- *T-cell defects* lead to susceptibility to intracellular pathogens, particularly viruses and some parasites. Inherited mutations that impair the generation of T_H1 cells (such as mutations in IL-12 or IFN-γ receptors, or the transcription factor STAT1) are associated with atypical mycobacterial infections. By contrast, defects that impair the generation of T_H17 cells (such as mutations in STAT3) are associated with chronic mucocutaneous candidiasis.

Even more common are acquired immunodeficiencies. Worldwide, the most common cause of immunodeficiency is infection with HIV, the cause of AIDS. While most organisms that infect people with AIDS were common pathogens before the era of HIV, others were uncommon (cryptococcus, pneumocystis), and one, Kaposi sarcoma herpesvirus (KSHV), also called human herpesvirus-8 (HHV-8), was discovered as a result of research in AIDS patients.

Other causes of acquired immunodeficiencies include infiltrative processes that suppress bone marrow function (such as leukemia), immunosuppressive drugs used to treat patients with autoimmune diseases and organ transplant recipients, as well as drugs used to treat cancer, and hematopoietic stem cell transplantation. Therapy to prevent rejection of organ transplants leads to severe immunosuppression, making transplant recipients very susceptible to infectious diseases. Patients receiving hematopoietic stem cell transplants have profound defects in innate and adaptive immunity during the time that it takes for the donated stem cells to engraft, and become susceptible to infection with almost any organism, including opportunistic organisms that seldom cause disease in healthy people (e.g., *Aspergillus* species and *Pseudomonas* species).

Decline of immune responses can result in reactivation of latent infection and severe pathologic manifestations. Such reactivation is seen in latent viral infections (e.g., herpesviruses) and some bacterial infections (e.g., tuberculosis). At least some of the increased incidence of certain infections in the elderly may be due to age-related declines in immune function.

Diseases of organ systems other than the immune system also can make patients susceptible to diseases due to specific microorganisms. People with cystic fibrosis commonly get respiratory infections with *P. aeruginosa, S. aureus*, and *Burkholdaria cepacia*. Lack of splenic function in people with sickle cell disease makes them susceptible to infection with encapsulated bacteria such as *S. pneumoniae*, which are normally opsonized and phagocytosed by splenic macrophages. Burns destroy skin, removing this barrier to microbes and allowing infection with pathogens such as *P. aeruginosa*. Finally, malnutrition can impair immune defenses.

Host Damage

Infectious agents establish infection and damage tissues by three mechanisms:

- They can contact or enter host cells and cause cell death directly, or cause changes in cellular metabolism and proliferation that can eventually lead to transformation.
- They may release toxins that kill cells at a distance, release enzymes that degrade tissue components, or damage blood vessels and cause ischemic necrosis.
- They can induce host immune responses that, though directed against the invader, cause additional tissue damage. As already mentioned, the defensive responses of the host constitute a double-edged sword: They are necessary to overcome the infection but at the same time may directly contribute to tissue damage.

Here we describe some of the mechanisms whereby viruses and bacteria damage host tissues.

Mechanisms of Viral Injury

Viruses can directly damage host cells by entering them and replicating at the host's expense. The predilection for viruses to infect certain cells and not others is called *tropism* and may be determined by physical factors, surface proteins that are required for viral entry, and other factors that are required for viral replication. Each is discussed below briefly.

A major determinant of tissue tropism is the presence of viral receptors on host cells. Viruses have surface proteins that bind to particular proteins found on the surface of host cells. Many of these host cell proteins normally function as receptors for host factors. For example, HIV glycoprotein gp120 binds to CD4 on T cells and to the chemokine receptors CXCR4 (mainly on T cells) and CCR5 (mainly on macrophages) (Chapter 6), while Epstein-Barr virus binds to complement receptor 2 (also known as CR2 or CD21) on B cells. Other tropisms are explained by different kinds of cell-lineage specific factors. For example, JC virus infection, which causes leukoencephalopathy (Chapter 28), is restricted to oligodendroglial cells in the CNS; this is because the expression of JC viral genes needed for a productive infection requires host transcription factors that are only expressed in glial cells, and not in neurons or endothelial cells.

Physical barriers also can contribute to tissue tropism. For example, enteroviruses replicate in the intestine in part because they can resist inactivation by acids, bile, and digestive enzymes. Rhinoviruses infect host cells only within the upper respiratory tract because they replicate optimally at the lower temperatures found in sites exposed to the ambient atmosphere.

Once viruses are inside host cells, they can damage or kill the cells by a number of mechanisms (Fig. 8-3):

- *Direct cytopathic effects.* Some viruses kill cells by preventing synthesis of critical host macromolecules (e.g., host cell DNA, RNA, or proteins), or by producing degradative enzymes and toxic proteins. For example, poliovirus inactivates cap-binding protein, which is essential for translation of host cell mRNAs but leaves translation of poliovirus mRNAs unaffected. Herpes simplex virus produces proteins that inhibit the synthesis of cellular DNA and mRNA, as well as other proteins that degrade host DNA. Viruses can induce cell death by a variety of means, including by activating so-called death receptors (members of the TNF receptor family) on the plasma membrane and by triggering the intracellular apoptotic machinery. During the course of productive viral infection, large amounts of viral proteins are synthesized in infected cells, including unfolded or