بسم الله الرحمن الرحيم

Infectious disease pathology

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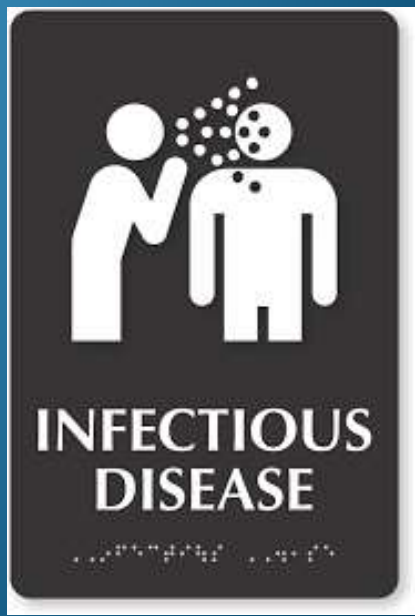
دانشکده پزشکی



- This chapter reviews the general principles of the pathogenesis of infectious disease and describes the characteristic histopathologic changes for different disease categories.

- 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:

elderly, AIDS , chronic diseases , receiving immunosuppressive drugs.

- In developing countries, unsanitary living conditions and malnutrition → infectious diseases that kills more than 10 million people each year.
- The most common victims: children with respiratory and diarrheal infections.

Categories of Infectious Agents

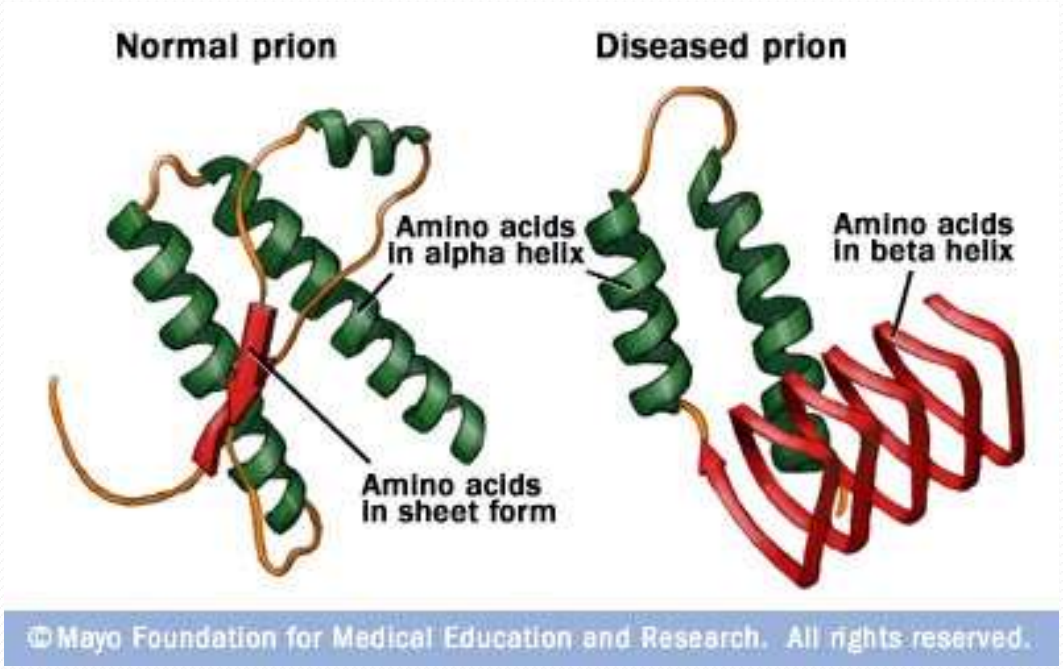
- **Prions**
- **Viruses**
- **Bacteria**
- **Fungi**
- **Protozoa**
- **Helminths**
- **Ectoparasites**

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

Prions

- Abnormal forms of a host protein termed *prion protein* (PrP).



Cause transmissible spongiform encephalopathies, including:

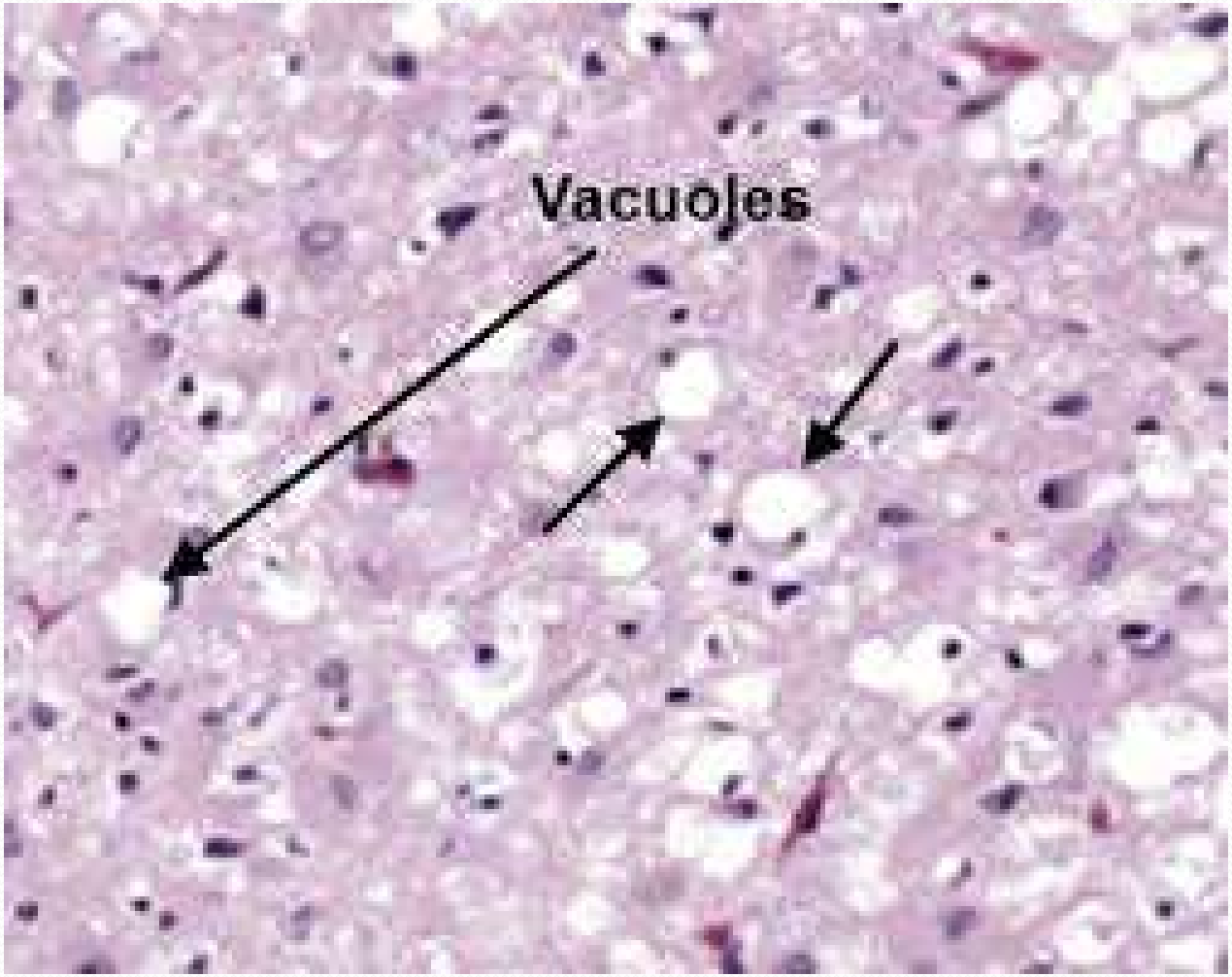
- **Kuru** (human cannibalism), Creutzfeldt-Jakob disease (CJD), bovine spongiform encephalopathy (BSE) ("mad cow disease"), and variant Creutzfeldt-Jakob disease (vCJD) (meat from BSE-infected cattle).

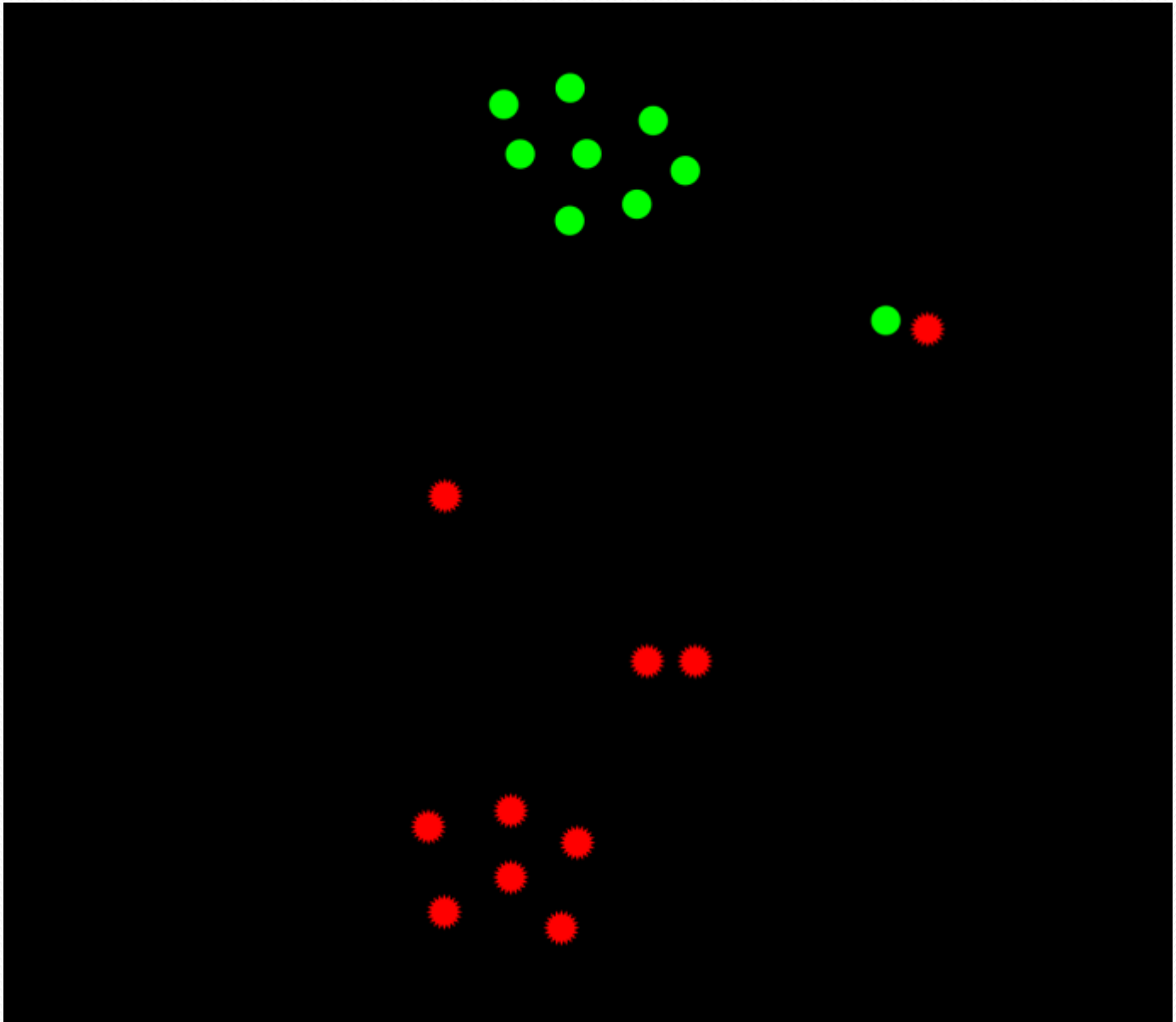
- PrP is found normally in neurons. Diseases occur when the PrP undergoes a conformational change that confers resistance to proteases.

- The protease-resistant PrP promotes conversion of the normal protease-sensitive PrP to the abnormal form.

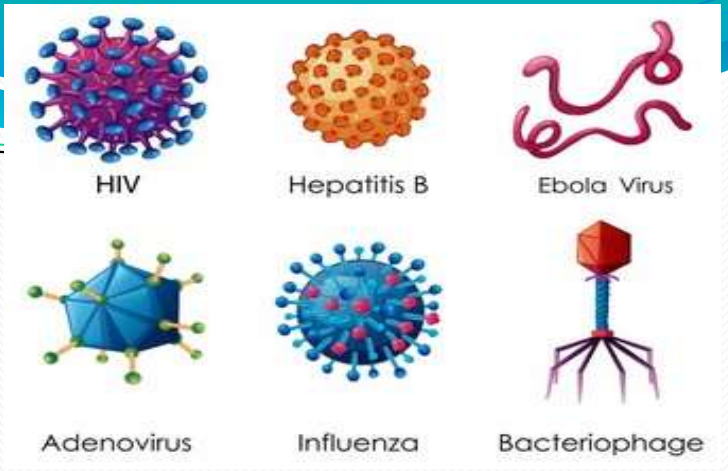
- Accumulation of abnormal PrP leads to neuronal damage and distinctive spongiform pathologic changes in the brain.
- Spontaneous and inherited mutations have been observed in the sporadic and familial forms of CJD, respectively.

- CJD can be transmitted from person to person iatrogenically, by surgery, organ transplantation, or blood transfusion.


Vacuoles

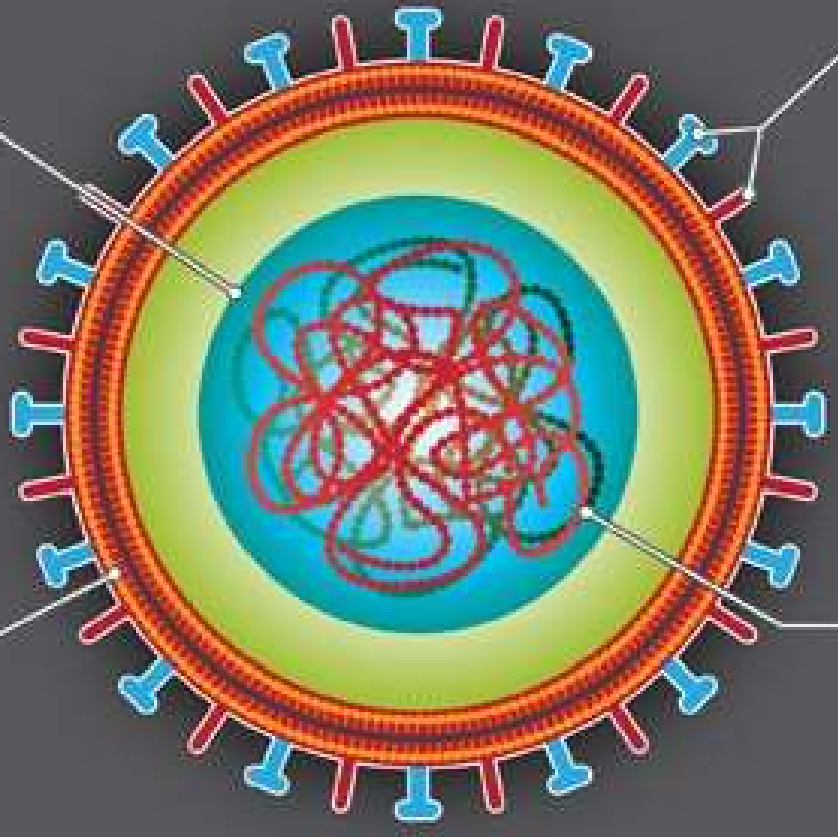


Viruses



- **Viruses :**are obligate intracellular agents that depend on the host's metabolic machinery for their replication.
- Viruses are classified by the type of nucleic acid they contain-either DNA or RNA and by the shape of their protein coat, or capsid, the presence or absence of a lipid envelope, their mode of replication, the preferred cell type for replication (called tropism), or the type of pathology they cause.

VIRUS STRUCTURE

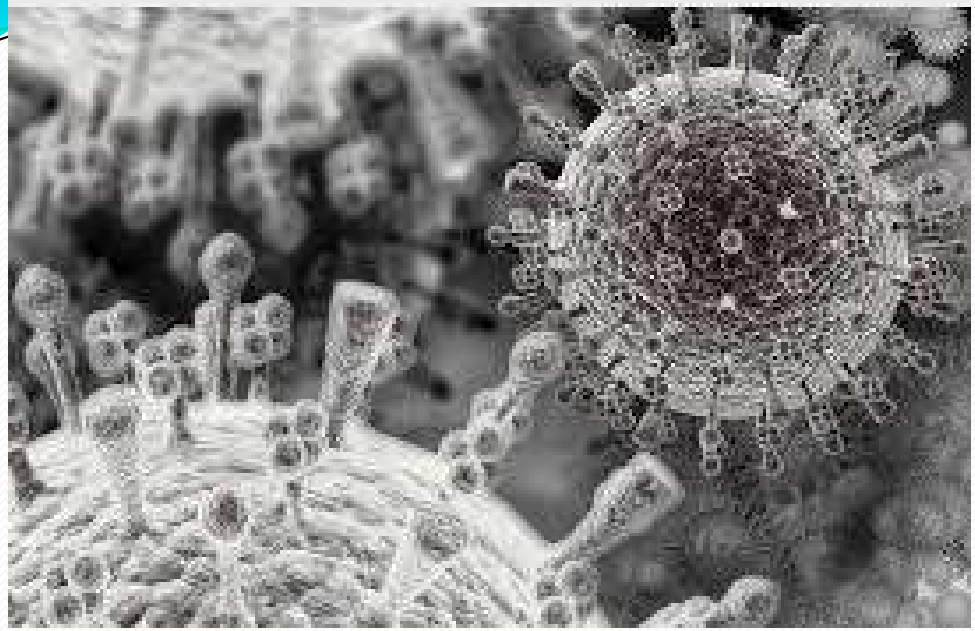


Capsid
The capsid contains the virus' genetic material (DNA or RNA)

Surface proteins
These help the virus recognise and bind to cells in the host organism

Viral envelope
The viral envelope is made from fatty lipid molecules taken from cells in the host

Virus genetic material (DNA or RNA)
The virus' genetic material contains the instructions for making new copies of the virus



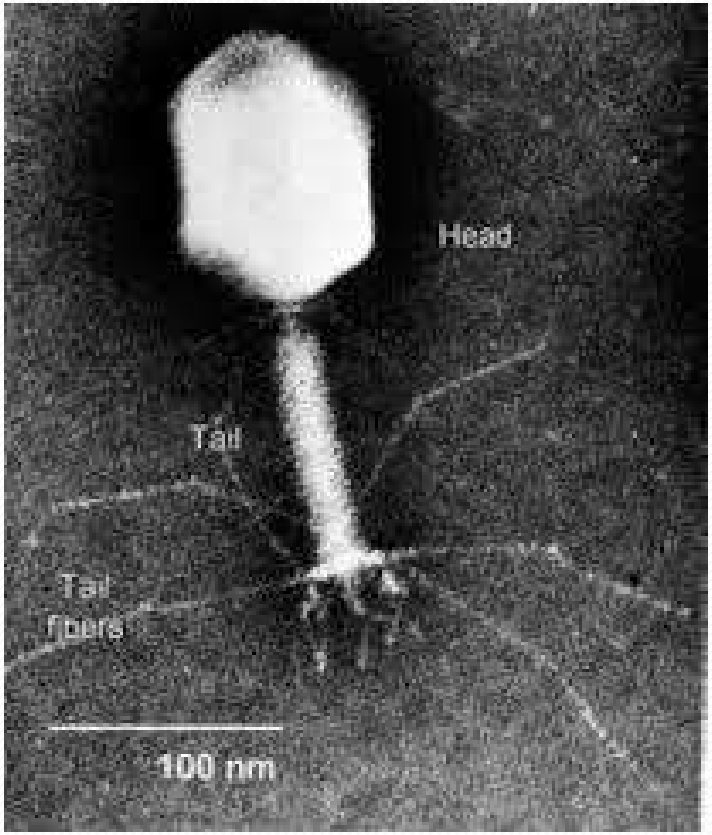

Head
Tail
Tail fibers
100 nm

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.

- 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

- CMV,HSV, smallpox and rabies

- many viruses (e.g., poliovirus) **do not** produce inclusions.

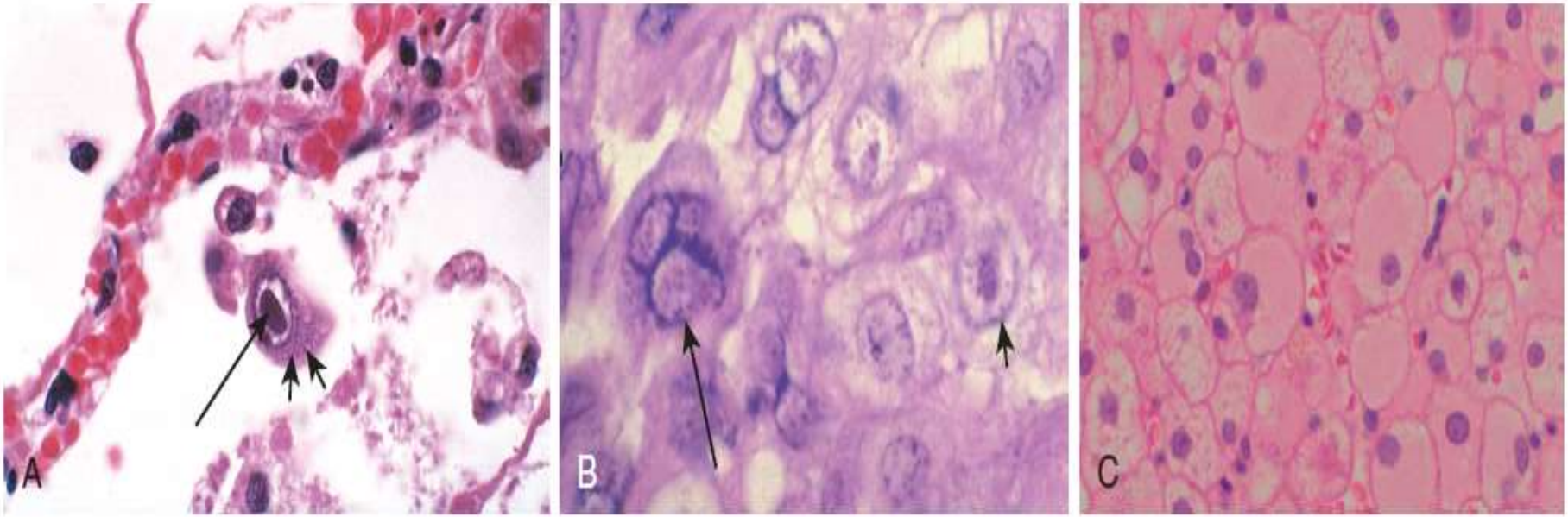


Figure 8–1 Examples of viral inclusions. **A,** Cytomegalovirus infection in the lung. Infected cells show distinct nuclear (*long arrow*) and ill-defined cytoplasmic (*short arrows*) inclusions. **B,** Varicella-zoster virus infection in the skin. Herpes simplex virus and varicella-zoster virus both 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).

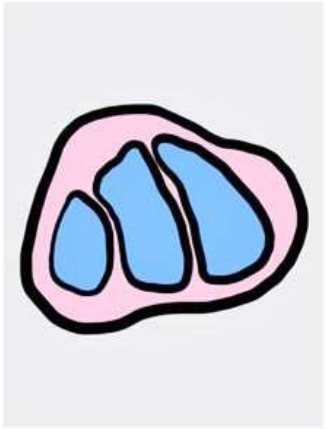
HSV Infection

Multinucleation

Moulding

Margination of chromatin

(Ground glass chromatin)

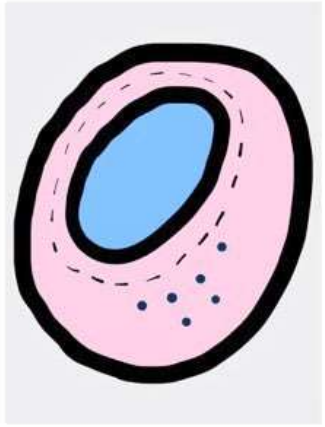


CMV Infection

Single, large, basophilic intranuclear inclusion

Perinuclear halo

Stippled cytoplasmic inclusions

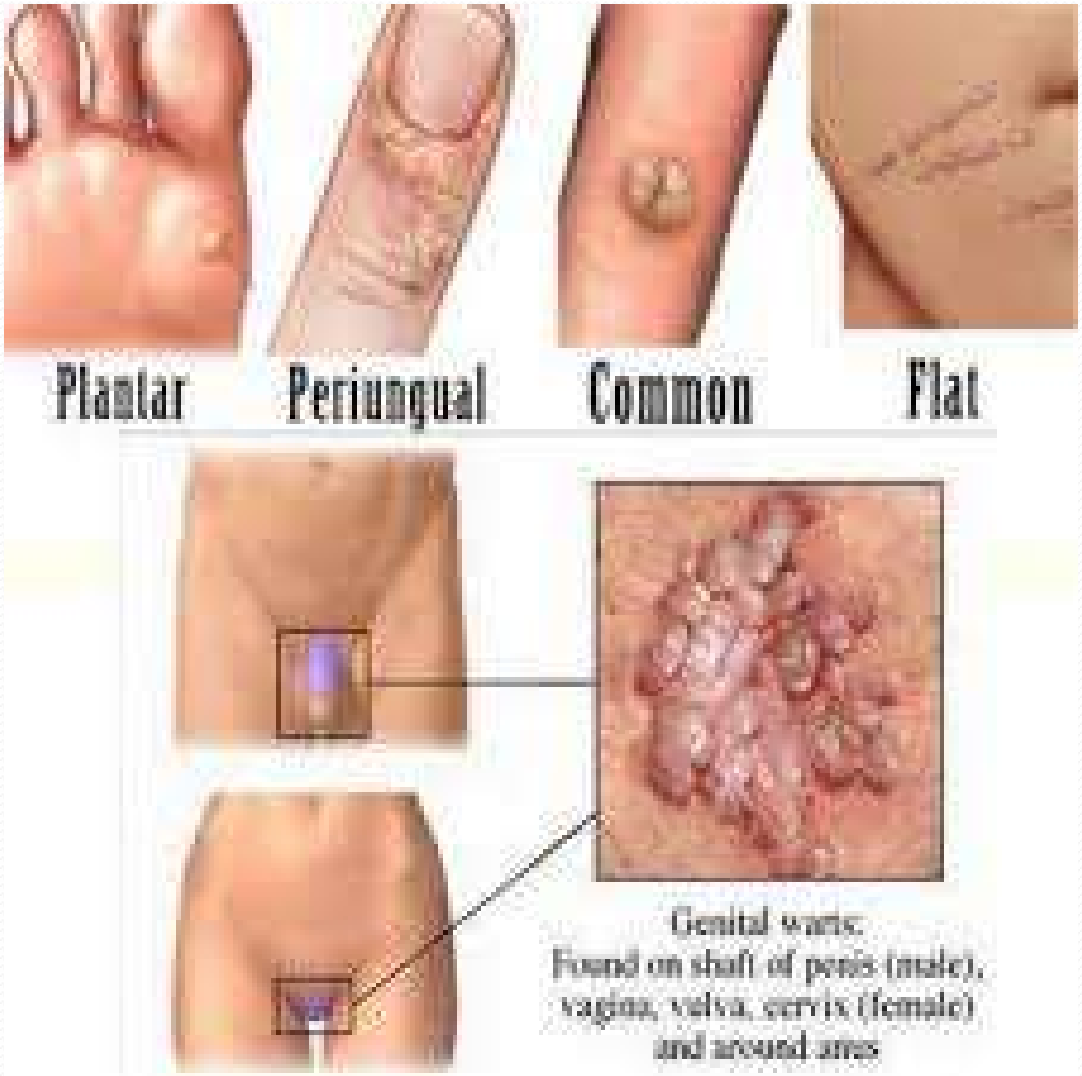


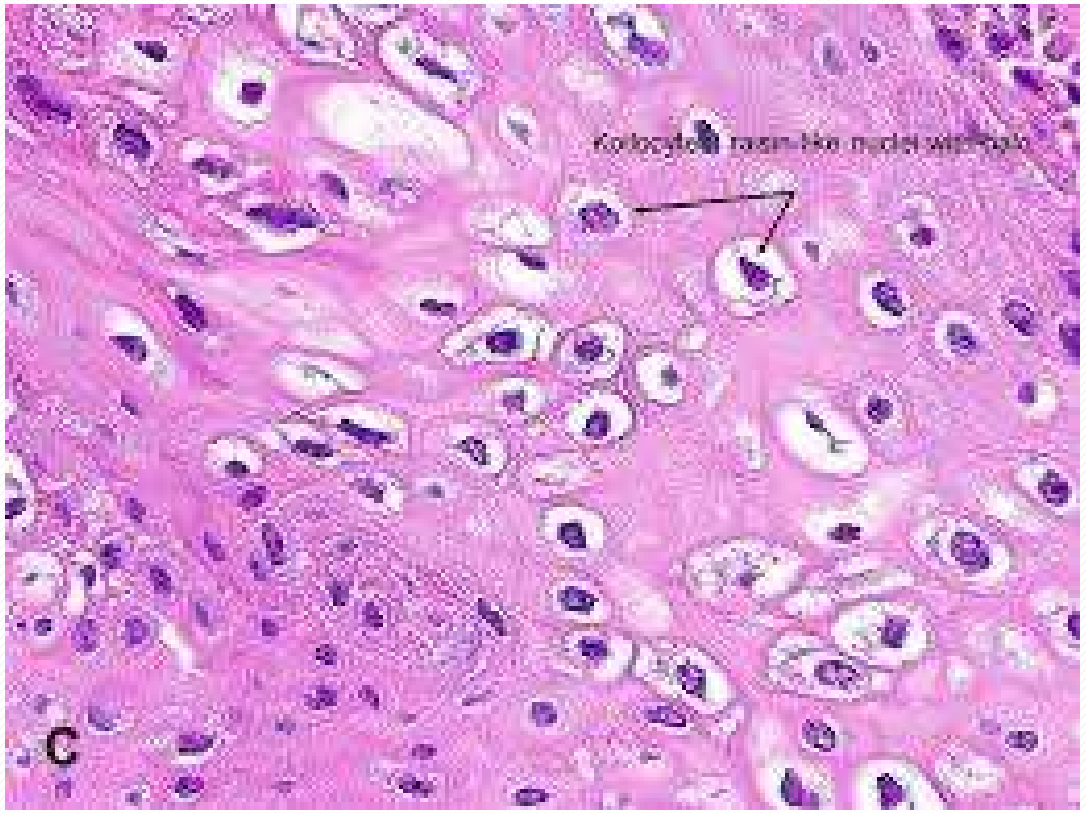
- Accounting for a large share of human infections, viruses can cause illnesses in several ways. Many viruses cause transient illnesses (e.g., colds, influenza).

- Other viruses are not eliminated from the body but persist for years, continuing to multiply and remaining demonstrable (e.g., chronic infection with hepatitis B virus)
- or surviving in some latent noninfectious form with the potential to be reactivated later:
- For example, the herpes zoster virus, the cause of chickenpox, may persist in the dorsal root ganglia and be periodically activated to cause the painful skin condition called *shingles*.

- Different species of viruses can produce the same pathologic features (e.g., upper respiratory tract infections), and a single virus (e.g., CMV) can produce different clinical manifestations depending on the host's resistance and age

- 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).


Plantar
Periungual
Common
Flat
Genital warts:
Found on shaft of penis (male),
vagina, vulva, cervix (female)
and around anus


C

Genital HPV Types

HPV TYPE	CLINICAL FINDINGS	CANCER POTENTIAL
6, **11**	genital warts, low grade genital lesions, RRP	Low (negligible)
40, 42, 43, 44, 54, 61, 70, 71, 72, 81	low grade genital lesions	Low (negligible)
16, **18**, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82	low & high grade genital lesions, cancer	High

Uncertain cancer potential:
HPV 26, 34, 53, 57, 66, 83

Bacteria

- Bacteria are prokaryotes, meaning that they have a cell membrane but lack membrane-bound nuclei and other membrane-enclosed organelles

- Bacteria have two forms of cell wall:(gram-negative organisms and gram-positive organisms). A normal healthy person is colonized by as many as 10^{12} bacteria on the skin, 10^{10} bacteria in the mouth, and 10^{14} bacteria in the alimentary tract

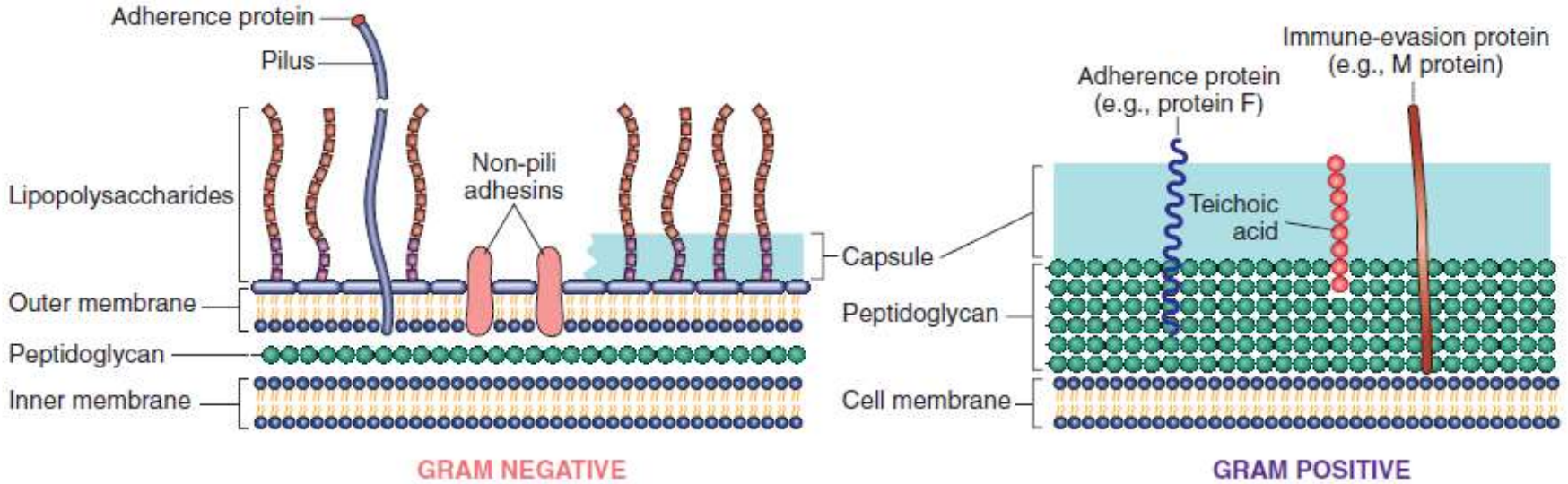
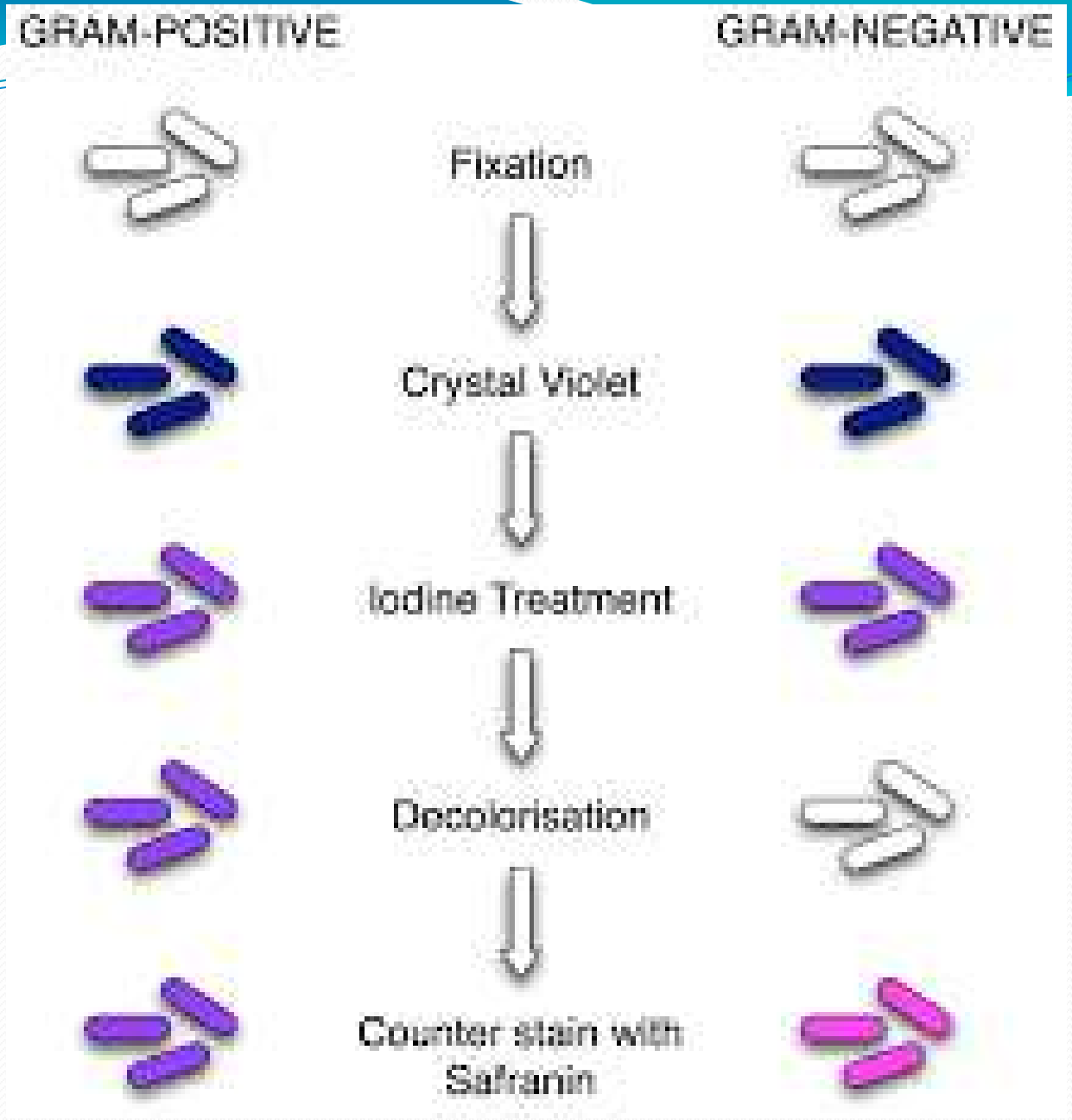
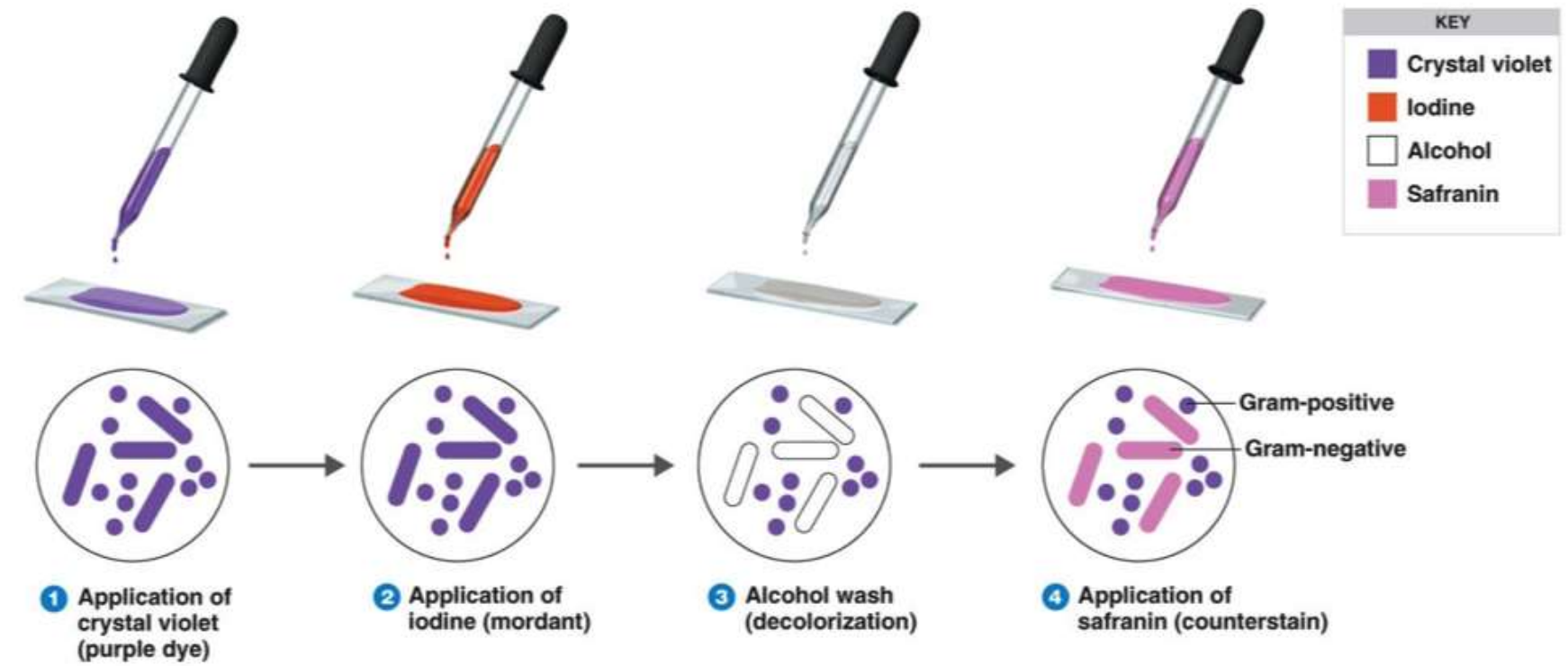
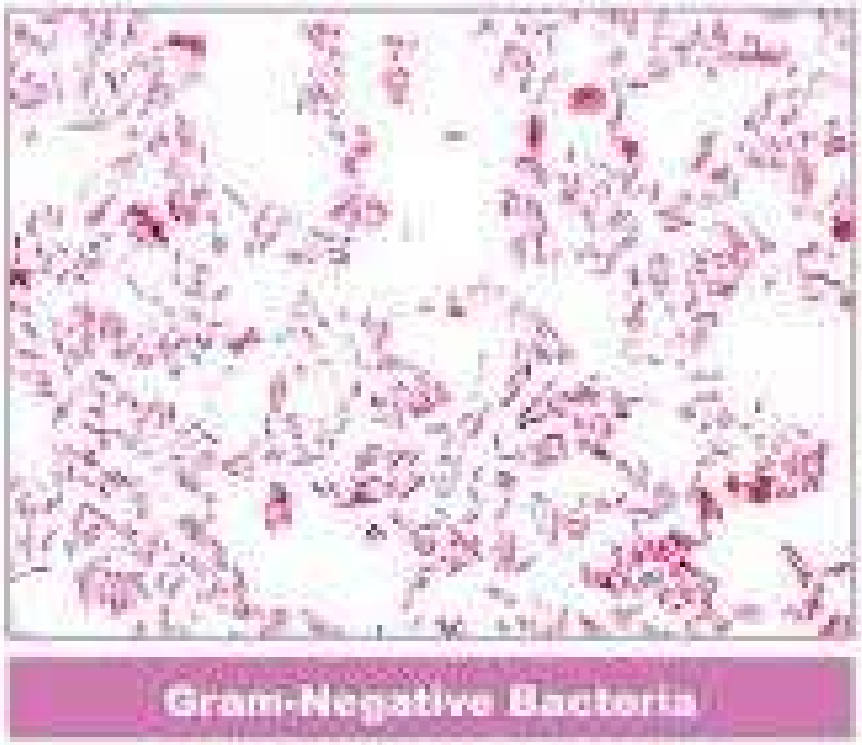


Figure 8–2 Molecules on the surface of gram-negative and gram-positive bacteria involved in the pathogenesis of infection.

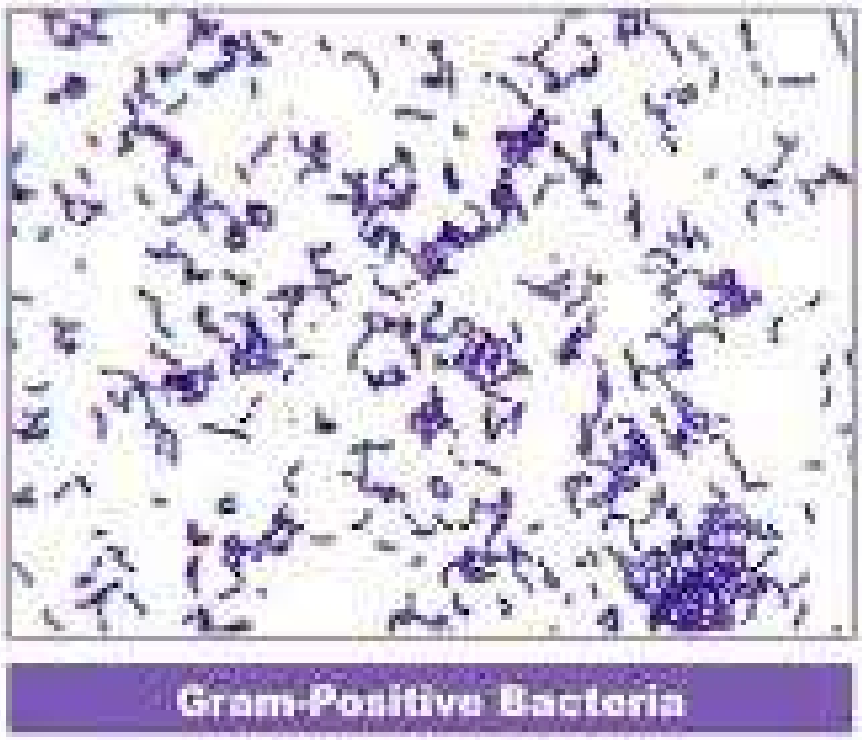
Gram stain


GRAM-POSITIVE
GRAM-NEGATIVE
Fixation
Crystal Violet
Iodine Treatment
Decolorisation
Counter stain with Safranin

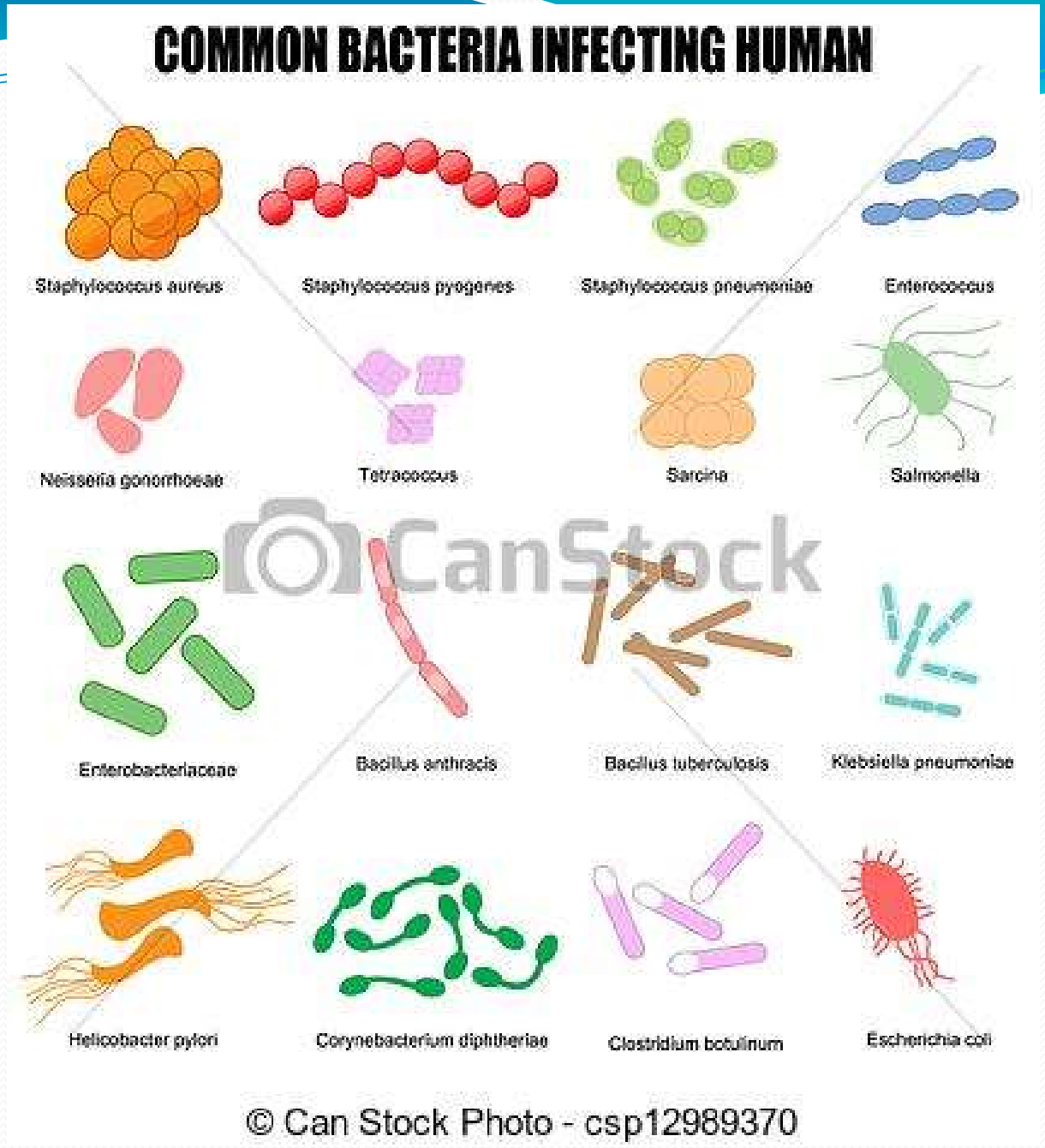

KEY
Crystal violet
Iodine
Alcohol
Safranin
Gram-positive
Gram-negative
1 Application of crystal violet (purple dye)
2 Application of iodine (mordant)
3 Alcohol wash (decolorization)
4 Application of safranin (counterstain)



Gram-Negative Bacteria



Gram-Positive Bacteria


COMMON BACTERIA INFECTING HUMAN
Staphylococcus aureus
Staphylococcus pyogenes
Staphylococcus pneumoniae
Enterococcus
Neisseria gonorrhoeae
Tetracoccus
Sarcina
Salmonella
Enterobacteriaceae
Bacillus anthracis
Bacillus tuberculosis
Klebsiella pneumoniae
Helicobacter pylori
Corynebacterium diphtheriae
Clostridium botulinum
Escherichia coli
© Can Stock Photo - csp12989370

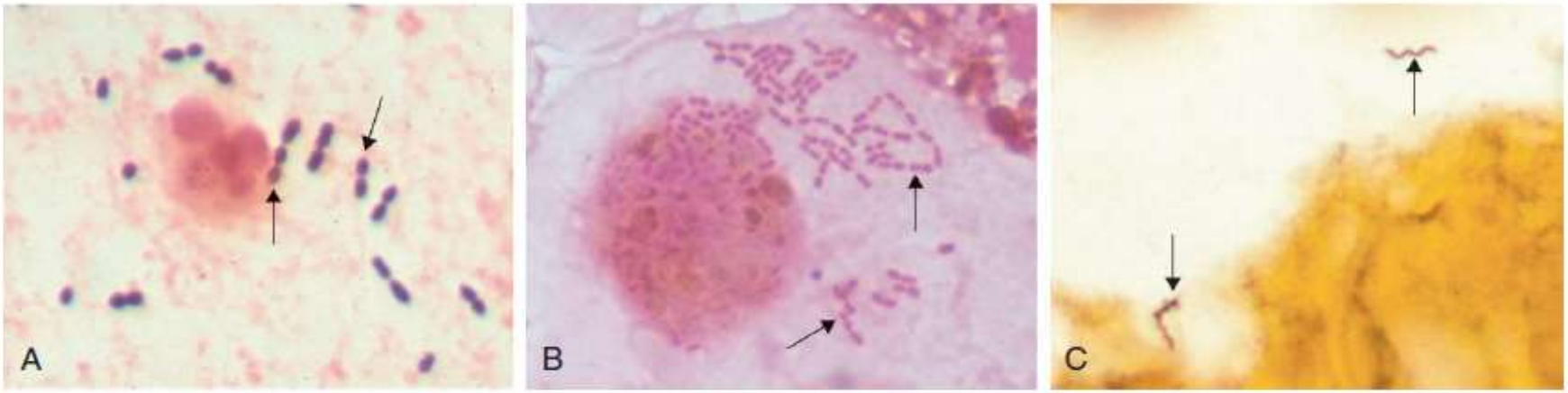


Figure 8–3 The variety of bacterial morphology. The bacteria are indicated by *arrows*. **A,** Gram stain preparation of sputum from a patient with pneumonia. Gram-positive, elongated cocci in pairs and short chains (*Streptococcus pneumoniae*) and a neutrophil are evident. **B,** Gram stain preparation 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.

Chlamydiae, Rickettsias, and Mycoplasmas

- These infectious agents are grouped together because they are similar to bacteria but lack certain structures or metabolic capabilities (they cannot synthesize ATP).
- Chlamydia and rickettsiae are obligate intracellular agents that replicate in phagosomes of epithelial cells and in the cytoplasm of endothelial cells, respectively.
- *C. trachomatis* is the leading infectious cause of female sterility (by scarring and narrowing the fallopian tubes) and blindness (by trachoma, a chronic inflammation of the conjunctiva that eventually scars and opacifies the cornea).
- *Mycoplasma and Ureaplasma* organisms do not have a rigid cell wall

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.

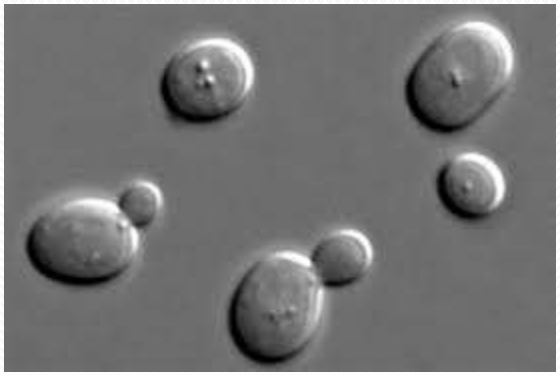
Normal microbiome

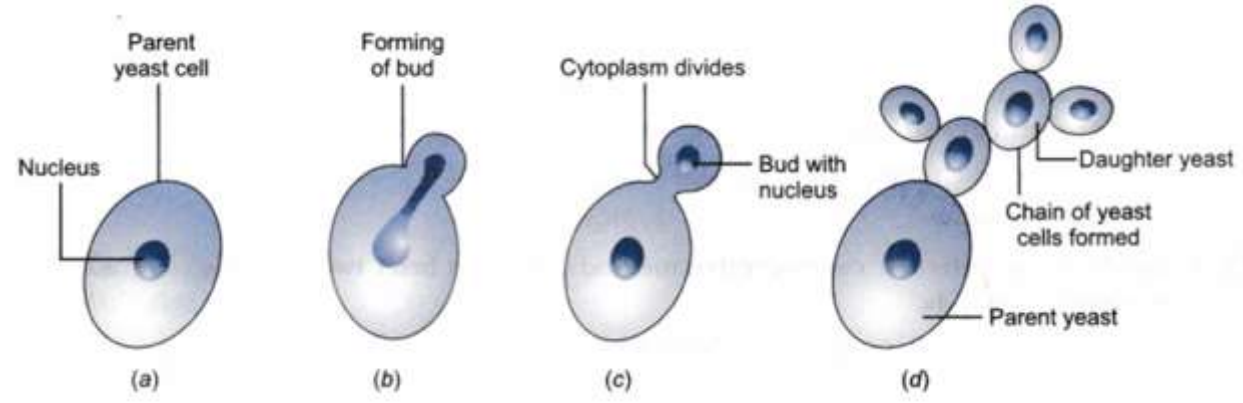
- The intestinal tract and skin normally are colonized by a large number and diversity of bacterial species.
- This ecosystem of microbes and their genes and products that humans live with is called the *microbiome*.
- In the intestinal tract, the microbiota are responsible not only for absorption of 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

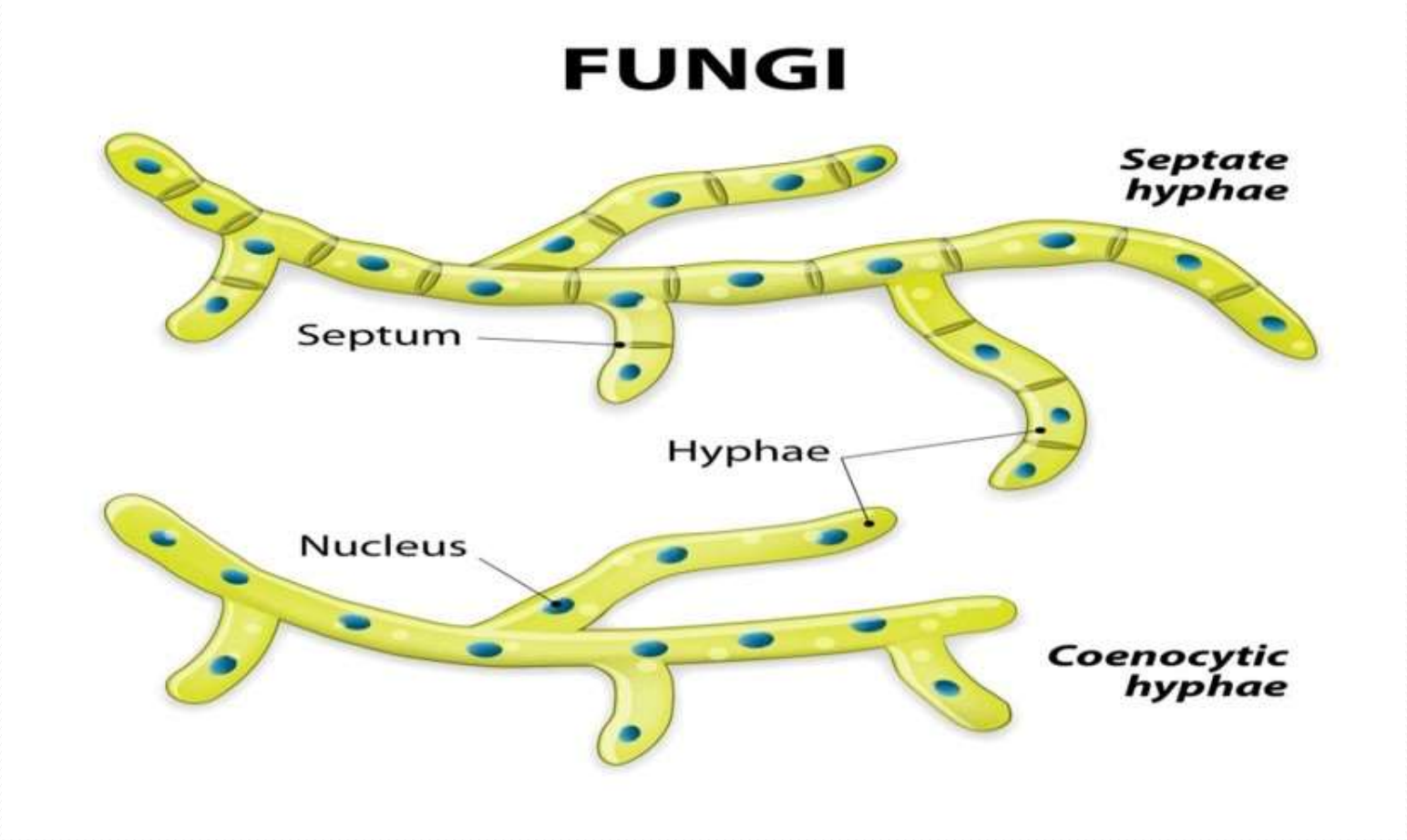
Fungi

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.

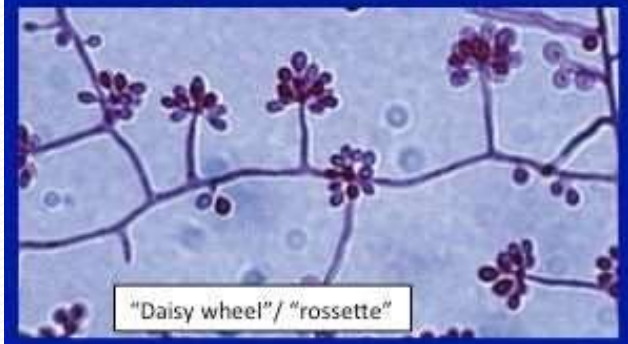



Parent
yeast cell
Nucleus
(a)
Forming
of bud
(b)
Cytoplasm divides
Bud with
nucleus
(c)
Daughter yeast
Chain of yeast
cells formed
Parent yeast
(d)


FUNGI
Septate hyphae
Septum
Hyphae
Nucleus
Coenocytic hyphae

- 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

Dimorphic fungi - II

Mold – 30^0 C		Yeast – 37^{0}C
 "Daisy wheel"/ "rossette"	*Sporothrix*	 "Cigar" bodies
Nonspecific	*Paracoccidioidomyces*	 Mariner's wheel
	*Penicillium Marneffei*	

- 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 to destroy vital organs in immunocompromised hosts but heal spontaneously or remain latent in otherwise normal hosts.
- Some deep fungal species are limited to a particular geographic region (e.g., *Coccidioides* in the Far West and *Histoplasma* in the Ohio River Valley).
- Opportunistic fungi (e.g., *Candida, Aspergillus, Mucor*, and *Cryptococcus)* by contrast, are ubiquitous contaminants.

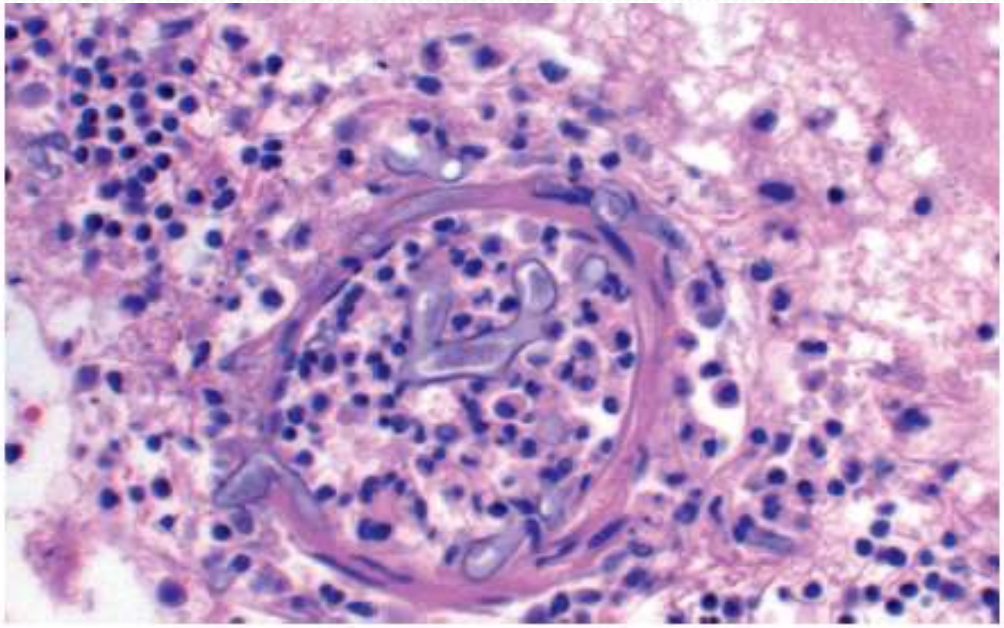


Figure 8–4 Meningeal blood vessels with angioinvasive *Mucor* species. Note the irregular width and near right-angle branching of the hyphae.

Protozoal parasites

- 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

- 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

- Their life cycles are complex. 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.

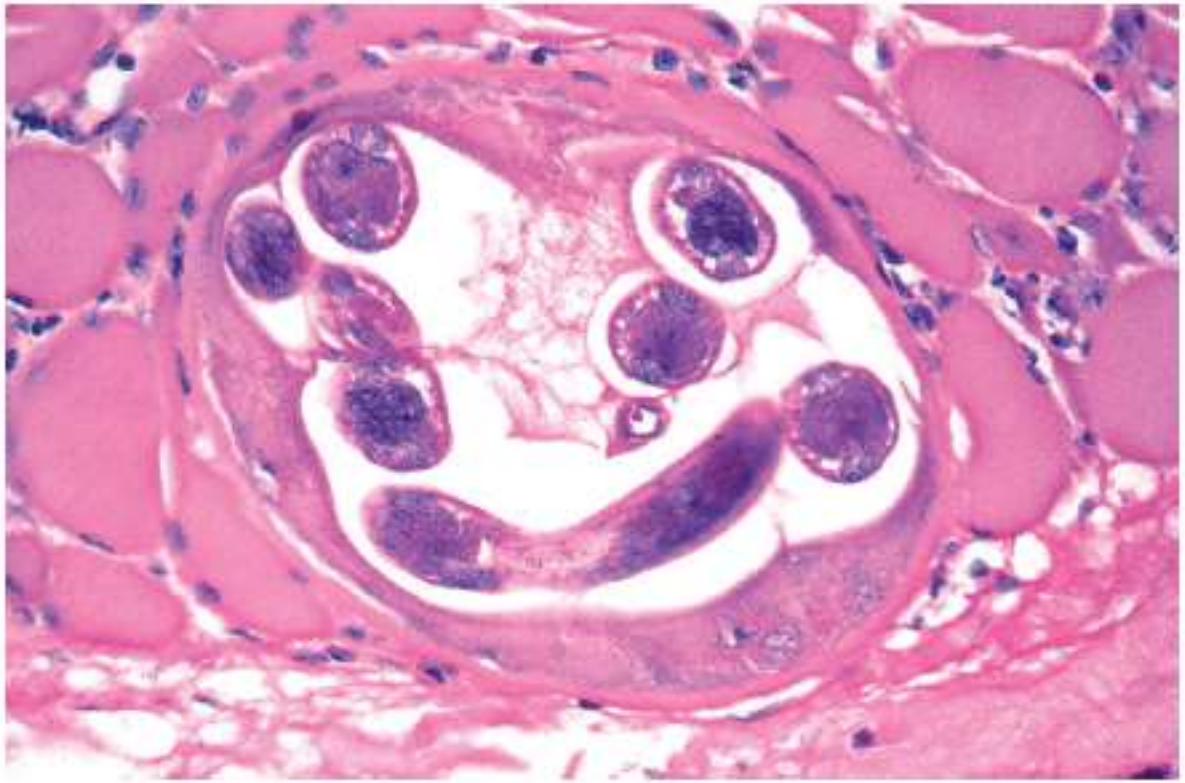


Figure 8–5 Coiled *Trichinella spiralis* larva within a skeletal muscle cell.

Helminths comprise three groups:

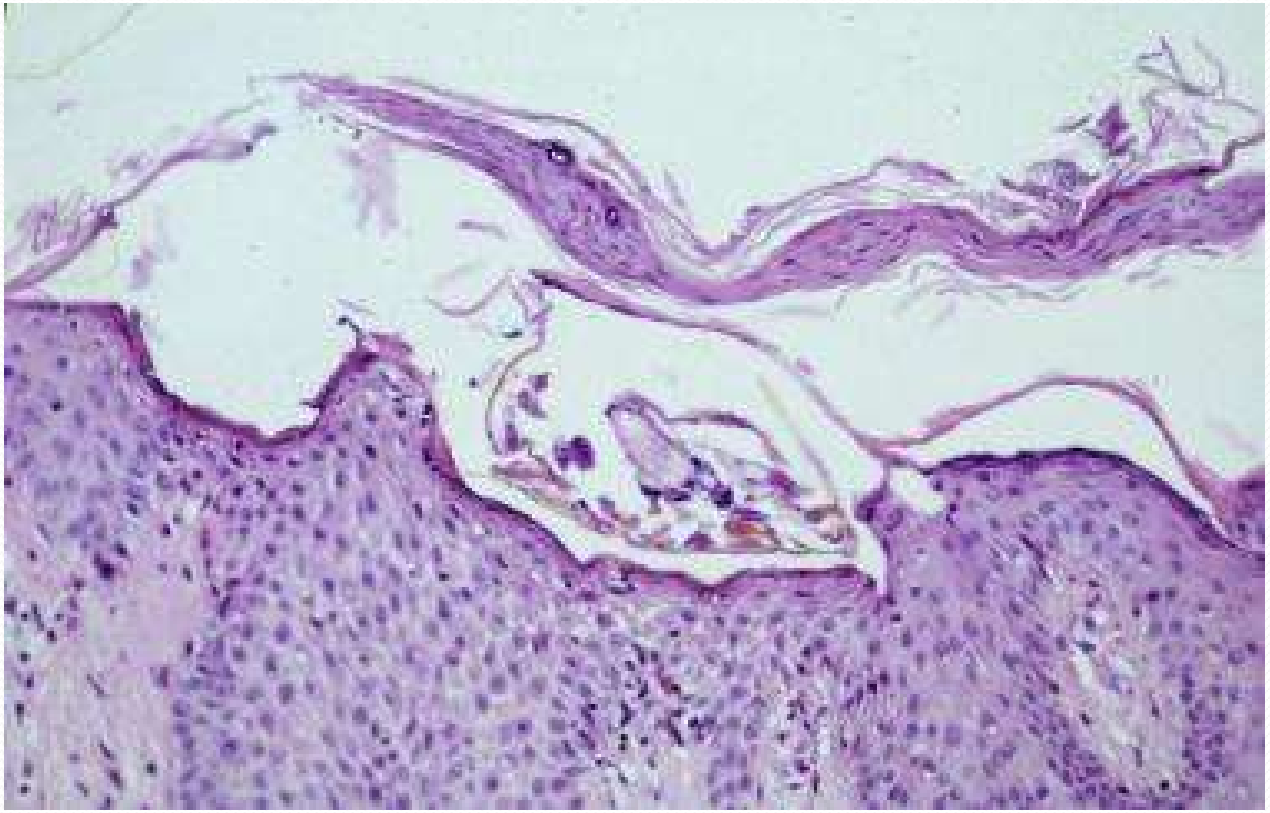
- Roundworms (nematodes)

- Tapeworms (cestodes)

- Flukes (trematodes)

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

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

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.

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

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).

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.*

- 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).

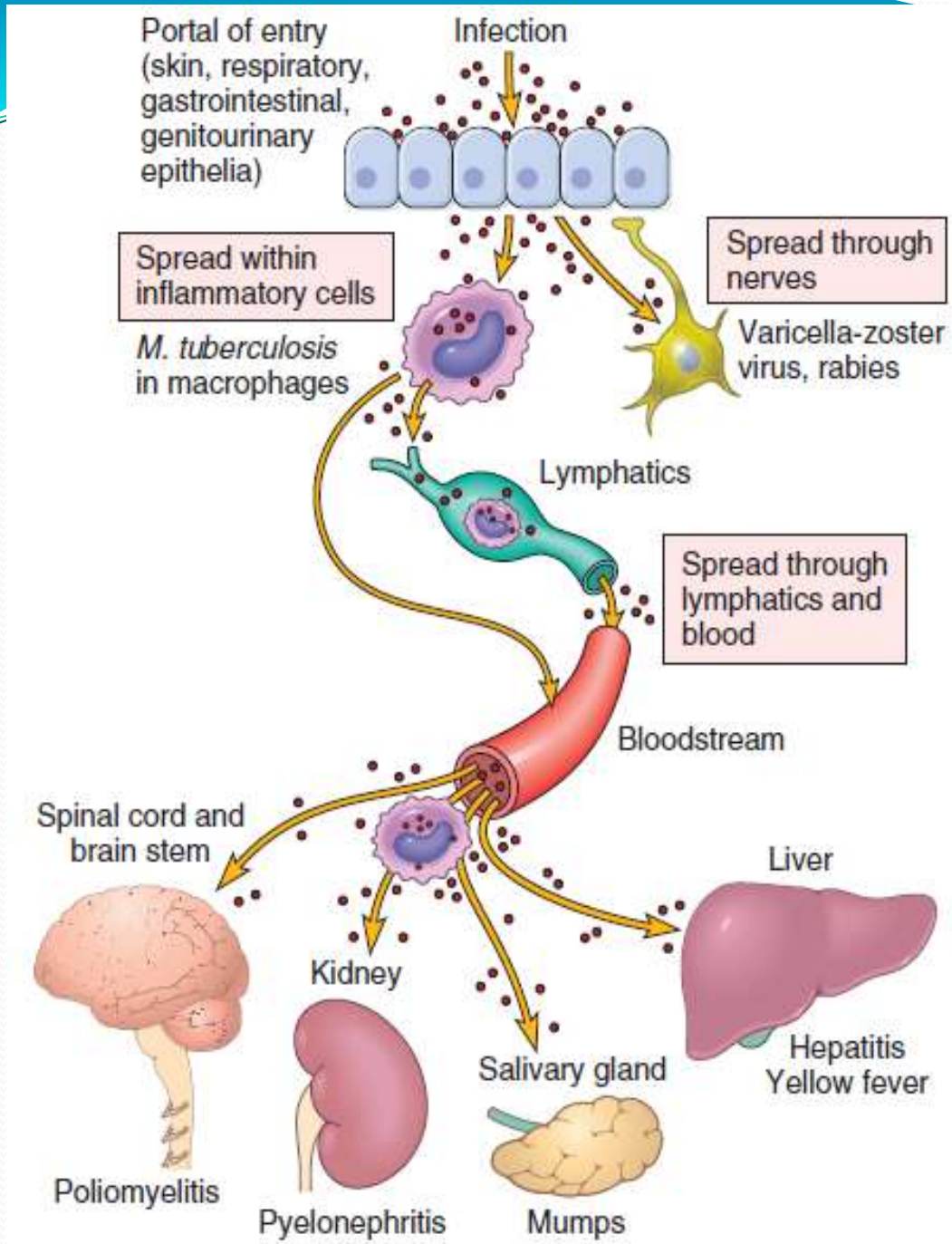


Figure 8–6 Routes of entry and dissemination of microbes. To enter the body, microbes penetrate epithelial or mucosal barriers. Infection may remain localized at the site of entry or spread to other sites in the body. Most common microbes (selected examples are shown) spread through the lymphatics or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

- 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 non virulent microbes 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.

Release from the Body and 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.

They are necessary to overcome the infection but at the same time may directly contribute to tissue damage.

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

- *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.

- 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).

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.
- Plasmids and bacteriophages (viruses) are genetic elements that spread between bacteria and can encode virulence factors, including toxins, or enzymes that confer antibiotic resistance.

- 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.

- *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.
- *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

- *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
- *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
- *Toxins that alter intracellular signaling or regulatory pathways*
- *Super antigens*
- *Neurotoxins* produced by *Clostridium botulinum* and *Clostridium tetani* inhibit release of neurotransmitters, resulting in paralysis
- Enterotoxins

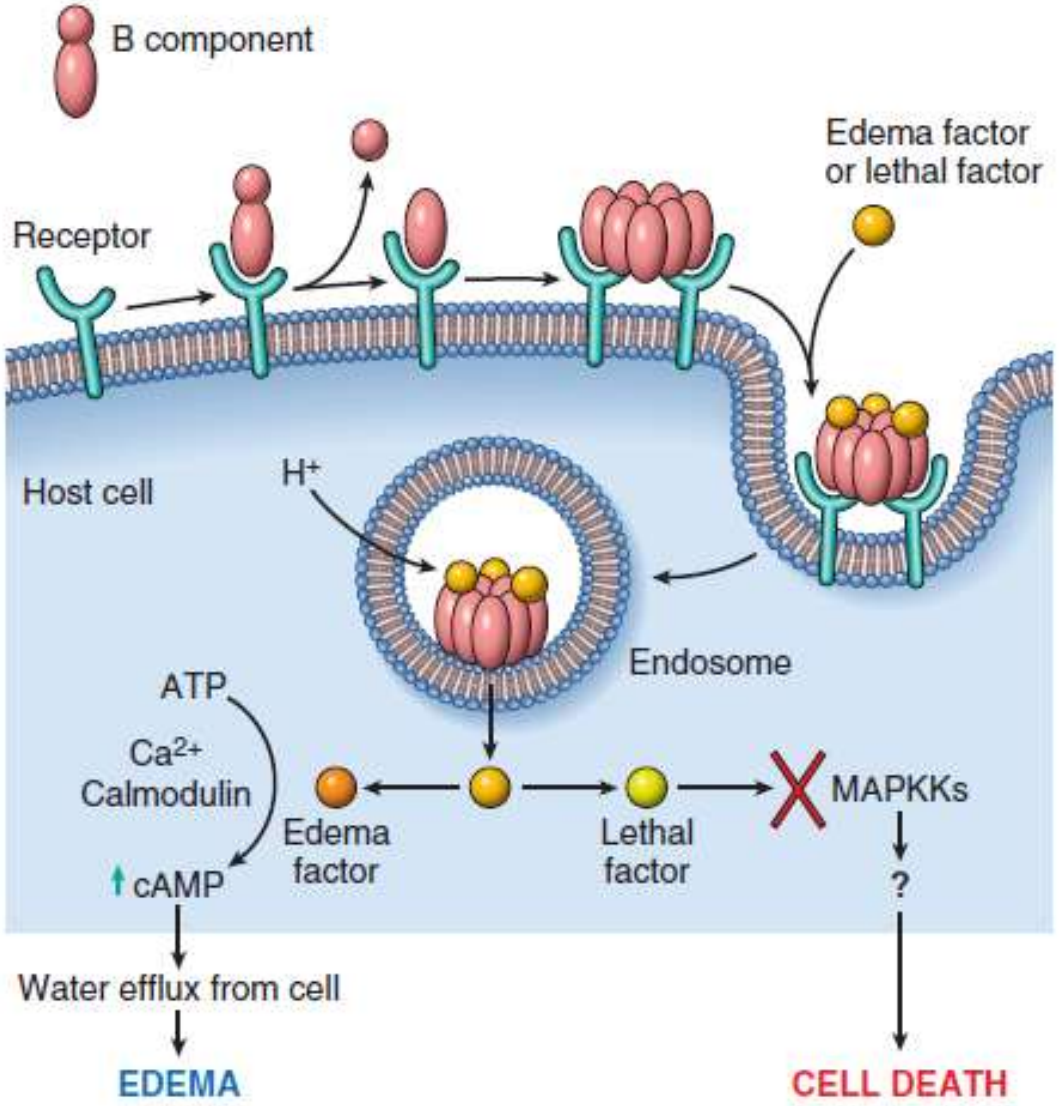


Figure 8–8 Mechanism of anthrax exotoxin action. The B component, also called "protective antigen," binds a cell-surface protein, is cleaved by a host protease, and forms a heptamer. Three A subunits of edema factor (EF) or lethal factor (LF) bind to the B heptamer, enter the cell, and are released into 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-

IMMUNE EVASION BY MICROBES

- Microorganisms have developed many means to resist and evade the immune system
- These mechanisms, which are important determinants of microbial virulence and pathogenicity, include:
- (1) antigenic variation (Changing surface proteins)
- (2) resistance to innate immune defenses (defensis, cathelicidins and thrombocidins are inactivated or down regulated)
- (3) impairment of effective T cell antimicrobial responses by specific or nonspecific immunosuppression.

Table 8-6 Mechanisms of Antigenic Variation

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

SPECTRUM OF INFLAMMATORY RESPONSES TO INFECTION

- **Suppurative (Purulent) Inflammation**
- This pattern is the reaction to acute tissue damage, characterized by increased vascular permeability and leukocytic infiltration, predominantly of neutrophils. 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.

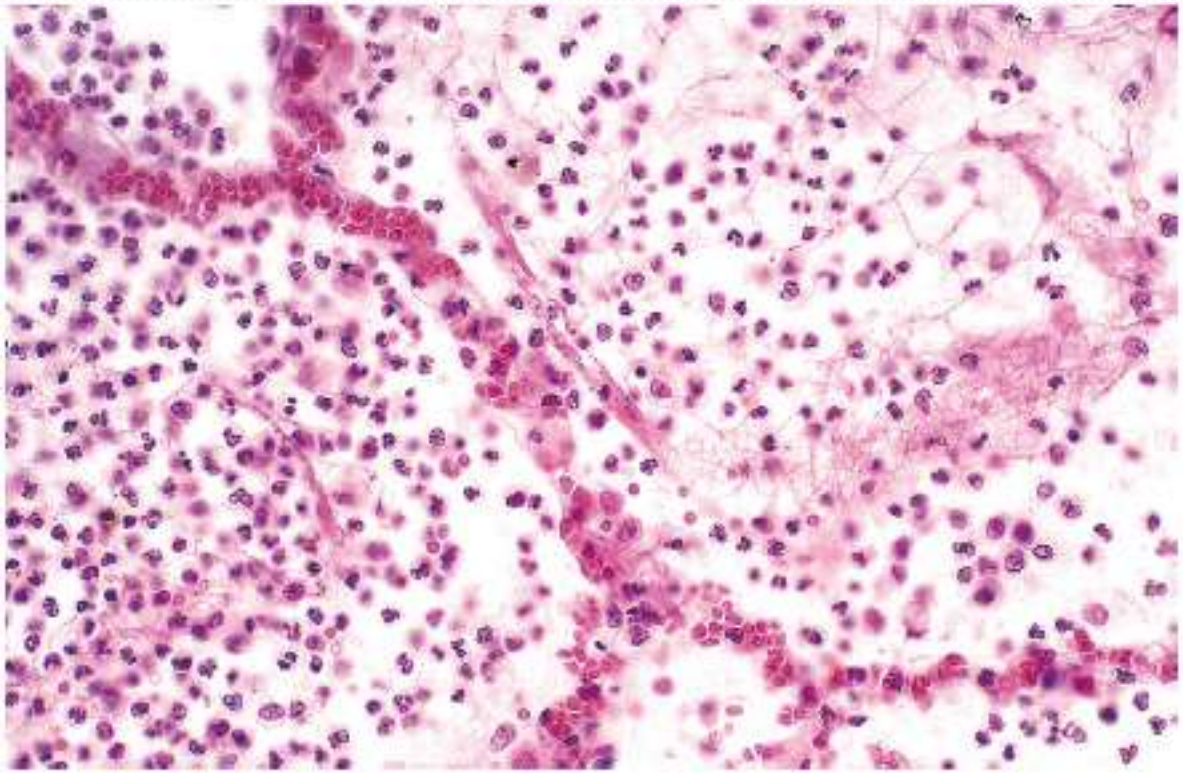


Figure 8–10 Pneumococcal pneumonia. Note the intra-alveolar polymorphonuclear exudate and intact alveolar septa.

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.

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

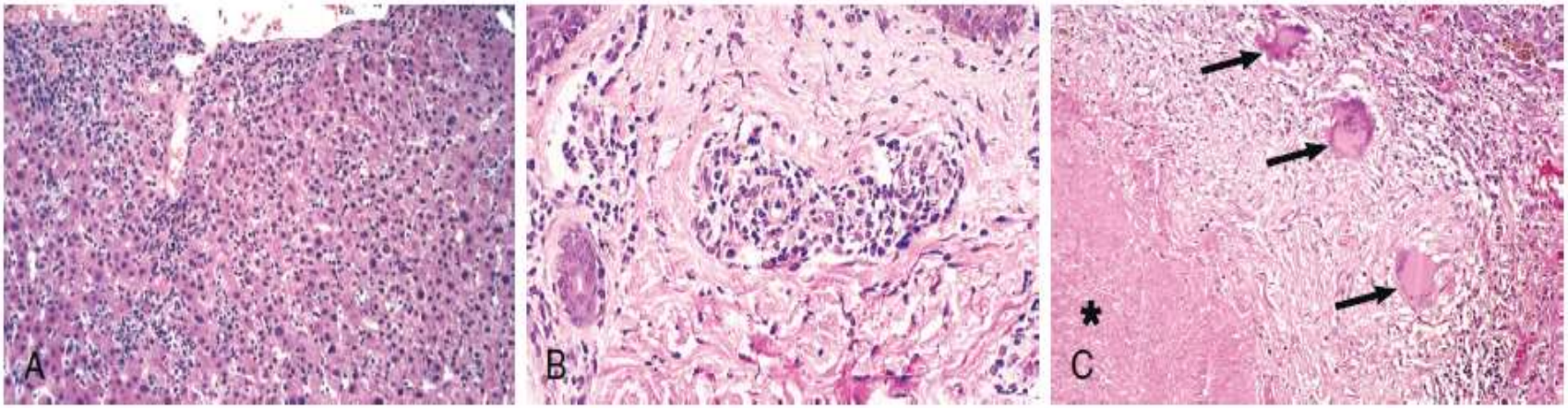
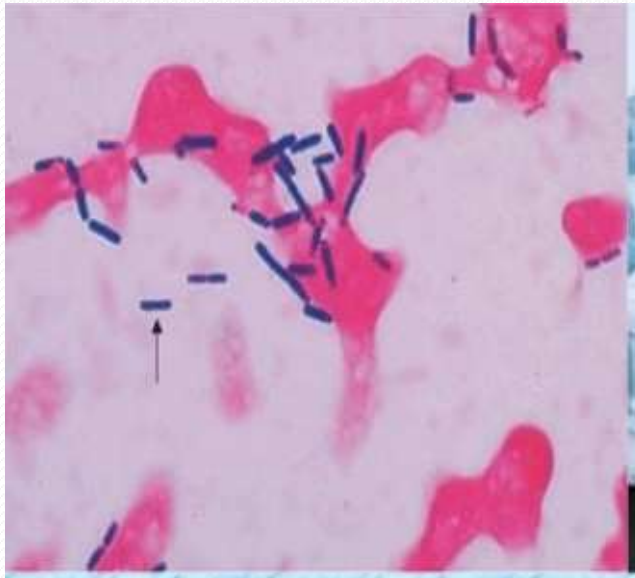


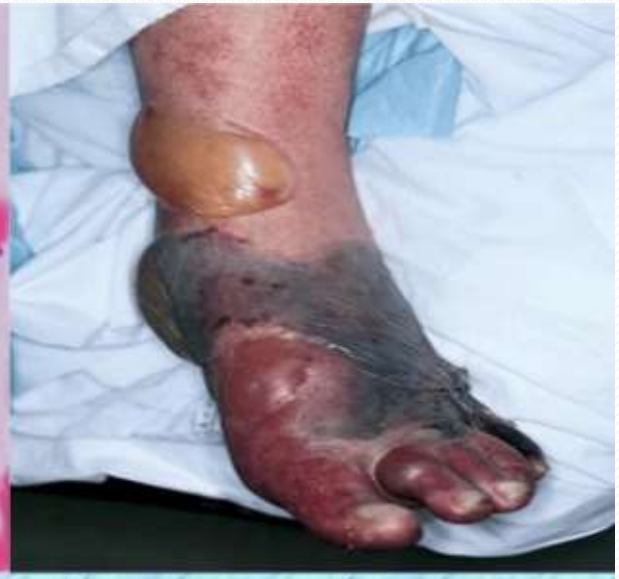
Figure 8–11 Mononuclear and granulomatous inflammation. **A,** Acute viral hepatitis characterized by a predominantly lymphocytic infiltrate. **B,** Secondary syphilis in the dermis with perivascular lymphoplasmacytic infiltrate and endothelial proliferation. **C,** Granulomatous inflammation in response 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.

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.



Clostridium perfringens
Gram stain
Arrow points to a large gram-positive rod



Gas gangrene. Note large area of necrosis on lateral aspect of foot. Necrosis mainly caused by lecithinase produced by Clostridium perfringens. Gas in tissue is a feature of gangrene produced by this anaerobic bacteria. A large gas and fluid-filled bulla is seen near the ankle.

- **Chronic Inflammation and Scarring**
- Many infections elicit chronic inflammation, which can either resolve with complete healing or lead to extensive scarring.

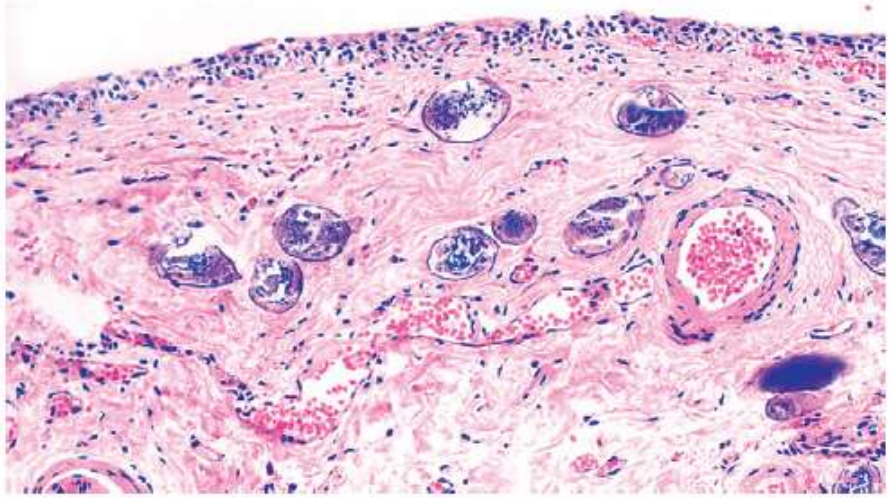


Figure 8–12 *Schistosoma haematobium* infection of the bladder with numerous calcified eggs and extensive scarring.

Infections in People with Immunodeficiencies

- Inherited or acquired defects in immunity 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 complementare 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 TH17 cell generation) are associated with **chronic mucocutaneous candidiasis**.

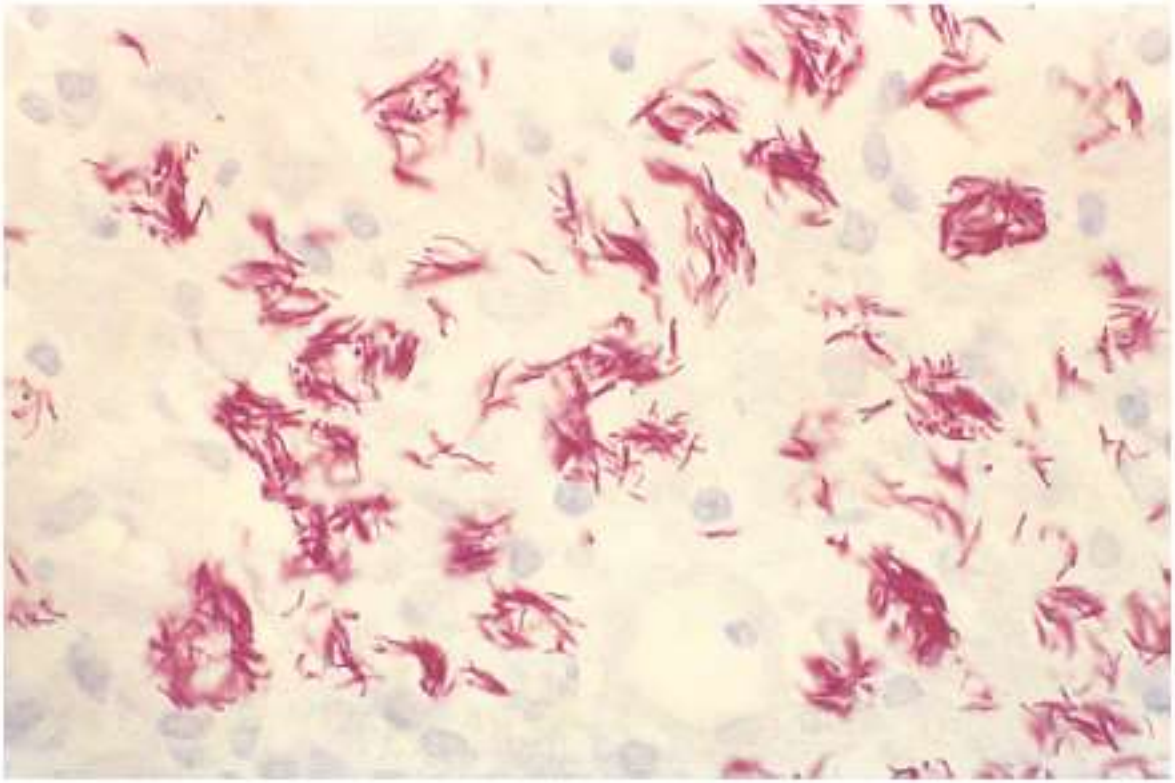


Figure 8–13 In the absence of appropriate T cell–mediated immunity, granulomatous host response does not occur. *Mycobacterium avium* infection in a patient with AIDS, showing massive intracellular macrophage infection with acid-fast organisms (filamentous and pink in this acid-fast stain preparation).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