Histoplasma capsulatum is a dimorphic fungus (Figure 46–3B) that grows in the yeast phase in tissue and in cultures incubated at 37°C. The mold phase grows in cultures incubated at 22° to 25°C and as a saprophyte in soil. There are three varieties of Histoplasma (capsulatum, duboisii, farciminosum), which vary in their geographic distribution. The yeast forms are small for fungi (2 to 4 μm) and reproduce by budding (blastoconidia). The mycelia are septate and produce microconidia and macroconidia. The diagnostic structure is termed the tuberculate macroconidium because of its thick wall and radial, finger-like projections (Figure 46–3A). Growth is obtained on blood agar, chocolate agar, and Sabouraud’s agar, but may take many weeks. The designation H capsulatum is actually a misnomer, because no capsules are formed. It comes from the halos seen around the yeasts in tissue sections, which are caused by a shrinkage artifact of routine histologic methods.

Histoplasmosis is limited to the endemic area, where most patients are asymptomatic or show only a fever and cough. If affected persons are seen by a physician, a pulmonary infiltrate and hilar adenopathy may or may not be evident on a radiograph. Progressive cases show extension in the lung or enlargement of lymph nodes, liver, and spleen.
PATHOGENIC FUNGI

EPIDEMIOLOGY

*H. capsulatum* grows in soil under humid climatic conditions, particularly soil containing bird or bat droppings. Inhalation of the mold microconidia, which are small enough (2 to 5 μm) to reach the terminal bronchioles and alveoli, is believed to be the mode of infection. The organism is particularly prevalent in certain temperate, subtropical, and tropical zones, and endemic areas are present in all continents of the world except Antarctica. The largest and best defined is the United States region drained by the Ohio and Mississippi Rivers (Figure 46–4). Over 50% of the residents of states in this area show radiologic evidence of previous infection, and in some locales, up to 90% demonstrate delayed-type hypersensitivity to *Histoplasma* antigens. Disturbances of bird roosts, bat caves, and soil have been associated with point source outbreaks. Persons in endemic areas whose employment (agriculture, construction) or avocation (spelunkers) brings them in contact with these sites are at increased risk. The infection is not transmitted from person to person. Disease is more common in men, but there are no racial or ethnic differences in susceptibility.

PATHOGENESIS

The hallmark of histoplasmosis is infection of the lymph nodes, spleen, bone marrow, and other elements of the reticuloendothelial system with intracellular growth in phagocytic macrophages. The initial infection is pulmonary, through inhalation of infectious conidia, which convert to the yeast form in the host. They attach to integrin and fibronectin receptors and are readily taken up by professional phagocytes. Dendritic cells kill the invading yeast cells, but inside neutrophils and macrophages they survive the effects of the oxidative burst and inhibit phagosome-lysosome fusion. Key features in this survival and multiplication are the ability of *H. capsulatum* to capture iron and calcium from the macrophage and to modulate phagolysosomal pH. The acidic pH required for optimal killing effect in the lysosome is elevated by *H. capsulatum* toward the less effective neutral range (pH 6.0 to 6.5). With continued growth, there is lymphatic spread and development of a primary lesion similar to that seen in tuberculosis. The extent of spread to the reticuloendothelial system within macrophages during primary infection is unknown, but such spread is presumed to occur. Most cases never advance beyond the primary stage, leaving only a calcified node as evidence of infection. As in tuberculosis, viable cells may remain in these old lesions and reactivate later, particularly if the person becomes immunocompromised. Pathologically, granulomatous inflammation with necrosis is prominent in pulmonary lesions, but *H. capsulatum* may be difficult to detect, even with special fungal stains. Extrapulmonary spread involves the reticuloendothelial system, with enlargement of the liver.