2011. Most of that increase has occurred in south-central Arizona, where most of that state's population resides, and in the southern San Joaquin Valley of California, a much less populated region. The factors causing this increase have not been fully elucidated; however, an influx of older individuals without prior coccidioidal infection appears to be involved. Other variables, such as climate change, construction activity, and increased awareness and reporting, may also be factors. Health care providers should consider coccidioidomycosis when evaluating persons with pneumonia who live in or have traveled to endemic areas.

PATHOGENESIS, PATHOLOGY, AND IMMUNE RESPONSE

On agar media and in the soil, *Coccidioides* organisms exist as filamentous molds. Within this mycelial structure, individual filaments (*hyphae*) elongate and branch, some growing upward. Alternating cells within the hyphae degenerate, leaving barrel-shaped viable elements called *arthroconidia*. Measuring ~2 by 5 μm, arthroconidia may become airborne for extended periods. Their small size allows them to evade initial mechanical mucosal defenses and reach deep into the bronchial tree, where infection is initiated in the nonimmune host.

Once in a susceptible host, the arthroconidia enlarge, become rounded, and develop internal septations. The resulting structures, called *spherules* (Fig. 237-1), may attain sizes of 200 μm and are unique to *Coccidioides*. The septations encompass uninuclear elements called *endospores*. Spherules may rupture and release packets of endospores that can themselves develop into spherules, thus propagating infection locally. If returned to artificial media or the soil, the fungus reverts to its mycelial stage.

Clinical observations and data from studies of animals strongly support the critical role of a robust cellular immune response in the host's control of coccidioidomycosis. Necrotizing granulomas containing spherules are typically identified in patients with resolved pulmonary infection. In disseminated disease, granulomas are generally poorly formed or do not develop at all, and a polymorphonuclear leukocyte response occurs frequently. In patients who are asymptomatic or in whom the initial pulmonary infection resolves, delayed-type hypersensitivity to coccidioidal antigens has been routinely documented.

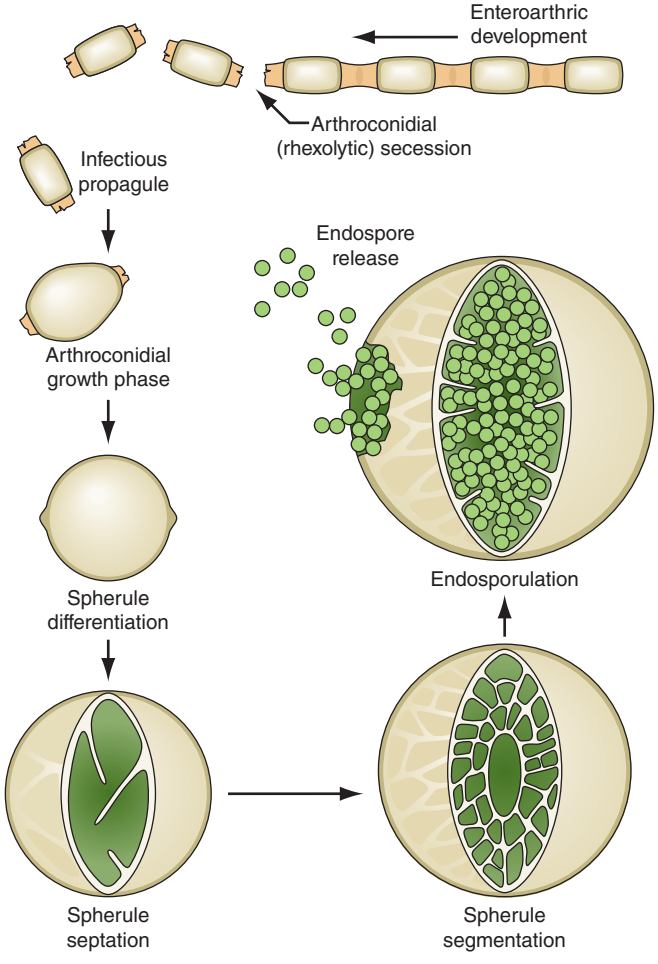

FIGURE 237-1 Life cycle of *Coccidioides*. *(From TN Kirkland, J Fierer: Emerg Infect Dis 2:192, 1996.)*

CLINICAL AND LABORATORY MANIFESTATIONS

Of infected individuals, 60% are completely asymptomatic, and the remaining 40% have symptoms that are related principally to pulmonary infection, including fever, cough, and pleuritic chest pain. The risk of symptomatic illness increases with age. Coccidioidomycosis is commonly misdiagnosed as community-acquired bacterial pneumonia.

There are several cutaneous manifestations of primary pulmonary coccidioidomycosis. Toxic erythema consisting of a maculopapular rash has been noted in some cases. Erythema nodosum (see Fig. 25e-40)—typically over the lower extremities—or erythema multiforme (see Fig. 25e-25)—usually in a necklace distribution—may occur; these manifestations are seen particularly often in women. Arthralgias and arthritis may develop. The diagnosis of primary pulmonary coccidioidomycosis is suggested by a history of night sweats or profound fatigue as well as by peripheral-blood eosinophilia and hilar or mediastinal lymphadenopathy on chest radiography. While pleuritic chest pain is common, pleural effusions occur in fewer than 10% of cases. Such effusions are invariably associated with a pulmonary infiltrate on the same side. The cellular content of these effusions is mononuclear in nature; *Coccidioides* is rarely grown from effusions.

In most patients, primary pulmonary coccidioidomycosis usually resolves without sequelae in weeks. However, several pneumonic complications may arise. Pulmonary nodules are residua of primary pneumonia. Generally single, frequently located in the upper lobes, and ≤4 cm in diameter, nodules are often discovered on a routine chest radiograph in an asymptomatic patient. Calcification is uncommon. Coccidioidal pulmonary nodules can be difficult to distinguish radiographically from pulmonary malignancies. Like malignancies, coccidioidal nodules often enhance on positron emission tomography. However, routine CT often demonstrates multiple nodules in coccidioidomycosis. Biopsy is often required to distinguish between these two conditions.

Pulmonary cavities occur when a nodule extrudes its contents into the bronchus, resulting in a thin-walled shell. These cavities can be associated with persistent cough, hemoptysis, and pleuritic chest pain. Rarely, a cavity may rupture into the pleural space, causing pyopneumothorax. In such cases, patients present with acute dyspnea, and the chest radiograph reveals a collapsed lung with a pleural air-fluid level. Chronic or persistent pulmonary coccidioidomycosis manifests with prolonged symptoms of fever, cough, and weight loss and is radiographically associated with pulmonary scarring, fibrosis, and cavities. It occurs most commonly in patients who already have chronic lung disease due to other etiologies.

In some cases, primary pneumonia presents as a diffuse reticulonodular pulmonary process (detected by plain chest radiography) in association with dyspnea and fever. Primary diffuse coccidioidal pneumonia may occur in settings of intense environmental exposure or profoundly suppressed cellular immunity (e.g., in patients with AIDS), with unrestrained fungal growth that is frequently associated with fungemia.

Clinical dissemination outside the thoracic cavity occurs in fewer than 1% of infected individuals. Dissemination is more likely to occur in male patients, particularly those of African-American or Filipino ancestry, and in persons with depressed cellular immunity, including patients with HIV infection and peripheral-blood CD4+ T cell counts of <250/μL; those receiving chronic glucocorticoid therapy; those with allogeneic solid-organ transplants; and those being treated with tumor necrosis factor α antagonists. Women who acquire infection during the second or third trimester of pregnancy also are at risk for disseminated disease. Common sites for dissemination include the skin, bone, joints, soft tissues, and meninges. Dissemination may follow symptomatic or asymptomatic pulmonary infection and may involve