigens from ragweed is correlated with the expression of the HLA class II allotype DRB1*1501. Such associations imply that certain HLA class II:peptide combinations predispose to stimulation of a T_H2 response.

10-8 IgE-mediated allergic reactions consist of an immediate response followed by a late-phase response

One way in which clinical allergists detect a person's sensitivity to allergens is to observe the reaction when small quantities of common allergens are injected into the skin. Substances to which a person is sensitive produce a characteristic inflammatory reaction called a **wheal and flare** at the site of injection within a few minutes (Figure 10.16, left panel). Substances to which the person is not allergic produce no such reaction. Because of its rapid appearance, the wheal and flare is called an **immediate reaction**. Such reactions are the direct consequence of IgE-mediated mast-cell degranulation in the skin. Released histamine and other mediators cause increased permeability of local blood vessels, whereupon fluid leaves the blood and produces local swelling (edema). The swelling produces the wheal at the injection site, and the increased blood flow into the surrounding area produces the redness that is the flare. Immediate reactions can last for up to 30 minutes and the relative intensity of the wheal and flare varies.

Some 6–8 hours after the immediate reaction has subsided, a second reaction—the **late-phase reaction**—occurs at the site of injection (see Figure 10.16, right panel). This consists of a more widespread swelling and is due to the leukotrienes, chemokines, and cytokines synthesized by mast cells after IgE-mediated activation.

Although skin tests are a good way of determining whether a patient has developed an allergen-specific IgE response, they cannot assess, for example, whether the response to a particular allergen is the cause of a patient's asthma—an allergic reaction in which the airways become inflamed, constricted, and blocked with mucus. To ascertain this, allergists make direct measurements of a person's breathing capacity in the absence and presence of inhaled allergen (Figure 10.17). On inhalation of an allergen to which a patient is sensitized, mucosal mast cells in the respiratory tract degranulate. The released mediators cause immediate constriction of the bronchial smooth muscle, which results in the expulsion of material from the lungs by

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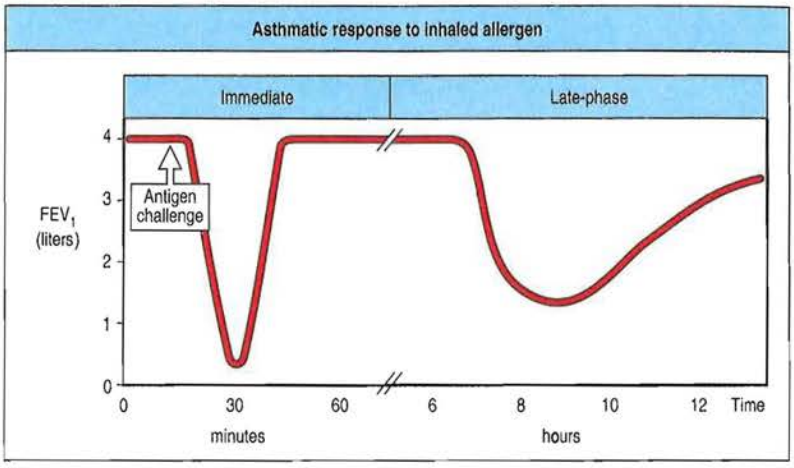


Figure 10.17 The course of an asthmatic response to inhaled allergen. The response is measured in terms of breathing capacity: the forced expiratory volume of air in 1 second (FEV_1). This is the maximum volume of air that a person can forcibly breathe out of the lungs in one second after taking a deep breath. The immediate response in the lungs finishes within an hour, to be followed some 6 hours later by the late-phase response.

coughing, and difficulty in breathing. As in the skin test, the immediate response in the lungs finishes within an hour, to be followed some 6 hours later by the late-phase response, which is due to leukotrienes and other mediators. In allergies to inhaled antigens, such as chronic asthma, the late-phase reaction is the more damaging. It induces the recruitment of leukocytes, particularly eosinophils and T_H2 lymphocytes, into the site and, if antigen persists, the late-phase response can easily develop into a chronic inflammatory response in which allergen-specific T_H2 cells promote eosinophilia and IgE production.

10-9 The effects of IgE-mediated allergic reactions vary with the site of mast-cell activation

When sensitized people are reexposed to an allergen, the effect of the IgE-mediated reaction varies depending on the allergen and the tissues with which it comes in contact. Only those mast cells at the site of exposure degranulate and, once released, the preformed mediators are short-lived. Their effects on blood vessels and smooth muscles are therefore confined to the immediate vicinity of the activated mast cells. The more sustained effects of the late-phase response are also restricted to the site of allergen exposure, because the leukotrienes and other induced mediators are also short-lived. The anatomy of the site of contact also determines how quickly the inflammatory reaction subsides. The tissues most commonly exposed to allergens are the mucosa of the respiratory and gastrointestinal tracts, the blood, and connective tissues. Airborne allergens irritate the respiratory tract and food-borne antigens the gastrointestinal tract; the blood and connective tissues receive allergens through insect bites and other wounds and also from absorption via the gut and respiratory mucosa (Figure 10.18).

For parasite infections, interactions between antigen, IgE, and mast cells trigger violent muscular contractions that can expel worms from the gastrointestinal tract and increase fluid flow to wash them out. In the lungs, the muscular spasms and increased mucus secretion that result from mast-cell activation can be seen as a way to expel organisms attached to respiratory epithelium, such as lung flukes. In allergy, this crude defense is mistakenly ranged against nonthreatening particles and proteins that are often smaller than any microorganism. The violence and power of the IgE-mediated response means that the clinical manifestations of an allergic reaction can vary markedly with the amount of IgE that a sensitized person has made, the amount of allergen triggering the reaction, and the route by which it entered

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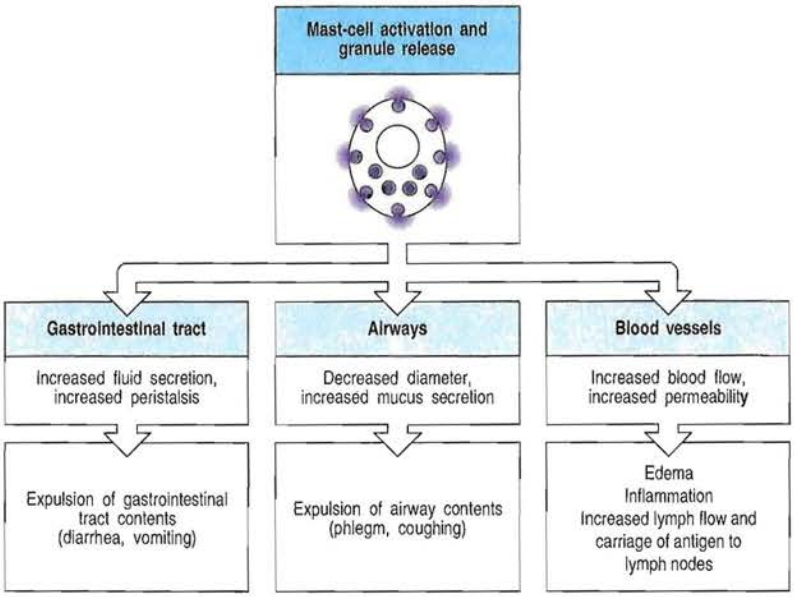


Figure 10.18 The physical effects of IgE-mediated mast-cell degranulation vary with the tissue exposed to allergen.

the body. In the next four sections we examine how allergic reactions vary when they occur in different tissues.

10-10 Systemic anaphylaxis is caused by allergens in the blood

When an allergen enters the bloodstream it can cause widespread activation of the connective tissue mast cells associated with blood vessels. This causes a dangerous hypersensitivity reaction called **systemic anaphylaxis**. During systemic anaphylaxis, disseminated mast-cell activation causes both an increase in vascular permeability and a widespread constriction of smooth muscle. Fluid leaving the blood causes the blood pressure to drop drastically, a condition called **anaphylactic shock**, and the connective tissues to swell. Damage is sustained by many organ systems and their function is impaired. Death is usually caused by asphyxiation due to constriction of the airways and swelling of the epiglottis (Figure 10.19). In the USA, more than 160 deaths a year are the result of anaphylaxis, which is the most extreme over-reaction of the body's defenses. Because this form of immunity is fatal rather than protective it was called '*ana*phylaxis', meaning anti-protection, to contrast with the '*pro*phylaxis' afforded by protective immunity.

Potential allergens are introduced directly into the blood by stings from wasps, bees, and other venomous insects; these account for about a quarter of the fatalities from anaphylaxis in the USA. Drug injections can also lead to anaphylaxis. Systemic anaphylaxis can also be provoked by food or drugs taken orally if the allergens that they contain are absorbed rapidly from the gut into the blood. Foods that can cause anaphylaxis include peanuts and brazil nuts. Anaphylactic reactions can be fatal, but treatment with an injection of epinephrine (adrenaline) will usually bring them under control. Epinephrine stimulates the reformation of tight junctions between endothelial cells. This reduces their permeability and prevents fluid loss from the blood, diminishing tissue swelling and raising blood pressure. Epinephrine also relaxes constricted bronchial smooth muscle and stimulates the heart (Figure 10.20). The danger of anaphylaxis is such that patients with known anaphylactic sensitivity to insect venoms or food are advised to carry a syringe full of epinephrine at all times.

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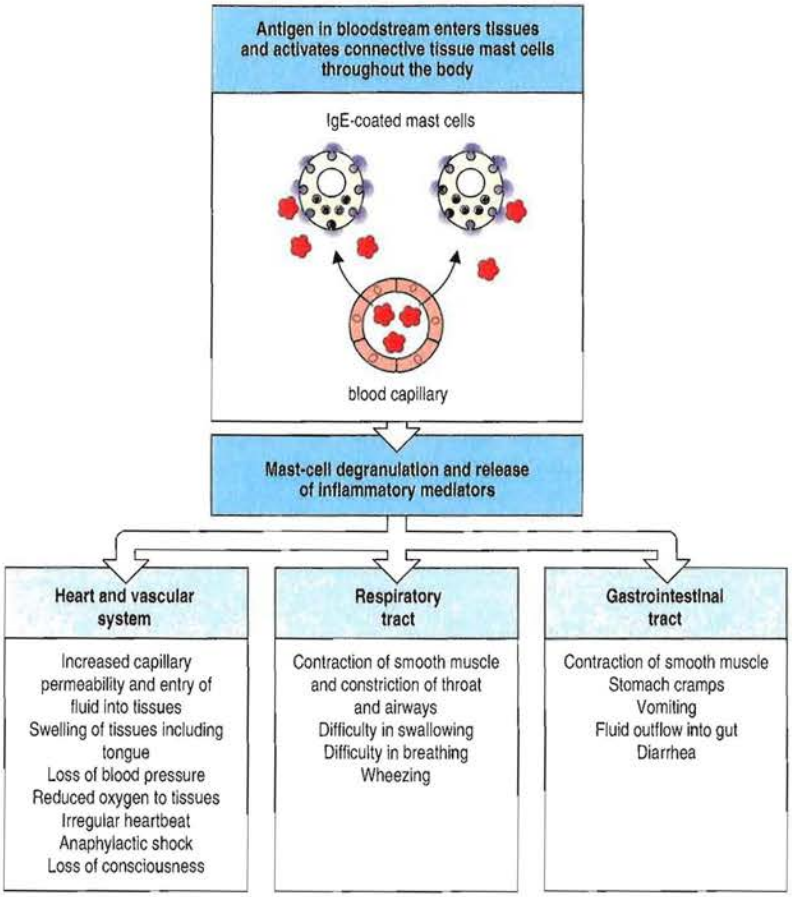


Figure 10.19 Systemic anaphylaxis is caused by allergens that reach the bloodstream and activate mast cells throughout the body.

The most common cause of systemic anaphylaxis is allergy to penicillin and related antibiotics, which accounts for about 100 fatalities a year in the USA. Penicillin is a small organic molecule with a reactive β-lactam ring. On ingestion or injection of the drug, the β-lactam ring can be opened up to produce covalent conjugates with proteins of the body, creating new 'foreign' epitopes. These modified proteins can then stimulate a variety of hypersensitivity reactions, as described in later sections. In some individuals, the response is dominated by T_H2 cells and thus by B cells producing IgE specific for the new epitopes. When penicillin is given to a person who has been sensitized in this manner, it causes anaphylaxis and even death. For this reason, clinicians take care to avoid prescribing any drug to patients who have a history of allergy to that drug. Unfortunately, penicillin cannot be modified to remove its allergic potential because the reactive β-lactam ring is essential for its antibiotic activity.

Reactions resembling anaphylaxis can occur in the absence of specific interaction between an allergen and IgE. Such **anaphylactoid reactions** are caused by other stimuli that induce mast-cell degranulation and can be occasioned by exercise or by certain drugs and chemicals. Anaphylactoid reactions are also treated with epinephrine.

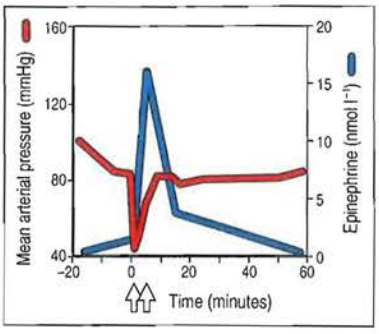


Figure 10.20 The change in blood pressure during systemic anaphylaxis and its treatment with epinephrine. Time 0 indicates the time at which the anaphylactic reaction was reported by the patient. The arrows indicate the times at which injections of epinephrine were given.

10-11 Rhinitis and asthma are caused by inhaled allergens

Allergens most commonly enter the body by inhalation. Mild allergies to inhaled antigens are common, being manifested as violent bursts of sneeezing

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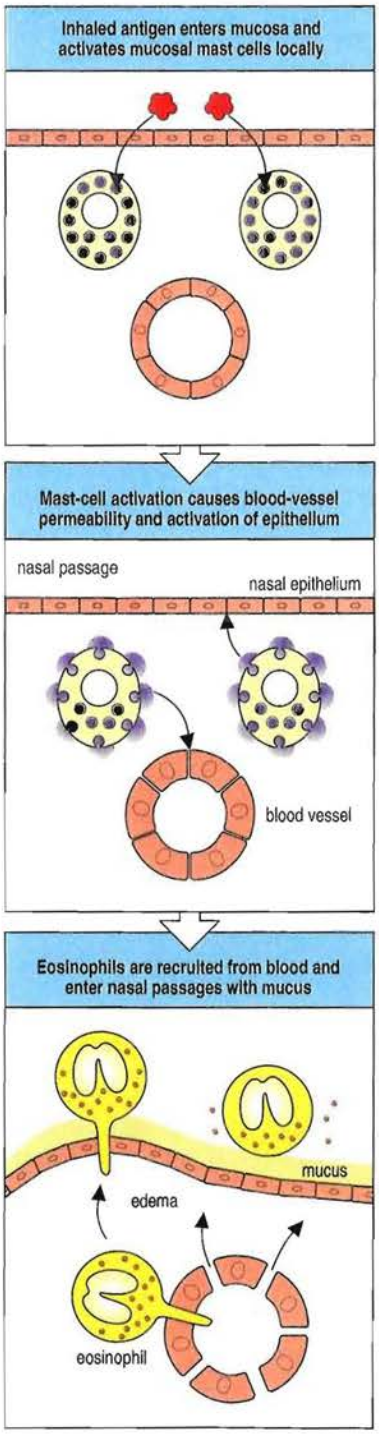


Figure 10.21 Allergic rhinitis is caused by allergens entering the respiratory tract. Histamine and other mediators released by activated mast cells increase the permeability of local capillaries and activate nasal epithelium to produce mucus. Eosinophils attracted into the tissues from the blood become activated and release their inflammatory mediators. Activated eosinophils are shed into the nasal passages.

and a runny nose, a condition called **allergic rhinitis** or hay fever. It is caused by allergens that diffuse across the mucous membrane of the nasal passages and activate mucosal mast cells beneath the nasal epithelium (Figure 10.21). Allergic rhinitis is characterized by local edema leading to obstruction of the nasal airways and a nasal discharge of mucus that is rich in eosinophils. There is also a generalized irritation of the nose due to histamine release. The reaction can extend to the ear and throat, and the accumulation of fluid in the blocked sinuses and eustachian tubes is conducive to bacterial infection. The same exposure to allergen that produces rhinitis can affect the conjunctiva of the eyes, where the reaction is called **allergic conjunctivitis**. It produces itchiness, tears, and inflammation. Although these reactions are uncomfortable and distressing, they are generally of short duration and cause no long-lasting tissue damage.

Much more serious is **allergic asthma**, a condition suffered by 130 million people worldwide, in which allergic reactions cause chronic difficulties in breathing, such as shortness of breath and wheezing. Asthma is triggered by allergens activating submucosal mast cells in the lower airways of the respiratory tract. Within seconds of mast-cell degranulation there is an increase in the fluid and mucus being secreted into the respiratory tract, and bronchial constriction due to contraction of the smooth muscle surrounding the airway. Chronic inflammation of the airways is a characteristic feature of asthma, involving a persistent infiltration of leukocytes, including T_H2 lymphocytes, eosinophils, and neutrophils (Figure 10.22). The overall effect of the asthmatic attack is to trap air in the lungs, making breathing more difficult. Patients with allergic asthma often need treatment, and asthmatic attacks can prove fatal.

Although allergic asthma is initially driven by a response to a specific allergen, the chronic inflammation that subsequently develops seems to be perpetuated in the absence of further exposure to the allergen. In **chronic asthma** the airways can become almost totally occluded by mucus plugs (Figure 10.23). A generalized hypersensitivity in the airways also develops, and environmental factors other than reexposure to specific allergen can trigger asthmatic attacks. Typically, the airways of chronic asthmatics are hyper-responsive to chemical irritants commonly present in air, such as cigarette smoke and sulfur dioxide. Disease can be exacerbated by immune responses to bacterial or viral infections of the respiratory tract, especially when they are dominated by T_H2 cells. For this reason, chronic asthma is classified as a type IV hypersensitivity reaction caused by T cells.

10-12 Urticaria, angioedema, and eczema are allergic reactions in the skin

Allergens that activate mast cells in the skin to release histamine cause raised itchy swellings called **urticaria** or **hives**. Urticaria means 'nettle-rash' and the word derives from *Urtica*, the Latin name for stinging nettles; the origin of the word hives is unknown. This reaction is essentially the same as the immediate wheal-and-flare reaction caused by the deliberate introduction of allergens into the skin in tests to determine allergy (see Section 10-8), which can also be produced by the injection of histamine alone (Figure 10.24). Activation of mast

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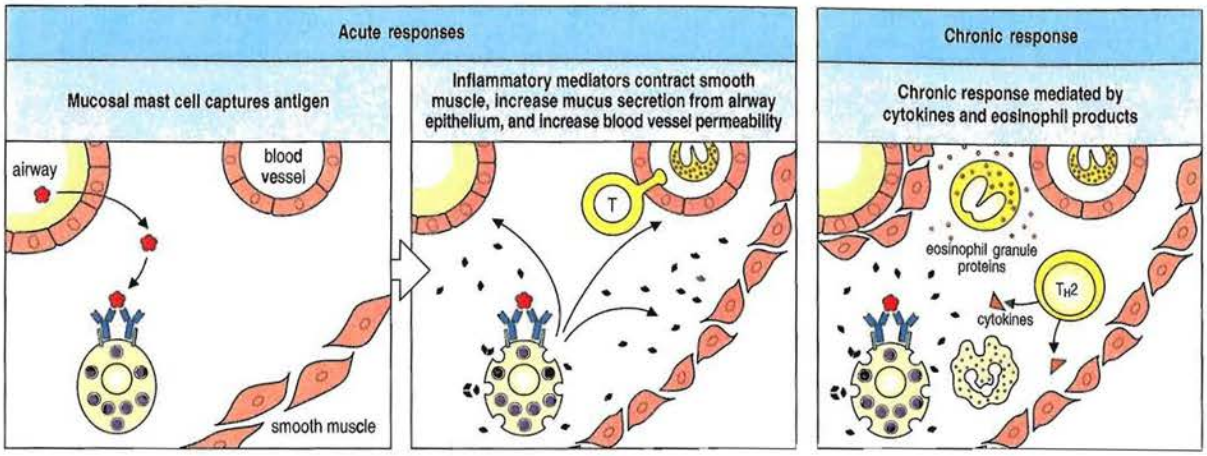


Figure 10.22 The acute response in allergic asthma leads to T_H2-mediated chronic inflammation of the airways. In sensitized individuals, mast cells carrying IgE specific for the allergen are present in the mucosa of the airways, as shown in the first panel. As shown in the second panel, cross-linking of specific IgE on the surface of mast cells by inhaled allergen triggers them to secrete inflammatory mediators, causing bronchial smooth muscle contraction and increased mucus secretion from mucosal epithelium, which together lead to airway obstruction. Increased blood vessel permeability also caused by inflammatory mediators leads to edema and an influx of inflammatory cells, including eosinophils and T_H2 lymphocytes. Activated mast cells and T_H2 cells secrete cytokines that also augment eosinophil activation and degranulation, which causes further tissue injury and influx of inflammatory cells, as shown in the third panel. The end result is chronic inflammation, which can then cause irreversible damage to the airways.

cells in deeper subcutaneous tissue leads to a similar but more diffuse swelling called **angioedema** (or angioneurotic edema). Urticaria and angioedema can arise as a result of any allergy to a food or drug if the allergen gets carried to the skin by the bloodstream, and they are among the many reactions that occur during systemic anaphylaxis. Insect bites are a common cause of urticaria, and such local reactions usually occur without inducing a more general anaphylaxis.

A more prolonged allergic response in the skin is observed in some atopic children. This condition is called **atopic dermatitis** or **eczema**. The word eczema is of Greek derivation and means to 'break out' or 'boil over'. The condition is characterized by an inflammatory response that causes a chronic and itching skin rash with associated skin eruptions and fluid discharge. This response has similarities to that occurring in the bronchial walls of asthmatics. Eczema frequently presents in families with a history of asthma and allergic rhinitis, and is often associated with high IgE levels. However, the severity of the dermatitis is not readily correlated with exposure to particular allergens or to the levels of allergen-specific IgE. Thus the etiology of eczema remains poorly understood. Neither is it understood why eczema usually clears in adolescence, whereas rhinitis and asthma more often persist throughout life.

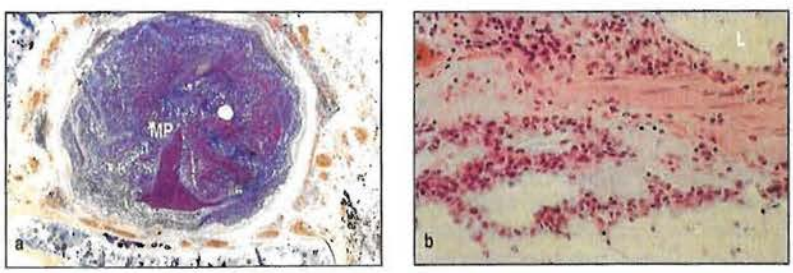
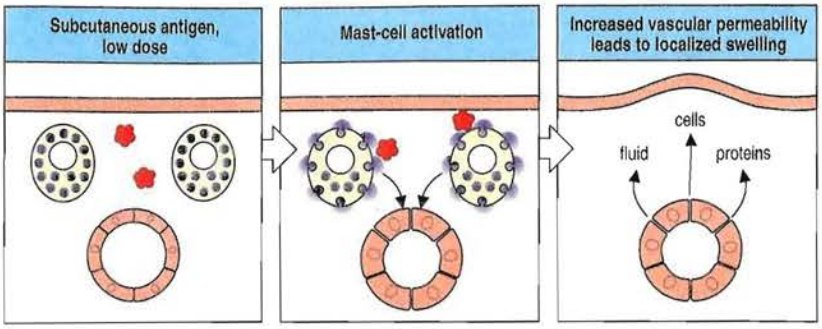


Figure 10.23 Inflammation of the airways in chronic asthma restricts breathing. Panel a shows a light micrograph of a section through the bronchus of a patient who died of asthma; there is almost total occlusion of the airway by a mucus plug (MP). The small white circle is all that is left of the lumen of the bronchus. In panel b, a light micrograph at higher magnification gives a closer view of the bronchial wall. It shows injury to the epithelium lining the bronchus, accompanied by a dense inflammatory infiltrate that includes eosinophils, neutrophils, and lymphocytes. L, lumen of the bronchus. Photographs courtesy of T. Krausz.

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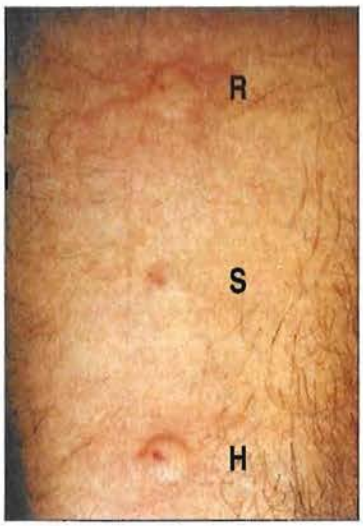


Figure 10.24 Allergen-induced release of histamine by mast cells in skin causes localized swelling. As shown in the panels on the left, allergen introduced into the skin of a sensitized individual causes mast cells in the connective tissue to degranulate. The histamine released dilates local blood vessels, causing rapid swelling due to leakage of fluid and proteins into tissues. The photograph shows the raised swellings (wheals) that appear 20 minutes after intradermal injections of ragweed pollen antigen (R) or histamine (H) into a person who is allergic to ragweed. The small wheal at the site of saline injection (S) is due to the volume of fluid injected into the dermis. Photograph courtesy of R. Geha.

10-13 Food allergies cause systemic effects as well as gut reactions

Humans probably eat a greater variety of foodstuffs than any other living animal. All human food is derived from plants and animals and contains a large number of different proteins, many of which are potentially immunogenic. As food passes down the gastrointestinal tract, the proteins are degraded by proteases into peptides of ever-decreasing size. These are a potential source of peptides for presentation to T_H2 cells. Despite the quantity and variety of food that humans eat, IgE is made against only an extremely small proportion of the proteins ingested. However, people sensitized to a particular protein will be allergic to any food containing that protein. Foods that commonly cause allergies include grains, nuts, fruits, legumes, fish, shellfish, eggs, and milk.

Once sensitized to a food allergen, any subsequent intake causes a marked and immediate reaction that can drive the person from the dining room. The allergen passes across the epithelial wall of the gut and binds to IgE on the mucosal mast cells associated with the gastrointestinal tract. The mast cells degranulate, releasing their mediators, principally histamine. The local blood vessels become permeable, and fluid leaves the blood and passes across the gut epithelium into the lumen of the gut. Meanwhile, contraction of smooth muscles of the stomach wall produces cramps and vomiting, while the same reaction in the intestine produces diarrhea (Figure 10.25). These reactions probably evolved originally to expel gut parasites; in the allergic reaction they serve to expel the allergen-containing food from the human body. This goal is indeed accomplished, but at the expense of dehydration, weakness, and waste of food.

In addition to allergic reactions localized in the gut, food allergens also produce reactions in other tissues, notably the skin. Depending on the timing and course of the gut reaction and of the uptake of allergen from the gut, allergen can enter the circulation and be transported elsewhere in the body. Mast cells in the connective tissue in the deeper layers of the skin tend to be activated by such blood-borne allergens, and their degranulation produces urticaria and angioedema. In this context, orally administered drugs behave similarly to food; they too can produce intestinal reactions, urticaria, and angioedema in sensitized individuals.

10-14 People with parasite infections and high levels of IgE rarely develop allergic disease

In tropical countries, parasitic helminth infections are endemic; more than 1 billion people worldwide are heavily and persistently infected. A universal feature of helminth infection is the stimulation of CD4 T_H2-like responses that produce raised levels of IgE, and increased numbers of eosinophils in the

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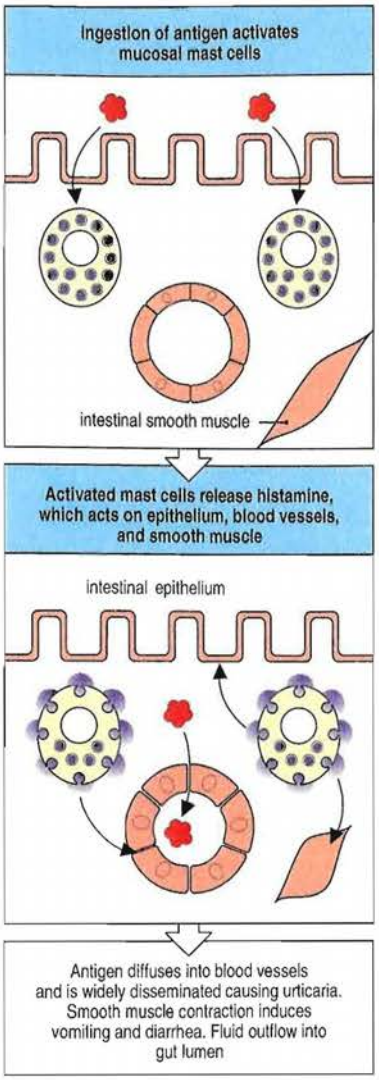


Figure 10.25 Ingested allergen can cause vomiting, diarrhea, and urticaria. Localized reactions are caused by histamine acting on intestinal epithelium, blood vessels and smooth muscles. Urticaria is caused by antigen that enters blood vessels and is carried to the skin.

blood and mast cells in tissues. Only a small fraction of the IgE is parasite-specific; the remainder is highly heterogeneous and represents the product of nonspecific, polyclonal B- and T-cell activation by the parasite. Despite the abundance and variety of IgE in their system, people with helminth infections are rarely afflicted by allergic disease.

Several facts may contribute to the resistance of helminth-infected individuals to allergy. One is that nonspecific IgE competes with parasite-specific IgE, or any allergen-specific IgE, for binding to the FcεRI receptors on mast cells, basophils, and activated eosinophils. This limits the extent to which parasite antigen binding to specific IgE triggers IgE-mediated effector mechanisms, allowing the parasite to escape killing by activated eosinophils or expulsion from the body by the action of activated mast cells. Another contributing factor is that T-cell responses are generally suppressed in chronic parasitic infections, probably owing to the participation of regulatory T cells and the inhibitory effects of IL-10, TGF-β, and nitric oxide.

For the populations of western Europe and North America, helminth and many other parasite infections have largely been eradicated. In these populations the prevalence of IgE-mediated allergy and asthma has been steadily increasing. The 'hygiene hypothesis' proposes that this increase has been caused by better hygiene, vaccination to prevent infection, and the increased use of antibiotics and other drugs to stop infections. Children are exposed to fewer and less heavy infections than were their parents, with the result that their immune systems are insufficiently used and become less successfully regulated. In other words, a lack of practice in dealing with real infections can reveal a propensity to perceive danger where it does not exist. Supporting the hygiene hypothesis are family studies showing that exposure of children to more infections, and at a younger age, reduces the likelihood that they will develop atopic allergic reactions.

10-15 Allergic reactions are prevented and treated by three complementary approaches

Three distinct strategies are used to reduce the effects of allergic disease. The first strategy is one of prevention—to modify a patient's behavior and environment so that contact with the allergen is avoided. Allergen-containing foods are avoided, houses are refurnished in ways that discourage mites, pets are kept outside, and desert vacations or sea cruises are taken during the pollen season.

The second strategy is pharmacological—to use drugs that reduce the impact of any contact with allergen. Such drugs block the effector pathways of the allergic response and limit the inflammation after IgE-induced activation of mast cells, eosinophils, and basophils. Antihistamines reduce rhinitis and urticaria by preventing histamine from binding to H1 histamine receptors on vascular endothelium and thus increasing vascular permeability. Corticosteroids, which suppress leukocyte function generally, are often administered topically or systemically to suppress the chronic inflammation of asthma, rhinitis, or eczema. Cromolyn sodium prevents the degranulation of activated mast cells and granulocytes and is inhaled by asthmatics as a prophylactic to prevent attacks. Epinephrine is used to treat anaphylactic reactions.

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The third strategy in the treatment of allergy is immunological—to prevent the production of allergen-specific IgE. One way of achieving this is to modulate the antibody response so that it shifts from one dominated by IgE to one dominated by IgG. A procedure called **desensitization**, which was first described in 1911 and is used in a similar way today, can achieve this for some patients and some allergies. Patients are given a series of allergen injections in which the dose is initially very small and is gradually increased. Successful treatments are associated with the production of allergen-specific antibodies of the IgG4 isotype, which, like IgE, is a product of a T_H2 response, and increased levels of IL-10. An occasional consequence of the injections used for desensitization is anaphylaxis, because the patient is being exposed to the allergen to which they are sensitized. For this reason 'allergy shots' should always be given under carefully controlled conditions in which patients are monitored for the early symptoms of systemic anaphylaxis and, if need be, given epinephrine.

A more recent approach to desensitization is to vaccinate patients with allergen-derived peptides that are known to be presented by HLA class II molecules to CD4 T_H2 cells. The aim is to induce anergy of allergen-specific T cells *in vivo* by decreasing the expression of the CD3:T-cell receptor complex at the T_H2 cell surface. In principle, the advantage of this method over the older approach is that anaphylaxis should never be triggered by the injections, as only the native allergen protein and not the peptide vaccine can interact with allergen-specific IgE. Factors complicating this approach are the HLA class II polymorphisms determining which allergen-derived peptides can be presented by any individual. Any vaccine with general applicability to a human population must contain sufficient different peptides so that an anergizing response can be produced irrespective of HLA class II type. Alternatively, vaccines could be custom-made from peptides selected on the basis of a patient's HLA class II type.

Because allergies are a prevalent and increasing problem for humans in the richer countries in the world, there is much interest within the biotechnology and pharmaceutical industries in developing new approaches to the relief or cure of allergy. One potential set of targets for drugs are the signaling pathways that cells of the immune system use to enhance the IgE response. For example, inhibitors of the cytokines IL-4, IL-5, or IL-13 could block such pathways. Conversely, the administration of cytokines that promote T_H1 responses could shift the antibody response away from IgE and towards IgG. In experiments on mice, IFN-γ and IFN-α have both been shown to reduce IL-4-stimulated IgE synthesis. The high-affinity IgE receptor is also a potential target for drugs that bind the receptor and prevent the arming of mast cells with allergen-specific IgE.

Summary

Type I hypersensitivity reactions are caused by protein allergens binding to IgE molecules and activating mast cells. The activated mast cells release a variety of chemical mediators that orchestrate a local state of inflammation. Smooth muscles constrict, blood vessels dilate, and eosinophils and basophils enter the affected area. The effects of IgE-mediated reactions vary with the route of allergen entry to the body and the tissue affected. Inhaled allergens, for example plant pollens and animal dander, activate mast cells in the respiratory tract. Rhinitis is caused by reactions in the upper airways; asthma by reactions in the lower airways. Insect stings deliver allergens into the skin, where mast-cell mediators cause hives and urticaria. Allergens in certain foods, such as peanuts or shrimp, trigger mast cells of the gastrointestinal tract, resulting in vomiting and diarrhea. When food allergens are absorbed into the blood they

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become disseminated throughout the body, causing systemic mast-cell activation and resulting in widespread urticaria or even systemic anaphylaxis. The violent reactions activated by IgE are believed to have evolved as a defense against parasites. In allergic reactions this defensive mechanism is misguidedly aimed at environmental proteins that pose no threat.

Type II, III, and IV hypersensitivity reactions

IgG antibodies and specific T cells can cause both acute and chronic adverse hypersensitivity reactions. A variety of different effector mechanisms are involved, which cause inflammatory reactions and tissue destruction.

10-16 Type II hypersensitivity reactions are caused by antibodies specific for altered components of human cells

Occasional side-effects seen after the administration of certain drugs are hemolytic anemia caused by the destruction of red blood cells, or thrombocytopenia caused by the destruction of platelets. These are examples of type II hypersensitivity reactions and have been associated with the antibiotic penicillin, quinidine (a drug used to treat cardiac arrhythmia), and methyldopa, which is used to reduce high blood pressure. In each case, chemically reactive drug molecules bind to surface components of red blood cells or platelets and create new epitopes to which the immune system is not tolerant (Figure 10.26).

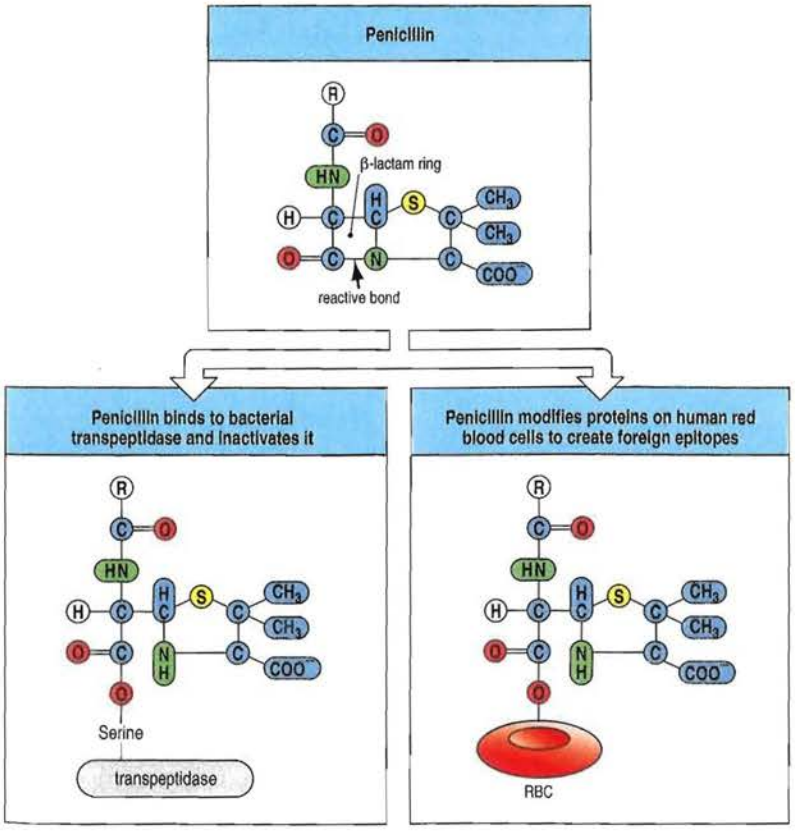
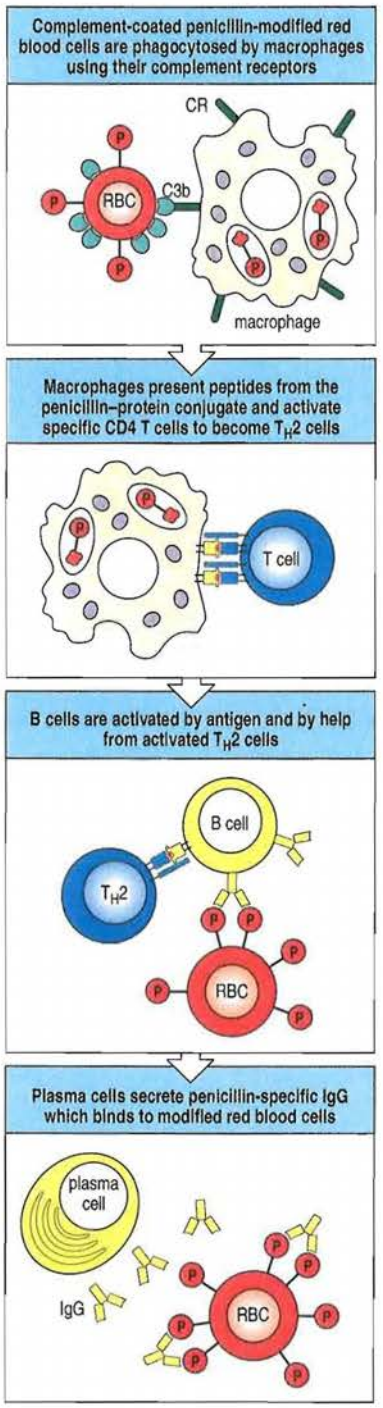


Figure 10.26 Penicillin and other small-molecule drugs can modify human cells so that they display foreign epitopes. Penicillin exerts its antibacterial action by mimicking the substrate for bacterial transpeptidase, which is required for bacterial cell wall synthesis. On binding to transpeptidase, a reactive bond in the β-lactam ring of penicillin opens and forms a covalent bond with an amino-acid residue in the active site of the transpeptidase, thereby inactivating the enzyme permanently (lower left panel). The same mechanism occasionally results in molecules of penicillin becoming covalently bonded to surface proteins of human cells (lower right panel). This modification of human proteins creates new epitopes that can act like foreign antigens. Red blood cells (RBC) are the cells most commonly modified in this way.

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Figure 10.27 Penicillin–protein conjugates stimulate the production of anti-penicillin antibodies. Red cells that have been covalently bonded to penicillin (P) are phagocytosed by macrophages, which process the penicillin-modified proteins and present peptide antigens to specific CD4 T cells. These are activated to become effector T_H2 cells, which stimulate antigen-specific B cells to produce antibodies against the penicillin-modified epitope.



These epitopes stimulate the formation of IgM and IgG antibodies that are specific for the conjugate of drug and cell-surface component.

The penicillin-modified red cells acquire a coating of the complement component C3b as a side-effect of complement activation by the bacterial infection for which the drug has been given. This facilitates their phagocytosis by macrophages via complement receptors. These cells process the penicillin-modified protein and present peptides from it to specific CD4 T cells, which are activated to become effector T_H2 cells. These then stimulate antigen-specific B cells to produce antibodies against the penicillin-modified epitope (Figure 10.27). Binding of antibodies to the drug-conjugated cells activates complement by the classical pathway, resulting in either cell lysis by the terminal complement components or receptor-mediated phagocytosis by macrophages in the spleen (Figure 10.28).

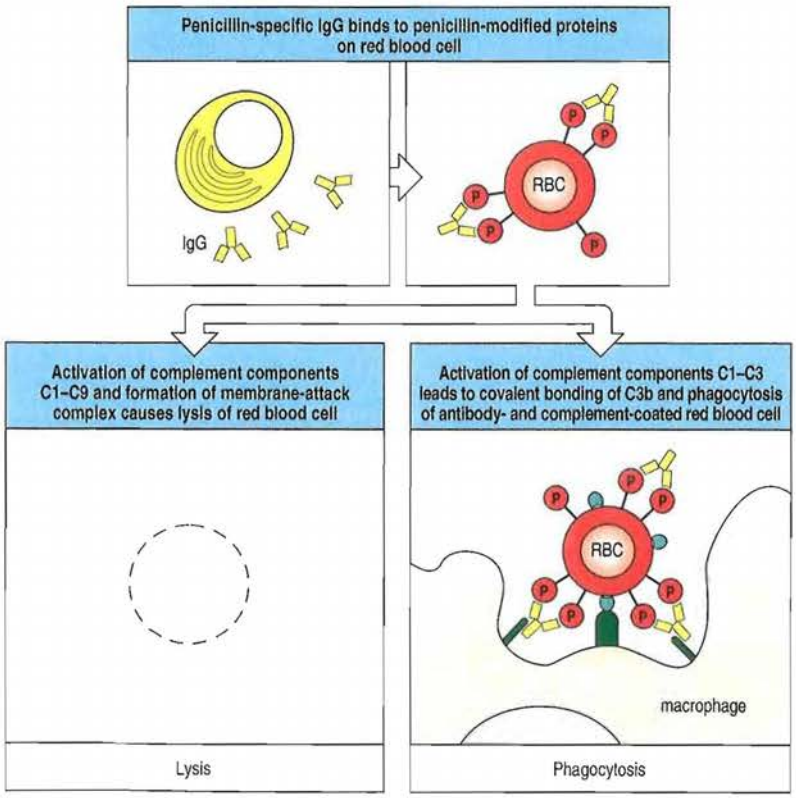


Figure 10.28 Binding of antibodies to penicillin-modified red cells makes them susceptible to complement-mediated lysis or to phagocytosis via Fc receptors and complement receptors.

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10-17 Type III hypersensitivity reactions are caused by immune complexes formed from IgG and soluble antigens

Complexes of soluble protein antigens and their high-affinity IgG antibodies are generated in almost all immune responses and in most situations they are cleared without causing tissue damage. Immune complexes vary greatly in size, from a simple complex of one antigen and one antibody molecule through to large aggregates containing millions of antigen and antibody molecules. The larger aggregates fix complement efficiently and are readily taken up by phagocytes and removed from the circulation. Smaller immune complexes are less efficient at fixing complement; they tend to circulate in the blood and become deposited in blood vessel walls. When these complexes accumulate at such sites, they become capable of fixing complement and initiating tissue-damaging inflammatory reactions through their interactions with the Fc receptors and complement receptors on circulating leukocytes. This type of hypersensitivity is called type III hypersensitivity. Complement activation produces C3a and C5a. The former stimulates mast cells to release histamine, causing urticaria; the latter recruits inflammatory cells into the tissue. Platelets accumulate around the site of immune-complex deposition, and the clots that they form cause the blood vessels to burst, producing hemorrhage in the skin.

The size of the immune complexes formed at a particular time and place is strongly influenced by the relative concentrations of soluble antigen and antibody (Figure 10.29). Whether large immune complexes can be formed also depends on the size and complexity of the antigen; most antigens that will be encountered in normal circumstances contain multiple epitopes and thus can, in principle, form extensive immune complexes by cross-linking antibodies. When antigen is in excess, as occurs early in the immune response, each antigen-binding site on an antibody binds an antigen molecule, producing small immune complexes that often contain a single antibody molecule and two antigen molecules. Late in the immune response, antibodies are in excess; in these circumstances each antigen molecule binds to several antibody molecules. At intermediate times, when the amounts of antigen and antibody are more evenly balanced, larger immune complexes are formed in

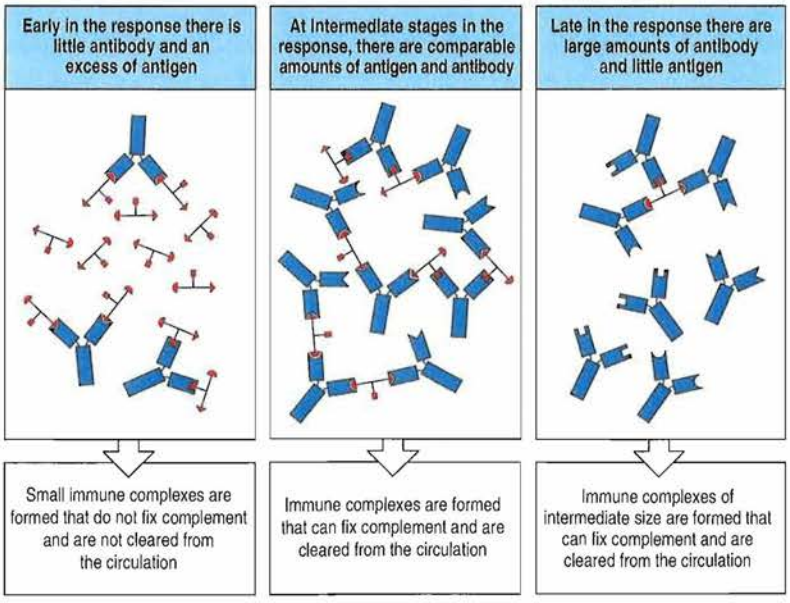


Figure 10.29 Immune complexes of different sizes and stoichiometries are formed during the course of an immune response.

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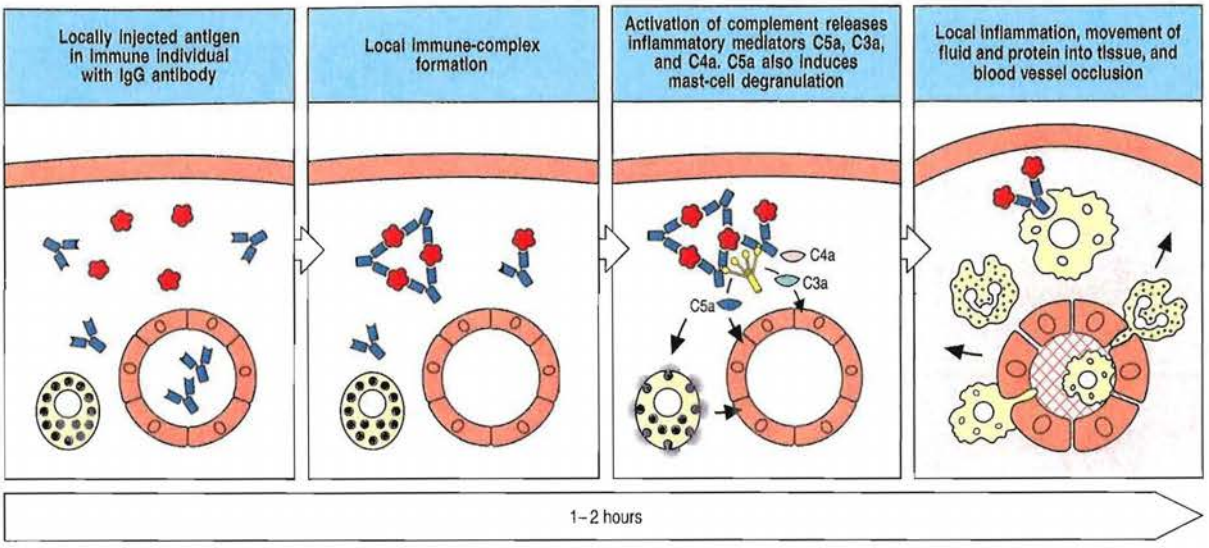


Figure 10.30 Localized deposition of immune complexes within a tissue causes a type III hypersensitivity reaction. In sensitized individuals, the introduction of allergen into a tissue leads to the formation of immune complexes with IgG in the extracellular fluid. The immune complexes activate complement and recruit inflammatory cells to the site, causing a hard swelling. Platelets accumulate in the capillary, leading to occlusion and rupture of the vessel, causing erythema.

which several antibody and antigen molecules are cross-linked. A minimum of two IgG molecules per complex is needed to fix complement, so it is at the beginning of the immune response, when soluble immune complexes fix complement poorly, that they are most likely to circulate in the blood and become deposited in blood vessel walls.

In people who have made IgG against a soluble protein, a type III hypersensitivity reaction can be experimentally induced in the skin by subcutaneous injection of the antigen. Specific IgG diffuses from the blood into the connective tissue at the site of injection and combines with antigen to form immune complexes. The complexes activate complement, creating an inflammatory reaction that draws leukocytes and antibodies into the site of injection. Here the Fc and complement receptors of leukocytes engage the immune complexes, activating the cells and further propagating the local inflammatory reaction. This type of reaction was first described by Nicholas-Maurice Arthus and is called an **Arthus reaction** (Figure 10.30). In humans, Arthus reactions usually appear as localized areas of erythema and hard swelling (induration) that subside within a day. Such reactions can often be seen at the site of injections used to desensitize IgE-mediated allergies. The dependence of the Arthus reaction on immune-complex interactions with Fc receptors is demonstrated by the failure to produce Arthus reactions in mice lacking the γ chain common to all Fc receptors.

10-18 Systemic disease caused by immune complexes can follow the administration of large quantities of soluble antigens

During the late nineteenth century and the first half of the twentieth century, diphtheria, scarlet fever, tetanus, and other life-threatening bacterial infections were treated by injecting patients with serum taken from horses that had been immunized with these bacteria or their toxins. The horse antibodies helped human patients to control and clear the infection but could also produce a systemic type III hypersensitivity reaction that became known as **serum sickness**. This condition occurred some 7–10 days after the administration of horse serum and was characterized by chills, fevers, rash, arthritis, vasculitis, and sometimes glomerulonephritis. The cause of serum sickness is the formation of antibodies against the foreign horse proteins and the

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Route	Resulting disease	Site of immune-complex deposition
Intravenous (high dose)	Vasculitis	Blood vessel walls
	Nephritis	Renal glomeruli
	Arthritis	Joint spaces
Subcutaneous	Arthus reaction	Perivascular area
Inhaled	Farmer's lung	Alveolar/capillary interface





Figure 10.31 The pathology of type III hypersensitivity reactions is determined by the sites of immune-complex deposition. The table shows the types of reaction that result from different routes of antigen entry to the body. Serum sickness follows the intravenous administration of large amounts of foreign antigen. Photographs show hemorrhage in the skin (panel a) and urticarial rash (panel b) resulting from serum sickness. Photographs courtesy of R. Geha.

deposition of small immune complexes in tissues; the symptoms depend on which tissues are affected (Figure 10.31).

Therapeutic administration of serum from immunized horses is rarely used today. One remaining application is the use of horses to prepare anti-venom antisera for neutralizing the effects of snake-bite. However, the symptoms of serum sickness are now seen in other circumstances in which patients have received an infusion of large amounts of a foreign protein. Transplant patients given mouse monoclonal antibodies specific for human T cells to prevent rejection can get serum sickness. It also occurs occasionally in patients who have had a myocardial infarction (heart attack) and are treated with the bacterial enzyme streptokinase to degrade their blood clots. Serum sickness can also result from the intravenous administration of large amounts of a drug such as penicillin, which binds to host proteins on, for example, erythrocytes (see Section 10-16) and provokes an IgG response. This type of reaction can occur in people with no history of allergy to penicillin. Drug-induced serum sickness is now the most common example of this condition.

The onset of serum sickness coincides with the synthesis of antibodies, which form immune complexes with the antigenic proteins. Because the serum is loaded with antigen, large quantities of immune complexes are formed and dispersed throughout the body. The complexes fix complement and activate leukocytes bearing Fc receptors or complement receptors. These activated cells create an inflammatory response that causes widespread damage (Figure 10.32).

The formation of immune complexes induces the clearance of the antigenic proteins by the normal phagocytic pathways; consequently, serum sickness is of limited duration unless additional injections of the foreign antigen are given. If a second dose of antigen is given after the effects of the first dose have subsided, a secondary response will follow, with disease symptoms being manifested within a day or two of the second injection.

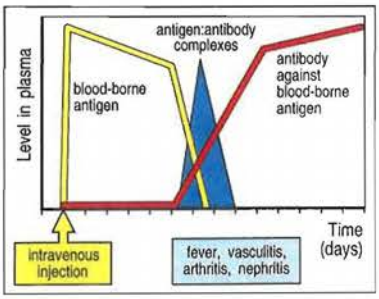


Figure 10.32 Serum sickness is a classic example of a transient immune-complex mediated syndrome. An injection of a large amount of a foreign antigen into the circulation leads to an antibody response. These antibodies form immune complexes with the circulating foreign antigens. The complexes are deposited in small blood vessels and activate complement and phagocytes, inducing fever and the symptoms of vasculitis, nephritis, and arthritis. All these effects are transient and resolve once the foreign antigen has been cleared.

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A disease similar to serum sickness can be seen in certain infections in which the immune system fails to clear the pathogen, and both the infection and the immune response persist. For example, in subacute bacterial endocarditis, or in chronic viral hepatitis, the multiplying pathogens continue to produce antigens, and plasma cells continue to make antibodies. Immune complexes are continually being generated, deposited, and cleared, processes that can cause injury to small blood vessels and nerves in many organs, including the skin and kidneys.

Some common inhaled antigens tend to provoke an IgG rather than an IgE response and cause type III hypersensitivity reactions. Continued exposure to the antigen leads to the formation of immune complexes and their deposition in the walls of the alveoli in the lungs. Such deposits stimulate an inflammatory response. The resulting accumulation of fluid, antigen, and cells impedes the lungs' normal function of gas exchange, and the patient experiences difficulty in breathing. Occupations in which workers are exposed daily to quantities of the same airborne antigens can lead to this condition. The immune systems of farm workers exposed to hay dust and mold spores are often provoked in this manner, giving rise to the occupational disease called **farmer's lung**. Without a change in work habits the continuing deposition of immune complexes in the alveolar membranes leads to irreversible lung damage.

10-19 Type IV hypersensitivity reactions are mediated by antigen-specific effector T cells

Hypersensitivity reactions caused by effector T cells specific for the sensitizing antigen are known as type IV hypersensitivity or **delayed-type hypersensitivity reactions** (**DTH**), because they occur 1–3 days after contact with antigen. This time course contrasts with those of antibody-mediated hypersensitivity, which are generally apparent within a few minutes. The amount of antigen required to elicit a type IV hypersensitivity reaction is 100–1000 times greater than that required to produce antibody-mediated hypersensitivity reactions. This difference reflects the intrinsic inefficiency in generating peptide epitopes from protein antigens for presentation by HLA molecules. Antigens that cause common type IV hypersensitivity reactions are shown in Figure 10.33.

The best studied example of a type IV hypersensitivity reaction is the **tuberculin test**, the clinical test used to determine whether a person has been infected with *Mycobacterium tuberculosis*. In the tuberculin test a small amount of protein antigen extracted from *M. tuberculosis* is injected intradermally or intracutaneously. People with immunity to *M. tuberculosis*—those

Type IV hypersensitivity reactions are mediated by antigen-specific effector T cells

Syndrome	Antigen	Consequence
Delayed-type hypersensitivity	Proteins: Insect venom Mycobacterial proteins (tuberculin, lepromin)	Local skin swelling: Erythema Induration Cellular infiltrate Dermatitis
Contact hypersensitivity	Haptens: Pentadecacatechol (poison ivy) Small metal ions: Nickel Chromate	Local epidermal reaction: Erythema Cellular infiltrate Contact dermatitis

Figure 10.33 Examples of common type IV hypersensitivity reactions. Hapten is the name given to any small molecule that when covalently bonded to a protein stimulates an immune response.

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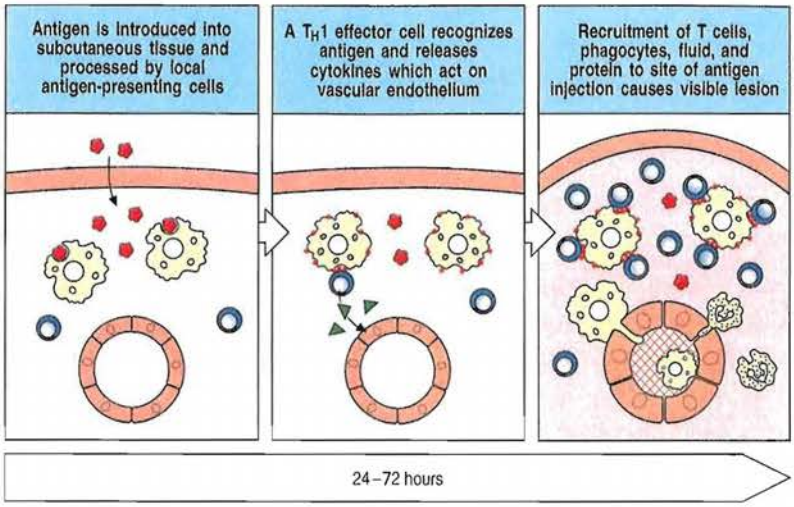


Figure 10.34 The stages and time course of a type IV hypersensitivity reaction. The first phase involves uptake, processing, and presentation of the antigen by local antigen-presenting cells. In the second phase, antigen-specific memory T cells produced during previous exposure to the antigen migrate into the site of injection and become activated. Because these antigen-specific cells are rare, and there is no inflammation to attract them into the site, it can take several hours for a T cell of the correct specificity to arrive. Activated T_H1 cells release mediators that activate local endothelial cells, recruiting an inflammatory cell infiltrate dominated by macrophages and causing the accumulation of fluid and protein. At this point, the lesion becomes apparent.

who have existing tuberculosis, or who have resolved an infection, or or who have been vaccinated with the BCG strain—develop an inflammatory reaction around the site of injection 24–72 hours later. The response is mediated by T_H1 cells that recognize peptides derived from the *M. tuberculosis* protein that are presented by HLA class II molecules. The peptides are presented by macrophages and dendritic cells in the vicinity of the injection and initially stimulate tuberculin-specific memory T cells that have left the blood and entered the tissue; these generate effector T_H1 cells locally. After activation, the T_H1 cells initiate further inflammatory reactions that recruit fluid, proteins, and other leukocytes to the site (Figure 10.34). Each of these phases takes several hours, accounting for the time taken before the response is seen or felt. The activated T_H1 cells produce cytokines that mediate these effects (Figure 10.35). In the United States the diagnostic value of the tuberculin skin test for existing infection currently outweighs the benefits of vaccination against tuberculosis, and hence vaccination is not routine. In the UK and

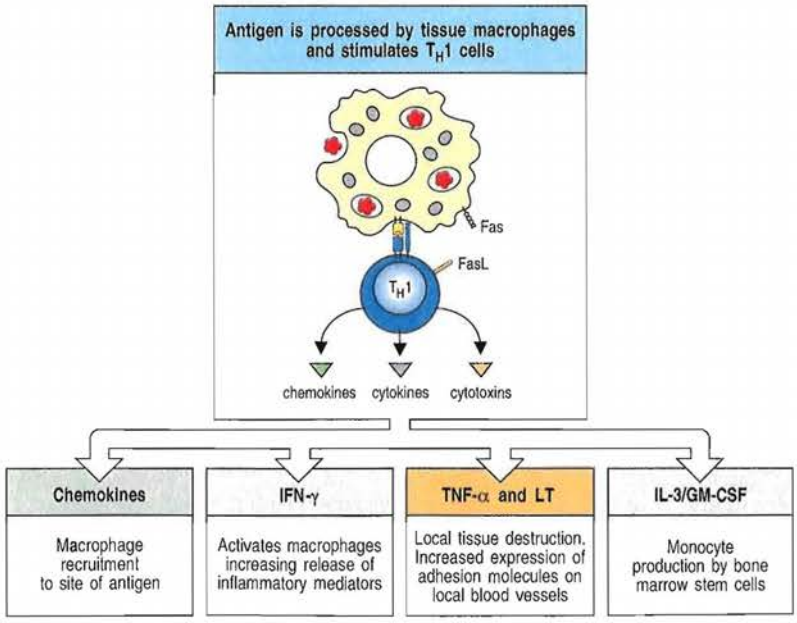


Figure 10.35 Most type IV hypersensitivity reactions are orchestrated by the cytokines released by T_H1 CD4 cells in response to antigen. Macrophages or tissue dendritic cells recruited to the site of inflammation by chemokines present antigen and amplify the response. The release of TNF-α and the cytotoxin lymphotoxin (LT, formerly known as TNF-β) affect local blood vessels through their effects on endothelial cells. IL-3 and GM-CSF stimulate the production of macrophages. IFN-γ and TNF-α activate macrophages. Macrophages are killed by LT and by the interaction of Fas on the macrophage with Fas ligand (FasL) on the T cell.

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some other European countries, BCG is given to children as one of their routine vaccinations. It is preceded by a tuberculin test, which serves to detect any preexisting infection or immunity.

Type IV hypersensitivity responses can be developed to a variety of antigens in the environment. For example, the dermatitis caused by contact with the North American plants poison ivy (*Toxicodendron radicans*; see Figure 10.1) and poison oak (*T. diversilobium*, whose leaves are oval and untoothed, or shaped rather like oak leaves on young plants) is due to a reaction of this type and involves both CD4 and CD8 T cells. The reaction is caused by pentadecacatechol, a small, highly reactive lipid-like molecule that is present in the leaves and roots of the plant and is easily transferred to human skin (Figure 10.36).

When a person contacts poison ivy, pentadecacatechol penetrates the outer layers of the skin and indiscriminately forms covalent bonds with extracellular proteins and skin cell-surface proteins. On degradation of the chemically modified proteins by skin macrophages and Langerhans' cells, antigenic peptides that carry the pentadecacatechol adduct are generated and presented by HLA class II molecules to T_H1 cells. The cytokines secreted by the T_H1 cells activate macrophages and produce inflammation (see Figure 10.35). When pentadecacatechol penetrates the skin it also crosses the plasma membranes of cells and chemically modifies intracellular proteins. The processing of such modified proteins results in the presentation of chemically modified peptides by HLA class I molecules to CD8 T cells. On activation, the CD8 T cells have the potential to kill any cells that contacted the chemical and present modified peptides on their surfaces.

On first contact with poison ivy, a person might experience only a minor or undetectable reaction. During this primary or sensitizing response, Langerhans' cells or dendritic cells carry pentadecacatechol-modified proteins to the draining lymph node, where the T-cell response is initiated. Once immunological memory has been developed, subsequent contacts with the plant yield unpleasant reactions of the type shown in Figure 10.36. The red, raised, weeping skin lesions are due to heavy infiltration of the contact sites with blood cells, combined with the localized destruction of skin cells and the extracellular matrix that holds the skin together. Because of the delayed nature of the reaction there is plenty of time for a person to transfer pentadecacatechol from the initial site of contact to other parts of the body, a process that often exacerbates the extent of the reaction.

The reaction to poison ivy is an example of **contact sensitivity**, so called because contact with the skin is necessary to initiate the allergic response. Contact sensitivity can also develop to coins, jewelry, and other metallic objects containing nickel. In this case the bivalent nickel ions are chelated by histidine in human proteins; processing of these proteins forms T-cell epitopes to which the immune system responds.



Figure 10.36 Physical contact with poison ivy transfers pentadecacatechol, which causes dermatitis. The chemical structure of pentadecacatechol is shown in the top panel. The photograph shows characteristic blistering skin lesions on the hand of a patient with dermatitis caused by contact with poison ivy (see Figure 10.1 for a photograph of the plant). Photograph courtesy of R. Geha.

Summary

Type II hypersensitivity reactions are mediated by IgG antibodies directed against cell-surface or matrix antigens and are commonly caused by drugs that are being given as treatment for other diseases. Because of their chemical reactivity, drugs bind to surface proteins of human cells, for example erythrocytes or platelets, creating new epitopes that stimulate an antibody response. On binding to the drug-modified cells, the antibodies activate complement, which leads to cell destruction. Type III hypersensitivity reactions are caused by soluble immune complexes formed by IgG binding to the

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soluble antigens against which they were made. They can be seen when nonhuman proteins, such as mouse monoclonal antibodies, are given therapeutically. Antibodies specific for the nonhuman proteins are made, and early in the response small immune complexes are formed that are not efficiently cleared from the circulation. These tend to deposit in blood vessels, where they activate complement and inflammation. Depending on the sites of activation, these reactions can cause vasculitis, nephritis, arthritis, or lung disease. Type IV hypersensitivity reactions are caused by effector T cells, often responding to reactive chemicals transferred into the skin by physical contact to cause a contact dermatitis. In some conditions, tissue damage is caused by the activation of macrophages by T_H1 cells and the actions of cytotoxic T cells; in others, such as chronic asthma, cytokines produced by T_H2 cells specific for an inhaled allergen activate eosinophils and other inflammatory cells.

Summary to Chapter 10

The immune system provides the body with powerful defenses against infection. These include adaptive immune responses that have the potential to respond to any structure that is not a normal part of the body. Inevitably, all humans develop adaptive immunity to some foreign substances, such as animal and plant proteins in foods, that are not associated with infection. In general, such immune responses are harmless, but this is not always so, and various allergies or hypersensitivities are caused by the immune system's overreactions to nonthreatening environmental antigens. A first exposure to an allergen is rarely noticeable, but hypersensitivity reactions are brought on by subsequent exposures in which the allergen interacts with previously formed antibodies or stimulates memory lymphocytes. Four types of hypersensitivity reaction are conventionally defined on the basis of the effector mechanisms that cause them. Hypersensitivity reactions of types I, II, and III are triggered by antibodies, whereas type IV hypersensitivity reactions are triggered by effector T cells. In all four types of reaction, recognition of the allergen triggers an unwanted inflammatory response of varying severity and duration.

Questions

Question 10–1

Identify four different ways that an individual may come into contact with an allergen and provide two examples of allergens for each type of contact. (Refer to Figure 10.1.)

Question 10–2

A. Describe how the components of the immune system involved differ between the following subsets of hypersensitivity reactions. (Refer to Figure 10.2.) (i) Type I versus type II/type III; (ii) type I/type II/type III versus type IV.

B. Describe how the antigens differ between the following subsets of hypersensitivity reactions. (i) Type I/type III versus type II; (ii) T_H1- or T_H2-dependent type IV versus type IV involving cytotoxic T cells.

Question 10–3

A. Describe in detail the effector mechanism responsible for mast-cell activation during a type I hypersensitivity reaction.

B. What are the products of mast-cell activation? (Refer to Figures 10.3 and 10.5.)

Question 10–4

A. What type of hypersensitivity reaction typically occurs when penicillin is administered to an allergic individual?

B. Describe in chronological order the events leading to this reaction.

C. What type of hypersensitivity reaction can penicillin cause in a nonallergic individual? (Refer to Figures 10.26, 10.27, 10.28, and 10.31.)

Question 10–5

Explain what causes farmer's lung and its pathology. State what type of hypersensitivity reaction is involved. (Refer to Figures 10.29, 10.30, and 10.31.)

Question 10–6

Describe four ways in which a type III hypersensitivity reaction differs from a type I reaction.

Question 10–7

A. What is the tuberculin test used for and how does it work?

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B. What type of hypersensitivity reaction is involved?

C. Why does vaccination render this test useless? (Refer to Figures 10.33, 10.34, and 10.35.)

Question 10–8

Most extracellular antigens are taken up and processed by antigen-presenting cells via phagolysosomes and presented with MHC class II molecules to T_H1 and T_H2 cells.

A. Explain how pentadecacatechol, the antigen responsible for the hypersensitivity reaction against poison ivy, is an exception to this route of antigen processing and gains entry into the cytosolic route of antigen processing.

B. Which T cells are activated and what is the immunological consequence? (Refer to Figures 10.33 and 10.36.)

Question 10–9

A. Explain the effects of histamine binding to the H1 receptor on smooth muscle, mucosal epithelia, and endothelial cells of blood vessels.

B Why are antihistamines used to treat chronic asthma and allergic rhinitis?

Question 10–10

An immunological strategy in the treatment of allergy is called desensitization. Explain (a) how desensitization is carried out and (b) the potential risk associated with this treatment.

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Chapter 11

Disruption of Healthy Tissue by the Immune Response



Chapter 10 described how hypersensitivity to harmless environmental antigens leads to acute or chronic disease, depending on the type of antigen and the frequency of exposure to it. In this chapter another set of chronic immunological diseases is considered, diseases caused by adaptive immunity that becomes misdirected at healthy cells and tissues of the body. Such diseases are known as **autoimmune diseases**, and many different types have been described. They are not uncommon; around 5% of the population of developed countries has one or more of these conditions, and their incidence is increasing. Autoimmune diseases can be caused by antibodies that perturb a normal physiological function or by inflammatory T cells that damage healthy cells or tissue at a rate that is beyond the capacity of the body to repair. When the targeted tissue is involved in essential day-to-day functions of the body, the autoimmune disease can become a threat to life.

Autoimmune diseases are caused by unwanted adaptive immune responses; they represent failures of the mechanisms that maintain **self-tolerance**—the prevention of attack on the body's own cells and tissues—in the populations of circulating B and T cells. Although much is known of the effects of autoimmune disease, less is understood about the events that break **tolerance** and cause an autoimmune response. The first part of the chapter describes some of the more common autoimmune diseases; the second part discusses some of the predisposing factors for autoimmune disease and the mechanisms by which tolerance can be broken and lead to disease.

Autoimmune diseases

There are many chronic diseases in which the immune system is active, often causing the affected tissues to be inflamed and abnormally infiltrated by lymphocytes and other leukocytes, but in which there seems to be no associated active infection. These diseases are caused by the immune system itself, which attacks cells and tissues of the body as though they were infected, causing chronic impairment of tissue and organ function. Chronic diseases of this kind are collectively known as autoimmune diseases because they are caused by immune responses directed towards autologous (self) components of the body. An immune response that causes an autoimmune disease is called an **autoimmune response** and it produces a state of **autoimmunity**.

Autoimmune diseases vary widely in the tissues they attack and the symptoms they cause. Some focus on a particular organ or cell type, others act

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systemically. For most autoimmune diseases the incidence differs between females and males, with females being more commonly affected. A defining characteristic of autoimmune diseases is the presence of antibodies and T cells specific for antigens expressed by the targeted tissue. These antigens are called **autoantigens** and are a subset of the self-antigens; the effectors of adaptive immunity that recognize them are known as **autoantibodies** and autoimmune T cells. The mechanisms of antigen recognition and effector function in autoimmunity are the same as those used in responding to pathogens and environmental antigens; the damaging responses are due to a variety of immune effector mechanisms.

11-1 The effector mechanisms of autoimmunity resemble those causing certain hypersensitivity reactions

Autoimmune diseases can be classified by the type of immunological effector mechanism causing the disease. Three kinds are distinguished, and their effector mechanisms correspond to three of the four types of hypersensitivity reactions described in Chapter 10. The first kind of autoimmune disease, corresponding to type II hypersensitivity (see Section 10-16, p. 331), is caused by antibodies directed against components of cell surfaces or the extracellular matrix; the second kind, corresponding to type III hypersensitivity (see Section 10-17, p. 333), is caused by the formation of soluble immune complexes that are deposited in tissues; the third kind, corresponding to type IV hypersensitivity (see Section 10-19, p. 336), is caused by effector T cells. Autoimmune diseases of all three kinds are described in Figure 11.1. Autoimmune diseases are never caused by IgE, the source of type I hypersensitivity reactions.

Autoimmunity corresponding to the type II hypersensitivity reaction is frequently directed at cells of the blood. In **autoimmune hemolytic anemia**, IgG and IgM antibodies bind to components of the erythrocyte surface, where they activate complement by the classical pathway, triggering the destruction of red cells. Complete activation of the classical pathway leads to formation of the membrane-attack complex and hemolysis—lysis of red cells. Alternatively, erythrocytes coated with antibody and C3b are cleared from the circulation, principally by Fc and complement receptors on phagocytes in the spleen (Figure 11.2). All mechanisms lead to a reduction in the red-cell count. This condition is called anemia, a term derived from Greek words meaning 'without blood.'

White blood cells can also be a target for autoantibodies and complement activation. Because nucleated cells are less susceptible than erythrocytes to complement-mediated lysis, the major effect of complement activation is to facilitate phagocyte-mediated clearance of white blood cells in the spleen. Patients who develop antibodies against neutrophil surface antigens suffer from reduced numbers of circulating neutrophils, a state called **neutropenia**. Blood cells that have bound antibody and complement are, however, still able to function, so one treatment used for patients with chronic autoimmunity to blood cells is splenectomy, which reduces the rate at which the opsonized cells are cleared from the blood.

Antibody responses to components of the extracellular matrix are uncommon, but can be very damaging when they occur. In **Goodpasture's syndrome**, IgG is formed against the α_3 chain of type IV collagen, the collagen found in basement membranes throughout the body. The antibodies deposit along the basement membranes of renal glomeruli and renal tubules, eliciting an inflammatory response in the renal tissue (Figure 11.3). These basement membranes are an essential part of the blood-filtering mechanism of the kidney and, as IgG and inflammatory cells accumulate, kidney function

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Autoimmune disease	Autoantigen	Consequence
Antibody against cell-surface or matrix antigens (type II)		
Autoimmune hemolytic anemia	Rh blood group antigens, I antigen	Destruction of red blood cells by complement and phagocytes, anemia
Autoimmune thrombocytopenia purpura	Platelet integrin gpIIb:IIIa	Abnormal bleeding
Goodpasture's syndrome	Non-collagenous domain of basement membrane collagen type IV	Glomerulonephritis, pulmonary hemorrhage
Pemphigus vulgaris	Epidermal cadherin	Blistering of skin
Acute rheumatic fever	Streptococcal cell wall antigens. Antibodies cross-react with cardiac muscle	Arthritis, myocarditis, late scarring of heart valves
Graves' disease	Thyroid-stimulating hormone receptor	Hyperthyroidism
Myasthenia gravis	Acetylcholine receptor	Progressive weakness
Insulin-resistant diabetes	Insulin receptor (antagonist)	Hyperglycemia, ketoacidosis
Hypoglycemia	Insulin receptor (agonist)	Hypoglycemia
Immune-complex disease (type III)		
Subacute bacterial endocarditis	Bacterial antigen	Glomerulonephritis
Mixed essential cryoglobulinemia	Rheumatoid factor IgG complexes (with or without hepatitis C antigens)	Systemic vasculitis
Systemic lupus erythematosus	DNA, histones, ribosomes, snRNP, scRNP	Glomerulonephritis, vasculitis, arthritis
T cell-mediated disease (type IV)		
Insulin-dependent diabetes mellitus	Pancreatic β-cell antigen	β-cell destruction
Rheumatoid arthritis	Unknown synovial joint antigen	Joint inflammation and destruction
Multiple sclerosis	Myelin basic protein, proteolipid protein	Brain degeneration. Paralysis
Celiac disease	Gluten modified by tissue transglutaminase	Malabsorption of nutrients Atrophy of intestinal villi

Figure 11.1 A selection of autoimmune diseases, the symptoms they cause, and the autoantigens associated with the immune response. The autoimmune diseases are classified as types II, III, and IV because their tissue-damaging effects are similar to those of hypersensitivity reactions types II, III, and IV respectively (see Chapter 10). snRNP, small nuclear ribonucleoprotein; scRNP, small cytoplasmic ribonucleoprotein.

becomes progressively impaired, leading to kidney failure and death if not treated. Treatment involves plasma exchange to remove existing antibodies and immunosuppressive drugs to prevent the formation of new ones. Although autoantibodies are deposited in the basement membranes of other organs, the high-pressure filtering of blood by renal glomeruli is the vital function most sensitive to their effects. Indeed, kidney damage by the immune system is responsible for one-quarter of all cases of end-stage renal failure.

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