Conferences and Reviews

Coccidioidomycosis

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Coccidioidomycosis is a systemic fungal infection endemic to the southwestern United States and other parts of the western hemisphere. Although producing a wide range of disorders in healthy persons, immunosuppression predisposes to especially severe disease. Thus, a knowledge of the pathogenesis of coccidioidal infections and its relation to the normal immune responses is useful to understand the diversity of problems that *Coccidioides immitis* may cause. Diagnosis usually requires laboratory studies such as fungal culture or specific serologic testing. Fortunately, many patients do not need to be treated for the infection to resolve. Therapy for the more severe forms of coccidioidal infection was once limited to amphotericin B but now includes azole antifungal agents. These expanded alternatives now require physicians to weigh many factors in determining the best management for specific patients.

(Galgiani JN: Coccidioidomycosis. West J Med 1993; 159:153-171)

About 100 years ago, an Argentinean soldier was reported by a medical intern and his teacher to have lesions resembling mycosis fungoides that contained an organism resembling protozoa.[1] Shortly thereafter, two more cases were recognized by Emmet Rixford, a Stanford surgeon.[2,3] Although Rixford correctly proposed that these unusual infections might have originated in the San Joaquin Valley of California, their true fungal cause was not discovered until later,[4] and the public health dimensions of the infection, currently about 100,000 cases per year, were not appreciated until the 1930s.[5]

Once a distinctly regional disease of the Southwest, coccidioidomycosis is no longer a disease to be comfortably ignored by physicians elsewhere.[6-12] The advancing epidemic of the acquired immunodeficiency syndrome (AIDS) and immunosuppressing medical therapies such as cancer chemotherapy and organ transplantation have made the reactivation of dormant coccidioidal infections increasingly likely in patients throughout the United States. Because such infections are often life-threatening, there is little tolerance for delays in diagnosis if treatment is to be helpful, and therefore more rapid methods for diagnosis, now under development, will be important additions to laboratory testing. In addition, new antifungal agents have become available, and these have increased the options for treatment. Many physicians, especially those who treat only occasional coccidioidal infections, have not had the opportunity to learn the best use for these new agents. Finally, interest in the natural history and pathogenesis of *Coccidioides immitis* is broadening as well, and there is a growing understanding of both diagnostic and T cell-stimulating fungal antigens.

In this review I aim to identify in detail some of these recent developments and integrate them into an overall understanding of the disease. It is hoped this will serve both as a resource for those who need an update on coccidioidomycosis since previous reviews[13-16] and as a stimulus for new work into areas where substantial questions remain.

Epidemiology

The endemic regions for C *immitis* lie exclusively in the western hemisphere and nearly all between the 40-degree latitudes north and south (Table 1). Within the United States, the low deserts of Arizona and the Central Valley of California are the most intensely endemic. Recently an Indian skeleton dated at more than 1,000 years old has been found to have lesions containing spherules and represents the first conclusive evidence of mycotic infection in prehistoric North America.[17] Outside of the United States, endemic regions have been identified in Mexico and areas of both Central and South America. With few exceptions, the regions of endemicity are characterized as the "Lower Sonoran Life Zone."[18] The climate is arid, with a yearly rainfall ranging from 5 to 20 inches, and it has hot summers, winters with few freezes, and alkaline soil.

Within regions endemic for *C immitis*, infection can occur without any specific predisposition. Past estimates of the annual endemic risk of infection have been derived from the prevalence of reactivity among children. In Kern County, California, for example, reactivity in 1939 was 55% in elementary school students and increased to 68% in high school students. By 1964, reactivity in elementary

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CF = complement-fixing [antigen]
CSF = cerebrospinal fluid
HIV = human immunodeficiency virus
IDCF = immunodiffusion complement-fixing
IDTP = immunodiffusion tube precipitin
Ig = immunoglobulin
TP = tube precipitin-reacting [antigen]

school was only 8% and increased to only 24% by high school.[19] This downward trend in rates has been corroborated by recent studies in the Tucson, Arizona, metropolitan area that have suggested that the annual risk is in the range of 2% to 4%.[20-22] Above this ambient risk, occupational dust exposure[23-26] and windstorms[27] have occasionally caused outbreaks.

TABLE 1.—*Geographic Regions Recognized as Endemic for* Coccidioides immitis

Geographic Region or Continent	*Specific Area*
United States	
Arizona	Southern deserts including the cities of Phoenix and Tucson
California	Parts within or near the Central Valley of the counties of Tehama, Butte, Glenn, Yolo, San Joaquin, Alameda, Stanislaus, Merced, Madera, Fresno, San Benito, Tulare, Kings, Monterey, Kern, San Luis Obispo, Los Angeles, Ventura, Riverside, Imperial, and San Bernardino; also the southernmost portion of San Diego County
Nevada	Southernmost tip
New Mexico	Portions of the southern third
Texas	Western portion, including the city of El Paso, and along the western Mexican border
Mexico	Adjacent to the western US border, western portions of the states of Sonora, Nayarit, Jalisco, and Michoacán, and central regions including Coahuila, Durango, and San Luis Potosí
Central America	The republics of Guatemala, Honduras, Nicaragua
South America	Argentina, Paraguay, Venezuela, Colombia, Brazil

In a review of the epidemiologic features of coccidioidomycosis, Pappagianis discusses the seasonal nature of new infections, which appear influenced by many factors including rainfall, sunlight, temperature, and the salt concentration of the soil.[28] How such factors can dramatically change the number of infections has been demonstrated by the record-breaking epidemic occurring in 1991 and 1992.[29] In Kern County alone, the reported number of cases exceeded 1,700 for the three months ending in November 1992,[30] and similar increases have been reported throughout the entire San Joaquin Valley. Neither of the two preceding winters' precipitation had been particularly heavy, a factor that has been associated with higher rates during the following summer.[26] An analysis of the timing of the rainfall has suggested a possible correlation between a greater-than-seasonal precipitation in the months of February and March and increased disease activity (Gavin Welch, Kern County Health Department, written communication, February 1993) (Table 2). Other climatic influences including the drought conditions of the past several years may also have contributed to the epidemic.

TABLE 2.—*Relationship of Annual Number of Reported Cases of Coccidioidomycosis in Kern County, California, for Years in Which February and March Precipitation Exceeded 4.00 inches**

Year	*Rainfall for February and March, inches*	*Reported Cases of* Coccidioides immitis *Infection, No.*
Normal (1982-1990)	1.9	253
1938	4.61	Not available
1978†	6.68	451
1991	4.33	1,181
1992	4.00	3,292

*Source of data: Gavin Welch, Kern County Health Department.
†Includes infections also attributed to winter dust storm (from Pappagianis and Einstein[27]).

Host-Parasite Biologic Processes

Mycology

Coccidioides immitis grows as mycelia in its saprobic form, producing arthroconidia that readily infect the lungs. Within the terminal bronchioles of the lung,[31] an arthroconidium sheds its hyphal outer wall layer and enlarges spherically, forming internal septations that contain endospores.[32-35] When mature spherules rupture, they release endospores in clumps embedded in a glycocalyx, and endospores continue in the spherule phase. If inoculated into saline solution or standard culture media, spherules revert to mycelial growth.[36] Using specialized techniques, spherules can be propagated in vitro,[37-39] and this has been useful for studies of spherule-associated antigens. The usual taxonomic classification based on a sexual phase has not been possible as both the mycelial and spherule phases of growth are asexual. An alternative approach using ribosomal subunit gene DNA homology has been employed to relate *C immitis* to other fungi.[40] In these studies, more than 1,700 bases of the 18S ribosomal gene were sequenced from strains of *C immitis*, five other human fungal pathogens, and four higher fungi. Of 1,565 sequence positions that could be aligned in all 10 taxa, 335 showed at least one substitution, and for *C immitis*, the fewest substitutions occurred in comparisons with *Blastomyces dermatitidis, Histoplasma capsulatum,* and *Trichophyton rubrum.* A tree of genetic relatedness illustrating the predicted evolutionary relationships is given in Figure 1. By this line of analysis, all of these pathogens would be classified as Ascomycetes.[41]

Pathogenesis and Innate Defenses

From studies in mice, only a few arthroconidia administered intranasally are necessary to produce an infection,[42] and it is surmised that most ambient infections of humans occur from only a single spore. Occasionally ex-

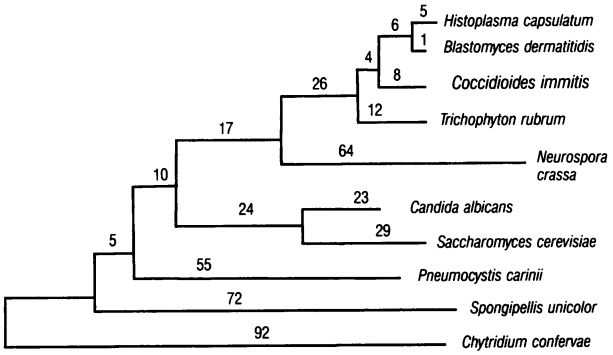


Figure 1.—This "tree" shows the genetic distances among species, based on pairwise substitutions among *Coccidioides immitis* and 9 other fungi. The number on each branch represents the number of DNA substitutions inferred to have been fixed on that branch (redrawn from Bowman et al[40]).

posure can be much more intense, such as during military maneuvers[26,43] or at archeologic excavation sites.[25,44,45] In these circumstances, the likelihood of symptoms and more widespread infection developing seems to be greater. After infection, the incubation period before initial symptoms ranges from one to three weeks.

Pathogenicity appears largely related to spherule resistance to eradication by even normal host defenses and to the inflammatory response that they engender. Fungal extracts can activate complement and attract human neutrophils in vitro.[46,47] These observations are consistent with the histologic finding of accumulated neutrophils, eosinophils, and other evidence of acute inflammation that is often present in portions of coccidioidal lesions.[48] Although measurable inhibition by neutrophils of arthroconidia and immature spherules has been reported, these effects are lost as spherules mature, and neutrophils show virtually no killing of any stage of coccidioidal growth.[36,49,50] The outer hyphal wall layer of arthroconidia may in part be responsible for the resistance to phagocytosis because physically shearing it from arthroconidia makes them more vulnerable to neutrophil ingestion.[51] Moreover, a protease capable of digesting antibodies and perhaps other opsonins has been isolated from spherules, and this might also increase the resistance to fungal attack.[52,53] Finally, the wall itself may provide a substrate to react with a variety of microbicidal intermediates that neutrophils release during the oxidative burst, thus blunting their otherwise lethal effects.[54] In combination, these observations suggest that the acute inflammatory response may slow fungal proliferation, but ultimately it is inadequate to arrest the disease process. Moreover, as new spherules are propagated within the infected tissue, they continue to be a source of acute inflammation, resulting in progressive suppuration and tissue destruction. Spherules of *C immitis* possess no known toxins,[55] nor is tissue infarction by vascular invasion a characteristic of coccidioidomycosis.[56]

Even though neutrophils are incompletely effective in controlling coccidioidal infection, other cellular defenses may play a greater role before antigenic stimulation of immunity. Using human peripheral blood natural killer cells or mononuclear leukocyte fractions enriched for monocytes, killing of endospores and arthroconidia, respectively, has been demonstrated even with leukocytes from patients without previous coccidioidal infection.[57-59] An interesting speculation arising from these observations is the possibility that these cellular defenses might eradicate early infections, conceivably without T-cell help. If this were the case, enhancement of T cell-independent defenses by response modifiers would be a potentially effective means of treating coccidioidal infections in patients with AIDS or others whose T lymphocytes are impaired.

T Cell-Mediated Immunity

A wide variety of studies have established T-lymphocyte immunity to *C immitis* as critical to the normal control of infections. An adoptive transfer of splenic lymphocytes from vaccinated mice protects recipient mice from lethal coccidioidal infections.[60] Cytokines including interferon gamma from such splenic lymphocytes promote macrophage killing of endospores in vitro,[61] and recombinant interferon gamma produces the same effect with murine peritoneal macrophages or human blood monocytes.[62,63] In humans, dermal delayed-type hypersensitivity, peripheral blood lymphocyte transformation, and the elaboration of interferon gamma to coccidioidal antigens are all evidence of T-cell immunity that normally develops after naturally acquired infection but is lacking where infection is progressive.[64-71] As is discussed later, patients with T-cell deficiencies are particularly vulnerable to widespread infections. Unrestricted infections may also occur in some patients who seem to have a selective susceptibility to coccidioidomycosis and do not exhibit generalized anergy.[72]

Despite all of these observations that implicate a T-cell requirement for controlling infection, details about how the T-cell response is regulated are largely unknown. Early studies of the protective effect of killed-spherule vaccines indicated that vaccination does not prevent infection but rather limits its spread.[73] More recently, comparisons of two inbred strains of mice, one sensitive and the other resistant to experimental coccidioidomycosis, indicate that both strains have delayed-type hypersensitivity early after infection. In mice of the sensitive strain, this reactivity is lost in association with increasing fungal antigenemia.[74,75] In other studies, serum containing analogous antigen activity was found to stimulate suppressor cells.[76] Whether similar events occur in humans is not known, although antigenemia and circulating immune complexes have been detected in patients during early and more chronic illness.[77-80] Serum antibodies also develop after infection, are of considerable diagnostic importance (discussed later), and to some extent, differences in the class of antibody response (especially immunoglobulin [Ig] E[81]) have been associated with differences in clinical illness. Even though there is no evidence that antibodies are protective, anti-idiotypic antibodies might be involved in T-cell regulation in coccidioidomycosis, as has been suggested in other diseases.[82]

Coccidioidal antigens used in past studies of T-cell re-

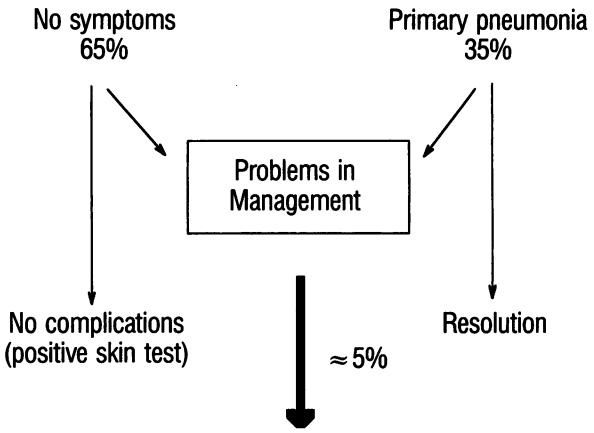
sponses have been complex heterogeneous preparations, and therefore a precise definition of the important antigens is only beginning to be learned. Kirkland and coworkers described a cell-wall antigen mixture from *C immitis* that stimulates a murine T-cell line derived from a mouse immunized with an attenuated strain of *C immitis*.[83] The T-cell line was also stimulated by mycelia-derived coccidioidin but not with exoantigens of spherules or irrelevant antigens. Also, a fusion protein was isolated from a mycelia-derived complementary DNA library that stimulated the T-cell line, and it is anticipated that a primary amino acid sequence will be learned from the continuation of that work. Another antigen has been isolated from the walls of spherules.[84,85] Apparently a glycoprotein in situ, the deglycosylated protein measures 33 kDa and reacts selectively with both antibodies and T lymphocytes from patients who have been infected with *C immitis*. Of additional interest, the expression of this protein is greatest in mature spherules and least in mycelia, a relationship that corresponds closely to differences in the potency of vaccines prepared from spherules or mycelia.[86,87] Work is now underway to learn the full-length sequence and to map regions that are important to both humoral and cellular responses.

Clinical Consequences of Infection

After infection is established, the range of subsequent manifestations is great (Figure 2). It is estimated that about two thirds of patients have no illness or at least have symptoms mild enough that medical attention is not sought. The only evidence of such infections is likely to be a positive coccidioidal skin test. The most common form of infection within the endemic regions is a subacute and usually self-limited pulmonary syndrome. In a few patients, however, the pneumonic process leads to various pulmonary sequelae, and in others, infection produces lesions outside the chest. Although these complications occur in only a small proportion of all infected patients, they are the most common manifestations seen by physicians outside of the endemic areas and may require extensive medical attention. Thus, keys to the appropriate management of patients with coccidioidomycosis are to recognize occurrences that are expected during a normal uncomplicated primary infection and, conversely, to identify as early as possible the cases of unusual or more extensive infection.

Pulmonary Infection

Initial manifestations. The clinical features of primary coccidioidal infection have recently been analyzed in 172 (97 male and 75 female) ambulatory University of Arizona students who were diagnosed during the four years before 1983 and their course compared with descriptions of previous cases.[88] The most frequent symptoms included fatigue (77%) and pulmonary symptoms of cough (64%), chest pain (53%), dyspnea (17%), and hemoptysis (4%). Fever was present in 46% of patients, arthralgia or myalgia was reported in 22%, and 22% had headache. There was a trend for symptoms to be more numerous in



Pulmonary	Extrapulmonary
ARDS	Skin lesions
Nodule	Abscesses
Cavity	Arthritis
Empyema	Osteomyelitis
Progression	Meningitis

Figure 2.—The diagram outlines the clinical spectrum of coccidioidomycosis. ARDS = adult respiratory distress syndrome

men than in women. The most common skin reactions were a diffuse maculopapular evanescent rash (16% in men, 7% in women) and erythema nodosum (3% in men and 23% in women). Erythema multiforme is also well recognized to occur in association with early infection and may be more common in children.[13] Chest radiographs showed associated abnormalities of pneumonia (41%), cavities (8%), or nodules (4%). Pleural effusions were not noted in these patients, but are part of the spectrum of primary infection.[89] Effusions are ipsilateral, and cultures of pleural biopsy specimens usually grow *C immitis*. In addition, hilar adenopathy, usually unilateral and previously commonly noted on chest radiographs,[90-92] was not addressed in this review. The peripheral blood leukocyte count usually was below 10×10^9 per liter (10,000 cells per μl), but eosinophilia (greater than 5% of the total) was noted in 27% of patients. Erythrocyte sedimentation rates were often elevated.

The typical pattern for initial illness is not easily distinguished from various other respiratory tract problems by symptoms or from a routine medical visit. Yozwiak and associates prospectively analyzed students with respiratory complaints for symptoms and routine laboratory abnormalities that were significantly associated with coccidioidal infection.[93] By multivariant analysis, the following six factors appeared to behave independently and were used to construct a probability index for this infection: erythrocyte sedimentation rate above 28 mm per hour, male sex, erythema nodosum, endemic residence of less than four years, duration of symptoms less than one week, and an absolute lymphocyte count of less than 1.6

$\times 10^6$ per liter (1,600 cells per μl) (Figure 3).[93] A small proportion of patients with coccidioidomycosis had all six factors present, and in those cases the scale was specific. For most patients, fewer factors were present, and the risk of infected and noninfected patients overlapped substantially. Thus, in general, diagnosis requires a specific laboratory evaluation, as is discussed in a later section.

Usual clinical course. Of 172 otherwise healthy college students, 161 recovered without therapy, and only 9 had pulmonary complications: slowly resolving pneumonia in 6, persistent cavity in 2, and ruptured cavity in 1.[88] This is also the result for most cases complicated by pleural effusion.[89] Despite this eventual resolution, there was considerable cost and attendant morbidity.[20] Even without specific antifungal therapy for most patients, the cost of medical services for these patients was estimated

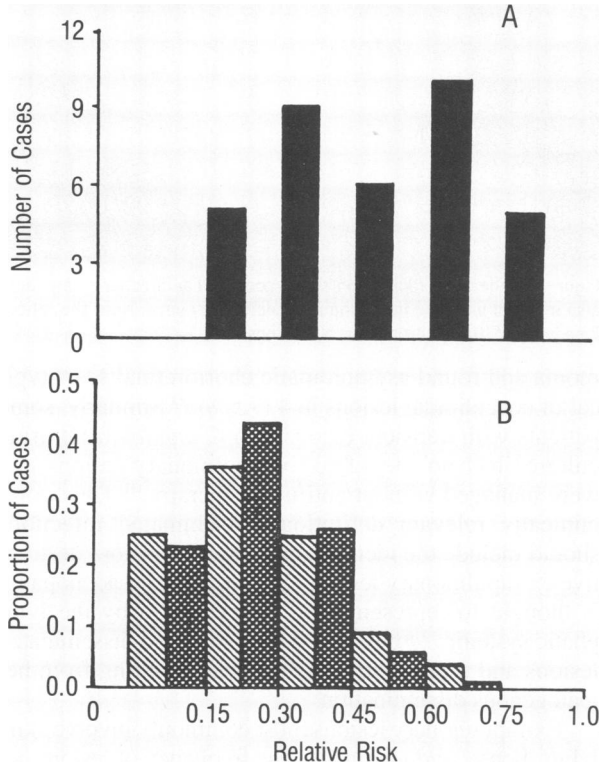


Figure 3.—The graphs show the distributions of the estimated likelihood of coccidioidal infection among 556 patients seeking medical attention for symptoms suggestive of coccidioidomycosis. The relative risk values are based on a standardized scale from 0 to 1 in which 1 represents the highest risk of disease. Graph A represents the relative risk distribution of 36 patients diagnosed with coccidioidomycosis. Graph B represents the relative risk distribution for those in whom the evaluation for coccidioidal infection was negative (hatched bars, n = 269 patients) and for those in whom infection was indeterminate (cross-hatched bars, n = 287 patients) (reprinted from Yozwiak et al,[93] with permission).

to be more than $70,000 (1983 dollars), and a similar cost was incurred in other patients without coccidioidomycosis in whom the diagnosis was entertained. The number of clinic visits required averaged more than six per student, about twice as many as for patients with mononucleosis, and management often extended for several months. Thus, even though the infection typically resolves, management commonly requires considerable attention over a protracted period of time.

Nodules. Coccidioidal pneumonia in about 5% to 7% of patients will evolve to form sharply circumscribed radiodense lesions, usually solitary and less than 6 cm in diameter. In most patients, these lesions are associated with no symptoms, and if a progression from the original coccidioidal pneumonia to the residual nodule is documented, then further evaluation is rarely necessary.

The major difficulty posed by these lesions is their resemblance to carcinoma. In a review of 200 solitary pulmonary nodules surgically resected from patients within the coccidioidal endemic region, 33.5% were found to be malignant.[94] Unfortunately, there are no accurate noninvasive means to exclude cancer. In 86% of persons with benign pulmonary nodules, serum anticoccidioidal antibodies are undetectable. Coccidioidal skin tests are often reactive, but this does not assure that the pulmonary lesion is not a second process. Because many of the lesions are peripheral, bronchoscopic biopsy frequently produces nondiagnostic tissue, and until recently most patients required a thoracotomy to remove the lesion. In reviewing the results from percutaneous fine-needle aspiration in 348 patients from medical centers within Phoenix, Arizona, Forseth and colleagues reported that 101 (29%) lesions yielded either spherules on smear or *C immitis* on culture,[95] thus saving the patient a more invasive procedure. Others have reported similar results.[96]

Cavities. Another possible sequela of the initial coccidioidal pneumonia is the development of a pulmonary cavity.[97,98] This occurs in about 5% of patients, and typical cavities are solitary, thin-walled, and peripheral (Figure 4). Cavitation is unusual in children[99,100] and less frequent in young adults than in older adults. The cavities are commonly asymptomatic, and about 50% will disappear within two years of their occurrence. Some cavities do cause problems, especially if radiographs show a surrounding infiltrate or an air-fluid level. Occasionally coccidioidal mycetoma can develop.[101-105] Common symptoms include cough, constant but relatively scant sputum production, chest pain in the region of the cavity, and hemoptysis. Fever, night sweats, or weight loss may also be present but are less frequent. Although infection occasionally spreads to contiguous segments of the lung, the process usually remains restricted to the original site of involvement. Diabetes mellitus is regarded as a risk for heightened morbidity associated with cavities,[106] but the documentation for this is not conclusive.

Considering the peripheral location of many coccidioidal cavities, rupture into the pleural space is a surprisingly infrequent event and most often develops in otherwise healthy young adults. In a series of 23 patients with this complication,[107] male patients outnumbered female patients 17 to 6, the median age was 24 years, 19 patients were white, and only 2 had diabetes mellitus. Of interest, only 8 patients had known of their infection before rupture. The symptoms are similar to those of a spontaneous pneumothorax, which is often the initial impression, leading to a possible delay in diagnosis. A useful differentiat-

ing point is the presence of an air-fluid level evident on chest radiograph in the pleural space that is typical of a ruptured cavity and unusual for a spontaneous pneumothorax. Once a ruptured cavity is identified, the mainstay of treatment is surgical repair.[107]

Diffuse coccidioidal pneumonia. Diffuse involvement of the lungs most commonly is the result of reticulonodular infiltrates (Figure 5) caused by hematogenous spread of the fungus[108] and is a manifestation of widespread infection. This is almost always a complication that occurs in immunocompromised patients, such as those with lymphoma, organ transplants, or AIDS.[22,109-111] Diffuse pneumonia can also be the result of primary infection developing in many parts of the lung simultaneously. Because ambient exposure within the endemic regions is unlikely to result in a high inoculum exposure, a history of unusually intense exposure rather than immunosuppression is more typical. In some instances, the radiographic differentiation of multicentric primary infections from diffuse reticulonodular infiltrates may be difficult.

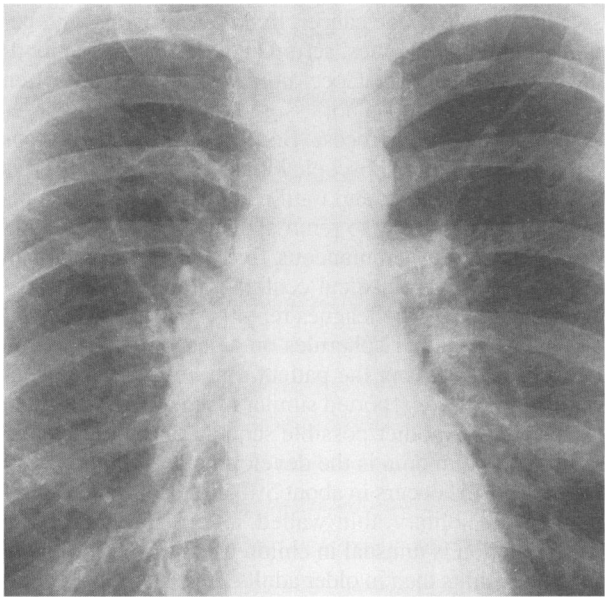


Figure 4.—The chest radiograph is from an otherwise healthy patient with pulmonary coccidioidomycosis. Note the thin-walled cavity in the upper lobe of the right lung.

A few patients have infections that progressively involve greater and greater portions of the lung.[112] Symptoms often persist for years and include weight loss and fever in addition to those directly referable to the chest. Radiographs are characterized by both inflammatory infiltrates and fibrosis, often including bilateral apical cavitation, and these features distinguish this process from the more acute forms of diffuse pulmonary involvement.

Manifestations of Extrapulmonary Lesions

Infections due to *C immitis* outside the chest are almost always the result of hematogenous spread from an initial pulmonary focus. The fungus may spread asymptomatically outside the lungs more frequently than is clinically appreciated. For example, Rodenbiker and coworkers performed full ophthalmologic examinations on 53 patients with previous self-limited coccidioidal pneumonia and found asymptomatic chorioretinal scars typical of coccidioidal lesions in 4 (7.5%).[113] Similarly, some patients with transient recovery of *C immitis* from urine cultures had no identified extrapulmonary lesions and were managed without antifungal therapy.[114] Thus, for a clinically relevant definition, disseminated infections should include the identification of one or more destructive extrapulmonary lesions. Supraclavicular adenopathy is thought to represent thoracic extension by the lymphatic system,[115,116] but should be considered disseminated lesions and treated similarly to those resulting from hematogenous dissemination.

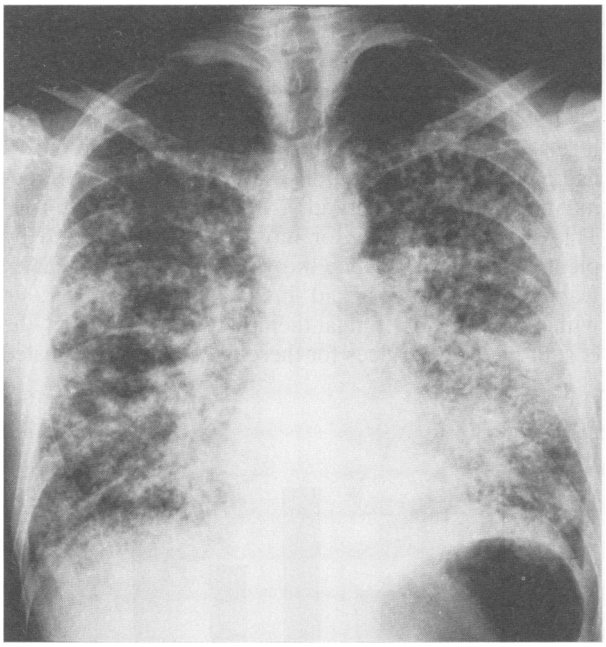


Figure 5.—The chest radiograph shows coccidioidal infection in a patient also infected with the human immunodeficiency virus. Note the reticulonodular infiltrates throughout both lungs.

Extrapulmonary lesions most commonly involve skin, joints, bones, and meninges. The frequency of lesions occurring in these various anatomic locations has been estimated in the past,[56,117] but many of the cases were identified because they were fatal, and it is possible that the record of disseminated infection is distorted as a result. A set of several hundred clinical case records was collected by an Armed Forces-Veterans Administration collaboration in the 1950s, before the availability of effective antifungal therapy, but a description of this group of patients has only recently been undertaken.[118] It is hoped that continued analysis of these records will provide a more quantitative picture of the various manifestations of disseminated infection.

Nonmeningeal sites of dissemination. The skin is the most common site of extrathoracic spread. Although cutaneous infections may occur anywhere, they often develop on the face (Figure 6). Papules and verrucous le-

sions are typical, but superficial plaques or subcutaneous abscesses also occur.[119] Symptoms associated with these lesions are often minor and evidence of acute inflammation on examination only slight. The histopathologic features of these varied lesions range from necrosis to granulomatous reactions and satellite lesions.[120] Skin biopsy of these lesions usually yields *C immitis* in culture, although finding spherules microscopically may be more difficult.

Bones and joints are also frequent sites of dissemination. Knee infection is common, often being a pure synovitis without evidence of bone involvement. In other cases, joint infections are more likely to have contiguous osteolytic lesions seen on x-ray films, most frequently involving vertebrae, wrists, hands, ankles, feet, pelvis, and long bones, in that order.[121,122]

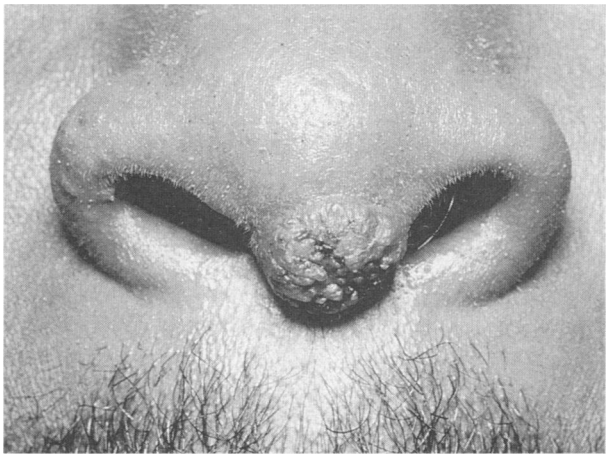


Figure 6.—A skin lesion is shown on a patient with disseminated coccidioidomycosis.

In addition to skin and skeletal infections, lesions can occur anywhere throughout the body. For example, recent reports have focused on infections of the sella turcica,[123] the eye,[124] the larynx,[125-127] the external ear,[128,129] the thyroid,[130] the peritoneum,[131,132] prosthetic grafts of the femoral artery,[133] the placenta during pregnancy,[134] the female genital tract,[135,136] intestinal tract,[137] the liver,[138,139] urinary bladder,[140] and other urologic sites.[141-143]

Meningitis. A recent review of the natural history of coccidioidal meningitis has focused on the clinical course of 25 patients with meningitis that was diagnosed before the availability of antifungal therapy.[118] In that analysis, the most common symptoms of central nervous system involvement were headache (76%), vomiting (32%), nuchal rigidity (26%), confusion (8%), and diplopia (8%). The chance that meningitis occurred as the sole site of dissemination or as one of numerous sites was about equal. Patients with multisite dissemination had a median survival of 2 months whereas those whose dissemination involved solely the meninges had a median survival of 11 months. This confirms earlier reports that coccidioidal meningitis is nearly always lethal in two years.[144-148] In addition, other reports have identified a few patients in whom signs of cerebral or spinal vasculitis develop.[149,150]

Initial cerebrospinal fluid (CSF) findings included leukocyte counts ranging from 98 to 1,250 $\times$ 10^6 cells per liter (98 to 1,250 cells per μl), and about two thirds of the cells were mononuclear. In a recent review it was noted that 70% of patients also have CSF eosinophilia (>10 $\times$ 10^6 cells per liter or >0.10 eosinophils).[151] An unexpected finding from this study was that CSF pleocytosis tended to fall over time. Although an explanation for this pattern is not certain, the decrease could result from fibrosis encapsulating the foci of inflammation. Other CSF findings included protein concentrations ranging from 0.61 to 2.52 grams per liter (61 to 252 mg per dl) and glucose concentrations ranging from 0.5 to 4.1 mmol per liter (9 to 74 mg per dl).

Hydrocephalus is a common complication of coccidioidal meningitis, and in children it is usually present at the time of diagnosis.[152] Although the presence of dilated lateral ventricles and other findings by computed tomographic scanning have been adequate for detecting this problem, magnetic resonance imaging has been necessary to evaluate the aqueduct of Sylvius for patency.[153] Often hydrocephalus is a communicating type, as shown in Figure 7. In such cases a lumboperitoneal shunt is feasible and may offer some advantages over a ventriculoperitoneal shunt, which was most commonly installed in the past.

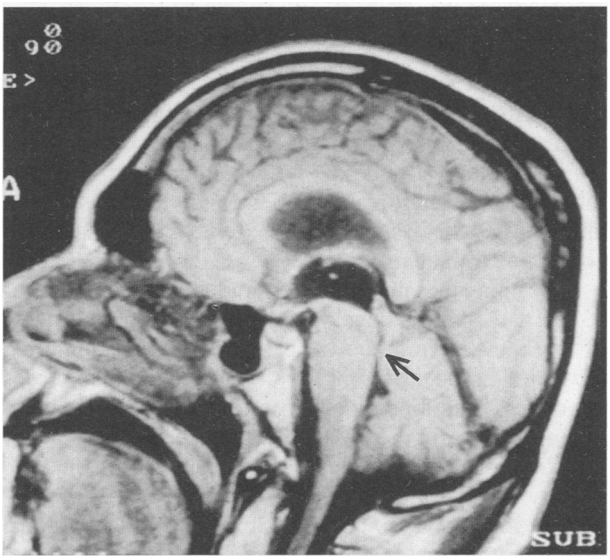


Figure 7.—A magnetic resonance image of a patient with coccidioidal meningitis complicated by hydrocephalus shows the third ventricle to be enlarged, but the aqueduct of Sylvius is patent, as indicated by the arrow.

Primary extrapulmonary inoculation. Rarely, cutaneous lesions can develop as the result of direct inoculation and do not represent extension from a pulmonary focus.[154-158] Primary cutaneous lesions develop painful suppurative sores, often with regional adenopathy, and usually heal without antifungal therapy.

Predispositions to Extrapulmonary Spread of Infection

Human immunodeficiency viral infection. Before 1987, only five patients with coccidioidal infection as a

complication of AIDS had been reported.[159-163] A report by Bronnimann and associates, however, described seven cases in Pima County, Arizona, and estimated that the annual risk of infection might be as high as 28% per year.[109] A subsequent prospective study has been carried out in the Phoenix and Tucson areas during a four-year period to determine more accurately the incidence of active coccidioidal infections occurring in patients infected with the human immunodeficiency virus (HIV).[164] Results from that study indicated with 95% confidence a risk of active infection to range from 8% to 41% during the period of study. This makes coccidioidomycosis one of the most frequent life-threatening complications for HIV-infected patients within the regions endemic for *C immitis*.

Why these rates are higher than for estimated skin-test-conversion rates for immunocompetent patients[21] or rates of infections for other immunosuppressed patient groups[22] is not clear. One possibility is that endemic exposure is higher than skin-test-conversion rates reflect. If this is the case, natural host defenses that normally prevent infection before T cell-dependent immunity is produced may be impaired in HIV-infected patients. An alternative explanation is that a reactivation of previously quiescent infections is contributing to the rates. Supporting this contention were the findings that overt infection was significantly associated with heightened immunodeficiency—$CD4^+$ count <250 cells $\times 10^6$ per liter, an established diagnosis of AIDS, and anergy to noncoccidioidal skin test antigens. Other factors, such as a history of previous coccidioidomycosis, prolonged residence within the endemic area, or the presence of a positive coccidioidal skin test, did not show a similar correlation as might be expected if reactivated latent disease was important. Clearly this issue needs resolving for physicians to counsel their patients.[165]

The clinical profile for coccidioidomycosis in HIV-infected patients was developed by a retrospective review of 77 previously unreported cases.[111] The most common presentation, occurring in 31 (40%) of the patients, was the radiographic finding of diffuse bilateral reticulonodular infiltrates (Figure 5). This was a serious illness for which the median survival was only one month, and the density of spherules within the lung tissue was great.[166] On the other hand, 20 patients (26%) had unilateral focal pulmonary infiltrates as their presenting complaint. Infections in these patients manifest a clinical course that would be difficult to distinguish from that of patients without HIV infection, and in this group during the period of follow-up after diagnosis, only 2 patients had died. Another 20 patients had various forms of extrathoracic dissemination including meningitis (9 patients), inguinal and other adenopathy (5 patients), skin lesions (4 patients), and hepatic lesions (2 patients). The course of these patients' infections varied widely, with many surviving for prolonged periods of time. In the remaining 6 patients, focal lesions were not evident and diagnosis was by serologic tests only. This last group also had more favorable survival times. Other complications have included peritonitis[131] and brain abscess.[167]

Many HIV-infected patients have had great difficulty handling coccidioidal infections, and for them treatment is critical. A few patients have been able to resolve their illness without treatment, and so it is possible that selected patients might be best served without an early initiation of therapy. As summarized in Table 3, treatment is nearly always indicated in patients with extrathoracic lesions, in patients with bilateral reticulonodular pulmonary lesions that are usually associated with fungemia, and in patients whose $CD4^+$ counts are low. On the other hand, because a positive skin test does not predict increased risk of reactivation, it is not in itself an indication for treatment. Moreover, a few patients who otherwise appear to be immunologically intact and to be handling their infection might well benefit from not beginning therapy. This last approach could save both cost and possible toxicity but is likely to produce anxiety in both patient and physician and would require close observation and frequent reevaluation.

TABLE 3.—*Guidelines for the Treatment of Patients Infected With the Human Immunodeficiency Virus Who Have Coccidioidomycosis*

Treatment indicated if
Extrathoracic dissemination
Diffuse pulmonary infection
Any infection in the presence of a $CD4^+$ count < 250 × 10^6/liter
Observation indicated if
Asymptomatic positive skin test
Localized pulmonary infection, $CD4^+$ count is normal, and illness is resolving

Organ and bone marrow-transplant recipients. A renal transplantation program was established in southern Arizona in 1970, and its experience with coccidioidomycosis developing in patients with kidney transplants was reviewed in 1980.[22] The annual risk of infection was approximately 6% in the first year after engraftment and decreased to about half of this for subsequent years, roughly comparable to estimates of skin-test-conversion rates for the general population in the same area. The difference in the first year has been thought to be related either to reactivation (analogous to the possibility with HIV-infected patients) or to higher levels of immunosuppressive medications. Despite the relatively low incidence, infections progressed to dissemination in 12 of 18 patients and to death in 10. A similar rate of infection occurred in heart-transplant recipients, but dissemination and death occurred less frequently than in patients receiving kidneys.[168,169]

Because specific instances of the reactivation of previous coccidioidal infection after organ transplantation have occurred at centers outside the regions endemic for the fungus,[170-172] the safety of proceeding with organ transplantation in patients with a history of infection is in question. Recently we reviewed the records of 656 organ recipients from our renal and cardiac transplantation programs and identified 9 cases of coccidioidal infections

that had occurred before the patients received their grafts.[173] Five of these patients received one or another form of antifungal therapy after transplantation; in this group, no recurrent infections developed. In contrast, four patients received no antifungal therapy, and in two of them, recurrent coccidioidomycosis developed, and they died as a result. In addition, both of these patients were on heightened immunosuppressive therapy for acute rejection, another factor that might have contributed to recurrence. Also identified in our review were 11 other patients with positive coccidioidal skin tests before they received heart transplants. None of these had postoperative antifungal therapy, and none have had the infection recur.

This experience represents a beginning at understanding this problem and can be used to formulate tentative guidelines for evaluating and managing transplant candidates (Table 4). First, as with HIV-infected patients, a reactive coccidioidal skin test is a poor predictor of reactivation after immunosuppression. Second, as part of the transplantation evaluation, an extensive residence and travel history should be obtained to identify those who need screening coccidioidal skin tests. Three of our patients, including the two who ultimately died of recurrent infection, were identified only by serologic screening. Finally, our findings suggest that those with past coccidioidomycosis or positive pretransplantation serologic tests may need postoperative antifungal therapy to prevent reactivation. Whether these recommendations should be modified or expanded in the future will require experience with the management and outcome of more cases. To facilitate the exchange of this information, a data base has been established at the University of Arizona that can be reached using my address (see reprint request footnote at beginning of article). It is hoped that physicians who have experience with organ transplantation in individual patients with previous coccidioidal infections will contribute their observations to this resource so that increasingly rational guidelines can be developed.

Other forms of immunosuppression. A seminal report establishing *C immitis* as an opportunistic pathogen was that of Deresinski and Stevens, who reviewed the experience at Stanford University Medical Center (Palo Alto, California). They noted that infections were more likely to disseminate in patients with Hodgkin's disease than in those without immunosuppressing diseases or treatments.[110] In another report from the University of Arizona, 16 of 126 coccidioidal infections treated at that center were in patients with malignant neoplasms, uremia, collagen-vascular diseases, or those who had received recent immunosuppressive drug therapy.[174] In the immunosuppressed group, the rate of dissemination was 50%, and all had received immunosuppressive therapy. In both reports, the severity of the infection was wide ranging, with some patients surviving more than three years after the onset of their infection despite immunosuppression. Although coccidioidomycosis has not been frequent in those receiving bone marrow transplants, three centers (two outside of the endemic regions) have each had a patient with this complication.[175]

TABLE 4.—*Guidelines to Prevent Recurrent Coccidioidomycosis After Organ Transplantation*

Patient Finding	*Disposition*
History of endemic exposure	Test for coccidioidal antibodies and consider giving antifungal drugs during treatment of acute rejection
Positive skin test	Same as for history of endemic exposure
History of coccidioidal illness	Give antifungal drugs after engraftment or if antibodies are detected

Other acquired predispositions. Pregnancy has been regarded as a risk for women, especially during the third trimester and the peripartum period. In reviewing 74 published reports and 41 unpublished cases from Pappagianis, Peterson and colleagues indicated that of 38 women in whom coccidioidomycosis was diagnosed in the third trimester, 26 (68%) had disseminated disease and 18 (47%) died.[176] With amphotericin B treatment of first- and second-trimester infections, mortality was 19% compared with 66% in untreated patients. In contrast, of 23 patients diagnosed during their first trimester, only 5 had disseminated disease and 3 died. Usually the infants were uninfected, although neonatal coccidioidomycosis has been reported.[177,178] These alarming statistics included early reports from central California in which the general health of some of the women was poorer than is likely the case today. Moreover, even with relatively low estimates of annual infection rates and the number of pregnancies per year within the endemic regions, the predicted number of serious infections from coccidioidomycosis is far greater than obstetricians practicing in these areas have found. This point was documented by Wack and co-workers by surveying the number of coccidioidal infections reported among 47,120 pregnancies.[179] Although 178 infections would be expected during the third trimester, assuming the annual risk is 3% and 50% of the women had not had a previous infection, these authors were able to find only 10. Four infections were presumptive diagnoses only, none resulted in death, the delivered infants were healthy (two women had elective abortions not related to infection), and only two infections progressed to dissemination. Nonetheless, both cases of disseminated infection occurred in women whose infection began late in their third trimester, other case reports continue to describe a similar pattern,[180-182] and recent in vitro studies have shown a blunted lymphocyte response to coccidioidal antigens near term and postpartum.[183] Taken together, these observations suggest that within the endemic area coccidioidal infections actually occur fairly infrequently during contemporary pregnancies. Moreover, when symptoms of coccidioidomycosis do occur late in or soon after pregnancy, they are often associated with serious complications.

Genetic factors. Whether certain racial groups are at higher risk of having disseminated lesions has been a topic of extensive debate. Disseminated infections have

developed in Filipinos, African Americans, Mexican Americans, and Native Americans out of proportion to their representation in the general population, and as a result it has been suggested that this might be due to genetic differences. From early data, Filipino patients accounted for 22% of the reported cases of dissemination whereas they constituted only 0.25% of the general population.[184] This proportion was 175 times higher than for whites. Critical analysis of the methods used in those reports has raised questions about whether the intensity of exposure, nutrition, or the presence of other diseases might be more important factors than race.[185] Observations during a severe California dust storm in 1977, in which exposure was unlikely to be biased, have reasserted that differences in a predisposition to dissemination between races do in fact exist. In one report, patients identified through contact with a reference serologic laboratory were categorized either as having disseminated infection or as being symptomatic without dissemination.[186] It was reported that infection in 53.8% of African-American patients and 38.4% of Asians (including Chinese, Japanese, Korean, and Vietnamese but excluding Filipinos) was classified as disseminated, in contrast to that in only 11.2% of white patients. A similar pattern with a smaller number of cases was reported from a naval base after the same dust storm.[187] Thus, at present it appears likely that African- and Asian-American patients are at greater risk than are whites.

Other evidence of genetic links to disseminated infection is derived from an association with specific blood groups. Deresinski and associates reported that disseminated infection was disproportionately common in patients with blood group B.[188] Similarly, Cohen and colleagues showed dissemination to be associated with both the B and AB blood groups in kidney transplant recipients or those undergoing hemodialysis.[22] The significance of this association has not been developed, although it is presumed to relate to the linkage of blood group antigens with immunoregulatory genes. If this is the case, then it would be expected that dissemination would also be associated with one or another HLA type. Although early studies have failed to demonstrate this,[189] contemporary typing methods have not been applied to the question.

Diagnostic Approaches

Culture of the Organism and Its Identification

The definitive method of establishing the diagnosis of coccidioidomycosis is by isolating the fungus from a clinical specimen. *Coccidioides immitis* is not fastidious and readily grows on most media used in clinical microbiology laboratories. It is also a fairly rapidly growing fungus, often detectable within five days and sometimes as early as two days after the medium has been inoculated.

Colonial structure of the mycelial phase is not diagnostic, and further studies are necessary to establish the identity of the organism. In the past, this was done by inoculating mice or using special in vitro procedures to produce endosporulating spherules[190,191] or by extracting mycelial growth with thimerosal (Merthiolate) to test for a species-specific antigen.[192,193] Another approach has been to grow specimens on a commercial medium that indicates the presence of *C immitis* by a color change. Unfortunately, this strategy has not yet become sufficiently specific for clinical use.[194] More recently, a species-specific DNA probe has become available in a commercial kit so that species can be identified on the day that growth is detected.[195]

Despite the value of recovering *C immitis* in culture, this poses a possible risk to laboratory personnel because the mycelial phase is highly infectious.[24,29] For this reason, if a mycelial organism is observed in a culture, the petri dish or container should not be opened except in a biologic containment cabinet and by experienced personnel. Similarly, if infection due to *C immitis* is suspected, clinicians should note that possibility on the laboratory request slip.

More rapid than culturing *C immitis* and equally specific are identifying spherules in infected tissue or cytologic preparations.[196-200] Although occasionally other structures may resemble spherules,[201,202] this seldom poses a problem. In difficult cases, viewing the hematoxylin-eosin–stained structures under fluorescent light can sometimes be helpful because *C immitis* will autofluoresce.[203] The direct examination of specimens is faster than growing *C immitis* in culture but is not as sensitive.[204] Therefore, both procedures should routinely be requested from the laboratory.

Antibody Detection

For the past half century, detecting anticoccidioidal antibodies has been an important means of establishing a diagnosis of coccidioidomycosis.[205,206] A thorough discussion of conventional testing procedures was published recently[207] and is beyond the scope of this review. It may be useful, however, to summarize the types of testing currently available, some new information emerging about the nature of the fungal antigens used to detect antibodies, and new approaches that are under development for future use.

The two major antigens used to detect anticoccidioidal antibodies are the tube precipitin-reacting (TP) antigen—so called because of the precipitin button that formed in the bottom of the test tube in the originally described "tube precipitin" test—and the complement-fixing (CF) antigen. During primary infections, IgM antibodies against the TP antigen are usually found in serum earlier than CF antibodies and disappear sooner, although exceptions to this rule can occur. In contrast, TP antibodies are not usually found in more chronic infections whereas CF antibodies are typical. The concentrations of TP antibodies have never been related to the prognosis. On the other hand, the concentration of CF antibodies is generally in proportion to the extent of disease, and by standardized laboratory procedures, detecting antibodies in dilutions greater than 16-fold is significantly associated with extrapulmonary infections. The ability of CF antibodies to activate complement and to persist for long periods is typical of IgG immunoglobulins.

TABLE 5.—*Commercially Available Diagnostic Tests for Coccidioidomycosis*

Commercial Kit Test	Correlation With Reference Tests: Tube Precipitin (TP)	Correlation With Reference Tests: Complement Fixation (CF)	Comment	Source
Immunodiffusion TP (IDTP)	Yes	No	Has largely supplanted the original TP, even in reference laboratories	Kaufman et al, 1985[208]; Huppert and Bailey, 1963[210]; Huppert and Bailey, 1965[212]
Immunodiffusion CF (IDCF)	No	Yes	Usually used as a screen with quantitation provided by CF test	Johnson et al, 1984[209]; Huppert and Bailey, 1965[211]; Wieden et al, 1983[214]
Latex	Yes	No	Screening test only; should always be confirmed	Huppert et al, 1968[219]
ELISA	Yes	Yes	New test; full validation awaits further documentation	Gade et al, 1992[221]

ELISA = enzyme-linked immunosorbent assay

Although the traditional methods for detecting anti-TP or anti-CF antibodies are well established, neither is available as a commercial kit, and both are difficult to adapt to general-purpose clinical serologic laboratories for occasional use. In their stead, dual immunodiffusion procedures that can be more readily supplied commercially have been developed as surrogate procedures to detect antibodies of the same specificity as the original TP and CF tests.[208-217] Although the immunodiffusion tests are considered to be highly specific and at least as sensitive as the original methods, this evolution has introduced some confusion in terms because there are two immunodiffusion tests, one mimicking the TP test (IDTP) and the other mimicking the CF test (IDCF), depending on the reagents used (Table 5).[208-212,214,219,221] Like the TP test, the IDTP results are reported qualitatively as either positive or negative. Usually the IDCF is also reported qualitatively, and, if positive, would be followed by the standard CF test to obtain quantitative results.

Other tests are available for detecting coccidioidal infections but are at this time of more limited value. Latex agglutination tests have been used with some degree of success and have been recommended by some as a rapid method for screening serum for more specific studies.[218-220] More recently, an enzyme-linked immunosorbent assay has been introduced that has also been proposed for screening and may be more specific than latex tests.[221] Although useful, the results from these methods have not yet been extensively correlated with results from TP or CF tests.

As useful as detecting anticoccidioidal antibodies has been for diagnosing coccidioidomycosis, negative studies do not exclude the diagnosis. This is especially the case early in the course of primary infection[80] or in immunosuppressed patients. For example, a third of patients with AIDS in whom bilateral reticulonodular pulmonary infiltrates develop have had undetectable anticoccidioidal antibodies by conventional tests.[111,222] More sensitive procedures such as radioimmunoassay or enzyme-linked immunosorbent assay may improve antibody detection but require much more purified antigens to avoid nonspecific activity. Purifying relevant antigens has not been easy because extracts of *C immitis* are complex and their glycoprotein nature has posed technical difficulties for good separation. In recent years, both TP and CF antigens have begun to be characterized in some detail.[215,217,223-227] As a result, it is possible that synthetic or recombinant antigens should become available as reagents in the future.

Fungal Antigen Detection

Rather than rely on a patient's humoral response, an alternative serologic approach to diagnosis is to assay for circulating antigens of the fungus itself, as has proved useful in histoplasmosis.[228,229] Several studies have reported detecting coccidioidal antigens in the serum of patients with either acute or chronic infections (Table 6).[77-80] The move from these observations to a clinically available procedure has not yet occurred, however. As with antibody detection, the availability of more purified reagents will likely result in assays that are within the competence of clinical laboratories.

Defining the Extent of Infection

Once a diagnosis has been established, it is important to determine whether the infection has spread beyond the chest and, if so, how extensively. As was discussed ear-

TABLE 6.—*Detecting Circulating Coccidioidal Antigen as a Diagnostic Test*

Cases	Findings	Source
Mice		
Acute infection	Transient antigenemia*	Cox and Kennell, 1988[75]
Patients		
Acute infection	>50% with antigen in first 2 weeks*	Galgiani et al, 1982[80]
Chronic pulmonary infection	73% with immune complexes containing coccidioidal antigen	Yoshinoya et al, 1980[77]
Disseminated infection	56% with antigen†	Weiner, 1983[78]

*Results were obtained using an enzyme-linked immunosorbent assay.
†Results were obtained using a radioimmunoassay.

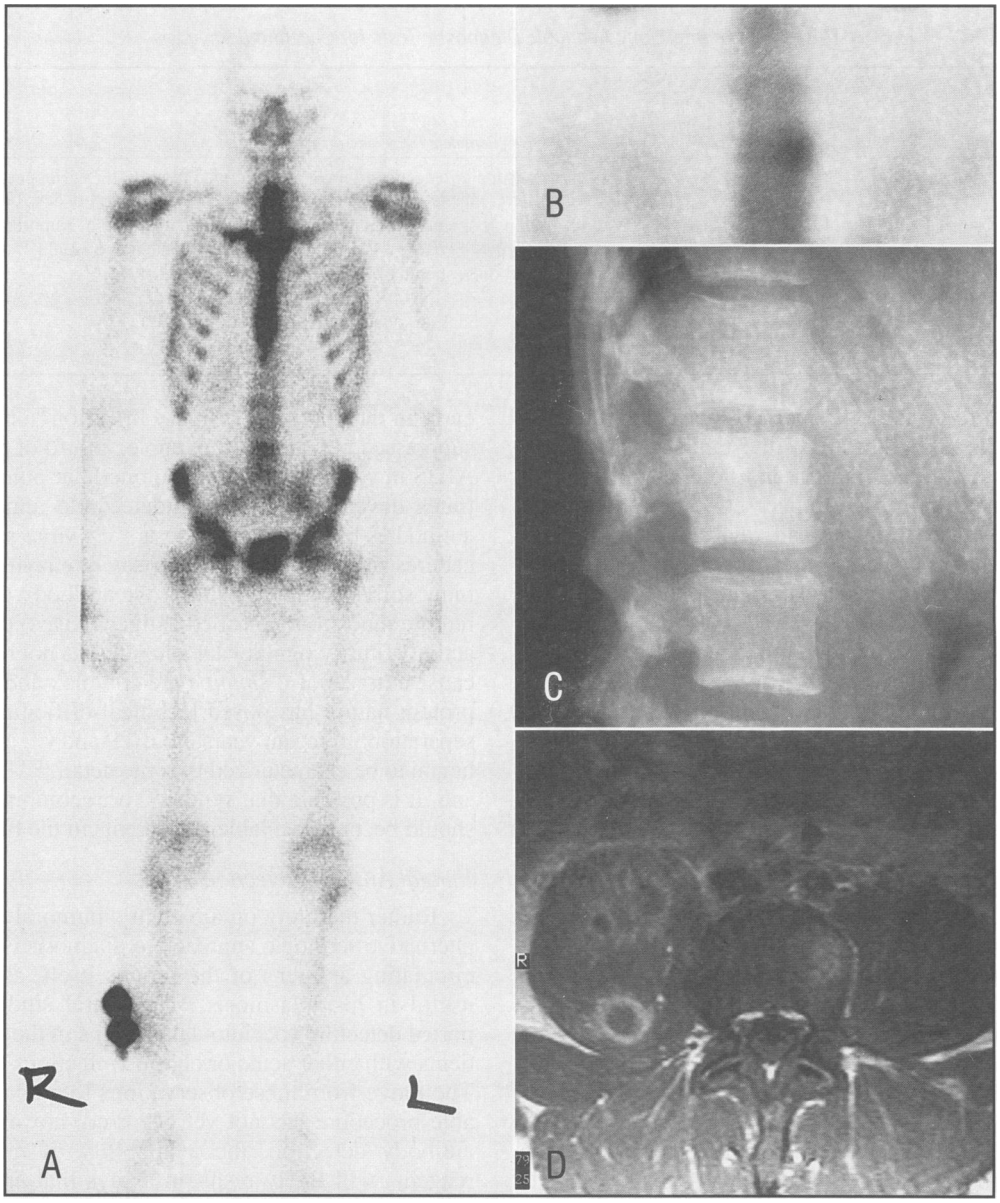


Figure 8.—Imaging techniques are shown that were used to define the extent of disseminated coccidioidomycosis in a patient. **A,** A bone scan was done because of a complaint of minor lower back pain; it showed subtly abnormal uptake in the second lumbar vertebra. **B,** Tomographic scanning of the second lumbar vertebra produced higher resolution and demonstrated asymmetry of the abnormal uptake. **C,** Planar radiographs confirmed a lytic lesion to be present in that region. **D,** Magnetic resonance imaging of the spine confirmed the findings in the second lumbar vertebra and also showed a lytic lesion in the fourth vertebra with associated abscesses in the surrounding muscles. These images were used to follow the progress of therapy and to determine the need for surgical debridement in addition to antifungal therapy. (A, B, and D are courtesy of Maria C. Tartak, MD, and Kelly McAleese, MD.)

lier, coccidioidal lesions often include an acute inflammatory component, and as a clinical correlate, they usually exhibit a focal nature. For this reason, a careful history and physical examination that detects no recent unexplained complaints of pain or evidence of inflammation is a sufficient evaluation for the possibility of extrathoracic spread for most patients with early respiratory tract infections. The presence of such symptoms should lead to more specific diagnostic imaging studies, which might include plain radiographs, computed tomographic scans, magnetic resonance studies, ultrasonograms, or nuclear isotope scans (Figure 8).[230,231] Headache is a frequent symptom of patients with early coccidioidal infections, and, fortunately, in most patients it does not indicate the presence of meningitis. But for patients with persistent headache or headache associated with nausea, vomiting, mental status changes, or other neurologic findings, a lumbar puncture is indicated to examine the CSF for the presence of pleocytosis, depressed glucose concentration, elevated protein concentration, or CF antibodies.

Therapeutic Strategies

Initial Pulmonary Infections

Clearly most primary coccidioidal infections resolve without therapy. Furthermore, despite the availability of new antifungal agents for the treatment of primary infections, there in fact exists no persuasive evidence that any treatment is useful for either shortening the course of the initial illness or preventing more serious problems from arising. Although it is likely that some patients with an initial infection would benefit from treatment, physicians within the endemic areas do not agree about who should be treated or for how long.

The patients for whom there is the most agreement are those whose T-cell immunity is deficient, as indicated earlier. The selection of therapy for such patients follows the guidelines I outline for extrapulmonary dissemination. A second group that is perhaps likely to benefit from therapy are those with infection produced by a large number of arthroconidia simultaneously because the likelihood of complications in this group appears to be higher than in persons with the usual endemic exposure.[44] The goal of such therapy is to inhibit fungal proliferation temporarily as host immune responses develop for continued control. Because rapidity of drug action may be important in this situation, many physicians think that amphotericin B is the preferred antifungal agent and that treatment should be continued for a cumulative dose of at least 1.0 gram (for a recent review of the use of amphotericin B, see Gallis and co-workers).[232] Once a patient has improved, therapy may be completed over an additional several months with an oral azole antifungal agent such as ketoconazole, fluconazole, or itraconazole.

Finally, there are other patients with symptoms and extent of pulmonary infection that are compelling, but the threshold for these indications is not the same for different physicians, and, again, there are no results from clinical trials to help with this decision. Patients in that category most likely should be given a trial of a month to a year of treatment with an oral azole agent.

Chronic Pulmonary and Extrapulmonary Dissemination (Excluding Meningitis)

In 1957, amphotericin B was first reported to be effective for the treatment of coccidioidomycosis in a patient with cutaneous lesions of the face.[233] Since then the documentation for amphotericin B efficacy in this disease has been surprisingly scant. Hardenbrook and Barriere reviewed the literature for amphotericin's efficacy in coccidioidomycosis, and these authors were able to identify 103 patients in 34 publications.[234] Only seven reports included more than four patients. Overall, 73 patients responded to treatment. These reports are complemented by more than three decades of unpublished experience that has resulted in a consensus that the most fulminant cases of coccidioidomycosis are best treated with amphotericin B. On the other hand, many patients do not have fulminant infections, but rather have chronic or subacute manifestations. This group of patients has been the focus of several clinical trials of azoles.[235-239] A review of newer antifungal agents and their pharmacology has been published recently.[240]

For the past decade a large collaborative effort, sponsored by the National Institute of Allergy and Infectious Diseases and now known as the Mycoses Study Group, has brought focus and systematic approaches to the study of coccidioidomycosis and to other invasive fungal infections. A workshop report published in 1980 laid the foundations by outlining study design requirements.[241] Over the past decade, a standardized approach has evolved for assessing response to therapy. The studies shown in Table 7 were not done for strict comparison.[237,239] Even so, comparison is useful to some extent because the studies were carried out by the same collaborative group and, except for the study of ketoconazole, they followed uniform methods of measuring response.

The 400-mg-per-day doses of itraconazole and fluconazole were similar to the 200-mg-per-day dose of Sch 39304. As shown in Table 7, relapses of responding patients were encountered after drugs were stopped, so the rates for durable responses were lower. It should be emphasized that the ketoconazole results were estimated using more stringent criteria of response, and, to a large extent, this difference may account for the discrepancy between its lower response rates as compared with those obtained with the newer agents. In fact, these results do not clearly indicate the superiority of any one of the newer drugs over ketoconazole. This may be a particularly important point to bear in mind because the newer agents are considerably more expensive and because none have yet obtained US Food and Drug Administration endorsement for the treatment of coccidioidomycosis.

Also shown in Table 7 are untoward events that were possibly attributable to the drugs used in the various studies. Using 400 mg per day, about 95% of patients could tolerate prolonged courses of ketoconazole, itraconazole, or fluconazole. When higher doses of ketoconazole were used, side effects clearly became more numerous. Not apparent from these figures are differences in minor but nonetheless discomforting gastrointestinal side effects, and, in general, most investigators think that the newer triazoles such as fluconazole and itraconazole are better tolerated than ketoconazole. In January 1993, the Mycoses Study Group began a randomized, double-blind study comparing the use of fluconazole with that of itraconazole, and it is hoped that results from this trial will better define the relative value of these two agents.

Meningitis

With the introduction of amphotericin B, survival with coccidioidal meningitis improved.[146,242-249] But to be effective, amphotericin B had to be administered repeatedly into the cerebrospinal space, and courses of treatment lasted many months or even years. Moreover, as reviewed by Labadie and Hamilton, overall reported survival was only 57%, varying substantially among different reports depending on the specific technique of drug

TABLE 7.—*Summary of Mycoses Study Group Trials With Azole Antifungal Drugs for the Treatment of Nonmeningeal Coccidioidomycosis*

Drug	Dose, mg/day	Patients, No.	Treatment Results: Response, %	Relapse, %	1 Year Remission, %	Stopped Due to Toxicity, %
Ketoconazole*	400	56	23†	9	21	6
	800	56	32†	44	18	17
Itraconazole‡	400	51	57	16	49	6
Fluconazole§	200	73	34	39	21	4§
	400	25	61	36	39	
Sch 39304‖	100 or 200	54	66	¶	¶	4

*From Galgiani et al.[239]
†Response was defined by a different method.
‡From Graybill et al.[237]
§Number represents the number of patients in whom drug toxicity for all doses combined limited their treatment.
‖Data represent work in progress and have not yet been published in final form.
¶Drug was withdrawn before completion of the study.

administration, drug dosing, patient factors, and length of observation.[246]

The possibility of substituting oral therapy with azoles was investigated soon after they were available, and some of the early experiences that followed are summarized in Table 8.[250-252] Ketoconazole has not proved widely applicable for this disease because at least 1,200 mg per day of the drug has been needed, and side effects at this dose often cannot be tolerated. In addition, in all of these reports, all but one patient received amphotericin B either concurrent with or before the azole. Thus, it was difficult to be sure how much of the response was attributable to the azole component of the therapy.

To resolve this situation, the Mycoses Study Group initiated a trial of fluconazole for the treatment of coccidioidal meningitis.[253] Only patients with untreated meningitis or active meningitis after previous therapy with amphotericin B failed were included, and during the study other antifungals were not administered. The dose of fluconazole was 400 mg per day, and treatment was evaluated by repeated measurements of CSF and other abnormalities using a predefined scoring system. By the fall of 1990, 50 patients were enrolled. By chance, exactly half of the enrolled patients had not received previous therapy, 41 were male, and 9 were HIV infected. The response for both groups combined was 79%, ranging from 70% for patients without previous therapy to 88% for patients who had relapsed after past treatment. In reviewing the baseline characteristics for the two groups, it appeared that by the time previously treated patients were enrolled in this study they had slightly milder disease, and it is possible that this difference may have accounted for that group's higher response rate. During the study, 10 responding patients have died of unrelated causes, including AIDS in 6 and stroke, pulmonary embolus, Hodgkin's disease, and urosepsis in the others. All of the other responders have now completed more than two years of therapy and are doing well. Of the 10 patients for whom therapy failed, 2 HIV-infected patients died, 2 patients were switched to amphotericin B, and 6 patients were continued on a regimen of fluconazole, but the dose was increased to 800 mg per day.

TABLE 8.—*Preliminary Reports of Azole Therapy for Coccidioidal Meningitis*

Azole Drug	Daily Oral Dose, mg	Relation to Amphotericin B Administration	Patients, No.: Treated	Improved
Ketoconazole*	≥ 1,200	Before	5	5
Fluconazole†	50-400	Concurrent	7	4
		Before	7	5
		None	1	1
Itraconazole‡	300-400	Concurrent	3	3
		Before	5	4

*From Craven et al.[250]
†From Tucker et al.[251]
‡From Tucker et al.[252]

Responses were generally achieved within eight months, and the rate of response was not affected by either HIV coinfection or the presence of hydrocephalus. In the first four months, improvement is most attributable to reduced symptoms, whereas the improvement of various CSF measurements occurred more gradually. From a practical standpoint, this meant that patients would start feeling better within a month or two, even though objective measures of improvement would take considerably longer to manifest.

It should also be appreciated that in some patients, not all evidence of disease activity has completely resolved even after many months of treatment. For example, of 20 responding patients who had lumbar punctures repeated 20 or more months after starting therapy, 5 still have leukocyte counts of 20 or more cells $\times 10^6$ per liter. Similarly, the glucose concentration was between 1.7 and 2.2 mmol per liter (31 and 39 mg per dl) in 3 patients, and the protein value was between 0.5 and 3.12 grams per liter (50 and 312 mg per dl) in 9 of 16 patients, none of whom had hydrocephalus. Overall, 15 patients had at least one of these CSF variables abnormal. Thus, despite the generally favorable pattern, there is also considerable heterogeneity in the rate and completeness of the resolution of evaluated abnormalities.

To summarize current treatment options for coccidioidal meningitis, fluconazole has emerged as an attrac-

tive alternative to intrathecal therapy. The response rate of 79% shown recently would seem at least as good as that for amphotericin B.[253] On the other hand, 21% of patients did not have a response at a dosage of 400 mg per day, so there is clearly room for additional improvement in the therapy for this disease. It is encouraging that some of the patients for whom therapy initially failed appeared to do better on higher doses of fluconazole, and perhaps additional dose-ranging studies will solve some of the residual problems. Alternatively, it may still be necessary to use amphotericin B in some patients. Finally, most investigators are reluctant to stop azole treatment, even after many years of therapy. In a recent compilation of 16 patients who have stopped therapy with any of several oral azoles, including ketoconazole, itraconazole, or fluconazole, 12 patients relapsed (David A. Stevens, MD, written communication, July 1993). Because adverse drug reactions with fluconazole have been few, it would seem advisable to continue therapy until more is known about the safety of discontinuing treatment.

Future Directions for Research

With the development of azoles for the treatment of coccidioidomycosis, considerably more options are available than were a decade ago. Even so, the disease remains a therapeutic challenge and one to test new antifungal drugs and new treatment strategies. Most recently, lipid or liposomal formulations of amphotericin B raise the hope of reduced toxicity, which in turn may permit the use of higher and more effective doses.[254] Another approach has been to identify entirely new classes of antifungal agents such as those that inhibit cell-wall synthesis.[255] The chitin synthase inhibitor, nikkomycin, is one such drug developed by Bayer, and this agent has proved to be an effective orally administered treatment of coccidioidomycosis in experimental murine infections.[256] Unfortunately, this promising drug has been withdrawn from clinical trials by the sponsor. One can only hope that this decision might be reconsidered or that another farsighted pharmaceutical manufacturer might step in to continue the drug's development. Another lead for new classes of antifungal drugs emanates from the observation that cyclosporine has in vitro and in vivo inhibitory effects on *C immitis*.[257] Although cyclosporine itself is too toxic to be used for its antimicrobial effects, other related compounds might be more selective.[258] Finally, a therapeutic role for interferon gamma has theoretical and experimental support.[62,63] Only time will tell whether this or another cytokine will find a place in the treatment of coccidioidomycosis.

In addition to the continued need for new therapies, our understanding of the biology of this pathogen remains incomplete. That most infected patients have the power to heal themselves should be strong stimulus to learn more about the details of the immune response. To do this will likely require the participation of scientists trained in modern immunologic, biochemical, and genetic approaches. Such studies will rightly be viewed as ambitious undertakings by scientists who have generally preferred to study less complex or more established experimental problems. On the other hand, the possibilities for unexpected findings are equally great, and it can only be hoped they will attract more fundamental work on this pathogen in the years ahead.

REFERENCES

1. Wernicke R: Ueber einen protozoenbefund bei mycosis fungoides (?). Zentralblatt Bakteriol 1892; 12:859-861
2. Rixford E: Case for diagnosis presented before the San Francisco Medico-Chirurgical Society, March 5, 1894. Occidental Med Times 1894; 8:326
3. Rixford E: A case of protozoic dermatitis. Occidental Med Times 1894; 8:704-707
4. Ophuls W: Further observations on a pathogenic mold formerly described as a protozoan (*Coccidioides immitis, Coccidioides pyogenes*). J Exp Med 1905; 6:443-486
5. Dickson EC, Gifford MA: Coccidioides infection (coccidioidomycosis)—II. The primary type of infection. Arch Intern Med 1938; 62:853-871
6. Cayce WR: Cases from the aerospace medicine residents' teaching file—Case #47: Primary pulmonary coccidioidomycosis. Aviat Space Environ Med 1991; 62:1200-1202
7. Ito H, Itaoka T, Onuki T, Yokoyama M, Yamamoto N, Nitta S: A case of pulmonary coccidioidomycosis. Nippon Kyobu Geka Gakkai Zasshi [Jpn J Thor Dis] 1991; 39:1222-1225
8. Lefler E, Weiler-Ravell D, Merzbach D, Ben-Izhak O, Best LA: Traveller's coccidioidomycosis: Case report of pulmonary infection diagnosed in Israel. J Clin Microbiol 1992; 30:1304-1306
9. Sekhon AS, Isaac-Renton J, Dixon JM, Stein L, Sims HV: Review of human and animal cases of coccidioidomycosis diagnosed in Canada. Mycopathologia 1991; 113:1-10
10. Babycos PB, Hoda SA: A fatal case of disseminated coccidioidomycosis in Louisiana. J La State Med Soc 1990;142:24-27
11. Taylor GD, Boettger DW, Miedzinski LJ, Tyrrell DLJ: Coccidioidal meningitis acquired during holidays in Arizona. Can Med Assoc J 1990; 142:1388-1390
12. Hughes CW, Kvale PA: Pleural effusion in Michigan caused by *Coccidioides immitis* after travel to an endemic area. Henry Ford Hosp Med J 1989; 37:47-49
13. Drutz DJ, Catanzaro A: Coccidioidomycosis—Parts I and II. Am Rev Respir Dis 1978; 117:559-585; 727-771
14. Ampel NM, Wieden MA, Galgiani JN: Coccidioidomycosis: Clinical update. Rev Infect Dis 1989; 11:897-911
15. Pappagianis D: Coccidioidomycosis, *In* Balows A, Hausler WJ Jr, Lennette EH (Eds): Laboratory Diagnosis of Infectious Diseases. Berlin, Springer Verlag, 1988, pp 600-623
16. Graybill JR: Treatment of coccidioidomycosis. Ann NY Acad Sci 1988; 544:481-487
17. Harrison WR, Merbs CF, Leathers CR: Evidence of coccidioidomycosis in the skeleton of an ancient Arizona Indian. J Infect Dis 1991; 164:436-437
18. Maddy KT: The geographic distribution of *Coccidioides immitis* and possible ecologic implications. Ariz Med 1958; 15:178-188
19. Larwood T: Further Drop in Kern County Coccidioidin Reactivity. Transactions of the Ninth Annual Coccidioidomycosis Conference, Los Angeles, California. Oakland, Calif, California Thoracic Society, 1964, pp 8-9
20. Kerrick SS, Lundergan LL, Galgiani JN: Coccidioidomycosis at a university health service. Am Rev Respir Dis 1985; 131:100-102
21. Dodge RR, Lebowitz MD, Barbee RA, Burrows B: Estimates of *C immitis* infection by skin test reactivity in an endemic community. Am J Public Health 1985; 75:863-865
22. Cohen IM, Galgiani JN, Potter D, Ogden DA: Coccidioidomycosis in renal replacement therapy. Arch Intern Med 1982; 142:489-494
23. Johnson WM: Occupational factors in coccidioidomycosis. J Occup Med 1981; 23:367-374
24. Pappagianis D: Coccidioidomycosis (San Joaquin or Valley Fever), *In* DiSalvo A (Ed): Occupational Mycoses. Philadelphia, Pa, Lea & Febiger, 1983, pp 13-28
25. Werner SB, Pappagianis D: Coccidioidomycosis in Northern California—An outbreak among archeology students near Red Bluff. Calif Med 1973; 119:10-20
26. Smith CE, Beard RR, Rosenberger HG, Whiting EG: Effect of season and dust control on coccidioidomycosis. JAMA 1946; 132:833-838
27. Pappagianis D, Einstein H: Tempest from Tehachapi takes toll or coccidioides conveyed aloft and afar. West J Med 1978; 129:527-530
28. Pappagianis D: Epidemiology of coccidioidomycosis. Curr Top Med Mycol 1988; 2:199-238
29. Centers for Disease Control (CDC): Coccidioidomycosis—United States 1991-1992. MMWR 1993; 42:21-24
30. Einstein HE, Johnson RH: Coccidioidomycosis: New aspects of epidemiology and therapy. Clin Infect Dis 1993; 16:349-356
31. Pappagianis D: Some characteristics of respiratory infection in man, *In*

Dimmick RL, Akers AB (Eds): An Introduction to Experimental Aerobiology. New York, NY, Wiley-Interscience, 1969, pp 390-406

32. Sun SH, Sekhon SS, Huppert M: Electron microscopic studies of saprobic and parasitic forms of *Coccidioides immitis*. Sabouraudia 1979; 17:265-273

33. Shaw JB, Wynn-Williams N: Infectivity of pulmonary tuberculosis in relation to sputum status. Am Rev Tuberc 1954; 69:724-732

34. Cole GT, Sun SH: Arthroconidium-spherule-endospore transformation in *Coccidioides immitis, In* Szaniszlo PJ (Ed): Fungal Dimorphism. New York, NY, Plenum Publishing, 1985, pp 281-333

35. Huppert M, Sun SH, Harrison JL: Morphogenesis throughout saprobic and parasitic cycles of *Coccidioides immitis*. Mycopathologia 1982; 78:107-122

36. Drutz DJ, Huppert M: Coccidioidomycosis: Factors affecting the host-parasite interaction. J Infect Dis 1983; 147:372-390

37. Converse JL: Growth of spherules of *Coccidioides immitis* in a chemically defined liquid medium (22144). Proc Soc Exp Biol Med 1955; 90:709-711

38. Converse JL, Besemer AR: Nutrition of the parasitic phase of *Coccidioides immitis* in a chemically defined liquid medium. J Bacteriol 1959; 78:231-239

39. Petkus AF, Baum LL, Ellis RB, Stern M, Danley DL: Pure spherules of *Coccidioides immitis* in continuous culture. J Clin Microbiol 1985; 22:165-167

40. Bowman BH, Taylor JW, White TJ: Molecular evolution of the fungi: Human pathogens. Mol Biol Evol 1992; 9:893-904

41. Bowman BH, Taylor JW, Brownlee AG, Lee J, Lu SD, White TJ: Molecular evolution of the fungi: Relationship of the *Basidiomycetes, Ascomycetes*, and *Chytridiomycetes*. Mol Biol Evol 1992; 9:285-296

42. Kong YCM, Levine HB, Madin SH, Smith CE: Fungal multiplication and histopathologic changes in vaccinated mice infected with *Coccidioides immitis*. J Immunol 1964; 92:779-790

43. Smith CE, Beard RR, Whiting EG, Rosenberger HG: Varieties of coccidioidal infection in relation to the epidemiology and control of the disease. Am J Public Health 1946; 36:1394-1402

44. Werner SB, Pappagianis D, Heindl I, Mickel A: An epidemic of coccidioidomycosis among archeology students in northern California. N Engl J Med 1972; 286:507-512

45. Pappagianis D: Coccidioides in the soil and the meninges. Calif Med 1973; 119:51-53

46. Galgiani JN, Isenberg RA, Stevens DA: Chemotaxigenic activity of extracts from the mycelial and spherule phases of *Coccidioides immitis* for human polymorphonuclear leukocytes. Infect Immun 1978; 21:862-865

47. Galgiani JN, Yam P, Petz LD, Williams PL, Stevens DA: Complement activation by *Coccidioides immitis*: In vitro and clinical studies. Infect Immun 1980; 28:944-949

48. Echols RM, Palmer DL, Long GW: Tissue eosinophilia in human coccidioidomycosis. Rev Infect Dis 1982; 4:656-664

49. Galgiani JN, Payne CM, Jones JF: Human polymorphonuclear-leukocyte inhibition of incorporation of chitin precursors into mycelia of *Coccidioides immitis*. J Infect Dis 1984; 149:404-412

50. Galgiani JN: Inhibition of different phases of *Coccidioides immitis* by human neutrophils or hydrogen peroxide. J Infect Dis 1986; 153:217-222

51. Frey CL, Drutz DJ: Influence of fungal surface components on the interaction of *Coccidioides immitis* with polymorphonuclear neutrophils. J Infect Dis 1986; 153:933-943

52. Cole GT, Zhu S, Pan S, Yuan L, Kruse D, Sun SH: Isolation of antigens with proteolytic activity from *Coccidioides immitis*. Infect Immun 1989; 57:1524-1534

53. Yuan L, Cole GT: Isolation and characterization of an extracellular proteinase of *Coccidioides immitis*. Infect Immun 1987; 55:1970-1978

54. Galgiani JN: Killing of *Coccidioides immitis* by hypochlorous acid or monochloramine. J Med Vet Mycol 1990; 28:173-181

55. Galgiani JN: Studies of the effects of spherulin from *Coccidioides immitis* on human polymorphonuclear leukocytes. Mycopathologia 1985; 90:107-111

56. Huntington RW Jr, Waldmann WJ, Sargent JA, O'Connell H, Wybel R, Croll D: Pathologic and clinical observations on 142 cases of fatal coccidioidomycosis with necropsy, *In* Ajello L (Ed): Coccidioidomycosis. Tucson, Univ of Arizona Press, 1967, pp 221-225

57. Petkus AF, Baum LL: Natural killer cell inhibition of young spherules and endospores of *Coccidioides immitis*. J Immunol 1987; 139:3107-3111

58. Ampel NM, Bejarano GC, Galgiani JN: Killing of *Coccidioides immitis* by human peripheral blood mononuclear cells. Infect Immun 1992; 60:4200-4204

59. Ampel NM, Galgiani JN: Interaction of human peripheral blood mononuclear cells with *Coccidioides immitis* arthroconidia. Cell Immunol 1991; 133:253-262

60. Beaman L, Pappagianis D, Benjamini E: Mechanisms of resistance to infection with *Coccidioides immitis* in mice. Infect Immun 1979; 23:681-685

61. Beaman L, Benjamini E, Pappagianis D: Activation of macrophages by lymphokines: Enhancement of phagosome-lysosome fusion and killing of *Coccidioides immitis*. Infect Immun 1983; 39:1201-1207

62. Beaman L: Effects of recombinant gamma interferon and tumor necrosis factor on in vitro interactions of human mononuclear phagocytes with *Coccidioides immitis*. Infect Immun 1991; 59:4227-4229

63. Beaman L: Fungicidal activation of murine macrophages by recombinant gamma interferon. Infect Immun 1987; 55:2951-2955

64. Cox RA, Vivas JR: Spectrum of in vivo and in vitro cell-mediated immune responses in coccidioidomycosis. Cell Immunol 1977; 31:130-141

65. Cox RA, Vivas JR, Gross A, Lecara G, Miller E, Brummer E: In vivo and in vitro cell-mediated responses in coccidioidomycosis—I. Immunologic responses of persons with primary, asymptomatic infections. Am Rev Respir Dis 1976; 114:937-943

66. Cole GT, Seshan KR, Franco M, Bukownik E, Sun SH, Hearn VM: Isolation and morphology of an immunoreactive outer wall fraction produced by spherules of *Coccidioides immitis*. Infect Immun 1988; 56:2686-2694

67. Cole GT, Kirkland TN, Franco M, et al: Immunoreactivity of a surface wall fraction produced by spherules of *Coccidioides immitis*. Infect Immun 1988; 56:2695-2701

68. Deresinski SC, Levine HB, Stevens DA: Soluble antigens of mycelia and spherules in the in vitro detection of immunity to *Coccidioides immitis*. Infect Immun 1974; 10:700-704

69. Catanzaro A, Spitler LE, Moser KM: Cellular immune response in coccidioidomycosis. Cell Immunol 1975; 15:360-371

70. Barbee RA, Hicks MJ: Clinical usefulness of lymphocyte transformation in patients with coccidioidomycosis. Chest 1988; 93:1003-1007

71. Ampel NM, Bejarano GC, Salas SD, Galgiani JN: In vitro assessment of cellular immunity in human coccidioidomycosis: Relationship between dermal hypersensitivity, lymphocyte transformation, and lymphokine production by peripheral blood mononuclear cells from healthy adults. J Infect Dis 1992; 165:710-715

72. Rea TH, Johnson R, Einstein H, Levan NE: Dinitrochlorobenzene responsivity: Difference between patients with severe pulmonary coccidioidomycosis and patients with disseminated coccidioidomycosis. J Infect Dis 1979; 139:353-356

73. Kong YM, Levine HB, Madin SH, Smith CE: Fungal multiplication and histopathologic changes in vaccinated mice infected with *Coccidioides immitis*—I. Immunology 1964; 92:779-790

74. Cox RA, Kennell W, Boncyk L, Murphy JW: Induction and expression of cell-mediated immune responses in inbred mice infected with *Coccidioides immitis*. Infect Immun 1988; 56:13-17

75. Cox RA, Kennell W: Suppression of T-lymphocyte response by *Coccidioides immitis* antigen. Infect Immun 1988; 56:1424-1429

76. Cox RA: Immunosuppression by cell wall antigens of *Coccidioides immitis*. Rev Infect Dis 1988; 10:S415-S418

77. Yoshinoya S, Cox RA, Pope RM: Circulating immune complexes in coccidioidomycosis—Detection and characterization. J Clin Invest 1980; 66:655-663

78. Weiner MH: Antigenemia detected in human coccidioidomycosis. J Clin Microbiol 1983; 18:136-142

79. Galgiani JN, Dugger KO, Ito JI, Wieden MA: Antigenemia in primary coccidioidomycosis. Am J Trop Med Hyg 1984; 33:645-649

80. Galgiani JN, Grace GM, Lundergan LL: New serologic tests for early detection of coccidioidomycosis. J Infect Dis 1991; 163:671-674

81. Cox RA, Baker BS, Stevens DA: Specificity of immunoglobulin E in coccidioidomycosis and correlation with disease involvement. Infect Immun 1982; 37:609-616

82. Aharoni R, Teitelbaum D, Arnon R, Puri J: Immunomodulation of experimental allergic encephalomyelitis by antibodies to the antigen-Ia complex. Nature 1991; 351:147-150

83. Kirkland TN, Zhu S, Kruse D, Hsu L, Seshan KR, Cole GT: *Coccidioides immitis* fractions which are antigenic for immune T lymphocytes. Infect Immun 1991; 59:3952-3961

84. Dugger KO, Galgiani JN, Ampel NM, et al: An immunoreactive apoglycoprotein purified from *Coccidioides immitis*. Infect Immun 1991; 59:2245-2251

85. Galgiani JN, Sun SH, Dugger KO, et al: An arthroconidial-spherule antigen of *Coccidioides immitis*: Differential expression during in vitro fungal development and evidence for humoral response in humans after infection or vaccination. Infect Immun 1992; 60:2627-2635

86. Levine HB, Cobb JM, Smith CE: Immunogenicity of spherule-endospore vaccines of *Coccidioides immitis* for mice. J Immunol 1961; 87:218-227

87. Levine HB, Kong YCM, Smith CE: Immunization of mice to *Coccidioides immitis*: Dose, regimen and spherulation stage of killed spherule vaccines. J Immunol 1965; 94:132-142

88. Lundergan LL, Kerrick SS, Galgiani JN: Coccidioidomycosis at a university outpatient clinic: A clinical description, *In* Einstein HE, Catanzaro A (Eds): Coccidioidomycosis. Proceedings of the Fourth International Conference. Washington, DC, National Foundation for Infectious Diseases, 1985, pp 47-54

89. Lonky SA, Catanzaro A, Moser KM, Einstein H: Acute coccidioidal pleural effusion. Am Rev Respir Dis 1976; 114:681-688

90. Birsner JW: The roentgen aspects of five hundred cases of pulmonary coccidioidomycosis. AJR Am J Roentgenol Rad Ther 1954; 72:556-573

91. Bayer AS: Fungal pneumonias; pulmonary coccidioidal syndromes (Part 1)—Primary and progressive primary coccidioidal pneumonias—Diagnostic, therapeutic, and prognostic considerations. Chest 1981; 79:575-583

92. Castellino RA, Blank N: Pulmonary coccidioidomycosis: The wide spectrum of roentgenographic manifestations. Calif Med 1968; 109:41-49

93. Yozwiak ML, Lundergan LL, Kerrick SS, Galgiani JN: Symptoms and routine laboratory abnormalities associated with coccidioidomycosis. West J Med 1988; 149:419-421

94. Read CT: Coin lesion, pulmonary: In the southwest (solitary pulmonary nodules). Ariz Med 1972; 29:775-781

95. Forseth J, Rohwedder JJ, Levine BE, Saubolle MA: Experience with needle biopsy for coccidioidal lung nodules. Arch Intern Med 1986; 146:319-320

96. Freedman SI, Ang EP, Haley RS: Identification of coccidioidomycosis of the lung by fine needle aspiration biopsy. Acta Cytol 1986; 30:420-424

97. Winn WA: A long-term study of 300 patients with cavitary abscess lesions of the lung of coccidioidal origin. Chest 1968; 54:S12-S16

98. Smith CE, Beard RR, Saito MT: Pathogenesis of coccidioidomycosis with special reference to pulmonary cavitation. Ann Intern Med 1948; 29:623-655

99. Richardson HB Jr, Anderson JA, McKay BM: Acute pulmonary coccidioidomycosis in children. J Pediatr 1967; 70:376-382

100. Carrada-Bravo T: Coccidioidomycosis in children. Bol Med Hosp Infant Mex 1989; 46:507-514

101. Rodriguez-Cintron W, Fraire AE, Greenberg SD, Stevens PM, Stager CE: Pulmonary coccidioidal pseudomycetoma. Diagn Microbiol Infect Dis 1992; 15:267-272

102. Thadepalli H, Salem FA, Mandel AK, Rambhatla K, Einstein HE: Pulmonary mycetoma due to *Coccidioides immitis*. Chest 1977; 71:429-430

103. Putnam JS, Harper WK, Greene JF Jr, Nelson KG, Zurek RC: *Coccidioides immitis*—A rare cause of pulmonary mycetoma. Am Rev Respir Dis 1975; 112:733-738

104. Rohatgi PK, Schmitt RG: Pulmonary coccidioidal mycetoma. Am J Med Sci 1984; 287:27-30

105. Winn RE, Johnson R, Galgiani JN, Butler C, Pluss J: Cavitary coccidioidomycosis with fungus ball formation: Diagnosis by fiberoptic bronchoscopy with coexistence of hyphae and spherules. Chest, in press

106. Baker EJ, Hawkins JA, Waskow EA: Surgery for coccidioidomycosis in 52 diabetic patients with special reference to related immunologic factors. J Thorac Cardiovasc Surg 1978; 75:680-687

107. Cunningham RT, Einstein H: Coccidioidal pulmonary cavities with rupture. J Thorac Cardiovasc Surg 1982; 84:172-177

108. Ampel NM, Ryan KJ, Carry PJ, Wieden MA, Schifman RB: Fungemia due to *Coccidioides immitis*—An analysis of 16 episodes in 15 patients and a review of the literature. Medicine (Baltimore) 1986; 65:312-321

109. Bronnimann DA, Adam RD, Galgiani JN, et al: Coccidioidomycosis in the acquired immunodeficiency syndrome. Ann Intern Med 1987; 106:372-379

110. Deresinski SC, Stevens DA: Coccidioidomycosis in compromised hosts—Experience at Stanford University Hospital. Medicine (Baltimore) 1974; 54:377-395

111. Fish DG, Ampel NM, Galgiani JN, et al: Coccidioidomycosis during human immunodeficiency virus infection—A review of 77 patients. Medicine (Baltimore) 1990; 69:384-391

112. Sarosi GA, Parker JD, Doto IL, Tosh FE: Chronic pulmonary coccidioidomycosis. N Engl J Med 1970; 283:325-329

113. Rodenbiker HT, Ganley JP, Galgiani JN, Axline SG: Prevalence of chorioretinal scars associated with coccidioidomycosis. Arch Ophthalmol 1981; 99:71-75

114. Defelice R, Wieden MA, Galgiani JN: The incidence and implications of coccidioidouria. Am Rev Respir Dis 1982; 125:49-52

115. Coburn JW: Scalene lymph node involvement in primary and disseminated coccidioidomycosis—Evidence of extrapulmonary spread in primary infection. Ann Intern Med 1962; 56:911-924

116. Jenkins DW Jr: Persistent adenopathy in coccidioidomycosis: An indication for therapy. South Med J 1977; 70:531-532

117. Forbus WD, Bestebreurtje AM: Coccidioidomycosis: A study of 95 cases of the disseminated type with special reference to the pathogenesis of the disease. Milit Surg 1946; 99:653-719

118. Vincent T, Galgiani JN, Huppert M, Salkin D: The natural history of coccidioidal meningitis: VA-Armed Forces Cooperative Studies, 1955-1958. Clin Infect Dis 1993; 16:247-254

119. Hobbs ER: Coccidioidomycosis. Dermatol Clin 1989; 7:227-239

120. Quimby SR, Connolly SM, Winkelmann RK, Smilack JD: Clinicopathologic spectrum of specific cutaneous lesions of disseminated coccidioidomycosis. J Am Acad Dermatol 1992; 26:79-85

121. Bried JH, Galgiani JN: *Coccidioides immitis* infections in bones and joints. Clin Orthop 1986; 211:235-243

122. Bayer AS, Guze LB: Coccidioidal synovitis: Clinical, diagnostic, therapeutic, and prognostic considerations. Semin Arthritis Rheum 1979; 8:200-211

123. Scanarini M, Rotilio A, Rigobello L, Pomes A, Parenti A, Alessio L: Primary intrasellar coccidioidomycosis simulating a pituitary adenoma. Neurosurgery 1991; 28:748-751

124. Rodenbiker HT, Ganley JP: Ocular coccidioidomycosis. Surv Ophthalmol 1980; 24:263-290

125. Hajare S, Rakusan TA, Kalia A, Gibson FB, Strunk CL: Laryngeal coccidioidomycosis causing airway obstruction. Pediatr Infect Dis J 1989; 8:54-56

126. Boyle JO, Coulthard SW, Mandel RM: Laryngeal involvement in disseminated coccidioidomycosis. Arch Otolaryngol Head Neck Surg 1991; 117:433-436

127. Ward PH, Berci G, Morledge D, Schwartz H: Coccidioidomycosis of the larynx in infants and adults. Ann Otol Rhinol Laryngol 1977; 86:655-660

128. Busch RF: Coccidioidomycosis of the external ear. Otolaryngol Head Neck Surg 1992; 107:491-492

129. Harvey RP, Pappagianis D, Cochran J, Stevens DA: Otomycosis due to coccidioidomycosis. Arch Intern Med 1978; 138:1434-1435

130. Loeb JM, Livermore BM, Wofsy D: Coccidioidomycosis of the thyroid. Ann Intern Med 1979; 91:409-411

131. Jamidar PA, Campbell DR, Fishback JL, Klotz SA: Peritoneal coccidioidomycosis associated with human immunodeficiency virus infection. Gastroenterology 1992; 102:1054-1058

132. Ampel NM, White JD, Varanasi UR, Larwood TR, Van Wyck DB, Galgiani JN: Coccidioidal peritonitis associated with continuous ambulatory peritoneal dialysis. Am J Kidney Dis 1988; 11:512-514

133. Schwartz DN, Fihn SD, Miller RA: Infection of an arterial prosthesis as the presenting manifestation of disseminated coccidioidomycosis: Control of disease with fluconazole. Clin Infect Dis 1993; 16:486-488

134. McCaffree MA, Altshuler G, Benirschke K: Placental coccidioidomycosis without fetal disease. Arch Pathol Lab Med 1978; 102:512-514

135. Bylund DJ, Nanfro JJ, Marsh WL Jr: Coccidioidomycosis of the female genital tract. Arch Pathol Lab Med 1986; 110:232-235

136. Saw EC, Smale LE, Einstein H, Huntington RW Jr: Female genital coccidioidomycosis. Obstet Gynecol 1975; 45:199-202

137. Weisman IM, Moreno AJ, Parker AL, Sippo WC, Liles WJ: Gastrointestinal dissemination of coccidioidomycosis. Am J Gastroenterol 1986; 81:589-593

138. Craig JR, Hillberg RH, Balchum OJ: Disseminated coccidioidomycosis—Diagnosis by needle biopsy of liver. West J Med 1975; 122:171-174

139. Howard PF, Smith JW: Diagnosis of disseminated coccidioidomycosis by liver biopsy. Arch Intern Med 1983; 143:1335-1338

140. Weinberg MG, Galgiani JN, Switzer RW, Vega E: Coccidioidomycosis of the urinary bladder, *In* Einstein HE (Ed): Coccidioidomycosis—Proceedings of the 4th International Conference. Washington, DC, National Foundation for Infectious Diseases, 1985, pp 355-359

141. Kuntze JR, Herman MH, Evans SG: Genitourinary coccidioidomycosis. J Urol 1988; 140:370-374

142. Dunne WM Jr, Ziebert AP, Donahoe LW, Standard P: Unexpected laboratory diagnosis of latent urogenital coccidioidomycosis in a nonendemic area. Arch Pathol Lab Med 1986; 110:236-238

143. Conner WT, Drach GW, Bucher WC Jr: Genitourinary aspects of disseminated coccidioidomycosis. J Urol 1975; 113:82-88

144. Abbott KH, Cutler OI: Chronic coccidioidal meningitis: Review of the literature and report of seven cases. Arch Pathol 1936; 21:320-330

145. Buss WC, Gibson TE, Gifford MA: Coccidioidomycosis of the meninges. Calif Med 1950; 72:167-169

146. Einstein HE, Holeman CW Jr, Sandidge LL, Holden DH: Coccidioidal meningitis—The use of amphotericin B in treatment. Calif Med 1961; 94:339-343

147. Schlumberger HG: A fatal case of cerebral coccidioidomycosis with cultural studies. Am J Med Sci 1945; 209:483-496

148. Sobel RA, Ellis WG, Nielsen SL, Davis RL: Central nervous system coccidioidomycosis: A clinicopathologic study of treatment with and without amphotericin B. Hum Pathol 1984; 15:980-995

149. Williams PL, Johnson R, Pappagianis D, et al: Vasculitic and encephalitic complications associated with *Coccidioides immitis* infection of the central nervous system in humans: Report of 10 cases and review. Clin Infect Dis 1992; 14:673-682

150. Wrobel CJ, Rothrock J: Coccidioidomycosis meningitis presenting as anterior spinal artery syndrome. Neurology 1992; 42:1840

151. Ragland AS, Arsura EL, Ismail Y, Johnson R: Eosinophilic pleocytosis in coccidioidal meningitis: Frequency and significance. Am J Med 1993; 95:in press

152. Harrison HR, Galgiani JN, Reynolds AF Jr, Sprunger LW, Friedman AD: Amphotericin B and imidazole therapy for coccidioidal meningitis in children. Pediatr Infect Dis 1983; 2:216-221

153. Wrobel CJ, Meyer S, Johnson RH, Hesselink JR: MR findings in acute and chronic coccidioidomycosis meningitis. AJNR Am J Neuroradiol 1992; 13:1241-1245

154. Carroll GF, Haley LD, Brown JM: Primary cutaneous coccidioidomycosis. Arch Dermatol 1977; 113:933-936

155. Schwartz RA, Lamberts RJ: Isolated nodular cutaneous coccidioidomycosis. J Am Acad Dermatol 1981; 4:38-46

156. Levan NE, Huntington RW Jr: Primary cutaneous coccidioidomycosis in agricultural workers. Arch Dermatol 1965; 92:215-220

157. Winn WA: Primary cutaneous coccidioidomycosis—Reevaluation of its potentiality based on study of three new cases. Arch Dermatol 1965; 92:221-228

158. Morwood DT, Nichter LS, Wong V: An unusual complication of an open-head injury: Coccidioidal meningitis. Ann Plast Surg 1989; 23:437-441

159. Kovacs A, Forthal DN, Kovacs JA, Overturf GD: Disseminated coccidioidomycosis in a patient with acquired immune deficiency syndrome. West J Med 1984; 140:447-449

160. Abrams DI, Robia M, Blumenfeld W, Simonson J, Cohen MB, Hadley WK: Disseminated coccidioidomycosis in AIDS. N Engl J Med 1984; 310:986-987

161. Roberts CJ: Coccidioidomycosis in acquired immune deficiency syndrome—Depressed humoral as well as cellular immunity. Am J Med 1984; 76:734-736

162. Levy RM, Bredesen DE, Rosenblum ML: Neurological manifestations of the acquired immunodeficiency syndrome (AIDS): Experience at UCSF and review of the literature. J Neurosurg 1985; 62:475-495

163. Salberg DJ, Venkatachalam H: Disseminated coccidioidomycosis presenting in AIDS. VA Practitioner 1986; 3:89-93

164. Ampel NM, Dols CL, Galgiani JN: Coccidioidomycosis during human immunodeficiency virus infection—Results of a prospective study in a coccidioidal endemic area. Am J Med 1993; 94:235-240

165. Galgiani JN, Ampel NM: Coccidioidomycosis in human immunodeficiency virus-infected patients. J Infect Dis 1990; 162:1165-1169

166. Graham AR, Sobonya RE, Bronnimann DA, Galgiani JN: Quantitative pathology of coccidioidomycosis in acquired immunodeficiency syndrome. Hum Pathol 1988; 19:800-806

167. Jarvik JG, Hesselink JR, Wiley C, Mercer S, Robbins B, Higginbottom P: Coccidioidomycotic brain abscess in an HIV-infected man. West J Med 1988; 149:83-86

168. Calhoun DL, Galgiani JN, Cukowski C, Copeland JG: Coccidioidomycosis in recent renal or cardiac transplant recipients, *In* Einstein HE, Catanzaro A (Eds): Coccidioidomycosis—Proceedings of the 4th International Conference on Coccidioidomycosis. Washington, DC, National Foundation for Infectious Diseases, 1985, pp 312-318

169. Hall KA, Sethi GK, Rosado LJ, Martinez JD, Huston CL, Copeland JG: Coccidioidomycosis and heart transplantation. J Heart Lung Transplant 1993; 12:525-526

170. Vartivarian SE, Coudron PE, Markowitz SM: Disseminated coccidioidomycosis—Unusual manifestations in a cardiac transplantation patient. Am J Med 1987; 83:949-952

171. Dodd LG, Nelson SD: Disseminated coccidioidomycosis detected by percutaneous liver biopsy in a liver transplant recipient. Am J Clin Pathol 1990; 93:141-144

172. Britt RH, Enzmann DR, Remington JS: Intracranial infection in cardiac transplant recipients. Ann Neurol 1981; 9:107-119

173. Hall KA, Copeland JG, Zukoski CF, Sethi GK, Galgiani JN: Markers of coccidioidomycosis prior to cardiac or renal transplantation and the risk of recurrent infection. Transplantation 1993; 55:1422-1425

174. Rutala PJ, Smith JW: Coccidioidomycosis in potentially compromised hosts: The effect of immunosuppressive therapy in dissemination. Am J Med Sci 1978; 275:283-295

175. Riley DK, Galgiani JN, O'Donnell MR, Ito JI, Beatty PG, Evans TG: Coccidioidomycosis in bone marrow transplant recipients. Transplantation 1994, in press

176. Peterson CM, Schuppert K, Kelly PC, Pappagianis D: Coccidioidomycosis and pregnancy. Obstet Gynecol Surv 1993; 48:149-156

177. Shafai T: Neonatal coccidioidomycosis in premature twins. Am J Dis Child 1978; 132:634

178. Bernstein DI, Tipton JR, Schott SF, Cherry JD: Coccidioidomycosis in a neonate: Maternal-infant transmission. J Pediatr 1981; 99:752-754

179. Wack EE, Ampel NM, Galgiani JN, Bronnimann DA: Coccidioidomycosis during pregnancy—An analysis of ten cases among 47,120 pregnancies. Chest 1988; 94:376-379

180. Walker MP, Brody CZ, Resnik R: Reactivation of coccidioidomycosis in pregnancy. Obstet Gynecol 1992; 79:815-817

181. Peterson CM, Johnson SL, Kelly JV, Kelly PC: Coccidioidal meningitis and pregnancy: A case report. Obstet Gynecol 1989; 73:835-836

182. McCoy MJ, Ellenberg JF, Killam AP: Coccidioidomycosis complicating pregnancy. Am J Obstet Gynecol 1980; 137:739-740

183. Barbee RA, Hicks MJ, Grosso D, Sandel C: The maternal immune response in coccidioidomycosis—Is pregnancy a risk factor for serious infection? Chest 1991; 100:709-715

184. Gifford MA, Buss WC, Douds RJ, Miller HE, Tupper RB: Data on coccidioides fungus infection, Kern County. Bakersfield, Calif, Kern County Dept Public Health Annual Report, 1936, p 39-54

185. Huppert M: Racism in coccidioidomycosis? Am Rev Respir Dis 1978; 118:797-798

186. Pappagianis D, Lindsay S, Beall S, Williams P: Ethnic background and the clinical course of coccidioidomycosis (Letter). Am Rev Respir Dis 1979; 120:959-961

187. Williams PL, Sable DL, Mendez P, Smyth LT: Symptomatic coccidioidomycosis following a severe natural dust storm. Chest 1979; 76:566-570

188. Deresinski SC, Pappagianis D, Stevens DA: Association of ABO blood group and outcome of coccidioidal infection. Sabouraudia 1979; 17:261-264

189. Scheer M, Opelz G, Terasaki P, Hewitt W: The Association of Disseminated Coccidioidomycosis and Histocompatibility Type. 13th Interscience Conference on Antimicrobial Agents and Chemotherapy, 1973, p 157

190. Sun SH, Huppert M, Vukovich KR: Rapid in vitro conversion and identification of *Coccidioides immitis*. J Clin Microbiol 1976; 3:186-190

191. Kaufman L: Laboratory methods for the diagnosis and confirmation of systemic mycoses. Clin Infect Dis 1992; 14(suppl 1):S23-S29

192. Kaufman L, Standard P: Improved version of the exoantigen test for identification of *Coccidioides immitis* and *Histoplasma capsulatum* cultures. J Clin Microbiol 1978; 8:42-45

193. Huppert M, Sun SH, Rice EH: Specificity of exoantigens for identifying cultures of *Coccidioides immitis*. J Clin Microbiol 1978; 8:346-348

194. Standard P, Kaufman L: Evaluation of Leathers-Awasthi medium for identifying *Coccidioides immitis* isolates. J Clin Microbiol 1987; 25:2428-2429

195. Stockman L, Clark KA, Hunt JM, Roberts GD: Evaluation of commercially available acridinium ester-labeled chemiluminescent DNA probes for culture identification of *Blastomyces dermatitidis, Coccidioides immitis, Cryptococcus neoformans,* and *Histoplasma capsulatum*. J Clin Microbiol 1993; 31:845-850

196. Buiuc D, Dobrescu A, Dobrescu G, Petrescu Z, Brănizteanu L: Further comment on the importance of microscopy in clinical microbiology—The argument for the diagnosis of the skin manifestations of histoplasmosis and coccidioidomycosis [in Rumanian]. Rev Med Chir Soc Med Nat Iasi 1990; 94:393-396

197. Wolfson D, Lee S: Coccidioidomycosis diagnosed from bone marrow smear. JAMA 1991; 266:707

198. Sobonya RE, Barbee RA, Wiens J, Trego D: Detection of fungi and other pathogens in immunocompromised patients by bronchoalveolar lavage in an area endemic for coccidioidomycosis. Chest 1990; 97:1349-1355

199. Sobonya RE, Barbee RA: Isolation of *Coccidioides immitis* from bronchoalveolar lavage is diagnostic of infection (Letter). Am Rev Respir Dis 1991; 143:451

200. Campbell SC, Winter JA, Bjelland JC, Wieden M, Sobonya RE, Galgiani JN: Coccidioidomycosis—Clinical Conference in Pulmonary Disease from the Tucson VA Medical Center and the University of Arizona. Chest 1982; 81:488-492

201. Watts JC, Chandler FW, Mihalov ML, Kammeyer PL, Armin AR: Giant forms of *Blastomyces dermatitidis* in the pulmonary lesions of blastomycosis: Potential confusion with *Coccidioides immitis*. Am J Clin Pathol 1990; 93:575-578

202. Berman JJ, Yost BA: Coccidioidomycosis versus pollen (Letter). South Med J 1989; 82:277

203. Graham AR: Fungal autoflorescence with ultraviolet illumination. Am J Clin Pathol 1983; 79:231-234

204. DiTomasso JP, Ampel NM: Diagnosis of Coccidioidomycosis During HIV Infection: Utility of Cytology, Culture, and Transbronchial Biopsy—Abstract No. PO-B09-1361. 9th International Conference on AIDS, Berlin, Germany. New York, NY, World Health Organization, 1993

205. Smith CE, Saito MT, Simons SA: Pattern of 39,500 serologic tests in coccidioidomycosis. JAMA 1956; 160:546-552

206. Smith CE, Whiting EG, Baker EE, Rosenberger HG, Beard RR, Saito MT: The use of coccidioidin. Am Rev Tuberc Pulmon Dis 1948; 57:330-360

207. Pappagianis D, Zimmer BL: Serology of coccidioidomycosis. Clin Microbiol Rev 1990; 3:247-268

208. Kaufman L, Standard PG, Huppert M, Pappagianis D: Comparison and diagnostic value of the coccidioidin heat-stable (HS and tube precipitin) antigens in immunodiffusion. J Clin Microbiol 1985; 22:515-518

209. Johnson JE, Jeffery B, Huppert M: Evaluation of five commercially available immunodiffusion kits for detection of *Coccidioides immitis* and *Histoplasma capsulatum* antibodies. J Clin Microbiol 1984; 20:530-532

210. Huppert M, Bailey JW: Immunodiffusion as a screening test for coccidioidomycosis serology. Sabouraudia 1963; 2:284-291

211. Huppert M, Bailey JW: The use of immunodiffusion tests in coccidioidomycosis—I. The accuracy and reproducibility of the immunodiffusion test which correlates with complement fixation. Am J Clin Pathol 1965; 44:364-368

212. Huppert M, Bailey JW: The use of immunodiffusion tests in coccidioidomycosis—II. An immunodiffusion test as a substitute for the tube precipitin test. Am J Clin Pathol 1965; 44:369

213. Huppert M, Bailey JW, Chitjian P: Immunodiffusion as a substitute for complement fixation and tube precipitin tests in coccidioidomycosis, *In* Ajello L (Ed): Coccidioidomycosis—The Second Symposium on Coccidioidomycosis. Tucson, University of Arizona, 1967, pp 221-225

214. Wieden MA, Galgiani JN, Pappagianis D: Comparison of immunodiffusion techniques with standard complement fixation assay for quantitation of coccidioidal antibodies. J Clin Microbiol 1983; 18:529-534

215. Zimmer BL, Pappagianis D: Immunoaffinity isolation and partial characterization of the *Coccidioides immitis* antigen detected by the tube precipitin and immunodiffusion-tube precipitin tests. J Clin Microbiol 1989; 27:1759-1766

216. Johnson SM, Pappagianis D: The coccidioidal complement fixation and immunodiffusion-complement fixation antigen is a chitinase. Infect Immun 1992; 60:2588-2592

217. Zimmer BL, Pappagianis D: Characterization of a soluble protein of *Coccidioides immitis* with activity as an immunodiffusion-complement fixation antigen. J Clin Microbiol 1988; 26:2250-2256

218. Pappagianis D, Krasnow RI, Beall S: False-positive reactions of cerebrospinal fluid and diluted sera wth the coccidioidal latex-agglutination test. Am J Clin Pathol 1976; 66:916-921

219. Huppert M, Peterson ET, Sun SH, Chitjian PA, Derrevere WJ: Evaluation of a latex particle agglutination test for coccidioidomycosis. Am J Clin Pathol 1968; 49:96-102

220. Yturraspe DJ: Clinical evaluation of a latex particle agglutination test and a gel diffusion precipitin test in the diagnosis of canine coccidioidomycosis. J Am Vet Med Assoc 1971; 158:1249-1256

221. Gade W, Ledman DW, Wethington R, Yi A: Serological responses to various *Coccidioides* antigen preparations in a new enzyme immunoassay. J Clin Microbiol 1992; 30:1907-1912

222. Antoniskis D, Larsen RA, Akil B, Rarick MU, Leedom JM: Seronegative disseminated coccidioidomycosis in patients with HIV infection. AIDS 1990; 4:691-693

223. Kruse D, Cole GT: A seroreactive 120-kilodalton β-1,3-glucanase of *Coccidioides immitis* which may participate in spherule morphogenesis. Infect Immun 1992; 60:4350-4363

224. Cox RA, Sun SH, Dolan MJ, Harrison JL: Localization of the tube precipitin and complement fixation antigens of *Coccidioides immitis* by immunoelectron microscopy with murine monoclonal antibodies. Infect Immun 1992; 60:3315-3324

225. Cole GT, Kruse D, Seshan KR: Antigen complex of *Coccidioides immitis* which elicits a precipitin antibody response in patients. Infect Immun 1991; 59:2434-2446

226. Cole GT, Kruse D, Zhu S, Seshan KR, Wheat RW: Composition, serologic reactivity, and immunolocalization of a 120-kilodalton tube precipitin antigen of *Coccidioides immitis*. Infect Immun 1990; 58:179-188

227. Kruse D, Cole GT: Isolation of tube precipitin antibody-reactive fractions of *Coccidioides immitis*. Infect Immun 1990; 58:169-178

228. Wheat LJ, Connolly-Stringfield P, Blair R, Connolly K, Garringer T, Katz BP: Histoplasmosis relapse in patients with AIDS: Detection using *Histoplasma capsulatum* variety *capsulatum* antigen levels. Ann Intern Med 1991; 115:936-941

229. Wheat LJ, Connolly-Stringfield P, Kohler RB, Frame PT, Gupta MR: *Histoplasma capsulatum* polysaccharide antigen detection in diagnosis and management of disseminated histoplasmosis in patients with acquired immunodeficiency syndrome. Am J Med 1989; 87:396-400

230. Stadalnik RC, Goldstein E, Hoeprich PD, dos Santos PAL, Lee KK: Diagnostic value of gallium and bone scans in evaluation of extrapulmonary coccidioidal lesions. Am Rev Respir Dis 1980; 121:673-676

231. Boddicker JH, Fong D, Walsh TE, Schillaci RF, Moniot AL, Catanzaro A: Bone and gallium scanning in the evaluation of disseminated coccidioidomycosis. Am Rev Respir Dis 1980; 122:279-287

232. Gallis HA, Drew RH, Pickard WW: Amphotericin B: 30 years of clinical experience. Rev Infect Dis 1990; 12:308-329

233. Fiese MJ: Treatment of disseminated coccidioidomycosis with amphotericin B—Report of a case. Calif Med 1957; 86:119-120

234. Hardenbrook MH, Barriere SL: Coccidioidomycosis: Evaluation of parameters used to predict outcome with amphotericin B therapy. Mycopathologia 1982; 78:65-71

235. Diaz M, Puente R, De Hoyos LA, Cruz S: Itraconazole in the treatment of coccidioidomycosis. Chest 1991; 100:682-684

236. Catanzaro A, Fierer J, Friedman PJ: Fluconazole in the treatment of persistent coccidioidomycosis. Chest 1990; 97:666-669

237. Graybill JR, Stevens DA, Galgiani JN, Dismukes WE, Cloud GA, NAIAD Mycoses Study Group: Itraconazole treatment of coccidioidomycosis. Am J Med 1990; 89:282-290

238. Tucker RM, Denning DW, Arathoon EG, Rinaldi MG, Stevens DA: Itraconazole therapy for nonmeningeal coccidioidomycosis: Clinical and laboratory observations. J Am Acad Dermatol 1990; 23(suppl):593-601

239. Galgiani JN, Stevens DA, Graybill JR, Dismukes WE, Cloud GA: Ketoconazole therapy of progressive coccidioidomycosis—Comparison of 400- and 800-mg doses and observations at higher doses. Am J Med 1988; 84:603-610

240. Como JA, Dismukes WE: Systemic antifungal therapy: Focus on new oral azole drugs. N Engl J Med 1993, in press

241. Dismukes WE, Bennett JE, Drutz DJ, Graybill JR, Remington JS, Stevens DA: Criteria for evaluation of therapeutic response to antifungal drugs. Rev Infect Dis 1980; 2:534-544

242. Pappagianis D, Crane R: Survival in coccidioidal meningitis since introduction of amphotericin B, *In* Ajello L (Ed): Coccidioidomycosis—Current Clinical and Diagnostic Status. Miami, Fla, Symposia Specialists, 1977, pp 223-237

243. Glynn KP, Alazraki NP, Waltz TA: Coccidioidal meningitis—Intrathecal treatment with hyperbaric amphotericin B. Calif Med 1973; 119:6-9

244. LeClerc M, Giammona ST: Coccidioidal meningitis—The use of amphotericin B intravenously and intrathecally by repeated lumbar punctures. West J Med 1975; 122:251-254

245. Winn WA: The treatment of coccidioidal meningitis—The use of amphotericin B in a group of 25 patients. Calif Med 1964; 101:78-89

246. Labadie EL, Hamilton RH: Survival improvement in coccidioidal meningitis by high-dose intrathecal amphotericin B. Arch Intern Med 1986; 146:2013-2018

247. Kelly PC, Sievers ML, Thompson R, Echols C: Coccidioidal meningitis: Results of treatment in 22 patients, *In* Ajello L (Ed): Coccidioidomycosis—Current Clinical and Diagnostic Status. Miami, Fla, Symposia Specialists, 1977, pp 239-251

248. Bouza E, Dreyer JS, Hewitt WL, Meyer RD: Coccidioidal meningitis—An analysis of thirty-one cases and review of the literature. Medicine (Baltimore) 1981; 60:139-172

249. Wrobel CJ, Alksne JF: Retromastoid cisternal Ommaya reservoir for intrathecal therapy of coccidioidomycosis meningitis—Technical note. J Neurosurg 1992; 77:476-477

250. Craven PC, Graybill JR, Jorgensen JH, Dismukes WE: High-dose ketoconazole for treatment of fungal infections of the central nervous system. Ann Intern Med 1983; 98:160-167

251. Tucker RM, Galgiani JN, Denning DW, et al: Treatment of coccidioidal meningitis with fluconazole. Rev Infect Dis 1990; 12(suppl 3):S380-S389

252. Tucker RM, Denning DW, Dupont B, Stevens DA: Itraconazole therapy for chronic coccidioidal meningitis. Ann Intern Med 1990; 112:108-112

253. Galgiani JN, Catanzaro A, Cloud GA, et al: Fluconazole therapy for coccidioidal meningitis. Ann Intern Med 1993; 119:28-35

254. Sharkey PK, Lipke R, Renteria A, et al: Amphotericin B lipid complex (ABLC) in treatment (Rx) of coccidioidomycosis, *In* Program and Abstracts of the 31st Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC, American Society for Microbiology, 1991, p 742A

255. Hector RF: Compounds active against cell walls of medically important fungi. Clin Microbiol Rev 1993; 6:1-21

256. Hector RF, Zimmer BL, Pappagianis D: Evaluation of nikkomycins X and Z in murine models of coccidioidomycosis, histoplasmosis, and blastomycosis. Antimicrob Agents Chemother 1990; 34:587-593

257. Kirkland TN, Fierer J: Cyclosporin A inhibits *Coccidioides immitis* in vitro and in vivo. Antimicrob Agents Chemother 1983; 24:921-924

258. High KP, Handschumacher RE: Immunity, microbial pathogenesis, and immunophilins: Finding the keys, now where are the locks? Infect Agents Dis 1992; 1:121-135