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. In the colon, 99.9% of bacteria are anaerobic, including *Bacteroides* species. Many bacteria remain extracellular when they invade the body, while others can survive and replicate either outside or inside of host cells (*facultative intracellular* bacteria) and some grow only inside host cells (*obligate intracellular* bacteria).

Chlamydiae, Rickettsiae, Mycoplasmas

These microbes are grouped together because, like other bacteria, they divide by binary fission and are sensitive to antibiotics, but they lack certain structures (e.g., *Mycoplasma* lack a cell wall) or metabolic capabilities (e.g., *Chlamydia* cannot synthesize adenosine triphosphate [ATP]). *Chlamydia* and *Rickettsiae* are obligate intracellular organisms that replicate in membrane-bound vacuoles in epithelial cells and the

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Figure 8-2 Molecules on the surface of Gram-negative and Gram-positive bacteria involved in pathogenesis. Not shown is the type 3 secretory apparatus of Gram-negative bacteria (see text).

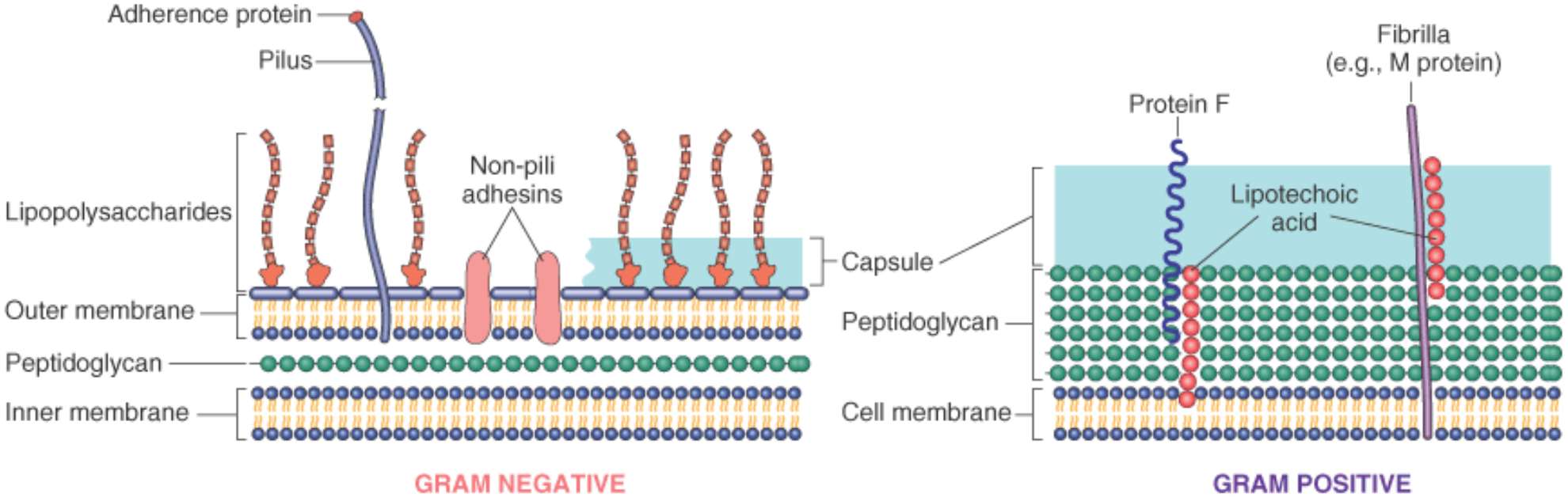

Figure 8-3 The variety of bacterial morphology. *A*, Gram stain of sputum from patient with pneumonia. There are Gram-positive cocci in clusters *(Staphylococcus aureus)* with degenerating neutrophils. *B*, Gram stain of sputum from a patient with pneumonia. Gram-positive, elongated cocci in pairs and short chains *(Streptococcus pneumoniae)* and a neutrophil is seen. *C*, Gram stain of *Clostridium sordellii* grown in culture. A mixture of Gram-positive and Gram-negative rods, many of which have subterminal spores (clear areas), are present. *Clostridia* species often stain as both Gram-positive and negative, although they are true Gram-positive bacteria. *D*, Gram stain of a bronchoalveolar lavage specimen showing Gram-negative intracellular rods typical of Enterobacteriaceae such as *Klebsiella pneumoniae* or *Escherichia coli*. *E*, Gram stain of urethral discharge from a patient with gonorrhea. Many Gram-negative diplococci *(Neisseria gonorrhoeae)* are present within a neutrophil. *F*, Silver stain of brain tissue from a patient with Lyme disease meningoencephalitis. Two helical spirochetes *(Borrelia burgdorferi)* are indicated by arrows. The panels are at different magnifications. *(D, Courtesy of Dr. Karen Krisher, Clinical Microbiology Institute, Wilsonville, OR. All other panels courtesy of Dr. Kenneth Van Horn.)*

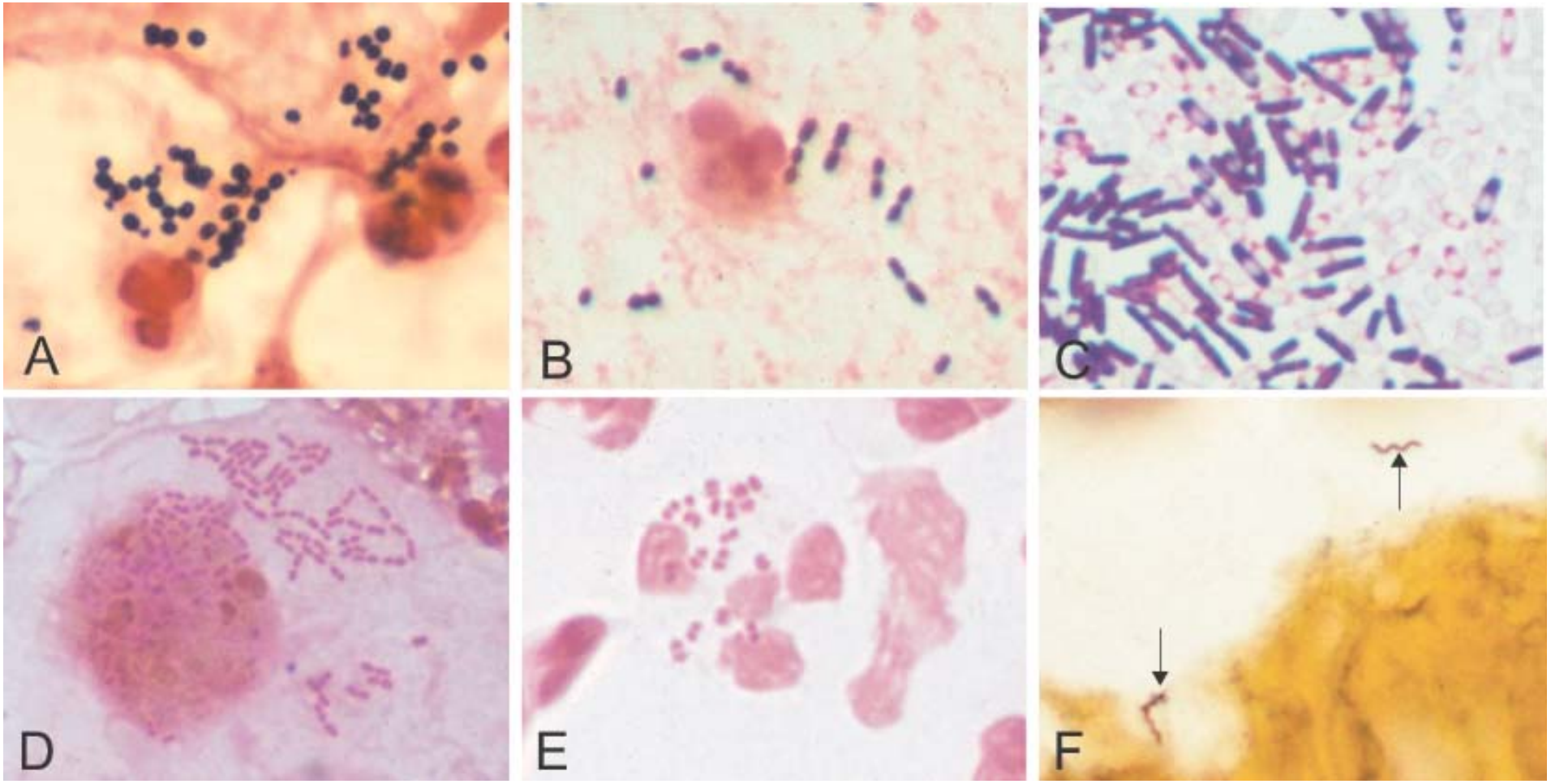

TABLE 8-6 -- Protozoa Pathogenic for Humans

Species	Order	Form, Size	Disease
Luminal or Epithelial			
Entamoeba histolytica	Amebae	Trophozoite 15–20 µm	Amebic dysentery; liver abscess
Balantidium coli	Ciliates	Trophozoite 50–100 µm	Colitis
Naegleria fowleri	Ameboflagellates	Trophozoite 10–20 µm	Meningoencephalitis
Acanthamoeba sp.	Ameboflagellates	Trophozoite 15–30 µm	Meningoencephalitis or ophthalmitis
Giardia lamblia	Mastigophora	Trophozoite 11–18 µm	Diarrheal disease, malabsorption
Isospora belli	Coccidia	Oocyst 10–20 µm	Chronic enterocolitis or malabsorption or both
Cryptosporidium sp.	Coccidia	Oocyst 5–6 µm	

Trichomonas vaginalis	Mastigophora	Trophozoite 10–30 µm	Urethritis, vaginitis
Bloodstream			
Plasmodium species	Hemosporidia	Trophozoites, schizonts, gametes (all small and inside red cells)	Malaria
Babesia microti, B. bovis	Hemosporidia	Trophozoites inside red cells	Babesiosis
Trypanosoma species	Hemoflagellates	Trypomastigote 14–33 µm	African sleeping sickness
Intracellular			
Trypanosoma cruzi	Hemoflagellates	Trypomastigote 20 µm	Chagas disease
Leishmania donovani	Hemoflagellates	Amastigote 2 µm	Kala-azar
Leishmania species	Hemoflagellates	Amastigote 2 µm	Cutaneous and mucocutaneous leishmaniasis
Toxoplasma gondii	Coccidia	Tachyzoite 4–6 µm (cyst larger)	Toxoplasmosis

immunosuppressed individuals do opportunistic fungi give rise to life-threatening infections characterized by tissue necrosis, hemorrhage, and vascular occlusion, with minimal to no inflammatory response. In addition, AIDS patients are victims of the opportunistic fungus *Pneumocystis jiroveci (carinii)*.

Protozoa

Parasitic protozoa are single-celled eukaryotes that are major causes of disease and death in developing countries (Table 8-6). Protozoa can replicate intracellularly within a variety of cells (e.g., *Plasmodium* in red blood cells, *Leishmania* in macrophages) or extracellularly in the urogenital system, intestine, or blood. *Trichomonas vaginalis* are flagellated protozoal parasites that are sexually transmitted and can colonize the vagina and male urethra. The most prevalent intestinal protozoans, *Entamoeba histolytica* and *Giardia lamblia*, have two forms: (1) motile trophozoites that attach to the intestinal epithelial wall and may invade and (2) immobile cysts that are resistant to stomach acids and are infectious when ingested. Blood-borne protozoa (e.g., *Plasmodium*, *Trypanosoma*, and *Leishmania*) are transmitted by insect vectors, in which they replicate before being passed to new human hosts. *Toxoplasma gondii* is acquired either by 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 intermediary host or vector. Thus, depending on parasite species, humans may harbor either adult worms (e.g., *Ascarus lumbricoides*) or immature stages (e.g., *Toxocara canis*) or asexual larval forms (e.g., *Echinococcus* species). Once adult worms take up residence in humans,

they do not multiply but generate eggs or larvae destined for the next phase of the cycle. An exception is *Strongyloides stercoralis*, the larvae of which can become infectious in the gut and cause overwhelming autoinfection in immunosuppressed persons. There are two important consequences of the lack of replication of adult worms: (1) Disease is often caused by inflammatory responses to the eggs or larvae rather than to the adults (e.g., schistosomiasis), and (2) disease is in proportion to the number of organisms that have infected the individual (e.g., 10 hookworms cause little disease, whereas 1000 hookworms cause severe anemia by consuming 100 mL of blood per day).

Ectoparasites

Ectoparasites are insects (lice, bedbugs, fleas) or arachnids (mites, ticks, spiders) that attach to and live on or in the skin. Arthropods may produce disease directly by damaging the human host or indirectly by serving as the vectors for transmission of an infectious agent into a human host. Some arthropods may cause itching and excoriations (e.g., pediculosis caused by lice attached to hair shafts, or scabies caused by mites burrowing into the stratum corneum). At the site of the bite, mouthparts may be found associated with a mixed infiltrate of lymphocytes, macrophages, and eosinophils. In addition, attached arthropods can be vectors for other pathogens. For example, deer ticks transmit the Lyme disease spirochete *Borrelia burgdorferi*.

TRANSMISSION AND DISSEMINATION OF MICROBES

Host Barriers to Infection

The outcome of infection is determined by the ability of the microbe to infect, colonize, and damage host tissues and the ability of host defense mechanisms to eradicate the infection. *Host barriers to infection prevent microbes from entering the body and consist of innate and adaptive immune defenses* [11] (see Fig. 6-1 , Chapter 6). Innate immune defense mechanisms exist before infection and respond rapidly to microbes. These mechanisms include physical barriers to infection, phagocytic cells and natural killer cells, and plasma proteins, including the complement system proteins and other mediators of inflammatory responses (cytokines, collectins, acute phase reactants). Adaptive immune responses are stimulated by exposure to microbes and increase in magnitude, speed, and effectiveness with successive exposures to microbes. Adaptive immunity is mediated by T and B lymphocytes and their products (Chapter 6).

Microbes can enter the host by inhalation, ingestion, sexual transmission, insect or animal bites, or injection. The first barriers to infection are intact host skin and mucosal surfaces and their secretory products. In general, respiratory, gastrointestinal, or genitourinary tract infections occur in healthy persons and are caused by relatively virulent microorganisms that are capable of damaging or penetrating intact epithelial barriers. In contrast, most skin infections in healthy persons are caused by less virulent organisms entering 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 (about 5.5) and the presence of fatty acids inhibit growth of microorganisms other than residents of the normal flora. Human skin is normally inhabited by a variety of bacterial and fungal species, including some potential opportunists, such as *Staphyloccus epidermidis* and *Canadida albicans*. Although skin is usually an effective barrier, certain types of fungi (dermatophytes) can infect the stratum corneum, hair, and nails, and a few microorganisms are able to traverse the unbroken skin. For example, *Schistosoma* larvae released from freshwater snails penetrate swimmers' skin by releasing collagenase, elastase, and other enzymes that dissolve the extracellular matrix. Most microorganisms, however, 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 can produce local or systemic infection (bacteremia). Needle sticks can expose the recipient to potentially infected blood and may transmit HBV, HCV, or HIV. Some pathogens penetrate the skin via an insect or animal bite. For instance, bites by fleas, ticks, mosquitoes, mites, and lice break the skin and transmit arboviruses (causes of yellow fever and encephalitis), rickettsiae (Rocky Mountain spotted fever), bacteria (plague, Lyme disease), protozoa (malaria, leishmaniasis), and helminths (filariasis). Animal bites can lead to infections with bacteria or with rabies virus.

Gastrointestinal Tract.

Most gastrointestinal pathogens are transmitted by food or drink contaminated with fecal material. Where hygiene fails, diarrheal disease becomes rampant.

Acidic gastric secretions are important defenses within the gastrointestinal tract and are lethal for many gastrointestinal pathogens.[11] Healthy volunteers do not become infected by *Vibrio cholerae* unless they are fed $10^{[11]}$ organisms, whereas volunteers given *Vibrio cholerae* and sodium bicarbonate have a 10,000-fold increase in susceptibility to cholera. In contrast, some ingested agents, such as *Shigella* and *Giardia* cysts, are relatively resistant to gastric acid; hence, as few as 100 organisms of each are sufficient to cause illness.

Other normal defenses within the gastrointestinal tract include (1) the viscous mucous layer covering the gut, (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 B cells located in mucosa-associated lymphoid tissues (MALT). These lymphoid aggregates are covered by a single layer of specialized epithelial cells called M cells. M cells are important for transport of antigens to MALT and for binding and uptake of numerous gut pathogens, including poliovirus, enteropathic *Escherichia coli, Vibrio cholerae, Salmonella typhi*, and *Shigella flexneri*. [12]

Infections via the gastrointestinal tract occur 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 unbalance the normal bacterial flora (e.g., in pseudomembranous colitis), or when there is stalled peristalsis or mechanical obstruction (e.g., in blind loop syndrome). Most enveloped viruses are killed by the bile and digestive enzymes, but nonenveloped viruses may be resistant (e.g., the hepatitis A virus, rotaviruses, reoviruses, and Norwalk agents).

Enteropathogenic bacteria elicit gastrointestinal disease by a variety of mechanisms:

- While growing on contaminated food, certain staphylococcal strains release powerful enterotoxins that cause food poisoning symptoms without any bacterial multiplication in the gut.
- *V. cholerae* and toxigenic *E. coli* multiply inside the mucous layer overlying the gut epithelium and release exotoxins that cause the gut epithelium to secrete high volumes of watery diarrhea.
- *Shigella, Salmonella*, and *Campylobacter* invade and damage the intestinal mucosa and lamina propria and so cause ulceration, inflammation, and hemorrhage, clinically manifested as dysentery.[13]
- *S. typhi* passes from the damaged mucosa through Peyer 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 patients. *Candida*, part of the normal gastrointestinal flora, shows a predilection for stratified squamous epithelium, causing oral thrush or membranous esophagitis, but may also disseminate to the stomach, lower gastrointestinal tract, and systemic organs.

The cyst forms of intestinal protozoa are essential for their transmission because cysts resist stomach acid. In the gut, cysts convert to motile trophozoites and attach to sugars on the intestinal epithelia through surface lectins. Thereafter, there is wide species variation. *Giardia lamblia* attaches to the epithelial brush border, whereas cryptosporidia are taken up by enterocytes, in which they form gametes and spores. *Entamoeba histolytica* causes contact-mediated cytolysis through a channel-forming pore protein and thereby ulcerates and invades the colonic mucosa. Intestinal helminths, as a rule, cause disease only when they are present in large numbers or in ectopic sites, for example, by obstructing the gut or invading and damaging the bile ducts *(Ascaris lumbricoides)*. Hookworms may cause iron deficiency anemia by chronic loss of blood sucked from intestinal villi; the fish tapeworm *Diphyllobothrium latum* can deplete its host of vitamin B_{12} , giving rise to an illness resembling pernicious anemia. Finally, the larvae of several helminth parasites pass through the gut briefly on their way toward another organ habitat; for example, *Trichinella spiralis* larvae preferentially encyst in muscle, *Echinococcus* species larvae in the liver or lung.

Respiratory Tract.

Some 10,000 microorganisms, including viruses, bacteria, and fungi, are inhaled daily by every city inhabitant. The distance these microorganisms travel into the respiratory system is inversely proportional to their size.[11] Large microbes are trapped in the mucociliary blanket that lines the nose and the upper respiratory tract. Microorganisms are trapped in the mucus secreted by goblet cells and are then transported by ciliary action to the back of the throat, where they are swallowed and cleared. Organisms 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.

Damage to the mucociliary defense results from repeated insults in smokers and patients with cystic fibrosis, while acute injury occurs in intubated patients and in those who aspirate gastric acid. Successful respiratory microbes evade the mucociliary defenses in part by attaching to 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. However, sialic acid binding prevents newly synthesized viruses from leaving the host cell. Influenza viruses have another cell surface protein, neuraminidase, which cleaves sialic acid and allows virus to release from the host cell. Neuraminidase also lowers the viscosity of mucus and facilitates viral transit within the respiratory tract. Interestingly, some anti-influenza drugs are sialic acid analogs that inhibit neuraminidase and prevent viral release from host cells.

Certain respiratory bacterial pathogens can impair ciliary activity. For instance, *Haemophilus influenza* and *Bordetella pertussis* elaborate toxins that paralyze mucosal cilia; *Pseudomonas aeruginosa*, a cause of severe respiratory infection in persons with cystic fibrosis, and *Mycoplasma pneumoniae* produce ciliostatic substances. Some bacteria such as *Streptococcus pneumoniae* or *Staphylococcus* species lack specific adherence factors and often gain access after viral infection causes loss of ciliated epithelium, making individuals who have had viral respiratory infection more susceptible to secondary bacterial respiratory infection. *Mycobacterium tuberculosis*, in contrast, gains its foothold in normal alveoli because it is able to escape phagocytic killing by macrophages. Growth requirements for microorganisms can determine their site of infection in the respiratory tract. For example, rhinoviruses, which cause the common cold, grow optimally at 33°C, the temperature of the nasal mucosa, but grow poorly at 37°C, the temperature of the lower respiratory tract. Finally, opportunistic fungi infect the lungs when cellular immunity is depressed or when leukocytes are reduced in number (e.g., *P. jiroveci* [*carinii*] in AIDS patients and *Aspergillus* species in chemotherapy patients).

Urogenital Tract.

The urinary tract is almost always invaded from the exterior via the urethra.[11] 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., gonococci, *E. coli*) adhere to the urinary epithelium. Anatomy is an important factor for infection. Women have more than 10 times as many urinary tract infections (UTIs) as men, because the distance between the urinary bladder and skin (i.e., the length of the urethra) is 5 cm, in contrast to 20 cm in men. Obstruction of urinary flow and/or reflux can compromise normal defenses and increase susceptibility to UTIs. UTIs can spread retrogradely from the bladder to the kidney and cause acute and chronic pyelonephritis, which is the major preventable cause of renal failure.

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 and make the vagina susceptible to infection. To be successful as pathogens, microorganisms have developed specific mechanisms for attaching to vaginal or cervical mucosa or enter via local breaks in the mucosa during sex (genital warts, syphilis).

Spread and Dissemination of Microbes

Some microorganisms proliferate locally, at the site of infection, whereas others penetrate the epithelial barrier and spread to other sites via the lymphatics, the blood, or nerves[11] (Fig. 8-4). Some of the superficial pathogens stay confined to the lumen of hollow viscera (e.g., cholera); others adhere to or proliferate exclusively in or on epithelial cells (e.g., papillomaviruses, dermatophytes). A variety of pathogenic bacteria, fungi, and helminths are invasive by virtue of their motility or ability to secrete lytic enzymes (e.g., streptococci and staphylococci secrete hyaluronidase, which degrades the extracellular matrix between host cells). Microbial spread initially follows tissue planes of least resistance and regional lymphatic and vascular anatomy. For example, staphylococcal infections may progress from a localized abscess or furuncle to regional lymphadenitis that sometimes leads to bacteremia and colonization of distant organs (heart, liver, brain, kidney, bone). Within the blood, microorganisms may be transported free or within host cells. Some viruses (e.g., poliovirus and HBV), most bacteria and fungi, some protozoa (e.g., African trypanosomes), and all helminths are transported free in the plasma. Leukocytes can carry herpesviruses, HIV, mycobacteria, and *Leishmania* and *Toxoplasma* organisms. Certain viruses (e.g., Colorado tick fever virus) and parasites (*Plasmodium* and *Babesia*) are carried by red blood cells. Viruses also may propagate

Figure 8-4 Routes of entry, dissemination, and release of microbes from the body. *(Adapted from Mims CA: The Pathogenesis of Infectious Disease, 4th ed. San Diego, CA, Academic Press, 1996.)*

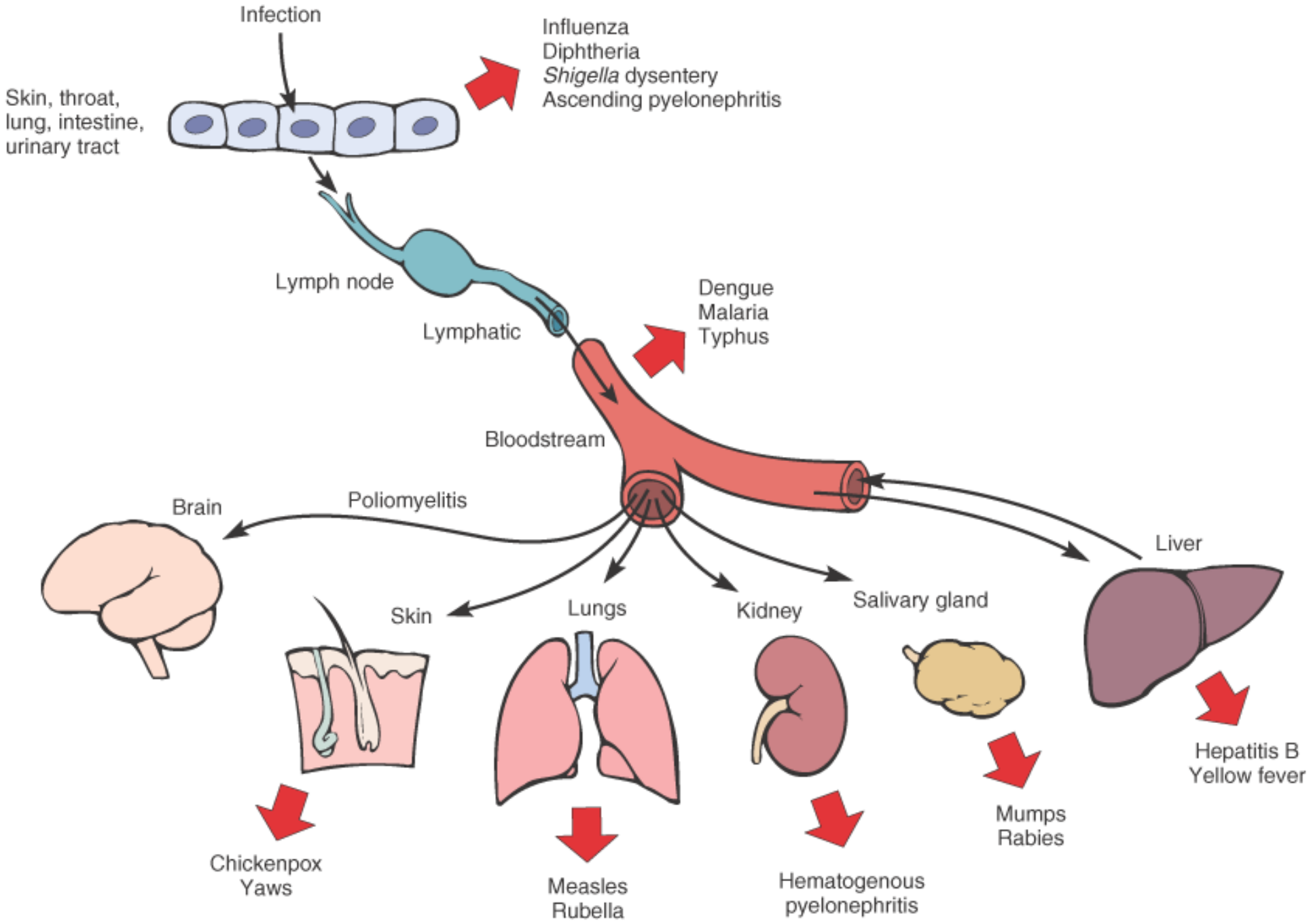

TABLE 8-7 -- Classification of Important Sexually Transmitted Diseases

	Disease or Syndrome and Population Principally Affected		
Pathogens	***Males***	***Both***	***Females***
Viruses			
••Herpes simplex virus		Primary and recurrent herpes, neonatal herpes	
••Hepatitis B virus		Hepatitis	
••Human papillomavirus	Cancer of penis (some cases)	Condyloma acuminatum	Cervical dysplasia and cancer, vulvar cancer
••Human immunodeficiency virus		Acquired immunodeficiency syndrome	
Chlamydiae			
••*Chlamydia trachomatis*	Urethritis, epididymitis, proctitis	Lymphogranuloma venereum	Urethral syndrome, cervicitis, bartholinitis, salpingitis and sequelae
Mycoplasmas			
••*Ureaplasma urealyticum*	Urethritis		
Bacteria			
••*Neisseria gonorrhoeae*	Epididymitis, prostatitis, urethral stricture	Urethritis, proctitis, pharyngitis, disseminated gonococcal infection	Cervicitis, endometritis, bartholinitis, salpingitis, and sequelae (infertility, ectopic pregnancy, recurrent salpingitis)
Treponema pallidum		Syphilis	
Haemophilus ducreyi		Chancroid	
Calymmatobacterium granulomatis		Granuloma inguinale (donovanosis)	
Shigella	* Enterocolitis		
Campylobacter	* Enterocolitis		
Protozoa			Vaginitis
••*Trichomonas vaginalis*	Urethritis, balanitis		
••*Entamoeba histolytica*	* Amebiasis		
••*Giardia lamba*	* Giardiasis		
Modified and updated from Krieger JN: Biology of sexually transmitted diseases. Urol Clin North Am 11:15, 1984.			

*Most important in homosexual populations.

Syphilis is discussed later in this chapter, and other STIs are described in Chapter 21 and Chapter 22 .

HOW MICROORGANISMS CAUSE DISEASE

Infectious agents establish infection and damage tissues in three ways:

- 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 cellular responses that, although directed against the invader, cause additional tissue damage, usually by immune-mediated mechanisms. Thus, as we discussed in Chapter 2 and Chapter 6 , the defensive responses of the host are a two-edged sword: They are necessary to overcome the infection but at the same time may directly contribute to tissue damage.

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

Mechanisms of Viral Injury

Viruses can directly damage host cells by entering them and replicating at the host's expense. The predilection for viruses to infect certain cells and not others is called tissue tropism and is determined by several factors, including (1) host cell receptors for the virus, (2) cellular transcription factors that recognize viral enhancer and promoter sequences, (3) anatomic barriers, and (4) local temperature, pH, and host defenses.[15] Each of these is described briefly.

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 gp120 binds to CD4 on T cells and to the chemokine receptors CXCR4 (mainly on T cells) and CCR5 (mainly on macrophages). Rhinoviruses bind to the same site on ICAM-1 as LFA-1, an integrin on the surface of lymphocytes that is an important adhesion molecule for lymphocyte activation and migration.[16] 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.

Another determinant of viral tropism is the ability of the virus to replicate inside some cells but not in others, and this is related to the presence of cell-type—specific transcription factors. For example, the JC virus, which causes leukoencephalopathy (Chapter 28), is restricted to oligodendroglia in the central nervous system because the promoter and enhancer DNA sequences upstream from the viral genes are active in glial cells but not in neurons or endothelial cells. Physical barriers also can contribute to tissue tropism. For example, enteroviruses replicate in the intestine in part because they can resist inactivation by acids, bile, and digestive enzymes. Rhinoviruses replicate only within the upper respiratory tract because they survive optimally at the lower temperature of the upper respiratory tract.

Once viruses are inside host cells, they can kill the cells and/or cause tissue damage in a number of ways (Fig. 8-5):

- Viruses may inhibit host cell DNA, RNA, or protein synthesis. For example, poliovirus inactivates cap-binding protein, which is essential for translation of host cell mRNAs, but leaves translation of poliovirus mRNAs unaffected.
- Viral proteins may insert into the host cell's plasma membrane and directly damage its integrity or promote cell fusion (HIV, measles virus, and herpesviruses).
- Viruses may lyse host cells. For example, respiratory epithelial cells are killed by influenza virus replication, liver cells by yellow fever virus, and neurons by poliovirus and rabies virus.
- Viruses may manipulate programmed cell death (apoptosis). Some virus-encoded proteins (including TAT and gp120 of HIV, adenovirus E1A) can induce cell death. In contrast,

some viruses encode one or more genes that inhibit apoptosis (e.g., homologues of the cellular *bcl-2* gene), suggesting that apoptotic cell death may be a protective host response to eliminate virus-infected cells. It has been hypothesized that viral antiapoptotic strategies may enhance viral replication, promote persistent viral infections, or promote virus-induced cancers.[17]

• Viral proteins on the surface of the host cells may be recognized by the immune system, and the host lymphocytes may attack the virus-infected cells. Acute liver failure during hepatitis B infection may be accelerated by cytotoxic T lymphocyte (CTL)-mediated destruction of infected hepatocytes (a normal response to clear the infection). FAS ligand on CTLs, which bind to FAS receptors on the surface of hepatocytes, also can induce apoptosis in target cells.[18]

• Viruses may damage cells involved in host antimicrobial defense, leading to secondary infections. For example, viral damage to respiratory epithelium predisposes to the subsequent development of pneumonia by *Streptococcus pneumoniae* and *Haemophilus influenzae*. HIV depletes CD4+ helper lymphocytes and thereby causes opportunistic infections.

• Viral killing of one cell type may cause the death of other cells that depend on them. For example, denervation by the attack of poliovirus on motor neurons causes atrophy and sometimes death of distal skeletal muscle supplied by such neurons.

• Some viruses can cause *cell proliferation and transformation* (e.g., EBV, HBV, human papillomavirus, or HTLV-1), resulting in cancer. The mechanisms of viral transformation are numerous and are discussed in Chapter 7 .

Figure 8-5 Mechanisms by which viruses cause injury to cells.

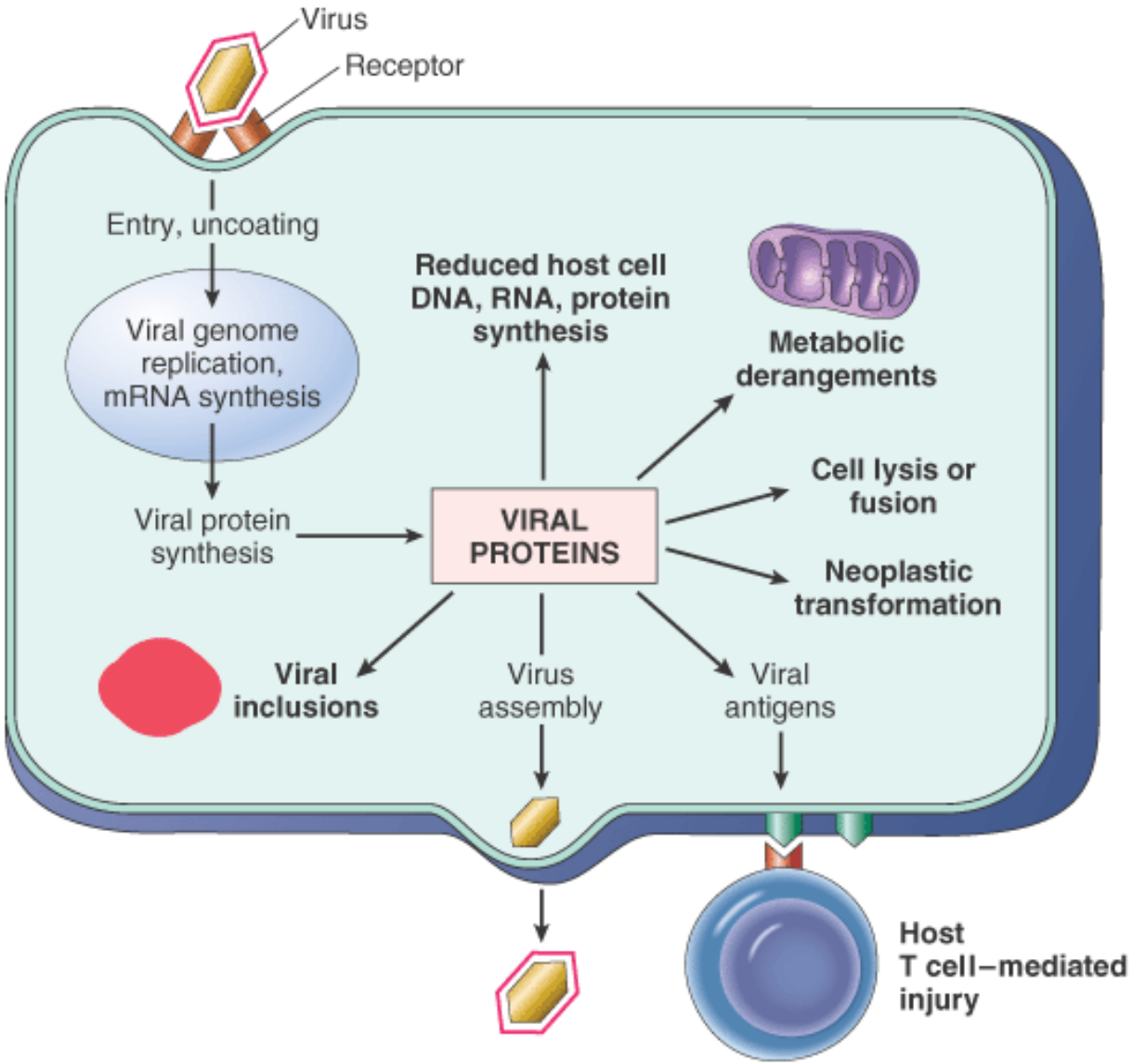

TABLE 8-8 -- Pathogens with Significant Antigenic Variation

Rhinoviruses	Colds
Influenza virus	Influenza
Neisseria gonorrhoeae	Gonorrhea
Borrelia hermsii	Relapsing fever
Borrelia burgdorferi	Lyme disease

Trypanosoma brucei	African sleeping sickness
Giardia lamblia	Giardiasis
Plasmodium falciparum	Severe malaria

neutrophils and macrophages.[33] The carbohydrate capsule on the surface of all the major bacteria that cause pneumonia or meningitis (pneumococcus, meningococcus, *Haemophilus influenzae*) makes them more virulent by shielding bacterial antigens and by preventing phagocytosis of the organisms by neutrophils. For example, *E. coli* with the sialic acid-containing K1 capsule causes meningitis in newborns. Sialic acid will not bind C3b, which is critical for activation of the alternative complement pathway, so the bacteria escape from complement-mediated lysis and opsonization-directed phagocytosis. Many bacteria make toxic proteins that kill phagocytes, prevent their migration, or diminish their oxidative burst. Bacteria also can circumvent immune defenses by covering themselves with host proteins. *S. aureus* are covered by protein A molecules that bind the Fc portion of antibodies and so inhibit phagocytosis. *Neisseria*, *Haemophilus*, and *Streptococcus* all secrete proteases that degrade antibodies. Another successful strategy for circumventing phagocytic defense mechanisms is to replicate within phagocytic cells. A number of viruses, rickettsias, some intracellular bacteria (including mycobacteria, Listeria, and Legionella), fungi (e.g., *Cryptococcus neoformans*), and protozoa (e.g., leishmania, trypanosomes, toxoplasmas) can multiply within phagocytes.

Viruses can produce molecules that inhibit innate immunity.[15] [35] [36] Some viruses (e.g., herpesviruses and poxviruses) produce proteins that block complement activation. Viruses have developed a large number of strategies to combat interferons (IFN), an early host defense against viruses. Some viruses produce soluble homologues of IFN-α/β or IFN-γ receptors that inhibit actions of extracellular IFNs, or produce proteins that inhibit intracellular JAK/STAT signaling downstream of IFN receptors or inactivate or inhibit dsRNA-dependent protein kinase (PKR), a key mediator of the antiviral effects of IFN. Viruses also can produce homologues of chemokines or chemokine receptors, and these can function as antagonists and inhibit recruitment of inflammatory cells to favor survival of viruses. Viruses also can produce soluble cytokine mimics (e.g., EBV produces a homologue of the immunosuppressive cytokine IL-10) or soluble cytokine receptor homologues.

Some microbes can 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, HCMV, and EBV) can bind to or alter localization of MHC class I proteins, impairing peptide presentation to CD8+ T cells[36] [37] (Fig. 8-6). 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 killer inhibitory receptors (Chapter 6). Similarly, herpesviruses can target MHC class II molecules for degradation, impairing antigen presentation to CD4+ T helper cells. Viruses also can infect lymphocytes and directly compromise their function. HIV infects CD4+ T cells, macrophages, and dendritic cells, and EBV infects B lymphocytes.

INFECTIONS IN IMMUNOSUPPRESSED HOSTS

Different types of immunosuppression affect different cells of the immune system. The opportunistic infections that an immunosuppressed person contracts depend on the types of

Figure 8-6 Inhibition of MHC expression by viruses. The steps at which different viruses inhibit the class I MHC antigen presentation pathway are shown. *(Modified with permission from Abbas AK, Lichtman AH: Cellular and Molecular Immunology, 5th ed., Philadelphia, Saunders, 2003.)*

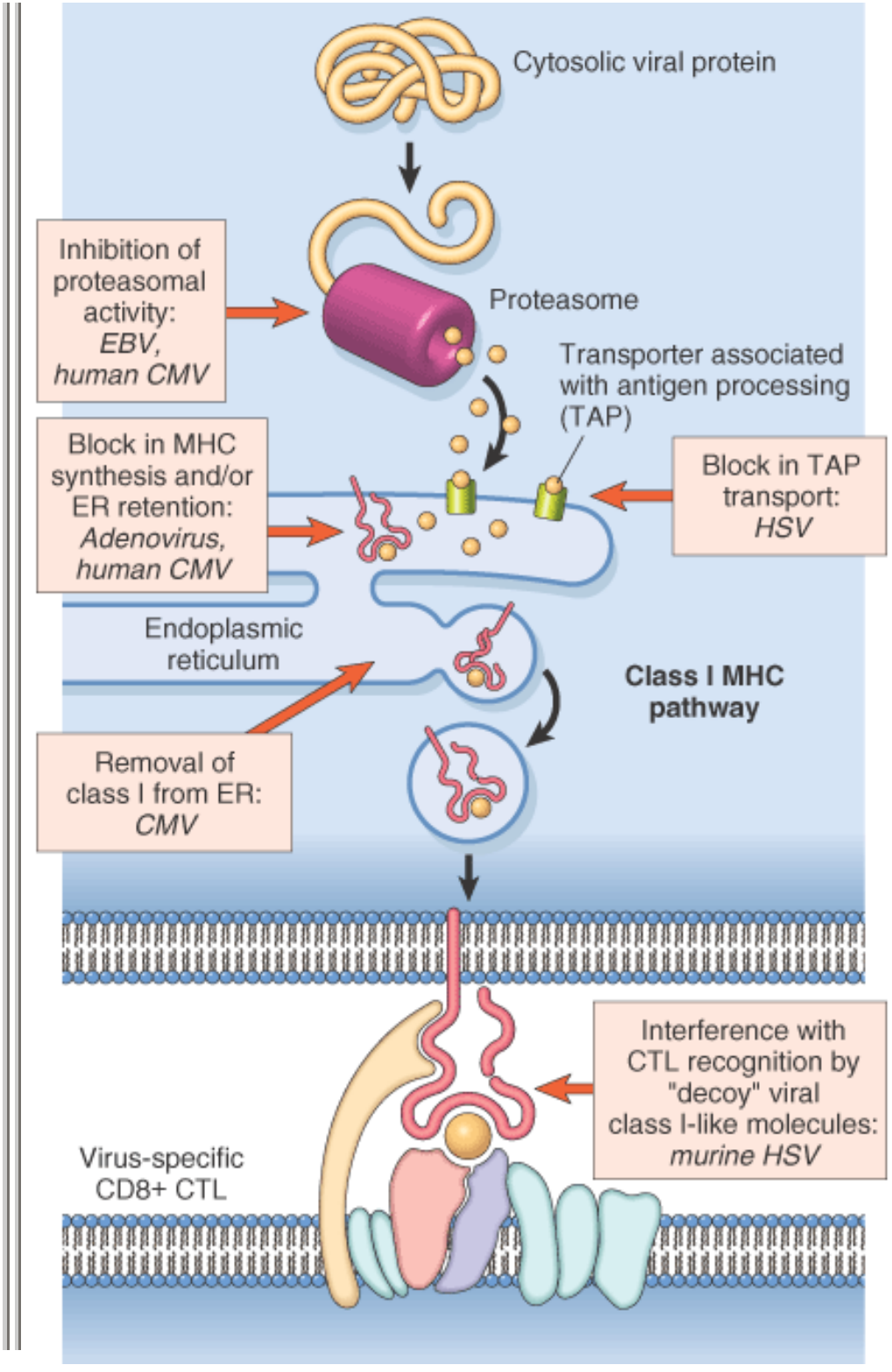
Cytosolic viral protein
Inhibition of proteasomal activity: *EBV, human CMV*
Proteasome
Transporter associated with antigen processing (TAP)
Block in MHC synthesis and/or ER retention: *Adenovirus, human CMV*
Block in TAP transport: *HSV*
Endoplasmic reticulum
Class I MHC pathway
Removal of class I from ER: *CMV*
Interference with CTL recognition by "decoy" viral class I-like molecules: *murine HSV*
Virus-specific CD8+ CTL

TABLE 8-9 -- Special Techniques for Diagnosing Infectious Agents

Gram stain	Most bacteria
Acid-fast stain	Mycobacteria, nocardiae (modified)
Silver stains	Fungi, legionellae, pneumocystis
Periodic acid-Schiff	Fungi, amebae
Mucicarmine	Cryptococci
Giemsa	Campylobacteria, leishmaniae, malaria parasites
Antibody probes	Viruses, rickettsiae
Culture	All classes
DNA probes	Viruses, bacteria, protozoa

of a lesion rather than at its center, particularly if there is necrosis.

Nucleic acid-based tests have become routine methods for detecting or quantifying several pathogens. Molecular diagnostics have become particularly important in the care of people infected with HIV.[40] Quantification of the viral RNA is an important guide to antiretroviral therapy. The management of hepatitis B and C infections is similarly guided by nucleic acid-based viral quantification or typing to predict resistance to antiviral drugs.

Nucleic acid amplification tests (NAATs), such as polymerase chain reaction (PCR) and transcription-mediated amplification, have become routine for diagnosis of gonorrhea, chlamydia, tuberculosis, and herpes encephalitis. In some cases, molecular assays are much more sensitive than conventional testing.[41] [42] PCR testing of cerebrospinal fluid (CSF) for herpes simplex virus encephalitis has a sensitivity of about 80%, while viral culture of CSF has a sensitivity of less than 10%. Similarly, NAATs for genital chlamydia detect 10% to 30% more infections than does conventional chlamydia culture. In other cases, such as gonorrhea, the sensitivity of NAAT testing is similar to that of culture.

SPECTRUM OF INFLAMMATORY RESPONSES TO INFECTION

In contrast to the vast molecular diversity of microbes, the morphologic patterns of tissue responses to microbes are limited, as are the mechanisms directing these responses. At the microscopic level, therefore, many pathogens produce identical reaction patterns, and few features are unique or pathognomonic for a particular microorganism. Moreover, it is the interaction between the microorganism and the host that determines the histologic features of the inflammatory response. Thus, pyogenic bacteria, which normally evoke vigorous leukocyte responses, may cause rapid tissue necrosis with little leukocyte exudation in a profoundly neutropenic host. Similarly, in a normal patient, *M. tuberculosis* causes well-formed granulomas with few mycobacteria present, whereas in an AIDS patient, the same mycobacteria multiply profusely in macrophages, which fail to coalesce into granulomas.

There are five major histologic patterns of tissue reaction in infections.

Suppurative (Polymorphonuclear) Inflammation

This pattern is the reaction to acute tissue damage, described in Chapter 2 , characterized by increased vascular permeability and leukocytic infiltration, predominantly of neutrophils (Fig. 8-7). The neutrophils are attracted to the site of infection by release of chemoattractants from the "pyogenic" bacteria that evoke this response, mostly extracellular Gram-positive cocci and Gram-negative rods. Massing of neutrophils forms pus. The sizes of exudative lesions vary from tiny microabscesses formed in multiple organs during bacterial sepsis secondary to a

colonized heart valve to diffuse involvement of entire lobes of the lung during pneumonia. How destructive the lesions are depends on their location and the organism involved. For example, pneumococci usually spare alveolar walls and cause lobar pneumonia that resolves

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Figure 8-7 Pneumococcal pneumonia. Note the intra-alveolar polymorphonuclear exudate and intact alveolar septa.

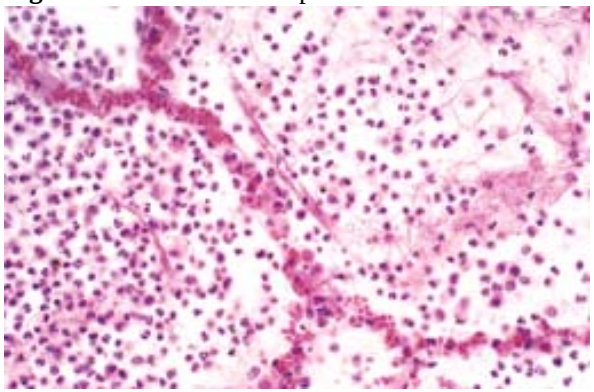


Figure 8-8 Secondary syphilis in the dermis with perivascular lymphoplasmacytic infiltrate and endothelial proliferation.

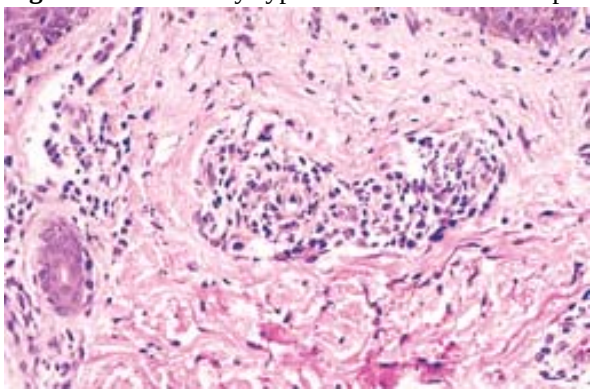


Figure 8-9 Herpesvirus blister in mucosa. See Figure 8-13 for viral inclusions.

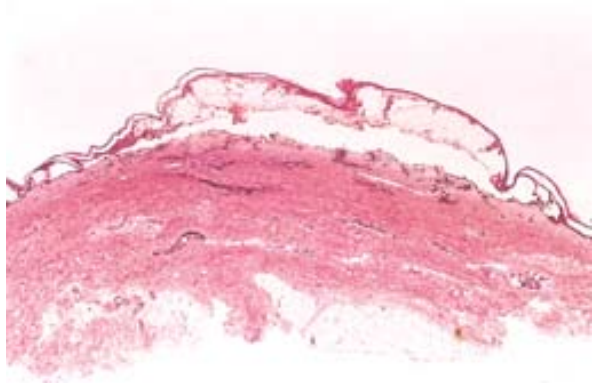


Figure 8-10 *Schistosoma haematobium* infection of the bladder with numerous calcified eggs and extensive scarring.

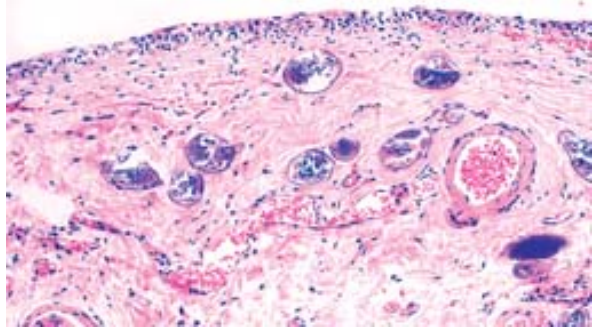


Figure 8-11 Measles giant cells in the lung. Note the glassy eosinophilic intranuclear inclusions.

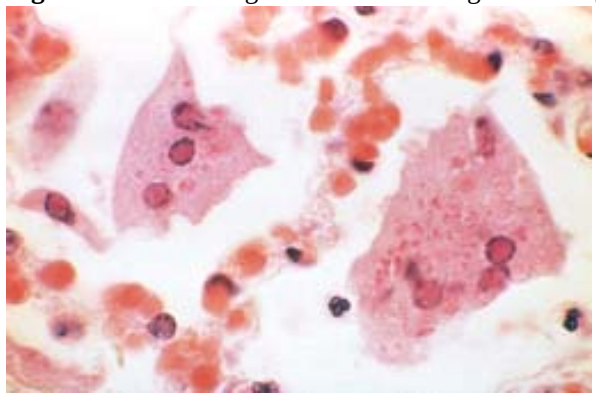


Figure 8-12 High-power view of cells from the blister in Figure 8-9 showing glassy intranuclear herpes simplex inclusion bodies.

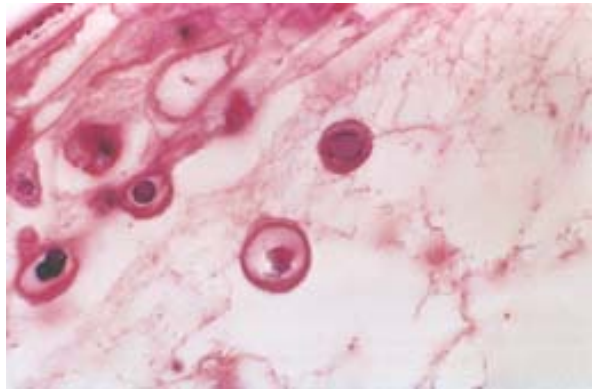


Figure 8-13 Cytomegalovirus: distinct nuclear and ill-defined cytoplasmic inclusions in the lung.

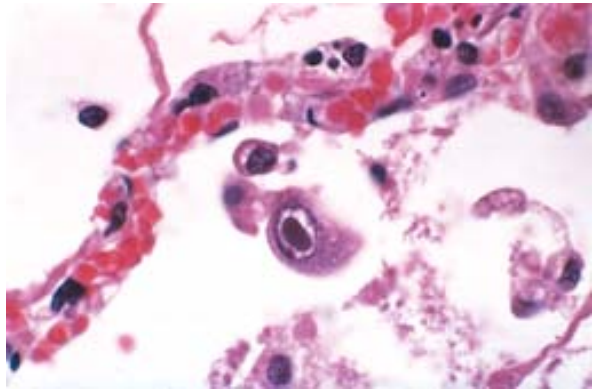


Figure 8-14 Skin lesion of chickenpox (varicella zoster virus) with intraepithelial vesicle.

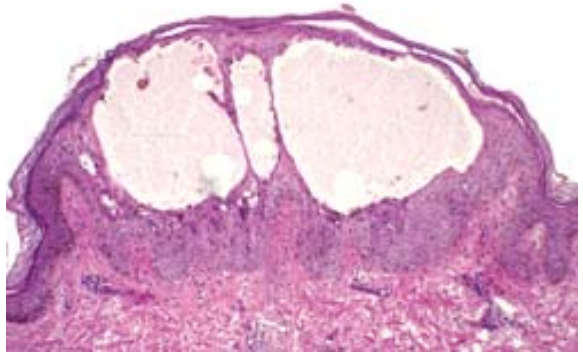


Figure 8-15 Dorsal root ganglion with varicella zoster virus infection. Note the ganglion cell necrosis and associated inflammation. *(Courtesy of Dr. James Morris, Radcliffe Infirmary, Oxford, England.)*

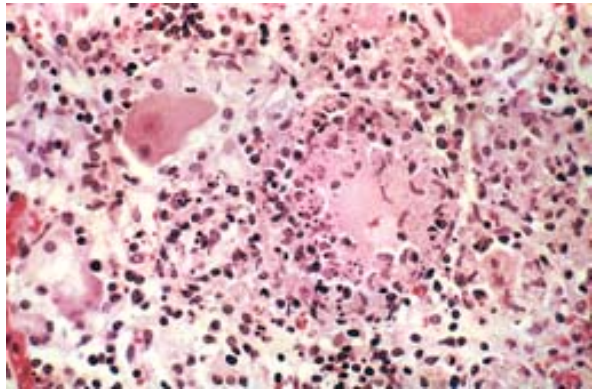


Figure 8-16 Pathways of transmission of the Epstein-Barr virus. In an individual with normal immune function, infection leads to mononucleosis. In the setting of cellular immunodeficiency, proliferation of infected B cells is uncontrolled and may cause B-cell neoplasms. One secondary genetic event that collaborates with Epstein-Barr virus (EBV) to cause B-cell transformation is a balanced 8;14 chromosomal translocation, which is seen in Burkitt lymphoma. EBV has also been implicated in the pathogenesis of nasopharyngeal carcinoma, Hodgkin disease, and certain other rare non-Hodgkin lymphomas.

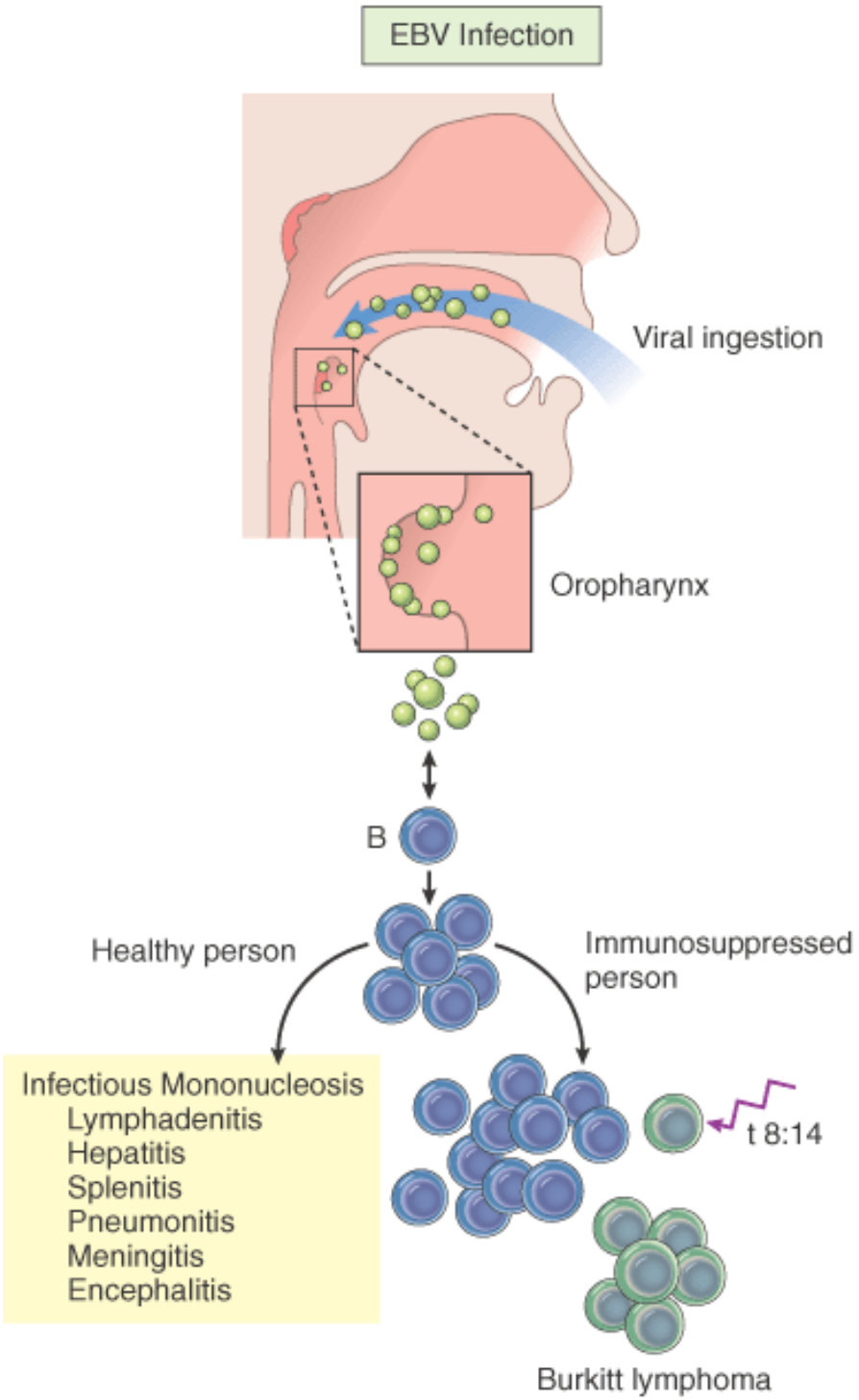


Figure 8-17 Atypical lymphocytes in infectious mononucleosis.

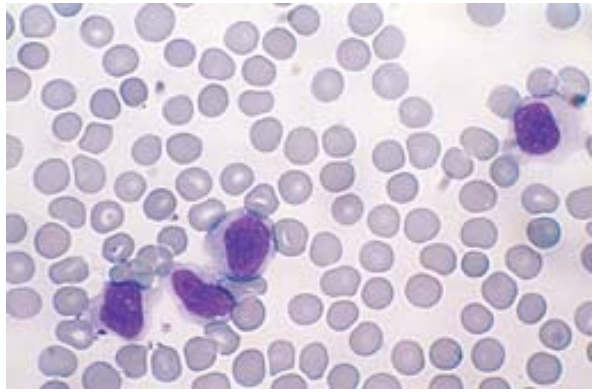
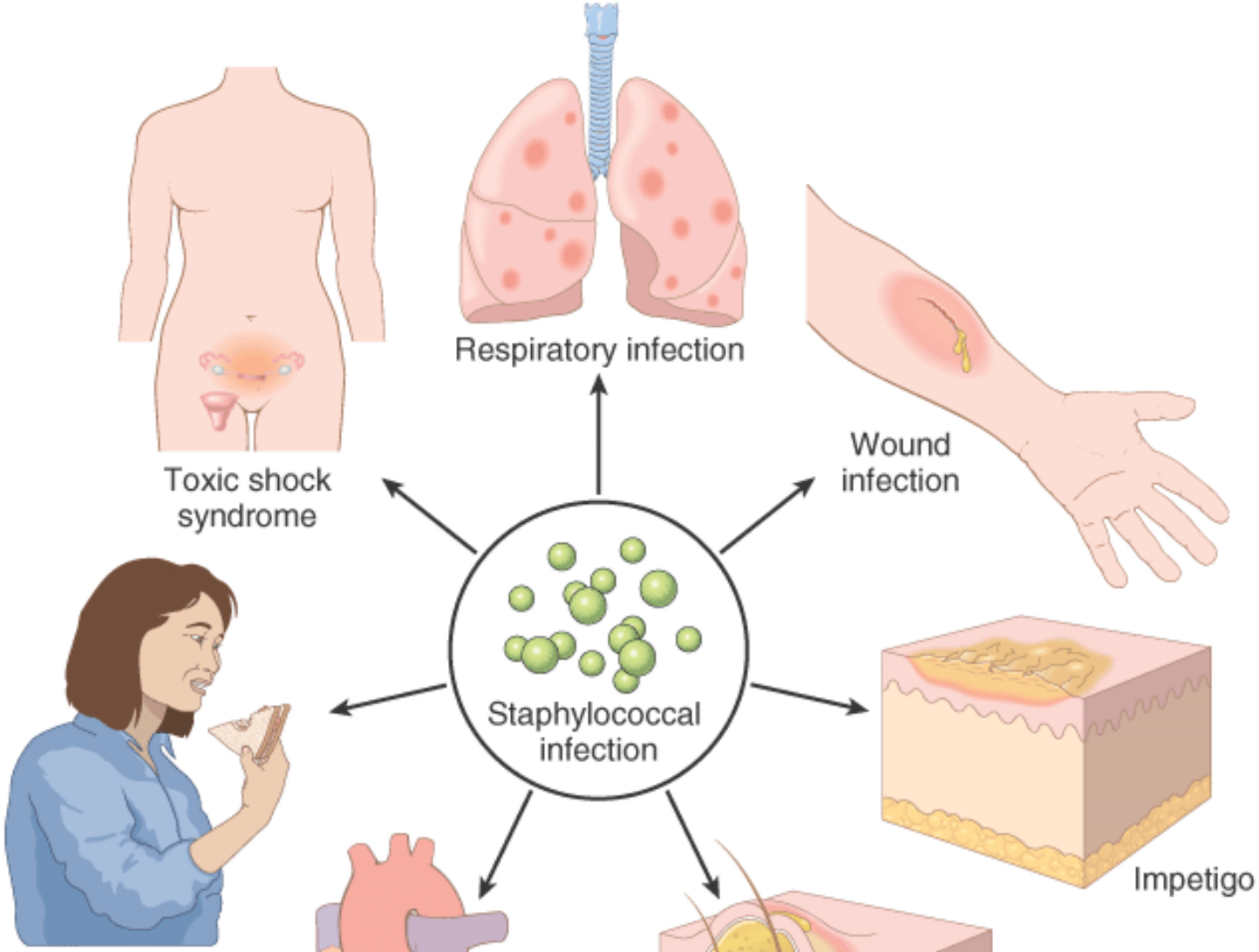


Figure 8-18 The many consequences of staphylococcal infection.



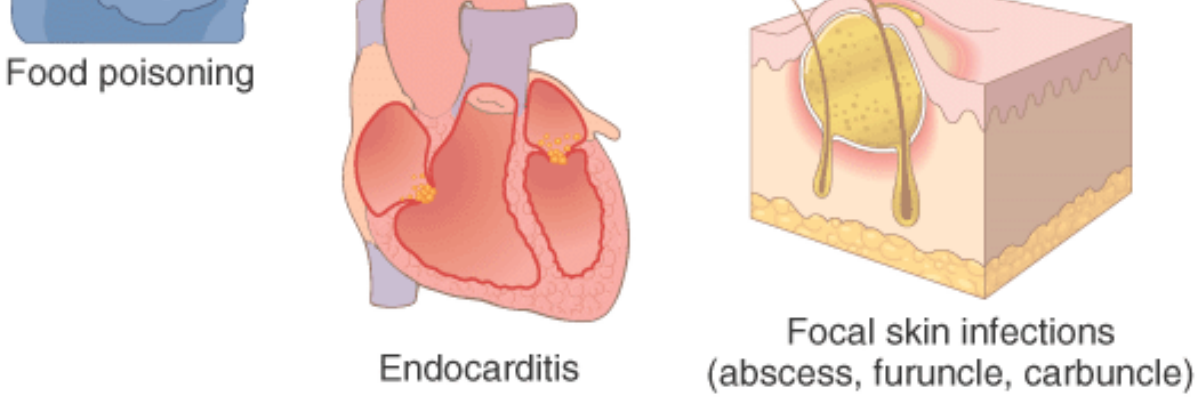


Figure 8-19 Staphylococcal abscess of the lung with extensive neutrophilic infiltrate and destruction of the alveoli (contrast with Figure 8-8).

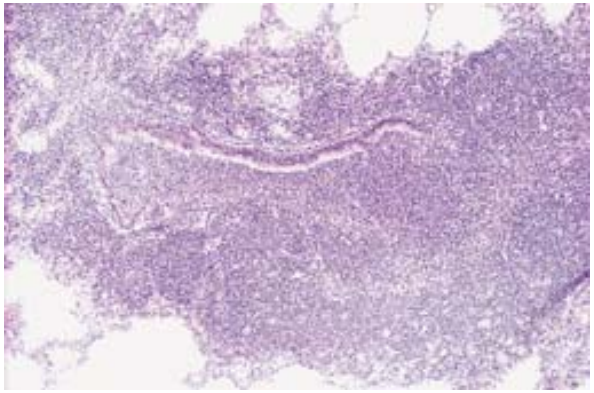


Figure 8-20 Streptococcal erysipelas.

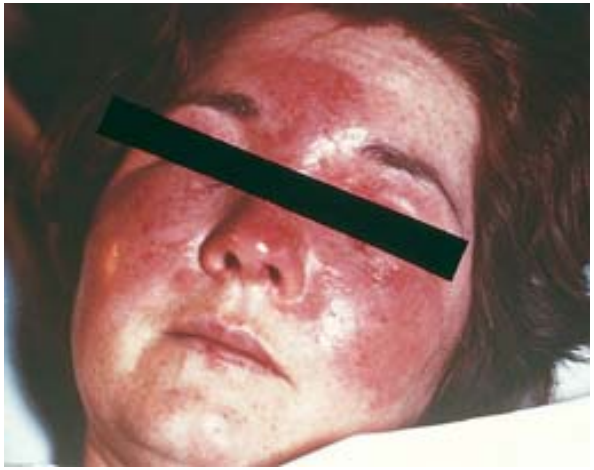


Figure 8-21 Membrane of diphtheria lying within a transverse bronchus (*A*) and forming a perfect cast (removed from the lung) of the branching respiratory tree (*B*).

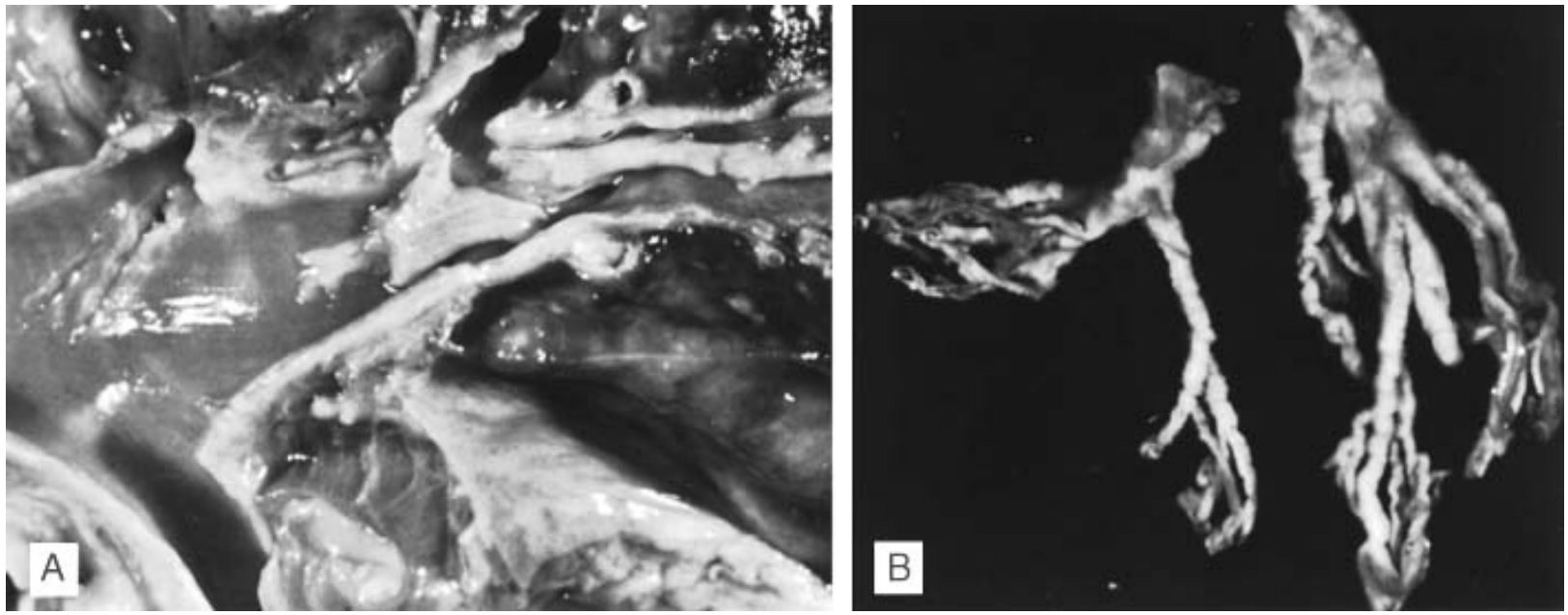


Figure 8-22 Mechanism of action of anthrax toxins. *(Adapted from Mourez et al: 2001: a year of major advances in anthrax toxin research. Trends Microbiol 10(6):287, 2002.)*

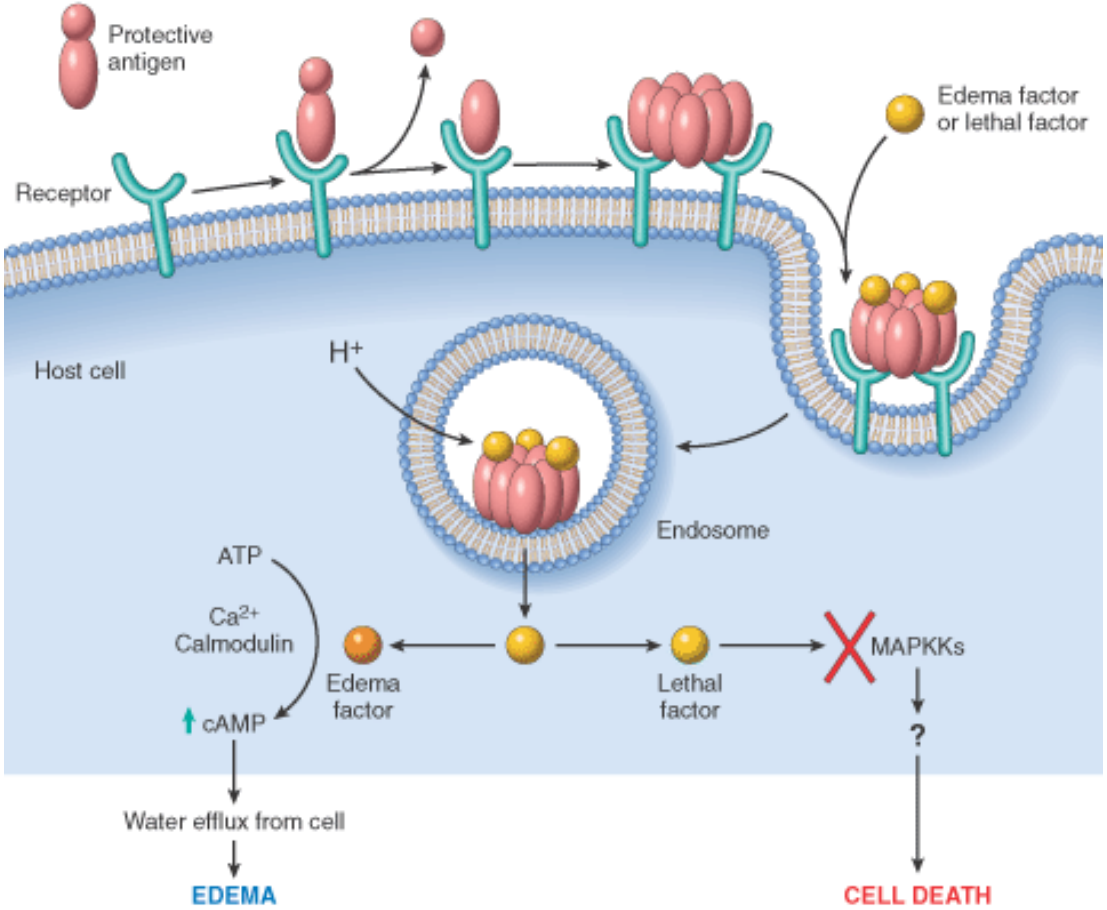


Figure 8-23 *B. anthracis* in the subcapsular sinus of a hilar lymph node of a patient who died of inhalational anthrax. *(Courtesy of Dr. Lev Grinberg, Department of Pathology, Hospital 40, Ekaterinburg, Russia and Dr. David Walker, UTMB Center for Biodefense and Emerging Infectious Diseases, Galveston, TX.)*

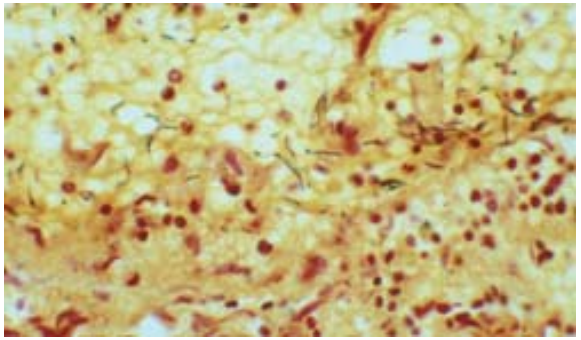


Figure 8-24 *Nocardia asteroides* in a Gram-stained sputum sample. Note the beaded, branched Gram-positive organisms and leukocytes. *(Courtesy of Dr. Ellen Jo Baron, Stanford University Medical Center, Stanford, CA.)*

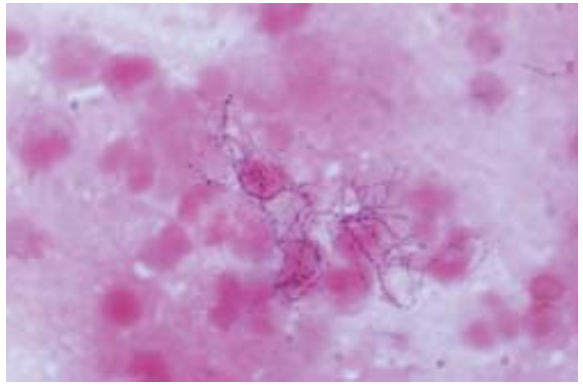


Figure 8-25 Gonococcal culture showing pili, as seen by scanning microscopy (*A*), and in clusters, as seen by transmission electron microscopy (*B*). *(Courtesy of Dr. John Swanson, Rocky Mountain Laboratories, Hamilton, MT.)*

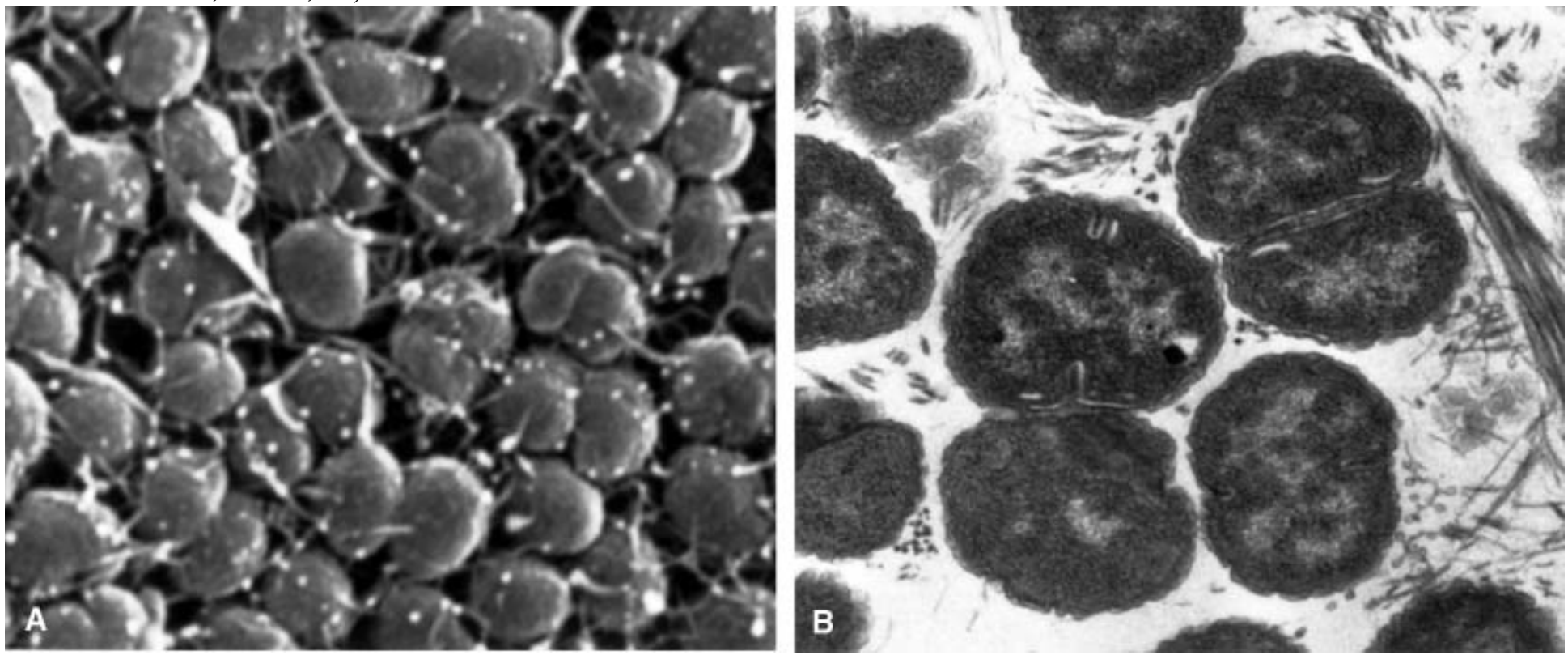


Figure 8-26 Whooping cough showing a haze of bacilli *(arrows)* etangled with the cilia of bronchial epithelial cells.

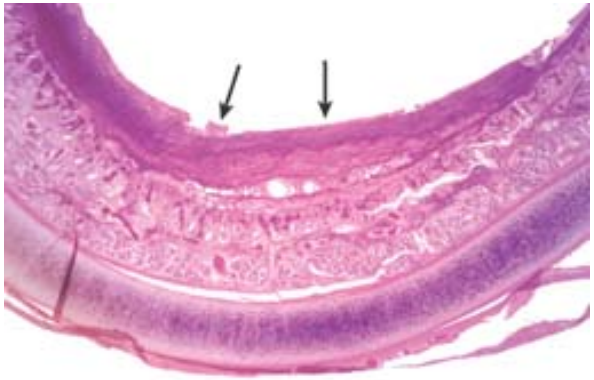


Figure 8-27 *Pseudomonas* vasculitis in which masses of organisms form a perivascular blue haze.

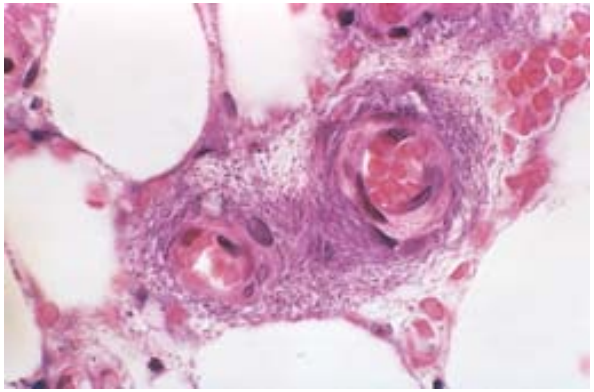


Figure 8-28 The sequence of events in primary pulmonary tuberculosis, commencing with inhalation of virulent *M. tuberculosis* and culminating with the development of cell-mediated immunity to the organism. *A*, Events occurring in the first 3 weeks after exposure. *B*, events thereafter. The development of resistance to the organism is accompanied by the appearance of a positive tuberculin test. Cells and bacteria are not drawn to scale. iNOS, inducible nitric oxide synthase; MHC, major histocompatibility complex; MTB, *M. tuberculosis*; NRAMP1, natural resistance-associated macrophage protein.

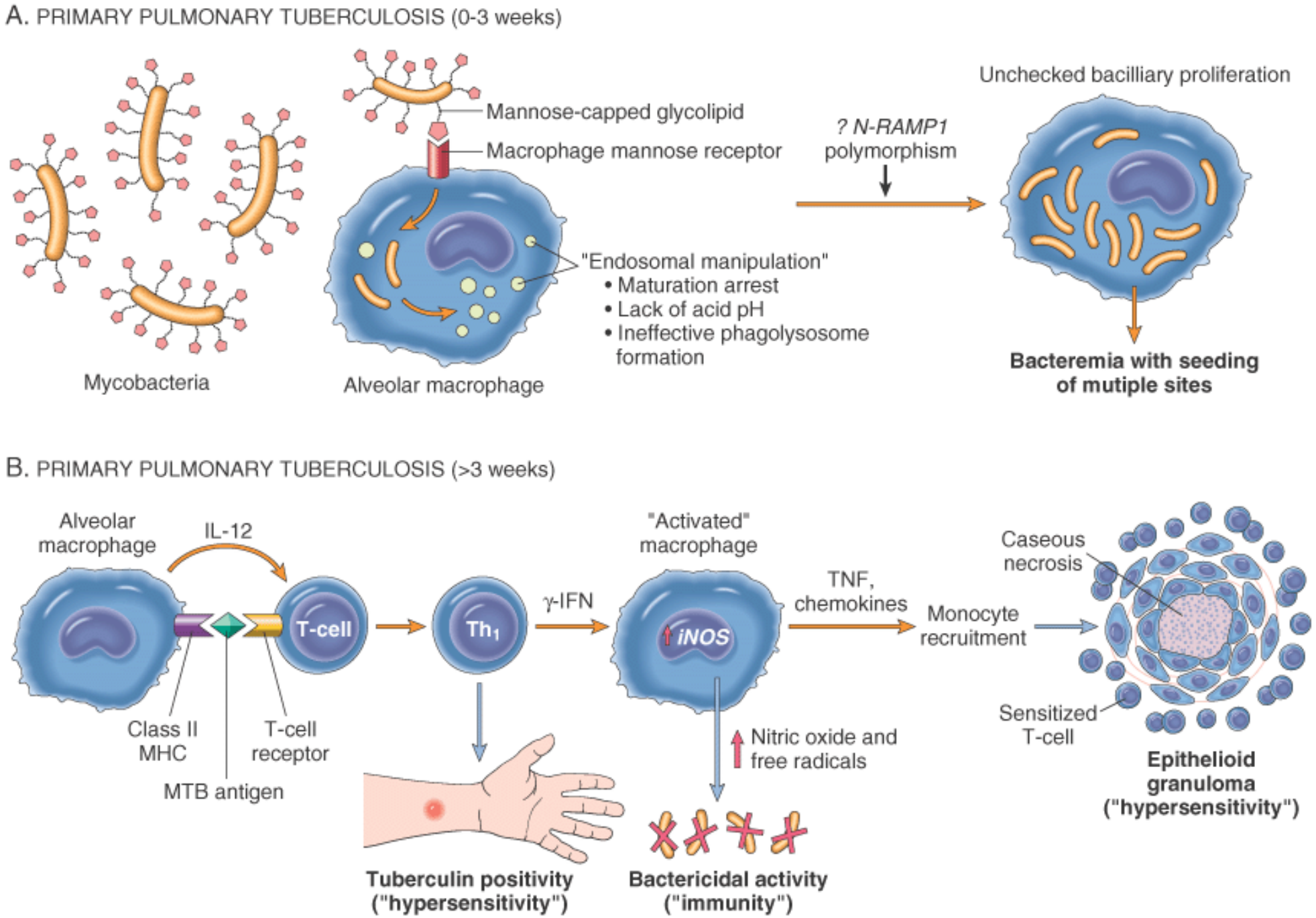


Figure 8-29 The natural history and spectrum of tuberculosis. *(Adapted from a sketch provided by Dr. R. K. Kumar, The University of New South Wales, School of Pathology, Sydney, Australia.)*

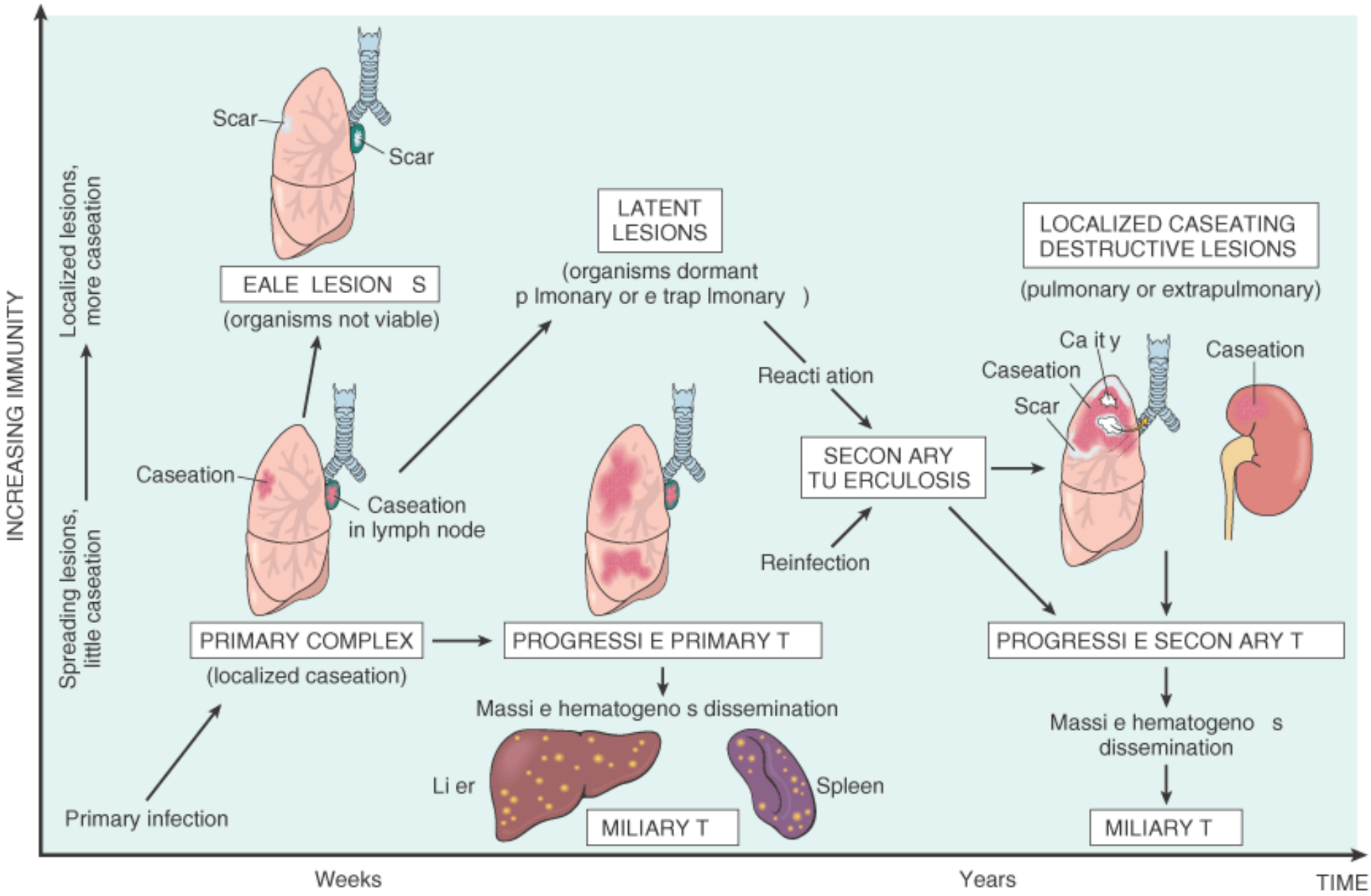


Figure 8-30 Primary pulmonary tuberculosis, Ghon complex. The gray-white parenchymal focus is under the pleura in the lower part of the upper lobe. Hilar lymph nodes with caseation are seen on the left.

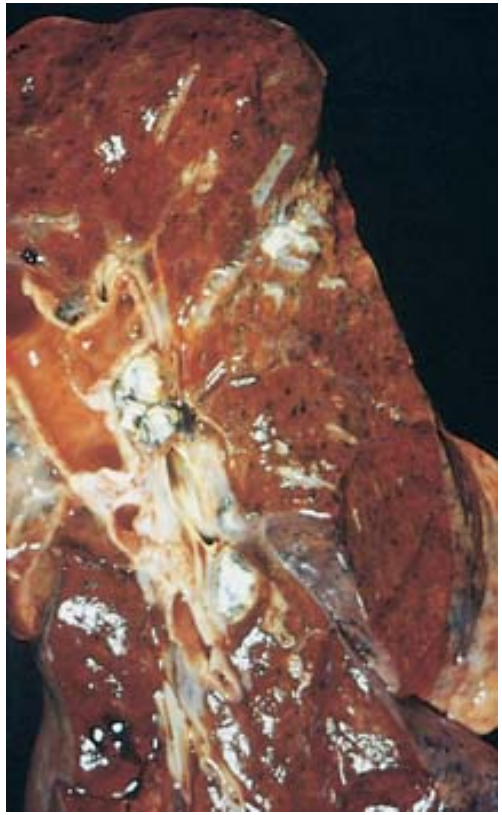


Figure 8-31 The morphologic spectrum of tuberculosis. A characteristic tubercle at low magnification (*A*) and in detail (*B*) illustrates central caseation surrounded by epithelioid and multinucleated giant cells. This is the usual response seen in patients who have developed cell mediated immunity to the organism. Occasionally, even in immunocompetent individuals, tubercular granulomas might not show central caseation (*C*); hence, irrespective of the presence or absence of caseous necrosis, special stains for acid-fast organisms need to be performed when granulomas are present in histologic section. In immunosuppressed individuals, tuberculosis may not elicit a granulomatous response ("nonreactive tuberculosis"); instead, sheets of foamy histiocytes are seen, packed with mycobacteria that are demonstrable with acid-fast stains (*D*). *(D, Courtesy of Dr. Dominick Cavuoti, Department of Pathology, University of Texas Southwestern Medical School, Dallas, TX.)*

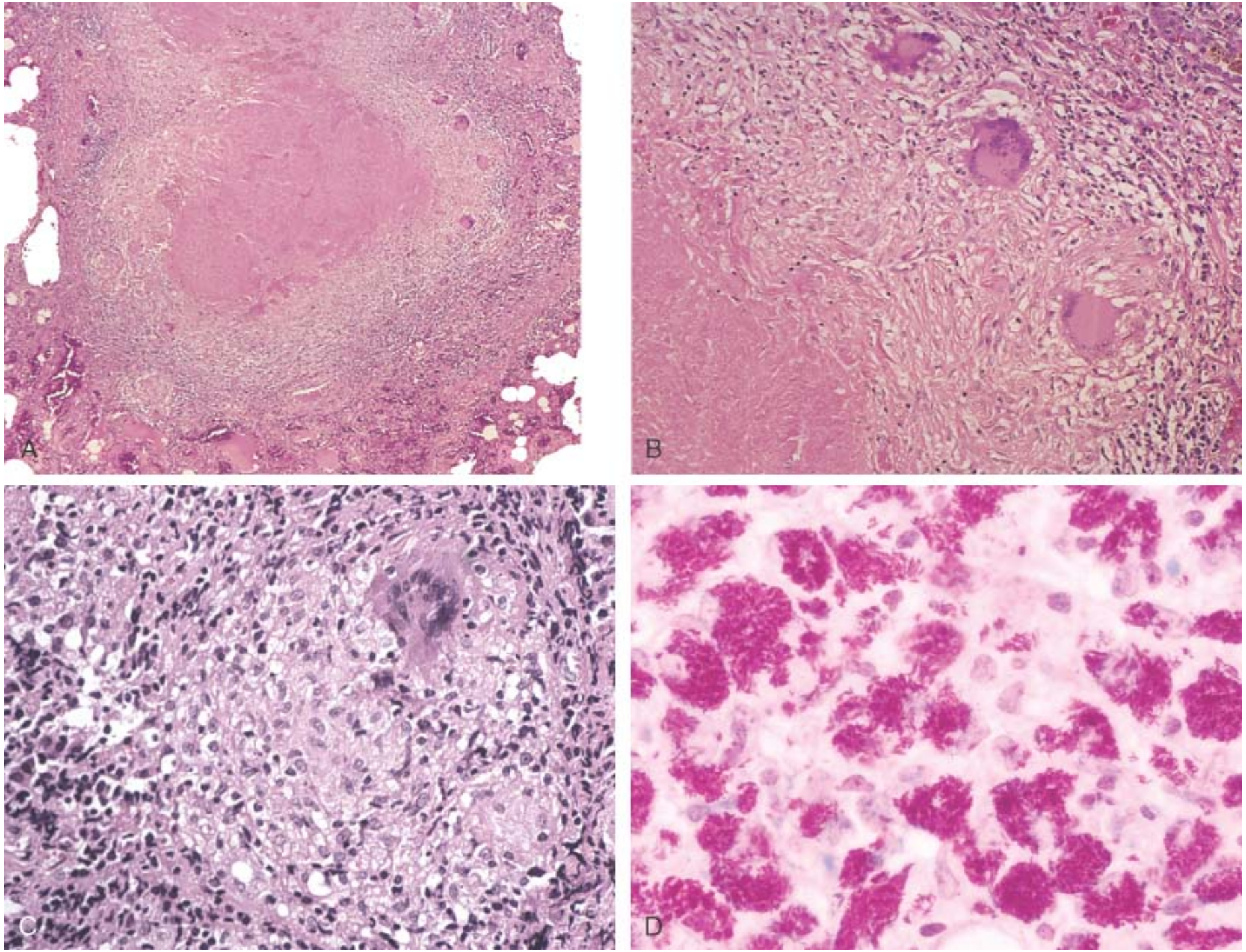


Figure 8-32 Secondary pulmonary tuberculosis. The upper parts of both lungs are riddled with gray-white areas of caseation and multiple areas of softening and cavitation.

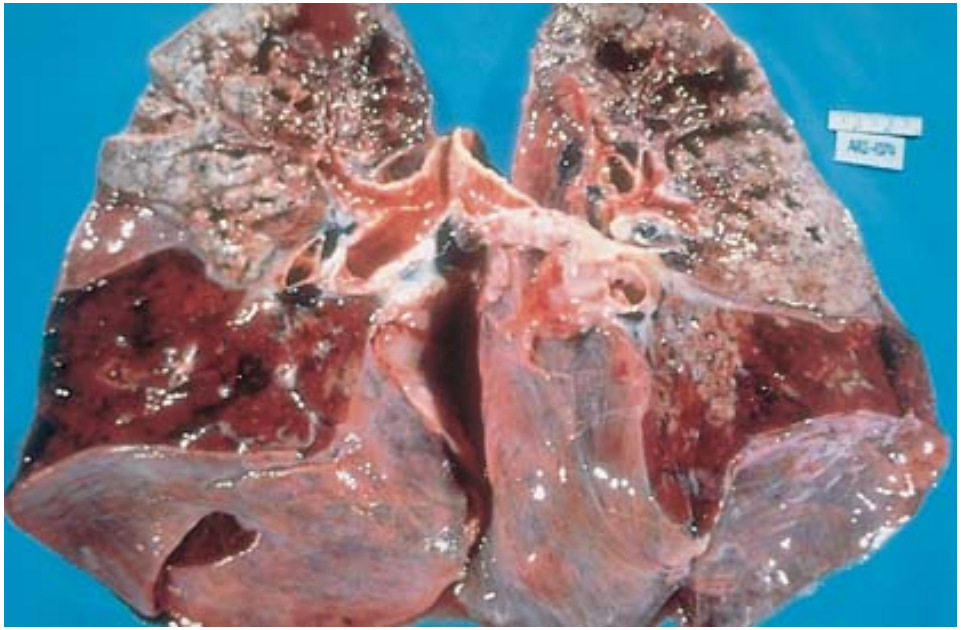


Figure 8-33 Miliary tuberculosis of the spleen. The cut surface shows numerous gray-white granulomas.

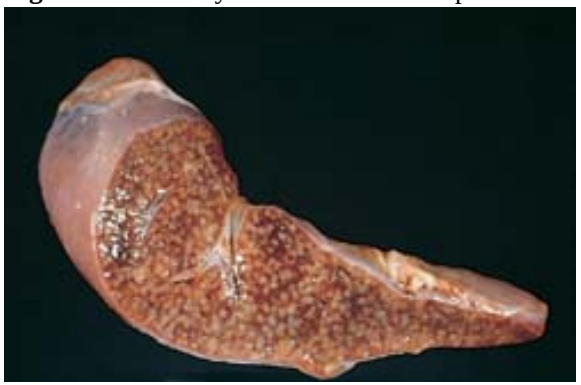


Figure 8-34 *Mycobacterium avium* infection in a patient with AIDS, showing massive infection with acid-fast organisms.

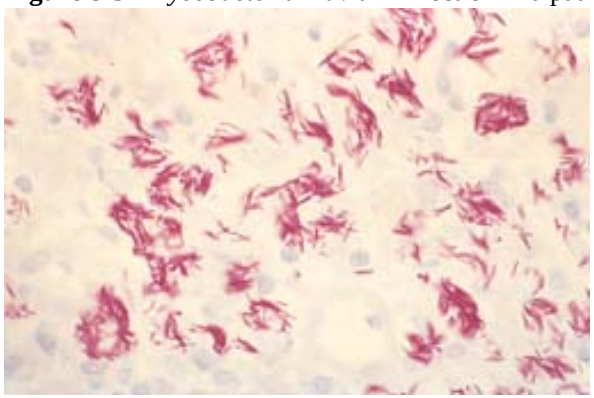


Figure 8-35 Leprosy. *A*, Peripheral nerve. Note the inflammatory cell infiltrates in the endoneural and epineural compartments. *B*, Cells within the endoneurium contain acid-fast positive lepra bacilli. *(Courtesy of E.P. Richardson, Jr. and U. De Girolami, Harvard Medical School.)*

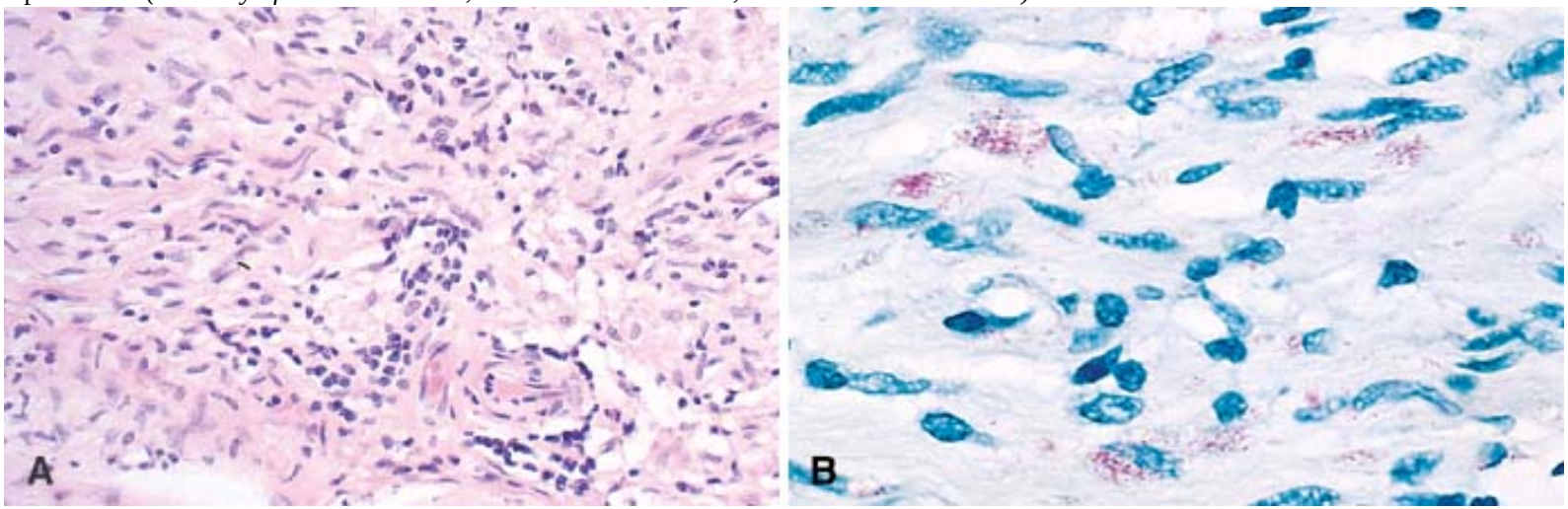


Figure 8-36 Lepromatous leprosy. Acid-fast bacilli ("red snappers") within macrophages.

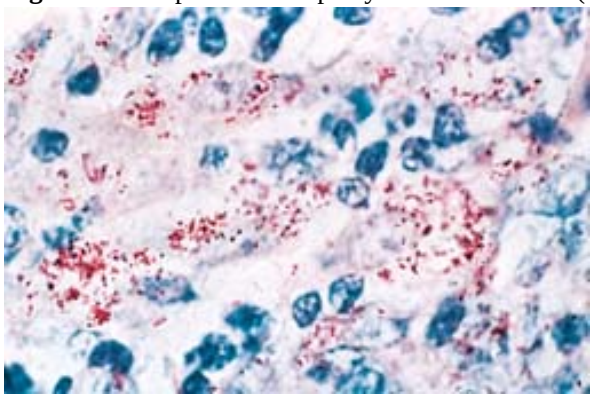


Figure 8-37 *Treponema pallidum* (dark-field microscopy) showing several spirochetes in scrapings from the base of a chancre. *(Courtesy of Dr. Paul Southern, Department of Pathology, University of Texas Southwestern Medical School, Dallas, TX.)*

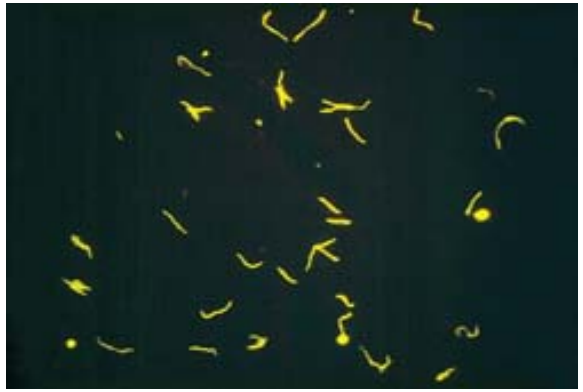


Figure 8-38 Protean manifestations of syphilis.

STAGE	PATHOLOGY	
Primary	Chancre	
Secondary	Palmar, rash	
	Lymphadenopathy	
	Condyloma latum	
Tertiary	Neurosyphilis:	Meningovascular
		Tabes dorsalis
		General paresis
	Aortitis:	Aneurysms
		Aortic regurgitation
	Gummas:	Hepar lobatum
		Skin, bone, others
Congenital	Late abortion or stillbirth	
	Infantile:	Rash
		Osteochondritis
		Periostitis
		Liver and lung fibrosis
	Childhood:	Interstitial keratitis
		Hutchinson teeth
		Eighth nerve deafness

Hutchinson teeth
Eighth nerve deafness

Figure 8-39 Syphilitic chancre in the scrotum (see Figure 8-8 for the histopathology of syphilis). *(Courtesy of Dr. Richard Johnson, Beth Israel-Deaconess Hospital, Boston, MA.)*

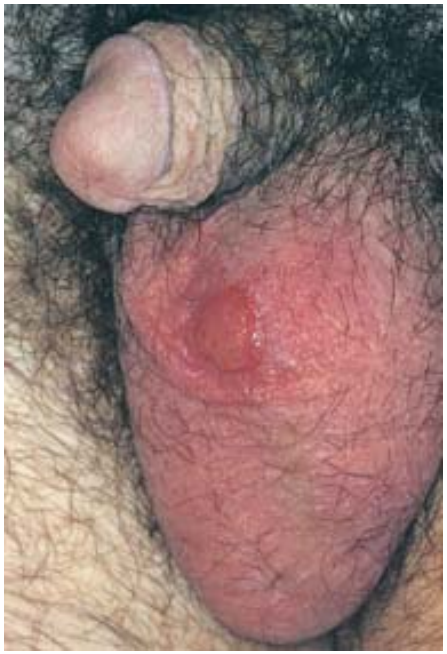


Figure 8-40 Trichrome stain of liver shows liver gumma (scar), stained blue, which is caused by tertiary syphilis (also known as hepar lobatum). Compare with nodules of alcoholic cirrhosis (Chapter 18).

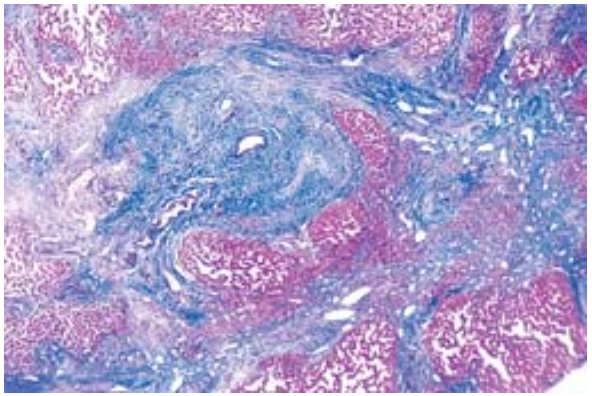


Figure 8-41 Tiny deer tick *(bottom)*, which transmits Lyme disease and Babesia and Ehrlichia organisms, contrasted with a larger dog tick *(top)*, which is not thought to transmit human infections. *(Courtesy of Dr. F.R. Matuschka, Free University of Berlin, Germany.)*

Figure 8-42 Clinical stages of Lyme disease.

STAGE 1

Acute illness (weeks)

- Tick bite—erythematous papule
- Erythema chronicum migrans
- Lymphadenitis

STAGE 2

Dissemination (weeks to months)

- CNS:
  - Meningoencephalitis
  - Cranial neuritis
- Cardiac:
  - Heart block
  - Pericarditis
  - Myocarditis

STAGE 3

Late chronic form

- Destructive chronic arthritis
- Acrodermatitis atrophicans
- Neuropathy

Figure 8-43 Boxcar-shaped Gram-positive *Clostridium perfringens* in gangrenous tissue.

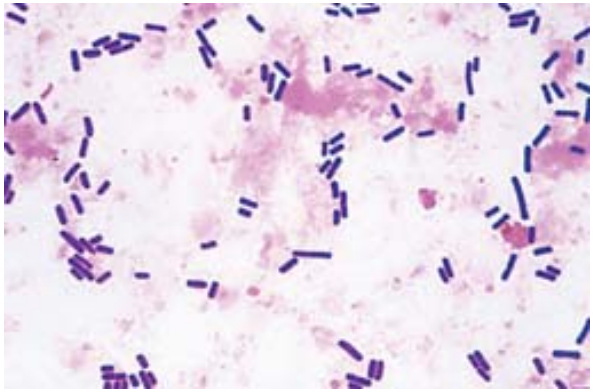


Figure 8-44 Peripheral blood granulocyte (band neutrophil) containing an Ehrlichia inclusion (*arrow*). *(Courtesy of Dr. Stephen Dumler, Johns Hopkins Medical Institutions, Baltimore, MD.)*

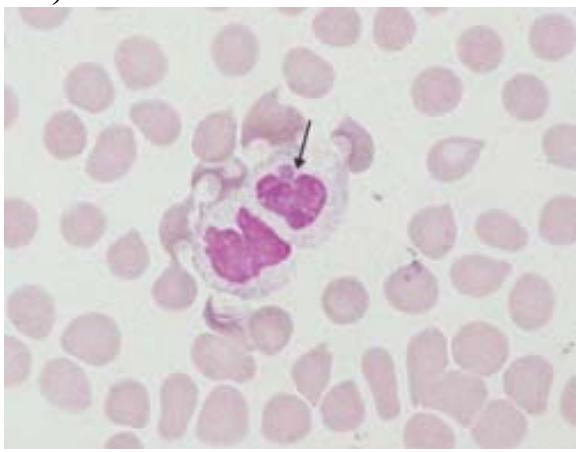


TABLE 8-10 -- Rickettsial Diseases and Pathogens

Typhus Group (No Eschar)				
Organism	***Disease***	***Geography***	***Transmission***	***Distinctive Features***
R. prowazekii	Epidemic typhus Brill-Zinsser disease	Worldwide (war, famine)	Louse feces	Endothelial infection; centrifugal rash; reactivation with mild disease
R. typhi	Murine typhus	Worldwide (rat related)	Rat flea feces	Similar to epidemic typhus, but mortality is lower
Spotted Fever Group				
Organism	***Disease***	***Geography***	***Transmission***	***Distinctive Features***
R. rickettsii	Rocky Mountain spotted fever	North and South America	Tick bite	Endothelia and vascular smooth muscle infected; centripetal rash, eschar rare
R. conorii	Boutonneuse fever	Africa, Southern Europe, India	Tick bite	Prominent eschar, tache noire

R. africae	Africa tick fever	Africa, Caribbean	Tick bite	Multiple eschars
R. sibirica	North Asia tick typhus	Eurasia	Tick bite	Typical spotted fever with eschar
R. japonica	Japanese spotted fever	Japan	Tick bite	Typical spotted fever with eschar
R. australis	Queensland tick typhus	Eastern Australia	Tick bite	Typical spotted fever with eschar
R. akari	Rickettsialpox	United States, Ukraine, Korea, Croatia	Mite bite	Mild spotted fever with eschar
R. felis	Similar to murine typhus	United States	Opossum flea	Similar to murine typhus
Orientia tsutsugamushi	Scrub typhus	Eastern Asia and Western Pacific region	Chigger bite	Eschar common, insects present in scrub vegetation
Ehrlichiosis Group				
Organism	***Disease***	***Geography***	***Transmission***	***Distinctive Features***
Ehrlichia chaffeensis	Monocytic ehrlichiosis	United States, Europe	Tick bite	Fever, lymphadenopathy, no eschar, rash in 40%
Anaplasma phagocytophilum and *E. ewingii*	Granulocytic ehrlichiosis	United States, Europe	Tick bite	Fever, lymphadenopathy, no eschar or rash

The innate immune response to rickettsial infection is mounted by natural killer cells, which produce γ-interferon, reducing bacterial proliferation. Cytotoxic T-lymphocyte responses are critical for elimination of rickettsial infections. IFN-γ and TNF, from activated natural killer cells, CD4+, and CD8+ T lymphocytes, stimulate the production of bactericidal nitric oxide. Cytotoxic T lymphocytes lyse infected cells, reducing bacterial proliferation. Rickettsial infections are diagnosed by immunostaining of organisms or by detection of antirickettsial antibodies in the serum.

Morphology

Typhus Fever.

In mild cases, the gross changes are limited to a rash and small hemorrhages due to the vascular lesions. In more severe cases, there may be areas of necrosis of the skin with gangrene of the tips of the fingers, nose, earlobes, scrotum, penis, and vulva. In such cases, irregular ecchymotic hemorrhages may be found internally, principally in the brain, heart muscle, testes, serosal membrane, lungs, and kidneys.

The most prominent microscopic changes are the small-vessel lesions that underlie the rash and the focal areas of hemorrhage and inflammation in the various organs and tissues affected. Endothelial swelling in the capillaries, arterioles, and venules may narrow the lumina of these vessels. A cuff of mononuclear inflammatory cells usually surrounds the affected vessel. The vascular lumina are sometimes thrombosed, but necrosis of the vessel wall is unusual in typhus compared with RMSF. Vascular thromboses lead to the gangrenous necroses of the skin and other structures in a minority of cases. In the brain, characteristic typhus nodules are composed of focal microglial proliferations with an infiltrate of mixed T lymphocytes and macrophages (Fig. 8-45).

Scrub typhus, or mite-borne infection, is usually a milder version of typhus fever. The rash is usually transitory or might not appear. Vascular necrosis or thrombosis is rare, but there may be a prominent inflammatory lymphadenopathy.

Rocky Mountain spotted fever.

A hemorrhagic rash that extends over the entire body, including the palms of the hands and soles of the feet, is the hallmark

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Figure 8-45 Typhus nodule in the brain.

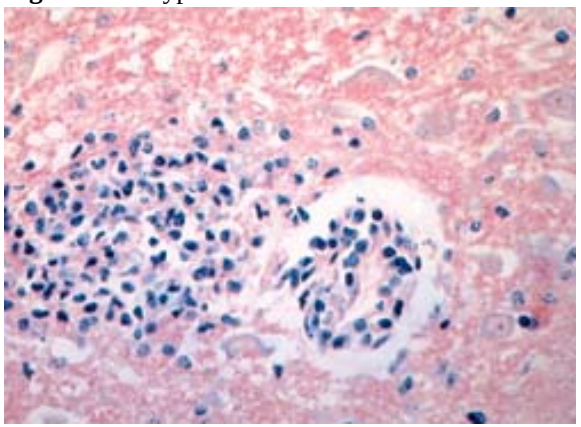


Figure 8-46 Rocky Mountain spotted fever with a thrombosed vessel and vasculitis.

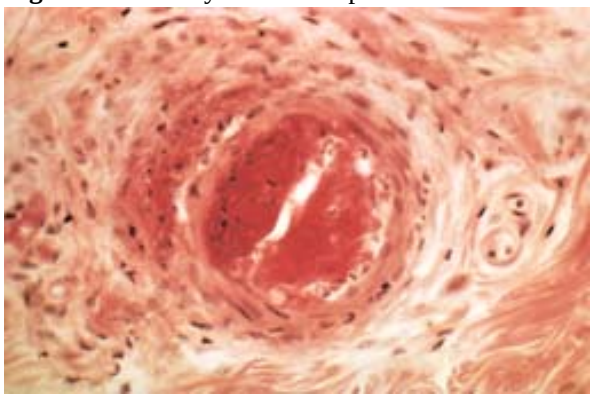


Figure 8-47 The morphology of *Candida* infections. *A*, Severe candidiasis of the distal esophagus. *B*, Silver stain of esophageal candidiasis reveals the dense mat of *Candida*. *C*, Characteristic pseudohyphae and blastoconidia (budding yeast) of *Candida*. *(C, Courtesy of Dr. Dominick Cuvuoti, Department of Pathology, University of Texas Southwestern Medical School, Dallas, TX.)*

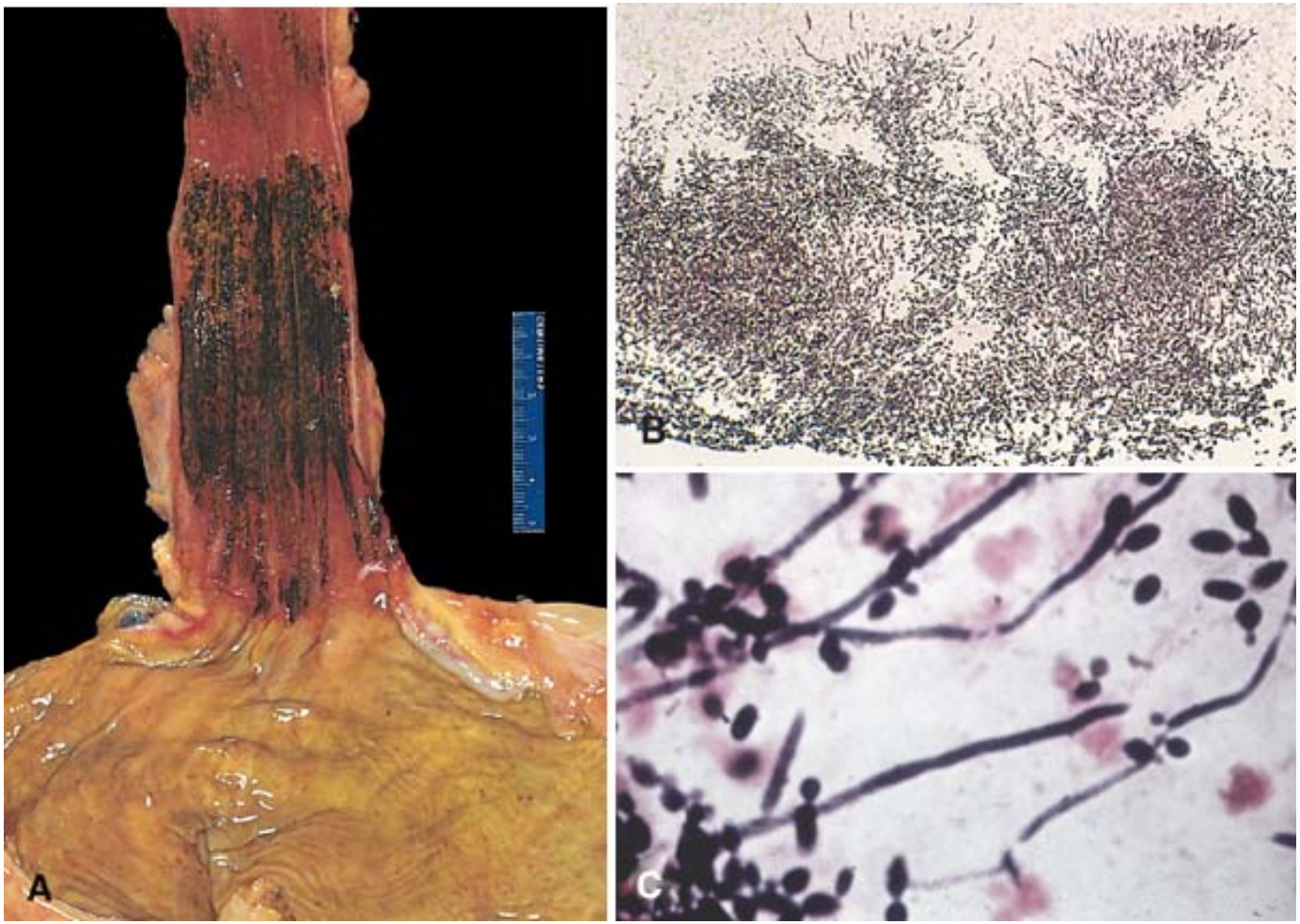


Figure 8-48 Mucicarmine stain of cryptococci (staining red) in a Virchow-Robin perivascular space of the brain (soap-bubble lesion).

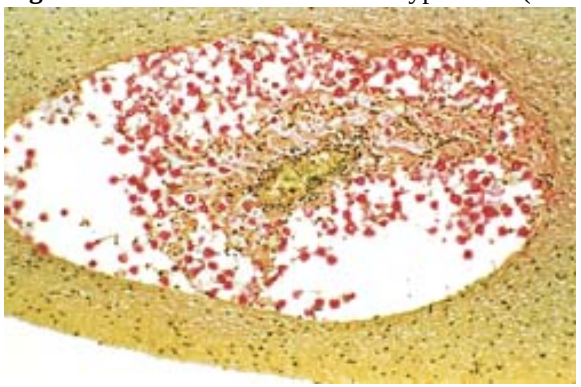


Figure 8-49 *Aspergillus* morphology. *A*, Invasive aspergillosis of the lung in a bone marrow transplant patient. *B*, Histologic sections from this case, stained with Gomori methenamine-silver (GMS) stain, show septate hyphae with acute-angle branching, features consistent with *Aspergillus*. Occasionally, *Aspergillus* may demonstrate fruiting bodies (inset) when it grows

in areas that are well aerated (such as the upper respiratory tract).

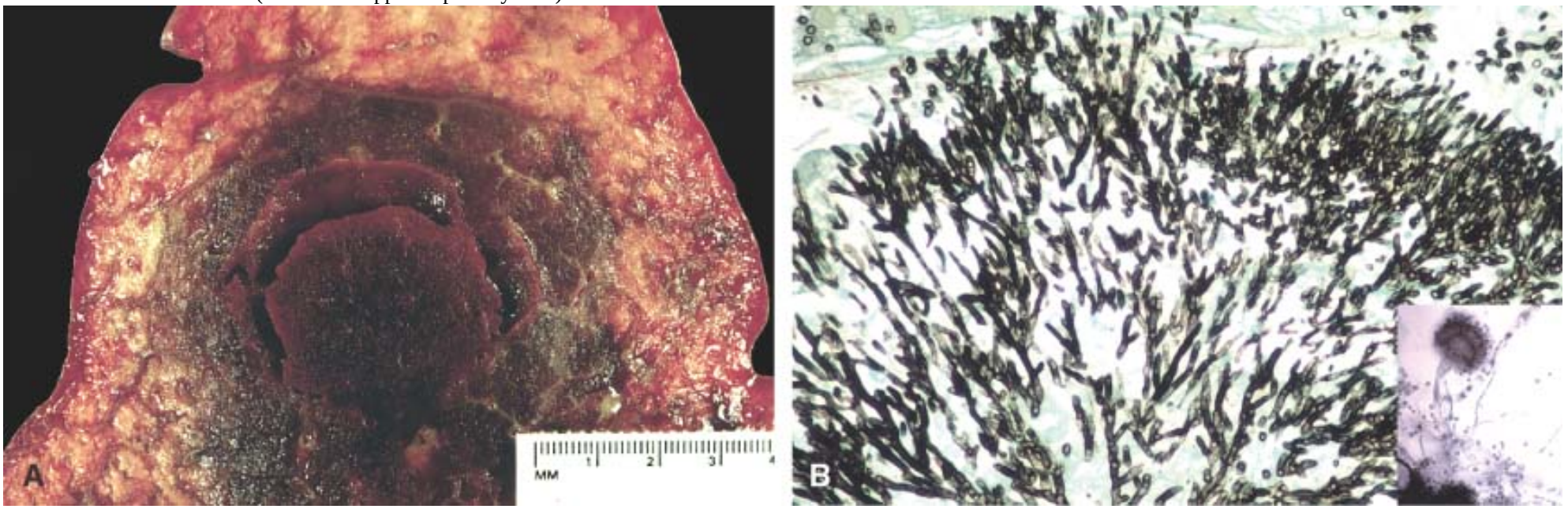


Figure 8-50 PAS stain of mucormycosis showing hyphae, which have an irregular width and right-angle branching, invading an artery wall.

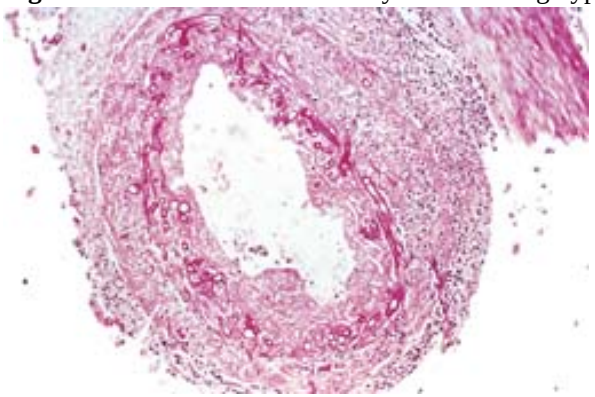


Figure 8-51 Life cycle of *Plasmodium falciparum*. *(Drawn by Dr. Jeffrey Joseph, Beth Israel-Deaconess Hospital, Boston, MA.)*

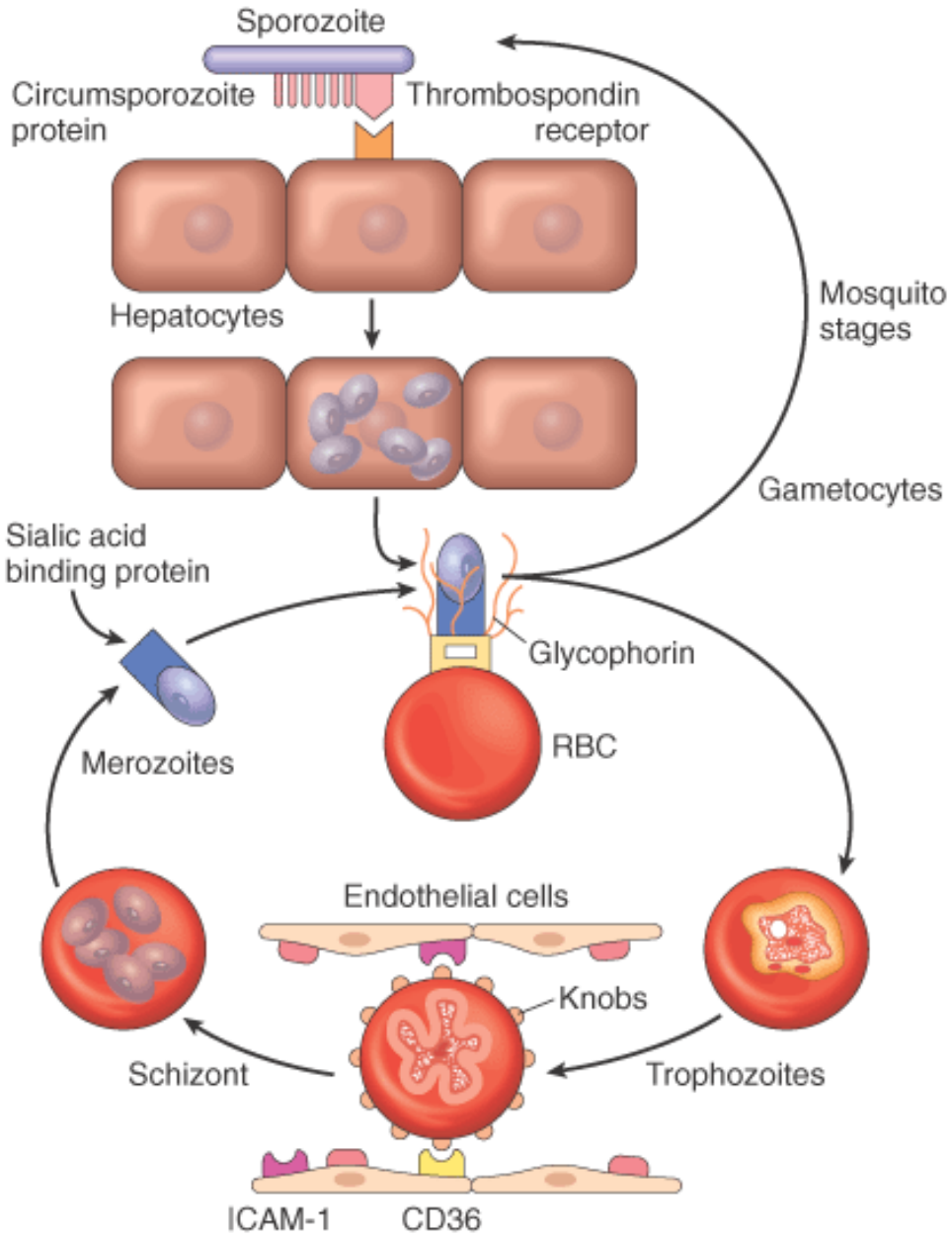


Figure 8-52 *P. falciparum*-infected red cells marginating within a vein in cerebral malaria.

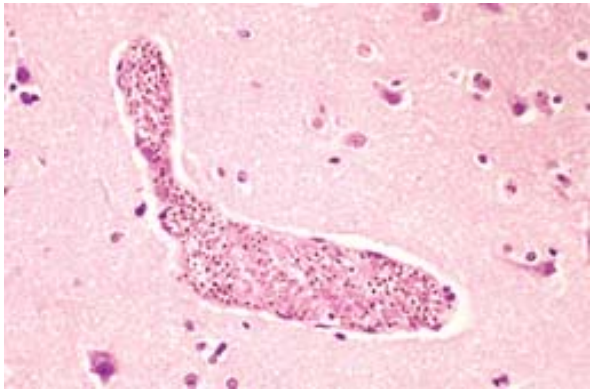


Figure 8-53 Erythrocytes with *Babesia*, including the distinctive Maltese cross form. *(Courtesy of Lynne Garcia, LSG and Associates, Santa Monica, CA.)*

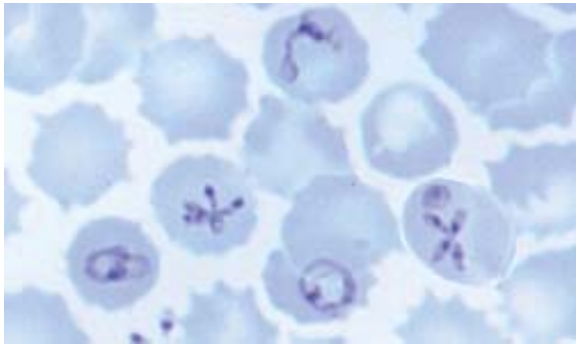


Figure 8-54 *Leishmania donovani* parasites within the macrophages of a lymph node in visceral leishmaniasis (kala-azar).

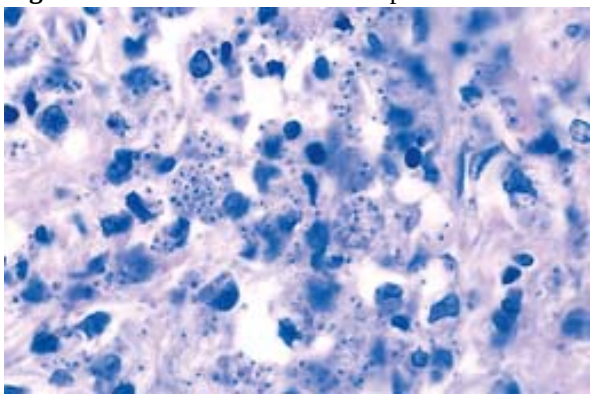


Figure 8-55 Slender bloodstream parasites of African trypanosomiasis.

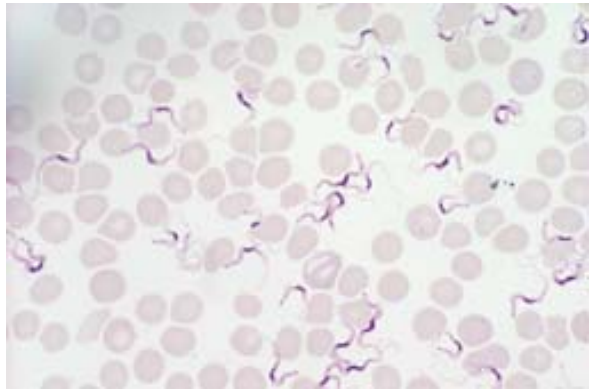


Figure 8-56 Strongyloides hyperinfection in a patient treated with high-dose cortisone. A female, her eggs and rhabditoid larvae are in the duodenal crypts; filariform larvae are entering the blood vessels and muscularis mucosa. *(Courtesy of Dr. Franz C. Von Lichtenberg, Brigham and Women's Hospital, Boston, MA.)*

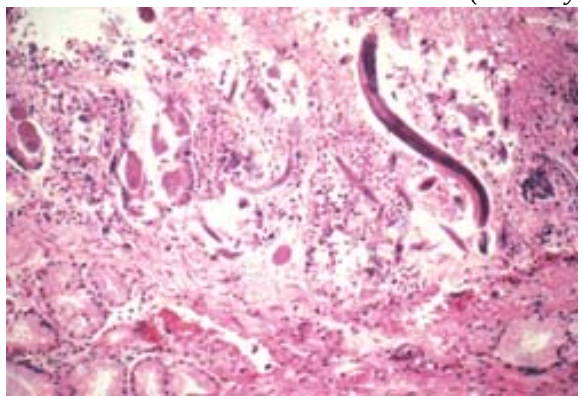


Figure 8-57 Portion of a cysticercus cyst.

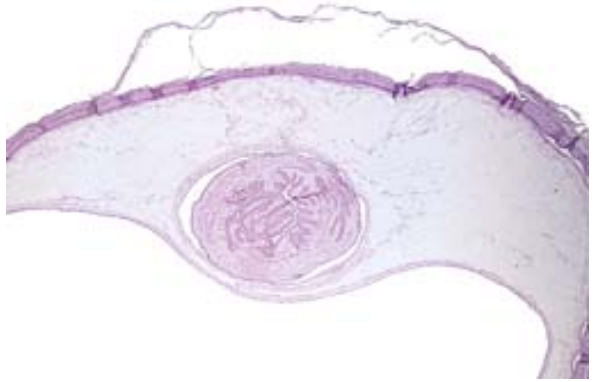


Figure 8-58 Coiled *Trichinella spiralis* larva within a skeletal muscle cell.

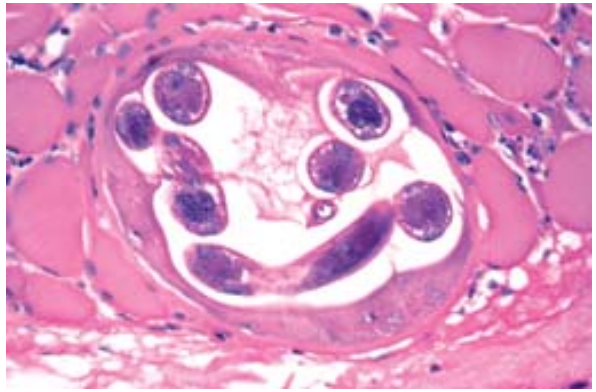


Figure 8-59 Schistosome life cycle.

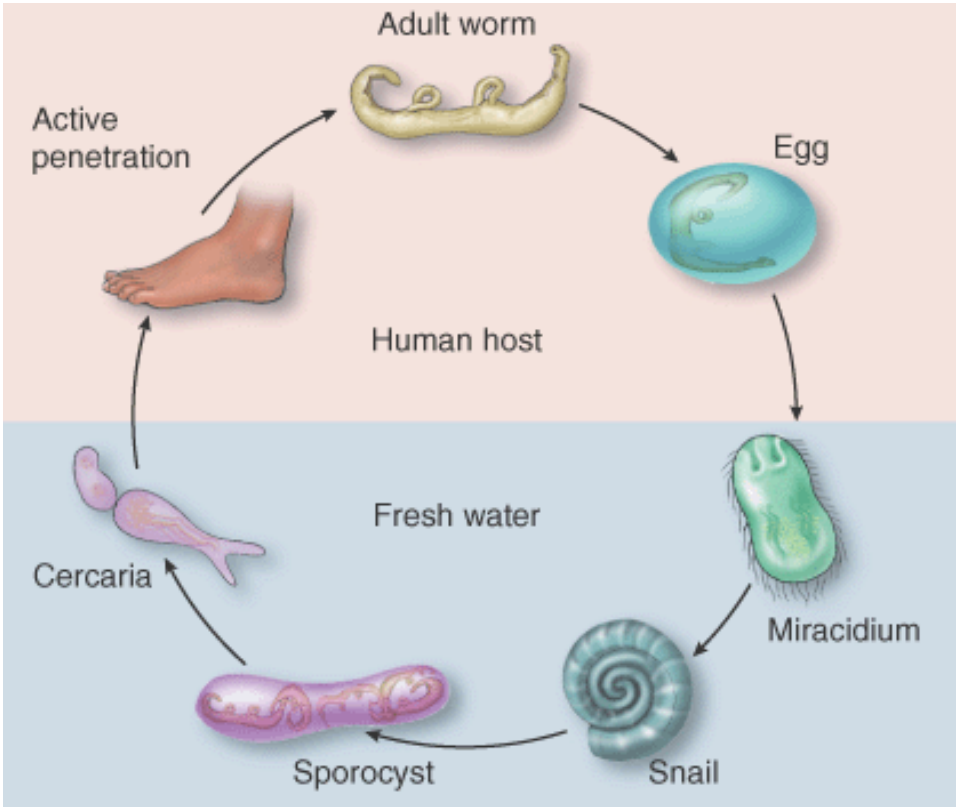


Figure 8-60 *Schistosoma mansoni* granuloma with a miracidium-containing egg *(center)* and numerous, adjacent, scattered eosinophils.

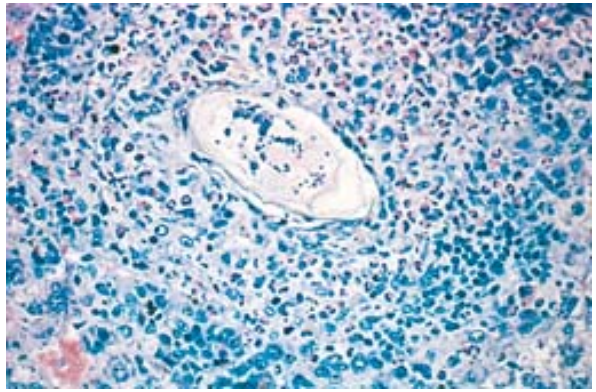


Figure 8-61 Pipe-stem fibrosis of the liver due to chronic *Schistosoma japonicum* infection.

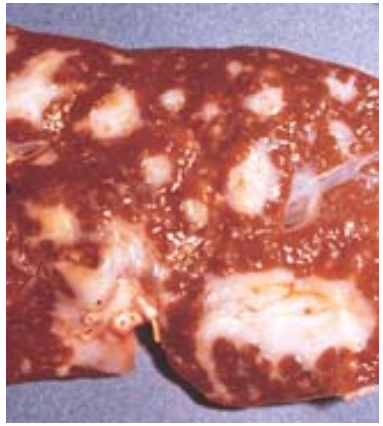


Figure 8-62 Massive edema and elephantiasis caused by filariasis of the leg. *(Courtesy of Dr. Willy Piessens, Harvard School of Public Health, Boston, MA.)*

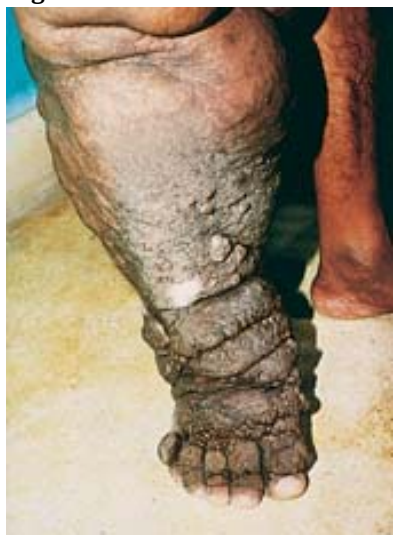
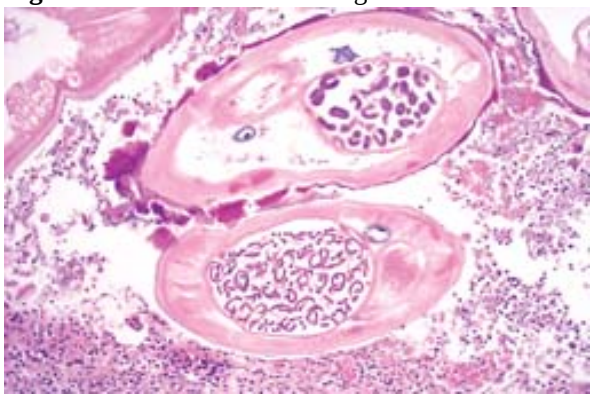


Figure 8-63 Microfilaria-laden gravid female of *Onchocerca volvulus* in a subcutaneous fibrous nodule.



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Chapter 9 - Environmental and Nutritional Pathology

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Environment and Disease

Environmental and occupational health encompasses the diagnosis, treatment, and prevention of injuries and illnesses resulting from exposure to exogenous chemical or physical agents. Such exposure may occur in the workplace, or people may voluntarily expose themselves to these hazards, for example, by abusing drugs or ethanol and smoking cigarettes. These personal habits may lead to involuntary exposure of fetuses and infants to drugs, ethanol, or environmental tobacco smoke.

People are often confused about the magnitude of the adverse health effects of exogenous physical and chemical agents. There is widespread concern about the potential chronic or delayed effects of exposure to low levels of contaminants in air, water, and food, and hence patients frequently seek advice and information from their health care

professionals about the risk of disease associated with specific environmental and occupational exposures. This chapter provides a basic foundation in the most important diseases associated with environmental and occupational exposures, emphasizing the mechanisms leading to these diseases. This framework will help physicians to recognize and treat injuries and

illness resulting from environmental and occupational exposures and to educate their patients about the risks of these exposures.[1]

RECOGNITION OF OCCUPATIONAL AND ENVIRONMENTAL DISEASES

Accidents, illness, and premature deaths threaten the health of 130 million workers in the United States. Occupational health risks are even greater in developing countries, where children and women constitute a larger proportion of the work force. In the United States, the annual rate of occupational injuries is 7400 per 100,000 workers. The overall fatality rate is 4.8 per 100,000 workers; the highest rates occur in the mining, agricultural, construction, transportation, and public utility industries. In addition to physical injury, occupational exposures contribute to a wide range of illnesses that may lead to premature death (Table 9-1). The magnitude of occupational diseases is most likely underestimated because workers and their employers fear economic or legal pressures, physicians may not recognize that an illness is work related, and there may be a long latent period between exposure and the development of clinical illness. Nevertheless, occupational diseases are preventable if there is adequate surveillance by state and federal governments, responsible leadership in industry, and access to health professionals trained in occupational safety and health.[1]

The magnitude and extent of illness related to environmental exposures are difficult to ascertain. The Environmental Protection Agency estimates that more than 80,000 chemicals are currently used in the United States; approximately 1500 are pesticides and 5500 are food additives that affect our water and food supplies. Although only 600 of these chemicals have been tested, 10% have produced cancer in at least one rodent species.[2] Industrial chemicals, production

TABLE 9-1 -- Reported Occupational Diseases in the United States in 1997

Disease	Number of Workers	Percentage
Repeated trauma	276,600	64
Skin disorders	57,900	13
Lung conditions due to toxic exposures	20,300	5
Physical injury	16,600	4
Poisoning	5100	1
Lung disease due to dusts	2900	1
All other illnesses	50,600	12
Total	430,000	100

Data from Levy BS, Wegman DH: Occupational health — an overview. In Levy BS, et al. (eds): Occupational Health. Recognizing and Preventing Work-Related Disease and Injury, fourth ed. Philadelphia, Lippincott Williams & Wilkins, 2000, p. 3; and Bureau of Labor Statistics, U.S. Department of Labor, www.hls.gov.

byproducts, and metals are commonly detected at hazardous waste sites (Table 9-2). There are currently 11,300 Superfund-designated waste sites in the United States. The potential human health hazards associated with exposure to chemical mixtures is a major concern.[2]

There is considerable difference in the magnitudes of exposure in the occupational and environmental settings. Occupational exposures affect a defined cohort of workers who are exposed to chemicals in the range of parts per million (ppm); by contrast, environmental exposures to these same chemicals in the air, water, or hazardous waste sites may be in the parts per billion (ppb) or parts per trillion (ppt) range. The health effects of such chronic, low-level exposures are unknown.

In the United States, four regulatory agencies determine exposure limits for environmental and occupational hazards: the Environmental Protection Agency, the Food and Drug

Administration (FDA), the Occupational Safety and Health Administration, and the Consumer Products Safety Commission. The Environmental Protection Agency regulates exposure to pesticides, toxic chemicals, water and air pollutants, and hazardous wastes. The FDA regulates drugs, medical devices, food additives, and cosmetics. The Occupational Safety and Health Administration mandates that employers (including hospitals and physicians) provide safe working conditions for employees. All other products sold for use in homes, schools, or recreation are regulated by the Consumer Products Safety Commission.

Physicians should be familiar with current approaches used by regulatory agencies in the United States and be prepared to explain the strengths and limitations of the scientific evidence in nontechnical terms. Health care providers must be prepared to counsel patients about the primary prevention of disease related to occupational and environmental exposures, taking into account potential synergistic effects of mixed exposures and individual genetic susceptibility. Prevention of tobacco smoking would prevent 80% to 90% of lung cancers; however, this objective has been difficult to achieve, especially in teenagers. Strategies for secondary prevention of lung cancer in former or current smokers (e.g., chemoprevention) have been disappointing so far.[3] Prevention of occupationally

TABLE 9-2 -- Common Chemicals at Hazardous Waste Sites

Acetone	DDT, DDE, DDD
Aldrin/Dieldrin	1,1 and 1,2-Dichloroethane
Arsenic	Lead
Barium	Mercury
Benzene	Methylene chloride
2-Butanone	Nickel
Cadmium	Pentachlorophenol
Carbon tetrachloride	Polychlorinated biphenyls
Chlordane	Tri- and Tetrachloroethylene
Chloroform	Toluene
Chromium	Vinyl Chloride
Cyanide	Zinc
Data from U.S. Environmental Protection Agency, www.epa.gov/superfund/resources/chemicals.htm.	

related diseases rests on defining and enforcing safe exposure levels, developing new technologies to reduce industrial exposures, and identifying less toxic substitutes for industrial and chemical agents. These strategies require a basic understanding of biochemical and molecular mechanisms of toxicity.

MECHANISMS OF TOXICITY

Toxicology is the scientific discipline that studies the detection, effects, and mechanisms of action of poisons and toxic chemicals. *Toxicity* is a relative phenomenon that depends on the inherent structure and properties of a chemical and on its dose. Dose-response curves are typically generated in laboratory animals exposed to various amounts of a chemical. A typical

dose-response curve for acute toxicity is illustrated in Figure 9-1 . In this example, a measurable response occurs at a dose of 0.1 mg/kg; this is defined as the *threshold dose*. To the left of this dose, at subthreshold levels, there is no measurable response. For this chemical, this is the *no observed effect level* and can be considered a safe dose. This information is used to establish a daily or annual *threshhold limit value* or *permissible exposure level* for occupational exposures. Frequently, a plateau is reached at higher doses; this is defined as the *ceiling effect*. It is uncertain whether carcinogens show a threshold effect or whether the dose-response curve should be extrapolated linearly to zero.[4]

Despite the inherent limitations of toxicity testing in animals, several important toxicologic principles have been established by this experimental approach. Exogenous chemicals are absorbed after ingestion, inhalation, or skin contact, and then distributed to various organs (Fig. 9-2). Chemicals are frequently metabolized, often by multiple enzymatic pathways, to products that may be more toxic or less toxic than the parent chemical. One or more of these products then interacts with the target macromolecule, resulting in a toxic effect.[5] The site of toxicity is frequently the site where metabolism or excretion of toxic metabolites occurs. The dose administered (external dose) may not be the same as the *biologic effective dose* delivered to the target organ and target macromolecule.

Figure 9-1 The dose-response curve for acute chemical toxicity. Th, threshold dose; STh, subthreshold levels. *(Data from Hughes WW: Essentials of Environmental Toxicology: The Effects of Environmentally Hazardous Substances on Human Health. Washington, DC, Taylor & Francis, 1996, p. 33.)*

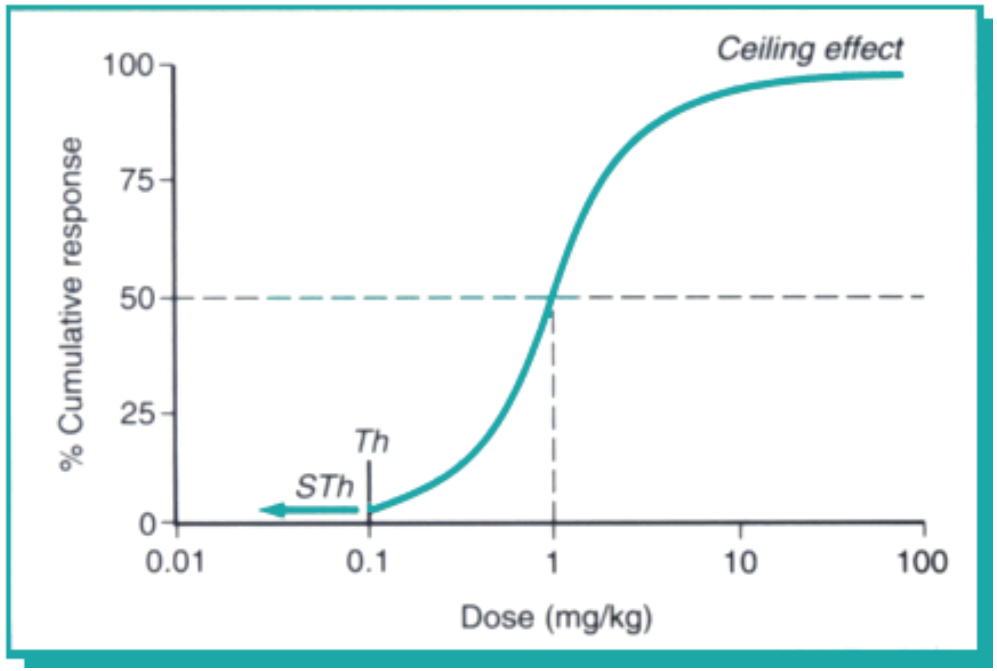

Figure 9-2 Absorption and distribution of toxicants. *(From Hodgson E, Levi PE: Absorption and distribution of toxicants. In Hodgson E, Levi PE [eds]: A Textbook of Modern Toxicology. Stamford, CT, Appleton & Lange, 1997, p. 52.)*

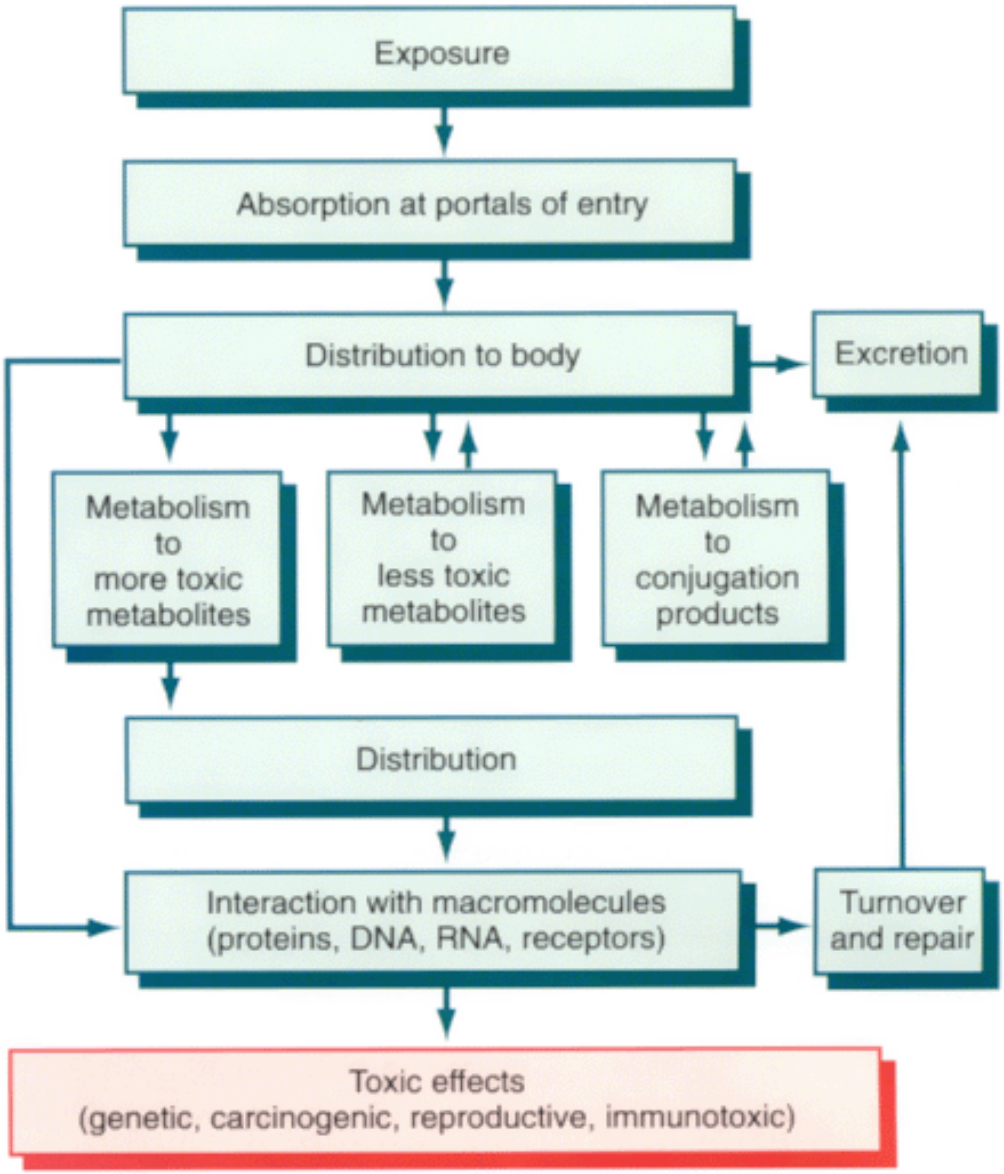

Figure 9-3 Biotransformation of lipophilic toxicants to hydrophilic metabolites. *(Adapted from Hodgson E: Metabolism of toxicants. In Hodgson E, Levi PE [eds]: A Textbook of Modern Toxicology. Stamford, CT, Appleton & Lange, 1997, p. 57.)*

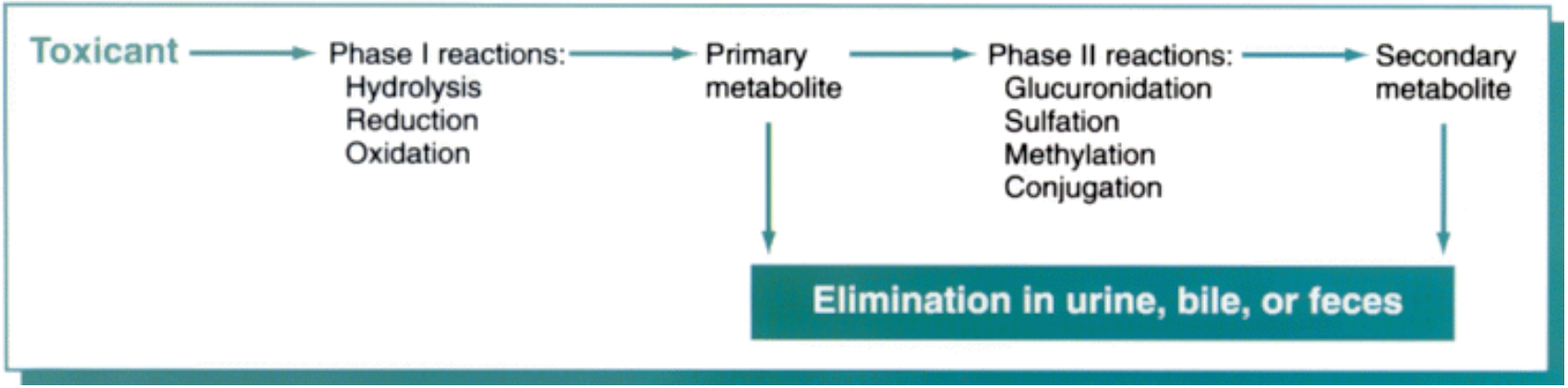

TABLE 9-3 -- Organ-Specific Carcinogens in Tobacco Smoke

Organ	Carcinogen
Lung, larynx	Polycyclic aromatic hydrocarbons
	4-(Methylnitrosoamino)-1-(3-pyridyl)-1-buta-none (NNK)
	Polonium 210
Esophagus	*N'*-Nitrosonornicotine (NNN)
Pancreas	NNK (?)
Bladder	4-Aminobiphenyl, 2-naphthylamine
Oral cavity (smoking)	Polycyclic aromatic hydrocarbons, NNK, NNN
Oral cavity (snuff)	NNK, NNN, polonium 210
Data from Szczesny LB, Holbrook JH: Cigarette smoking. In Rom WH (ed): Environmental and Occupational Medicine, 2nd ed. Boston, Little, Brown, 1992, p. 1211.	

such synergism is the increase in risk of lung cancer in cigarette smokers exposed to asbestos.[13]

Mainstream cigarette smoke inhaled by the smoker is composed of a particulate phase and a gas phase; tar is the total particulate phase without water or nicotine. There are 0.3 to 3.3 billion particles per milliliter of mainstream smoke and more than 4000 constituents, including 43 known carcinogens. Examples of the organ-specific carcinogens found in tobacco smoke and snuff are listed in Table 9-3 . In addition to these chemical carcinogens, cigarette smoke contains carcinogenic metals such as arsenic, nickel, cadmium, and chromium; potential promoters such as acetaldehyde and phenol; irritants such as nitrogen dioxide and formaldehyde; cilia toxins such as hydrogen cyanide; and carbon monoxide. Carbon monoxide is a colorless, odorless gas produced during incomplete combustion of fossil fuels or tobacco. It has 200 times higher affinity for hemoglobin than oxygen does and it impairs release of oxygen from hemoglobin. Thus, carbon monoxide exposure decreases the delivery of oxygen to peripheral tissues. Carbon monoxide also binds to other heme-containing proteins such as myoglobin and cytochrome oxidase. Nicotine is an important constituent of cigarette smoke. It is an alkaloid that readily crosses the blood-brain barrier and stimulates nicotine receptors in the brain. It is also responsible for the acute pharmacologic effects associated with tobacco use that are most likely mediated by catecholamines: increased heart rate and blood pressure, increased coronary artery blood flow, increased contractility and cardiac output, and mobilization of free fatty acids. Nicotine is responsible for tobacco addiction.

The inhaled agents in cigarette smoke may act directly on the mucous membranes, may be swallowed in saliva, or may be absorbed into the bloodstream from the abundant alveolar

capillary bed. By various routes of delivery, the constituents of cigarette smoke act on distant target organs and cause a variety of systemic diseases, listed in Table 9-4 . The greatest numbers of deaths attributable to cigarette smoking are due to lung cancer, ischemic heart disease, and chronic obstructive lung disease. Lung cancer is caused by multiple carcinogens and promoters in cigarette smoke. As described in Chapter 15 , specific preneoplastic changes are found in the tracheobronchial lining of cigarette smokers. These cellular changes

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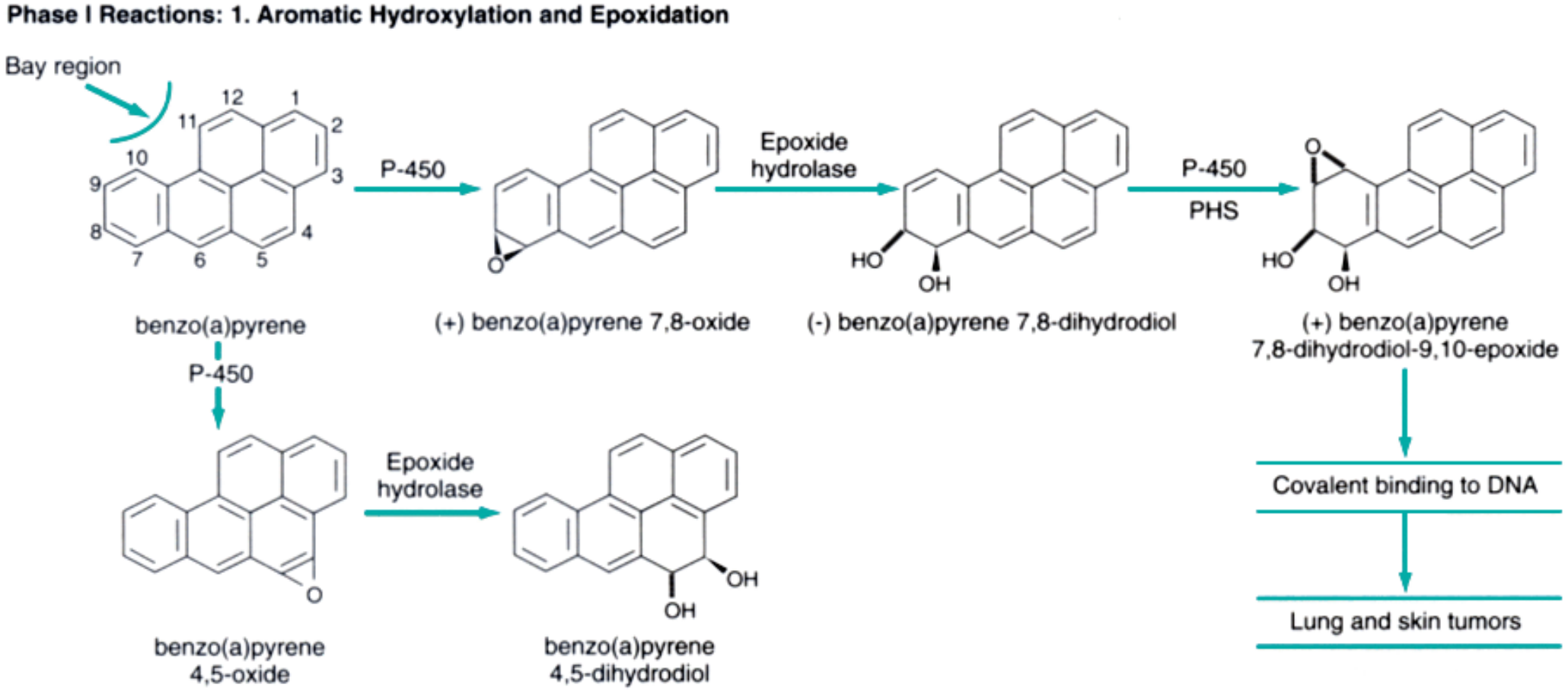
Figure 9-4a *A,* Xenobiotic metabolism: phase I reactions. FMO, flavin-containing monooxygenase; PHS, prostaglandin-H synthases.



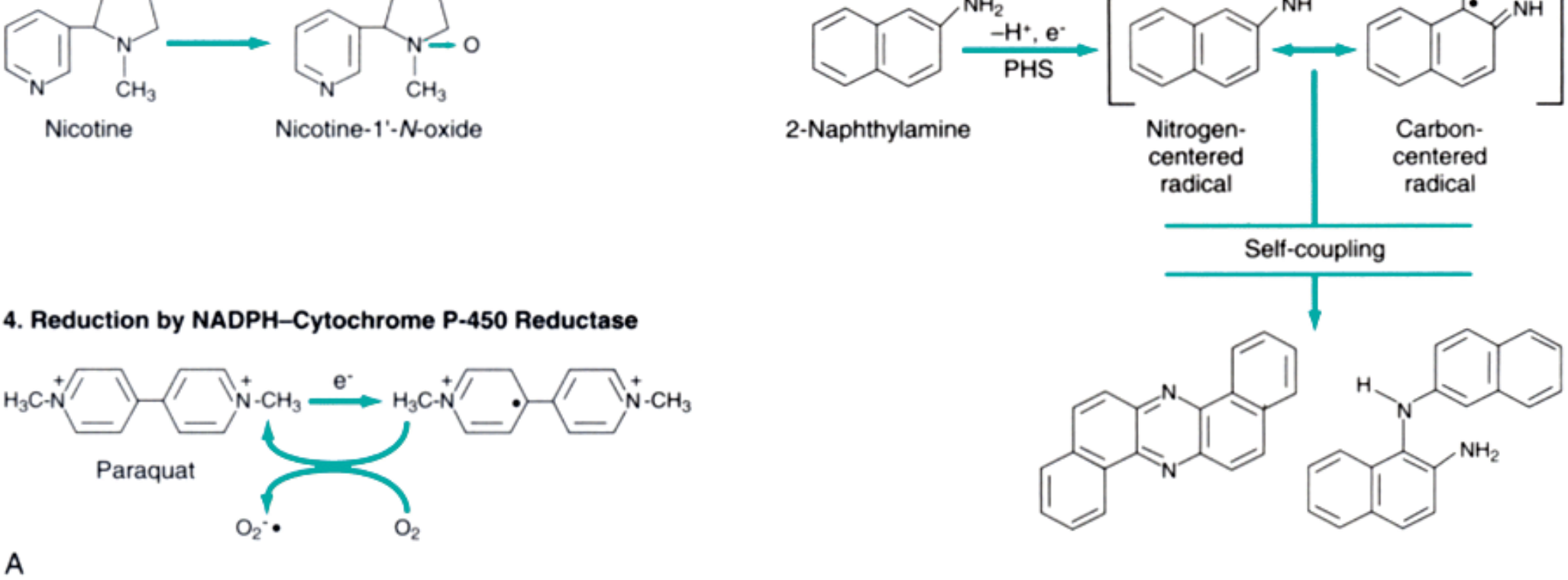


Figure 9-4b *B,* Xenobiotic metabolism: phase II reactions (see text for details). *(Adapted from Parkinson A: Biotransformation of xenobiotics. In Klaasen CD [ed]: Casarett and Doull's Toxicology: The Basic Science of Poisons, 5th ed. New York, McGraw-Hill, 1996, pp. 113–186; and Hodgson E, Levi PE [(eds]: A Textbook of Modern Toxicology. Stamford, CT, Appleton & Lange, 1997, pp. 57, 95.)*

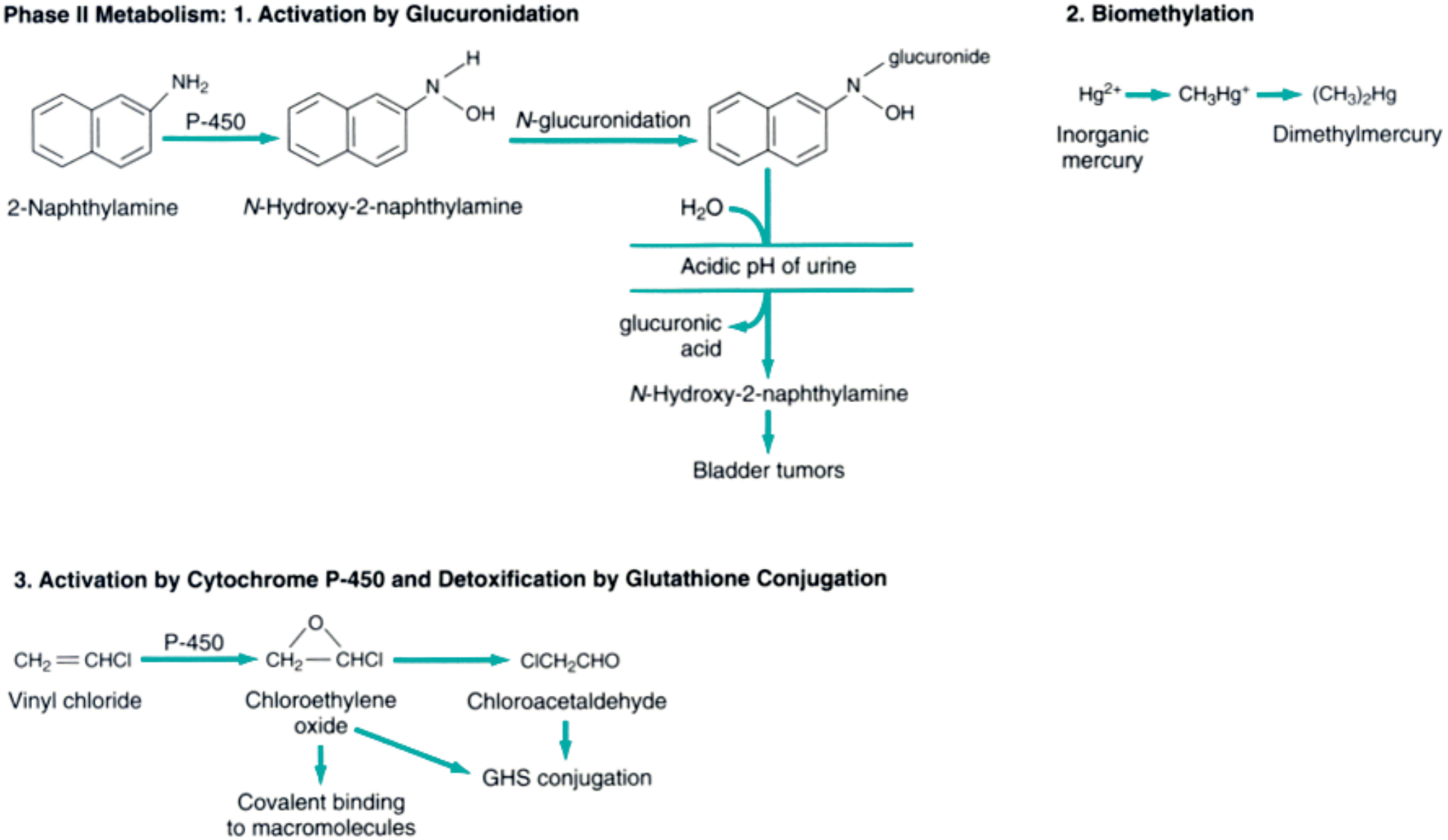


TABLE 9-4 -- Deaths per Year Attributable to Cigarette Smoking in the United States

	Number of Deaths	
Cause of Death	***Men***	***Women***
Cancer	102,812	54,664
Cardiovascular disease	90,906	57,699

Respiratory disease	53,713	44,429
Residential fires	589	377
Perinatal deaths	598	407
Lung cancer and heart disease attributable to passive smoking	15,517	22,536
Total	264,135	80,112

Data from CDC. Annual smoking-attributable mortality, years of potential life lost, and economic costs—United States, 1995–1999. MMWR 51:300, 2002.

exposure to silica, coal dust, grain dust, cotton dust, and welding fumes.

Tobacco use also increases the prevalence of peptic ulcers; smoking impairs healing of ulcers and increases the likelihood of recurrence. Smoking may also increase pyloric reflux and decrease bicarbonate secretion from the pancreas.

In addition to the health hazards of mainstream tobacco smoke, there are risks associated with exposure to sidestream smoke, also called passive smoking or environmental tobacco smoke (ETS). In 1986, two reports issued by the National Research Council and the Surgeon General concluded that ETS increases the risk of lung cancer, ischemic heart disease, and acute myocardial infarction.[14] The Environmental Protection Agency classified ETS as a known human carcinogen in 1992. ETS is especially hazardous for infants and young children. Maternal smoking increases the incidence of sudden infant death syndrome. Young children in households of cigarette smokers suffer from an increased incidence of respiratory and ear infections and exacerbation of asthma.

Alcohol Abuse

Ethanol is the most widely used and abused agent throughout the world. There are 15 to 20 million alcoholics in the United States; approximately 100,000 deaths in the United States are attributed to alcohol abuse per year, with an economic cost of $100 to $130 billion.[15] Ethanol is ingested in alcoholic beverages such as beer, wine, and distilled spirits. A blood alcohol concentration of 80 to 100 mg/dL is the legal

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definition for driving under the influence of alcohol in many states. Approximately 3 ounces (44 ml) of ethanol are required to produce this blood alcohol level in a 70-kg person. This is equivalent to 12 ounces of fortified wine, 8 bottles of beer (12 ounces each), or 6 ounces of 100-proof whiskey. In occasional drinkers, a blood alcohol level of 200 mg/dL produces inebriation, with coma, death, and respiratory arrest at 300 to 400 mg/dL. Habitual drinkers can tolerate blood alcohol levels up to 700 mg/dL. This metabolic tolerance is partially explained by a fivefold to tenfold induction of the cytochrome P-450 xenobiotic-metabolizing enzyme CYP2E1. Such induction increases the metabolism of ethanol as well as that of other drugs and chemicals, including cocaine and acetaminophen. Although no specific receptor for ethanol has been identified, chronic use results in psychologic and physical dependence. The biologic basis for ethanol addiction is unknown, although genetic factors may be involved.

Ethanol is metabolized to acetaldehyde by alcohol dehydrogenase in the gastric mucosa and liver, and by cytochrome P-450 (CYP2E1) and catalase in the liver (Fig. 9-5). Acetaldehyde is converted to acetic acid by aldehyde dehydrogenase. There are genetic polymorphisms in aldehyde dehydrogenase that affect ethanol metabolism; approximately 50% of Chinese, Vietnamese, and Japanese people have reduced activity of this enzyme due to a point mutation that converts glutamine to lysine at amino acid 487. These ethnic groups also rapidly convert ethanol to acetaldehyde, which builds up and triggers a facial flushing syndrome. Women have lower levels of gastric alcohol dehydrogenase activity than men do; therefore, they may develop higher blood alcohol levels than men after drinking the same quantity of ethanol.[15]

The metabolism of ethanol is directly responsible for most of its toxic effects. In addition to its acute action as a

Figure 9-5 Metabolism of ethanol. ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase. *(From Parkinson A: Biotransformation of xenobiotics. In Klassen CD [ed]: Casarett and Doull's Toxicology: The Basic Science of Poisons, 5th ed. New York, McGraw-Hill, 1996, p. 128.)*

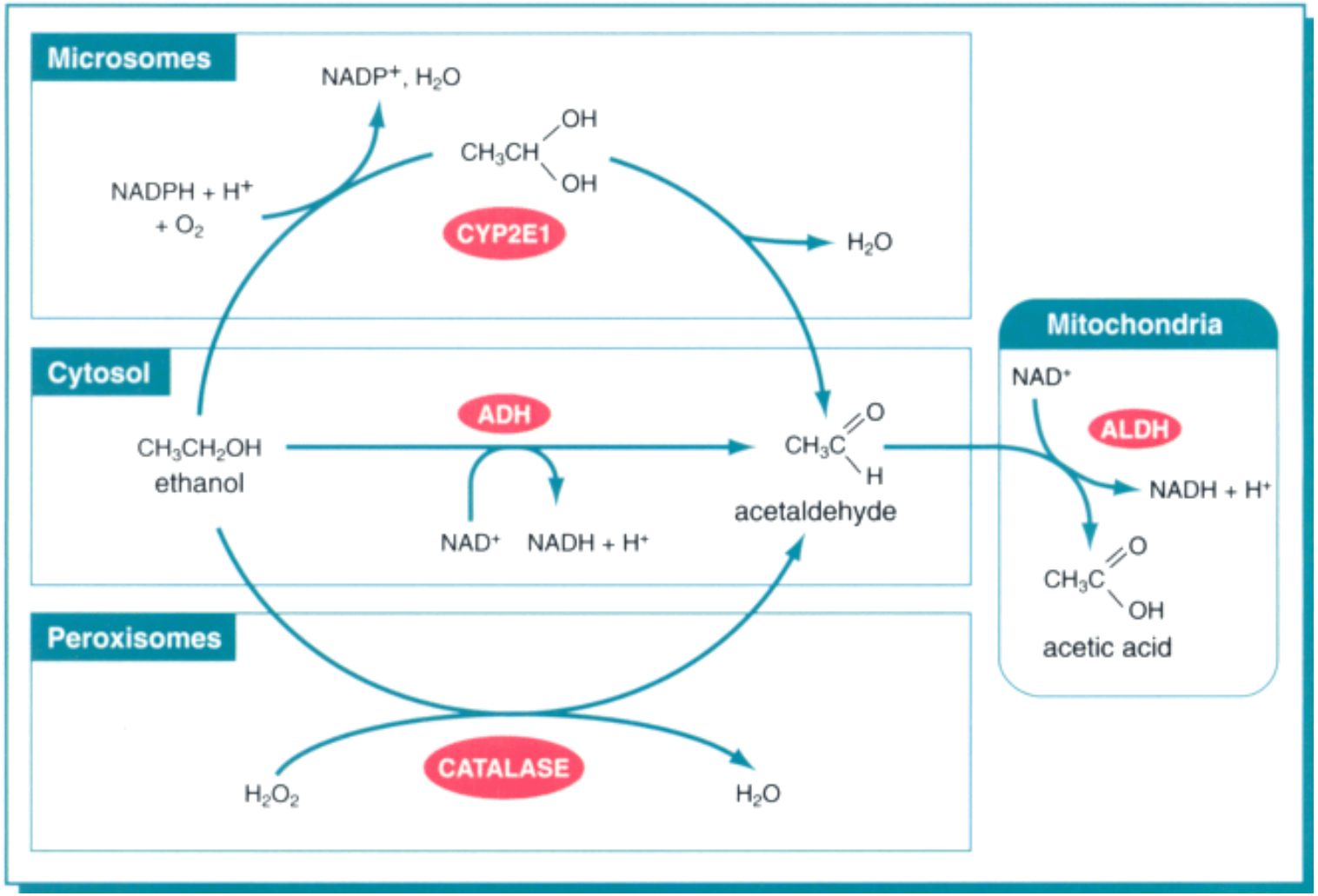

TABLE 9-5 -- Mechanisms of Disease Caused by Ethanol Abuse

Organ System	Lesion	Mechanism
Liver	Fatty change	Toxicity
	Acute hepatitis	
	Alcoholic cirrhosis	

Nervous system	Wernicke syndrome	Thiamine deficiency
	Korsakoff syndrome	Toxicity and thiamine deficiency
	Cerebellar degeneration	Nutritional deficiency
	Peripheral neuropathy	Thiamine deficiency
Cardiovascular system	Cardiomyopathy	Toxicity
	Hypertension	Vasopressor
Gastrointestinal tract	Gastritis	Toxicity
	Pancreatitis	Toxicity
Skeletal muscle	Rhabdomyolysis	Toxicity
Reproductive system	Testicular atrophy	?
	Spontaneous abortion	?
Fetal alcohol syndrome	Growth retardation	Toxicity
	Mental retardation	
	Birth defects	

Data from Rubin E: Alcohol abuse. In Craighead JE (ed): Pathology of Environmental and Occupational Disease. St. Louis, Mosby-Year Book, 1996, p. 249; and Lewis DD, Woods SE: Fetal alcohol syndrome. Am Fam Physician 50:1025, 1994.

central nervous system depressant, chronic ethanol use can cause a wide range of systemic effects (Table 9-5). Some of these chronic effects can be attributed to specific vitamin deficiencies; for example, damage to the peripheral and central nervous systems is related to thiamine deficiency, whereas

other systemic effects result from direct toxicity. The effects of ethanol on various organ systems are discussed next.

Liver.

Ethanol can cause fatty change, acute alcoholic hepatitis, and cirrhosis. *Fatty change* is an acute, reversible manifestation of ethanol ingestion. In chronic alcoholism, fat accumulation can cause massive enlargement of the liver. The biochemical mechanisms responsible for fat accumulation in hepatocytes are the following:

- Catabolism of fat by peripheral tissues is increased, and there is increased delivery of free fatty acids to the liver.
- Metabolism of ethanol in the cytosol and of its derivative, acetaldehyde, in the mitochondria converts the oxidized form of nicotinamide adenine dinucleotide (NAD^+) to the reduced form (NADH); an excess of NADH over NAD stimulates lipid biosynthesis.
- Oxidation of fatty acids by mitochondria is decreased.
- Acetaldehyde forms adducts with tubulin and impairs function of microtubules, resulting in decreased transport of lipoproteins from the liver.

Acute alcoholic hepatitis is another potentially reversible form of liver injury (Chapter 18). Although fatty change is asymptomatic except for liver enlargement, alcoholic hepatitis can produce fever, liver tenderness, and jaundice. On histologic examination, there are focal areas of hepatocyte necrosis and cell injury manifest by fat accumulation and alcoholic hyalin, or Mallory bodies. Neutrophils accumulate around foci of necrosis (Fig. 9-6). Ethanol and its metabolites are directly toxic to hepatocytes; this toxicity is believed to be mediated by glutathione depletion, mitochondrial injury, altered metabolism of methionine, and cytokine release from Kupffer cells.[16] Hepatocellular necrosis, as well as fibrosis, begins around the central vein, suggesting that hypoxia may contribute to this injury. With chronic ethanol use, 10% to 15% of alcoholics develop irreversible liver damage, or *alcoholic cirrhosis*. This is characterized by a hard, shrunken liver with formation of micronodules of regenerating hepatocytes surrounded by dense bands of collagen (Fig. 9-7). Alcoholic cirrhosis is a serious, potentially fatal disease accompanied by weakness, muscle wasting, ascites, gastrointestinal hemorrhage, and coma. Perisinusoidal fibrosis occurs initially, with

Figure 9-6 Acute alcoholic hepatitis. The liver cells show cytoplasmic accumulation of fat and hyalin *(arrow)*. A scattered inflammatory infiltrate is present. *(MEDCOM © 1976.)*

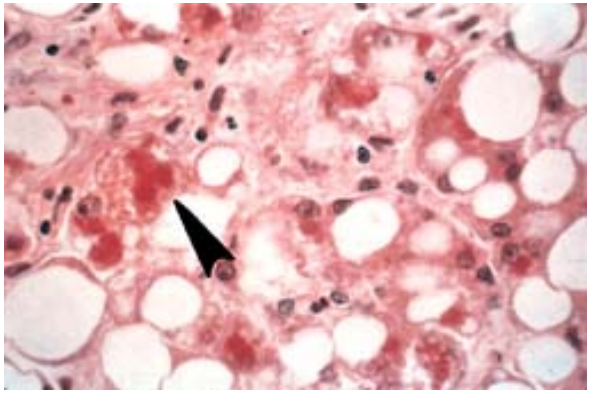

Figure 9-7 Micronodular cirrhosis is a late complication of chronic alcoholism. The liver architecture is distorted by regenerating nodules of hepatocytes surrounded by dense bands of fibrous tissue that stain blue (Masson trichrome stain). *(Courtesy of Dr. Steve Kroft, Department of Pathology, Southwestern Medical School, Dallas, TX.)*

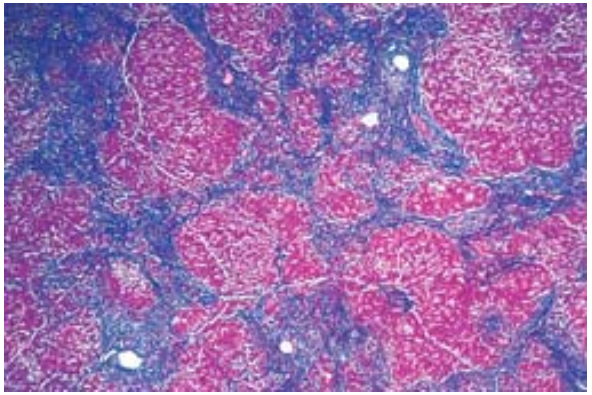

TABLE 9-6 -- Common Drugs of Abuse

Class	Molecular Target	Example
Opioid narcotics	Mu opioid receptor (agonist)	Heroin, hydromorphone (Dilaudid)
		Oxycodone (Percodan, Percocet, Oxycontin)
		Methadone (Dolophine)

		Meperidine (Demerol)
Sedative-hypnotics	$GABA_A$ receptor (agonist)	Barbiturates
		Ethanol
		Methaqualone (Quaalude)
		Glutethimide (Doriden)
		Ethchlorvynol (Placidyl)
Psychomotor stimulants	Dopamine transporter (antagonist)	Cocaine
		Amphetamine
	Serotonin receptors (toxicity)	3,4-methylenedioxymethamphetamine (MDMA, ecstasy)
Phencyclidine-like drugs	NMDA glutamate receptor channel (antagonist)	Phencyclidine (PCP, angel dust)
		Ketamine
Cannabinoids	CBI cannabinoid receptors (agonist)	Marijuana
		Hashish
Nicotine	Nicotine acetylcholine receptor (agonist)	Tobacco products
Hallucinogens	Serotonin 5-HT_2 receptors (agonist)	Lysergic acid diethylamide (LSD)
		Mescaline
		Psilocybin
Data from Hyman SE: A 28-year-old man addicted to cocaine. JAMA 286:2586, 2001.		

more slowly than ethanol, resulting in initial symptoms of intoxication, followed by toxic effects after several hours or days. *Methanol* is metabolized to formaldehyde and formic acid, resulting in metabolic acidosis, dizziness, vomiting, blurred vision or blindness, and respiratory depression. Methanol has been proposed as a gasoline additive or substitute, but there is concern that chronic inhalation of methanol-containing fumes may cause central nervous system depression. The lethal dose of *ethylene glycol* is only 1.4 mL/kg; it is metabolized by alcohol dehydrogenase to aldehydes, glycolate, oxalate, and lactate. If a person survives the initial toxicity, acute renal failure may occur several days later because of obstruction of the kidney tubules by calcium oxalate crystals. Acute methanol or ethylene glycol poisoning is treated by administration of ethanol, which slows the production of toxic metabolites.

Drug Abuse

Drug abuse, addiction, and overdose are serious public health problems. In a recent survey, 8% to 23% of teenagers reported marijuana use, and 2% reported cocaine use during the previous month. A National Comorbidity Survey conducted in 1995 discovered that 7.5% of US residents 15 to 54 years old had a history of drug dependence. Risk factors for drug use include family history, male sex, psychiatric disorders, ethanol abuse, easy access to drugs, and peer pressure.[21] The molecular targets of many commonly abused drugs have recently been identified, as summarized in Table 9-6 . Identification of specific neurotransmitter pathways that may activate reward circuits in the brain, as diagrammed in Figure 9-8 , may lead to more effective therapies for drug abuse and addiction. [19]

Sedative-Hypnotics.

Ethanol is the most widely abused central nervous system depressant, as discussed before. Barbiturates are circulated illegally and are known as downers. They

Figure 9-8 Effects of cocaine on neurotransmitters. Cocaine inhibits the reuptake of the neurotransmitters dopamine and norepinephrine in the central and peripheral nervous systems.

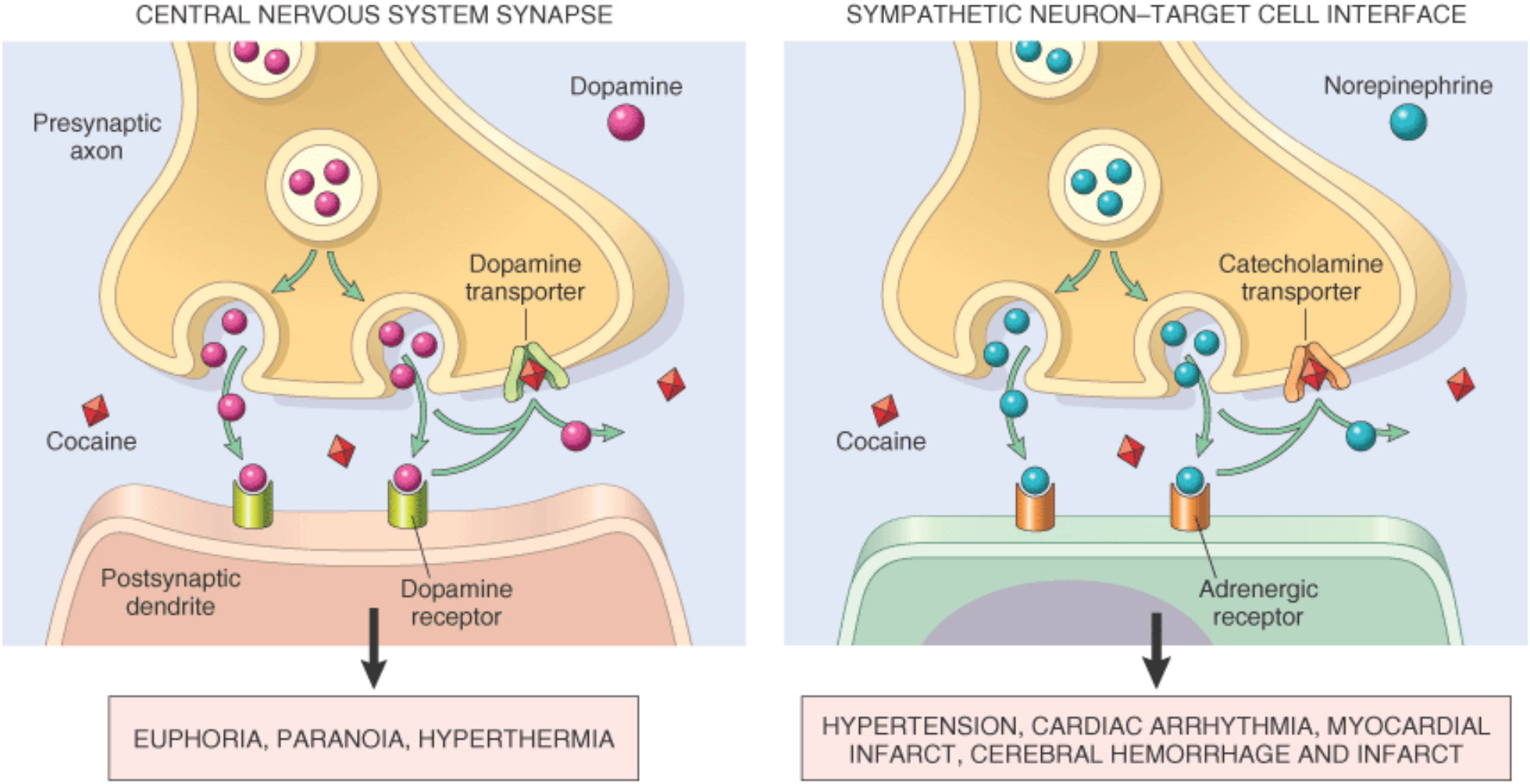

TABLE 9-7 -- Mechanisms of Adverse Drug Reactions

Mechanism	Example	Adverse Effect
Toxicity due to overdose	Acetaminophen	Liver necrosis and failure

Predictable reaction based on pharmacologic mechanism	Nonselective, nonsteroidal anti-inflammatory drugs	Peptic ulcer
Altered drug metabolism related to:		
••Thiopurine S-methyltransferase deficiency	Azathioprine	Bone marrow failure
••Cytochrome P-450 CYP2C9 variants	Oral anticoagulants	Bleeding
••Cytochrome P-450 CYP2D6 variants	Some antipsychotic drugs	Excessive sedation; parkinsonism
••N-acetyltransferase, slow acetylator phenotype	Hydralazine	Lupus
Idiopathic	Chloramphenicol	Aplastic anemia

and numbness. PCP characteristically induces nystagmus. High doses can induce coma lasting a few hours up to 10 days. Lysergic acid diethylamide (LSD) is a potent synthetic drug usually taken orally. It is absorbed rapidly and produces psychic effects, visual illusions, and altered perception for up to 12 hours. In high doses, LSD can cause death.

THERAPEUTIC DRUGS

An adverse drug reaction is defined as a toxic or undesired response to a drug used at therapeutic doses to prevent, diagnose, or treat disease. It is estimated that approximately 2 million hospitalized patients suffered from serious adverse drug reactions in 1994, resulting in 106,000 deaths. These estimates are conservative because they do not include errors in drug dosage or administration or patient noncompliance.[24] In Table 9-7 , adverse drug reactions are classified on the basis of their underlying mechanisms. Predictable reactions are based on the known toxicity or mechanism of action of a drug; these reactions are usually related to dose. Individual variations or polymorphisms in drug-metabolizing enzymes contribute to variable responses to drug therapy and an increased incidence of side effects. At least 5% of commonly prescribed drugs are metabolized by the cytochrome P-450 CYP1A2 pathway; approximately 12% of Caucasians carry variant alleles that reduce drug metabolism by this pathway. [25] *Pharmacogenomics* is a new field that uses genotyping to predict and prevent adverse drug reactions; for example, children with leukemia are screened for thiopurine methyltransferase variants to determine the optimal dose of azathiopurine,[26] and genotyping for the cytochrome P-450 CYP2D6 enzyme will help individualize doses of antipsychotic drugs to reduce side effects.[27] In contrast to these predictable types of adverse drug reactions, idiopathic or idiosyncratic reactions are rare and unpredictable, although the consequences may be severe or even fatal.

Herbal medicines are widely used in the United States and throughout the world; although many of these preparations have been shown to be effective in short-term trials, there is lack of quality control in this industry and few long-term studies of effectiveness and safety. As summarized in Table 9-8 , the most commonly used herbal medicines in the United States can produce adverse effects, including allergic or hypersensitivity reactions, and potentially serious interactions with prescription drugs.[28]

Oral Contraceptives and Hormone Replacement Therapy

Estrogens, alone or in combination with progestin, have been widely used for over 35 years as oral contraceptives or as hormone replacement therapy by perimenopausal and postmenopausal women. Most oral contraceptives combine synthetic ethinyl estradiol or mestranol with a progestin or use progestin alone; hormone replacement therapy uses natural estrogens alone or in combination with progesterone. Recent epidemiologic evidence has clarified the potential benefits and risks of these widely used drugs.

Oral Contraceptives.

There has been considerable concern and controversy about the safety of oral contraceptives, especially in relation to breast cancer. Two population-based, case-control studies, the Cancer and Steroid Hormone Study published in 1986 and the Women's Contraceptive and Reproductive Experiences Study published in 2002, explored the association between past or current use of oral contraceptives and breast cancer. [29] The most recent study included women between ages 35 and 64 diagnosed with breast cancer between 1994 and 1998. Potential effects of duration, formulations containing a high dose of estrogen, and family history of breast cancer were compared in women diagnosed with breast cancer or in control women without cancer. Past or current use of oral contraceptives was not found to be associated with an increased risk of breast cancer in white or black women in the United States.[30] Previous studies of other hormone-responsive cancers have also shown no increased risk of cancer; in fact, oral contraceptive use was found to decrease the risk of endometrial and ovarian cancers. In contrast, women infected with human papillomavirus have an increased risk of developing cervical cancer if they use oral contraceptives, although this risk may be related to other lifestyle factors (Chapter 22).

Uncommon adverse effects of oral contraceptives include:

- *Venous thrombosis and pulmonary embolism.* Oral contraceptives increase the risk of thrombosis; this risk is higher in carriers of mutations in factor V or prothrombin,[26] as described in Chapter 4 . The older, high-dose preparations incurred a greater risk, but a smaller risk persists even with the low-estrogen-containing oral contraceptives. The newer, third-generation oral contraceptives that combine low-dose estrogen with synthetic progestins confer an even higher risk.
- *Cardiovascular disease.* Estrogens and progestins have opposing effects on high-density lipoprotein (HDL) and low-density lipoprotein (LDL) levels. The overall effect on lipoproteins depends on the preparations used, especially the dose of progestin in the formulation. Recent epidemiologic evidence suggests that nonsmoking healthy women younger than age 45 who use the newer low-estrogen formulations do not have an increased risk of atherosclerosis or myocardial infarction. However, the risk of myocardial infarction is increased in women older than age 35 who smoke. The risk of ischemic stroke is also increased, regardless of age or smoking history.
- *Liver tumors.* Benign hepatic adenomas may occur, especially in older women who have used oral contraceptives for prolonged periods. These tumors may rupture and cause intra-abdominal bleeding.

TABLE 9-8 -- Adverse Effects of Herbal Medicines

Example	Adverse Effects	Drug Interactions
Echinacea	Allergic reactions	None described
Ginkgo	Headache, nausea	Potentiates anticoagulants
Ginseng	Headache, insomnia, euphoria, diarrhea	Interacts with monamine oxidase inhibitors, hypoglycemic drugs, anticoagulants
Saw palmetto	Constipation, decreased libido, urine retention	None described
St. John's wort	Allergic reactions, nausea, photosensitivity	Accelerated drug metabolism (oral contraceptives, anticoagulants)

Data from Ernst E: The risk-benefit profile of commonly used herbal therapies: ginkgo, St. John's wort, ginseng, echinacea, saw palmetto, and kava. Ann Intern Med 136:42, 2002.

Hormone Replacement Therapy.

In the United States, approximately one third of perimenopausal and postmenopausal women use hormone replacement therapy (HRT), either estrogen in combination with a progestin or a natural estrogen alone. There has been recent controversy about the risks and benefits of HRT. Short-term benefits include reduction in symptoms that accompany menopause, including hot flashes, vaginal dryness, and sleep disturbances. Long-term benefits include maintenance of bone mineral density and prevention of osteoporotic fractures. The major controversies surrounding HRT are the potential increased risk of cancer versus the potential benefits associated with prevention of ischemic heart disease and dementia. Recent results from the Women's Health Initiative and the Heart and Estrogen/Progestin Replacement Study have provided new information about the risks and benefits of HRT:[31]

• *Cancer*. Unopposed estrogen therapy greatly increases the risk of endometrial hyperplasia and cancer; therefore, most postmenopausal women now use estrogen in combination with a progestin. This combination drastically reduces or eliminates the risk of endometrial cancer. The risk of colon cancer was reduced in women who used HRT in some studies, but not in the Heart and Estrogen/Progestin Replacement Study. Recent results from the Women's Health Initiative indicate an increased risk of breast cancer in women who used HRT combined therapy for 5 years.
• *Venous thrombosis and pulmonary embolism.* The risk of thromboembolic events, including deep vein thrombosis,

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pulmonary embolism, stroke, and retinal thrombosis, is elevated approximated twofold in HRT users, especially within the first 2 years.
• *Cardiovascular disease.* The recent Women's Health Initiative reported an approximate 29% increased risk of myocardial infarction, especially during the first year of combined HRT use. This is in contrast to earlier studies in which either no effect or slight protection against cardiovascular diseases was reported. Methodologic differences probably underlie these divergent results. [32]
• *Cholecystitis.* There is an increased risk of gallbladder disease in HRT users that increases with time.
• *Dementia.* The current studies are not adequate to evaluate whether HRT use prevents dementia.

Overall, the risks and benefits associated with the use of oral contraceptives and HRT must be evaluated for each individual patient in the context of her overall health, individual risk factors, and family history.

Acetaminophen

When taken in large doses, this widely used nonprescription analgesic and antipyretic causes *hepatic necrosis*. The window between the usual therapeutic dose (0.5 gm) and the toxic dose (15 to 25 gm) is large, however, and the drug is ordinarily safe in adults. Doses should be reduced for infants and children, especially in the setting of fever, reduced food intake, or dehydration, since these conditions may predispose to liver injury.[33] Toxicity begins with nausea, vomiting, diarrhea, and sometimes shock, followed in a few days by evidence of jaundice; with serious overdosage, liver failure ensues, with centrilobular necrosis that may extend to the entire lobule. Some patients show evidence of concurrent renal and myocardial damage.

Aspirin (Acetylsalicylic Acid)

Overdose may result from accidental ingestion by young children; in adults, overdose is frequently suicidal. The major untoward consequences are metabolic with few morphologic changes. At first respiratory alkalosis develops, followed by metabolic acidosis that often proves fatal before anatomic changes can appear. Ingestion of as little as 2 to 4 gm by children or 10 to 30 gm by adults may be fatal, but survival has been reported after doses five times larger.

TABLE 9-9 -- National Ambient Air Quality Standards: Sources and Number of People at Risk

Pollutant	Primary Standard	Tons Emitted (Millions)	People at Risk (Millions)
Ozone	0.08 ppm 8 hr average	Not applicable	143••
Nitrogen oxides	0.053 ppm annual arithmetic mean	25	Not available
Sulfur dioxide	0.03 ppm annual arithmetic mean	19	0.3
Particulates (PM_{10})	50 µg/µL annual arithmetic mean	24	8.7

Carbon monoxide	9 ppm 8 hr average	97	31••
Lead	1.5 µg/µL quarterly average	30	2.5

Data from U.S. Environmental Protection Agency: epa.gov/oar/oaqps, www.scorecard.org/env-releases, the American Lung Association: www.lungusa.org/air, and Goldman LR: Environmental health and its relationship to occupational health. In Levy BS, et al. (eds): Occupational Health. Recognizing and Preventing Work-Related Disease and Injury, fourth ed. Philadelphia, Lippincott Williams & Wilkins, 2000, p. 51.

Chronic aspirin toxicity (salicylism) may develop in persons who take 3 gm or more daily, the dose required to treat chronic inflammatory conditions. Chronic salicylism is manifested by headache, dizziness, ringing in the ears (tinnitus), difficulty in hearing, mental confusion, drowsiness, nausea, vomiting, and diarrhea. The central nervous system changes may progress to convulsions and coma. The morphologic consequences of chronic salicylism are varied. Most often there is an acute erosive gastritis (Chapter 17), which may produce overt or covert gastrointestinal bleeding and lead to gastric ulceration. A bleeding tendency may appear concurrently with chronic toxicity, because aspirin acetylates platelet cyclooxygenase and blocks the ability to make thromboxane A_2 , an activator of platelet aggregation. Petechial hemorrhages may appear in the skin and internal viscera, and bleeding from gastric ulcerations may be exaggerated.

Proprietary analgesic mixtures of aspirin and phenacetin or its active metabolite, acetaminophen, when taken for a span of years, have caused renal papillary necrosis, referred to as *analgesic nephropathy* (Chapter 20).

OUTDOOR AIR POLLUTION

Air pollution is a serious problem in the United States and many other industrialized countries. In the United States, the Environmental Protection Agency is charged with identification and regulation of pollutants in the ambient air that may cause adverse health effects. The current National Ambient Air Quality Standards for the six major pollutants are listed in Table 9-9 . Despite federal and state regulations, many cities and regions in the United States currently do not meet these primary standards. Epidemiologic research, human clinical studies, and animal toxicologic studies continue to provide evidence for adverse health effects of ambient air pollutants, even at exposure levels below the current standards. The major sources of ambient air pollutants are:

- *Combustion of fossil fuels.* These are divided into mobile sources such as motor vehicles, stationary sources such as power plants and factories, and other sources such as barbecues and fireplaces. Tailpipe emissions from motor vehicles are a complex mixture of carbon monoxide, oxides of nitrogen, hydrocarbons, diesel exhaust particles, and other particulates including lead oxide from tetraethyl lead contained in leaded gasoline.

- *Photochemical reactions.* Oxides of nitrogen and volatile hydrocarbons interact in the atmosphere to produce ozone (O_3) as a secondary pollutant.
- *Power plants.* These release sulfur dioxide (SO_2) and particulates into the atmosphere. Coal and oil contain sulfur, leading to atmospheric formation of sulfates. Automobiles release oxides of nitrogen, leading to atmospheric formation of nitrates. Aerosolized acid sulfates contribute to acid rain.
- *Waste incinerators, industry, smelters.* These point sources release acid aerosols, metals, mercury vapor, and organic compounds that may be hazardous for human health. One example of the numerous hazardous chemicals emitted by these sources is methyl isocyanate that was accidentally released at Bhopal in India in 1984, resulting in 3000 deaths due to pulmonary edema. Some of the air toxins, such as polycyclic aromatic hydrocarbons, are known carcinogens.[34]

Lungs are the major target of common outdoor air pollutants; especially vulnerable are children, asthmatics, and people with chronic lung or heart disease, as summarized in Table 9-10 . The serious toxicity associated with lead exposure is discussed subsequently under Industrial Exposures. The major air pollutants and the mechanisms responsible for their adverse health

effects are summarized briefly.[34]

Ozone.

Ozone is a major component of smog that accompanies summer heat waves over much of the United States. Exposure of exercising children and adults to as little as 0.08 ppm produces cough, chest discomfort, and inflammation in the lungs. Asthmatics are especially sensitive and require more frequent visits to emergency rooms and more hospitalizations during smog episodes. It is not known whether these acute changes lead to chronic, irreversible lung injury. Ozone is highly reactive and oxidizes polyunsaturated lipids to hydrogen peroxide and lipid aldehydes. These products act as irritants and induce release of inflammatory mediators,

TABLE 9-10 -- Health Effects of Outdoor Air Pollutants

Pollutant	Populations at Risk	Effects
Ozone	Healthy adults and children	Decreased lung function
		Increased airway reactivity
		Lung inflammation
	Athletes, outdoor workers	Decreased exercise capacity
	Asthmatics	Increased hospitalizations
Nitrogen dioxide	Healthy adults	Increased airway reactivity
	Asthmatics	Decreased lung function
	Children	Increased respiratory infections
Sulfur dioxide	Healthy adults	Increased respiratory symptoms
	Patients with chronic lung disease	Increased mortality
		Increased hospitalization
	Asthmatics	Decreased lung function
Acid aerosols	Healthy adults	Altered mucociliary clearance
	Children	Increased respiratory infections
	Asthmatics	Decreased lung function
		Increased hospitalizations
Particulates	Children	Increased respiratory infections
		Decreased lung function
	Patients with chronic lung or heart disease	Excess mortality
	Asthmatics	Increased attacks

Data from Bascom R, et al: Health effects of outdoor air pollution, Am J Respir Crit Care Med 153:3, 477, 1996.

cause increased epithelial permeability and reactivity of the airways, and decrease ciliary clearance. The highest inhaled dose is delivered at the bronchoalveolar junction; however, ozone also causes inflammation of the upper respiratory tract.

Nitrogen Dioxide.

Oxides of nitrogen include NO and NO_2 . These have lower reactivity than ozone. Nitrogen dioxide dissolves in water in the airways to form nitric and nitrous acids, which damage the airway epithelial lining. Children and patients with asthma have increased susceptibility to nitrogen dioxide; there is a wide variation in individual responses to this pollutant.

Sulfur Dioxide.

This pollutant is highly soluble in water; it is absorbed in the upper and lower airways, where it releases H^+ , HSO_3^- (bisulfite), and SO_3^- (sulfite), which cause local irritation.

Acid Aerosols.

Primary combustion products of fossil fuels are emitted by tall smoke stacks at high altitudes and are transported by air. In the atmosphere, sulfur and nitrogen dioxide are oxidized to sulfuric acid and nitric acid, respectively, which are dissolved in water droplets or adsorbed to particulates. These acid aerosols are irritants to the airway epithelium and alter mucociliary clearance. Asthmatics have decreased lung function and increased hospitalizations when exposed to acid aerosols, although there is a wide variation in airway responses.

Particulates.

As discussed in Chapter 15 , the deposition and clearance of particulates inhaled into the lungs depend on their size. Ambient particulates are highly heterogeneous in size and in chemical composition. It is uncertain which characteristics of ambient particulates contribute to their adverse health effects. Recent epidemiologic and toxicologic studies suggest that ultrafine particles (less than 0.1 μm in aerodynamic diameter) are more hazardous. They contribute to increased morbidity and mortality, especially among infants, the elderly, and people with chronic cardiopulmonary disease. The mechanisms responsible for these adverse health effects are suspected to involve: (1) systemic cytokine release

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associated with pulmonary inflammation; (2) increased blood viscosity; and (3) autonomic changes associated with variable heart rates and arrhythmias.[35]

INDOOR AIR POLLUTION

Rising energy costs during the past 30 years have led to increased insulation and decreased ventilation of homes, which elevates the level of indoor air pollutants. The health hazards of environmental tobacco smoke have already been discussed. Other sources of indoor air pollutants are gas cooking stoves and furnaces, wood stoves, construction materials, furniture, radon, allergens associated with pets, dust mites, and fungal spores and bacteria. The major categories of indoor air pollutants and their health effects are summarized in Table 9-11 and discussed briefly next.[36]

Carbon Monoxide.

This odorless, colorless gas is a byproduct of combustion produced from burning gasoline, oil, coal, wood, and natural gas. It is also a major pollutant in tobacco smoke, and its untoward

effects were discussed earlier along with cigarette smoking. Here we should note that carbon monoxide levels in ambient air should not exceed 9 ppm; however, indoor levels of 2 to 4 ppm have been measured in homes during the winter. Such carbon monoxide pollution of indoor air can reduce exercise capacity and aggravate myocardial ischemia. Higher levels can cause poisoning manifested as headaches, dizziness, loss of motor control, and coma. Approximately 900 accidental deaths due to asphyxia are caused by indoor carbon monoxide pollution each year in the United States.

Nitrogen Dioxide.

Gas stoves and kerosene space heaters can raise indoor levels of nitrogen dioxide to 20 to 40 ppm in homes; this is several orders of magnitude higher than outdoor air levels. Children are more susceptible to the untoward

TABLE 9-11 -- Health Effects of Indoor Air Pollutants

Pollutant	Populations at Risk	Effects
Carbon monoxide	Adults and children	Acute poisoning
Nitrogen dioxide	Children	Increased respiratory infections
Wood smoke	Children	Increased respiratory infections
Formaldehyde	Adults and children	Eye and nose irritation, asthma
Radon	Adults and children	Lung cancer
Asbestos fibers	Maintenance and abatement workers	Lung cancer, mesothelioma
Manufactured mineral fibers	Maintenance and construction workers	Skin and airway irritation
Bioaerosols	Adults and children	Allergic rhinitis, asthma

Data from Lambert WE, Samet JM: Indoor air pollution. In Harber P, et al (eds): Occupational and Environmental Respiratory Disease. St. Louis, Mosby-Year Book, 1996, p. 784; and Menzies D, Bourbeau J: Building-related illnesses. N Engl J Med 337:1524, 1997.

effects of nitrogen dioxide. It impairs lung defenses and is hence associated with increased respiratory infections.

Wood Smoke.

This is a complex mixture of nitrogen oxides, particulates, and polycyclic aromatic hydrocarbons. High concentrations of wood smoke in poorly ventilated homes can increase the incidence of respiratory infections in children.

Formaldehyde.

This highly soluble, volatile chemical has been used in the manufacture of many consumer products, including textiles, pressed wood, furniture, and urea formaldehyde foam insulation. Although indoor levels are usually less than 1 ppm, it can cause acute irritation of the eyes and upper respiratory tract and exacerbation of asthma. Formaldehyde is frequently emitted with acrolein and acetaldehyde, which may have additive or synergistic irritant effects. Additional volatile organic compounds that may be present at low levels in indoor air include benzene, tetrachloroethylene, polycyclic aromatic hydrocarbons, and chloroform. The potential for toxicity or carcinogenicity at these exposure levels is low, although occupational exposure to these volatile compounds can be hazardous. Formaldehyde at high doses (6 to 14 ppm) has produced nasal tumors in rats.[37]

Radon.

Radon, a radioactive gas, is a decay product of uranium widely distributed in the soil. Radon gas emanating from the earth is prevalent in homes. Indoor levels of radon average around 1.5 pCi/L; approximately 4% of homes have an annual average level greater than 4 pCi/L. Radon gas is inhaled into the lungs; its decay products emit alpha radiation, which has been associated with lung cancer in miners. According to some estimates, the low levels found in indoor air account for 10,000 lung cancers per year in the United States.[38]

Asbestos Fibers.

Homes and public buildings built before the 1970s in the United States contain asbestos insulation, pipe covers, ceiling tiles, and flooring. If these materials are non-friable and undisturbed, low levels of fibers can be measured in indoor air. Maintenance and abatement workers who repair or remove asbestos-containing materials are at risk for lung cancer and mesothelioma if they do not use respirators. [39] [40]

Manufactured Mineral Fibers.

Fiberglass has been widely used as an asbestos substitute for home insulation. Low levels of these fibers can be measured in indoor air. Maintenance and construction workers can develop skin and lung irritation when using these materials. [41]

Bioaerosols.

Aerosolization of bacteria responsible for *Legionella* pneumonia has been associated with contaminated heating and cooling systems in public buildings (Chapter 8). More common hazards in indoor air are allergens associated with pets, dust mites, cockroaches, fungi, and molds. These allergens cause allergic rhinitis and exacerbate asthma. [41]

The etiology of the so-called *sick building syndrome*, or *multiple chemical sensitivity syndrome*, is less clear. In some cases, high levels of one or more of these indoor air pollutants may be responsible. In most cases, poor ventilation is at fault.[41]

INDUSTRIAL EXPOSURES

For centuries, physicians have recognized that occupational exposures contribute to human disease. The spectrum of human diseases associated with occupational exposures is summarized in Table 9-12 . Almost all organ systems can be affected, resulting in acute toxicity or irritation, hypersensitivity

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reactions, chronic toxicity, fibrosis, and cancer. The chronic effects of occupational exposures are complex; they include degenerative changes in the nervous system, reproductive dysfunction, lung fibrosis, and cancer. The mechanisms responsible for these effects are not well understood. Some examples of acute and chronic diseases resulting from occupational exposures and potential hazards of environmental exposures are discussed in the following sections.

Volatile Organic Compounds

Large volumes of organic solvents and vapors are used in industry and in homes. These chemicals are known as volatile organic compounds (VOCs). They are used in manufacturing, degreasing, and dry cleaning and as components of paint removers and aerosol sprays. VOCs and petroleum products such as kerosene, mineral oil, and turpentine are stored in

underground tanks. Surface spills and leakage from storage tanks can cause contamination of underground water supplies. In general, high levels of exposure encountered in industry cause headache, dizziness, and liver or kidney toxicity. At lower levels of exposure, there is concern about potential carcinogenicity and adverse reproductive effects. Some VOCs and their adverse effects are described next.

Aliphatic Hydrocarbons.

These compounds are the most widely used industrial solvents and dry-cleaning agents. All of these chemicals are readily absorbed through the lungs, skin, and gastrointestinal tract. In addition to acute central nervous system depression, they can cause liver and kidney toxicity. Common examples of these chemicals are chloroform and carbon tetrachloride; both are carcinogenic in rodents. Methylene chloride, another such chemical, is used in paint

TABLE 9-12 -- Human Diseases Associated with Occupational Exposures

Organ	Effect	Toxicant
Cardiovascular system	Heart disease	Carbon monoxide, lead, solvents, cobalt, cadmium
Respiratory system	Nasal cancer	Isopropyl alcohol, wood dust
	Lung cancer	Radon, asbestos, silica, bis(chloromethyl)ether, nickel, arsenic, chromium, mustard gas
	Chronic obstructive lung disease	Grain dust, coal dust, cadmium
	Hypersensitivity	Beryllium, isocyanates
	Irritation	Ammonia, sulfur oxides, formaldehyde
	Fibrosis	Silica, asbestos, cobalt
Nervous system	Peripheral neuropathies	Solvents, acrylamide, methyl chloride, mercury, lead, arsenic, DDT
	Ataxic gait	Chlordane, toluene, acrylamide, mercury
	Central nervous system depression	Alcohols, ketones, aldehydes, solvents
	Cataracts	Ultraviolet radiation
Urinary system	Toxicity	Mercury, lead, glycol ethers, solvents
	Bladder cancer	Naphthylamines, 4-aminobiphenyl, benzidine, rubber products
Reproductive system	Male infertility	Lead, phthalate plasticizers
	Female infertility	Cadmium, lead
	Teratogenesis	Mercury, polychlorinated biphenyls
Hematopoietic system	Leukemia	Benzene, radon, uranium
Skin	Folliculitis and acneiform dermatosis	Polychlorinated biphenyls, dioxins, herbicides
	Cancer	Ultraviolet radiation
Gastrointestinal tract	Liver angiosarcoma	Vinyl chloride

Data from Leigh JP, et al: Occupational injury and illness in the United States. Estimates of costs, morbidity, and mortality. Arch Intern Med 157:1557, 1997; Mitchell FL: Hazardous waste. In Rom WN (ed): Environmental and Occupational Medicine, 2nd ed. Boston, Little, Brown, 1992, p. 1275; and Levi PE: Classes of toxic chemicals. In Hodgson E, Levi PE (eds): A Textbook of Modern Toxicology, Stamford, CT, Appleton & Lange, 1997, p. 229.

removers and aerosols. In enclosed areas, high concentrations of methylene chloride can be reached because it is highly volatile. Methylene chloride is metabolized by cytochrome P-450 to carbon dioxide and carbon monoxide. Carbon monoxide can form carboxyhemoglobin, causing respiratory depression and death. Perchloroethylene and related compounds are widely used in the dry-cleaning industry. Acute exposure causes central nervous system depression, confusion, dizziness, impaired gait, and nausea. Repeated exposures may cause dermatitis. Perchloroethylene is a potential human carcinogen.

Petroleum Products.

Gasoline, kerosene, mineral oil, and turpentine are highly volatile and are a common cause of poisoning in children. Inhalation of these vapors causes dizziness, incoordination, and central nervous system depression.

Aromatic Hydrocarbons.

Benzene, toluene, and xylene are widely used solvents in the rubber and shoe industries and in printing and paper-coating. Although toluene and xylene are not carcinogenic, inhalation of benzene is hazardous because it can cause bone marrow toxicity, aplastic anemia, and acute leukemia. Benzene is metabolized by the cytochrome P-450 system in liver, producing benzoquinone and muconaldehyde. These metabolic products are believed to cause bone marrow toxicity.

Polycyclic Aromatic Hydrocarbons

Polycyclic aromatic hydrocarbons are among the most potent chemical carcinogens (Chapter 7). The carcinogenicity of these compounds was recognized in 1775, with the description of scrotal cancer in English chimney sweepers exposed to soot. A variety of polycyclic aromatic hydrocarbons characterized

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by three or more fused benzene rings are produced by combustion of fossil fuels; high-temperature processing of coke, coal, and crude oil; and iron and steel foundries. Benzo[a]pyrene is the prototype of polycyclic aromatic hydrocarbons. As described earlier (see Fig. 9-4*A*), it is metabolized by cytochrome P-450, prostaglandin H synthetase, and epoxide hydrolase, an inducible microsomal enzyme in the liver. Activated epoxide intermediates bind to DNA; these adducts have been used as markers of polycyclic aromatic hydrocarbon exposure. Occupational exposure to polycyclic aromatic hydrocarbons is associated with an increased risk of lung and bladder cancers.[42] Cigarette smoking is another important source of benzo[a] pyrene. Mutations in the *p53* tumor-suppressor gene found in lung cancers associated with cigarette smoking are most commonly G:C→T:A transversions. This mutational spectrum is consistent with metabolism of benzo[a]pyrene to reactive intermediates that attack deoxyguanines on the nontranscribed DNA strand.[7]

Plastics, Rubber, and Polymers

Millions of tons of synthetic plastics, rubber, and polymers are produced throughout the world. These products are then fabricated into latex fabrics, pipe, cables, flooring, home and recreational products, medical products, and containers. In 1974, occupational exposure to vinyl chloride monomers used to produce polyvinyl chloride resins was found to be associated with angiosarcoma of the liver. Vinyl chloride is a colorless gas that is flammable and explosive. Before the polymerization step in the manufacturing of polyvinyl chloride, it can be absorbed through the skin or lungs. Vinyl chloride is metabolized by the cytochrome P-450 system in the liver to chloroacetaldehyde. This metabolite covalently binds to DNA and is mutagenic. Exposure of rubber workers to 1,3-butadiene

TABLE 9-13 -- Toxic and Carcinogenic Metals

Metal	Disease	Occupation
Lead	Renal toxicity	Battery and ammunition workers, foundry workers, spray painting, radiator repair
	Anemia, colic	
	Peripheral neuropathy	
	Insomnia, fatigue	
	Cognitive deficits	
Mercury	Renal toxicity	Chlorine-alkali industry
	Muscle tremors, dementia	
	Cerebral palsy	
	Mental retardation	
Arsenic	Cancer of skin, lung, liver	Miners, smelters, oil refinery workers, farm workers
Beryllium	Acute lung irritant	Beryllium refining, aerospace manufacturing, ceramics
	Chronic lung hypersensitivity	
	? Lung cancer	
Cobalt and tungsten carbide	Lung fibrosis	Toolmakers, grinders, diamond polishers
	Asthma	
Cadmium	Renal toxicity	Battery workers, smelters, welders, soldering
	? Prostate cancer	
Chromium	Cancer of lung and nasal cavity	Pigment workers, smelters, steel workers
Nickel	Cancer of lung and nasal sinuses	Smelters, steel workers, electroplating

Data from Levi PE: Classes of toxic chemicals. In Hodgson E, Levi PE (eds): A Textbook of Modern Toxicology. Stamford, CT, Appleton & Lange, 1997, p. 229; and Sprince NL: Hard metal disease. In Rom WN (eds): Environmental and Occupational Medicine, 2nd ed. Boston, Little, Brown, 1992, p. 791.

has been shown to be associated with an increased risk of leukemia. Plastics are widely used in consumer products, including food and beverage containers. Public exposure to plasticizers, such as phthalate esters, and to additives such as bisphenol-A raises concern about potential adverse reproductive effects of these synthetic chemicals. Phthalate esters have been shown to induce testicular injury in rats, and bisphenol-A mimics the proliferative effects of estrogen.

Metals

Occupational exposure to metals in mining and manufacturing is associated with acute and chronic toxicity, as well as carcinogenicity, as summarized in Table 9-13 .[43] Occupational as

well as environmental exposure to lead continues to be a serious public health problem. Agricultural exposure to arsenic-containing pesticides is discussed subsequently. The pulmonary effects of beryllium are described in Chapter 15 . The health effects of inorganic and organic mercury were discussed earlier in this chapter under "Mechanisms of Toxicity." The untoward effects of some of the remaining metals listed in Table 9-13 are described here.

Lead.

More than 4 million tons of lead are produced each year for use in batteries, alloys, exterior red lead paint, and ammunition. Workers employed in these industries as well as in mining, smelting, spray painting, recycling, and radiator repair are exposed to lead. In some countries, tetraethyl lead is still used as a gasoline additive, thus polluting the air. *Inhalation is the most important route of occupational exposure.* Environmental sources of lead are urban air due to use of leaded gasoline, soil contaminated with exterior lead paint, the water supply due to lead plumbing, and house dust in homes with interior lead paint. Consumers may be exposed to lead-glazed ceramics, lead solder in food and soft drink cans, and illegally

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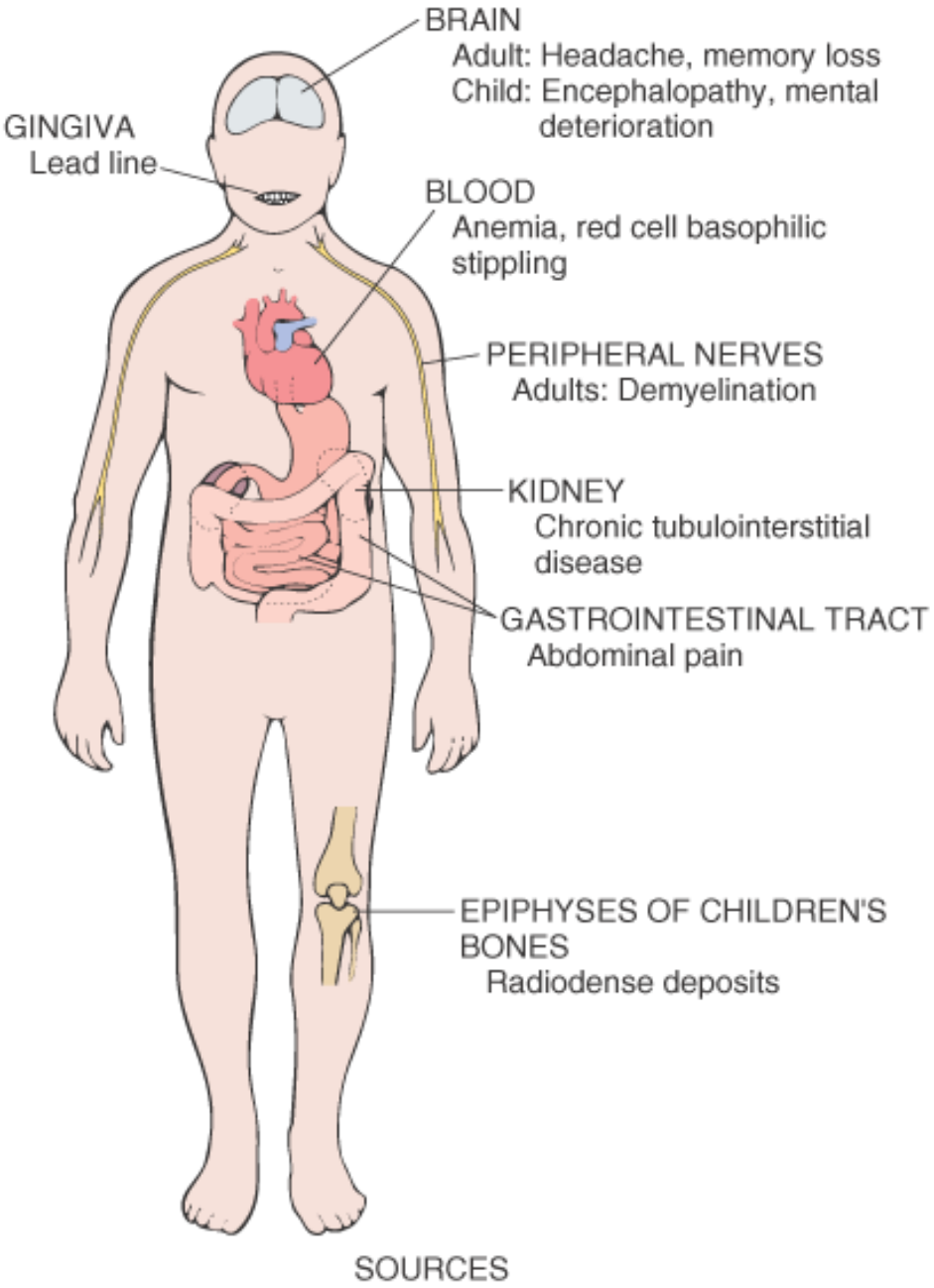
produced alcoholic beverages (moonshine). Lead ingested in this manner is absorbed through the gastrointestinal tract. Intestinal absorption of lead is enhanced by calcium, iron, or zinc deficiency; compared with adults, the absorption is greater in children and infants and hence they are particularly vulnerable to lead toxicity. Absorbed lead is mainly (80% to 85%) taken up by bone and developing teeth in children; the blood accumulates 5% to 10%, and the remainder is distributed throughout the soft tissues. Lead clears rapidly from blood, but that deposited in bones has a half-life of 30 years. Thus, the presence of lead in blood indicates recent exposure, and it does not allow the determination of total body burden. The toxicity of lead is related to its multiple biochemical effects:

- *High affinity for sulfhydryl groups.* The most important enzymes inhibited by lead due to this mechanism are involved in heme biosynthesis: δ-aminolevulinic acid dehydratase and ferroketolase. These enzymes catalyze the incorporation of iron into the heme molecule, and hence patients develop hypochromic anemia.
- *Competition with calcium ions.* As a divalent cation, lead competes with calcium and is stored in bone. It also interferes with nerve transmission and brain development.
- *Inhibition of membrane-associated enzymes.* Lead inhibits 5'-nucleotidase activity and sodium-potassium ion pumps, leading to decreased survival of red blood cells (hemolysis), renal damage, and hypertension.
- *Impaired production* of 1,25-dihydroxyvitamin D, the active metabolite of vitamin D.

Lead contributes to multiple chronic health effects, illustrated in Figure 9-9 . *Injury to the central and peripheral nervous systems* causes headache, dizziness, memory deficits, and decreased nerve conduction velocity. *Blood changes* occur early and are characteristic. Because lead interferes with heme biosynthesis, it causes a microcytic hypochromic anemia; punctate basophilic stippling of erythrocytes is characteristic. There is also an element of hemolysis because lead inhibits membrane-associated red cell enzymes. Because lead inhibits incorporation of iron into heme, the iron is displaced, and zinc protoporphyrin is formed. Thus, an elevated blood level of zinc protoporphyrin or its product, free erythrocyte protoporphyrin, is an important indicator of lead poisoning. *Gastrointestinal symptoms* include colic and anorexia. The kidneys are a major route of excretion of lead. Acutely, there is *damage to the proximal tubules*, with intranuclear lead inclusions and clinical evidence of renal tubule dysfunction. Chronically, lead can cause diffuse interstitial fibrosis, gout, and renal failure. Even in the absence of overt clinical symptoms of kidney damage, lead causes hypertension. Lead can cause infertility in men due to testicular injury; failure of implantation of the fertilized ovum can occur in women.[44]

Infants and children are especially vulnerable to lead toxicity. It is estimated by the CDC that in the year 2000 approximately 454,000 children in the United States had blood lead levels greater than 10 µg/dL. A recent study indicates that even below this level there is an inverse correlation between blood lead concentration and IQ scores. Very slightly elevated blood levels (~3 µg/dL) in young females have also been reported to delay puberty.[45] Thus, lead toxicity continues to be a matter of concern. Lead may be mobilized from the maternal skeleton during pregnancy and it readily crosses the placental barrier. Hence

Figure 9-9 Consequences of lead exposure.



Battery burning
Urban soil
Newsprint
Automotive exhaust

TABLE 9-14 -- Health Effects of Agricultural Pesticides

Category	Example	Effects and Disease Associations
Insecticides	Organochlorines	Neurotoxicity; hepatotoxicity
	••DDT	
	••Chlordane	
	••Lindane	
	••Methoxychlor	
	Organophosphates	Neurotoxicity; delayed neuropathy
	••Parathion	
	••Diazinon	
	••Malathion	
	Carbamates	Neurotoxicity (reversible)
	••Aldicarb	
	••Carbaryl	
	Botanical agents	Paresthesia; lung irritant; allergic dermatitis
	••Nicotine	
	••Pyrethrins	
	••Rotenone	
Herbicides	Arsenic compounds	Hyperpigmentation; gangrene; anemia; sensory neuropathy; cancer
	Dinitrophenols	Hyperthermia; sweating
	Chlorophenoxy herbicides	
	••2,4-D and 2,4,5-T	? Lymphoma; sarcoma
	••TCDD	Fetotoxicity; immunotoxicity; cancer
	Paraquat	Acute lung injury
	Atrazine	? Cancer
	Alachlor	? Cancer
Fungicides	Captan	? Reproductive toxicity
	Maneb	

	Benomyl	
Rodenticides	Fluoroacetate	Cardiac and respiratory failure
	Warfarin	Hemorrhage
	Strychnine	Respiratory failure
Fumigants	Carbon disulfide	Cardiac toxicity
	Ethylene dibromide	Neurotoxicity
	Phosphine	Lung edema; brain damage
	Chloropicrin	Eye irritation; lung edema; arrhythmias

Data from Hodgson E: Introduction to toxicology. In Hodgson E, Levi PE (eds): A Textbook of Modern Toxicology. Stamford, CT, Appleton & Lange, 1997, p. 1; and Levi PE: Classes of toxic chemicals. In Hodgson E, Levi PE (eds): A Textbook of Modern Toxicology. Stamford, CT, Appleton & Lange, 1997, p. 229.

soil and water supplies. Environmental contamination is a threat to wildlife; some pesticides undergo bioaccumulation and persist in wildlife and humans for decades. Bioaccumulation and biopersistence are characteristic of organochlorines, such as DDT (dichlorodiphenyltrichloroethane), and dioxins, such as TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin). There is considerable controversy about the adverse health effects of these persistent pesticides and their metabolites, especially concerning their relationship to breast cancer,[48] reproductive abnormalities,[49] and cognitive deficits.[50]

Agricultural pesticides are divided into five categories, depending on the target pest: insecticides, herbicides, fungicides, rodenticides, and fumigants (Table 9-14). All pesticides are toxic to some plant or rodent species; at higher doses, they can also be toxic to farm animals, pets, and humans. In general, herbicides used to control weeds have low acute toxicity for mammals; fungicides are characterized as moderately toxic. Acute toxicity of insecticides for mammals ranges from low to high. For example, DDT was widely used as an insecticide in the 1940s and 1950s because it has low acute toxicity for humans. However, DDT persists in the environment and accumulates in the food chain. Birds that ingested DDT-contaminated insects and fish suffered reproductive defects. DDT and its major metabolite, DDE

(1,1-dichloro-2,2-bis(*p*-chlorophenyl) ethylene), accumulate in fat tissue and have been detected in human milk. Organochlorines, as well as industrial chemicals such as polychlorinated biphenyls (PCBs), are weakly estrogenic. Some of these chemicals are carcinogenic in rodents and cause reproductive dysfunction in amphibians, birds, and fish.[48] Although several epidemiologic studies have not found increased levels of DDE or PCBs in women with breast cancer compared with matched control subjects, there is still concern that these persistent organochlorines, other potentially estrogenic pesticides, and natural phytoestrogens in plants such as soybeans may have adverse reproductive effects in humans. The mechanisms of action of these xenoestrogens, alone or in combination, in the development of cancer and in reproductive dysfunction are unknown.[48] [49]

The major health effects of the most common agricultural pesticides are summarized in Table 9-14 . Selected examples are discussed here.

• *Organochlorines*, such as DDT, have low acute toxicity for humans; however, they bioaccumulate and persist in the environment and in fat tissue. These chemicals are absorbed through the skin, gastrointestinal tract, and lungs. As alluded to earlier, the role of DDT and its metabolites as an endocrine-disrupting agent is controversial. *Chlordane* is representative of cyclodienes that are used to control termites and other soil insects. Acute toxicity causes hypothermia, tremor, and convulsions. Chlordane also causes immune dysfunction and may act as a nongenotoxic carcinogen. These effects may contribute to the increased incidence of lymphoma observed in some farm workers. *Lindane* is an isomer

of benzene hexachloride that is used to control lice and scabies, as a wood preservative, and as a household fumigant. It has been reported to cause immune dysfunction and reproductive problems in women.

• *Organophosphates* are irreversible inhibitors of cholinesterases resulting in abnormal transmission at peripheral and central nerve endings. These chemicals are absorbed through the skin, gastrointestinal tract, and lungs. Up to 40% of farm workers in the United States show measurable inhibition of red blood cell or plasma cholinesterase activity; fatalities have been reported from organophosphate exposure. *Carbamates* are reversible inhibitors of cholinesterase that produce acute neurotoxic effects similar to those of organophosphate insecticides. Carbaryl (Sevin) is potentially mutagenic and teratogenic because it poisons the mitotic spindle.

• *Herbicides* like the dioxin TCDD has received much attention. During the Vietnam War, the defoliant Agent Orange was contaminated with TCDD. A chemical factory explosion in Seveso, Italy, in 1976 caused local environmental contamination and human exposure to TCDD, resulting in chloracne and an increased incidence of leukemia, lymphoma, and sarcomas. TCDD and structurally similar dioxins are also produced in the paper pulp industry using chlorine bleach and by waste incinerators. Low doses of dioxin are present in our food, soil, and water. In some laboratory animals, TCDD is highly toxic, immunosuppressive, teratogenic, and carcinogenic. The sensitivity of some strains of laboratory mice to dioxin is linked to the aryl hydrocarbon hydroxylase receptor. TCDD can induce liver cytochrome P-450 enzyme activity, increase estrogen metabolism, and interfere with development of the male reproductive tract. TCDD also decreases thyroxine levels in adult rats. Extrapolation of these multiple adverse effects observed in laboratory animals to low-dose exposure of humans is difficult.[51]

• *Rodenticides* are highly toxic chemicals with restricted use. The major health threat is death from suicidal or accidental ingestion.

TABLE 9-15 -- Natural Toxins

Category	Example	Source	Effects and Associated Diseases
Mycotoxins	Ergot alkaloids	*Claviceps* fungi	Gangrene, convulsions, abortion
	Aflatoxins	*Aspergillus flavus*	Liver cancer
	Tricothecenes	*Fusarium, Trichoderma*	Diarrhea, ataxia
Phytotoxins	Cycasin	Cycad flour	Amyotrophic lateral sclerosis
	Monocrotaline	*Senecio* plants	Hepatitis
	Safrole	Black pepper; oil of Sassafras	Cancer
	Solanine	Solanaceae plants (potato)	Neurotoxin
Animal toxins	Venoms	Snakes	Cardiotoxin, neurotoxin
		Bees	Direct toxicity, cardiotoxin
	Saxitoxin	Dinoflagellates	Neurotoxin, paralysis
	Ciguatoxin	Dinoflagellates	Paresthesia, paresis, vomiting, diarrhea
	Tetrodotoxin	Puffer fish	Neurotoxin, shock

Data from Hodgson E: Introduction to toxicology. In Hodgson E, Levi PE (eds): A Textbook of Modern Toxicology. Stamford, CT, Appleton & Lange, 1997, p. 1.

NATURAL TOXINS

In addition to manufactured pesticides, potent toxins and carcinogens are present in the natural environment, as summarized in Table 9-15 . These mycotoxins and phytotoxins may contaminate foods. For example, cycad flour is used in arid climates. This plant contains the toxin cycasin (methylazoxymethanol β-glucoside). If the plant and seeds are cut into small pieces, soaked in water, and dried, the toxin is leached. However, if these precautions are not followed, a degenerative neurologic disorder (amyotrophic lateral sclerosis) is produced by

ingestion of cycasin. Animal toxins can be ingested by eating fish, snails, or mollusks. The most common poisoning results from eating tropical fish and snails that have ingested dinoflagellates containing ciguatoxin. Ciguatera

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poisoning can be severe and occurs in the South Pacific and the Caribbean. Paralytic shellfish poisoning occurs in North America after eating mollusks that have ingested dinoflagellates that contain saxitoxin. Aflatoxin B_1 is produced by fungi that contaminate peanuts, corn, and cottonseed. It is a potent carcinogen that contributes to the high incidence of liver cancer in some regions of Africa and the Far East (Chapter 7 and Chapter 18).

RADIATION INJURY

Radiation is energy distributed across the electromagnetic spectrum as waves (long wavelengths, low frequency) or particles (short wavelengths, high frequency). The types, frequencies, and biologic effects of electromagnetic radiation are summarized in Table 9-16 . Approximately 80% of radiation is derived from natural sources, including cosmic radiation, ultraviolet light, and natural radioisotopes, especially radon gas. The remaining 20% is derived from manufactured sources that include instruments used in medicine and dentistry, consumer products that emit radio waves or microwaves, and nuclear power plants. The potentially catastrophic effects of radiation are most vividly illustrated by the effects of nuclear explosions. The atomic bombs dropped on Hiroshima and Nagasaki in 1945 not only caused acute injury and death but also increased incidence of various cancers among the survivors. Numerous historical incidents document the deleterious effects of therapeutic radiation. For example, early in the 20th century, American radiologists experienced an increased incidence of aplastic anemia and neoplasms of the skin, brain, and hematopoietic system. Children who were treated with radiation for an enlarged thymus or benign skin lesions between 1910 and 1959 suffered from an increased incidence of thyroid abnormalities, thyroid tumors, and leukemias and lymphomas. Exposure of the fetus to radiation can produce mental retardation, congenital anomalies, leukemia, and solid tumors. Investigation of these deliberate or accidental exposures to radiation led to an understanding of the relationship between the dose and timing of radiation and the acute and chronic health effects. However, in general, these historical exposures were higher than radiation currently received by the general population from natural and manufactured sources,

TABLE 9-16 -- Ionizing and Nonionizing Electromagnetic Radiation

Frequency (Hz)	Radiation	Biologic Effects
1–50	Electric power	?
10^6 –10^{11}	Radio waves and radar	Thermal effects, cataracts
10^9 –10^{10}	Microwaves	Lens opacities
10^{11} –10^{14}	Infrared	Cataracts
10^{15}	Visible light	Retinal burns (lasers)
10^{15} –10^{18}	Ultraviolet light	Skin burns, cancer
10^{18} –10^{20}	X-rays and gamma rays	Acute and delayed injury; cancer
10^{27}	Cosmic radiation	?

by patients undergoing diagnostic procedures such as mammography or chest radiography, and by nuclear power plant workers. Unfortunately, fear of widespread radiation exposure following a terrorist attack reinforces the importance of understanding the mechanisms and clinical manifestations of radiation injury.[52] Despite our understanding of the health effects of

high doses of radiation, the potential adverse effects of low doses are controversial. Furthermore, accidents at nuclear power plants in Windscale, England, in 1957, at Three Mile Island in Pennsylvania in 1979, and at Chernobyl in the former Soviet Union in 1986 perpetuate public anxiety about excess cancers associated with the medical, commercial, and military uses of radioactivity.[53]

Electromagnetic radiation characterized by long wavelengths and low frequencies is described as *nonionizing radiation*. Electric power, radio waves and microwaves, infrared, and ultraviolet light are examples of nonionizing radiation. They produce vibration and rotation of atoms in biologic molecules. Radiation energy of short wavelengths and high frequency can ionize biologic target molecules and eject electrons. X-rays, gamma rays, and cosmic rays are forms of *ionizing radiation*. Ionizing radiation can be in the form of electromagnetic waves, such as x-rays produced by a roentgen tube or gamma rays emitted from natural sources, or particles that are released by natural decay of radioisotopes or by artificial acceleration of subatomic particles. *Particulate radiation* is classified by the type of particles emitted: alpha particles, beta particles or electrons, protons, neutrons, mesons, or deuterons. The energy of these particles is measured in million electron volts (MeV). Radioisotopes decay by emission of alpha or beta particles or by capture of electrons. In the case of radon gas, unstable daughter nuclei are produced that subsequently disintegrate, releasing alpha particles. *Alpha particles* consist of two neutrons and two protons; they have strong ionizing power but low penetration because of their large size. In contrast, *beta particles* are electrons emitted from the nucleus of an atom; these have weaker ionizing power but higher penetration than alpha particles. The decay of radioisotopes is expressed by the *curie* (Ci), 3.7×10^{10} disintegrations per second, or the *becquerel* (Bq), 1 disintegration per second. The rate of decay of radioisotopes is usually expressed as the half-life ($t_{1/2}$) and ranges from a few seconds to centuries. Internal deposition of radioisotopes with long half-lives is especially dangerous because it results in continuous release of radioactive particles and gamma rays. For example, radium was used to paint watch dials and treat cancer in the first half of the 20th century; its long half-life of 1638 years and ability to be concentrated in the skeleton result in delayed appearance of bone tumors.

Ionizing Radiation

The dose of ionizing radiation is measured in several units:

- *roentgen:* unit of charge produced by x-rays or gamma rays that ionize a specific volume of air
- *rad:* the dose of radiation that will produce absorption of 100 ergs of energy per gram of tissue; 1 gm of tissue exposed to 1 roentgen of gamma rays is equal to 93 ergs
- *gray* (Gy): the dose of radiation that will produce absorption of 1 joule of energy per kilogram of tissue; 1 Gy corresponds to 100 rad

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- *rem:* the dose of radiation that causes a biologic effect equivalent to 1 rad of x-rays or gamma rays
- *sievert* (Sv): the dose of radiation that causes a biologic effect equivalent to 1 Gy of x-rays or gamma rays; 1 Sv corresponds to 100 rem.[53]

These measurements do not directly quantify energy transferred per unit of tissue and therefore do not predict the biologic effects of radiation. The following terms provide a better approximation of such information.

- *Linear energy transfer* (LET) expresses energy loss per unit of distance traveled as electron volts per micrometer. This value depends on the type of ionizing radiation. LET is high for alpha particles, less so for beta particles, and even less for gamma rays and x-rays. Thus, alpha and beta particles penetrate short distances and interact with many molecules within that short distance. Gamma rays and x-rays penetrate deeply but interact with relatively few molecules per unit distance. It should be evident that if equivalent amounts of energy entered the body in the form of alpha and gamma radiation, the alpha particles would induce heavy damage in a restricted area, whereas gamma rays would dissipate energy over a longer course and produce considerably less damage per unit of tissue.
- *Relative biologic effectiveness* (RBE) is simply a ratio that represents the relationship of the LETs of various forms of irradiation to cobalt gamma rays and megavolt x-rays, both of which have an RBE of unity (1).

In addition to the physical properties of the radioactive material and the dose, the biologic effects of ionizing radiation depend on several factors:

• Dose rate: a single dose can cause greater injury than divided or fractionated doses that allow time for cellular repair.
• Since DNA is the most important subcellular target of ionizing radiation, rapidly dividing cells are more radiosensitive than are quiescent cells. Hematopoietic cells, germ cells, gastrointestinal epithelium, squamous epithelium, endothelial cells, and lymphocytes are highly susceptible to radiation injury; bone, cartilage, muscle, and peripheral nerves are more resistant.
• A single dose of external radiation administered to the whole body is more lethal than regional doses with shielding. For example, the median lethal dose (LD_{50}) of ionizing radiation is 2.5 to 4.0 Gy (250 to 400 rad), whereas doses of 40 to 70 Gy (4000 to 7000 rad) can be delivered in a fractionated manner during several weeks for cancer therapy.
• Cells in the G_2 and mitotic phases of the cell cycle are most sensitive to ionizing radiation.
• Different cell types differ in the extent of their adaptive and reparative responses.
• Since ionizing radiation produces oxygen-derived radicals from the radiolytic cleavage of water (Chapter 1), cell injury induced by x-rays and gamma rays is enhanced by hyperbaric oxygen. Halogenated pyrimidines can also increase radiosensitivity to tumor cells. Conversely, free radical scavengers and antioxidants protect against radiation injury.

Cellular Mechanisms of Radiation Injury.

The acute effects of ionizing radiation range from overt necrosis at high doses (>10 Gy), killing of proliferating cells at intermediate doses (1 to 2 Gy), and no histopathologic effect at doses less than 0.5 Gy. Subcellular damage does occur at these lower doses, primarily targeting DNA; however, most cells show adaptive and reparative responses to low doses of ionizing radiation. If cells undergo extensive DNA damage or if they are unable to repair this damage, they undergo apoptosis (Chapter 7). Surviving cells may show delayed effects of radiation injury: mutations, chromosome aberrations, and genetic instability. These genetically damaged cells may become malignant; tissues with rapidly proliferating cell populations are especially susceptible to the carcinogenic effects of ionizing radiation. Most cancers induced by ionizing radiation have occurred after doses greater than 0.5 Gy. Acute cell death, especially of vascular endothelial cells, can cause delayed organ dysfunction several months or years after radiation exposure. In general, this delayed injury is caused by a combination of atrophy of parenchymal cells, ischemia due to vascular damage, and fibrosis.[53] Acute and delayed effects of ionizing radiation are listed in Table 9-17 , and their mechanisms are described next.

Acute Effects.

Ionizing radiation can produce a variety of lesions in DNA, including DNA-protein cross-links, cross-linking of DNA strands, oxidation and degradation of bases, cleavage of sugar-phosphate bonds, and single-stranded or double-stranded DNA breaks. This damage may be produced directly by particulate radiation, x-rays, or gamma rays or indirectly by oxygen-derived free radicals or soluble products derived from peroxidized lipids.[54] Even relatively low doses of ionizing radiation (less than 0.5 Gy) induce alterations in gene expression in some target cell populations. Free radicals generated directly or indirectly by exposure to ionizing radiation may produce oxidant stress that activates transcription factors (such as NF-κB) that increase gene expression.[55] DNA damage itself stimulates the expression of several genes involved in DNA repair, cell-cycle arrest, and apoptosis. As discussed in Chapter 7 , the tumor-suppressor gene *p53* is activated after many different forms of DNA damage. The end-points resulting from activation of this p53-mediated DNA damage response are discussed in Chapter 7 . Briefly, activation of p53 induces cell-cycle arrest, DNA repair and, in some cases, apoptosis. Apoptosis of microvascular endothelial cells may be the primary target of acute radiation in the GI tract, resulting in secondary damage to intestinal crypt stem cells[56] and the GI syndrome (see Table 9-18).

Fibrosis.

An important delayed complication of ionizing radiation, usually at doses used for cancer therapy, is replacement of normal parenchymal tissue by fibrosis, resulting in scarring and loss of function. These fibrotic changes may be secondary to ischemic injury caused by vascular damage, death of parenchymal cells, or deletion of stem cells.[57] The mechanisms responsible for fibrosis have been explored in a murine model of radiation-induced pulmonary fibrosis using microarray analysis of gene expression. Up-regulation of chemokines that recruit inflammatory cells to the lungs as well as cytokines and growth factors involved in fibroblast activation and collagen deposition are central components of radiation-induced fibrosis.[58] As described in Chapter 3 , these chemokines, cytokines, and growth factors also play important roles in wound healing.

TABLE 9-17 -- Acute Injury and Delayed Complications Caused by Ionizing Radiation

Organ	Acute Injury	Delayed Complications
Bone marrow	Atrophy	Hypoplasia, leukemia
Skin	Erythema	Atrophy of epidermis and fibrosis of dermis; cancer
Heart	—	Interstitial fibrosis
Lung	Edema, endothelial and epithelial cell death	Interstitial and intra-alveolar fibrosis; cancer
Gastrointestinal tract	Edema, mucosal ulcers	Ulcers; fibrosis; strictures; adhesions; cancer
Liver	Veno-occlusive disease	Cirrhosis; liver tumors
Kidney	Vasodilation	Cortical atrophy, interstitial fibrosis
Urinary bladder	Mucosal erosion	Submucosal fibrosis; cancer
Brain	Edema, necrosis	Necrosis of white matter, gliosis; brain cancer
Testis	Necrosis	Tubular atrophy
Ovary	Atresia of follicles	Stromal fibrosis
Thyroid	—	Hypothyroidism; cancer
Breast	—	Fibrosis; cancer
Thymus, lymph nodes	Atrophy	Lymphoma

Carcinogenesis.

Occupational or accidental exposures to ionizing radiation produce an increased incidence of various types of cancer, including skin cancers, leukemia, osteogenic sarcomas, and lung cancer. There is usually a latent period of 10 to 20 years before appearance of these cancers. In survivors of the atomic blasts at Hiroshima and Nagasaki, all types of leukemias were especially common, with the exception of chronic lymphocytic leukemia. Exposure of children to irradiation causes an increased incidence of breast and thyroid cancers as well as gastrointestinal and urinary tract tumors. The nuclear power accident at Chernobyl in 1986 caused more than 50 deaths, with estimated exposures of 50 to 300 rad. More than 20,000 people were exposed to up to 40 rem. As early as 1990, an increased incidence of thyroid cancer was seen in exposed children. Approximately 2 million people living near Three Mile Island were exposed to low doses of 100 mrem in 1979; no adverse effects have yet been reported. Workers in the nuclear energy industry and in health care and research are exposed annually to doses ranging from 1 to 9 mSv. The annual maximal permissible exposure level for

TABLE 9-18 -- Clinical Features of the Acute Radiation Syndrome

Category	Whole-Body Dose (rem)	Symptoms	Prognosis

Subclinical	••<200	Mild nausea and vomiting	100% survival
		Lymphocytes <1500/µL	
Hematopoietic	200–600	Intermittent nausea and vomiting	Infections
		Petechiae, hemorrhage	May require bone marrow transplant
		Maximum neutrophil and platelet depression in 2 wk	
		Lymphocytes <1000/µL	
Gastrointestinal	600–1000	Nausea, vomiting, diarrhea	Shock and death in 10–14 days even with replacement therapy
		Hemorrhage and infection in 1–3 wk	
		Severe neutrophil and platelet depression	
		Lymphocytes <500/µL	
Central nervous system	••>1000	Intractable nausea and vomiting	Death in 14–36 hr
		Confusion, somnolence, convulsions	
		Coma in 15 min–3 hr	
		Lymphocytes absent	

these workers is 50 mSv or 1 rem. There is uncertainty about the potential carcinogenic risk at these low exposures because the shape of the dose-response curve is unknown.

The mechanisms responsible for the delayed carcinogenic effects of ionizing radiation are not completely understood. The latent period between acute exposure to ionizing radiation and the delayed appearance of cancer may be due to a phenomenon called *induced genetic instability*. Quantitative analysis of mutation rates in irradiated cells in culture shows that mutations continue to be expressed in surviving cells after several generations. Accumulation of these delayed mutations may be the result of persistent DNA lesions that are not repaired or due to an epigenetic mechanism, such as altered methylation at CpG sites or shortening of telomeres. Delayed chromosome aberrations are also observed after exposure to ionizing radiation, especially in human lymphocytes.[59] These mechanisms may be responsible for induction of secondary cancers, especially leukemias, in cancer patients treated with radiation therapy.

Clinical Manifestations of Exposure to Ionizing Radiation

The clinical effects of ionizing radiation depend on the dose, duration, and mode of exposure. These are described next.

Acute, Whole-Body Exposure.

Whole-body irradiation is potentially lethal; the clinical manifestations are dose dependent and described as the *acute radiation syndrome* or *radiation sickness*. On the basis of calculated doses delivered in nuclear reactor accidents or the atomic bombing of Japan, the LD_{50} at 60 days for humans exposed to a single dose of x-rays or gamma radiation is 2.5 to 4.0 Gy (250 to

400 rad). Depending on the dose, four clinical syndromes are produced: a subclinical or prodromal syndrome, hematopoietic syndrome, gastrointestinal syndrome, or central nervous system syndrome. These are summarized in Table 9-18 . The acute symptoms are manifestations of the high sensitivity of rapidly proliferating tissues, such as the lymphohematopoietic cells and gastrointestinal epithelium, to acute radiation-induced necrosis or apoptosis (Fig. 9-10). If the patient survives the acute radiation syndrome, sublethally injured cells may repair the radiation damage, and the necrotic or apoptotic cells may be replaced by the progeny of more radioresistant stem cells.

Effects of Radiation Therapy.

External radiation is delivered to malignant neoplasms at fractionated doses up to 40 to 70 Gy (4000 to 7000 rad), with shielding of adjacent normal tissues. Radiation therapy, especially when it is delivered to the chest or abdomen, can cause acute radiation sickness and neutrophil and platelet depression. These patients may experience transient fatigue, vomiting, and anorexia that may require reduction of the dose. Acutely, radiation therapy may shrink the tumor mass and relieve pain or compression of adjacent tissues. Unfortunately, cancer patients treated with radiation therapy may develop sterility, a secondary malignant neoplasm, or delayed radiation injury (described later).[53]

Effects on Growth and Development.

The developing fetus and young children are highly sensitive to growth and developmental abnormalities induced by ionizing radiation. Four susceptible phases can be defined:

Figure 9-10 Atrophy of the thymus gland after exposure to ionizing radiation. The right panel shows a normal thymus with deeply staining cortex and pale staining medulla; the left panel shows depletion of lymphocytes with preservation of (pink, concentric) Hassall corpuscles. *(American Registry of Pathology © 1990.)*

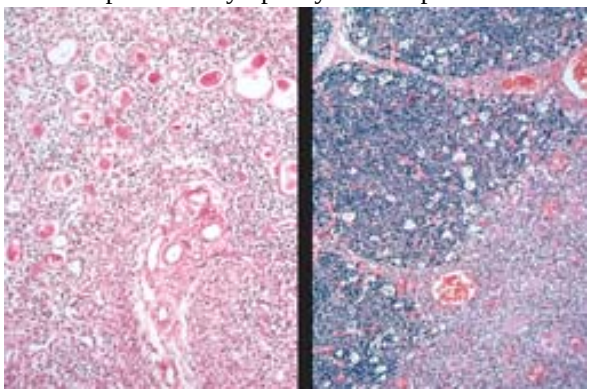

Figure 9-11 Acute vascular injury with fibrinoid necrosis and edema after exposure to ionizing radiation. *(American Registry of Pathology © 1990.)*

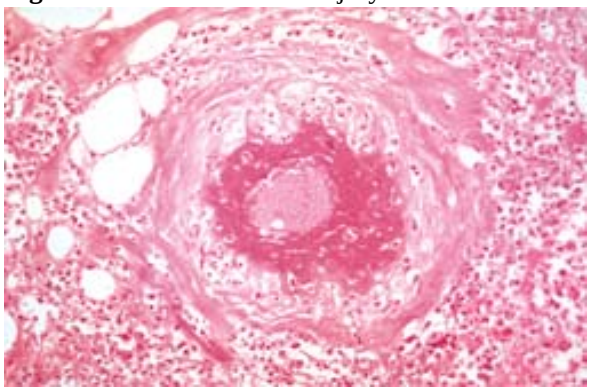

Figure 9-12 Chronic vascular injury with subintimal fibrosis occluding the lumen. *(American Registry of Pathology © 1990.)*

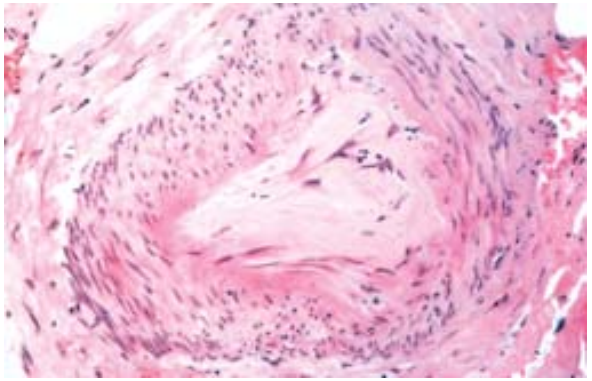

Figure 9-13 Chronic radiation dermatitis with atrophy of the epidermis, dermal fibrosis, and telangiectasia of the subcutaneous blood vessels. *(American Registry of Pathology © 1990.)*

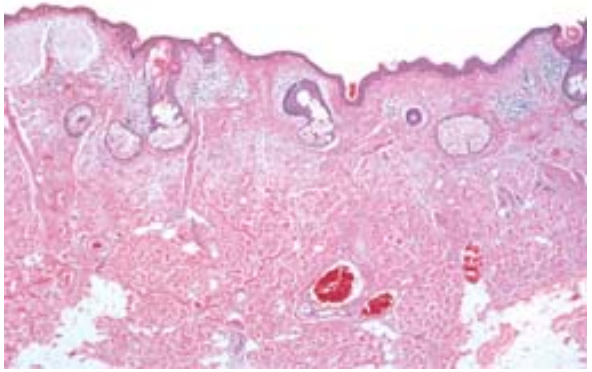

Figure 9-14 Extensive mediastinal fibrosis after radiotherapy for carcinoma of the lung. Note the markedly thickened pericardium. *(From the teaching collection of the Department of Pathology, Southwestern Medical School, Dallas, TX.)*

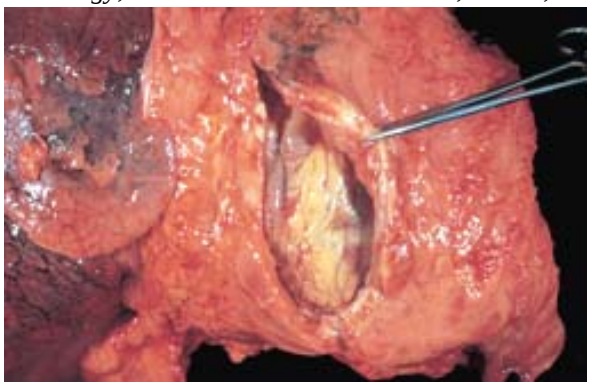

Figure 9-15 Radiation fibrosis of the breast stroma after radiotherapy for infiltrating ductal carcinoma. The nests of remaining tumor cells are pleomorphic and multinucleated. *(American Registry of Pathology © 1990.)*

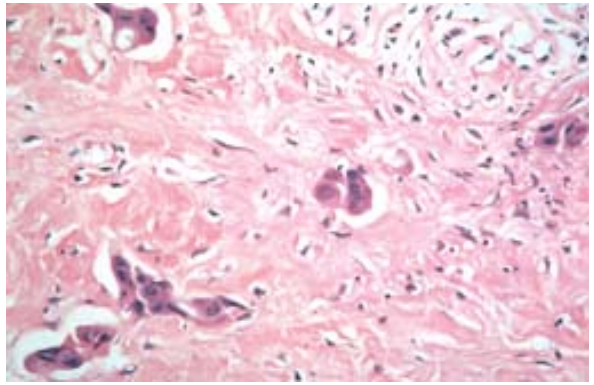

TABLE 9-19 -- Acute and Delayed Effects of Ultraviolet Radiation

Radiation	Wavelength (nm)	Acute Effects	Delayed Effects
UVA	320–400	Erythema 8–48 hr	Tanning
		Depletion of Langerhans cells	? Skin cancer
		Pigment darkening	
		Dermal inflammation	
UVB	290–320	Erythema 3–24 hr	Tanning
		Apoptosis of keratinocytes	Solar elastosis
		Depletion of Langerhans cells	Premature aging
			Actinic keratosis
			Skin cancer
UVC	200–290		? Skin cancer

Data from Rosen CF: Ultraviolet radiation. In Craighead JE (ed): Pathology of Environmental and Occupational Disease. St. Louis, Mosby-Year Book, 1996, p. 193.

Ultraviolet Radiation

Solar radiation spans the spectrum of wavelengths between 200 and 4000 nm, including ultraviolet, visible, and infrared radiation. Ultraviolet radiation is divided into ultraviolet A (UVA), ultraviolet B (UVB), and ultraviolet C (UVC); 3% to 5% of the total solar radiation that penetrates the earth's surface is ultraviolet radiation. Ozone in the atmosphere is an important protective agent against ultraviolet radiation because it completely absorbs all UVC and partially absorbs UVB. Chlorofluorocarbons, used commercially as propellants, as solvents, and in refrigerators and air conditioners, interact with and deplete ozone. Such depletion is predicted to contribute to an increase in UVB and possibly UVC exposure, thus triggering a 2% to 4% increase in the incidence of skin cancers. Some protection from the effects of UV light is afforded by window glasses: they absorb UVB radiation, but they transmit UVA radiation. Sunblocks and sunscreens offer greater protection because they absorb or block UVB and UVA to variable degrees. There are two major health effects of ultraviolet radiation: premature aging of the skin and skin cancer (Table 9-19). The carcinogenic effects of ultraviolet light are discussed in Chapter 7 . Here we focus on other effects of ultraviolet radiation.

The acute effects of UVA and UVB are short-lived and reversible. They include erythema, pigmentation, and injury to Langerhans cells and keratinocytes in the epidermis. The kinetics and chemical mediators of these reactions differ in response to UVA and UVB. Depending on the intensity and length of exposure, erythema, edema, and acute inflammation are mediated

by release of histamine from mast cells in the dermis, synthesis of arachidonic acid metabolites, and the production of pro-inflammatory cytokines like IL-1. UVA produces oxidation of melanin with transient, immediate

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darkening, especially in individuals with darker skin. Tanning induced by UVA and UVB is due to a delayed increase in the number of melanocytes, elongation and extension of dendritic processes, and transfer of melanin to keratinocytes. Tanning induced by UVB is protective against subsequent exposures; tanning induced by UVA provides limited protection. Both UVA and UVB deplete Langerhans cells and thus reduce the processing of antigens introduced through the epidermis. UVB causes apoptosis of keratinocytes in the epidermis, resulting in dyskeratotic, sunburn cells.

Repeated exposures to ultraviolet radiation give rise to changes in the skin that are characteristic of premature aging (e.g., wrinkling, solar elastosis, and irregularities in pigmentation). In contrast to ionizing radiation that increases deposition of collagen in the dermis, ultraviolet radiation causes degenerative changes in elastin and collagen, leading to wrinkling, increased laxity, and a leathery appearance. These connective tissue alterations accumulate over time and are largely irreversible. They are caused by increased expression of the elastin gene, increased expression of matrix metalloproteinases that degrade collagen, and induction of a tissue inhibitor of matrix metalloproteinase. The end result of these changes in connective tissue enzymes is degradation of type I collagen fibrils and disorganization and degeneration of the dermal connective tissue[61] (Fig. 9-16).

Skin damage induced by UVB is believed to be caused by the generation of reactive oxygen species and by damage to endogenous chromophores such as melanin. Ultraviolet radiation also damages DNA, resulting in the formation of pyrimidine dimers between adjacent pyrimidines on the same DNA strand. Other forms of DNA damage, for example, formation of pyrimidine-pyrimidone (6-4) photoproducts, single-stranded breaks, and DNA-protein cross-links, are also noted.[61] A unique spectrum of mutations has been identified in premalignant and malignant skin lesions in humans,

Figure 9-16 Solar elastosis with basophilic degeneration of the connective tissue in the upper layer of the dermis. *(American Registry of Pathology © 1990.)*

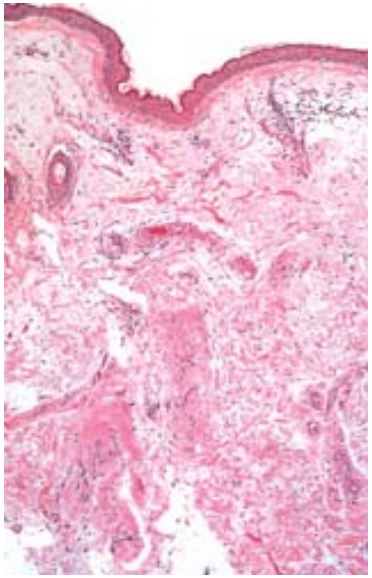

TABLE 9-20 -- Adult Mortality Rates in the United States, Ages 25–44, in 1998

	Rate per 100,000 population		
Cause	***Hispanic***	***Black***	***White***
Unintentional injuries	33.4	40.1	31.6
Cancer	16.8	38.0	25.3
Homicide	13.1	36.2	4.7
Human immunodeficiency virus	12.1	43.3	4.8
Heart disease	10.3	43.5	18.3
Suicide	7.8	—	17.0
Total	130.2	303.7	139.4

Data from CDC Fact Book, 2000/2001, Department of Health and Human Services, Centers for Disease Control and Prevention.

abuse, is a major concern in the United States. Hence, firearm safety and access are important matters of public health.[66]

Injuries caused by the physical environment, resulting from human activities as well as from external forces, can be divided into four categories: mechanical force, heat and cold, electrical injuries, and high altitudes.

Mechanical Force

Mechanical force may inflict soft-tissue injuries, bone injuries, and head injuries. Injuries of the bones and of the head are considered in Chapter 28 . Soft-tissue injuries can be superficial, involving mainly the skin, or deep, associated with visceral damage. The skin injuries can be further described as follows.

Abrasion.

This type of skin injury represents basically a scrape, in which the superficial epidermis is torn off by friction or force (Fig. 9-17). Regeneration without scarring usually occurs promptly unless infection complicates the process.

Figure 9-17 Abrasion. Note the superficial tears in the epidermis. There is bleeding under the skin as well. *(From the teaching collection of the Department of Pathology, Southwestern Medical School, Dallas, TX.)*

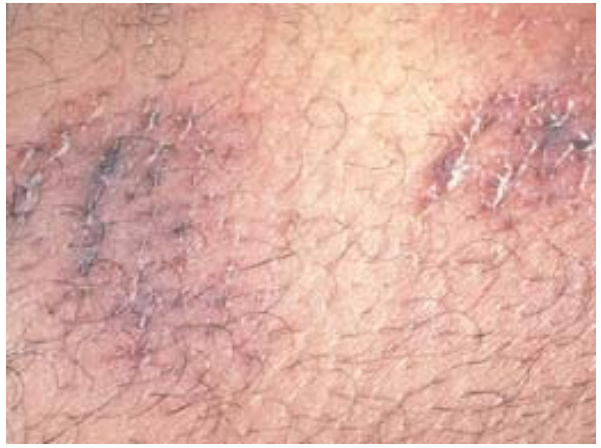

Figure 9-18 Laceration of the scalp. The bridging strands of the fibrous tissue are evident. *(From the teaching collection of the Department of Pathology, Southwestern Medical School, Dallas, TX.)*

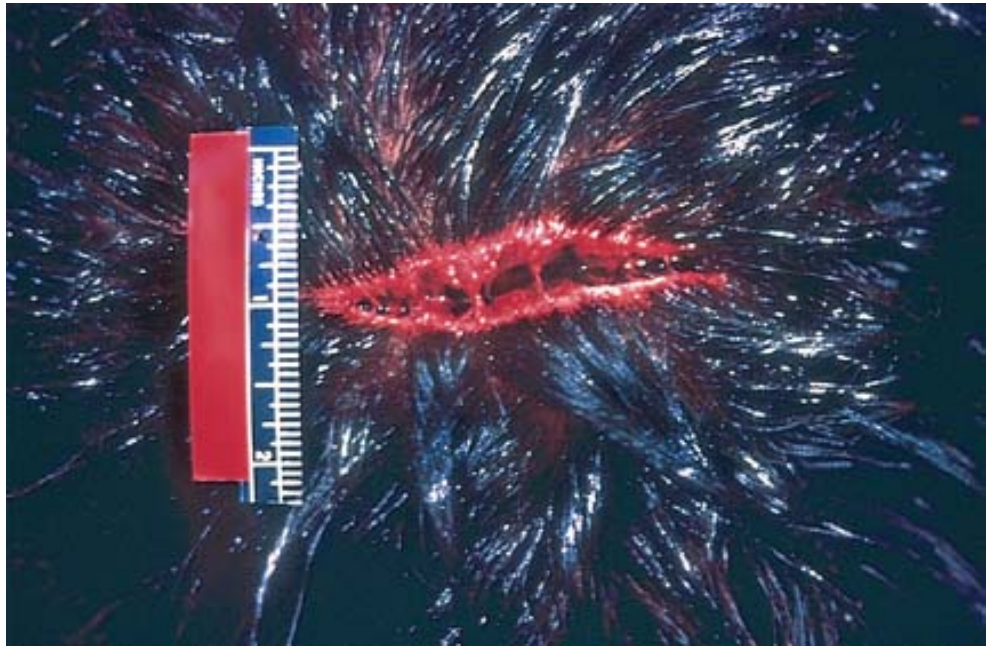

Figure 9-19 Contusion resulting from blunt trauma. The skin is intact, but there is hemorrhage in subcutaneous vessels, producing extensive discoloration. *(From the teaching collection of the Department of Pathology, Southwestern Medical School, Dallas, TX.)*

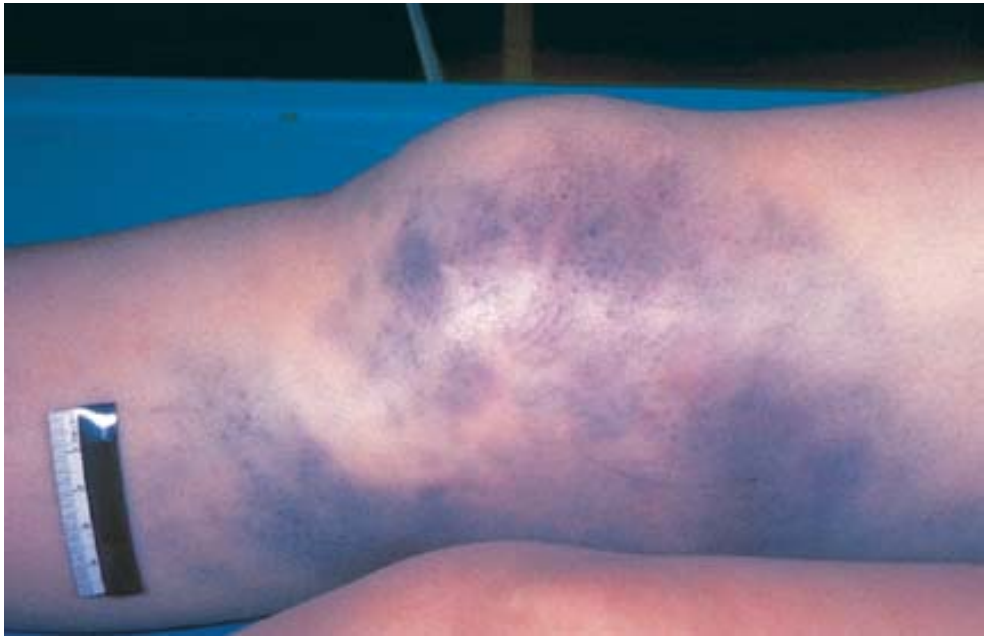

Figure 9-20 *A,* Gunshot wound of entry from a long distance. *(From the teaching collection of the Department of Pathology, Southwestern Medical School, Dallas, TX.) B,* An entry gunshot wound at close range revealing the prominent black discoloration produced by unburned powder, heat, and smoke as well as the more peripheral stippling resulting from larger particles of unburned powder. *(Courtesy of George Katsas, MD, Forensic Pathologist, Boston, MA.)*

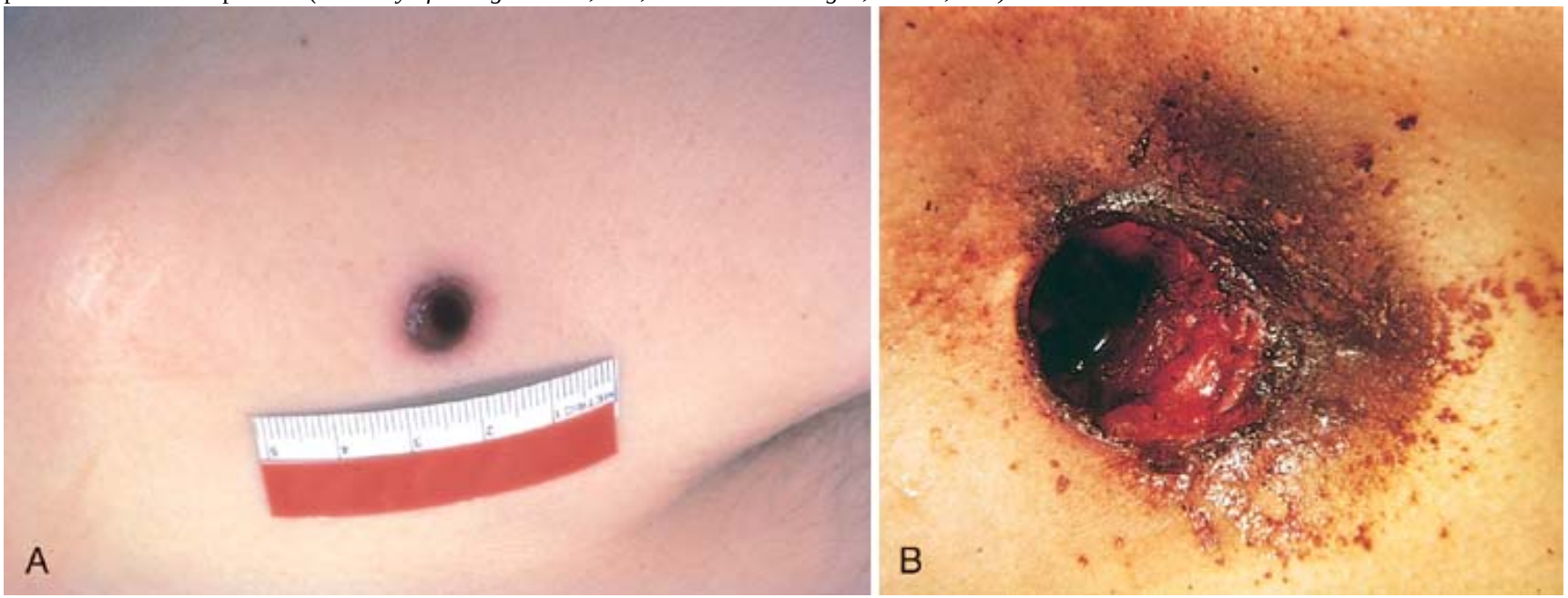

Figure 9-21 Kwashiorkor. The infant shows generalized edema, seen in the form of puffiness of the face, arms, and legs.

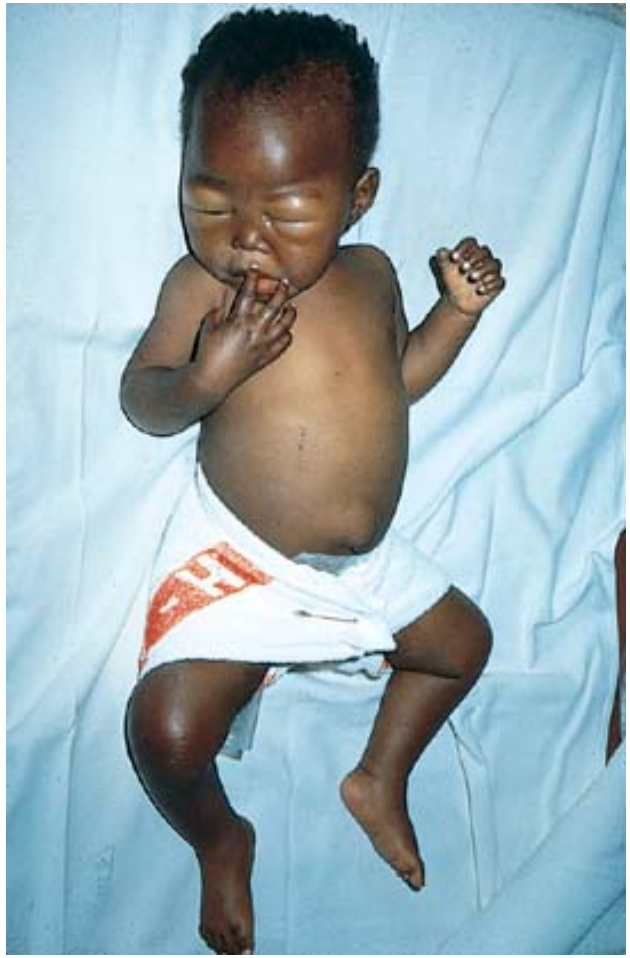

TABLE 9-21 -- Comparison of Severe Marasmus-Like and Kwashiorkor-Like Secondary Protein-Energy Malnutrition

Syndrome	Clinical Setting	Time Course	Clinical Features	Laboratory Findings	Prognosis
Marasmus-like protein-energy malnutrition	Chronic illness (e.g., chronic lung disease, cancer)	Months	History of weight loss	Normal or mildly reduced serum proteins	Variable; depends on underlying disease
			Muscle wasting		
			Absent subcutaneous fat		
Kwashiorkor-like protein-energy malnutrition	Acute, catabolic illness (e.g., severe trauma, burns, sepsis)	Weeks	Normal fat and muscle	Serum albumin <2.8 gm/dL	Poor
			Edema		
			Easily pluckable hair		

Data from Bennett JC, Plum F (eds): Cecil Textbook of Medicine, 20th ed. Philadelphia, WB Saunders, 1996, p. 1156.

weak and bedridden may show physical signs of protein and energy malnutrition: (1) depletion of subcutaneous fat in the arms, chest wall, shoulders, or metacarpal regions; (2) wasting of the quadriceps femoris and deltoid muscles; and (3) ankle or sacral edema.

Bedridden or hospitalized malnourished patients have an increased risk of infection, sepsis, impaired wound healing, and death after surgery.[68] The biochemical mechanisms responsible for secondary PEM in patients with cachexia are complex. In contrast to patients with anorexia nervosa, described next, patients with cachexia show loss of fat as well as muscle mass, which may occur before a decrease in appetite. Cachectic patients show increased expenditure of resting energy; in contrast, in chronic starvation, the basal metabolic rate is decreased. Cytokines produced by the host during sepsis, for example, or by tumors have been postulated to be involved in cachexia: tumor necrosis factor, interleukin-1, interleukin-6, and interferon-γ. In addition, as discussed in Chapter 7 , lipid- and protein-mobilizing factors have been isolated from animals and people with cancer cachexia.[69]

Morphology.

The central anatomic changes in PEM are (1) growth failure; (2) peripheral edema in kwashiorkor; and (3) loss of body fat and atrophy of muscle, more marked in marasmus.

The **liver** in kwashiorkor, but not in marasmus, is enlarged and fatty; superimposed cirrhosis is rare.

In kwashiorkor (rarely in marasmus), the **small bowel** shows a decrease in the mitotic index in the crypts of the glands, associated with mucosal atrophy and loss of villi and microvilli. In such cases, concurrent loss of small intestinal enzymes occurs, most often manifested as disaccharidase deficiency. Hence, infants with kwashiorkor initially may not respond well to a full-strength, milk-based diet. With treatment, the mucosal changes are reversible.

The **bone marrow** in both kwashiorkor and marasmus may be hypoplastic, mainly because of decreased numbers of red cell precursors. How much of this derangement is due to a deficiency of protein and folates or to reduced synthesis of transferrin and ceruloplasmin is uncertain. Thus, anemia is usually present, most often hypochromic microcytic anemia, but a concurrent deficiency of folates may lead to a mixed microcytic-macrocytic anemia.

The **brain** in infants who are born to malnourished mothers and who suffer PEM during the first 1 or 2 years of life has been reported by some observers to show cerebral atrophy, a reduced number of neurons, and impaired myelinization of the white matter, but there is no universal agreement on the validity of these findings.

Many **other changes** may be present, including (1) thymic and lymphoid atrophy (more marked in kwashiorkor than in marasmus); (2) anatomic alterations induced by intercurrent infections, particularly with all manner of endemic worms and other parasites; and (3) deficiencies of other required nutrients, such as iodine and vitamins.

Anorexia Nervosa and Bulimia

Anorexia nervosa is self-induced starvation, resulting in marked weight loss; bulimia is a condition in which the patient binges on food and then induces vomiting. These eating disorders occur primarily in previously healthy young women who have developed an obsession with attaining thinness.

The clinical findings in anorexia nervosa are generally similar to those in severe PEM. In addition, effects on the endocrine system are prominent. *Amenorrhea*, resulting from decreased secretion of gonadotropin-releasing hormone (and subsequent decreased secretion of luteinizing hormone and follicle-stimulating hormone), is so common that its presence is a diagnostic feature for the disorder. Other common findings, related to decreased thyroid hormone release, include cold intolerance, bradycardia, constipation, and changes in the skin and hair. The skin becomes dry and scaly and may be yellow because of excess carotene in the blood. Body hair may be increased but is usually fine and pale (lanugo). Bone density is decreased, most likely owing to low estrogen levels, which mimic the postmenopausal acceleration of osteoporosis. As expected with severe PEM, anemia, lymphopenia, and hypoalbuminemia may be present. A major complication of anorexia nervosa is an increased susceptibility to cardiac arrhythmia and sudden death, resulting in all likelihood from hypokalemia.

In bulimia, binge eating is the norm. Huge amounts of food, principally carbohydrates, are ingested, only to be followed by induced vomiting. Although menstrual irregularities are

common, amenorrhea occurs in less than 50% of bulimia patients, probably because weight and gonadotropin levels are maintained near normal. The major medical complications relate to continual induced vomiting and include (1) electrolyte imbalances (hypokalemia), which predispose the patient to cardiac arrhythmias; (2) pulmonary aspiration of gastric contents; and (3) esophageal and cardiac rupture.

Vitamin Deficiencies

Thirteen vitamins are necessary for health; four—A, D, E, and K—are fat-soluble, and the remainder are water-soluble. The distinction between fat- and water-soluble vitamins is important, because although fat-soluble vitamins are more readily stored in the body, they are likely to be poorly absorbed in gastrointestinal disorders of fat malabsorption (Chapter 17). Small amounts of some vitamins can be synthesized endogenously—vitamin D from precursor steroids; vitamin K and biotin by the intestinal microflora; and niacin from tryptophan, an essential amino acid—but the rest must be supplied in the diet. A deficiency of vitamins may be primary (dietary in origin) or secondary (because of disturbances in intestinal absorption, transport in the blood, tissue storage, or metabolic conversion). In the following sections, the major vitamins, together with their well-defined deficiency states, are discussed individually (with the exception of vitamin B_{12} and folate, which are discussed in Chapter 13) beginning with the fat-soluble vitamins. However, deficiencies of a single vitamin are uncommon, and the expression of a deficiency of a combination of vitamins may be submerged in concurrent PEM. A summary of all the essential vitamins, along with their functions and deficiency syndromes, is presented in Table 9-22 .

Vitamin A.

Vitamin A is actually a group of related natural and synthetic chemicals that exert a hormone-like activity or function. The relationship of some important members of this

TABLE 9-22 -- Vitamins: Major Functions and Deficiency Syndromes

Vitamin	Functions	Deficiency Syndromes
Fat-Soluble		
Vitamin A	A component of visual pigment	Night blindness, xerophthalmia, blindness
	Maintenance of specialized epithelia	Squamous metaplasia
	Maintenance of resistance to infection	Vulnerability to infection, particularly measles
Vitamin D	Facilitates intestinal absorption of calcium and phosphorus and mineralization of bone	Rickets in children
		Osteomalacia in adults
Vitamin E	Major antioxidant; scavenges free radicals	Spinocerebellar degeneration
Vitamin K	Cofactor in hepatic carboxylation of procoagulants—factors II (prothrombin), VII, IX, and X; and protein C and protein S	Bleeding diathesis
Water-Soluble		
Vitamin B_1 (thiamine)	As pyrophosphate, is coenzyme in decarboxylation reactions	Dry and wet beriberi, Wernicke syndrome, ?Korsakoff syndrome

Vitamin B_2 (riboflavin)	Converted to coenzymes flavin mononucleotide and flavin adenine dinucleotide, cofactors for many enzymes in intermediary metabolism	Ariboflavinosis, cheilosis, stomatitis, glossitis, dermatitis, corneal vascularization
Niacin	Incorporated into nicotinamide adenine dinucleotide (NAD) and NAD phosphate, involved in a variety of redox reactions	Pellagra—three "D's": dementia, dermatitis, diarrhea
Vitamin B_6 (pyridoxine)	Derivatives serve as coenzymes in many intermediary reactions	Cheilosis, glossitis, dermatitis, peripheral neuropathy
Vitamin B_{12}	Required for normal folate metabolism and DNA synthesis	Combined system disease (megaloblastic pernicious anemia and degeneration of posterolateral spinal cord tracts)
	Maintenance of myelinization of spinal cord tracts	
Vitamin C	Serves in many oxidation-reduction (redox) reactions and hydroxylation of collagen	Scurvy
Folate	Essential for transfer and use of 1-carbon units in DNA synthesis	Megaloblastic anemia, neural tube defects
Pantothenic acid	Incorporated in coenzyme A	No nonexperimental syndrome recognized
Biotin	Cofactor in carboxylation reactions	No clearly defined clinical syndrome

group is presented in Figure 9-22 . *Retinol*, perhaps the most important form of vitamin A, is the transport form and, as the retinol ester, also the storage form. It is oxidized in vivo to the aldehyde *retinal* (the form used in visual pigment) and the acid *retinoic acid*. Important dietary sources of vitamin A are animal derived (e.g., liver, fish, eggs, milk, butter). Yellow and leafy green vegetables such as carrots, squash, and spinach supply large amounts of carotenoids, many of which are provitamins that can be metabolized to active vitamin A in vivo; the most important of these is beta-carotene. A widely used term, *retinoids*, refers to both natural and synthetic chemicals that are structurally related to vitamin A but do not necessarily have vitamin A activity.

As with all fats, the digestion and absorption of carotenes and retinoids require bile, pancreatic enzymes, and some level of antioxidant activity in the food. *Retinol*, whether derived from ingested esters or from beta-carotene (through an intermediate oxidation step involving retinal), is transported in chylomicrons to the liver for esterification and storage. More than 90% of the body's vitamin A reserves are stored in the liver, predominantly in the perisinusoidal stellate (Ito) cells. In normal persons who consume an adequate diet, these reserves are sufficient for at least 6 months' deprivation. *Retinoic acid*, on the other hand, can be absorbed unchanged; it represents a small fraction of vitamin A in the blood and is active in epithelial differentiation and growth but not in the maintenance of vision.

Figure 9-22 Interrelationships of retinoids and their major functions.

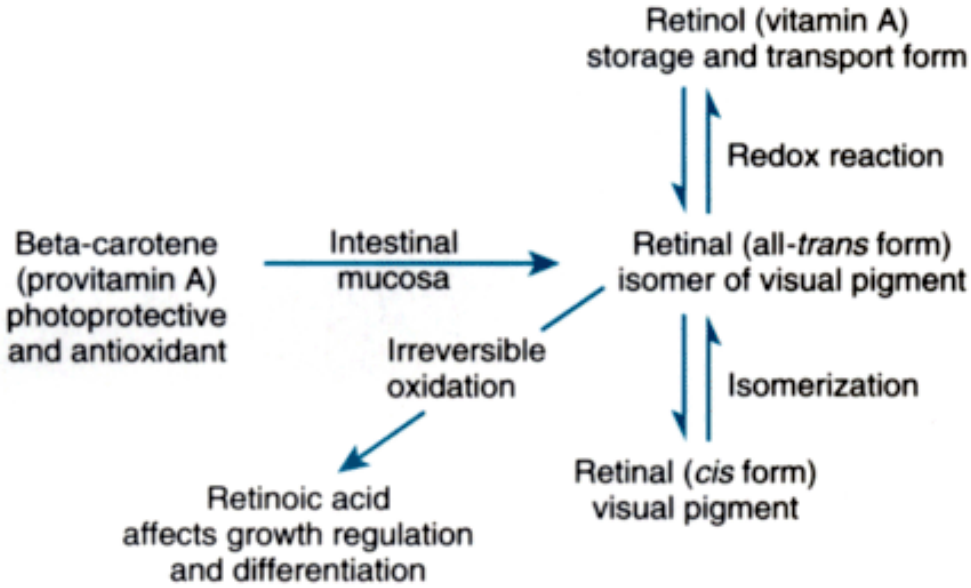

Figure 9-23 Vitamin A deficiency: its major consequences in the eye and in the production of keratinizing metaplasia of specialized epithelial surfaces, and its possible role in potentiating neoplasia.