the patient on the basis of preference and availability. Fluconazole given orally at 150 mg has the advantage of not requiring repeated intravaginal application. Nystatin is a polyene that has been used for both oropharyngeal thrush and vaginal candidiasis. Useful agents in other classes include ciclopirox olamine, haloprogin, terbinafine, naftifine, tolnaftate, and undecylenic acid.

236 Histoplasmosis

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ETIOLOGY

Histoplasma capsulatum, a thermal dimorphic fungus, is the etiologic agent of histoplasmosis. In most endemic areas, *H. capsulatum* var. *capsulatum* is the causative agent. In Africa, *H. capsulatum* var. *duboisii* also is found; var. *duboisii* can be differentiated from var. *capsulatum* as the *duboisii* yeasts are larger. In Central and South America, histoplasmosis is common and is caused by clades of *H. capsulatum* var. *capsulatum* that differ genetically from those involved elsewhere.

Mycelia—the naturally infectious form of *Histoplasma*—have a characteristic appearance, with microconidial and macroconidial forms. Microconidia are oval and are small enough (2–4 μm) to reach the terminal bronchioles and alveoli. Shortly after infecting the host, mycelia transform into the yeasts that are found inside macrophages and other phagocytes. The yeast forms are characteristically small (2–5 μm), with occasional narrow budding. In the laboratory, mycelia are best grown at room temperature, whereas yeasts are grown at 37°C on enriched media.

EPIDEMIOLOGY

Histoplasmosis is the most prevalent endemic mycosis in North America. Although this fungal disease has been reported throughout the world, its endemicity is particularly notable in certain parts of North, Central, and South America; Africa; and Asia. In Europe, histoplasmosis is diagnosed fairly often, mostly in emigrants from or travelers to endemic areas on other continents. In the United States, the endemic areas spread over the Ohio and Mississippi river valleys. This pattern is related to the humid and acidic nature of the soil in these areas. Soil enriched with bird or bat droppings promotes the growth and sporulation of *Histoplasma.* Disruption of soil containing the organism leads to aerosolization of the microconidia and exposure of humans nearby. Activities associated with high-level exposure include spelunking, excavation, cleaning of chicken coops, demolition and remodeling of old buildings, and cutting of dead trees. Most cases seen outside of highly endemic areas represent imported disease—e.g., cases reported in Europe after travel to the Americas, Africa, or Asia.

PATHOGENESIS AND PATHOLOGY

Infection follows inhalation of microconidia (Fig. 236-1). Once they reach the alveolar spaces, microconidia are rapidly recognized and engulfed by alveolar macrophages. At this point, the microconidia transform into budding yeasts (Fig. 236-2), a process that is integral to the pathogenesis of histoplasmosis and is dependent on the availability of calcium and iron inside the phagocytes. The yeasts are capable of growing and multiplying inside resting macrophages. Neutrophils and then lymphocytes are attracted to the site of infection. Before the development of cellular immunity, yeasts use the phagosomes as a vehicle for translocation to local draining lymph nodes, whence they spread hematogenously throughout the reticuloendothelial system. Adequate cellular immunity develops ~2 weeks after infection. T cells produce interferon γ to assist the macrophages in killing the organism and controlling the progression of disease. Interleukin 12 and tumor necrosis factor α (TNF-α) play an essential role in cellular immunity to *H. capsulatum*. In the immunocompetent host, macrophages, lymphocytes, and epithelial cells eventually organize and form granulomas that contain the organisms. These granulomas typically fibrose and calcify; calcified mediastinal lymph nodes and hepatosplenic calcifications are frequently found in healthy individuals from endemic areas. In immunocompetent hosts, infection with *H. capsulatum* confers some immunity to reinfection. In patients with impaired cellular immunity, the infection is not contained and can disseminate. Progressive disseminated histoplasmosis (PDH) can involve multiple organs, most commonly the bone marrow, spleen, liver (Fig. 236-3), adrenal glands, and mucocutaneous membranes. Unlike latent tuberculosis, latent histoplasmosis rarely reactivates.

Structural lung disease (e.g., emphysema) impairs the clearance of pulmonary histoplasmosis, and chronic pulmonary disease can result. This chronic process is characterized by progressive inflammation, tissue necrosis, and fibrosis mimicking cavitary tuberculosis.

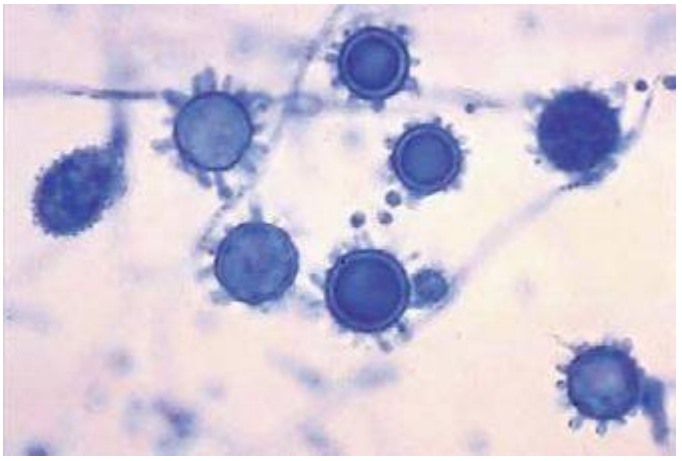

FIGURE 236-1 **Spiked spherical conidia of *H. capsulatum*** (lactophenol cotton blue stain).

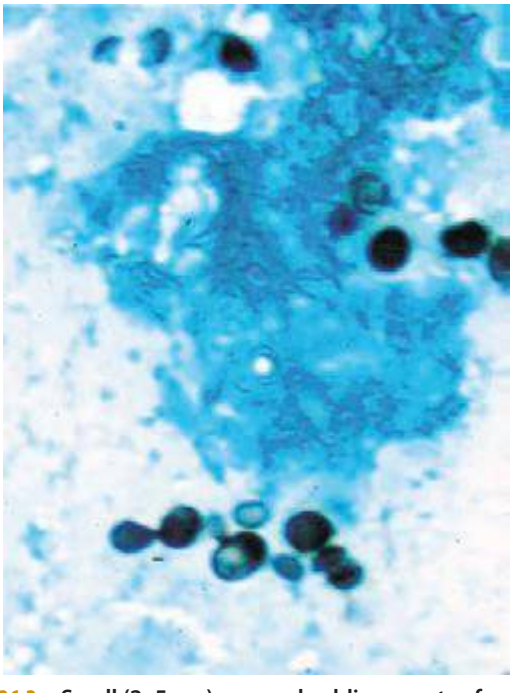

FIGURE 236-2 **Small (2–5 μm) narrow budding yeasts of *H. capsulatum*** from bronchoalveolar lavage fluid (Grocott's methenamine silver stain).