Fungi

CC14

LIST OF DISEASES WITH ORGAN INVOLVED,
MALARIA, KALA-AZAR--------PROTOZOA (UNIT- 5)

TINEAPEDIS, HISTOPLASMOSIS,CANDIDASIS- FUNGAL DISEASES(UNIT-6)

20

I. OVERVIEW

Fungi are a diverse group of saprophytic (deriving nourishment from dead organic matter) and parasitic eukaryotic organisms. Although formerly considered to be plants, they are now assigned their own kingdom, Mycota. Virtually all organisms are subject to fungal infection. Of some 200,000 fungal species, only about 100 have pathogenic potential for humans. Of these, only a few species account for most clinically important fungal infections (Figure 20.1). Human fungal diseases (mycoses) are classified by the location on or in the body where the infection occurs. They are called cutaneous when limited to the epidermis, subcutaneous when the infection penetrates significantly beneath the skin, and systemic when the infection is deep within the body or disseminated to internal organs. Systemic mycoses can be further divided into those that are caused by true pathogenic fungi capable of infecting healthy individuals and those that are opportunistic, infecting primarily those individuals who have predisposing conditions, such as immunodeficiency or debilitating diseases (for example, diabetes, leukemia, and Hodgkin and other lymphomas). Fungi produce and secrete a variety of unusual metabolic products, some of which, when ingested, are highly toxic to animals, including humans. Thus, fungi can cause poisoning as well as infection. Lastly, fungal spores, which are critical for dispersal and transmission of the fungus, are also important as human allergenic agents.

II. CHARACTERISTICS OF MAJOR FUNGAL GROUPS

Fungi can be distinguished from other infectious organisms such as bacteria or viruses because they are eukaryotes (that is, they have a membrane-enclosed nucleus and other organelles). Fungi have no chlorophyll or chloroplasts, thus distinguishing them from plants. Their characteristic structures, habitats, and modes of growth and reproduction are used to distinguish different groups among fungi.

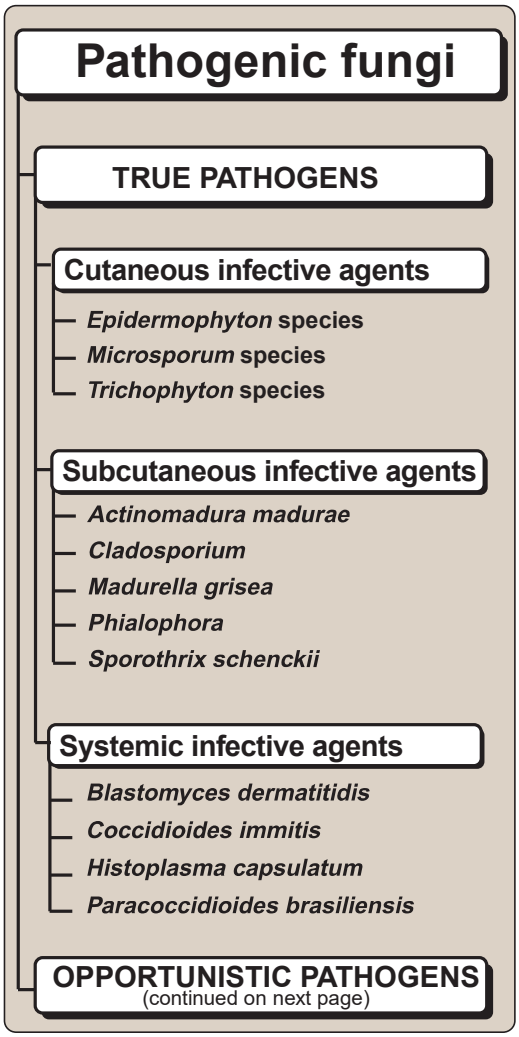

Figure 20.1
Classification of pathogenic fungi (figure continues on next page).

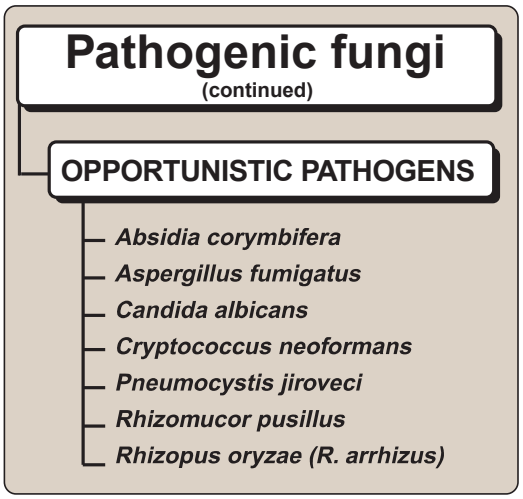

Figure 20.1 (continued)
Classification of pathogenic fungi.

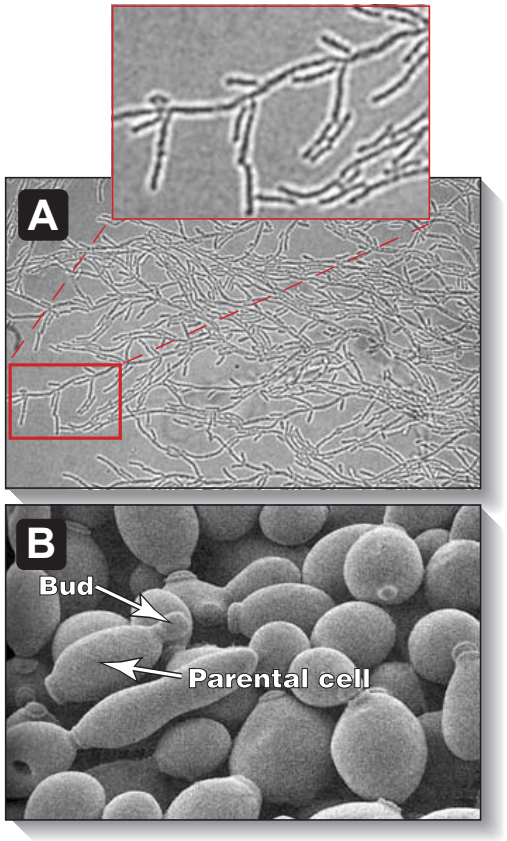

Figure 20.2
A. Filamentous (mold-like) fungi (light micrograph). B. Budding yeast-like fungi (scanning electron micrograph).

A. Cell wall and membrane components

The fungal cell wall and cell membrane are fundamentally different from those of bacteria and other eukaryotes. Fungal cell walls are composed largely of chitin, a polymer of N-acetylglucosamine, rather than peptidoglycan, which is a characteristic component of bacterial cell walls. Fungi are, therefore, unaffected by antibiotics (for example, penicillin) that inhibit peptidoglycan synthesis. The fungal membrane contains ergosterol rather than the cholesterol found in mammalian membranes. These chemical characteristics are useful in targeting chemotherapeutic agents against fungal infections. Many such agents interfere with fungal membrane synthesis or function. For example, amphotericin B and nystatin bind to ergosterol present in fungal cell membranes. There they form pores that disrupt membrane function, resulting in cell death. Imidazole antifungal drugs (clotrimazole, ketoconazole, miconazole) and triazole antifungal agents (fluconazole and itraconazole) interact with the P450 enzyme 14 α-sterol-demethylase to block demethylation of lanosterol to ergosterol. Because ergosterol is a vital component of fungal cell membranes, disruption of its biosynthesis results in cell death.

B. Habitat and nutrition

All fungi are chemoheterotrophs, requiring some preformed organic carbon source for growth. Fungi do not ingest food particles as do organisms such as protozoa (see p. 217) but depend upon transport of soluble nutrients across their cell membranes. To obtain these soluble nutrients, fungi secrete degradative enzymes (for example, cellulases, proteases, nucleases) into their immediate environment, which enable them to live saprophytically on organic waste. Therefore, the natural habitat of almost all fungi is soil or water containing decaying organic matter. Some fungi can be parasitic on living organisms. However, these parasitic infections usually originate from the individual's contact with fungus-contaminated soil, an exception being *Candida*, which is part of the normal human mucosal flora (see p. 7).

C. Modes of fungal growth

Most fungi exist in one of two basic morphologic forms (that is, either as filamentous mold or unicellular yeast). However, some fungi are dimorphic and can switch between these two forms in response to environmental conditions.

1. **Filamentous (mold-like) fungi:** The vegetative body, or thallus, of mold-like fungi is typically a mass of threads with many branches (Figure 20.2A). This mass is called a mycelium, which grows by branching and tip elongation. The threads (hyphae) are actually tubular cells that, in some fungi, are partitioned into segments (septate), whereas, in other fungi, the hyphae are uninterrupted by crosswalls (nonseptate). Even in septate fungi, however, the septae are perforated so that the cytoplasm of the hyphae is continuous. When hyphal filaments become densely packed, the mycelium may have the appearance of a cohesive tissue (for example, as seen in the body of a mushroom).

2. **Yeast-like fungi:** These fungi exist as populations of single, unconnected, spheroid cells, not unlike many bacteria, although they are some 10 times larger than a typical bacterial cell (see Figure 20.2B). Yeast-like fungi generally reproduce by budding.

3. **Dimorphic fungi:** Some fungal species, especially those that cause systemic mycoses, are dimorphic, being yeast-like in one environment and mold-like in another. Conditions that can affect morphology include temperature and carbon dioxide level. Examples of dimorphic fungi include *Blastomyces dermatiditis* and *Histoplasma capsulatum*.

D. Sporulation

Sporulation is the principal means by which fungi reproduce and spread through the environment. Fungal spores are metabolically dormant, protected cells, released by the mycelium in enormous numbers. They can be borne by air or water to new sites, where they germinate and establish colonies. Spores can be generated either asexually or sexually (Figure 20.3).

1. **Asexual sporulation:** Asexual spores (conidia) are formed by mitosis in or on specialized hyphae (conidiophores) as shown in

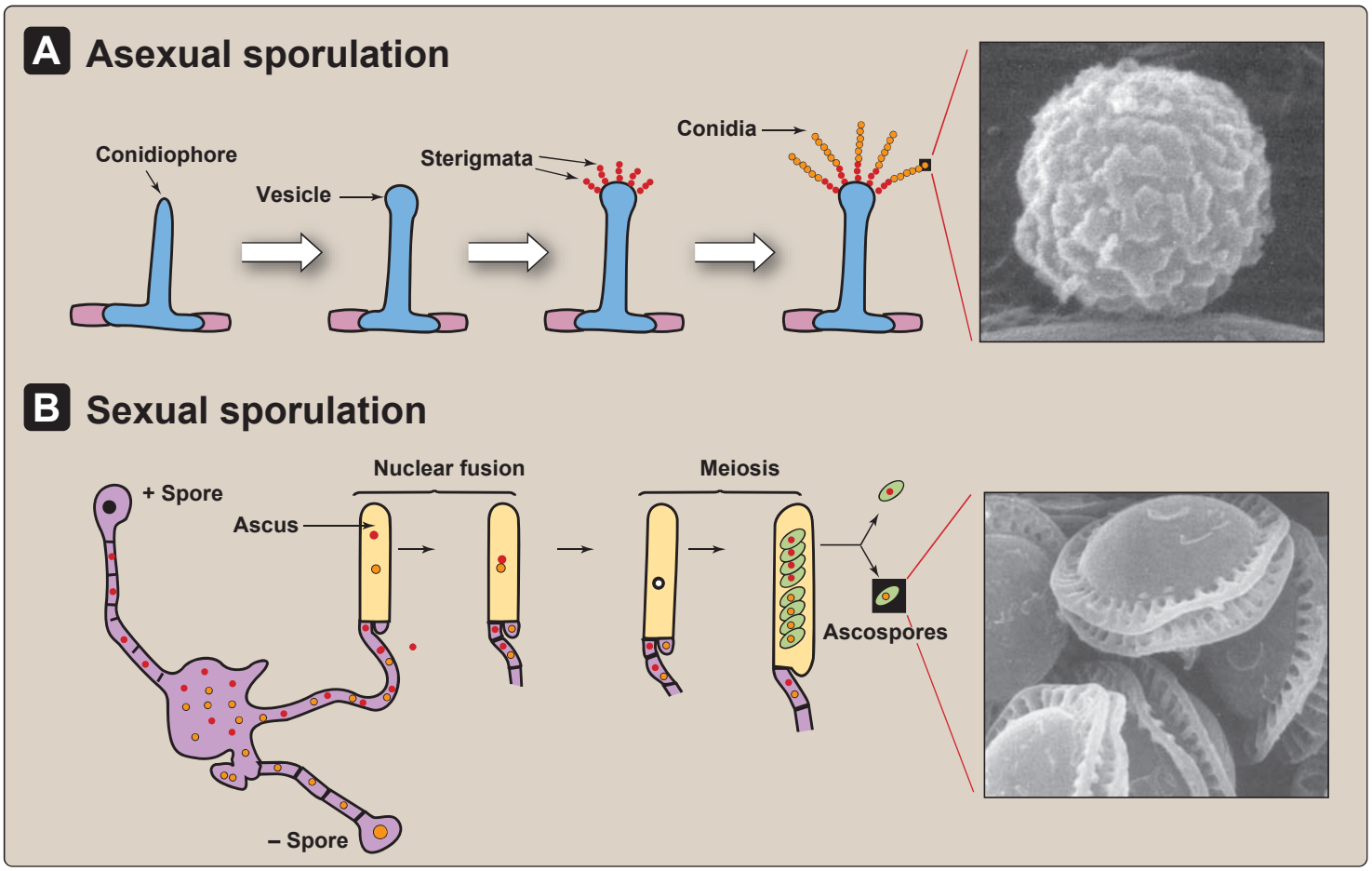

Figure 20.3
Sporulation among *Aspergillus nidulans*. A. Asexual. B. Sexual.

Figure 20.3A. The color of a typical fungal colony seen on bread, fruit, or culture plate is caused by the conidia, which can number tens of millions per cm^3 of surface. Because they are easily detached from their underlying mycelial mats, conidia can become airborne and, therefore, are a major source of fungal infection (see p. 209).

2. **Sexual sporulation:** This process is initiated when a haploid nucleus from each of two compatible strains of the same species fuse to form a transient diploid (see Figure 20.3B). The products of meiosis of this transient diploid become sexual spores (ascospores). Compared to asexual sporulation, sexual sporulation is relatively rare among human fungal pathogens. Spores, especially sexual spores, often have a characteristic shape and surface ornamentation pattern that may serve as the primary or only means of species identification.

E. Laboratory identification

Most fungi can be propagated on any nutrient agar surface. The standard medium is Sabouraud dextrose agar, which, because of its low pH (5.0), inhibits bacterial growth while allowing fungal colonies to form (Figure 20.4). Various antibacterial antibiotics can also be added to the medium to further inhibit bacterial colony formation. Cultures can be started from spores or hyphal fragments. Identification is usually based on the microscopic morphology of conidial structures. Clinical samples may be pus, blood, spinal fluid, sputum, tissue biopsies, or skin scrapings. These specimens can also be rapidly evaluated histologically by direct staining techniques to identify hyphae or yeast forms. Serologic tests and immunofluorescent techniques are also useful in identification of fungi from clinical isolates.

Figure 20.4
Colonies of *Candida albicans* grown on Sabouraud dextrose agar.

III. CUTANEOUS (SUPERFICIAL) MYCOSES

Also called dermatophytoses, these common diseases are caused by a group of related fungi, the dermatophytes. Dermatophytes fall into three genera, each with many species: *Trichophyton*, *Epidermophyton*, and *Microsporum*.

A. Epidemiology

The causative organisms of the dermatophytoses are often distinguished according to their natural habitats: anthropophilic (residing on human skin), zoophilic (residing on the skin of domestic and farm animals), or geophilic (residing in the soil). Most human infections are by anthropophilic and zoophilic organisms. Transmission from human to human or animal to human is by infected skin scales on inanimate objects. Only the pathogenic fungi are capable of human-to-human spread.

B. Pathology

A defining characteristic of the dermatophytes is their ability to use keratin as a source of nutrition. This ability allows them to infect ker-

atinized tissues and structures, such as skin, hair, and nails. There is some specificity, however. Although all three genera attack the skin, *Microsporum* does not infect nails, and *Epidermophyton* does not infect hair. None invades underlying, nonkeratinized tissue.

C. Clinical significance

Dermatophytoses are characterized by itching, scaling skin patches that can become inflamed and weeping. Specific diseases are usually identified according to affected tissue (for example, scalp, pubic area, or feet), but a given disease can be caused by any one of several organisms, and some organisms can cause more than one disease, depending, for example, on the site of infection or condition of the skin. The following are the most commonly encountered dermatophytoses.

1. **Tinea pedis ("athlete's foot"):** Organisms most often isolated from infected tissue are *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum*. The infected tissue is initially between the toes but can spread to the nails, which become yellow and brittle. Skin fissures can lead to secondary bacterial infections with consequent lymph node inflammation (Figure 20.5A).

2. **Tinea corporis ("ringworm"):** Organisms most often isolated are *E. floccosum* and several species of *Trichophyton* and *Microsporum*. Lesions appear as advancing rings with scaly centers (see Figure 20.5B). The periphery of the ring, which is the site of active fungal growth, is usually inflamed and vesiculated. Although any site on the body can be affected, lesions most often occur on nonhairy areas of the trunk.

3. **Tinea capitis ("scalp ringworm"):** Several species of *Trichophyton* and *Microsporum* have been isolated from scalp ringworm lesions, the predominant infecting species depending on the geographic location of the patient. In the United States, for example, the predominant infecting species is *Trichophyton tonsurans*. Disease manifestations range from small, scaling patches, to involvement of the entire scalp with extensive hair loss (see Figure 20.5C). The hair shafts can become invaded by *Microsporum* hyphae, as demonstrated by their green fluorescence in long-wave ultraviolet light (Wood lamp).

4. **Tinea cruris ("jock itch"):** Causative organisms are *E. floccosum* and *T. rubrum*. Disease manifestations are similar to ringworm, except that lesions occur in the moist groin area, where they can spread from the upper thighs to the genitals (see Figure 20.5D).

5. **Tinea unguium (onychomycosis):** The causative organism is most often *T. rubrum*. Nails thicken and become discolored and brittle. Treatment must continue for 3 to 4 months until all infected portions of the nail have grown out and are trimmed off (see Figure 20.5E).

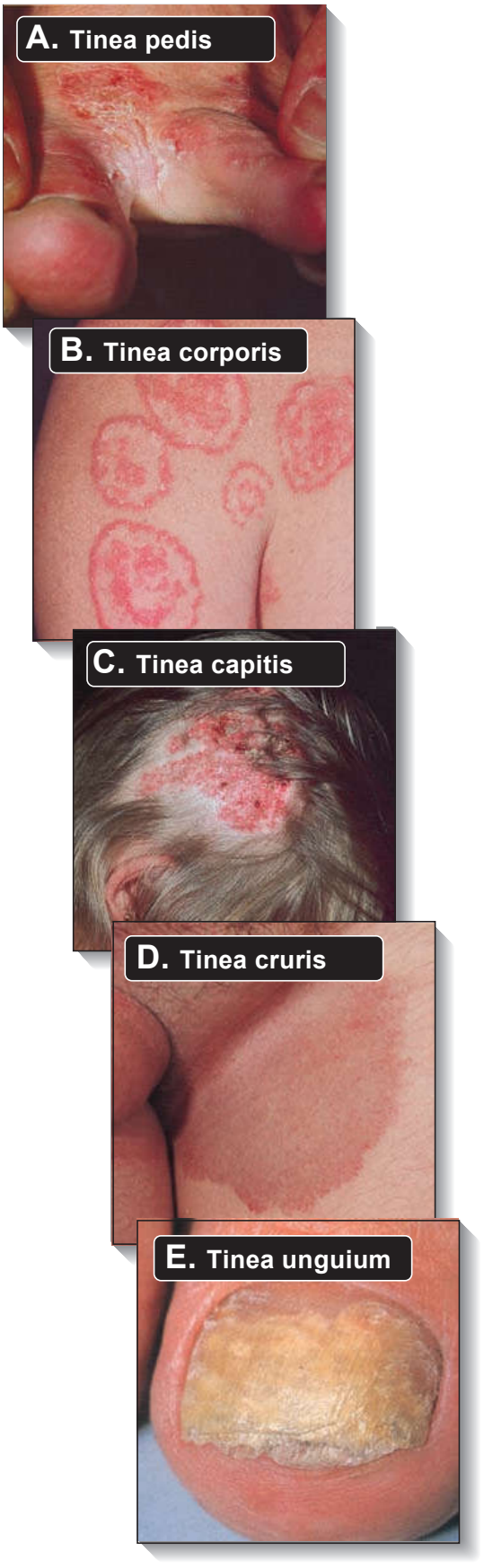

Figure 20.5
Cutaneous mycoses.

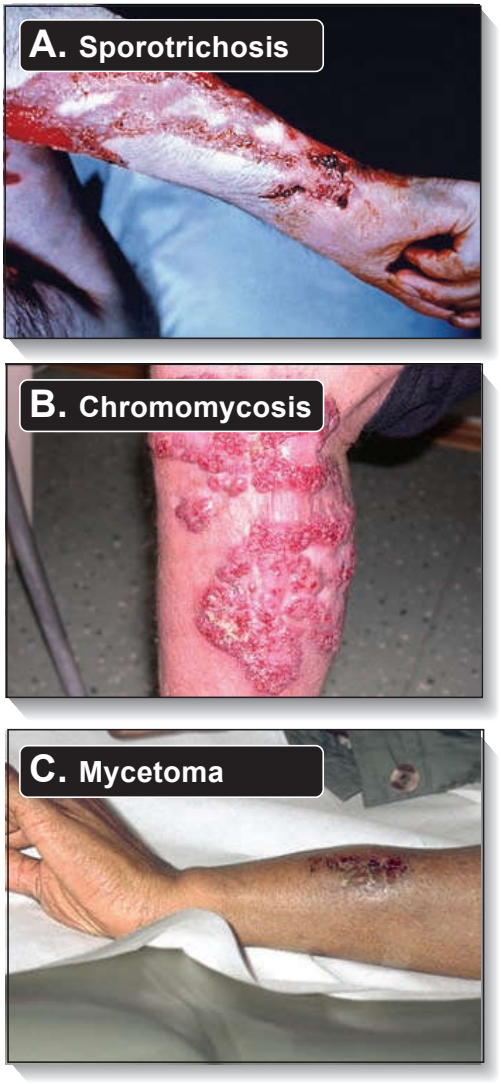

Figure 20.6
Subcutaneous mycoses.
A. Sporotrichosis. The forearm of a gardener exhibiting the cutaneous-lymphatic form of sporotrichosis.
B. Chromomycosis showing multiple plaques on the lower leg.
C. Mycetoma of the arm.

D. Treatment

Removal of infected skin, followed by topical application of antifungal antibiotics, such as miconazole and clotrimazole, is the first course of treatment. Refractory infections usually respond well to oral griseofulvin and itraconazole. Infections of the hair and nails usually require systemic (oral) therapy. Terbinafine is the drug of choice for onychomycosis.

IV. SUBCUTANEOUS MYCOSES

Subcutaneous mycoses are fungal infections of the dermis, subcutaneous tissue, and bone. Causative organisms reside in the soil and decaying or live vegetation.

A. Epidemiology

Subcutaneous fungal infections are almost always acquired through traumatic lacerations or puncture wounds. Sporotrichosis, for example, is often acquired from the prick of a thorn. As expected, these infections are more common in individuals who have frequent contact with soil and vegetation and wear inadequate protective clothing. The subcutaneous mycoses are not transmissible from human to human.

B. Clinical significance

With the rare exception of sporotrichosis, which shows a broad geographic distribution in the United States, the common subcutaneous mycoses discussed below are confined to tropical and subtropical regions.

1. **Sporotrichosis:** This infection, characterized by a granulomatous ulcer at the puncture site, may produce secondary lesions along the draining lymphatics (Figure 20.6A). The causative organism, *Sporothrix schenckii*, is a dimorphic fungus that exhibits the yeast form in infected tissue (see Figure 20.7) and the mycelial form upon laboratory culture. In most patients, the disease is self-limiting but may persist in a chronic form. Dissemination to distant sites is possible in patients with deficiencies in T-cell function (such as in AIDS and lymphomas). Oral itraconazole is the drug of choice.

2. **Chromomycosis:** Also called chromoblastomycosis, this infection is characterized by warty nodules that spread slowly along the lymphatics and develop crusty abscesses (see Figure 20.6B). Pathogens causing this mycosis include several species of pigmented soil fungi (for example, *Phialophora* and *Cladosporium)*, and the infection is most commonly seen in the tropics. Treatment is difficult. Surgical removal of small lesions is effective but must be performed cautiously and with wide margins to prevent dissemination. More advanced stages of the disease are treated with itraconazole and terbinafine.

3. **Mycetoma ("Madura foot"):** Mycetoma appears as a localized abscess, usually on the feet, but is not limited to the lower extremity (see Figure 20.6C). The abscess discharges pus, serum, and blood through sinuses (in this usage, sinus means "abnormal channel"). The infection can spread to the underlying bone and results in crippling deformities . The pathogenic agents are various soil fungi. Most common are *Madurella grisea* and *Exophiala jeanselmei*. Mycetomas appear similar to the lesions of chromomycosis, but the defining characteristic of mycetoma is the presence of colored grains, composed of compacted hyphae, in the exudate. The color of the grains (black, white, red, or yellow) is characteristic of the causative organism and, therefore, useful in identifying the particular pathogen. There is no effective chemotherapy for fungal mycetoma. Treatment is usually surgical excision.

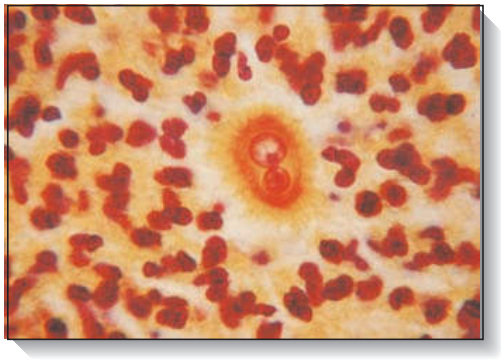

Figure 20.7
Tissue section showing the budding yeast *Sporothrix schenckii.*

V. SYSTEMIC MYCOSES

The organisms responsible for systemic mycoses fall into two general categories: 1) those that infect normal healthy individuals ("true" pathogens) and 2) those that primarily infect debilitated, and/or immunocompromised individuals ("opportunistic pathogens," see p. 385). In the United States, coccidioidomycosis, histoplasmosis, and blastomycosis are the most common systemic mycotic infections in the immunocompetent host. These infections occur in defined geographic areas where fungal pathogens are found in the soil and can be aerosolized. Clinical manifestations closely resemble those seen in tuberculosis in that asymptomatic primary pulmonary infection is common, whereas chronic pulmonary or disseminated infection is rare. The fungi causing these diseases are uniformly dimorphic, exhibiting the yeast form in infected tissue and the mycelial form in culture or in their natural environment.

A. Epidemiology and pathology

Entry into the host is by inhalation of airborne spores, which germinate in the lungs. From the lungs, dissemination can occur to any organ of the body, where the fungi can invade and destroy tissue (Figure 20.8).

B. Clinical significance

In spite of the seemingly grave nature of potentially systemic disease, most cases of coccidioidomycosis, histoplasmosis, and paracoccidioidomycosis in otherwise healthy patients present only mild symptoms and are self-limiting. In immunosuppressed patients, however, the same infections can be life threatening.

1. **Coccidioidomycosis:** Caused by *Coccidioides immitis*, most cases of coccidioidomycosis occur in the arid areas of southwestern United States (Figure 20.9) and Central and South America. Initial infection with *C. immitis* can cause fever with varying degrees of respiratory illness (called "Valley fever" because of its prevalence in the San Joaquin Valley of the southwestern United States). In the soil, the fungus generates spores by septation of

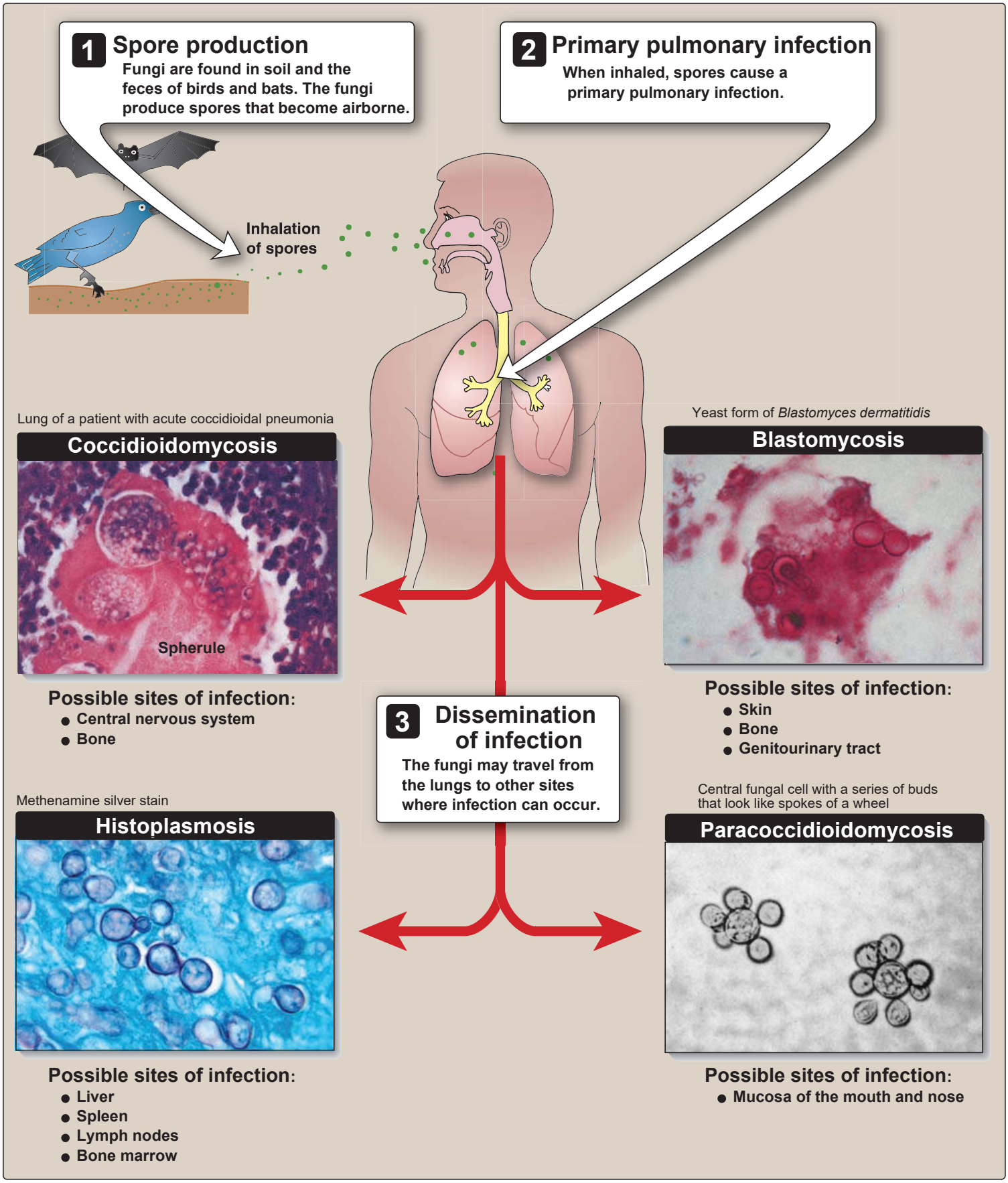

Figure 20.8
Systemic mycoses.

hyphal filaments (arthrospores). These spores become readily airborne and enter the lungs, where they germinate and develop into large (20 to 40 μm) spherules filled with many endospores. Rupture of the spherule releases the endospores, each of which can spread by the bloodstream and then form a new spherule. In cases of disseminated disease, lesions occur most often in the bones and the central nervous system, where they result in meningitis. The spores from the hyphal filaments are easily spread, so cultivation carries a significant risk of accidental infection of laboratory personnel.

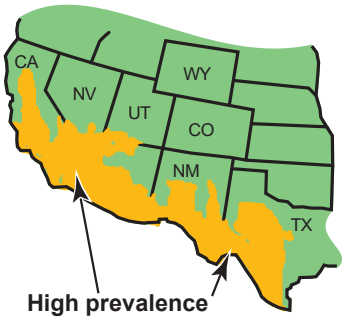

Figure 20.9
Geographic prevalence of coccidioidomycosis in the United States.

2. **Histoplasmosis:** Histoplasmosis is caused by *Histoplasma capsulatum*. In the soil, the fungus generates conidia, which, when airborne, enter the lungs and germinate into yeast-like cells. These yeast cells are engulfed by macrophages, in which they multiply. Pulmonary infections may be acute but relatively benign and self-limiting, or they can be chronic, progressive, and fatal. Dissemination is rare but can occur in older adults, the very young, and patients with deficiencies in T-cell function. Disseminated disease results in invasion of cells of the reticuloendothelial system, which distinguishes this organism as the only fungus to exhibit intracellular parasitism. Definitive diagnosis is by isolation and culture of the organism, which is a slow process (4 to 6 weeks), or by detection of exoantigen in urine specimens. The disease occurs worldwide but is most prevalent in central North America, especially the Ohio and Mississippi River Valleys (Figure 20.10). Soils that are laden with bird, chicken, or bat droppings are a rich source of *H. capsulatum* spores. Local epidemics of the disease can occur, in particular, in areas where construction has disturbed bird, chicken, and bat roosts. AIDS patients who live in or travel through endemic areas are especially at risk. The wide range of clinical manifestations of histoplasmosis makes it a particularly complex disease, often resembling tuberculosis.

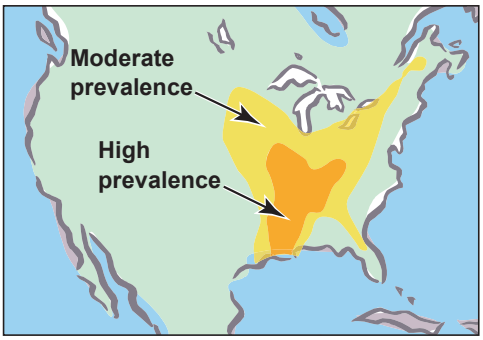

Figure 20.10
Endemic areas of histoplasmosis in North America.

3. **Blastomycosis:** *Blastomyces dermatitidis* causes blastomycosis. Like *Histoplasma,* the fungus produces microconidia, most often in the soil, which become airborne and enter the lungs. There they germinate into thick-walled yeast cells that often appear with unipolar, broad-based buds. Although initial pulmonary infections (Figure 20.11) rarely disseminate to other sites, when dissemination does occur, secondary sites include skin (70 percent), bone (30 percent), and the genitourinary tract (20 percent), where they manifest as ulcerated granulomas. Definitive diagnosis is accomplished by isolation and culture of the organism. Identifiable colonies can be obtained in 1 to 3 weeks, but identity can be established more rapidly by subjecting the young mycelial colonies to an exoantigen test. Infections are most common in the South Central and South Eastern United States and are much more common in adult males than in females or children.

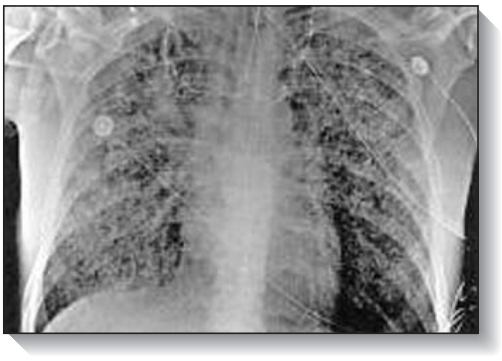

Figure 20.11
Chest radiograph showing a diffuse reticulonodular infiltrate of the lungs in a male landscaper. Bronchoalveolar lavage recovered *Blastomyces dermatitidis*.

4. **Paracoccidioidomycosis**: Also called South American blastomycosis, paracoccidioidomycosis is caused by *Paracoccidioides brasiliensis*. The clinical presentation is much like that of histoplasmosis and blastomycosis except that the most common sec-

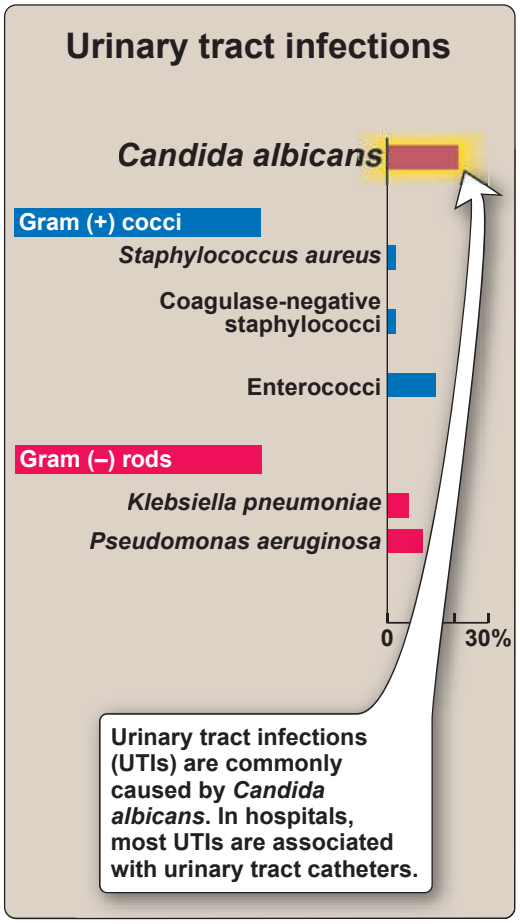

Figure 20.12
Commonly reported pathogens from urinary tract infections in patients in adult medical intensive care units.

ondary site of infection is the mucosa of the mouth and nose, where painful, destructive lesions may develop. Like other dimorphic pathogens, morphologic identification via conidia is slow, but the yeast form observed in infected tissue or exudates has a characteristic appearance resembling a ship's steering wheel, caused by the presence of multiple buds (see Figure 20.8). The disease is restricted to Central and South America, and over 90 percent of patients with symptomatic disease are mature males. It is speculated that estrogen may inhibit formation of the yeast form.

C. Laboratory identification

These diseases are not communicable from one person to another. However, laboratory cultures should be handled cautiously, especially those of *C. immitis*, because, under culture conditions, the fungi revert to the spore-bearing, infectious form. Because these organisms have slow growth rates, morphologic identification of the characteristic conidia can take several weeks. Histological examination of body fluids (sputum, pus, draining fistulas) for the presence of yeasts, hyphae, or conidia allows for rapid identification of the fungal etiological agent prior to the availability of culture results. A rapid method for identifying the four systemic pathogens discussed above is the exoantigen test in which cell-free antigens produced by young mycelial colonies (or liquid cultures) are detected by immunodiffusion assay. The exoantigen test can also be applied to urine specimens collected from patients suffering from histoplasmosis. Polymerase chain reaction is another rapid, accurate diagnostic method that detects specific fungal DNA sequences.

D. Treatment

Systemic mycoses are usually treated with amphotericin B, sometimes in combination with flucytosine. Ketoconazole, fluconazole and intraconazole are also used, depending on the infecting organism and the stage and site of the disease.

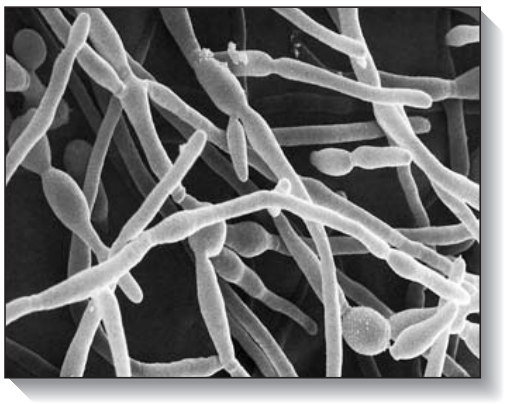

Figure 20.13
Candida albicans.

VI. OPPORTUNISTIC MYCOSES

Opportunistic mycoses afflict debilitated or immunocompromised individuals but are rare in healthy individuals. The use of immunosuppressive drugs for organ transplantation and chemotherapy in cancer treatment, and the high number of immunodeficient individuals caused by the AIDS epidemic have resulted in significant expansion of the immunocompromised population as well as increased spectrum of opportunistic fungal pathogens. Fungal infections represent approximately 15 percent of all nosocomial infections (infections that are a result of treatment in a hospital) in intensive care units in the United States, with *Candida* species being the most commonly occurring fungal nosocomial pathogen (Figure 20.12). The opportunistic mycoses most commonly encountered today include the following.

A. Candidiasis (candidosis)

Candidiasis is caused by the yeast *Candida albicans* and other *Candida* species, which are normal body flora found in the skin, mouth, vagina, and intestines. Although considered a yeast, *C. albicans* is dimorphic and can form a true mycelium (Figure 20.13). Infections occur when competing bacterial flora are eliminated, for example, by antibacterial antibiotics, allowing the yeast to overgrow. *Candida* infections have various manifestations, depending on the site and the degree of immunoincompetence of the patient. For example, oral candidiasis (thrush) presents as raised, white plaques on the oral mucosa, tongue, or gums (Figure 20.14). The plaques can become confluent and ulcerated and spread to the throat. Most HIV-positive individuals eventually develop oral candidiasis, which often spreads to the esophagus. The latter condition is considered an indicator of full-blown AIDS. Vaginal candidiasis presents as itching and burning pain of the vulva and vagina, accompanied by a white discharge. Systemic candidiasis is a potentially life-threatening infection that occurs in debilitated individuals, cancer patients (with neutropenia secondary to chemotherapy), individuals on systemic corticosteroids, and patients treated with broad-spectrum antibiotics, especially those with long intravenous catheters. Systemic candidiasis may involve the gastrointestinal (GI) tract, kidneys, liver, and spleen. Both oral and vaginal infections are treated topically with nystatin or clotrimazole. Depending on the severity and extent of a candidal infection, treatment with an azole drug, such as ketoconazole, fluconazole, and itraconazole, may be given orally or intravenously. Amphotericin B by itself or in combination with flucytosine is used in systemic disease. Echinocandins, such as caspofungin, micafungin and anidulafungin are active against *Aspergillus* and most *Candida*, including those species resistant to azoles.

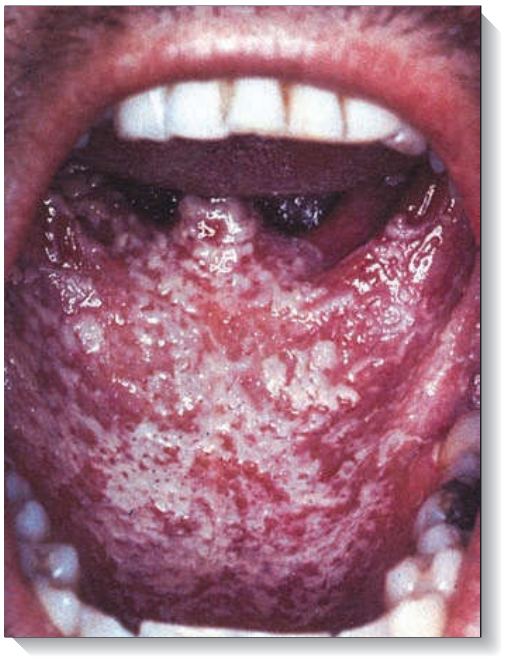

Figure 20.14
Oral candidiasis (thrush).

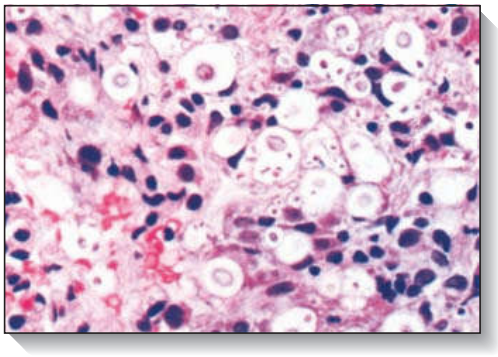

Figure 20.15
Cryptococcus neoformans. [Note: Capsules are visible because they do not take up the hematoxylin and eosin stain].

B. Cryptococcosis

Cryptococcosis is caused by the yeast *Cryptococcus neoformans* (Figure 20.15), which is found worldwide. The organism is especially abundant in soil containing bird (especially pigeon) droppings, although the birds are not infected. The organism has a characteristic polysaccharide capsule that surrounds the budding yeast cell, which is observable on a background of India ink (see Figure 34.26). A positive capsule stain on cerebrospinal fluid can give a quick diagnosis of cryptococcal meningitis, but false negatives are common. A latex agglutination test is also available. The most common form of cryptococcosis is a mild, subclinical lung infection. In immunocompromised patients, the infection often disseminates to the brain and meninges, with fatal consequences. However, about 20% of patients with cryptococcal meningitis have no obvious immunologic defect. In AIDS patients, cryptococcosis is the second most common fungal infection (after candidiasis) and is potentially the most serious. The antifungal drugs used to treat cryptococcosis are amphotericin B and flucytosine, the precise treatment regimen depending on the stage of disease, site of infection, and whether the patient has AIDS. When the CD4 cell count in an AIDS patient falls below 100 cells per μl, cryptococcal infection is so likely that fluconazole is used prophylactically.

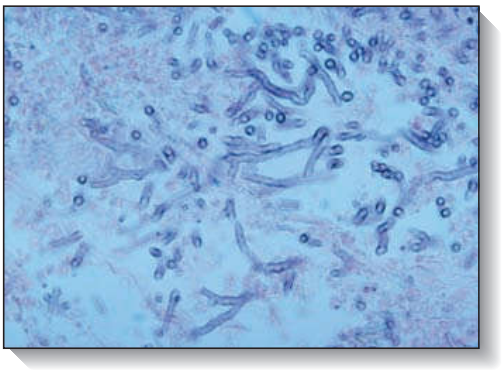

Figure 20.16
Aspergillus species.

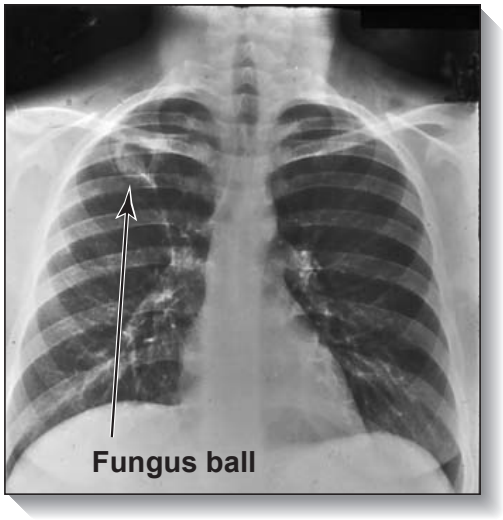

Figure 20.17
Fungus ball.

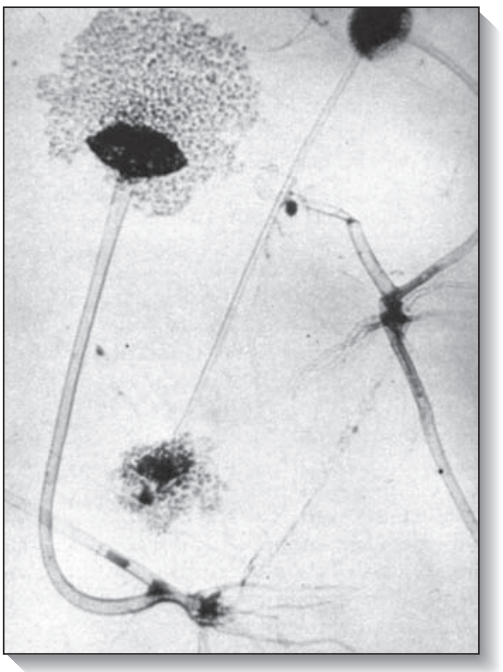

Figure 20.18
Rhizopus oryzae.

C. Aspergillosis

Aspergillosis is caused by several species of the genus *Aspergillus* but primarily by *Aspergillus fumigatus*. *Aspergillus* is rarely pathogenic in the normal host but can produce disease in immunosuppressed individuals and patients treated with broad-spectrum antibiotics. The disease has a worldwide distribution. Aspergilli are ubiquitous, growing only as filamentous molds (Figure 20.16) and producing prodigious numbers of conidiospores. They reside in dust soil, and decomposing organic matter. In fact, hospital outbreaks affecting neutropenic patients (that is, those with decreased neutrophils in their blood) have been traced to dust from neighboring construction work. Aspergillosis manifests itself in several forms, depending in part on the patient's immunologic status.

1. **Acute aspergillus infections:** The most severe, and often fatal, form of aspergillosis is acute invasive infection of the lung, from which the infection can be disseminated to the brain, GI tract, and other organs. A less severe, noninvasive lung infection gives rise to a fungus ball (aspergilloma), a mass of hyphal tissue that can form in lung cavities derived from prior diseases such as tuberculosis (Figure 20.17). Although the lung is the most common primary site of infection, the eye, ear, nasal sinuses, and skin can also be primary sites.

2. **Diagnosis and treatment:** Definitive diagnosis of an aspergillus infection is afforded by detection of hyphal masses and isolation of the organism from clinical samples. *Aspergillus* hyphae characteristically form V-shaped branches (septate hyphae that branch at a 45-degree angle, see Figure 20.16) that are distinguished from *Mucor* species, which form right-angle branches. Also, septa are present in *Aspergillus* hyphae but absent from those of *Mucor*. In culture, the spore-bearing structures of the aspergilli are unmistakable, but, because these organisms are so ubiquitous, external contamination of clinical samples can give false-positives. Treatment of *Aspergillus* infections is typically by amphotericin B and surgical removal of fungal masses or infected tissue. The antifungal drugs miconazole, ketoconazole, and fluconazole have not proven useful, although itraconazole has been used with some effectiveness for *Aspergillus* osteomyelitis.

D. Mucormycosis

Mucormycosis is caused most often by *Rhizopus oryzae* (also called *R. arrhizus*), as shown in Figure 20.18, and less often by other members of the order Mucorales, such as *Absidia corymbifera* and *Rhizomucor pusillus*. Like the aspergilli, these organisms are ubiquitous in nature, and their spores are found in great abundance on rotting fruit and old bread. *Mucor* infections occur worldwide but are almost entirely restricted to individuals with some underlying predisposing condition, such as burns, leukemias, or acidotic states such as diabetes mellitus. The most common form of the disease, which can be fatal within 1 week, is rhinocerebral mucormycosis, in which the infection begins in the nasal mucosa or sinuses and pro-

gresses to the orbits, palate, and brain. Because the disease is so aggressive, many cases are not diagnosed until after death. Treatment is based on high-dose amphotericin B but must be accompanied, when possible, by surgical debridement of necrotic tissue and correction of the underlying predisposing condition. Antifungal drugs other than amphotericin have not proven useful. With early diagnosis and optimal treatment, about half of diabetic patients survive rhinocerebral mucormycosis, but prognosis is very poor for leukemic patients.

E. Pneumocystis jiroveci

Pneumocystis jiroveci pneumonia is caused by a yeast-like fungus called *P. jiroveci* (formerly, *P. carinii*) as shown in Figure 20.19. The disease is still often referred to as PCP, for *P. carinii* pneumonia. Before the use of immunosuppressive drugs and the onset of the AIDS epidemic, infection with this organism was a rare occurrence. It is one of the most common opportunistic diseases of individuals infected with HIV-1 (see Figure 33.10) and almost 100 percent fatal if untreated.

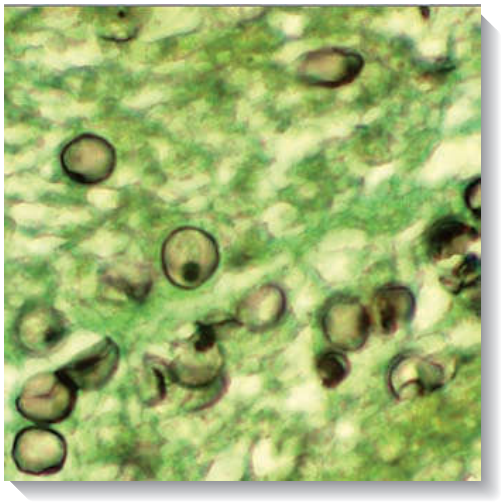

Figure 20.19
Silver stain of *Pneumocystis jiroveci* cysts in tissue from a patient with AIDS.

1. **Classification:** Previously, *P. jiroveci* was considered a protozoan, but recent molecular homology studies of both protein and nucleic acid sequences indicate that *P. jiroveci* is a fungus related to the ascomycetous yeasts. However, ergosterol, which is an essential component of most fungal membranes, is lacking in *P. jiroveci*. It has so far not been possible to cultivate *P. jiroveci in vitro*, limiting understanding of its life cycle.

2. **Pathology:** The infectious form and the natural reservoir of this organism have not been identified, but they must be ubiquitous in nature because almost 100 percent of children worldwide have antipneumocystis antibodies. The disease is not transmitted from person to person. Instead, development of *P. jiroveci* in immunodeficient patients is thought to be by activation of preexisting dormant cells in the lungs. The encysted forms induce inflammation of alveoli, resulting in production of an exudate that blocks gas exchange. Figure 20.20 shows typical radiographic findings in *Pneumocystis* pneumonia.

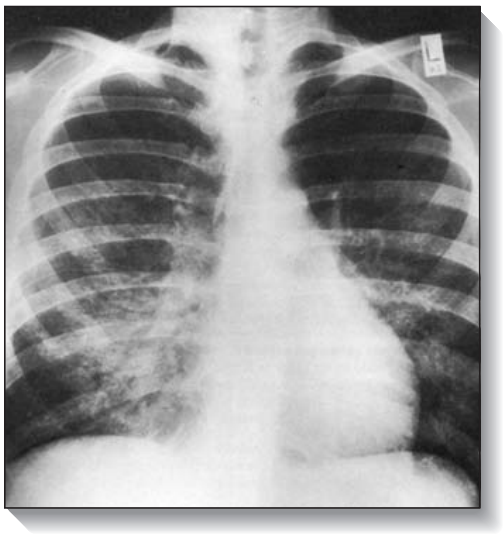

Figure 20.20
Pneumocystis pneumonia.

3. **Diagnosis and treatment:** Because *P. jiroveci* cannot be cultivated, diagnosis is based on microscopic examination of biopsied lung tissue or washings. The most effective therapy is a combination of sulfamethoxazole and trimethoprim, which is also used prophylactically to prevent infection in AIDS patients. Aggressive treatment can spare about half of patients. Because the mechanism of action of many antifungal drugs, such as amphotericin, involves interfering with ergosterol synthesis or function, these drugs are useless for fungi that lack ergosterol.

Study Questions

Choose the ONE correct answer.

20.1 A component of the cell membrane of most fungi is:

A. cholesterol.
B. chitin.
C. ergosterol.
D. peptidoglycan.
E. keratin.

Correct answer = C. Ergosterol in fungi is the functional equivalent of cholesterol in higher organisms. Peptidoglycan is a component of the bacterial cell wall, whereas chitin is a component of the cell wall of fungi. [Note: Chitin also comprises the exoskeletons of insects and crustacea.] Keratin is the major protein of hair and nails

20.2 A physician visiting a rural Latin American village finds that many mature males but few immature males or females of any age are afflicted by a particular fungal disease. What is likely to be the diagnosis?

A. Mycetoma
B. Blastomycosis
C. Paracoccidioidomycosis
D. Mucormycosis
E. Histoplasmosis

Correct answer = C. For some reason, possibly hormonal, this disease favors mature males.

20.3 A fungus that can attack hair is:

A. *Trichophyton*.
B. *Rhizopus*.
C. *Microsporum*.
D. *Sporothrix*.
E. *Epidermophyton*.

Correct answer = C. All attack skin, but only *Microsporum* attacks hair.

20.4 A farmer in Mississippi presents with a chronic cough. Chest radiograph reveals an opaque mass, and biopsy of the lung shows macrophages with multiple yeast forms. Which one of the following diagnoses is most likely?

A. Coccidioidomycosis
B. Histoplasmosis
C. Blastomycosis
D. Paracoccidioidomycosis
E. Sporotrichosis

Correct answer = B. Histoplasmosis is caused by *Histoplasma capsulatum*. In the soil, the fungus generates conidia, which, when airborne, enter the lungs and germinate into yeast-like cells. These yeast cells are engulfed by macrophages, in which they multiply. Pulmonary infections may be acute but relatively benign and self-limiting, or it may be chronic, progressive, and fatal. Dissemination is rare but results in invasion of reticuloendothelial system cells, which distinguishes this organism as the only fungus to exhibit intracellular parasitism. The disease occurs worldwide but is most prevalent in central North America, especially the Ohio and Mississippi River Valleys.

Protozoa

21

I. OVERVIEW

Protozoa are a diverse group of unicellular, eukaryotic organisms. Many have evolved structural features (organelles) that mimic the organs of multicellular organisms. Reproduction is generally by mitotic binary fission, although in some protozoal species, sexual (meiotic) reproduction with several variations occurs as well. Only a few of the many tens of thousands of protozoan species are pathogenic for humans. Those discussed in this chapter are listed in Figure 21.1. These pathogens are of two general kinds: those that parasitize the intestinal and urogenital tracts and those that parasitize blood cells and tissues. Protozoal infections are common in developing tropical and subtropical regions where sanitary conditions and control of the vectors of transmission are poor. However, with increased world travel and immigration, protozoal diseases are no longer confined to specific geographic locales. Because they are eukaryotes, protozoa, like fungi, have metabolic processes closer to those of the human host than to prokaryotic bacterial pathogens. Protozoal diseases are, therefore, less easily treated than bacterial infections because many antiprotozoal drugs are toxic to the human host.

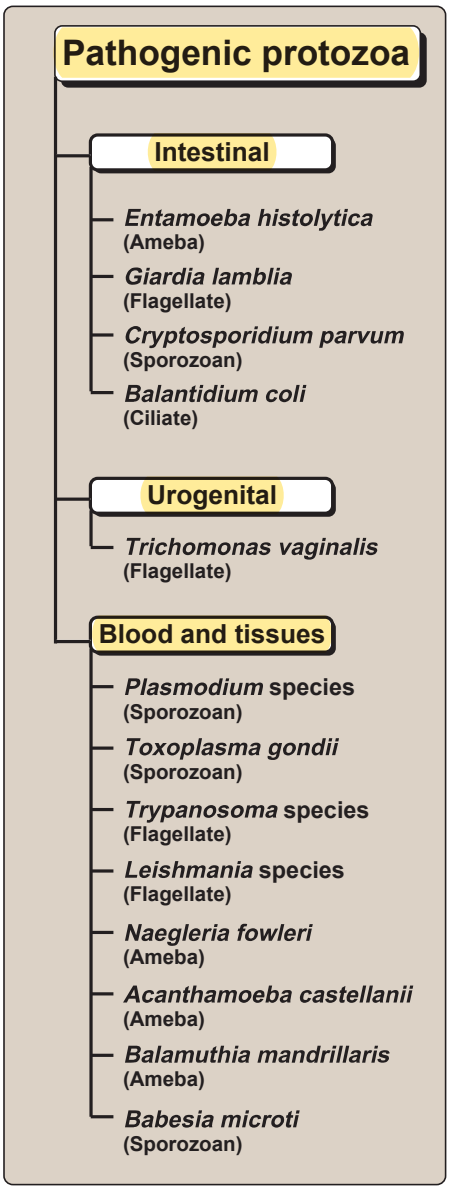

Figure 21.1
Clinically relevant protozoa, classified according to site of infection.

II. CLASSIFICATION OF CLINICALLY IMPORTANT PROTOZOA

Among the pathogenic protozoa, there are important common features that are clinically relevant. For example, many protozoa have both a dormant, immotile cyst stage that permits survival when environmental conditions are hostile and a motile, actively feeding and reproducing, vegetative (trophozoite) stage. For convenience, protozoa are classified according to mode of locomotion. The clinically relevant protozoa are divided into four groups (Figure 21.2).

A. Amebas

Amebas move by extending cytoplasmic projections (pseudopodia) outward from the main cell body. A single cell can have several pseudopodia projecting in the same general direction, with the remainder of the cytoplasm flowing into the pseudopodia. Amebas feed by engulfing food particles with their pseudopodia. Some amebas have flagella as well.

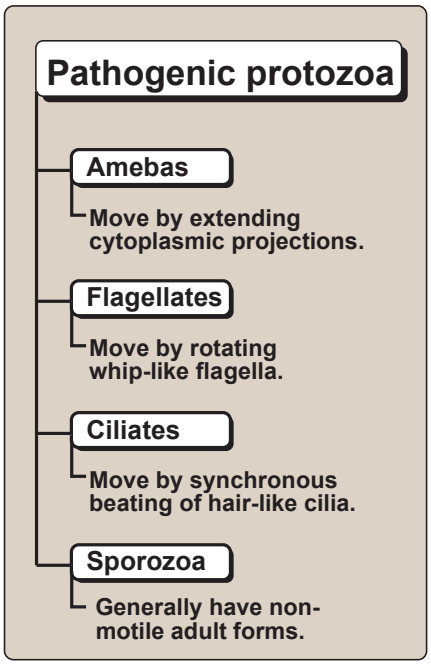

Figure 21.2
The four major protozoal groups, classified according to mode of locomotion.

B. Flagellates

Flagellates move by means of two or more whiplike projections (flagella) that rotate and propel the cells through their liquid environment. Some flagellates, for example *Trichomonas vaginalis*, also have undulating membranes that assist in swimming. Flagellates ingest food particles through an oral groove called a cytostome.

C. Ciliates

Ciliates move by means of many hairlike projections (cilia) arranged in rows that cover the cell surface and beat in synchrony, propelling the cell much like a row boat. Most ciliates have cytostomes that pass food particles through a cytopharynx and finally into vacuoles where digestion takes place. Although there are some 7,000 species of ciliates, only *Balantidium coli* is pathogenic for humans, and the disease, balantidiasis, is rare.

D. Sporozoa

Sporozoans (also called apicomplexa) are obligate, intracellular parasites. Although they generally have nonmotile adult forms, in some species, male gametes have flagella. An example of a sporozoan is *Plasmodium vivax* (see p. 221), which causes malaria. Sporozoans can have complex life cycles with more than one host. The definitive host is that which harbors the sexually reproducing stage, whereas the intermediate host provides the environment in which asexual reproduction occurs.

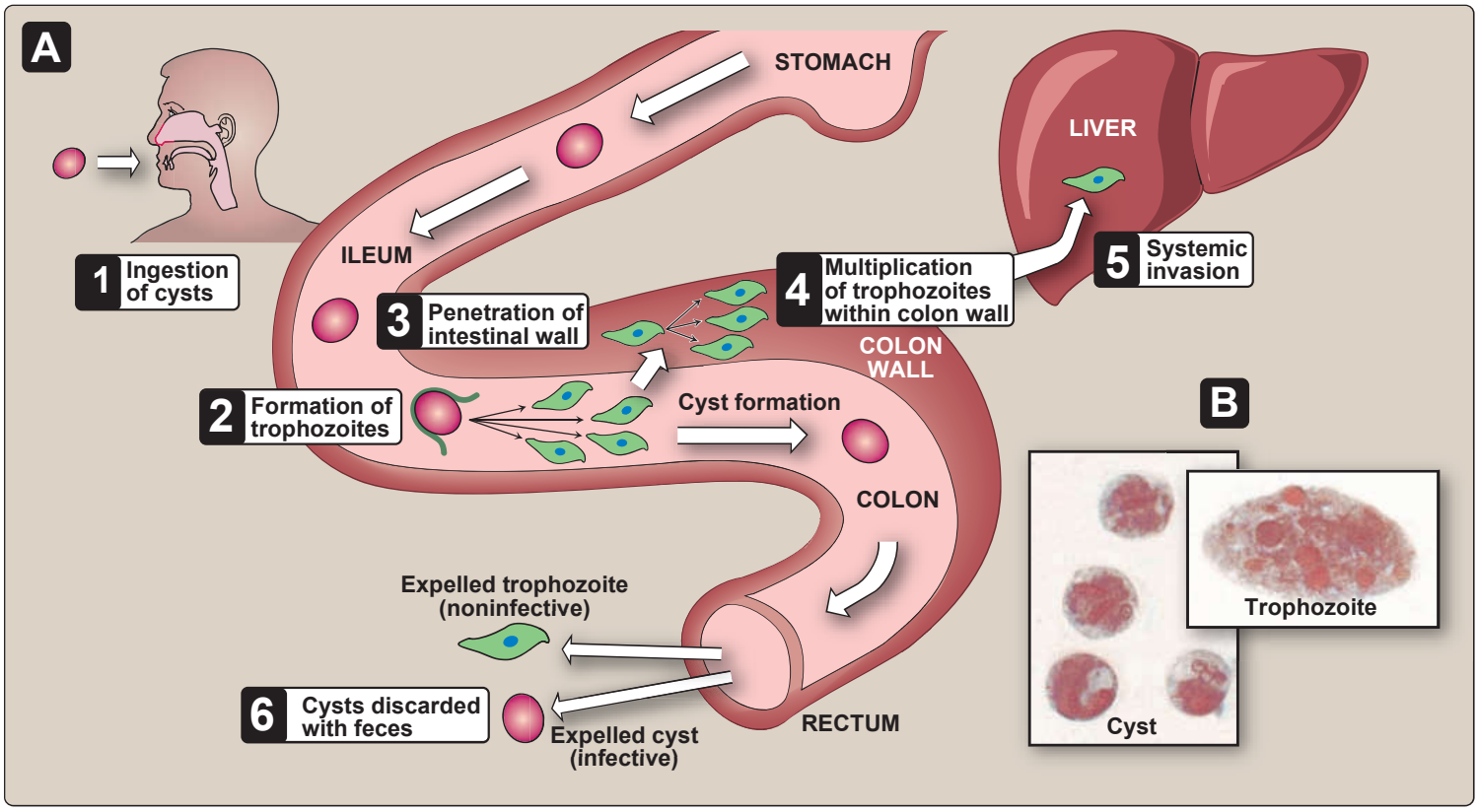

Figure 21.3
A. Life cycle of *Entamoeba histolytica*. B. Photomicrographs of trophozoite and cyst forms.

III. INTESTINAL PROTOZOAL INFECTIONS

There are four principal protozoal intestinal parasites: the ameba, *Entamoeba histolytica*; the flagellate, *Giardia lamblia*; the sporozoan, *Cryptosporidium* (several species); and *Balantidium coli* (the only ciliate protozoan to cause human disease). Each pathogen causes diarrhea, which, although similar, differ in the site of infection, its severity, and secondary consequences.

A. Amebic dysentery (*Entamoeba histolytica*)

Ingested cysts from contaminated food or water form trophozoites in the small intestine (Figure 21.3). These pass to the colon, where they feed on intestinal bacteria, and may invade the epithelium, potentially inducing ulceration. The parasite can further spread to the liver and cause abscesses. In the colon, trophozoites form cysts that pass in the feces. Amebic cysts are resistant to chlorine concentrations used in most water treatment facilities. Diagnosis is made by examination of fecal samples for motile trophozoites or cysts (Figure 21.4). Serologic test kits are useful when microscopic examination is negative. Liver abscesses should be biopsied from the abscess edge where the active amebas accumulate. Mild cases of luminal amebic dysentery are treated with iodoquinol, paromomycin, or diloxanide furoate. More severe cases, including liver infections, are treated with metronidazole (which also has antibacterial activity) in combination with chloroquine and/or diloxamide furoate or emetine. Up to 80% of infections due to *E. histolytica* are asymptomatic. These asymptomatic cyst-passers are a source of infection to others and may not be detected because they are asymptomatic.

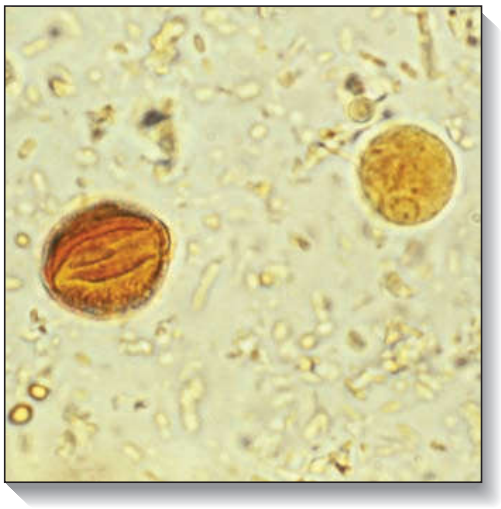

Figure 21.4
Entamoeba histolytica cysts.

B. Giardiasis (*Giardia lamblia*)

Giardiasis is the most commonly diagnosed parasitic intestinal disease in the United States. Similar to *E. histolytica*, *G. lamblia* has two life-cycle stages: the binucleate trophozoite that has four flagella and the drug-resistant, four-nucleate cyst. Ingested cysts form trophozoites in the duodenum, where they attach to the wall but do not invade (Figure 21.5). *Giardia* infections are often clinically mild, although in some individuals, massive infection may damage the duodenal mucosa. Because the *Giardia* parasite preferentially inhabits the duodenum, fecal examination may be negative. A commercial enzyme-linked immunosorbent assay to measure *Giardia* antigen in fecal material has proven useful. Metronidazole is an effective treatment. *G. lamblia* cysts are resistant to chlorine concentrations used in most water treatment facilities, as is true for *E. histolytica*.

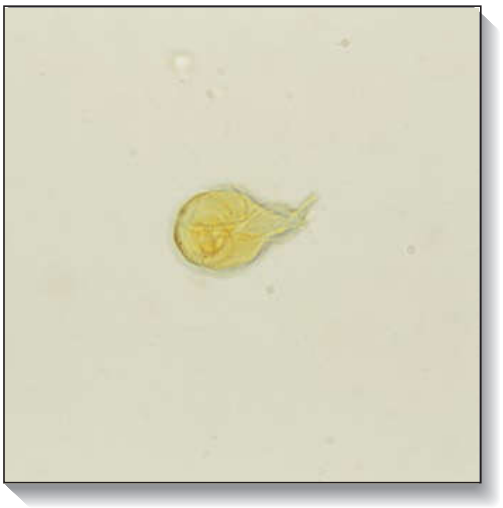

Figure 21.5
Giardia lamblia trophozoite in stool sample.

C. Cryptosporidiosis (*Cryptosporidium* species)

Cryptosporidium is an intracellular parasite that inhabits the epithelial cells of the villi of the lower small intestine. The source of infection is often the feces of domestic animals, and farm run-off has been implicated as a source of *Cryptosporidium* contamination of drinking water. Asymptomatic to mild cases are common, and, if the immune system of the patient is normal, the disease usually

resolves without therapy. However, in immunocompromised individuals (for example, those with AIDS), infection may be severe and intractable, although paromomycin has provided some improvement. Diagnosis is made by acid-fast staining of the tiny (4 to 6 μm) oocysts in fresh stool samples.

D. Balantidiasis (*Balantidium coli*)

Balantidiasis is caused by the ciliate protozoon *B. coli*, which causes dysentery by infecting the large intestine. *B. coli* is locally invasive, causing colonic ulcers. Although these may perforate, leading to peritonitis, it is unlike *E. histolytica* in that it is very rarely associated with spread to distant organs. Manifestations can range from asymptomatic carriage to abdominal discomfort and mild diarrhea to acute dysentery with blood and pus in the stool. The life cycle includes both trophozoite and cyst forms, and identification of either in the stool can be diagnostic. The cysts, which are the infective stage, can be found in contaminated water and are not inactivated by chlorination. Pigs are the natural reservoir of *B. coli*. The infection can be treated with tetracyclines or metronidizole. A summary of intestinal protozoal infections is shown in Figure 21.6.

Entamoeba histolytica

- **Infects colon with secondary infection of liver.**
- **Infected patients pass noninfectious trophozoites as well as infectious cysts in stools.**
- **Diagnosis by presence of characteristic cysts (containing one to four nuclei) in stools.**
- **Therapy: Iodoquinol, metronidazole.**

Giardia lamblia

- **Infection usually results from drinking contaminated water.**
- **Infects duodenum, with incubation time of about 10 days.**
- **Acute infection shows sudden onset with foul smelling, watery diarrhea.**
- **Diagnosis by presence of cysts or trophozoites in stools.**
- **Therapy: Metronidazole.**

Cryptosporidium parvum

- **Infects lower small intestine.**
- **Organisms are intracellular parasites in epithelial cells of intestinal villi.**
- **Diagnosis by modified acid-fast stain of stool sample.**
- **Therapy: Paromomycin (often not effective).**

Balantidium coli

- **Causes dysentery by infecting the large intestine, forming ulcers.**
- **Not invasive.**
- **Diagnosis by presence of cysts or trophozoites in stools.**
- **Therapy: Tetracyclines or metronidazole.**

Figure 21.6
Summary of intestinal protozoal infections.

IV. UROGENITAL TRACT INFECTION: TRICHOMONIASIS

Trichomoniasis is caused by *Trichomonas vaginalis* (Figure 21.7). Trichomoniasis is the most common protozoal urogenital tract infection of humans. The trichomonads are pear-shaped flagellates, with undulating membranes. There is no cyst form in the life cycle of Trichomonas. Several nonpathogenic species, including *Trichomonas tenax* and *Trichomonas hominis*, can be found in the human mouth and intestines, respectively. These species, which are part of the normal flora, are not easily distinguished morphologically from the pathogenic species, *T. vaginalis*. In females, it causes inflammation of the mucosal tissue of the vagina, vulva, and cervix, accompanied by a copious, yellowish, malodorous discharge. Less commonly, it infects the male urethra, prostate, and seminal vesicles, producing a white discharge. The disease is largely sexually transmitted, and both (or all) sexual partners should be treated. Because the optimum pH for growth of this organism is about 6.0, *T. vaginalis* does not thrive in the normal, acidic vagina, which has a pH of about 4.0. Abnormal alkalinity of the vagina, therefore, favors acquisition of the disease. Diagnosis is made by detection of motile trophozoites in vaginal or urethral secretions. If the concentration of parasites is too low to be observed directly, laboratory culture can be used to obtain observable organisms. Effective treatment is afforded by metronidazole. Figure 21.8 summarizes urogenital infections caused by *T. vaginalis.*

V. BLOOD AND TISSUE PROTOZOAL INFECTIONS

The major protozoal diseases that involve the blood and internal organs are malaria (*Plasmodium* species), toxoplasmosis (*Toxoplasma* species), trypanosomiasis (*Trypanosoma* species), and leishmaniasis (*Leishmania* species). *Plasmodium* and *Toxoplasma* are sporozoans (apicomplexa), whereas *Trypanosoma* and *Leishmania* are flagellates,

sometimes referred to as hemoflagellates. Three free-living amebas cause amoebic encephalitis in humans. *Babesia microcoti* causes babesiosis, which is transmitted to humans by the bite of an *Ixodes* tick and results in a red blood cell (RBC) infection, similar to that caused by *Plasmodium* species.

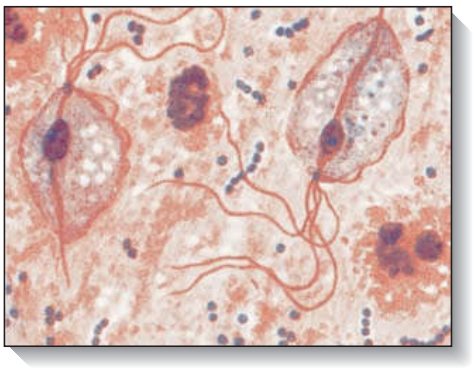

Figure 21.7
Trichomonas vaginalis.

A. Malaria (*Plasmodium falciparum* and other species)

Malaria is an acute infectious disease of the blood, caused by one of five species of the protozoal genus, *Plasmodium*, which is a sporozoan. *P. falciparum* accounts for some 15 percent of all malaria cases, and *P. vivax* for 80 percent of malarial cases. The plasmodial parasite is transmitted to humans through the bite of a female *Anopheles* mosquito or by an infected, blood-contaminated, needle. Sporozoans reproduce asexually in human cells by a process called schizogony, in which multiple nuclear divisions are followed by envelopment of the nuclei by cell walls producing merozoites. These, in turn, become trophozoites. Sexual reproduction occurs in the mosquito, where new spores (sporozoites) are formed. *Plasmodium knowlesi* causes malaria, at least in some parts of Asia. In addition to mosquito bites and blood-contaminate needles, blood transfusion is a potentially important mode of transmission, at least in parts of the world in which screening of bank blood may not be as assiduous as it is in the United States.

1. **Pathology and clinical significance:** Plasmodium sporozoites are injected into the bloodstream, where they rapidly migrate to the liver. There they form cyst-like structures containing thousands of merozoites. Upon release, the merozoites invade RBCs, using hemoglobin as a nutrient. Eventually, the infected RBCs rupture, releasing merozoites that can invade other erythrocytes. If large numbers of RBCs rupture at roughly the same time, a paroxysm (sudden onset) of fever can result from the massive release of toxic substances. A predictable consequence of RBC lysis is anemia, which is typical of *Plasmodium* infections. *P. falciparum* is the most dangerous plasmodial species. It can cause a rapidly fulminating disease, characterized by persistent high fever and orthostatic hypotension. Infection can lead to capillary obstruction and death if treatment is not prompt. *P. malariae*, *P. vivax*, and *P. ovale* cause milder forms of the disease, probably because they invade either young or old red cells, but not both. This is in contrast to *P. falciparum*, which invades cells of all ages. Even today, malarial infection is a common and serious disease and in 2010 is estimated to have caused about 655,000 deaths worldwide. A summary of the life cycle of *Plasmodium* is shown in Figure 21.9.

2. **Diagnosis and treatment:** Diagnosis depends on detection of the parasite inside RBCs (Figure 21.10). Thick blood smears stained with Giemsa stain provide the most sensitive visual test. Thin blood smears, in which more detail can be discerned, are used to determine the species involved, which is important in planning a course of therapy. Serologic tests are usually too slow for diagnosis of acute disease. Drug treatment is determined by the *Plasmodium* species that is causing the infection.

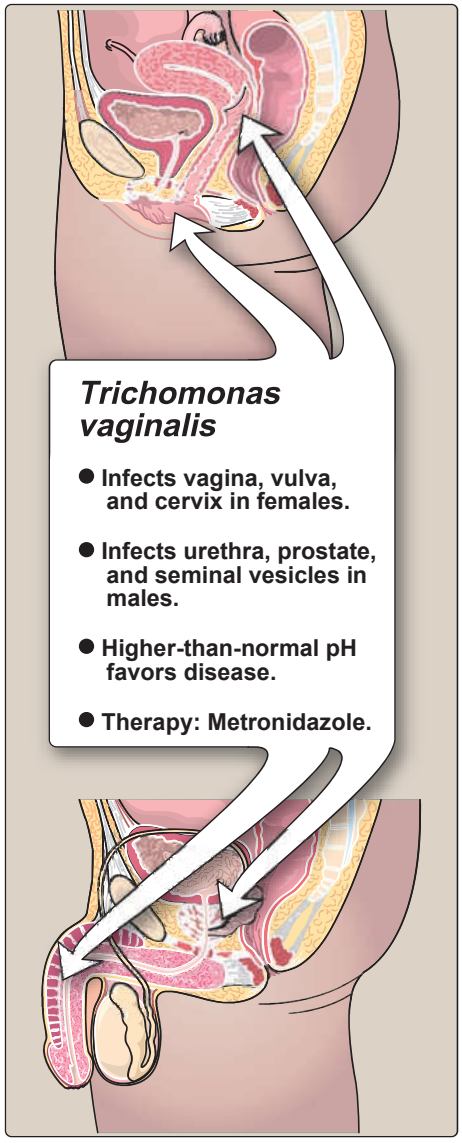

Figure 21.8
Summary of urogenital infection.

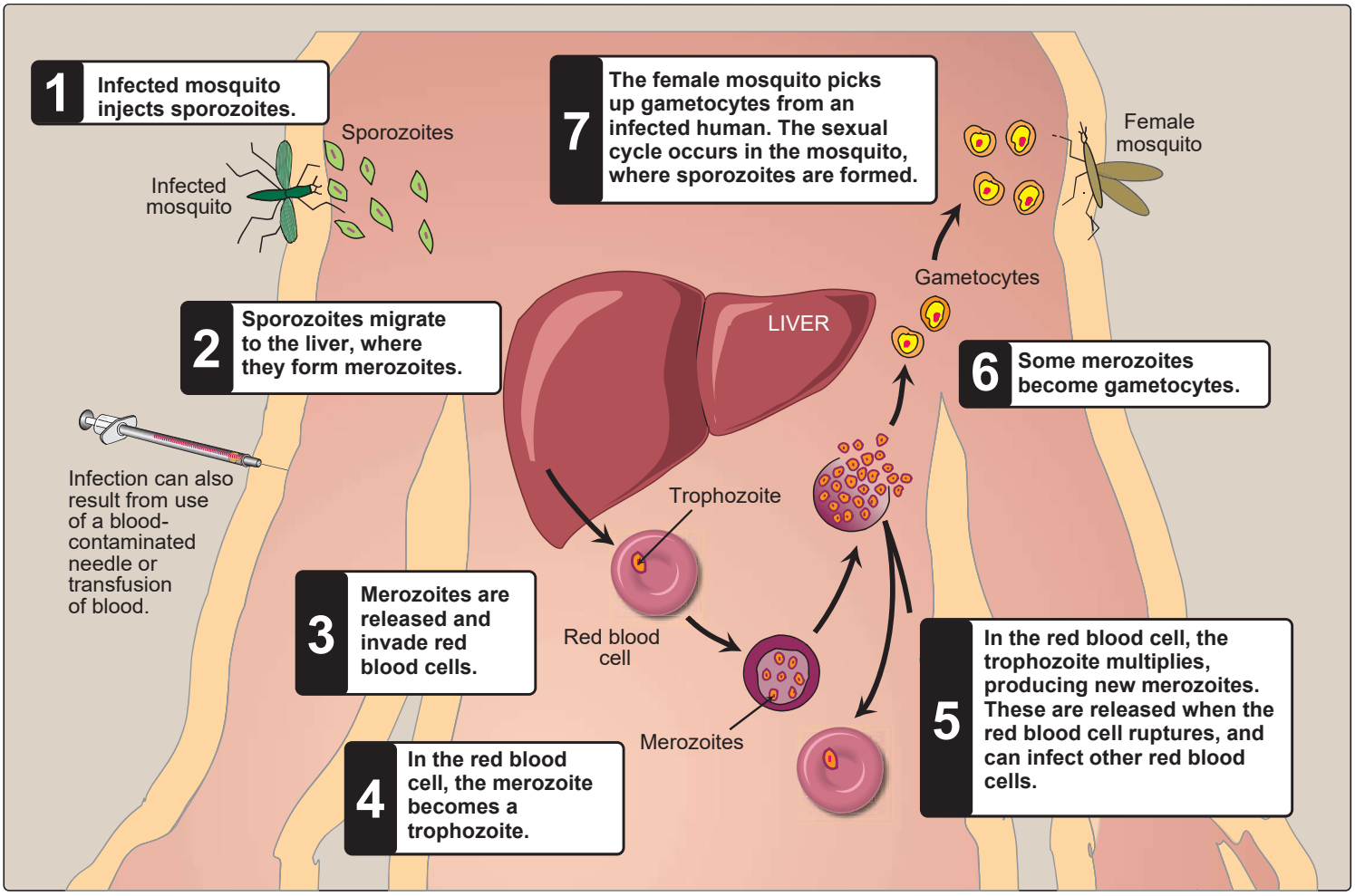

Figure 21.9
Life cycle of the malarial parasite, *Plasmodium falciparum*.

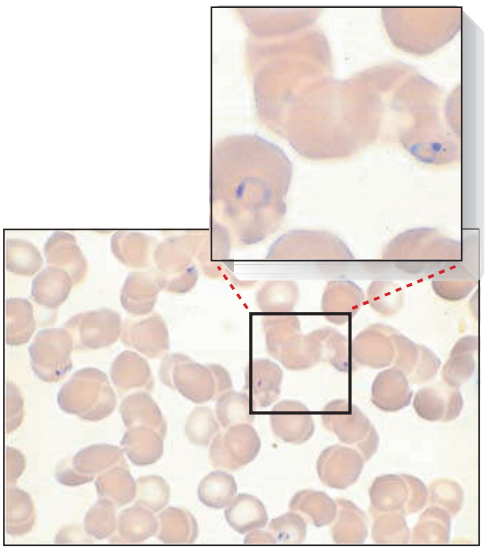

Figure 21.10
Ring form of *Plasmodium falciparum* in red blood cell.

Because *P. falciparum* has no exoerythrocytic phase, it needs only to be treated with quinine, artemisin, mefloquine or doxycycline, depending on resistance patterns in the given geographic location. Chloroquine resistance is so prevalent among *P. falciparum* that it is almost never used for this organism any more. For *ovale* or *vivax* infections, after treatment with chloroquine, a two-week course of primaquine is necessary to achieve a "radical cure" by eliminating exoerythrocytic organisms that persist in the liver. If, in the geographic location of infection, there is chloroquine resistance among *P. vivax* or *P. ovale*, then an alternative drug must be used prior to radical cure. Before treatment with primaquine, patients should be screened for glucose 6-phosphate dehydrogenase deficiency as individuals with deficiency of this enzyme develop hemolytic anemia, sometimes very severe, when treated with primaquine.

B. Toxoplasmosis (*Toxoplasma gondii*)

Toxoplasma gondii is an intracellular sporozoan, distributed worldwide, that infects all vertebrate species, although the definitive host is the cat. Humans can become infected by the accidental ingestion of oocysts present in cat feces, by eating raw or undercooked meat, congenitally from an infected mother, or from a blood transfusion.

1. **Pathology and clinical significance:** There are two kinds of *Toxoplasma* trophozoites found in human infections: rapidly growing tachyzoites ("tachy-" = rapid) that are seen in body fluids in early, acute infections, and slowly growing bradyzoites ("brady-" = slow) that are contained in cysts in muscle and brain tissue and in the eye. Tachyzoites directly destroy cells, particularly parenchymal and reticuloendothelial cells, whereas bradyzoites released from ruptured tissue cysts cause local inflammation with blockage of blood vessels and necrosis. Infections of normal human hosts are common and usually asymptomatic. However, they can be very severe in immunocompromised individuals, who may also suffer recrudescence (relapse) of the infection. Congenital infections can also be severe, resulting in stillbirths, brain lesions, and hydrocephaly, and they are a major cause of blindness in newborns.

2. **Diagnosis and treatment:** The initial diagnostic approach involves detection of parasites in tissue specimens, but this may often be inconclusive. With the recent availability of commercial diagnostic kits, serologic tests to identify toxoplasma are now routinely used. These include tests for *Toxoplasma*-specific immunoglobulin (Ig) G and IgM. The treatment of choice for this infection is the antifolate drug pyrimethamine, given in combination with sulfadiazine. For patients who can not receive sulfa drugs, clindamycin can be added to pyrimethamine.

C. Trypanosomiasis (various trypanosome species)

Trypanosomiasis refers to two chronic, eventually fatal, diseases (African sleeping sickness and American trypanosomiasis) caused by several trypanosome species. Some of the differences between these diseases and the available chemotherapeutic agents are summarized in Figure 21.11.

1. **Pathology and clinical significance:** African sleeping sickness is caused by the closely related flagellates, *Trypanosoma brucei gambiense* or *Trypanosoma brucei rhodesiense* (Figure 21.12). These parasites are injected into humans by the bite of the tsetse fly, producing a primary lesion, or chancre. The organism then spreads to lymphoid tissue and reproduces extracellularly in the blood. Later, the parasite invades the central nervous system (CNS), causing inflammation of the brain and spinal cord, mediated by released toxins. This inflammation produces the characteristic lethargy and, eventually, continuous sleep and death. American trypanosomiasis (Chagas disease), caused by *Trypanosoma cruzi*, occurs in Central and South America. Unlike African forms of the disease, infection is not transmitted by insect bite but rather by insect feces contaminating the conjunctiva or a break in the skin. The first symptom is a granulomatous lesion at the site of entry by the pathogen, followed by an acute disease characterized by fever and hepatosplenomegaly. Subsequently the disease may go into remission but reappear as digestive system problems. Potential, long term complications include cardiomyopathy and megacolon.

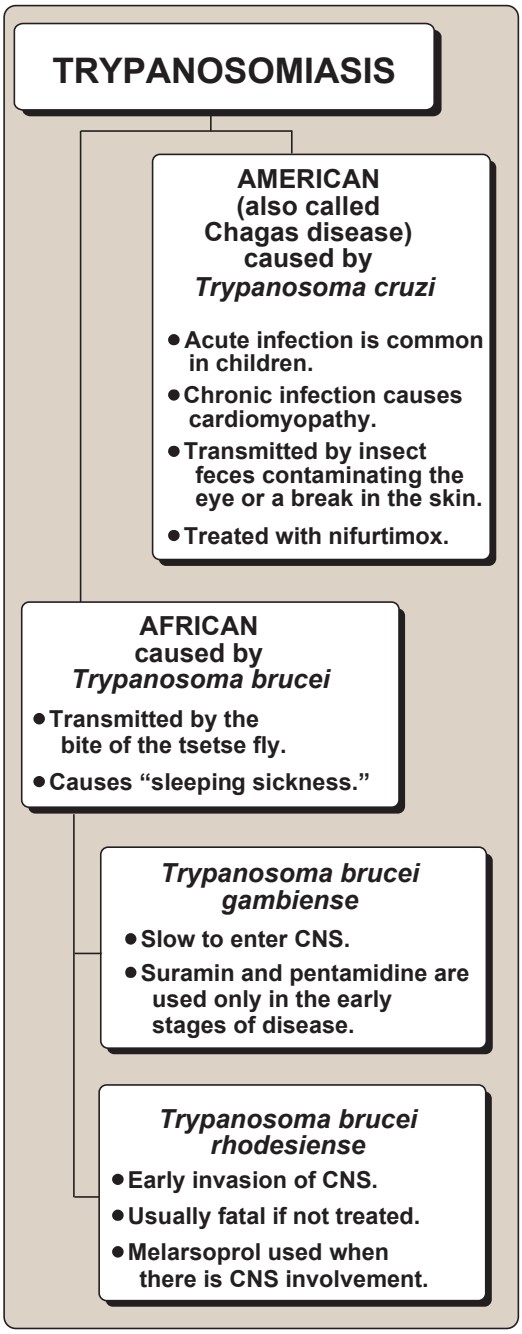

Figure 21.11
Summary of trypanosomiasis. CNS = central nervous system.

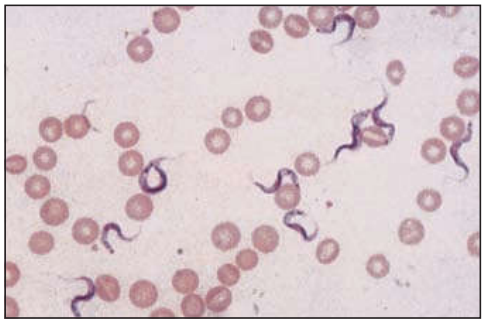

Figure 21.12
Trypanosoma brucei.

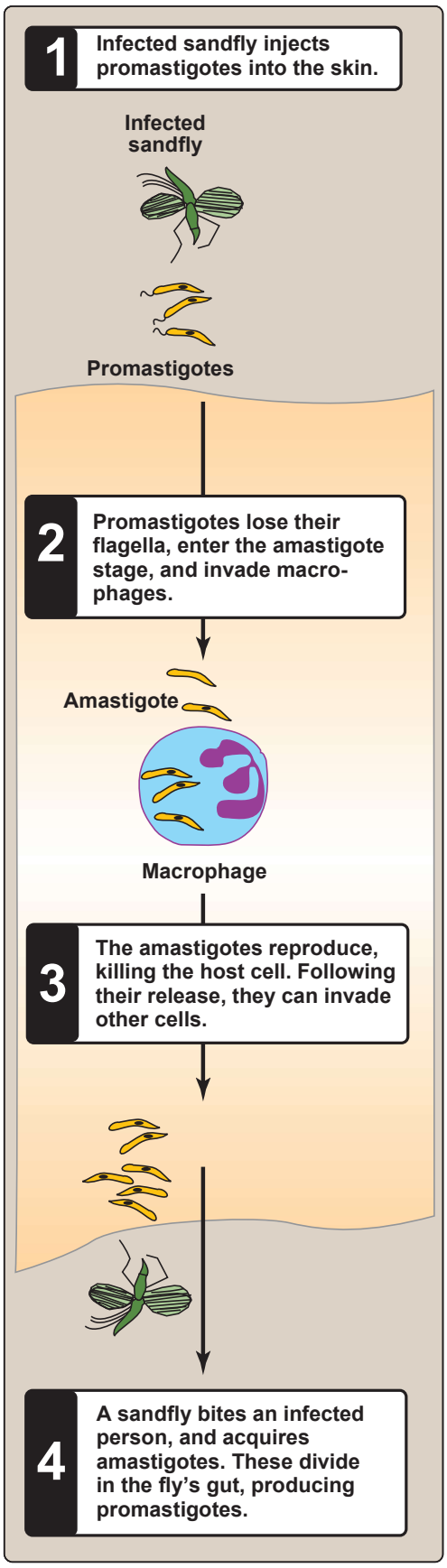

Figure 21.13
Life cycle of *Leishmania*.

2. Diagnosis and treatment: Diagnosis of African trypanosomiasis is made primarily by detection of motile trypanosomes in Giemsa-stained smears of body fluids (for example, blood, cerebrospinal fluid, and lymph node aspirates). Highly specific serologic tests are also available for diagnostic confirmation. Early-stage African trypanosomiasis is treated with suramin or pentamidine. Melarsoprol is used in late-stage disease when the CNS is involved. American trypanosomiasis is treated with nifurtimox, but the drug's effectiveness is limited.

D. Leishmaniasis (various *Leishmania* species)

Leishmaniasis refers to a group of infections caused by the flagellate protozoa of the genus *Leishmania*. About half a million new cases are reported each year, and it is estimated that 12 million people are currently infected with this parasite. There are three clinical types of leishmaniasis: cutaneous, mucocutaneous, and visceral. The various infective organisms are indistinguishable morphologically but can be differentiated biochemically. Two subgenera are recognized (*Leishmania leishmania* and *Leishmania viannia*), each with several species. Any species has the potential to cause one of three clinical manifestations. The natural reservoir of the parasite varies with geography and species but is usually wild rodents, dogs, and humans. Transmission to humans is by the bite of the female sandfly of the genus *Phlebotomus* or *Lutzomyia*. The life cycle of *Leishmania* is shown in Figure 21.13.

1. Cutaneous leishmaniasis (local name, "oriental sore"): This disease is caused by *Leishmania tropica* in North and West Africa, Iran, and Iraq. The cutaneous form of the disease is characterized by ulcerating single or multiple skin sores (Figure 21.14). Most cases spontaneously heal, but the ulcers leave unsightly scars. In Mexico and Guatemala, the cutaneous form is due to *Leishmania mexicana*, which produces single lesions that rapidly heal.

2. Mucocutaneous leishmaniasis (local name, espundia): This disease is caused by *Leishmania viannia brasiliensis* in Central and South America, especially the Amazon regions. In this form of the disease, the parasite attacks tissue at the mucosal-dermal junctions of the nose and mouth, producing multiple lesions. Extensive spreading into mucosal tissue can obliterate the nasal septum and the buccal cavity, ending in death from secondary infection.

3. Visceral leishmaniasis (local name, kala-azar): This disease is caused by *Leishmania donovani* in India, East Africa, and China. In the visceral disease, the parasite initially infects macrophages, which, in turn, migrate to the spleen, liver, and bone marrow, where the parasite rapidly multiplies. Symptoms include intermittent fevers and weight loss. The spleen and liver enlarge, and jaundice may develop. Mortality is nearly 100% within 2 years if the disease is untreated. In some cases, complications resulting from secondary infection and emaciation result in death.

4. Diagnosis and treatment: Diagnosis is made by examination of Giemsa-stained tissue and fluid samples for the nonflagellated

form (amastigote), which is the only form of the organism that occurs in humans and other mammals. Cutaneous and mucocutaneous disease can be diagnosed from tissue samples taken from the edges of lesions or lymph node aspirates. Visceral disease is more difficult to diagnose, requiring liver, spleen, or bone marrow biopsy. Serologic tests (for example, indirect fluorescent antibody, see p. 28, and complement fixation, see p. 26) are used by the Centers for Disease Control and Prevention. The treatment of leishmaniasis is difficult because the available drugs have considerable toxicity and high failure rates. Pentavalent antimonials, such as sodium stibogluconate, are the conventional therapy, with pentamidine and amphotericin B as second-line agents.

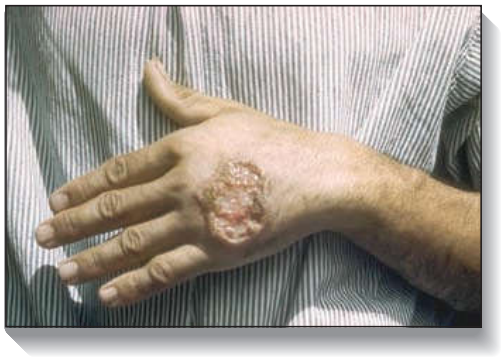

Figure 21.14
Skin ulcer due to leishmaniasis, on the hand of a Central American adult.

E. Amebic encephalitis (*Naegleria fowleri*, *Acanthamoeba castellanii,* and *Balamuthia mandrillaris*)

Several environmental amebae are capable of causing fatal CNS infections in humans. *Naegleria fowleri* can cause primary amebic meningoencephalitis (PAM) in immunocompetent individuals. The ameba exists in one of three morphological forms: flagellate, trophozoite, or cyst. The trophozoite (the infectious form found in fresh water) enters via the nasal cavity, generally infecting swimming children. From the nasal passages, the ameba directly invades the brain by way of the cribriform plate. The pathogen causes necrotic lesions in the brain, and the infection results in death within a few days of symptom onset. Symptoms initially include headache, fever, and nausea. More than 95 percent of cases are fatal, despite appropriate therapy with amphotericin B. *Acanthamoeba* species, also free-living amebas, cause granulomatous amebic encephalitis (GAE), which is not as rapidly progressing as PAM. However, like PAM, GAE is often fatal. *Acanthamoeba* species also cause cutaneous acanthamoebiasis, particularly in immunocompromised individuals. Acanthamoeba keratitis is an infection of the cornea, which is most often seen in contact lens wearers who suffer a traumatic eye injury. The source of the ameba is the contact lens solution, but, in immunocompetent persons, damage to the cornea is a prerequisite to infection. *Balamuthia mandrillaris* is also a free-living ameba capable of causing encephalitis (BAE). Acquisition of the pathogen is thought to be from water or soil with subsequent hematogenous spread to the brain. As with the other amebic encephalitides, infection in both immunocompetent and immunocompromised persons is likely to be fatal. Several cases of BAE were reported in 2010 in recipients of solid organ transplants.

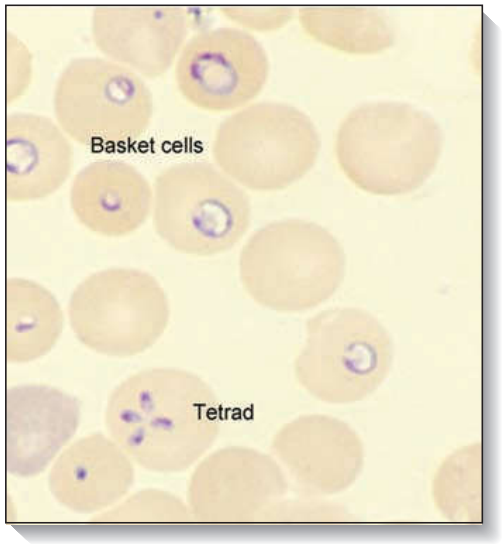

Figure 21.15
Wright-stained peripheral blood smear from a newborn with probable congenital *Babesia microti* infection.The smear shows parasites of variable size and morphologic appearance.

F. Babesiosis (*Babesia microti*)

B. microti is a protozoan transmitted by the bite of an *Ixodes* tick, which is the same arthropod vector that transmits Lyme disease. The reservoirs for both pathogens are small mammals and deer. *Babesia* infects RBCs in the human accidental host, multiplying within these cells and ultimately causing RBC lysis. Similar to *Plasmodium* species, *Babesia* species generate ring-like trophozoites within erythrocytes (Figure 21.15), which are diagnostic. The infection does not spread beyond the erythrocytes, but symptoms are related to loss of RBCs (anemia) and clearance of the cell

debris (hepatosplenomegaly and jaundice).

Study Questions

Choose the ONE correct answer.

21.1 The protozoal trophozoite phase is characterized by:

A. metabolic dormancy.
B. toxin production.
C. active feeding and reproduction.
D. flagellar locomotion.
E. residence in the intermediate host.

Correct answer = C. The trophozoite is, generally speaking, the active phase, in contrast to the cyst, which is the dormant phase. In some species, several varieties of trophozoites are recognized, such as the tachyzoites and bradyzoites of *Toxoplasma gondii*.

21.2 The definitive host of a parasite is the host:

A. in which asexual reproduction occurs.
B. in which sexual reproduction occurs.
C. that is obligatory for the parasite.
D. that is capable of destroying the parasite.
E. that is the vector organism that transports a parasite from an uninfected to an infected host.

Correct answer = B. Sexual reproduction occurs in the definitive host, whereas asexual reproduction occurs in the intermediate host. For example, in the case of malarial *Plasmodium*, the definitive host is the mosquito, and the intermediate host is the human. In most cases, both hosts are obligatory for propagation of the parasite.

21.3 *Plasmodium falciparum*, which causes malaria, is an example of:

A. an ameboid protozoan.
B. a sporozoan.
C. a flagellate.
D. a ciliate.
E. a schizont.

Correct answer = B. The sporozoans are also called apicomplexa because of the presence of a complex of organelles at the cell tip that facilitates penetration of the parasite into host tissue. A schizont is not a taxonomic group but a mass of trophozoites.

21.4 A U.S. businessman who has recently returned home from Haiti suddenly develops a periodic high fever followed by orthostatic hypotension. What is the likely preliminary diagnosis?

A. Chagas disease
B. Giardiasis
C. Syphilis
D. Malaria
E. Toxoplasmosis

Correct answer = D. All of the signs point to malaria, especially the periodicity of the fever that results from synchronous rupturing of large numbers of red blood cells.

21.5 A 22 year old female visits her gynecologist complaining of a foul-smelling vaginal discharge and severe itching. A specimen was collected and examined it by light microscopy revealing highly motile, nucleated cells with multiple flagella. What is the most likely causative agent of this infection?

A. *Balantidium coli*
B. *Plasmodium falciparum*
C. *Toxoplasma gondii*
D. *Giardia lamblia*

Correct answer = E. The symptoms are consistent with the sexually transmitted infection caused by *Trichomonas vaginalis*. This protozoal flagellate is highly motile and easily distinguished from other sexually transmitted disease pathogens by light microscopy. The other protozoal pathogens listed do not cause diseases that present with genitourinary tract symptoms.