Chapter 13

Failures of the Body’s Defenses

Most pathogens that threaten the human body are prevented from establishing infection, and 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 compete successfully against 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 and how the immune system is affected. 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 at which 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 can 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.
13-1 Genetic variation within some species of pathogens prevents effective long-term immunity

Antibodies directed against macromolecules on the surface 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 surface. One such pathogen is the bacterium *Streptococcus pneumoniae*, which causes pneumonia. 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 of *S. pneumoniae*, a person will have made antibodies that prevent reinfection with that type but will not prevent primary infection with another type (Figure is11.1/13.1). *S. pneumoniae* is a common cause of bacterial pneumonia because its genetic variation prevents individuals from developing 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.

13-2 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 the 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 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)
Neutralizing antibody binding to hemagglutinin prevents virus V from infecting cells of person P

While infecting person Q, virus V mutates to give virus V* with altered hemagglutinin

Virus V* infects person P because antibody made against V does not neutralize V*

Figure is11.2/13.2 Evolution of new influenza variants by antigenic drift. Upon infection with influenza strain V, person P produced antibodies against various epitopes of the viral hemagglutinin. Some antibodies are neutralizing (green); others are not (blue). When person P is further exposed to strain V, the neutralizing antibodies prevent the virus from infecting cells (left panel). In the course of infecting person Q, viral strain V mutates to give strain V*, which differs from V by one amino acid substitution (yellow) in the hemagglutinin (center panel). This amino-acid difference eliminates the epitope recognized by neutralizing antibodies made against strain V. Consequently, strain V* influenza virus can infect cells of person P without interference from the antibodies made against strain V (right panel). To clear this second influenza infection, person P must mount a primary immune response that makes neutralizing antibodies against strain V*. The viral neuraminidase (not shown) undergoes antigenic drift in a similar manner.

and the virus is cleared from the system by a combination of cell-mediated immunity and antibodies. The pattern of infection of influenza virus characteristically causes epidemics, in which the virus spreads rapidly through a local population and then abruptly subsides. Long-term survival of the influenza virus is ensured by the generation of new viral strains that evade the protective immunity acquired by human hosts 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 emerge regularly and cause an influenza epidemic every other winter or so. An individual's protective immunity to influenza is determined by the strain of virus to which they were first exposed—the phenomenon of 'original antigenic sin' (see Section 11-13, p. XX). 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 who suffer most at any particular time will be the very young, who have no previous exposure to influenza virus, and 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 is11.2/13.2).

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 inflict more severe disease and a greater mortality than the viruses emerging from antigenic drift. The influenza strains that cause pandemics are recombinant viruses that derive some of their RNA genome 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 the strains to 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 were simultaneously infected with both avian and human viruses. If such a recombinant virus jumps back into humans it has a tremendous competitive advantage, and in sweeping through the human population it will rapidly replace other influenza strains. Recombinant influenza viruses can similarly cause epidemics in bird populations and are greatly feared by poultry farmers. This mode of evolution is called **antigenic shift** (Figure 13.3/13.3).

13-3 Trypanosomes use gene rearrangement to change their surface antigens

Mutation and recombination are not the only methods 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. A good example is *Trypanosoma brucei*, the African trypanosome that is the major cause of sleeping sickness. The life cycle of the trypanosome involves both mammalian and insect hosts. Insect bites transmit trypanosomes to humans, in whom the parasites replicate in 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 genome contains more than 1000 genes encoding these **variable surface glycoproteins (VSGs)**.

At any time, an individual trypanosome produces only one form of VSG. This is because the 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** in which the gene in the expression site is excised and replaced by a copy of a different but homologous gene (Figure 13.4/13.4). 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 will 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, one of which will come to dominate the trypanosome population. In time, the number of trypanosomes expressing the new dominant form is sufficient to stimulate the production of antibodies, which clear the new dominant form. This allows a further form to dominate, and so the cycle continues.

This mechanism of immune evasion causes trypanosome infections to produce a dramatic cycling in the number of parasites within an infected person (see Figure 13.4, 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 completely replaced by cattle and other domesticated animals, as has occurred in many parts of the world. 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.

Gene conversion enables similar strategies of antigenic variation to be 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 the 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.

13-4 Herpesviruses 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
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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 herpesviruses. 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 the epithelial tissue (Figure 11.5/13.5). Viral replication in epithelial cells and the 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.

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The herpesvirus 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 herpesvirus 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 9.3, p. 251). 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.

### 13-5 Some pathogens sabotage or subvert immune defense mechanisms

Pathogens also exploit the immune-system cells that are ranged against them. *Mycobacterium tuberculosis* commandeers the macrophage’s pathway of phagocytosis for its own purposes. On being phagocytosed, *M. tuberculosis* prevents the fusion of phagosome and lysosome, thus protecting itself from the bactercidal 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 parasite *Toxoplasma gondii*, the cause of toxoplasmosis, creates its own specialized environment within the cells that it infects. This protozoan encloses itself in an impenetrable membrane-enclosed vesicle that does not fuse with other vesicles or membranes of the cell. Such isolation prevents *T. gondii*-derived peptides from binding to MHC molecules and stimulating a T-cell response to the parasite. 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 1.4, p. XX), 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 the capture of cellular genes encoding cytokines or cytokine receptors, which when expressed by the virus can divert the immune response, the synthesis of proteins that inhibit complement fixation, and the synthesis of proteins that inhibit antigen processing and presentation by MHC class I molecules. Examples of defensive mechanisms used by herpesviruses and poxviruses are shown in Figure is11.6/13.6.

Major players in the immune response to viral infections are NK cells and CD8 T cells, killer lymphocytes whose development and function are dependent upon MHC class I molecules. For this reason many viruses have evolved subversive mechanisms for interfering with the synthesis and expression of MHC class I. The herpesvirus human cytomegalovirus (CMV) is particularly rich in such mechanisms: it has 10 proteins that interfere in diverse ways to diminish the capacity of MHC class I molecules to stimulate NK-cell and CD8 T-cell responses against CMV-infected cells (Figure is11.7/13.7). One group of these saboteurs affect MHC class I molecules in diverse ways: by causing their degradation, by interfering with the proteasome, by interfering with the TAP or tapasin proteins, or by retaining MHC class I molecules in the endoplasmic reticulum—all mechanisms that prevent the presentation of viral antigens to CD8 T cells. Such mechanisms that reduce MHC class I expression should
favor an NK-cell response against the infected cells that are now lacking self-MHC class I (see Chapter 12). However, a second group of saboteurs interfere with the inhibitory NK-cell receptors CD94:NKG2A and LILRB1, which sense missing self-MHC class I, and with the activating NKG2D receptor, which recognizes the ligands MIC and ULBP (see Figure 12.2).

Human CMV is an extremely well-adapted human pathogen that infects more than half the population of the United States. Most of these 150 million people are unaware of their infection, because the virus causes few symptoms on initial infection and thereafter exists in a latent state, during which it is comfortably controlled by the combined activities of NK cells and CD8 T cells. In the healthy CMV-infected person there is a well-tuned balance in which the virus survives and multiplies with little expense to the host. In contrast, CMV causes life-threatening disease in immunocompromised individuals: the young, the elderly, the transplant recipient on immunosuppressive drugs, and people infected with HIV. CMV is the commonest infection affecting patients who have had a bone marrow transplant or hematopoietic stem-cell transplant, and if not treated with antiviral drugs it is fatal. CMV infects a wide range of human cell types and is spread via physical contact of bodily fluids.

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<th>Specific mechanism</th>
<th>Result</th>
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<td>Inhibition of humoral immunity</td>
<td>Virally encoded Fc receptor</td>
<td>Blocks effector functions of antibodies bound to infected cells</td>
<td>Herpes simplex</td>
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<td></td>
<td>Virally encoded complement receptor</td>
<td>Blocks complement-mediated effector pathways</td>
<td>Cytomegalovirus</td>
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<tr>
<td></td>
<td>Virally encoded complement control protein</td>
<td>Inhibits complement activation of infected cell</td>
<td>Vaccinia</td>
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<tr>
<td>Inhibition of inflammatory response</td>
<td>Virally encoded chemokine receptor homolog</td>
<td>Sensitizes infected cells to effects of some chemokines; advantage to virus unknown</td>
<td>Cytomegalovirus</td>
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<td>Virally encoded soluble cytokine receptor, e.g. IL-1 receptor homolog, TNF receptor homolog, IFN-γ receptor homolog</td>
<td>Blocks effects of cytokines by inhibiting their interaction with host receptors</td>
<td>Vaccinia</td>
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<td>Viral inhibition of adhesion molecule expression, e.g. LFA-3, ICAM-1</td>
<td>Blocks adhesion of lymphocytes to infected cells</td>
<td>Epstein–Barr virus</td>
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<td>Protection from NFκB activation by short sequences that mimic TLRs</td>
<td>Blocks inflammatory responses elicited by IL-1 or bacterial pathogens</td>
<td>Vaccinia</td>
</tr>
<tr>
<td>Blocking of antigen processing and presentation</td>
<td>Inhibition of MHC class I upregulation by IFN-γ</td>
<td>Impairs recognition of antigen-presenting cells by CD4 T cells</td>
<td>Herpes simplex</td>
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<td></td>
<td>Inhibition of peptide transport by TAP</td>
<td>Blocks peptide association with MHC class I</td>
<td>Herpes simplex</td>
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<tr>
<td>Immunosuppression of host</td>
<td>Virally encoded cytokine homolog of IL-10</td>
<td>Inhibits T11 lymphocytes, reduces IFN-γ production</td>
<td>Epstein–Barr virus</td>
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</tbody>
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![Figure is11.6/13.6 Mechanisms by which herpesviruses and poxviruses subvert the immune response. Herpes simplex, cytomegalovirus, and Epstein–Barr viruses are herpesviruses; vaccinia and rabbit myxoma virus are poxviruses.](image)

<table>
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<tr>
<th>HCMV protein</th>
<th>Subversive effect on the immune response</th>
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<tbody>
<tr>
<td>US2</td>
<td>Transports HLA class I to cytoplasm for degradation by proteasome</td>
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<tr>
<td>US3</td>
<td>Retains HLA class I in the endoplasmic reticulum by blocking tapasin function</td>
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<tr>
<td>US6</td>
<td>Inhibits TAP ATPase activity and function</td>
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<tr>
<td>US10</td>
<td>Binds HLA class I and slows its transport from the endoplasmic reticulum to the cell surface</td>
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<tr>
<td>US11</td>
<td>Targets newly synthesized HLA class I heavy chains for degradation in the cytoplasm</td>
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<tr>
<td>US12</td>
<td>Inhibits NK-cell recognition of infected cells by binding to the ULBP ligands of NKG2D</td>
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<td>UL16</td>
<td>MHC class I heavy-chain homolog that binds to the inhibitory NK-cell receptor LILRB1</td>
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<tr>
<td>UL18</td>
<td>The UL40 leader peptide binds HLA-E and subverts CD94:NKG2A monitoring of HLA-A,-B,-C expression</td>
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<tr>
<td>UL83</td>
<td>Blocks access to the proteasome and the generation of MHC class I binding peptides</td>
</tr>
<tr>
<td>UL142</td>
<td>Downregulates the expression of the MIC-A and MIC-B ligands of NKG2D</td>
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![Figure is11.7/13.7 Human cytomegalovirus interferes with the expression of MHC class I molecules in many different ways.](image)
Bacterial superantigens stimulate a massive but ineffective CD4 T-cell response

Some species of Gram-positive bacteria, notably *Staphylococcus aureus* and *Streptococcus pyogenes*, secrete potent toxins, which at minuscule concentrations induce a violent disruption of an infected person’s immune system. Because these small bacterial protein toxins activate so many different T-cell clones they are called superantigens. The mayhem is caused by the nonspecific activation of numerous clones of CD4 T cells, which involves 2–20% of the body’s CD4 T cells and excessive production of IL-2, interferon (IFN)-γ, and TNF-α. Between them, the staphylococci and streptococci make more than 30 different superantigens. What they all have in common are binding sites that allow the superantigen to cross-link an MHC class II molecule on an antigen-presenting cell with the T-cell receptor on a CD4 T cell.

The soluble superantigen first forms a stable interaction with an MHC class II molecule on the antigen-presenting cell. Subsequently, when a circulating CD4 T cell investigates the antigen-presenting cell to search for its specific antigen, a second site on the superantigen binds to the variable domain of the T-cell receptor Vβ chain. Then, at a third site, the superantigen binds to the T cell’s CD28 co-stimulatory receptor and does so in a way that does not interfere with the interaction of CD28 with its B7 ligand (Figure is11.8/13.8). By this mechanism, superantigens can substitute for the specific antigenic peptide and assemble a complex of T-cell receptor, co-receptor, and co-stimulatory receptor that will fully activate the CD4 T cell (see Section 8-5, p. XX). The various superantigens activate different subsets of CD4 T cells because they have different binding specificities for human Vβ chains. Thus, *S. aureus toxic shock syndrome toxin-1* (TSST-1) binds to β chains containing a Vβ2 gene segment and can activate all CD4 T cells bearing T-cell receptors with this type of β chain. In contrast, *S. aureus enterotoxin B* (SEB) activates all CD4 T cells expressing Vβ1.1, 3.2, 6.4, and 15.1 chains.

Eating food contaminated with *S. aureus* is a common cause of food poisoning. Several hours after enjoying the meal, the diner experiences different emotions while suffering episodes of violent vomiting and diarrhea as the mucosal immune system responds to the activation of CD4 T cells by bacterial superantigens. This response has the effect of flushing the bacteria and its toxins from the gastrointestinal tract, which benefits the host and raises the question of why bacteria have repeatedly evolved superantigens that target CD4 T cells, lymphocytes that are not involved in the immediate response to infection. One possibility is that a massive, and non-physiological, adaptive immune response at the onset of infection confuses the innate immune response. In this case, the bacteria would be able to evade the immune system and continue to grow and multiply.
scenario, the cytokines poured out by the CD4 T cells interfere with the capacity of neutrophils and macrophages to phagocytose the bacteria that have crossed the mucosa and are about to establish infection in the tissues.

13-7 Subversion of IgA action by bacterial IgA-binding proteins

*Staphylococcus aureus* is an adept and opportunistic pathogen that possesses numerous virulence factors which interfere with human defenses and promote the bacterial colonization of invaded tissue. In addition to the superantigens, *S. aureus* secretes a family of structurally related *staphylococcal superantigen-like proteins* (SSLPs) that subvert and compromise human immunity in a variety of ways. The purpose of staphylococcal superantigen-like protein 7 (SSLP7) is to prevent monomeric IgA from delivering the bacteria to phagocytes. In the absence of SSLP7, IgA binds to a bacterium with its Fab arms and to FcαRI on neutrophils and macrophages with its Fc region. This activates the phagocyte to engulf and destroy the bacterium bound to the Fc receptor. SSLP7 has binding sites for the Fc region of IgA and for the C5 complement protein. These interactions create a large constrained complex in which IgA binding to FcαRI and complement-mediated killing of the bacterium are both prevented (Figure n13.100/13.9). Over evolutionary time, there

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**Figure n13.100/13.9 Evasion of IgA-mediated defense by staphylococcal superantigen-like protein 7.** The upper panel shows how the combination of specific IgA and FcαRI on phagocytes causes the elimination of bacteria that cross a mucosal barrier and infect the underlying tissue. The lower panel shows how this mechanism for disposing of bacteria is thwarted by the SSLP7 protein of *S. aureus*. By binding to both C5 and the Fc region of IgA, SSLP7 prevents IgA from binding to FcαRI or activating complement-mediated killing of the bacteria (not shown).
has been a perpetual arms race between bacterial pathogens and their mammalian hosts. The host selects for new IgA variants that do not bind the bacterial SSLP, which in turn leads to selection for a new SSLP that binds to the latest version of IgA.

**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.

**Inherited immunodeficiency diseases**

Inherited defects in genes for components of the immune system cause **primary immunodeficiency diseases**, which reveal themselves by enhanced susceptibility to infection or autoimmunity. Primary immunodeficiency diseases are distinguished from **secondary immunodeficiency diseases**, which are due not to defective genes but to environmental factors, such as immunosuppressive drugs, that adversely impact the immune system. Before the advent of antibiotic therapy during the 1940s, most individuals with inherited immune defects died from infection during infancy or early childhood. Because so 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, numerous 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.

13-8 **Rare primary immunodeficiency diseases reveal how the human immune system works**

In dissecting the immune system of the laboratory mouse, immunologists ‘knock out’ a selected gene and examine the immunodeficiency syndrome that this causes. Equivalent human gene knockouts are provided by more than 200 primary immunodeficiency syndromes. Around 50 of these were described in the past 5 years, and the rate of discovery is increasing with the application of complete genome sequencing. Treating and studying these patients have made invaluable contributions to knowledge of the human immune system. It is no coincidence that in almost all the previous chapters of this book, one or more primary immunodeficiency syndromes have been used to illustrate the functions of particular proteins and the effects of their absence (Figure is11.9/13.10). For some genes their deletion from human and mouse genomes leads to similar immunodeficiencies, whereas for other genes the knockout phenotypes are unpredictably different. Most of the human conditions are very rare and are caused by mutant genes that have no selective benefit for the people who carry them. They usually occur in small populations that are
geographically or culturally isolated and in which there are traditions of marriage within the group. Recent advances in genetics and genomics have made the precise identification of the genes responsible for immunodeficiency

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<tr>
<td>Asplenia</td>
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<tr>
<td>C3 deficiency (see Figure 13.13 for other complement immunodeficiencies)</td>
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<tr>
<td>Factor I deficiency</td>
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<tr>
<td>Deficiencies of C5, C6, C7, C8, or C9</td>
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<td>Paroxysmal nocturnal hemoglobinuria</td>
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<td>NEMO deficiency (X-linked hypohidrotic ectodermal dysplasia and immunodeficiency)</td>
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<td>Chronic granulomatous disease</td>
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<td>MBL deficiency</td>
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<td>NK-cell deficiency</td>
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<td>Hyper-IgM deficiency</td>
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<td>IgG2 deficiency</td>
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<td>SCID (see Figure 13.16 for the different causes of SCID)</td>
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<td>Omenn syndrome</td>
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<td>MHC class I deficiency (bare lymphocyte syndrome type I)</td>
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<td>IPEX (immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome)</td>
</tr>
<tr>
<td>ZAP-70 deficiency</td>
</tr>
<tr>
<td>C4A or C4B</td>
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<tr>
<td>Selective IgA deficiency</td>
</tr>
</tbody>
</table>

Figure is11.9/13.10 Mechanisms of human immunity are revealed by the study of inherited immunodeficiency syndromes. This figure shows the immunodeficiency syndromes mentioned previously in this book (with references to the relevant sections), their gene defects, and the effects they have on the immune system.
syndromes much easier; now the more challenging task is for doctors in the field to recognize a novel form of immunodeficiency syndrome when they see it. International collaborations help in the identification and treatment of these patients.

Whereas most of the primary immunodeficiencies listed in Figure 13.10 were discovered in patients with severe disease and are caused by exceedingly rare mutant alleles, defects in other immune-system genes are more frequent and have less dramatic effects. Examples of the latter are defective MHC class I alleles, or the lack of an A or a B isotype of complement component C4 (see Section 9-18), which confers either an increased susceptibility to the autoimmune disease systemic lupus erythematosus (lack of A) or a somewhat heightened vulnerability to infection (lack of B). An extreme example is the gene-content variation of haplotypes encoding the KIR gene family of NK-cell receptors (see Section 12-7), which means that most people lack at least one KIR and its functions. Usually, those immune-system genes that can be lost with no drastic effect on immune function are members of multigene families in which another family member can, to some extent, compensate for the defective gene. In some cases this type of variability may represent a compromise, in that there are some benefits associated with having or lacking a particular gene.

13-9 **Inherited immunodeficiency diseases are caused by dominant, recessive, or X-linked gene defects**

All primary immunodeficiency diseases can be classified into three types: dominant, recessive, or X-linked. Syndromes due to a **dominant** defective allele show up in children who inherit a normal, functional allele from one parent and the defective allele from the other parent. Disease occurs because the abnormal properties of the defective allele interfere with and dominate over the functions provided by the normal allele. In contrast, a disease caused by a **recessive** allele is only manifested in patients who inherit the defective allele from both parents. Individuals who have one defective allele and one normal allele are healthy and are called **carriers** of the disease trait. In recessive diseases, the defective allele does not interfere with the function of the normal allele. A key difference between dominant and recessive disease traits lies in the fate of heterozygous individuals: for a dominant trait they get the disease, for a recessive trait they do not.

**X-linked diseases** are caused by recessive defects in genes on the X chromosome. Because males have only one X chromosome and females have two, the disease occurs in all males who inherit an X chromosome with a defective allele, but it will not show up in their sisters even if they inherit the same X chromosome. Disease occurs in females only when they inherit a defective X chromosome from both parents. X-linked diseases, of which we have already met three (see Figure 13.9), are therefore far more frequent in boys than in girls. For these traits only women serve as healthy carriers. Any disease caused by a dominant allele on an X chromosome would occur at equal frequency in boys and girls.

Dominance is most commonly seen when the defective gene encodes a protein that functions in a dimer or a larger protein complex. In such cases, the incorporation of one defective subunit can reduce or destroy the capacity of the complex to function. 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 the mutation first occurred. Thus, most of the severe inherited immunodeficiency syndromes that have been identified are due to recessive mutations in single genes. The known immunodeficiencies that are due to dominant mutations tend to be less severe and are caused by a reduction in a function rather than its loss.
13-10 Recessive and dominant mutations in the IFN-γ receptor cause diseases of differing severity

IFN-γ, the major cytokine that activates macrophages, is made by NK cells during the innate immune response and by T<sub>H1</sub> CD4 T cells and CD8 cytotoxic T cells during the adaptive immune response. When IFN-γ binds to IFN-γ receptors on a macrophage surface, the cell is induced to make changes in gene expression and become better at engulfing and killing bacteria (see Section 8-18, p. XX). The IFN-γ receptor is a dimer of two polypeptides, IFNγR1 and IFNγR2, which both associate with tyrosine kinases—Jak1 and Jak2, respectively. Functional IFN-γ is also a dimer, and binding of the dimeric cytokine to sites on the IFNγR1 polypeptide cross-links two molecules of the receptor to initiate the signaling cascade (Figure is11.10/13.11, first panel).

The response of macrophages to IFN-γ is crucial for defense against intravascular bacteria, such as mycobacteria, and both dominant and recessive mutations in IFNγR1 have been identified in patients suffering from persistent mycobacterial infections (Figure 13.11, second and third panels). Both types of mutation cause the condition of IFN-γ receptor deficiency. The recessive alleles contain mutations that prevent any expression of IFNγR1 at the cell surface. The macrophages and monocytes of patients with two recessive alleles carry only IFNγR2 at their surfaces and are unresponsive to IFN-γ (see Figure 13.11, second and fourth panels). For this group of patients the disease is usually more severe and appears at an earlier age. Heterozygotes are healthy because the protein made from the defective allele does not interfere with that made from the normal allele, which assembles with IFNγR2 and moves to the cell surface as functional IFN-γ receptor (see Figure 13.11, first panel).

In the dominant mutants, IFNγR1 is truncated such that much of the cytoplasmic tail, which binds Jak1 and initiates signaling, is missing. The truncated IFNγR1 associates with IFNγR2 protein and is taken to the surface as a receptor that binds IFN-γ but cannot transduce a signal. At the cell surface, these defective receptors compete for IFN-γ with the normal receptors that

![Figure 11.10/13.11](Figure 11.10/13.11 The impact of recessive and dominant mutations in the IFN-γ receptor on monocyte activation. Receptors for IFN-γ are composed of a dimer of IFNγR1 and IFNγR2. Two such dimers must be cross-linked by IFN-γ binding to the IFNγR1 chain for signaling to be triggered (first panel). Recessive mutant alleles of IFNγR1 produce a mutant chain that does not reach the surface. Thus, cells from patients homozygous for a recessive mutation have only IFNγR2 at the surface, lack IFNγR1 function, and cannot respond to IFN-γ (second panel). Heterozygotes for such a mutation produce sufficient numbers of wild-type chains to assemble enough functional receptors for a normal response to IFN-γ, as in the first panel. Dominant mutant alleles of IFNγR1 produce a mutant chain lacking a signaling domain. This chain can assemble into a dimer and bind IFN-γ but cannot signal (third panel). Heterozygotes for a dominant mutation make a small number of functional receptors composed entirely of wild-type chains, but most receptors are nonfunctional. Thus their response to IFN-γ is defective (third panel). The fourth panel compares the results of IFN-γ stimulation of blood monocytes from normal, homozygous recessive, and heterozygous dominant patients.)
incorporate IFNγR1 made from the normal allele (see Figure 13.11, third panel). This competition is further weighted against the functional receptors because the absence of the cytoplasmic domain from IFNγR1 prevents the mutant receptor from being recycled by endocytosis. It therefore accumulates at the cell surface, at levels fivefold higher than the normal receptor. Because of the interference by the mutant receptors, the response of patients’ macrophages and monocytes to IFN-γ is much reduced compared with healthy people, but it is greater than in patients carrying two recessive alleles (see Figure 13.11, fourth panel). Because of this difference, dominant mutants cause a less severe immunodeficiency, which tends to be detected at a later age.

13-11 Antibody deficiency leads to poor clearing of extracellular bacteria

The major threat to patients lacking antibodies is infection by pyogenic bacteria. These encapsulated bacteria, which include *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Staphylococcus aureus*, are not recognized by the phagocytic receptors of macrophages and neutrophils, so they frequently escape immediate elimination by the innate immune response. Such infections are normally cleared when the bacteria are opsonized by specific antibody and complement and then taken up and killed by phagocytes. For patients lacking antibodies, infections with pyogenic bacteria tend to persist unless treated with antibiotics.

The first immunodeficiency disease to be described was 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 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 development and differentiation of pre-B cells (see Figure 6.12, p. XX). Males inheriting an X chromosome with a mutant allele of the BTK gene are unable to produce functional B cells. Although BTK is also expressed in monocytes and T cells, these cells are not obviously compromised by its absence in patients with XLA.

Women with one functional and one nonfunctional copy of the BTK gene are healthy, but they pass XLA on to half of their male children. In all females, one X chromosome is randomly inactivated in every cell. For all women, each X chromosome is inactivated in 50% of the pre-B cells. In women who are not XLA carriers both pools of pre-B cells develop to give a population of mature B cells in which each X chromosome is inactivated in 50% of cells. In contrast, for carriers of XLA, the only pre-B cells that can develop are those that express the functional BTK allele and inactivate the mutant allele. Consequently, all the mature B cells in XLA carriers have inactivated the same X chromosome. By using genetic markers that distinguish between the two X chromosomes, the women in families with a history of XLA, or of any other X-linked syndrome, can be typed as carriers or non-carriers of the genetic disease (Figure is11.11/13.12).

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. 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, XLA patients are given monthly injections of **gamma globulin**, an antibody-containing preparation made from the plasma of healthy blood


13-12 Diminished production of antibodies also results from inherited defects in T-cell help

Diminished production of antibodies is also a symptom of defective genes encoding the membrane-associated cytokine CD40 ligand. As discussed in Chapter 9, 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, 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 and there are no germinal centers in the secondary lymphoid tissues (see Figure 9.17, p. XX). The blood of these patients has extremely low amounts of IgG, IgA, and IgE combined with abnormally high amounts of IgM. 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. As in XLA patients (see Section 13-11), regular injections of gamma globulin help to prevent infections, and antibiotics are used to treat their infections.

Macrophage activation by effector CD4 T cells also depends on the interaction of CD40 on the macrophage with CD40 ligand on the T cell (see Section 8-18).
In patients with X-linked hyper-IgM syndrome this interaction does not occur, which impairs the macrophage production of granulocyte–macrophage colony-stimulating factor (GM-CSF), a cytokine that stimulates the development of neutrophils in the bone marrow and their release into the circulation. In immunocompetent individuals, the immune response to infection increases the number of white blood cells in the blood, a state called leukocytosis, but this does not occur in patients lacking CD40 ligand. On the contrary, their blood can become profoundly deficient in neutrophils, a state called neutropenia that often leads to severe sores and blisters in the mouth and throat. Being always infested with bacteria, the integrity of these mucosal tissues depends on perpetual surveillance of their microbiota by neutrophils. The sores and blisters experienced by patients with X-linked hyper-IgM syndrome can be cured by intravenous administration of GM-CSF.

13-13 Complement defects impair antibody-mediated immunity and cause immune-complex disease

All effector functions that antibodies recruit to clear pathogens and their antigens are facilitated by complement activation. Consequently, the spectra of infections associated with deficiencies in complement and antibody production overlap substantially. Defects in the activation of C3, and in C3 itself, result in susceptibility to a wide range of pyogenic infections, emphasizing the importance of C3 as an opsonin that promotes the efficient elimination of bacteria by phagocytes. In contrast, defects in C5–C9, the terminal complement components that form the membrane-attack complex, have few 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 is11.12/13.13 lists the effects of the absence of complement components and complement inhibitory proteins.

The early components of the classical pathway are necessary for the elimination of immune complexes. As discussed in Section 9-20, p. XX, the 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, which capture the complexes with the CR1 complement receptor that binds to C4b and 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 to 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. This condition is called immune-complex disease.

Deficiencies in the proteins that control complement activation can also have major effects. People deficient for factor I in effect lack C3. Because factor I is absent, the conversion of C3 to C3b runs unchecked, and supplies of C3 are rapidly depleted (see Section 2-4, p. XX). Patients who lack properdin (factor P), a plasma protein that enhances the activity of the alternative pathway by stabilizing the C3 convertase, have a heightened susceptibility to Neisseria, because reduced C3 deposition impedes formation of the membrane-attack complex, the machinery used to kill the bacteria. In contrast, a deficiency in decay-accelerating factor (DAF) or CD59 causes an autoimmune-like condition. Lacking the protection conferred by DAF or CD59, the cells of these patients activate the alternative pathway of complement. The resultant complement-mediated lysis of erythrocytes causes the disease paroxysmal nocturnal hemoglobinuria (see Section 2-7, p. XX).

Hereditary angioedema (HAE) is an autosomal dominant disease caused by a deficiency of the complement regulator C1 inhibitor (C1INH). The disease is...
characterized by episodic bouts of subepithelial swelling of the face, larynx, and abdomen. The swelling around the larynx can lead to death by suffocation. C1 inhibitor affects serine proteases such as C1r and C1s by binding to the active site and forming a covalent bond that irreversibly inactivates the enzyme. In patients deficient in C1 inhibitor the classical pathway is overactive, resulting in abnormally low levels of C2 and C4 in the blood and an abnormally high production of the vasoactive C2a fragment. As well as participating in the regulation of complement activation, C1INH also controls serine proteases involved in blood clotting. In patients with HAE, the blood-clotting pathways are also overactive, resulting in abnormally high levels of the vasoactive peptide bradykinin. The combined actions of C2a and bradykinin cause fluid to leak out of the blood into the tissues, causing the edema that characterizes HAE.

C1 inhibitor is a member of a large family of serine and cysteine protease inhibitors called the **serpins**. By acting as a pseudosubstrate, each molecule of the inhibitor poisons the active site of a protease molecule (Figure is11.13/13.14). The genetic dominance of HAE does not arise from the C1 protein’s participation in a multisubunit complex, as is the case in IFN-γ receptor deficiency (see Section 13-10); instead, it occurs because one good copy of the C1INH gene cannot make sufficient inhibitor to control the complement and clotting cascades. HAE is treated with infusions of recombinant C1INH protein, some of which is purified from the milk of rabbits made transgenic for the human C1INH gene.

**13-14 Defects in phagocytes result in enhanced susceptibility to bacterial infection**

Phagocytosis mediated by macrophages and neutrophils is the principal method by which the immune system gets rid of infecting bacteria and other microbes. Any deficiency that compromises phagocyte activity has profound effects on the immune system’s capacity to clear infection (Figure is11.14/13.15). One such syndrome is due to mutation of the CD18 gene and is known as **leukocyte adhesion deficiency**. CD18 is the β2 subunit of the leukocyte integrins, which comprise the CR3, CR4, and LFA-1 adhesion molecules that are necessary for neutrophils and monocytes to leave the blood and enter sites of infection (see Section 3-8, p. XX). In children with leukocyte adhesion deficiency, these cells are unable to enter infected tissues where they are needed to dispose of the offending pathogen. Because CR3 and CR4 are also complement receptors, a second problem is that the phagocytes are unable to engulf bacteria opsonized with complement (see Section 3-9, p. XX). Children with leukocyte adhesion deficiency have recurrent and persistent infections with pyogenic bacteria that respond poorly to antibiotics and are not cleared by seemingly normal B-cell and T-cell responses. These children suffer successive infections and usually succumb during the first 2 years of life.
The capacity of phagocytes to kill ingested bacteria can also be blunted by a single defective gene. In **chronic granulomatous disease (CGD)**, the antibacterial activity of phagocytes is compromised by their inability to produce the superoxide radical \( \text{O}_2^- \) (see Section 3-9, p. XX). Mutations affecting any of the four proteins of the NADPH oxidase system can produce the 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. This lack of phagocyte function has effects in many different organs as well as leading to persistent and recurrent bacterial infections. The mutations causing this disease are in the \( CHS1 \) gene on chromosome 1, which encodes the lysosomal trafficking protein that is critical for lysosome function.

### 13-15 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 (Figure n13.101/13.16). 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, so the SCID phenotype can arise from defects in any one of a number of genes. Deficiency of **adenosine deaminase (ADA)** or **purine nucleoside phosphorylase (PNP)**, which are enzymes involved in purine degradation, account for 15% of SCID patients. The absence of these enzymes causes an accumulation
of nucleotide metabolites in all types of human cell, but the effects are particularly toxic to developing T cells and, to much lesser extent, to developing B cells. Infants with these immunodeficiencies have an underdeveloped thymus that contains few lymphocytes. ADA and PNP deficiencies are autosomal recessively inherited (Figure 11.15/13.17).

Because of the unique 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 one we consider here is due to mutation in the X-linked gene that encodes the common gamma chain (γc), a shared signaling component of the cell-surface receptors for IL-2, IL-4, IL-7, IL-9, and IL-15. (This γ chain of cytokine receptors is not the same as the γ chain associated with Fc receptors). When one of these cytokines binds to its receptor, γc interacts with the protein kinase Jak3 to produce intracellular signals (see Figure 8.22, p. XX). In the absence of a functional γ chain, none of the five cytokines can induce receptor signaling and so, predictably, the result is SCID. A very similar, but autosomally inherited, immunodeficiency occurs in patients who lack Jak3. The phenotype of SCID is so severe that affected infants survive only if they are kept isolated in a pathogen-free environment until their immune system has been replaced by hematopoietic cell transplantation and the passive administration of antibodies.

Another X-linked deficiency of T-cell function is Wiskott–Aldrich syndrome (WAS), a syndrome involving the impairment of platelets as well as lymphocytes. It shows up in childhood as a history of recurrent infections but is less severe than those in SCID patients. It is due to mutation in the WASP/WAS protein, a gene that encodes a protein involved in cellular signaling and cytoskeletal function. Patients with WAS have a combination of immune deficiencies and abnormalities of platelet function, which can lead to easy bruising and spontaneous bleeding. The WASP protein is crucial for the proper function of lymphocytes, particularly in the production of antibodies and the activation of T cells.

### Severe combined immunodeficiency syndromes and related conditions

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Defective gene/protein</th>
<th>Functional effect</th>
<th>Clinical effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenosine deaminase deficiency</td>
<td>ADA/adenosine deaminase</td>
<td>Build-up of toxic metabolites, resulting in death of T cells and B cells</td>
<td>Extreme susceptibility to infections of all types, including opportunistic infections (SCID), which is lethal in infancy if not treated</td>
</tr>
<tr>
<td>Radiation-sensitive SCID (see Section 5-2)</td>
<td>RAG1, RAG2, and other proteins involved in V(D)J recombination</td>
<td>Failure of V(D)J recombination, Non-production of T cells and B cells</td>
<td></td>
</tr>
<tr>
<td>X-linked SCID</td>
<td>IL2RG/common γ chain</td>
<td>Defects in cytokine signaling, resulting in the non-development of T cells and NK cells</td>
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</tr>
<tr>
<td>Janus 3 kinase (Jak3) deficiency</td>
<td>JAK3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omenn syndrome (see Section 5-2, p. xxx)</td>
<td>RAG1, RAG2 (80% loss of function), and other proteins involved in V(D)J recombination</td>
<td>Deficient V(D)J recombination, Non-production of T cells and B cells</td>
<td>SCID, chronic inflammation</td>
</tr>
<tr>
<td>Complete DiGeorge syndrome (see Section 7-1, p.xxx)</td>
<td>Associated with microdeletions of 22q11.2 region on chromosome 22</td>
<td>Defective thymus development and T-cell production</td>
<td>Cardiac defects, SCID</td>
</tr>
<tr>
<td>Wiskott–Aldrich syndrome (WAS)</td>
<td>WASP/WAS protein</td>
<td>Defective cytoskeletal function impairs lymphocyte function and interaction</td>
<td>Antibody deficiency, increased susceptibility to infections; thrombocytopenia with small platelets</td>
</tr>
<tr>
<td>MHC class II deficiency</td>
<td>Transcriptional activators acting at elements common to all HLA class II genes</td>
<td>Non-production of all HLA class II molecules, resulting in defective CD4 T-cell development in the thymus</td>
<td>Increased susceptibility to pyogenic and opportunistic infections</td>
</tr>
<tr>
<td>MHC class I deficiency</td>
<td>TAP1, TAP2</td>
<td>Impaired production of HLA class I molecules, resulting in failure of CD8 T cells to develop in the thymus</td>
<td>Repeated respiratory viral infections</td>
</tr>
</tbody>
</table>

![Figure n13.101/13.16 SCID and other severe immunodeficiencies related to an absence of T-cell function.](image)

![Figure is11.15/13.17 Adenosine deaminase (ADA) deficiency is inherited in an autosomal fashion.](image)
immunologically severe than SCID. The patients have normal levels of T and B cells but they cannot make good antibody responses and are therefore kept on a course of gamma-globulin injections (see Section 13-11). The relevant gene on the X chromosome encodes the Wiskott-Aldrich syndrome protein (WASP). This protein is involved in the cytoskeletal reorganization that is needed before T cells can deliver cytokines and signals to the B cells, macrophages, and other target cells with which they must intimately interact during their development and participation in the immune response (see Figure 8.26, p. XX).

Lack of HLA class II molecules also causes a serious immunodeficiency. The deficiency was originally 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, but is now more often called MHC class II deficiency. In these patients, CD4 T cells fail to develop (see Section 7-10, p. XX), which compromises most aspects of adaptive immunity. MHC class II deficiency arises from defects in transcriptional regulators that are essential for the expression of all the HLA class II genes. 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.

Defects in either of the two genes encoding the TAP peptide transporter (see Section 5-10, p. XX) 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 MHC class I deficiency, is less severe than the immunodeficiency caused by the absence of HLA class II, its principal effect being the selective loss of CD8 T cells (see Section 7-10, p. XX) 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 cause autosomally inherited forms of SCID or a related immunodeficiency called Omenn syndrome, depending on the particular defect (see Section 5-2, p. XX). These include the RAG-1 and RAG-2 proteins, the nuclease Artemis, and the DNA-dependent protein kinase (DNA-PK).

### 13-16 Some inherited immunodeficiencies lead to specific disease susceptibilities

Patients who lack the IFN-γ receptor suffer persistent and sometimes fatal infections of common intracellular bacteria, such as the ubiquitous nontuberculous strain of mycobacterium, *Mycobacterium avium* (see Section 13-10). **IL-12 receptor deficiency**, in which the receptor for the cytokine IL-12 is non-functional, produces a similar susceptibility to intracellular bacterial infections. In the innate immune response there is a mutual activation of NK cells and macrophages (Figure is11.16/13.18, left panel). This involves the IL-12 secreted by macrophages binding to the IL-12 receptor of NK cells and stimulating them to secrete IFN-γ. The IFN-γ then binds to the IFN-γ receptor on macrophages and activates phagocytosis and the secretion of proinflammatory cytokines. In the absence of a functioning IL-12 receptor, this cycle of mutual reinforcement cannot begin.

In the adaptive immune response, IL-12 secreted by macrophages binds to the IL-12 receptors of T cells, helping to induce the differentiation of T_{H1} cells from activated antigen-specific naive CD4 T cells (see Section 8-10, p. XX). On interacting with antigen on the macrophage surface, T_{H1} cells secrete IFN-γ, which acts on the macrophage to strengthen its activation, and thus leads to the destruction of the intracellular bacteria (Figure 13.18, right panel). IL-12
also acts on cytotoxic T cells, inducing them to also produce IFN-γ and maintain both macrophage activation (see Section 8-16, p. XX) and an environment favoring the differentiation of TH1 cells. So, again, in the absence of a functional IL-12 receptor this mutual activation of macrophage and effector T cells cannot get started. Unable to make an effective innate or adaptive immune response to intracellular bacteria, people lacking the IL-12 receptor suffer persistent infections with common strains of mycobacteria. When undiagnosed immunodeficient individuals, lacking either the IL-12 receptor or IFN-γ receptor, were vaccinated against tuberculosis with the Calmette–Guérin vaccine strain of live Mycobacterium bovis, the vaccine caused disseminated infection and disease. Even this weak and normally nonpathogenic strain of mycobacterium could not be controlled without functional IL-12 and IFN-γ receptors.

As we saw in Section 13-4, many healthy people maintain a persistent EBV infection of B cells, which is held in check by NK cells and EBV-specific T cells. For patients with a defect in the X-linked gene called SH2D1A, this balance is never achieved and childhood EBV infections can be severe and even progress to lymphoma. This immunodeficiency, which affects mostly boys, is called X-linked lymphoproliferative syndrome because it involves an ineffective proliferation of NK cells and T cells. 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 not yet clear.

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 pathogens. 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. The virus now known to cause AIDS, the human immunodeficiency virus (HIV), was first isolated in 1983. 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 relatively new disease to the medical profession and also to the human species. The earliest evidence for HIV comes from samples of 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, a type of monkey. In neither of these species, and 39 other species of African monkey, 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 (Figure is1.28/13.19). The World Health Organization currently estimates that some 35 million people are infected with HIV (Figure i11.19/13.20). 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—2.3 million new infections in 2012—and tens of millions of people will die from AIDS in the years to come.

Figure is1.28/13.19 HIV infection is widespread on all the inhabited continents. In 2012 there were about 35.3 million adults and children living with HIV/AIDS (black numbers) worldwide, including about 2.3 million new cases of HIV infection (blue numbers). About 1.6 million people died from AIDS in that year (red numbers). Data from Global Report: UNAIDS Report on the Global AIDS Epidemic 2013 (UNAIDS; 2013).

Figure is11.19/13.20 The number of people living with HIV infection worldwide is still increasing, but seems to be reaching a maximum.
**Figure is11.20/13.21** The virion of human immunodeficiency virus (HIV). The upper panel is an electron micrograph showing three virions. The lower panel is a diagram of a single virion. gp120 and gp41 are virally encoded envelope glycoproteins of molecular masses 120 kDa and 41 kDa, respectively. Photograph courtesy of Hans Gelderblom.

13-17 HIV is a retrovirus that causes a slowly progressing chronic 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 virus-encoded envelope proteins (Figure is11.20/13.21). HIV is an example of a retrovirus, so named because these viruses use an RNA genome to direct the synthesis of a DNA intermediate, a procedure backward or ‘retro’ from that used by most biological entities. 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 listed in Figure is11.21/13.22. 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. In the course of infecting a human cell, HIV recruits 273 human proteins to serve its own purpose. Many of these proteins are used to prevent the human system from terminating the HIV infection.

Around 8% of the human genome is made up of retrovirus-like sequences. These sequences are called endogenous retroviruses because they have become permanently integrated into the human genome and because transcripts from endogenous retroviruses are found in all human tissues. In contrast, HIV is an exogenous retrovirus. Like the herpesviruses (see Section 13-4), the retroviruses have a long history of exploiting humans and other primate species, and during that time they have evolved numerous and ingenious mechanisms for evading human immune systems. It is thus possible that the endogenous retroviruses, which are now part of self, actually contribute to the difficulties in halting infection by the exogenous and pathogenic retrovirus HIV.

In almost all people, HIV produces an infection that cannot be successfully terminated by the immune system and which continues throughout life. 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. From 1983 until 1997 there was no effective treatment for HIV, and during that period much was learnt of the natural course of HIV infection and the immune response that it provokes. At the present time, HIV is the most extensively studied human infectious disease.

13-18 HIV infects CD4 T cells, macrophages, and dendritic cells

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. Most infections take place across a mucosal surface.

Macrophages, dendritic cells, and CD4 T cells are vulnerable to HIV infection because they express CD4, which the virus exploits as its cellular receptor. Chimpanzees, our closest living relatives, are resistant to HIV infection because of a small difference in the structure of their CD4 glycoprotein compared with ours. CD4 attaches to the spikes on the outer surface of the virus. These spikes are trimers of the envelope glycoprotein, which is a heterodimer of the gp41 and gp120 transmembrane glycoproteins. The two proteins are made as a single polypeptide, which is then cleaved by a host protease to give gp41 and gp120. The gp120 component of the spike binds tightly to human CD4, enabling virions to attach to CD4-expressing cells. Before the virus can enter the cell, gp120 must also bind a co-receptor in the host-cell membrane. Once the co-receptor is bound, the gp41 component of the envelope glycoprotein fuses the viral membrane with the host-cell membrane, allowing the viral genome and associated proteins to enter the cytoplasm of the now infected cell.

The viral co-receptors are normal human chemokine receptors that HIV subverts to further its own propagation. There are different variants of HIV, and the cell types that they infect depend largely upon which co-receptor they bind. The HIV variants that spread infection from one person to another bind to the co-receptor CCR5 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 co-receptor CXCR4 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 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 infected CD4 T cell to be activated. Activation induces the synthesis of the transcription factor NFkB, 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 is11.21/13.22).

13-19 In the twentieth century, most HIV-infected people progressed in time to get AIDS

Immediately after becoming infected with HIV, a person can either be asymptomatic or experience a transient ‘flu-like’ illness. In either case, the virus becomes abundant in the blood, while the number of circulating CD4 T cells
declines markedly (Figure 11.23/13.24). 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.
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 obtained during the time before effective treatments were available, show that most HIV-infected individuals are destined to progress to AIDS in the absence of effective medical intervention (Figure is11.24/13.25). 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.

13-20 Genetic deficiency of the CCR5 co-receptor for HIV confers resistance to infection

Some people who are heavily exposed to HIV never become infected. Similarly, 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. 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

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**Figure is11.23/13.24** 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. The disease then enters the symptomatic phase. When CD4 T-cell counts fall below 200 cells/µl, the patient is said to have AIDS.

**Figure is11.24/13.25** Once an HIV infection is established, it usually leads to AIDS. Hemophilia is an inherited disease in which the blood clots poorly; any wound can cause excessive bleeding and be potentially fatal. Hemophilia is treated by regular intravenous infusions of clotting factors purified from the blood of healthy donors. In the early 1980s, when the AIDS epidemic was under way but its cause was still unknown, some seemingly healthy blood donors were infected with HIV. The virus from their donations contaminated several batches of clotting factor, and many hemophiliacs became infected with HIV. The graph shows the progression to AIDS of HIV-infected and uninfected hemophiliacs born before or after 1943. HIV infection almost inevitably leads to AIDS, as seen from the linear plots, which do not taper off. The rate of progression to AIDS increases with the patients’ age. [Q1] Perhaps explain the difference between the red and yellow lines?
frame, premature termination of translation, and a nonfunctional protein. This deletion variant, called CCR5-Δ32, is present only in Caucasian populations, in which 10% of the population is heterozygous for the variant and 1% is homozygous. Only people who are homozygous for CCR5-Δ32 resist HIV infection.

The importance of functional CCR5 for maintaining an HIV infection was dramatically demonstrated by a case reported in 2009 of an HIV-infected person who developed acute myelogenous leukemia and needed a hematopoietic stem-cell transplant. For this transplant the unrelated HLA-matched donor was also chosen to be homozygous for CCR5-Δ32. In this transplant, the entire immune system of the patient was repopulated with hematopoietic cells that lacked the CCR5 co-receptor. When this was achieved, the HIV in this patient ran out of cells to infect and so the virus died out. As well as driving the leukemia into remission, the stem-cell transplant cured the patient’s HIV infection. Up to now, this is the only example of someone being cured of an HIV infection.

CCR5 is a receptor for the chemokines CCL3 (MIP-1α), CCL4 (MIP-1β), and CCL5 (RANTES). That almost everyone has a functional CCR5 gene argues for this receptor having made useful contributions to human immunity and survival. However, for individuals exposed to HIV, the 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 mild form of immunodeficiency, like some of those 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 a component of the immune system that was useful in fighting past wars with 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 variant was at high frequency in Caucasians before the HIV epidemic argues for this mutation having enhanced human survival in Europe during previous epidemics of infectious disease. Both plague and smallpox have been advanced as the agent that first drove the CCR5 deletion to high frequency. In the current age, HIV will probably have its strongest selective effect in sub-Saharan Africa, where some 25 million people are infected with HIV and where HIV-infected individuals constitute more than 30% of the population of several countries. Because treatment is rarely available for African patients, mortality rates remain high and survival will be greatly enhanced by any genetic variants that prevent infection or reduce the severity of disease.

13-21 HLA and KIR polymorphisms influence the progression to AIDS

A feature of the early years of the AIDS epidemic was that a majority of those infected and diagnosed were young, well-educated people living in affluent countries. Thousands of these individuals were recruited into longitudinal studies that have correlated the clinical progression of HIV infection with genetic polymorphisms of the immune system. In addition to showing that HLA homozygosity speeds the progression to AIDS (see Figure 5.39, p. XX), these studies showed that the HLA-B*27 and HLA-B*57 allotypes slow the progression. Contributing to this effect, the HIV peptides presented by these HLA-B*27 and HLA-B*57 allotypes stimulate stronger CD8 T-cell responses to HIV-infected cells than peptides presented by other HLA-B allotypes.
Another property that the HLA-B*27 and HLA-B*57 allotypes have in common is the Bw4 epitope, the ligand for the NK-cell receptor KIR3DL1/S1. Combinations of Bw4+ HLA-B allotypes and KIR3DL1/S1 allotypes are associated with different rates of progression to AIDS. The most favorable combinations are HLA-B*57 with high-expressing allotypes of KIR3DL1, and HLA-B*27 with low-expressing KIR3DL1 allotypes (Figure is11.25/13.26). These correlations suggest that the type of NK-cell response at the start of an HIV infection affects the relative success of the subsequent adaptive response.

About 1 in 300 of HIV-infected people are able to control the infection to the point at which HIV RNA is undetectable in their blood using the standard clinical assay. These people, who suppress the infection and maintain their health for decades, are called elite controllers. In addition, around 7% of people infected with HIV maintain a low viremia with 2000 copies or fewer of viral RNA per milliliter of blood. These people also maintain health and are called viremic controllers. Whole-genome comparison of the controllers with the progressors, who progress to AIDS, showed that the most significant factor is the HLA-B type. Of the controllers, 67% had HLA-B*13, -B*27, -B*57, or -B*58, compared with 37% of the progressors.

13-22 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\textsubscript{H}1 and T\textsubscript{H}2 cells, B cells that make neutralizing antibodies, and CD8 cytotoxic T cells that kill virus-infected cells (Figure is11.26/13.27). However, the virus is rarely eliminated. One reason that keeps the virus ahead of the human immune response is its high rate of mutation throughout the course of an infection.

HIV and other retroviruses have high mutation rates because their reverse transcriptases lack proofreading mechanisms like those of 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, which coexist within the infected person.

The presence of variant viruses increases the difficulty of terminating the infection by immune mechanisms. A successful neutralizing antibody will select for the survival of viral variants that lack 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 an effective vaccine. It also limits the effectiveness of antiviral drugs. Good targets for drugs are the reverse transcriptase, which is essential for the synthesis of provirus, and the viral protease that cleaves large viral polyproteins to give the individual enzymes and proteins. Inhibitors of reverse transcriptase and protease have been found, and these drugs prevent the further infection of healthy cells. Unfortunately, mutation inevitably produces HIV variants with proteins resistant to the action of the drugs (Figure 11.27/13.28). One situation in which a relatively short course of drug treatment has long-term benefit is pregnancy. Treating HIV-infected pregnant women with zidovudine, an inhibitor of the viral reverse transcriptase, can prevent HIV transmission to their children in utero and at birth.

Because HIV so easily escapes from the effects of any single drug, several antiviral drugs are now used together in what is called combination therapy. 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), was introduced in 1997 and has proved effective at reducing the abundance of virus (the viral load) (Figure 11.28/13.29) and retarding disease progression. The drugs do not stop virus production by cells that have already been infected, but they 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 (Figure 11.29/13.30). At this point no naive or effector 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, because the virus quickly re-emerges in patients who stop taking their medicine.

HAART has been a life-changing therapy for HIV patients in the industrialized countries where it is available. At present, a 20-year-old who becomes infected with HIV and is given HAART will not die from AIDS and can expect to live for 50 more years. However, HAART does not restore HIV-infected individuals completely to health because they have increased risk of bone, cardiovascular, kidney, liver, and neurological diseases. In the context of HAART, HIV infection becomes a chronic inflammatory disease that originates in the gut and spreads to other tissues and organs. A variety of anti-inflammatory drugs are under test for their capacity to prevent and alleviate this new form of HIV-mediated disease.

**13-23 Clinical latency is a period of active infection and renewal of CD4 T cells**

The administration of antiviral drugs to HIV-infected individuals uncovered the active nature of the infection during the period of clinical latency. Within 2
days of starting a course of drugs, the amount of virus in the blood decreases markedly. At the same time, the number of CD4 T cells increases substantially (see Figure 13.28). This shows two things: 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 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.

**11-24 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. With time, however, a steady decline in the number of CD4 T cells is evident, showing how the virus gradually wins this war of attrition. Eventually, CD4 T cell numbers become so low that immune responses to all foreign antigens are compromised and HIV-infected people become exceedingly susceptible to other infections—at this stage they have progressed to AIDS. Because CD4 T cells are central to every aspect of adaptive immunity, the vulnerability of AIDS patients to infection resembles that of children with inherited SCID.

The infections that most frequently affect patients with AIDS are caused by commensal microorganisms that live either in or on the body and are actively controlled by healthy people. When they infect, such agents are called opportunistic pathogens, and the infections they cause are known as opportunistic
infections (Figure is11.30/13.31). There is a rough hierarchy in the times at which particular opportunistic infections occur in AIDS, which correlates with the order in which the different types of immunity collapse. Immunity mediated by CD4 T_H1 cells is generally lost before either the antibody or cytotoxic CD8 T-cell response.

The oral and respiratory tracts are soft tissues loaded with microorganisms, and in many patients with AIDS they are the sites 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 herpesviruses that are no longer controlled by CD8 T cells. Such diseases include shingles caused by varicella-zoster, B-cell lymphoma caused by EBV, and an endothelial tumor called Kaposi’s sarcoma, caused by the HHV8 herpesvirus. *Pneumocystis jirovecii*, a common environmental fungus that rarely troubles healthy people, is frequently the cause of pneumonia and death for AIDS patients. In the later stages of AIDS, reactivation of CMV 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 provide only temporary respite and also have their own deleterious effects. Eventually, the tissue damage that results from the combined effect of HIV infection, opportunistic infections, and medical intervention causes death.

A minority of HIV-infected individuals make antibodies that neutralize many strains of HIV

Although enormous resources have been invested in seeking a vaccine for HIV, the results have been generally disappointing. One encouraging result from a clinical trial reported in 2009 was that antibody recognizing the gp120 component of the envelope protein could provide protection against HIV infection. A second encouraging observation is that 1 in 500 HIV-infected individuals make small amounts of antibodies that bind and neutralize a broad range of HIV-1 strains. These individuals are called elite neutralizers, and the antibodies they make are termed broadly neutralizing antibodies. Such antibodies are not made during the primary response to HIV infection, but emerge only when a person has been infected for 2 years or longer, after their immune system has been stimulated by several HIV strains that successively emerge from the selection exerted by strain-specific antibodies. In following up these observations, techniques were developed for isolating B cells that make broadly neutralizing antibodies from the blood of elite neutralizers. Then by cloning and expressing cDNA encoding the heavy and light chains of these antibodies it became possible to make large quantities of many broadly neutralizing antibodies and define their specificity, structure, and common properties.

Most broadly neutralizing antibodies recognize one of four epitopes of the envelope glycoprotein of HIV-1 (Figure n13.102/13.32). These are all highly conserved regions that have biological importance for the virus. For example, one of the epitopes is the site on gp120 that binds CD4. A distinguishing property of broadly neutralizing antibodies is that their variable regions have many more somatic mutations than other antibodies. The heavy-chain variable regions of high-affinity antibodies typically have 10–20 mutations, whereas
40–80 mutations are present in the heavy-chain variable regions of broadly neutralizing antibodies. Such numbers indicate that the B cells making broadly neutralizing antibodies have over time been subject to several separate rounds of antigen-mediated somatic mutation (see Section 9-7, p. XX). Unlike other antibodies, the broadly neutralizing antibodies acquire mutations in framework regions as well as in the CDR loops, and these substitutions contribute to the neutralizing function. A further difference is that variable regions of the broadly neutralizing antibodies acquire insertions and deletions, leading to some of the antibody heavy chains having unusually long CDR loops. These loops enable the antibody to penetrate the glycans that shield the viral spikes and gain access to bind to gp120. A feature of some broadly neutralizing antibodies is that they react with a variety of structurally unrelated antigenic molecules, and are said to be polyreactive. It is suggested that polyreactivity increases the probability that the antibodies will bind with both their antigen-binding sites—one site binding to gp120, the other to another component of the virus or the infected human cell. This is a potential problem because there are only 15 spikes and 45 envelope proteins on the surface of the virus. One example of a polyreactive antibody binds to both CD4 and gp120.

Current research on broadly neutralizing antibodies is exploring two complementary clinical applications. The first is to design vaccines that will favor the production of these antibodies; the second is to infuse infected people, or people at risk of exposure to HIV, with the antibodies in a passive immunization. At the present time there is cautious optimism that successful application of broadly neutralizing antibodies will eventually bring the HIV epidemic under control.

Summary

The past 30 years has seen a worldwide epidemic of infectious disease caused by the human immunodeficiency virus (HIV), in which more than XXXX million people have died. HIV infects CD4 T cells, macrophages, and dendritic cells, and uses the CD4 glycoprotein as its receptor and the CCR5 chemokine receptor as its co-receptor. 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. This property facilitated the spread of infection, which is mainly by sexual transmission. Patients with AIDS succumb to a range of opportunistic infections and to a much lesser extent from virus-associated cancers.

Some people are resistant to infection by HIV because they lack the CCR5 co-receptor. Of the people infected with HIV, a small fraction control the virus and can maintain their health. Particular HLA-B and KIR alleles correlate with this capacity to control HIV. Until 1997, to be infected with HIV was a death sentence. In that year, highly active anti-retroviral therapy (HAART) was introduced, which involves a combination of drugs, each inhibiting an enzyme essential for viral replication. This highly successful therapy prevents progression to AIDS and allows HIV-infected individuals to live a normal lifespan.

No person who becomes infected with HIV ever gets rid of the virus. HIV subverts the human genome to serve its own ends and rapidly mutates its own genome so that the immune response made by the human host can be easily evaded. These viral tactics have thwarted a 30-year quest for a vaccine against HIV. After several years of infection with HIV, some people make small amounts of antibodies that have the capacity to neutralize a broad range of HIV strains. Such antibodies give hope for new strategies for vaccination strategies and passive immunization.
Summary to Chapter 13

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 in which 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 cytomegalovirus 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.

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 immunodeficiencies are very rare, which is 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 been exploiting the human species for less than a century, but it already had an arsenal of effective adaptations that were acquired during its previous 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 is now at pandemic proportions within the human population. Only a minority of people are resistant to HIV, either because their cells cannot be infected or because they have genetic variants of HLA, KIR, and other immune-system genes that allow them to control the infection and prevent the progress to AIDS. Combination therapy with anti-retroviral drugs prevents the progression to AIDS and allows HIV-infected people to lead long lives. No effective vaccine for HIV has been made, but new strategies for active and passive immunization, involving broadly neutralizing antibodies, are currently under intensive investigation.