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CHAPTER 8

General Pathology of Infectious Diseases

CHAPTER CONTENTS

This chapter reviews the general principles of the pathogenesis of infectious disease and describes the characteristic histopathologic changes for different disease categories. Infections that involve specific organs are discussed in other chapters of this book.

GENERAL PRINCIPLES OF MICROBIAL PATHOGENESIS

Infectious diseases remain an important health problem in the United States and worldwide despite the availability and use of effective vaccines and antibiotics. In the United States, 2 of the top 10 leading causes of death are attributable to infection (pneumonia and septicemia). Infectious diseases are particularly important causes of death among the elderly, people with the acquired immunodeficiency syndrome (AIDS), persons with chronic diseases, and patients receiving immunosuppressive drugs. In developing countries, unsanitary living conditions and malnutrition contribute to a massive burden of infectious diseases that kills more than 10 million people each year. Tragically, the most common victims are children with respiratory and diarrheal infections.

Categories of Infectious Agents

Infectious agents belong to a wide range of classes and vary greatly in size, ranging from prion protein aggregates of under 20 nm to 10-m tapeworms (Table 8–1).

Prions

Prions are composed of abnormal forms of a host protein termed *prion protein* (PrP). These agents cause transmissible spongiform encephalopathies, including kuru (associated with human cannibalism), Creutzfeldt-Jakob disease (CJD), bovine spongiform encephalopathy (BSE) (better known as "mad cow disease"), and variant Creutzfeldt-Jakob disease (vCJD) (probably transmitted to humans through consumption of meat from BSE-infected cattle). PrP is found normally in neurons. Diseases occur when the PrP undergoes a conformational change that confers resistance to proteases. The protease-resistant PrP promotes conversion of the normal protease-sensitive PrP to the abnormal form, explaining the infectious nature of these diseases. Accumulation of abnormal PrP leads to neuronal damage and distinctive spongiform pathologic changes in the brain. Spontaneous and inherited mutations in PrP that make it resistant to proteases have been observed in the sporadic and familial forms of CJD, respectively. CJD can be transmitted from person to person iatrogenically, by surgery, organ transplantation, or blood transfusion. These diseases are discussed in detail in Chapter 22.

Viruses

Viruses are obligate intracellular parasites that depend on the host cell's metabolic machinery for their replication. They consist of a nucleic acid genome surrounded by a protein coat (called a capsid) that is sometimes encased in a lipid membrane. Viruses are classified by their nucleic acid genome (DNA or RNA but not both), the shape of the capsid (icosahedral or helical), the presence or absence of

Table 8–1 Classes of Human Pathogens

Taxonomic Category	Size	Propagation Site(s)	Example(s)	Disease(s)
Prions	<20 nm	Intracellular	Prion protein	Creutzfeldt-Jacob disease
Viruses	20–300 nm	Obligate intracellular	Poliovirus	Poliomyelitis
Bacteria	0.2–15 μm	Obligate intracellular Extracellular Facultative intracellular	*Chlamydia trachomatis* *Streptococcus pneumoniae* *Mycobacterium tuberculosis*	Trachoma, urethritis Pneumonia Tuberculosis
Fungi	2–200 μm	Extracellular Facultative intracellular	*Candida albicans* *Histoplasma capsulatum*	Thrush Histoplasmosis
Protozoa	1–50 μm	Extracellular Facultative intracellular Obligate intracellular	*Trypanosoma gambiense* *Trypanosoma cruzi* *Leishmania donovani*	Sleeping sickness Chagas disease Kala-azar
Helminths	3 mm–10 m	Extracellular Intracellular	*Wuchereria bancrofti* *Trichinella spiralis*	Filariasis Trichinosis

a lipid envelope, their mode of replication, the preferred cell type for replication (called tropism), or the type of pathology they cause (Table 8–2). Some viral components and particles aggregate within infected cells and form characteristic inclusion bodies, which may be seen with the light microscope and are useful for diagnosis (Fig. 8–1). For example, cytomegalovirus (CMV)-infected cells are enlarged and show a large eosinophilic nuclear inclusion and smaller basophilic cytoplasmic inclusions; herpesviruses form a large nuclear inclusion surrounded by a clear halo; and both smallpox and rabies viruses form characteristic cytoplasmic inclusions. However, many viruses (e.g., poliovirus) do not produce inclusions.

Accounting for a large share of human infections, viruses can cause illnesses in several ways. Many viruses cause transient illnesses (e.g., colds, influenza). Other viruses are not eliminated from the body and persist within cells of the host for years, either continuing to multiply (e.g., chronic infection with hepatitis B virus [HBV]) or surviving in some nonreplicating form (termed *latent infection*) with the potential to be reactivated later. For example, herpes zoster virus, the cause of chickenpox, can enter dorsal root ganglia and establish latency there and later be periodically activated to cause shingles, a painful skin condition. Some viruses are involved in transformation of a host cell into a benign or malignant tumor (e.g., human papillomavirus [HPV]-induced benign warts and cervical carcinoma). Different species of viruses can produce the same clinical picture (e.g., upper respiratory infection); conversely, a single virus can cause different clinical manifestations depending on host age or immune status (e.g., CMV).

Table 8–2 Selected Human Viral Diseases and Their Pathogens

Organ System	Pathogen	Disease(s)
Respiratory	Adenovirus	Upper and lower respiratory tract infections, conjunctivitis
	Rhinovirus	Upper respiratory tract infection
	Influenza viruses A, B	Influenza
	Respiratory syncytial virus	Bronchiolitis, pneumonia
Digestive	Mumps virus	Mumps, pancreatitis, orchitis
	Rotavirus	Childhood gastroenteritis
	Norovirus	Gastroenteritis
	Hepatitis A virus	Acute viral hepatitis
	Hepatitis B virus	Acute or chronic hepatitis
	Hepatitis D virus	*With hepatitis B virus infection*: acute or chronic hepatitis
	Hepatitis C virus	Acute or chronic hepatitis
	Hepatitis E virus	Acute viral hepatitis
Systemic		
With skin eruptions	Measles virus	Measles (rubeola)
	Rubella virus	German measles (rubella)
	Varicella-zoster virus	Chickenpox, shingles
	Herpes simplex virus type 1	Oral herpes ("cold sore")
	Herpes simplex virus type 2	Genital herpes
With hematopoietic disorders	Cytomegalovirus	Cytomegalic inclusion disease
	Epstein-Barr virus	Infectious mononucleosis
	HIV-1 and HIV-2	AIDS
Skin/genital warts	Papillomavirus	Condyloma; cervical carcinoma
Central nervous system	Poliovirus	Poliomyelitis
	JC virus	Progressive multifocal leukoencephalopathy (opportunistic)

AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

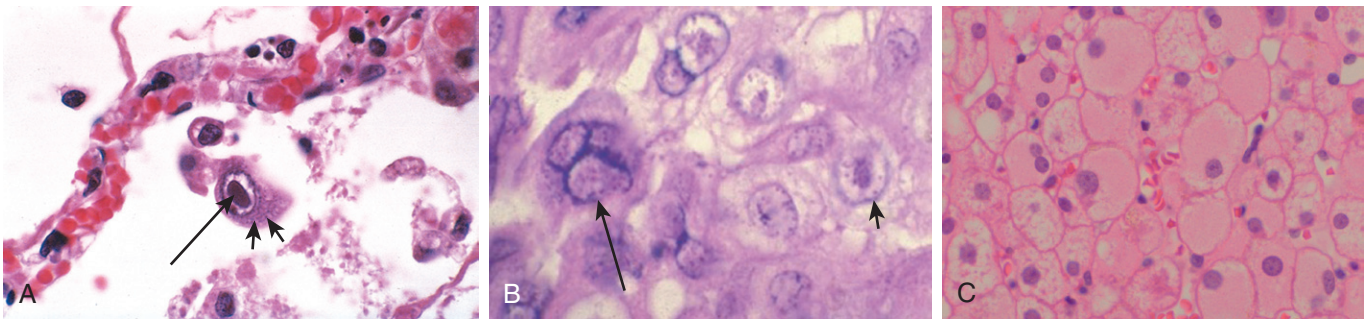

Figure 8–1 Examples of viral inclusions. **A,** Cytomegalovirus infection in the lung. Infected cells show distinct nuclear (*long arrow*) and ill-defined cytoplasmic (*short arrows*) inclusions. **B,** Varicella-zoster virus infection in the skin. Herpes simplex virus and varicella-zoster virus both cause characteristic cytopathologic changes, including fusion of epithelial cells, which produces multinucleate cells with molding of nuclei to one another (*long arrow*), and eosinophilic haloed nuclear inclusions (*short arrow*). **C,** Hepatitis B viral infection in liver. In chronic infections, infected hepatocytes show diffuse granular ("ground-glass") cytoplasm, reflecting accumulated hepatitis B surface antigen (HBsAg).

Bacteria

Bacterial infections are common causes of disease (Table 8–3). Bacteria are prokaryotes, meaning that they have a cell membrane but lack membrane-bound nuclei and other membrane-enclosed organelles. Most bacteria are bound by a cell wall consisting of peptidoglycan, a polymer of long sugar chains linked by peptide bridges surrounding the cell membrane. There are two common forms of cell wall structure: a thick wall that retains crystal-violet stain (gram-positive bacteria) and a thin cell wall surrounded by an outer membrane (gram-negative bacteria) (Fig. 8–2). Bacteria are classified by Gram staining (positive or negative), shape (spherical ones are cocci; rod-shaped ones are bacilli) (Fig. 8–3), and need for oxygen (aerobic or anaerobic). Motile bacteria have flagella, which are long helical filaments extending from the cell surface that rotate and move the bacteria. Some bacteria possess pili, another kind of surface projection that can attach bacteria to host cells or extracellular matrix. Bacteria synthesize their own DNA, RNA, and proteins, but they depend on the host for favorable growth conditions. Many bacteria remain extracellular when they grow in the host, while others survive and replicate either outside or inside of host cells (*facultative intracellular* bacteria) and some grow only inside host cells (*obligate intracellular* bacteria).

Normal healthy people can be colonized by as many as 10^{12} bacteria on the skin, 10^{10} bacteria in the mouth, and 10^{14} bacteria in the gastrointestinal tract. Bacteria colonizing the skin include *Staphylococcus epidermidis* and *Propionibacterium acnes,* the cause of acne. Aerobic and anaerobic bacteria in the mouth, particularly *Streptococcus mutans*, contribute to dental plaque, a major cause of tooth decay. There are over 3,000 taxa of bacteria in the normal intestinal flora of an individual human, but only a small subset, mainly anaerobes, account for the great majority.

Chlamydia and *Rickettsia* are obligate intracellular bacteria which replicate inside membrane-bound vacuoles in epithelial and endothelial cells, respectively. These bacteria get most or all of their energy source, ATP, from the host cell. *Chlamydia trachomatis* is the most frequent infectious cause of female sterility (by scarring and narrowing of the fallopian tubes) and blindness (by chronic inflammation of the conjunctiva that eventually causes scarring and opacification of the cornea). Rickettsiae injure the endothelial cells in which they grow, causing a hemorrhagic vasculitis, often visible as a rash, but they also may injure the central nervous system (CNS), with potentially fatal outcome, as in Rocky Mountain spotted fever and epidemic typhus. Rickettsiae are transmitted by arthropod vectors, including

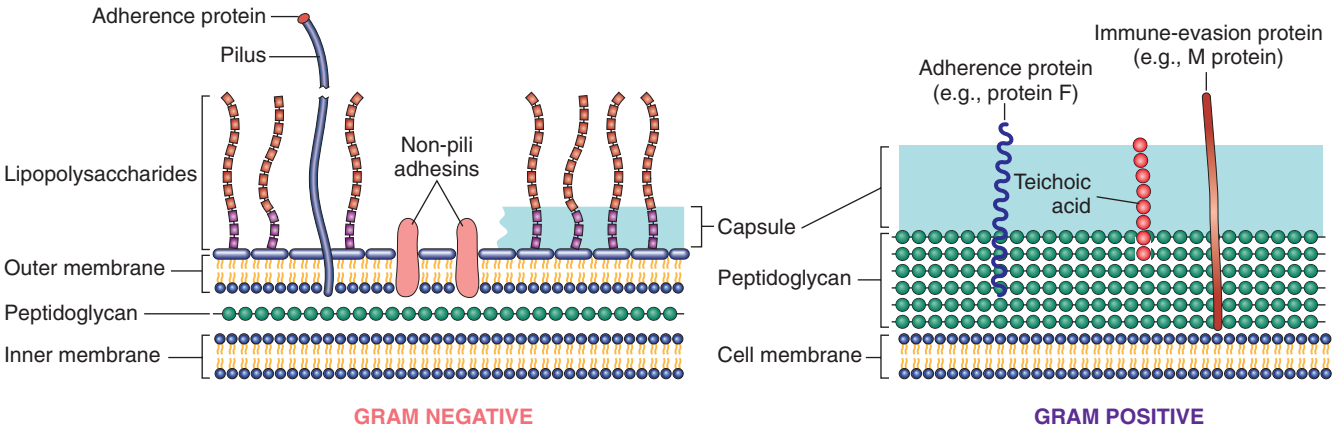

Figure 8–2 Molecules on the surface of gram-negative and gram-positive bacteria involved in the pathogenesis of infection.

Table 8–3 Selected Human Bacterial Diseases and Their Pathogens

Clinical/Microbiologic Category	Species	Frequent Disease Presentation(s)
Infections by pyogenic cocci	*Staphylococcus aureus, Staphylococcus epidermidis*	Abscess, cellulitis, pneumonia, sepsis
	Streptococcus pyogenes	Pharyngitis, erysipelas, scarlet fever
	Streptococcus pneumoniae (pneumococcus)	Lobar pneumonia, meningitis
	Neisseria meningitidis (meningococcus)	Meningitis
	Neisseria gonorrhoeae (gonococcus)	Gonorrhea
Gram-negative infections	*Escherichia coli,* Klebsiella pneumoniae**	Urinary tract infection, wound infection, abscess, pneumonia, sepsis, shock, endocarditis
	*Enterobacter (Aerobacter) aerogenes**	
	Proteus spp. (*Proteus mirabilis, Proteus morgagni*)*	
	Serratia marcescens, Pseudomonas* spp. (*Pseudomonas aeruginosa*),* *Bacteroides* spp. (*Bacteroides fragilis*)	
	Legionella spp. (*Legionella pneumophila*)	Legionnaires disease
Contagious childhood bacterial diseases	*Haemophilus influenzae*	Meningitis, upper and lower respiratory tract infections
	Bordetella pertussis	Whooping cough
	Corynebacterium diphtheriae	Diphtheria
Enteric infections	Enteropathogenic *E. coli, Shigella* spp., *Vibrio cholerae*	Invasive or noninvasive gastroenterocolitis
	Campylobacter jejuni, Campylobacter coli	
	Yersinia enterocolitica	
	Salmonella spp.	
	Salmonella typhi	Typhoid fever
Clostridial infections	*Clostridium tetani*	Tetanus (lockjaw)
	Clostridium botulinum	Botulism (paralytic food poisoning)
	Clostridium perfringens, Clostridium septicum	Gas gangrene, necrotizing cellulitis
	*Clostridium difficile**	Pseudomembranous colitis
Zoonotic bacterial infections	*Bacillus anthracis*	Anthrax
	Yersinia pestis	Bubonic plague
	Francisella tularensis	Tularemia
	Brucella melitensis, Brucella suis, Brucella abortus	Brucellosis (undulant fever)
	Borrelia recurrentis	Relapsing fever
	Borrelia burgdorferi	Lyme disease
Treponemal infections	*Treponema pallidum*	Syphilis
Mycobacterial infections	*Mycobacterium tuberculosis, M. bovis*	Tuberculosis
	Mycobacterium leprae	Leprosy
	Mycobacterium kansasii, Mycobacterium avium complex**	Atypical mycobacterial infections
Actinomycetal infections	*Nocardia asteroides**	Nocardiosis
	Actinomyces israelii	Actinomycosis

*Important opportunistic infections.

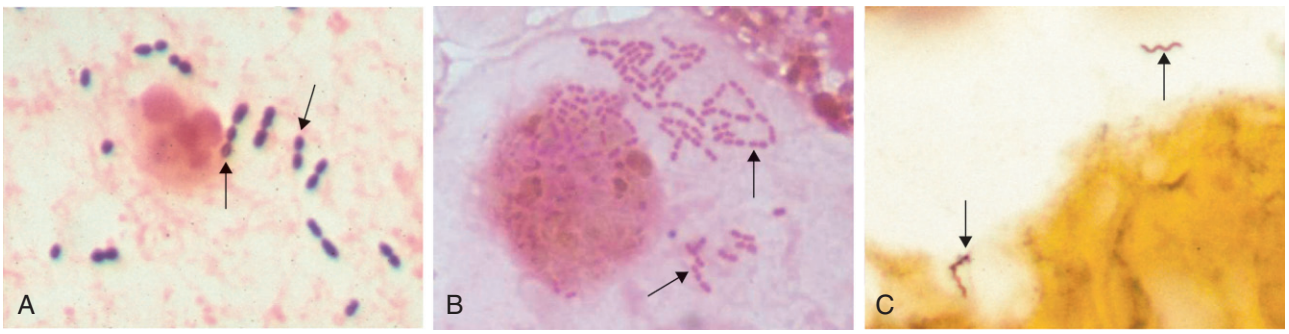

Figure 8–3 The variety of bacterial morphology. The bacteria are indicated by *arrows*. **A,** Gram stain preparation of sputum from a patient with pneumonia. Gram-positive, elongated cocci in pairs and short chains (*Streptococcus pneumoniae*) and a neutrophil are evident. **B,** Gram stain preparation of a bronchoalveolar lavage specimen showing gram-negative intracellular rods typical of members of Enterobacteriaceae such as *Klebsiella pneumoniae* or *Escherichia coli*. **C,** Silver stain preparation of brain tissue from a patient with Lyme disease meningoencephalitis. Two helical spirochetes (*Borrelia burgdorferi*) are indicated by *arrows*. **A, B,** and **C** are at different magnifications.

(B, Courtesy of Dr. Karen Krisher, Clinical Microbiology Institute, Wilsonville, Oregon. A and C, Courtesy of Dr. Kenneth Van Horn, Focus Diagnostics, Cypress, California.)

lice (in epidemic typhus), ticks (in Rocky Mountain spotted fever and ehrlichiosis), and mites (in scrub typhus).

Mycoplasma and the related genus *Ureaplasma* are unique among extracellular bacterial pathogens in that they do not have a cell wall. These are the tiniest free-living organisms known (125 to 300 nm).

Normal Microbiome. The intestinal tract and skin normally are colonized by a large number and diversity of bacterial species. Until recently, little was known about these species because most normal flora cannot be cultured. New techniques of microbial identification and speciation relying on ribosomal RNA sequencing have revealed normal microbial flora to be remarkably complex. This veritable ecosystem of microbes and their genes and products that humans live with is called the *microbiome*. In the intestinal tract, the microbiota are responsible not only for absorption of digested foods but also for maintaining the integrity of the epithelium and the normal functioning of the intestinal immune system, and for competitively inhibiting invasion and colonization by potentially pathogenic microbes. Depletion of the microbiome or change in its composition has been implicated in inflammatory bowel disease, the development of allergies, and increased incidence of various systemic autoimmune diseases.

Fungi

Fungi are eukaryotes that possess thick, chitin-containing cell walls and ergosterol-containing cell membranes. Fungi can grow either as rounded yeast cells or as slender, filamentous hyphae. Hyphae may be septate (with cell walls separating individual cells) or aseptate, which is an important distinguishing characteristic in clinical material. Some of the most important pathogenic fungi exhibit thermal dimorphism; that is, they grow as hyphal forms at room temperature but as yeast forms at body temperature. Fungi may produce sexual spores or, more commonly, asexual spores called *conidia*. The latter are produced on specialized structures or fruiting bodies arising along the hyphal filament.

Fungi may cause superficial or deep infections.

- Superficial infections involve the skin, hair, and nails. Fungal species that cause superficial infections are called *dermatophytes.* Infection of the skin is called *tinea*; thus, *tinea pedis* is "athlete's foot" and *tinea capitis* is scalp ringworm. Certain fungi invade the subcutaneous tissue, causing abscesses or granulomas sometimes called mycetomas.
- Deep fungal infections can spread systemically and invade tissues, destroying vital organs in immunocompromised hosts, but usually resolve or remain latent in otherwise normal hosts.

Fungi are divided into endemic and opportunistic species.

- Endemic fungi are invasive species that are limited to particular geographic regions (e.g., *Coccidioides* in the southwestern United States, *Histoplasma* in the Ohio River Valley).
- By contrast, opportunistic fungi (e.g., *Candida, Aspergillus, Mucor, Cryptococcus*) are ubiquitous organisms that either colonize individuals or are encountered from environmental sources. In immunodeficient individuals, opportunistic fungi give rise to life-threatening invasive infections characterized by tissue necrosis, hemorrhage, and vascular occlusion, with little or no inflammatory response (Fig. 8–4). Patients with AIDS often are infected by the opportunistic fungus *Pneumocystis jiroveci* (previously called *Pneumocystis carinii*).

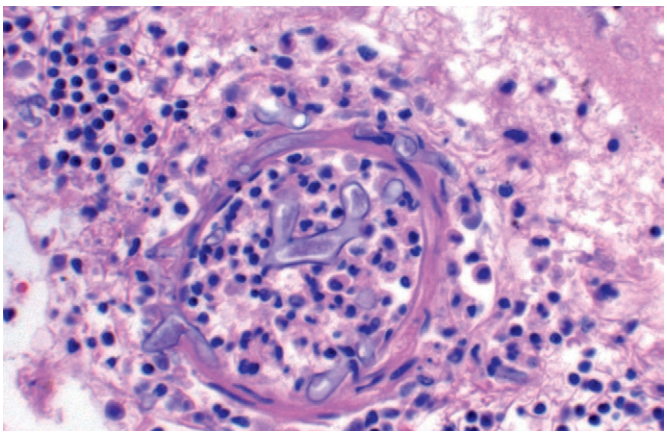

Figure 8–4 Meningeal blood vessels with angioinvasive *Mucor* species. Note the irregular width and near right-angle branching of the hyphae. *(Courtesy of Dr. Dan Milner, Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts.)*

Protozoa

Protozoa are single-celled eukaryotes that are major causes of disease and death in developing countries. Protozoa can replicate intracellularly within a variety of cells (e.g., *Plasmodium* in red cells, *Leishmania* in macrophages) or extracellularly in the urogenital system, intestine, or blood. *Trichomonas vaginalis* organisms are sexually transmitted flagellated protozoal parasites that often colonize the vagina and male urethra. The most prevalent intestinal protozoans, *Entamoeba histolytica* and *Giardia lamblia,* are ingested as nonmotile *cysts* in contaminated food or water and become motile *trophozoites* that attach to intestinal epithelial cells. Bloodborne protozoa (e.g., *Plasmodium*, *Trypanosoma*, *Leishmania*) are transmitted by insect vectors, in which they replicate before being passed to new human hosts. *Toxoplasma gondii* is acquired either through contact with oocyst-shedding kittens or by eating cyst-ridden, undercooked meat.

Helminths

Parasitic worms are highly differentiated multicellular organisms. Their life cycles are complex; most alternate between sexual reproduction in the definitive host and asexual multiplication in an intermediate host or vector. Thus, depending on the species, humans may harbor adult worms (e.g., *Ascaris lumbricoides*), immature stages (e.g., *Toxocara canis*), or asexual larval forms (e.g., *Echinococcus* spp.). Once adult worms take up residence in humans, they usually do not multiply but they produce eggs or larvae that are usually passed out in stool. Often, the severity of disease is in proportion to the number of infecting organisms. For example, a burden of 10 hookworms is associated with mild or no clinical disease, whereas 1000 hookworms consume enough blood to cause severe anemia. In some helminthic infections, such as schistosomiasis, disease is caused by inflammatory responses to the eggs or larvae, rather than to the adults.

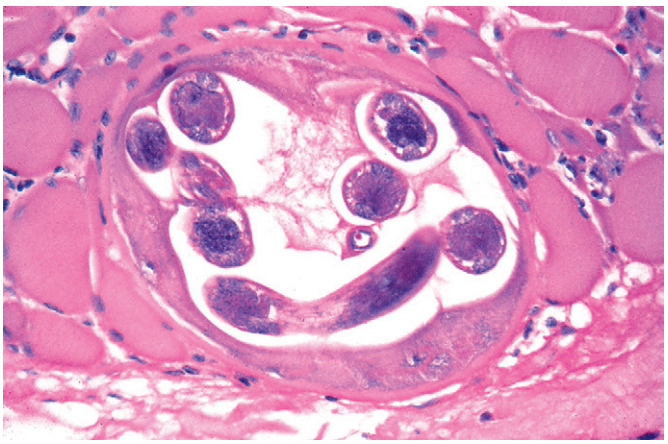

Figure 8–5 Coiled *Trichinella spiralis* larva within a skeletal muscle cell.

Helminths comprise three groups:

- *Roundworms* (*nematodes*) are circular in cross-section and nonsegmented. Intestinal nematodes include *Ascaris lumbricoides*, *Strongyloides stercoralis*, and hookworms. Nematodes that invade into tissue include the filariae and *Trichinella spiralis* (Fig. 8–5).
- *Tapeworms* (*cestodes*) have a head (scolex) and a ribbon of multiple flat segments (proglottids). They adsorb nutrition through their tegument and do not have a digestive tract. They include the fish, beef, and pork tapeworms, found in the human intestine. The larvae that develop after ingestion of eggs of certain tapeworms can cause cystic disease within tissues (*Echinoccus granulosus* larvae cause *hydatid* cysts; pork tapeworm larvae produce cysts called cysticerci in many organs).
- *Flukes* (*trematodes*) are leaf-shaped flatworms with prominent suckers that are used to attach to the host. They include liver and lung flukes and schistosomes.

Ectoparasites

Ectoparasites are insects (lice, bedbugs, fleas) or arachnids (mites, ticks, spiders) that attach to and live on or in the skin. Diseases caused directly by arthropods are characterized by itching and excoriations, such as pediculosis caused by lice attached to hairs, or scabies caused by mites burrowing into the stratum corneum. At the site of the bite, mouth parts may be found associated with a mixed infiltrate of lymphocytes, macrophages, and eosinophils. Arthropods also can serve as vectors for other pathogens, such as *Borrelia burgdorferi*, the agent of Lyme disease, which is transmitted by deer ticks.

SPECIAL TECHNIQUES FOR IDENTIFYING INFECTIOUS AGENTS

Some infectious agents can be seen in hematoxylin and eosin (H&E)–stained sections (e.g., the inclusion bodies formed by CMV and herpes simplex virus (HSV); bacterial clumps, which usually stain blue; *Candida* and *Mucor* among the fungi; most protozoans; all helminths). Many infectious agents, however, are best visualized by special stains that identify organisms on the basis of particular characteristics of their cell wall or coat—Gram, acid-fast, silver, mucicarmine, and Giemsa stains—or after labeling with specific antibodies (Table 8–4). Organisms are usually best visualized at the advancing edge of a lesion rather than at its center, particularly if there is necrosis.

Table 8–4 Special Techniques for Identifying Infectious Agents

Technique	Infectious Agent(s)
Gram stain	Most bacteria
Acid-fast stain	Mycobacteria, nocardiae (modified)
Silver stains	Fungi, legionellae, *Pneumocystis*
Periodic acid–Schiff	Fungi, amebae
Mucicarmine	Cryptococci
Giemsa	Leishmaniae, *Plasmodium*
Antibodies	All classes
Culture	All classes
DNA probes	All classes

Acute infections can be diagnosed serologically by detecting pathogen-specific antibodies in the serum. The presence of specific immunoglobulin M (IgM) antibody shortly after the onset of symptoms is often diagnostic. Alternatively, specific antibody titers can be measured early ("acute") and again at 4 to 6 weeks ("convalescent") after infection; a four-fold rise in titer usually is considered diagnostic. Assays for serum antibodies are very useful for the diagnosis of hepatitis caused by viruses.

Nucleic acid–based tests, collectively called *molecular diagnostics*, are used routinely to detect pathogens. Nucleic acid amplification techniques, such as polymerase chain reaction (PCR) and transcription-mediated amplification, are used for diagnosis of gonorrhea, chlamydial infection, tuberculosis, and herpes encephalitis. Molecular assays are much more sensitive than conventional testing for some pathogens. PCR testing of cerebrospinal fluid (CSF) for HSV encephalitis has a sensitivity of about 80%, whereas viral culture of CSF has a sensitivity of less than 10%. Similarly, nucleic acid tests for genital *Chlamydia* detect 10% to 30% more infections than does conventional *Chlamydia* culture. For other infections, such as gonorrhea, the sensitivity of nucleic acid testing is similar to that of culture. Quantitative nucleic acid amplification tests are used to guide the medical management of infections with human immunodeficiency virus (HIV), HBV and hepatitis C virus (HCV).

NEW AND EMERGING INFECTIOUS DISEASES

A surprising number of new infectious agents continue to be discovered. The infectious causes of some important diseases were previously unrecognized, because some of the infectious agents are difficult to culture; examples include *Helicobacter pylori* gastritis and peptic ulcer disease, HBV and HCV, and Legionnaires disease (pneumonia). Some infectious agents are relatively new to humans—for example, HIV, which causes AIDS, and *B. burgdorferi*, which causes Lyme disease. Other infections have become much more common because of immunosuppression caused by AIDS or therapy to prevent transplant rejection and for some cancers (e.g., Kaposi sarcoma, *Mycobacterium*

avium complex, P. jiroveci). Finally, infectious diseases that are common in one geographic area may be introduced into a new area. For example, West Nile virus has been common in Europe, Asia, and Africa for years but was first described in the United States in 1999.

Several factors contribute to the emergence of infectious diseases:

- Human behavior affects the spread and demographics of infections. AIDS was first recognized in the United States as predominantly a disease of homosexual men and drug abusers, but heterosexual transmission is now more common. In sub-Saharan Africa, the area of the world with the highest number of AIDS cases, it is predominantly a heterosexual disease.
- Changes in the environment occasionally drive rates of infectious diseases. Deforestation of the eastern United States has led to massive increases in deer and mice, which carry the ticks that transmit Lyme disease, babesiosis, and ehrlichiosis. Global warming has also had an impact on the spread of infections. For example, the mosquitoes that carry Dengue fever, which used to be confined to the U.S.-Mexican border, are now found in 28 states.
- Pathogens adapt rapidly to selective pressures exerted by widespread use (and overuse) of antibiotics. Antibiotic resistance has developed and is now common in *Mycobacterium tuberculosis*, *Neisseria gonorrhoeae*, and *Staphylococcus aureus*. Similarly, development of drug-resistant parasites has dramatically increased the morbidity and mortality associated with *Plasmodium falciparum* infection in Asia, Africa, and Latin America.

Table 8–5 Potential Agents of Bioterrorism

Category A Diseases and Agents
Anthrax: *Bacillus anthracis*
Botulism: *Clostridium botulinum* toxin
Plague: *Yersinia pestis*
Smallpox: *Variola major* virus
Tularemia: *Francisella tularensis*
Viral hemorrhagic fevers: filoviruses (e.g., Ebola, Marburg) and arenaviruses (e.g., Lassa, Machupo)
Category B Diseases and Agents
Brucellosis: *Brucella* spp.
Epsilon toxin of *Clostridium perfringens*
Food safety threats: *Salmonella* spp., *Escherichia coli* O157:H7, *Shigella*, others
Glanders: *Burkholderia mallei*
Melioidosis: *Burkholderia pseudomallei*
Psittacosis: *Chlamydia psittaci*
Q fever: *Coxiella burnetii*
Ricin toxin from castor beans (*Ricinus communis*)
Staphylococcal enterotoxin B
Typhus fever: *Rickettsia prowazekii*
Viral encephalitis: alphaviruses (e.g., Venezuelan equine encephalitis, Eastern equine encephalitis, Western equine encephalitis)
Water safety threats: *Vibrio cholerae*, *Cryptosporidium parvum*, others
Category C Diseases and Agents
Emerging infectious disease threats: Nipah virus, hantavirus, possibly others

Adapted from Centers for Disease Control and Prevention Information (www.bt.cdc.gov/bioterrorism/2011).

AGENTS OF BIOTERRORISM

Sadly, the anthrax attacks in the United States in 2001 transformed the theoretical threat of bioterrorism into reality. The Centers for Disease Control and Prevention (CDC) has evaluated the microorganisms that pose the greatest danger as weapons on the basis of the efficiency with which disease can be transmitted, how difficult the microorganisms are to produce and distribute, what can be done to defend against them, and the extent to which they are likely to alarm the public and produce widespread fear. Based on these criteria, the CDC has ranked bioweapons into three categories, designated A, B, and C (Table 8–5).

The agents in the highest-risk category A can be readily disseminated or transmitted from person to person, typically cause diseases that can carry a high mortality rate with potential for major public health impact, may cause pandemics leading to public panic and social disruption, and are likely to require special action for public health preparedness. For example, the smallpox virus is a category A agent because of its high transmissibility, case mortality rates of 30% or greater, and the lack of effective antiviral therapy. Smallpox readily spreads from person to person, mainly through respiratory secretions and by direct contact with virus in skin lesions. After an incubation period of 7 to 17 days, the usual presenting manifestations are high fever, headache, and backache, followed by a rash, which first appears on the mucosa of the mouth and pharynx, face, and forearms and spreads to the trunk and legs. The rash initially is vesicular and later becomes pustular. Because affected persons are contagious during the incubation period, smallpox virus can rapidly spread throughout an unprotected population. Since routine smallpox vaccination ended in the United States in 1972, immunity has waned, leaving the population highly susceptible. Concern that smallpox could be used for bioterrorism has led to reinstitution of vaccination for some medical and military personnel.

Category B agents are moderately easy to disseminate, cause disease associated with moderate morbidity but low mortality, and require specific diagnostic and disease surveillance. Many of these agents can be spread in food or water. Category C agents include emerging pathogens that could be engineered for mass dissemination because of ease of availability, production, and dissemination; the potential for high morbidity and mortality; and great impact on health.

TRANSMISSION AND DISSEMINATION OF MICROBES

Routes of Entry of Microbes

Microbes can enter the host through breaches in the skin, inhalation, ingestion, or sexual transmission. The first defenses against infection are intact skin and mucosal surfaces, which provide physical barriers and produce

antimicrobial substances. In general, respiratory, gastrointestinal, or genitourinary tract infections that occur in otherwise healthy persons are caused by relatively virulent microorganisms that are capable of damaging or penetrating intact epithelial barriers. By contrast, most skin infections in healthy persons are caused by less virulent organisms that enter the skin through damaged sites (cuts and burns).

Skin

The dense, keratinized outer layer of skin is a natural barrier to infection, and the low pH of the skin (less than 5.5) and the presence of fatty acids inhibit growth of microorganisms other than the normal flora. Skin normally is inhabited by bacteria and fungi, including potential opportunists, such as *S. aureus* and *Candida albicans.*

Most microorganisms penetrate through breaks in the skin, including superficial pricks (fungal infections), wounds (staphylococci), burns (*Pseudomonas aeruginosa*), and diabetic and pressure-related foot sores (multibacterial infections). Intravenous catheters in hospitalized patients provide portals for local or systemic infection. Needle sticks can expose the recipient to infected blood and transmit HBV, hepatitis C virus (HCV), or HIV. Some pathogens penetrate the skin via an insect or animal bite. Bites by fleas, ticks, mosquitoes, mites, and lice break the skin and transmit arboviruses (causes of yellow fever and encephalitis), bacteria (plague, Lyme disease, Rocky Mountain spotted fever), protozoa (malaria, leishmaniasis), and helminths (filariasis). Animal bites can lead to infections with bacteria or certain viruses, such as rabies. Only a few microorganisms are able to traverse the unbroken skin. For example, *Schistosoma* larvae released from freshwater snails penetrate swimmers' skin by releasing enzymes that dissolve the extracellular matrix. Certain fungi (dermatophytes) can infect intact stratum corneum, hair, and nails.

Gastrointestinal Tract

Gastrointestinal pathogens are transmitted by food or drink contaminated with fecal material. When hygiene fails, as may occur with natural disasters such as floods and earthquakes, diarrheal disease becomes rampant.

Acidic gastric secretions are important defenses and are lethal for many gastrointestinal pathogens. Healthy volunteers do not become infected by *Vibrio cholerae* unless they are fed 10^{11} organisms, but neutralizing the stomach acid reduces the infectious dose by 10,000-fold. By contrast, some ingested agents, such as *Shigella* and *Giardia* cysts, are relatively resistant to gastric acid, so fewer than 100 organisms of each can cause illness.

Other normal defenses within the gastrointestinal tract include (1) the layer of viscous mucus covering the intestinal epithelium, (2) lytic pancreatic enzymes and bile detergents, (3) mucosal antimicrobial peptides called defensins, (4) normal flora, and (5) secreted IgA antibodies. IgA antibodies are made by plasma cells located in mucosa-associated lymphoid tissue (MALT). These lymphoid aggregates are covered by a single layer of specialized epithelial cells called M cells, which are important for transport of antigens to MALT. Numerous gut pathogens use M cells to enter the host from the intestinal lumen, including poliovirus, enteropathic *Escherichia coli, V. cholerae, Salmonella typhi*, and *Shigella flexneri*.

Infection via the gastrointestinal tract occurs when local defenses are weakened or the organisms develop strategies to overcome these defenses. Host defenses are weakened by low gastric acidity, by antibiotics that alter the normal bacterial flora (e.g., in pseudomembranous colitis), or when there is stalled peristalsis or mechanical obstruction. Viruses that can enter the body through the intestinal tract (e.g., hepatitis A, rotavirus) are those that lack envelopes, because enveloped viruses are inactivated by bile and digestive enzymes.

Enteropathogenic bacteria cause gastrointestinal disease in several ways:

- *S. aureus* can contaminate and grow in food, where it releases powerful enterotoxins that, when ingested, cause food poisoning without any bacterial multiplication in the gut.
- *V. cholerae* and enterotoxigenic *E. coli* bind to the intestinal epithelium and multiply in the overlying mucous layer, where they release exotoxins that cause epithelial cells to secrete large volumes of fluid, resulting in watery diarrhea.
- *Shigella*, *Salmonella*, and *Campylobacter* invade locally and damage the intestinal mucosa and lamina propria, causing ulceration, inflammation, and hemorrhage—changes manifested clinically as dysentery.
- *Salmonella typhi* passes from the damaged mucosa through Peyer's patches and mesenteric lymph nodes and into the bloodstream, resulting in a systemic infection.

Fungal infection of the gastrointestinal tract occurs mainly in immunologically compromised persons. *Candida*, part of the normal gastrointestinal flora, shows a predilection for stratified squamous epithelium, causing oral thrush or membranous esophagitis, but also may spread to the stomach, lower gastrointestinal tract, and other organs.

Intestinal protozoa are transmitted as cysts, which resist stomach acid. In the gut, cysts convert to motile trophozoites and attach to sugars on the intestinal epithelia through surface lectins. What happens next differs among protozoa. *Giardia lamblia* attaches to the epithelial brush border, whereas cryptosporidia are taken up by enterocytes, in which they form gametes and oocysts. *E. histolytica* kills host cells by contact-mediated cytolysis through a channel-forming pore protein, with consequent ulceration and invasion of the colonic mucosa. *Intestinal helminths* cause disease when they are present in large numbers or by reaching ectopic sites, for example, by obstructing the gut or invading and damaging the bile ducts (*Ascaris lumbricoides*). Hookworms cause iron deficiency anemia by sucking blood from intestinal villi; *Diphyllobothrium*, the fish tapeworm, causes anemia by depriving the host of vitamin B_{12}. Finally, larvae of several helminths pass through the gut briefly on their way to another organ; for example, *Trichinella spiralis* larvae preferentially encyst in muscle, and *Echinococcus* larvae grow in the liver or lung.

Respiratory Tract

A large number of microorganisms, including viruses, bacteria, and fungi, are inhaled daily by every person. In many cases, the microbes are inhaled in dust or aerosol particles.

The distance these particles travel into the respiratory system is inversely proportional to their size. Large particles are trapped in the mucociliary blanket that lines the nose and the upper respiratory tract. Microorganisms trapped in the mucus secreted by goblet cells are transported by ciliary action to the back of the throat, where they are swallowed and cleared. Particles smaller than 5 µm travel directly to the alveoli, where they are phagocytosed by alveolar macrophages or by neutrophils recruited to the lung by cytokines.

Microorganisms that invade the normal healthy respiratory tract have developed specific mechanisms to overcome mucociliary defenses or to avoid destruction by alveolar macrophages. Some successful respiratory viruses evade these defenses by attaching to and entering epithelial cells in the lower respiratory tract and pharynx. For example, influenza viruses possess hemagglutinin proteins that project from the surface of the virus and bind to sialic acid on the surface of epithelial cells. This attachment induces the host cell to engulf the virus, leading to viral entry and replication within the host cell.

Certain bacterial respiratory pathogens, including *Haemophilus influenzae*, *Mycoplasma pneumoniae*, and *Bordetella pertussis*, release toxins that impair ciliary activity. Some bacteria lack the ability to overcome the defenses of the healthy lung and can cause respiratory infections only in compromised hosts. *S. pneumoniae* and *S. aureus* can cause pneumonia subsequent to influenza, because the viral infection causes loss of the protective ciliated epithelium. Chronic damage to mucociliary defense mechanisms occurs in smokers and people with cystic fibrosis, while acute injury occurs in intubated patients and in those who aspirate gastric acid.

Some respiratory pathogens avoid phagocytosis or destruction after phagocytosis. M. tuberculosis, for example, gains its foothold in alveoli because it escapes killing within the phagolysosomes of macrophages. Opportunistic fungi infect the lungs when cellular immunity is depressed or when leukocytes are reduced in number (e.g., *P. jiroveci* in patients with AIDS, *Aspergillus* spp. after chemotherapy).

Urogenital Tract

The urinary tract is almost always invaded from the exterior by way of the urethra. The regular flushing of the urinary tract with urine serves as a defense against invading microorganisms. Urine in the bladder is normally sterile, and successful pathogens (e.g., *N. gonorrhoeae, E. coli*) adhere to the urinary epithelium. Anatomy plays an important role in infection. Women have more than 10 times as many urinary tract infections as in men because the distance between the urinary bladder and skin (i.e., the length of the urethra) is 5 cm in women, in contrast with 20 cm in men. Obstruction of urinary flow or reflux can compromise normal defenses and increase susceptibility to urinary tract infections. Urinary tract infections often spread in retrograde fashion from the bladder to the kidney and cause acute and chronic pyelonephritis.

From puberty until menopause the vagina is protected from pathogens by a low pH resulting from catabolism of glycogen in the normal epithelium by lactobacilli. Antibiotics can kill the lactobacilli, allowing overgrowth of yeast, with resultant vaginal candidiasis.

Spread and Dissemination of Microbes Within the Body

Some microorganisms proliferate locally, at the site of initial infection, whereas others penetrate the epithelial barrier and spread to distant sites by way of the lymphatics, the blood, or nerves (Fig. 8–6). Pathogens that cause superficial infections stay confined to the lumen of hollow viscera (e.g., *Vibrio cholerae*) or adhere to or proliferate exclusively in or on epithelial cells (e.g., papillomaviruses, dermatophytes).

Microbes can spread within the body in several ways:

- Some extracellular bacteria, fungi, and helminths secrete lytic enzymes which destroy tissue and allow direct invasion. For example, *S. aureus* secretes hyaluronidase, which degrades the extracellular matrix between host cells. Invasive microbes initially follow tissue planes of least resistance and drain to regional lymphatics. *S. aureus* may travel from a localized abscess to the draining lymph nodes. This can sometimes lead to bacteremia and spread to deep organs (heart, bone).
- Microorganisms may be spread in the blood or lymph either free in extracellular fluid or within host cells. Some viruses (e.g., poliovirus, HBV), most bacteria and

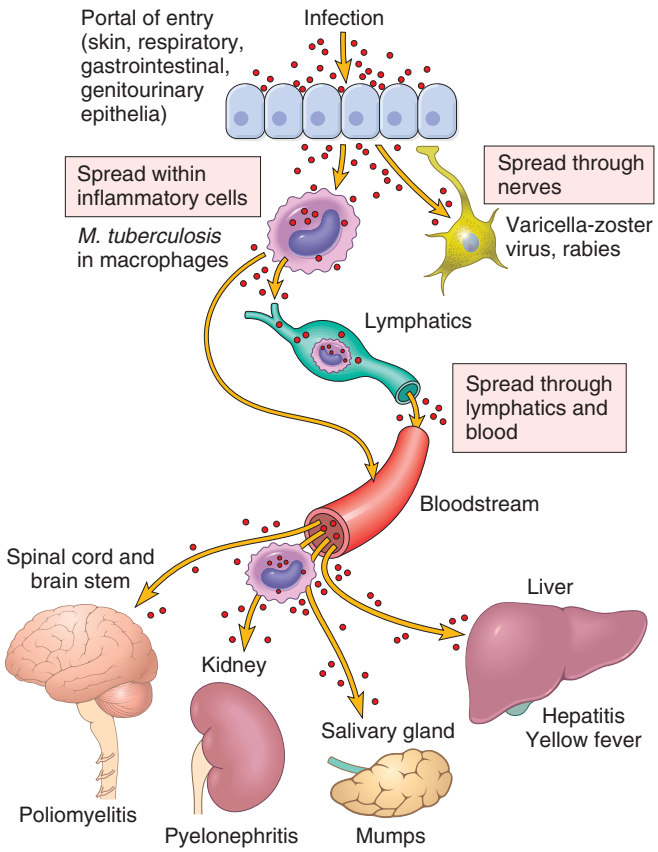

Figure 8–6 Routes of entry and dissemination of microbes. To enter the body, microbes penetrate epithelial or mucosal barriers. Infection may remain localized at the site of entry or spread to other sites in the body. Most common microbes (selected examples are shown) spread through the lymphatics or bloodstream (either freely or within inflammatory cells). However, certain viruses and bacterial toxins also may travel through nerves.

(Adapted from Mims CA: The Pathogenesis of Infectious Disease, 4th ed. San Diego, Academic Press, 1996.)

fungi, some protozoa (e.g., African trypanosomes), and all helminths are transported in blood, free in the plasma. Leukocytes can carry herpesviruses, HIV, mycobacteria, *Leishmania,* and *Toxoplasma.* The parasites *Plasmodium* and *Babesia* are carried within red blood cells.

- Most viruses spread locally from cell to cell by replication and release of infectious virions, but others may propagate from cell to cell by causing fusion of host cells, or by transport within nerves (as with rabies virus and varicella-zoster virus).

Spread of pathogens in the blood can have inconsequential or dire consequences. Infectious foci seeded by blood can be single and large (as with an abscess or tuberculoma) or multiple and tiny (as with miliary tuberculosis or *Candida* microabscesses). Sporadic bloodstream invasion by low-virulence or nonvirulent microbes (e.g., during brushing of teeth) is common but is quickly controlled by normal host defenses. By contrast, disseminated viremia, bacteremia, fungemia, or parasitemia by virulent pathogens is a serious danger and manifests as fever, low blood pressure, and multiple other systemic signs and symptoms of sepsis. Massive bloodstream invasion by bacteria can rapidly lead to fatal sepsis, even in previously healthy persons.

The major manifestations of infectious disease may appear at sites distant from the point of microbe entry. For example, varicella-zoster and measles viruses enter through the airways but cause rashes in the skin; poliovirus enters through the intestine but kills motor neurons to cause paralysis. *Schistosoma mansoni* parasites penetrate the skin but eventually localize in blood vessels of the portal system and mesentery, damaging the liver and intestine. *Schistosoma hematobium* localizes to the urinary bladder and causes cystitis. The rabies virus travels from the site of a bite by a rabid animal to the brain by retrograde transport in sensory neurons, where it then causes encephalitis and death.

Release from the Body and Transmission of Microbes

Transmission depends on the hardiness of the microbe. Some microbes can survive for extended periods in dust, food, or water. Bacterial spores, protozoan cysts, and thick-shelled helminth eggs can survive in a cool and dry environment. Less hardy microorganisms must be quickly passed from person to person, often by direct contact.

For transmission of disease, the mode of exit of a microorganism from the host's body is as important as entry into it. Every fluid or tissue that is normally secreted, excreted, or shed is used by microorganisms to leave the host for transmission to new victims.

- Skin flora, such as *S. aureus,* and pathogens, including the dermatophyte fungi, are shed in the desquamated skin. Some sexually transmitted pathogens are transmitted from genital skin lesions.
- Viruses that replicate in the salivary glands and are spread in saliva include mumps virus, cytomegalovirus, and rabies virus.
- Viruses and bacteria that are part of the normal respiratory flora or cause respiratory tract infections are shed in respiratory secretions during talking, coughing, and sneezing. Most respiratory pathogens, including influenza viruses, spread in large respiratory droplets, which travel no more than 3 feet. A few organisms, including *M. tuberculosis* and varicella-zoster virus, are spread from the respiratory tract by the airborne route in small respiratory droplets or within dust particles, which can travel long distances.
- Organisms shed in stool include many pathogens that replicate in the lumen or epithelium of the gut, such as *Shigella, Giardia lamblia,* and rotavirus. Pathogens that replicate in the liver (hepatitis A virus) or gallbladder (*Salmonella* serotype typhi) enter the intestine in bile and are shed in stool.
- Pathogens which exit the body in the blood are transmitted by invertebrate vectors, medical practices (blood transfusion, reuse of equipment) or sharing of needles by intravenous drug abusers. Bloodborne parasites, including *Plasmodium* spp. and arboviruses, are spread by biting insects.
- Urine is the usual mode of exodus from the human host by only a few organisms, including *Schistosoma haematobium,* which grows in the veins of the bladder and releases eggs that reach the urine.
- Sexually transmitted infections (STIs) infect and spread from the urethra, vagina, cervix, rectum, or oral pharynx. Organisms that cause STIs depend on direct contact for person-to-person spread because these pathogens do not survive in the environment. Transmission of STIs often is by asymptomatic people who do not realize that they are infected. Infection with one STI increases the risk for additional STIs, mainly because the risk factors are the same for all STIs. STIs are described in Chapters 17 and 18.
- Vertical transmission is from mother to fetus or newborn child, and occurs by three main anatomic routes. *Placental-fetal transmission* is most likely to occur when the mother has primary infection with a pathogen during pregnancy. The damage that occurs depends on the developmental stage of the fetus. For example, rubella infection during the first trimester can cause heart malformation, mental retardation, cataracts, or deafness in the infant, while little damage is caused by rubella infection during the third trimester. Vertical transmission also occurs during *passage of the neonate through the birth canal* (e.g., gonococcal or chlamydial conjunctivitis) or *through maternal milk* (e.g., CMV and HBV). Diagnosis of STIs in pregnant women is critical, because vertical transmission of STIs often can be prevented by treatment of the mother or newborn. For example, maternal transmission of HIV is the major cause of AIDS in children; it most often occurs prenatally, during delivery. Antiretroviral treatment of pregnant women with HIV infection and treatment of the newborn can reduce the rate of transmission of HIV to children from 25% to less than 2%.

Microbes also can be transmitted from animal to human (resulting in *zoonotic infections*), either through direct contact or consumption of animal products or indirectly by an invertebrate vector.

SUMMARY

Transmission of Microbes

- Transmission of infections can occur by contact (direct and indirect), respiratory droplets, fecal-oral route, sexual transmission, vertical transmission from mother to fetus or newborn, or insect/arthropod vectors.
- A pathogen can establish infection if it possesses virulence factors that overcome normal host defenses or if the host defenses are compromised.
- Host defenses against infection include:
  - *Skin:* tough keratinized barrier, low pH, fatty acids
  - *Respiratory system:* alveolar macrophages and mucociliary clearance by bronchial epithelium, IgA
  - *Gastrointestinal system:* acidic gastric pH, viscous mucus, pancreatic enzymes and bile, defensins, IgA, and normal flora
  - *Urogenital tract:* repeated flushing and acidic environment created by commensal vaginal flora

HOW MICROORGANISMS CAUSE DISEASE

Infectious agents establish infection and damage tissues by any of three mechanisms:

- They can contact or enter host cells and directly cause cell death.
- 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, although directed against the invader, cause additional tissue damage. Thus, as discussed in Chapters 2 and 4, the defensive responses of the host can be a mixed blessing. They are necessary to overcome the infection but at the same time may directly contribute to tissue damage.

Described next are 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 manifestations of viral infection are largely determined by the tropism of the virus for specific tissues and cell types.

- *A major determinant of tissue tropism is the presence of viral receptors on host cells.* Viruses possess specific cell surface proteins that bind to particular host cell surface proteins. Many viruses use normal cellular receptors of the host to enter cells. 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 4). In some cases, host proteases are needed to enable binding of virus to host cells; for instance, a host protease cleaves and activates the influenza virus hemagglutinin.
- The ability of the virus to replicate inside some cells but not in others depends on the presence of cell type–specific transcription factors that recognize viral enhancer and promoter elements. For example, the JC virus, which causes leukoencephalopathy (Chapter 22), replicates specifically in oligodendroglia in the CNS, because the promoter and enhancer DNA sequences regulating viral gene expression are active in glial cells but not in neurons or endothelial cells.
- Physical circumstances, such as chemicals and temperature, 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 cells only within the upper respiratory tract because they replicate optimally at the lower temperatures characteristic of this site.

Once viruses are inside host cells, they can damage or kill the cells by a number of mechanisms (Fig. 8–7):

- *Direct cytopathic effects.* Viruses can kill cells by preventing synthesis of critical host macromolecules, by producing degradative enzymes and toxic proteins, or by inducing apoptosis. For example, poliovirus blocks synthesis of host proteins by inactivating cap-binding protein, which is essential for translation of host cell messenger RNAs (mRNAs) but leaves translation of poliovirus mRNAs unaffected. HSV produces proteins that inhibit synthesis of cellular DNA and mRNA and

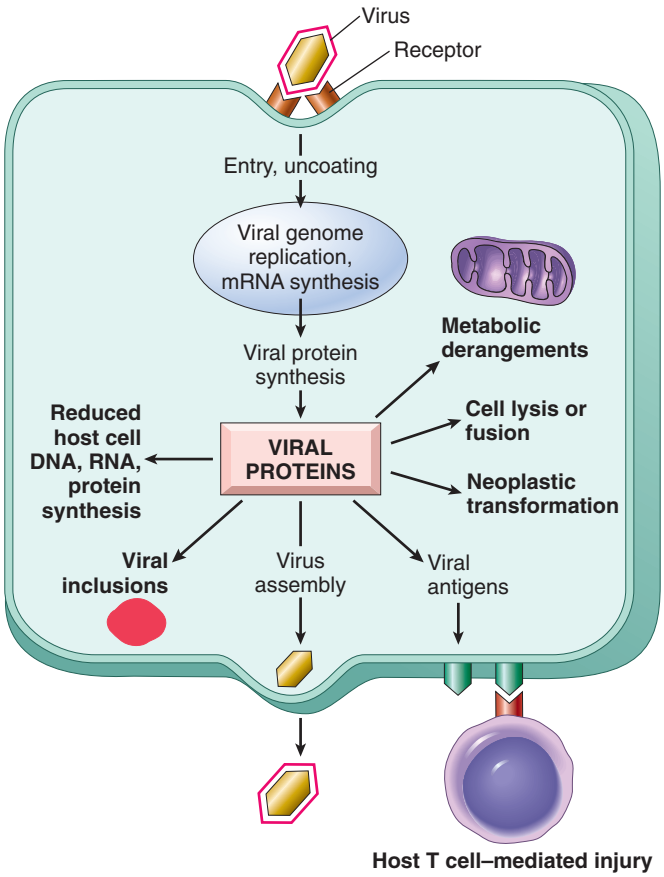

Figure 8–7 Mechanisms by which viruses cause injury to cells.

other proteins that degrade host DNA. Some viruses can stimulate apoptosis by production of proteins that are proapoptotic (e.g., HIV vpr protein). Viral replication also can trigger apoptosis of host cells by cell-intrinsic mechanisms, such as perturbations of the endoplasmic reticulum during virus assembly, which can activate proteases that mediate apoptosis (caspases).

- *Antiviral immune responses.* Viral proteins on the surface of host cells may be recognized by the immune system, and lymphocytes may attack virus-infected cells. Cytotoxic T lymphocytes (CTLs) are important for defense against viral infections, but CTLs also can be responsible for tissue injury. Acute liver failure during hepatitis B infection may be accelerated by CTL-mediated destruction of infected hepatocytes (a normal response to clear the infection).
- *Transformation of infected cells* into benign or malignant tumor cells. Different oncogenic viruses can stimulate cell growth and survival by a variety of mechanisms, including expression of virus-encoded oncogenes, antiapoptotic strategies, and insertional mutagenesis (in which the insertion of viral DNA into the host genome alters the expression of nearby host genes). The mechanisms of viral transformation are numerous and are discussed in Chapter 5.

Mechanisms of Bacterial Injury

Bacterial Virulence

Bacterial damage to host tissues depends on the ability of the bacteria to adhere to host cells, invade cells and tissues, or deliver toxins. Pathogenic bacteria have virulence genes that encode proteins conferring these properties. Virulence genes frequently are found grouped together in clusters called *pathogenicity islands*. A small number of virulence genes can determine whether a bacterium is harmful. The *Salmonella* strains that infect humans are so closely related that they are a single species, but a small number of virulence genes determine whether an isolate of *Salmonella* causes life-threatening typhoid fever or self-limited gastroenteritis.

Plasmids and bacteriophages (viruses) are genetic elements that spread between bacteria and can encode virulence factors, including toxins, or enzymes that confer antibiotic resistance. Bacteriophages or plasmids can convert otherwise nonpathogenic bacteria into virulent ones. Exchange of these elements between bacteria can endow the recipient with a survival advantage and/or the capacity to cause disease. Plasmids or transposons encoding antibiotic resistance can convert an antibiotic-susceptible bacterium into a resistant one, making effective therapy difficult.

Populations of bacteria also can act together in ways that alter their virulence.

- Many species of bacteria coordinately regulate gene expression within a large population by *quorum sensing,* in which specific genes, such as virulence genes, are expressed when bacteria reach high concentrations. This in turn may allow bacteria growing in discrete host sites, such as an abscess or consolidated pneumonia, to overcome host defenses. *S. aureus* coordinately regulates virulence factors by secreting *autoinducer peptides.* As the bacteria grow to increasing concentrations, the level of the autoinducer peptide increases, stimulating exotoxin production.
- Communities of bacteria can form *biofilms* in which the organisms live within a viscous layer of extracellular polysaccharides that adhere to host tissues or devices such as intravascular catheters and artificial joints. Biofilms make bacteria inaccessible to immune effector mechanisms and increase their resistance to antimicrobial drugs. Biofilm formation seems to be important in the persistence and relapse of infections such as bacterial endocarditis, artificial joint infections, and respiratory infections in people with cystic fibrosis.

Bacterial Adherence to Host Cells

Bacterial surface molecules that bind to host cells or extracellular matrix are called *adhesins.* Diverse surface structures are involved in adhesion of various bacteria (Fig. 8–2). *Streptococcus pyogenes* has protein F and teichoic acid projecting from its cell wall that bind to fibronectin on the surface of host cells and in the extracellular matrix. Other bacteria have filamentous proteins called pili on their surfaces. Stalks of pili are structurally conserved, whereas amino acids on the tips of the pili vary and determine the binding specificity of the bacteria. Strains of *E. coli* that cause urinary tract infections uniquely express a specific P pilus, which binds to a gal(α1–4)gal moiety expressed on uroepithelial cells. Pili on *N. gonorrhoeae* bacteria mediate adherence of the bacteria to host cells and also are targets of the host antibody response. Variation in the type of pili expressed is an important mechanism by which *N. gonorrhoeae* escapes the immune response.

Virulence of Intracellular Bacteria

Facultative intracellular bacteria usually infect epithelial cells (*Shigella* and enteroinvasive *E. coli*), macrophages (*M. tuberculosis, M. leprae*), or both (*S. typhi*). The growth of bacteria in cells may allow them to escape from certain immune effector mechanisms, such as antibodies and complement, or may facilitate spread of the bacteria in the body, as when macrophages carry *M. tuberculosis* from the lung to other sites.

Bacteria have evolved a number of mechanisms for entering host cells. Some bacteria use the host immune response to enter macrophages. Coating of bacteria with antibodies or the complement protein C3b (opsonization) elicits phagocytosis of bacteria by macrophages. Like many bacteria, *M. tuberculosis* activates the alternative complement pathway, resulting in opsonization with C3b and uptake by host macrophages in which the mycobacteria live. Some gram-negative bacteria use a *type III secretion system* to enter epithelial cells. This system consists of needle-like structures projecting from the bacterial surface that bind and form pores in the host cell membrane through which proteins are injected that mediate rearrangement of the cell cytoskeleton and facilitate bacterial entry. Finally, bacteria such as *Listeria monocytogenes* can manipulate the cell cytoskeleton to spread directly from cell to cell, perhaps allowing the bacteria to evade immune defenses.

Intracellular bacteria have different strategies for interacting with the host cell. *Shigella* and *E. coli* inhibit host

protein synthesis, replicate rapidly, and lyse the host cell within hours. Although most bacteria in macrophages are killed when the phagosome fuses with the acidic lysosome to form a phagolysosome, certain bacteria elude this host defense. For example, *M. tuberculosis* blocks fusion of the lysosome with the phagosome, allowing the bacteria to proliferate unchecked within the macrophage. Other bacteria avoid destruction in macrophages by escaping from the phagosome. *L. monocytogenes* produces a pore-forming protein called listeriolysin O and two phospholipases that degrade the phagosome membrane, allowing the bacteria to escape into the cytoplasm.

Bacterial Toxins

Any bacterial substance that contributes to illness can be considered a toxin. Toxins are classified as endotoxins, which are components of the bacterial cell, and exotoxins, which are proteins that are secreted by the bacterium.

Bacterial endotoxin is a lipopolysaccharide (LPS) that is a component of the outer membrane of gram-negative bacteria (Fig. 8–2). LPS is composed of a long-chain fatty acid anchor, termed lipid A, connected to a core sugar chain, both of which are very similar in all gram-negative bacteria. Attached to the core sugar is a variable carbohydrate chain (O antigen), which is used diagnostically to serotype strains of bacteria. Lipid A binds to CD14 on the surface of host leukocytes, and the complex then binds to Toll-like receptor 4 (TLR4), a pattern recognition receptor of the innate immune system that transmits signals that promote cell activation and inflammatory responses. Responses to LPS can be both beneficial and harmful to the host. The response is beneficial in that LPS activates protective immunity in several ways, including induction of important cytokines and chemoattractants (chemokines) of the immune system, as well as increased expression of costimulatory molecules, which enhance T lymphocyte activation. However, high levels of LPS play an important role in septic shock, disseminated intravascular coagulation (DIC), and acute respiratory distress syndrome, mainly through induction of excessive levels of cytokines such as TNF (Chapter 4).

Exotoxins are secreted proteins that cause cellular injury and disease. They can be classified into broad categories by their mechanism and site of action.

- *Enzymes.* Bacteria secrete a variety of enzymes (proteases, hyaluronidases, coagulases, fibrinolysins) that act on their respective substrates in vitro, but their role in disease is understood in only a few cases. For example, exfoliative toxins are proteases produced by *S. aureus* that cleave proteins known to hold keratinocytes together, causing the epidermis to detach from the deeper skin.
- *Toxins that alter intracellular signaling or regulatory pathways.* Most of these toxins have an active (A) component with enzymatic activity and a binding (B) component that binds cell surface receptors and delivers the A protein into the cell cytoplasm. The effect of these toxins depends on the binding specificity of the B domain and the cellular pathways affected by the A domain. A-B toxins are made by many bacteria including *Bacillus anthracis, V. cholerae,* and *Corynebacterium diphtheriae.* The mechanism of action of the A-B anthrax toxin is well understood (Fig. 8–8). Anthrax toxin has two alternate A components, edema factor (EF) and lethal factor (LF), which enter cells following binding to the B component and mediate different pathologic effects.
- *Superantigens* stimulate very large numbers of T lymphocytes by binding to conserved portions of the T cell receptor, leading to massive T lymphocyte proliferation and cytokine release. The high levels of cytokines lead to capillary leak and consequent shock. Superantigens made by *S. aureus* and *S. pyogenes* cause toxic shock syndrome (TSS).
- *Neurotoxins* produced by *Clostridium botulinum* and *Clostridium tetani* inhibit release of neurotransmitters, resulting in paralysis. These toxins do not kill neurons; instead, the A domains cleave proteins involved in secretion of neurotransmitters at the synaptic junction. Tetanus and botulism can result in death from respiratory failure due to paralysis of the chest and diaphragm muscles.
- Enterotoxins affect the gastrointestinal tract in different ways to cause varied effects, including nausea and vomiting (*S. aureus*), voluminous watery diarrhea (*V. cholerae*), or bloody diarrhea (*C. difficile*).

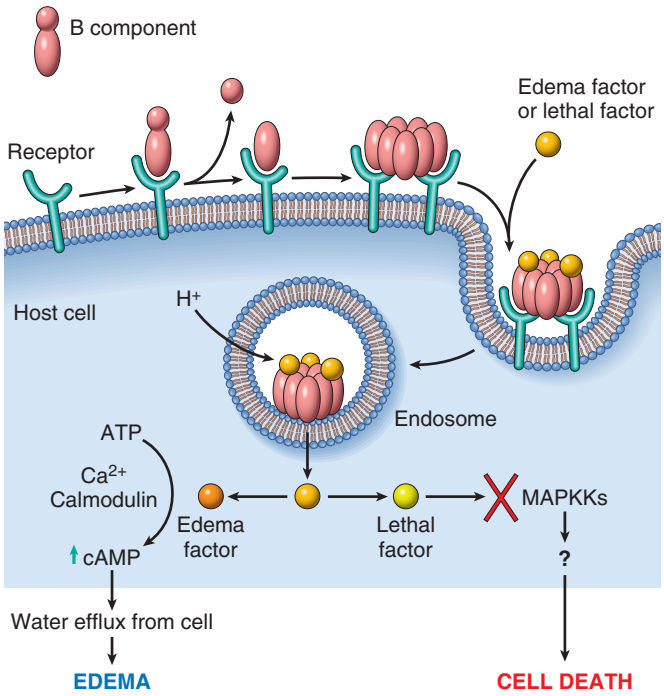

Figure 8–8 Mechanism of anthrax exotoxin action. The B component, also called "protective antigen," binds a cell-surface protein, is cleaved by a host protease, and forms a heptamer. Three A subunits of edema factor (EF) or lethal factor (LF) bind to the B heptamer, enter the cell, and are released into the cytoplasm. EF binds calcium and calmodulin to form an adenylate cyclase that increases intracellular cAMP, which causes efflux of water and interstitial edema. LF is a protease that destroys mitogen-activated protein kinase kinases (MAPKKs), leading to cell death. cAMP, cyclic adenosine monophosphate.

Injurious Effects of Host Immune Responses

As mentioned earlier, the host immune response to microbes can sometimes be the cause of tissue injury. The granulomatous inflammatory reaction to *M. tuberculosis* is

a delayed hypersensitivity response that sequesters the bacilli and prevents spread, but also produces tissue damage (caseous necrosis) and fibrosis. Similarly, the liver damage from HBV and HCV infection of hepatocytes is due mainly to the immune response to the infected liver cells and not to cytopathic effects of the virus. The humoral immune response to microbes also can have pathologic consequences. For example, poststreptococcal glomerulonephritis, which can develop after infection with *S. pyogenes,* is caused by antistreptococcal antibodies that bind to streptococcal antigens to form immune complexes, which deposit in renal glomeruli and produce nephritis. Thus, antimicrobial immune responses can have both beneficial and pathologic consequences.

Recent clinical, epidemiologic, and experimental studies suggest that infections may be associated with a wide variety of chronic inflammatory disorders as well as cancer. In some chronic inflammatory diseases, such as inflammatory bowel disease (Chapter 14), an important early event may be compromise of the intestinal epithelial barrier, which enables the entry of both pathogenic and commensal microbes and their interactions with local immune cells, resulting in inflammation. The cycle of inflammation and epithelial injury may be the basis for the disease, with microbes playing the central role. Certain viruses (HBV, HCV) and bacteria (*H. pylori*) that are not known to carry or to activate oncogenes are associated with cancers, presumably because these microbes trigger chronic inflammation with subsequent repair, which provides fertile ground for the development of cancer (Chapter 5).

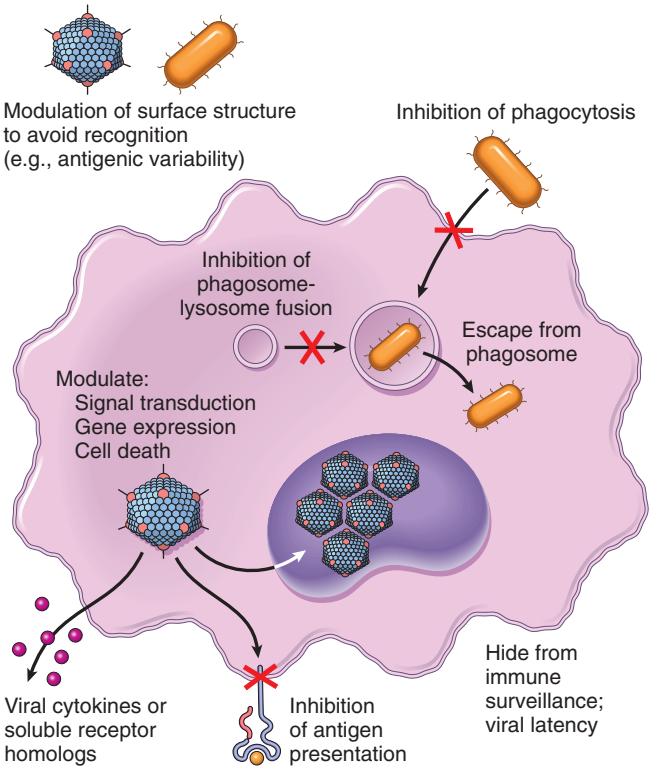

Figure 8–9 An overview of mechanisms used by viral and bacterial pathogens to evade innate and adaptive immunity.
(Modified with permission from Finlay B, McFadden G: Anti-immunology: evasion of the host immune system by bacterial and viral pathogens. Cell 124:767–782, 2006.)

SUMMARY

How Microorganisms Cause Disease

- Diseases caused by microbes involve an interplay of microbial virulence and host responses.
  - Infectious agents can cause cell death or dysfunction by directly interacting with the cell.
  - Injury may be due to local or systemic release of bacterial products, including endotoxins (LPS), exotoxins, or superantigens.
  - Pathogens can induce immune responses that cause tissue damage. Absence of an immune response may reduce the damage induced by some infections; conversely, immunocompromise can allow uncontrolled expansion of opportunistic agents or of microorganisms that can directly cause injury.

IMMUNE EVASION BY MICROBES

Humoral and cellular immune responses that protect the host from most infections are discussed in Chapter 4. Not surprisingly, microorganisms have developed many means to resist and evade the immune system (Fig. 8–9). These mechanisms, which are important determinants of microbial virulence and pathogenicity, include (1) antigenic variation, (2) resistance to innate immune defenses, and (3) impairment of effective T cell antimicrobial responses by specific or nonspecific immunosuppression.

Some microbes can evade immune responses by varying the antigens they express. Neutralizing antibodies block the ability of microbes to infect cells and recruit effector mechanisms to kill pathogens. To escape recognition, microbes use many strategies that involve genetic mechanisms for generating antigenic variation. The low fidelity of viral RNA polymerases (in HIV and many respiratory viruses including influenza virus) and reassortment of viral genomes (influenza viruses) create viral antigenic variation (Table 8–6). The spirochete *Borrelia recurrentis* repeatedly switches its surface antigens, and *Borrelia burgdorferi*, the

Table 8-6 Mechanisms of Antigenic Variation

Mechanism	Example	
	Agent(s)	Disease
High mutation rate	HIV	AIDS
	Influenza virus	Influenza
Genetic reassortment	Influenza virus	Influenza
	Rotavirus	Diarrhea
Genetic rearrangement (e.g., gene recombination, gene conversion, site-specific inversion)	*Borrelia burgdorferi*	Lyme disease
	Neisseria gonorrhoeae	Gonorrhea
	Trypanosoma spp.	African sleeping sickness
	Plasmodium spp.	Malaria
Large diversity of serotypes	Rhinoviruses	Colds
	Streptococcus pneumoniae	Pneumonia
		Meningitis

cause of Lyme disease, uses similar mechanisms to vary outer membrane proteins. *Trypanosoma* species have many genes for their major surface antigen, VSG, and can vary the expression of this surface protein. At least 80 different serotypes of *S. pneumoniae*, each with a different capsular polysaccharide, have been recognized.

Some microbes have devised methods for actively resisting immune defenses.

- Cationic antimicrobial peptides, including defensins, cathelicidins, and thrombocidins, provide important initial defenses against invading microbes. These peptides bind the bacterial membrane and form pores, killing the bacterium by hypoosmotic lysis. Bacterial pathogens (*Shigella* spp., *S. aureus*) avoid killing by making surface molecules that resist binding of antimicrobial peptides, or that inactivate or downregulate antimicrobial peptides by various mechanisms.
- Phagocytosis and killing of bacteria by polymorphonuclear leukocytes or neutrophils (PMNs) and monocytes constitute a critical host defense against extracellular bacteria. The carbohydrate capsule on the surface of many bacteria that cause pneumonia or meningitis (*S. pneumoniae, N. meningitidis, H. influenzae*) makes them more virulent by preventing phagocytosis of the organisms by neutrophils. Proteins on the surface of bacteria that inhibit phagocytosis include proteins A and M, expressed by *S. aureus* and *S. pyogenes,* respectively. Many bacteria make proteins that kill phagocytes, prevent their migration, or diminish their oxidative burst.
- *Viruses can produce molecules that inhibit innate immunity.* Viruses have developed a large number of strategies to combat interferons (IFNs), which are mediators of early host defense against viruses. Some viruses produce soluble homologues of IFN-α/β or IFN-γ receptors that bind to and inhibit actions of secreted IFNs, or produce proteins that inhibit intracellular JAK/STAT signaling downstream of IFN receptors. Viruses also may inactivate or inhibit double-stranded RNA–dependent protein kinase (PKR), a key mediator of the antiviral effects of IFN. Some viruses encode within their genomes homologues of cytokines, chemokines, or their receptors that act in various ways to inhibit immune responses. Finally, viruses have developed strategies to block apoptosis in the host cell, which may give the viruses time to replicate, persist or transform host cells.
- *Some microbes produce factors that decrease recognition of infected cells by CD4+ helper T cells and CD8+ cytotoxic T cells.* For example, several DNA viruses (e.g., herpesviruses, including HSV, CMV, and EBV) can bind to or alter localization of major histocompatibility complex (MHC) class I proteins, impairing peptide presentation to CD8+ cells. Downregulation of MHC class I molecules might make it likely that virus-infected cells would be targets for NK cells. However, herpesviruses also express MHC class I homologues that act as effective inhibitors of NK cells by engaging inhibitory receptors (Chapter 4). Herpesviruses can target MHC class II molecules for degradation, impairing antigen presentation to CD4+ T helper cells. Viruses also can infect leukocytes to directly compromise their function (e.g., HIV infects CD4+ T cells, macrophages, and dendritic cells).

SUMMARY

Immune Evasion by Microbes

After bypassing host tissue barriers, infectious microorganisms must also evade host innate and adaptive immunity mechanisms to successfully proliferate and be transmitted to the next host. Strategies include:

- Antigenic variation
- Inactivating antibodies or complement
- Resisting phagocytosis (e.g., by producing a capsule)
- Suppressing the host adaptive immune response (e.g., by inhibiting MHC expression and antigen presentation)

SPECTRUM OF INFLAMMATORY RESPONSES TO INFECTION

In contrast with the vast molecular diversity of microbes, the morphologic patterns of tissue responses to microbes are limited, as are the mechanisms directing these responses. Therefore, many pathogens produce similar reaction patterns, and few features are unique to or pathognomonic for a particular microorganism. It is the interaction between the microbe and the host that determines the histologic features of the inflammatory response.

There are five major histologic patterns of tissue reaction in infections: suppurative, mononuclear/granulomatous, cytopathic-cytoproliferative, necrosis, and chronic inflammation/scarring.

Suppurative (Purulent) Inflammation

This pattern is the reaction to acute tissue damage, characterized by increased vascular permeability and leukocytic infiltration, predominantly of neutrophils (Fig. 8–10). The neutrophils are attracted to the site of infection by release of chemoattractants from the "pyogenic" bacteria and host cells. Neutrophil enzymes cause liquefactive necrosis (Chapter 1).

MORPHOLOGY

Collections of neutrophils give rise to localized liquefactive necrosis, forming **abscesses.** The necrotic tissue and

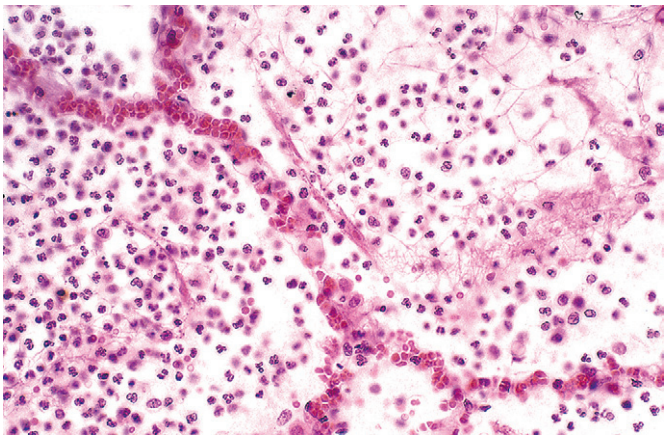

Figure 8–10 Pneumococcal pneumonia. Note the intra-alveolar polymorphonuclear exudate and intact alveolar septa.

inflammatory cells constitute pus, and bacteria that evoke pus formation are called "pyogenic." Typically, these are extracellular bacteria. The sizes of such lesions can vary from tiny microabscesses formed by bacteria seeding from an infected heart valve, to distended, pus-filled fallopian tubes caused by *N. gonorrhoeae*, to diffuse involvement of the meninges during *H. influenzae* infection, to entire lobes of the lung during pneumonia. The extent to which the lesions are destructive depends on their location and the organism involved. Thus, *S. pneumoniae* usually spares alveolar walls in the lung, and even lobar streptococcal pneumonias typically resolve completely without permanent damage (Fig. 8–10). On the other hand, *S. aureus* and *Klebsiella pneumoniae* destroy alveolar walls and form abscesses that heal with scar formation. Bacterial pharyngitis resolves without sequelae, whereas untreated acute bacterial infection can destroy a joint in a few days.

Mononuclear and Granulomatous Inflammation

Diffuse, predominantly mononuclear, interstitial infiltrates are a common feature of all chronic inflammatory processes, but development of such changes as an acute process often constitutes a response to viruses, intracellular bacteria, or intracellular parasites. In addition, spirochetes and some helminths provoke chronic mononuclear inflammatory responses.

MORPHOLOGY

Which mononuclear cell predominates within the inflammatory lesion depends on the host immune response to the organism. Thus, lymphocytes predominate in HBV infection (Fig. 8–11, *A*), whereas plasma cells are common in the primary and secondary lesions of syphilis (Fig. 8–11, *B*). The presence of these lymphoid cells reflects cell-mediated immune responses against the pathogen or pathogen-infected cells. Granulomatous inflammation is a distinctive form of mononuclear inflammation usually evoked by infectious agents that resist eradication (e.g., *M. tuberculosis, Histoplasma capsulatum,* schistosome eggs) but nevertheless are capable of stimulating strong T cell–mediated immunity. Granulomatous inflammation (Chapter 2) is characterized by accumulation of activated macrophages called "epithelioid" cells, which may fuse to form giant cells. In some cases, there is a central area of caseous necrosis (Fig. 8–11, *C*).

Cytopathic-Cytoproliferative Reaction

Cytopathic-cytoproliferative reactions usually are produced by viruses. The lesions are characterized by cell necrosis or cellular proliferation, usually with sparse inflammatory cells.

MORPHOLOGY

Some viruses replicate within cells and make viral aggregates that are visible as inclusion bodies (e.g., herpesviruses or adenovirus) or induce cells to fuse and form multinucleated cells called polykaryons (e.g., measles virus or herpesviruses) (Fig. 8–1). Focal cell damage in the skin may cause epithelial cells to become detached, forming blisters. Some viruses can cause epithelial cells to proliferate (e.g., venereal warts caused by HPV or the umbilicated papules of molluscum contagiosum caused by poxviruses). Finally, viruses can contribute to the development of malignant neoplasms (Chapter 5).

Tissue Necrosis

Clostridium perfringens and other organisms that secrete powerful toxins can cause such rapid and severe necrosis (gangrenous necrosis) that tissue damage is the dominant feature.

MORPHOLOGY

Because few inflammatory cells are present, necrotic lesions resemble infarcts with disruption or loss of basophilic nuclear staining and preservation of cellular outlines. Clostridia often are opportunistic pathogens that are introduced into muscle tissue by penetrating trauma or infection of the bowel in a neutropenic host. Similarly, the parasite *E. histolytica* causes colonic ulcers and liver abscesses characterized by extensive tissue destruction and liquefactive necrosis without a prominent inflammatory infiltrate. By entirely different mechanisms, viruses can cause widespread necrosis of host cells associated with inflammation, as exemplified by destruction of the temporal lobes of the brain by HSV or the liver by HBV.

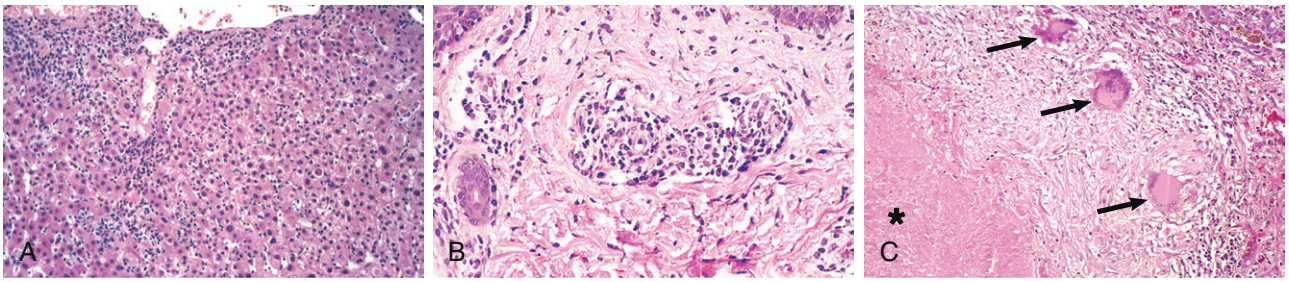

Figure 8–11 Mononuclear and granulomatous inflammation. **A,** Acute viral hepatitis characterized by a predominantly lymphocytic infiltrate. **B,** Secondary syphilis in the dermis with perivascular lymphoplasmacytic infiltrate and endothelial proliferation. **C,** Granulomatous inflammation in response to tuberculosis. Note the zone of caseation (*asterisk*), which normally forms the center of the granuloma, with a surrounding rim of activated epithelioid macrophages, some of which have fused to form giant cells (*arrows*); this in turn is surrounded by a zone of activated T lymphocytes. This high-magnification view highlights the histologic features; the granulomatous response typically takes the form of a three-dimensional sphere with the offending organism in the central area.

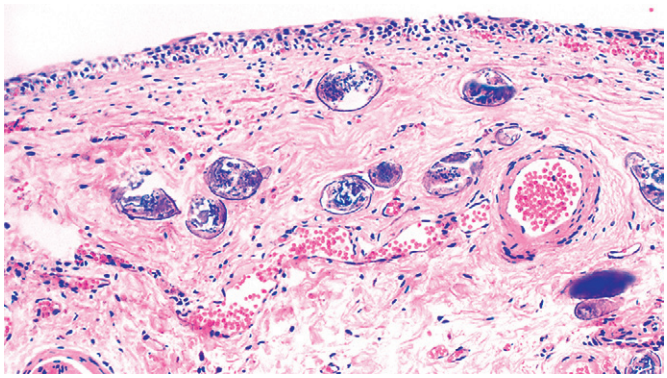

Figure 8–12 *Schistosoma haematobium* infection of the bladder with numerous calcified eggs and extensive scarring.

Chronic Inflammation and Scarring

Many infections elicit chronic inflammation, which can either resolve with complete healing or lead to extensive scarring.

MORPHOLOGY

Sometimes an exuberant scarring response is the major cause of dysfunction. For example, schistosome eggs cause "pipe-stem" fibrosis of the liver or fibrosis of the bladder wall (Fig. 8–12). *M. tuberculosis* causes constrictive fibrous pericarditis. Chronic HBV infection may cause cirrhosis of the liver, in which dense fibrous septa surround nodules of regenerating hepatocytes.

The patterns of tissue reactions described above are useful guidelines for analyzing microscopic features of infectious processes, but in practice it must be remembered that different types of host reactions often occur at the same time. For example, the lung of a patient with AIDS may be infected with CMV, which causes cytolytic changes, and, at the same time, by *Pneumocystis,* which causes interstitial inflammation. Similar patterns of inflammation also can be seen in tissue responses to physical or chemical agents and in inflammatory conditions of unknown cause (Chapter 2). Finally, in immunocompromised persons, the absence of a host inflammatory response frequently eliminates some of the histologic clues about the potential nature of infecting microorganism(s).

Infections in People with Immunodeficiencies

Inherited or acquired defects in immunity (Chapter 4) often impair only part of the immune system, rendering the affected persons susceptible to specific types of infections. Patients with antibody deficiency, as in X-linked agammaglobulinemia, contract severe bacterial infections by extracellular bacteria and a few viral infections (rotavirus and enteroviruses). Patients with T cell defects are susceptible to infections with intracellular pathogens, notably viruses and some parasites. Patients with deficiencies in early complement components are particularly susceptible to infections by encapsulated bacteria, such as *S. pneumoniae,* whereas deficiencies of the late components of complement are associated with *Neisseria* infections. Deficiencies in neutrophil function lead to increased infections with *S. aureus,* some gram-negative bacteria, and fungi. People with inherited deficiencies in mediators of innate and adaptive immunity sometimes show strikingly selective susceptibility to specific types of infections. These patterns reveal the essential roles of particular molecules in mediating protective immunity to specific microorganisms. For example, patients with mutations in signaling molecules downstream of several TLRs are prone to pyogenic bacterial diseases, particularly with *S. pneumoniae* infections. Impaired TLR3 responses are associated with childhood HSV encephalitis. Inherited defects in IL-17 immunity (such as mutations in STAT3, a transcription factor needed for T_H17 cell generation) are associated with chronic mucocutaneous candidiasis.

Acquired immunodeficiencies have a variety of causes, the most important being infection with HIV, which causes AIDS (Chapter 4). HIV infects and kills CD4+ helper T lymphocytes, leading to profound immunosuppression and a multitude of infections. Other causes of acquired immunodeficiency include infiltrative processes that suppress bone marrow function (e.g., leukemia), immunosuppressive drugs (such as those used to treat certain autoimmune diseases), and hemopoietic stem cell transplantation. Diseases of organ systems other than the immune system also can make patients susceptible to disease due to specific microorganisms. People with cystic fibrosis commonly get respiratory infections caused by *P. aeruginosa.* Lack of splenic function in persons with sickle cell disease makes them susceptible to infection with encapsulated bacteria such as *S. pneumoniae.* Burns destroy skin, removing this barrier to microbes, allowing infection with pathogens such as *P. aeruginosa.* Finally, malnutrition impairs immune defenses.

MORPHOLOGY

Patients with antibody, complement, or neutrophil defects may acquire severe local bacterial infections that do not elicit any significant neutrophilic infiltrate. In these patients, the identity of the causative organism may only be inferred by culture or appearance on special stains. Although many viral cytopathic effects (e.g., cell fusion or inclusions) (Fig. 8–1) may still be present, viral infections in immunocompromised hosts may not engender the anticipated mononuclear inflammatory response. In patients with AIDS who have no helper T cells and cannot mount normal cellular responses, organisms that would otherwise cause granulomatous inflammation (e.g., *M. avium complex*) fail to do so (Fig. 8–13).

SUMMARY

Patterns of Host Responses to Microbes

- In normal (immunocompetent) persons, the patterns of host responses are fairly stereotypical for different classes of microbes; these response patterns can be used to infer possible causal organisms.

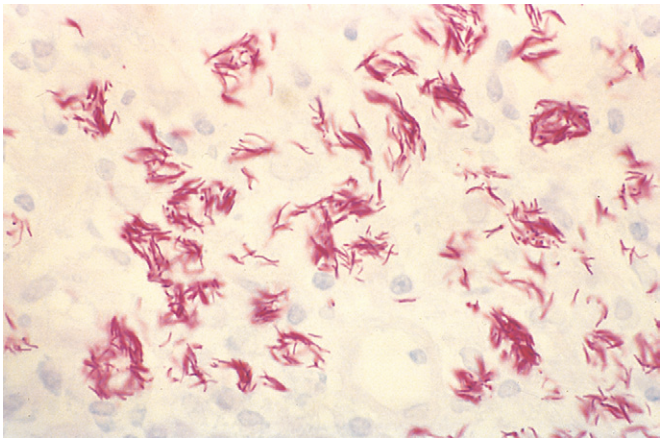

Figure 8–13 In the absence of appropriate T cell–mediated immunity, granulomatous host response does not occur. *Mycobacterium avium* infection in a patient with AIDS, showing massive intracellular macrophage infection with acid-fast organisms (filamentous and pink in this acid-fast stain preparation). The intracellular bacteria persist and even proliferate within macrophages, because there are inadequate T cells to mount a granulomatous response. AIDS, acquired immunodeficiency syndrome.

- Neutrophil-rich acute suppurative inflammation is typical of infections with many bacteria ("pyogenic" bacteria) and some fungi.
- Mononuclear cell infiltrates are common in many chronic infections and some acute viral infections.
- Granulomatous inflammation is the hallmark of infection with *Mycobacterium tuberculosis* and certain fungi.
- Cytopathic and proliferative lesions are caused by some viruses.
- Chronic inflammation and scarring represent the final common pathway of many infections.

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