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Diagnosis of Pulmonary Coccidioidal Infections

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SUMMARY

A wide variety of pulmonary lesions may be caused by coccidioidomycosis. Suspicion of coccidioidomycosis may be substantiated by careful clinical-epidemiological histories. The first laboratory procedure should be a coccidioidin skin test. If the reaction to the test is positive, serological tests are next. Also, if there is no reaction to coccidioidin, serological tests are still indicated if dissemination is suspected. The more severe the infection, the greater the probability of establishing a diagnosis serologically. In only three-fifths of patients with coccidioidal cavities can the diagnosis be fixed serologically. In such patients if differential skin tests are not conclusive, attempt should be made to recover the fungus. However, this is accompanied by great risk of laboratory infection. Eosinophilia and accelerated erythrocyte sedimentation are only circumstantial items of evidence, as is the appearance of the pulmonary roentgenogram.

COCCIDIOIDOMYCOSIS enters the differential diagnosis whether a pulmonary lesion is discovered during the course of clinical illness or as the consequence of routine or mass x-ray surveys. In either event clinical and epidemiological histories are the first steps in ariving at the diagnosis.

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CLINICAL SPECTRUM

Approximately 40 per cent of naturally-acquired human coccidioidal infections are accompanied by symptoms.[27] Most common are pleurisy, fever, malaise, cough, anorexia, backache, and night sweats. Not infrequently toxic erythema also develops. The patient may be prostrated or he may have only transient malaise. The pleural pain may be so severe as to be mistaken for that of coronary occlusion, nephrolithiasis, cholecystitis or fractured rib, or it may be so mild as to be only a sensation of oppression or tightness in the chest. In some instances the headache of coccidioidomycosis has been attributed to brain tumor or poliomyelitis. The toxic erythema has been confused with measles or scarlet fever. Five per cent of infections in males and as high as 25 per cent[27] of infections in females are accompanied by erythema nodosum or erythema multiforme, often associated with arthralgia. The arthralgia has caused confusion with rheumatic fever. Coccidioidal erythema nodosum must be distinguished from other sensitizing causes such as primary tuberculosis, streptococcosis or drug reactions. However, it is a useful sentinel which even can be used as an index for estimating incidence of coccidioidal infections. The erythema multiforme, which occurs especially on the upper extremities, thorax and face, is more apt to cause confusion and on several occasions has led to a diagnosis of smallpox. Pleural effusion, which is occasionally "silent," is generally associated with the initial infection although where a peripherally-located coccidioidal cavity breaks into the pleural space, hydropneumothorax develops secondary to the bronchopleural fistula.[31] This complication gen-

erally occurs months or years after the initial infection.

While coccidioidal dissemination usually occurs within a few months of the primary infection, a pulmonary lesion may not have been present or frequently has regressed so that the pulmonary roentgenogram is within normal limits when dissemination is diagnosed. It is noteworthy that dissemination occurs most frequently in dark-skinned males, in at least 1 in 100 infections of Negro males as compared with 1 in 400 of white males.[27] Dissemination is least frequent in white females except, as Vaughan suggested,[37] when infection is acquired during the last trimester of pregnancy.

Those are the highlights of the clinical spectrum of primary infection and the epidemiological aspects of disseminated coccidioidomycosis which provide for an index of suspicion.

An additional word should be said with respect to clinical history for coccidioidal pulmonary cavitation. As Winn[40] pointed out, most cavitations are "cyst-like" and silent. Hemoptysis frequently is associated with the condition, but rarely are the lesions progressive nor is the patient comparable to a person with either tuberculous cavitation or disseminating coccidioidomycosis.[31] Similarly, if a pulmonary lesion is proved to be a coccidioidal residual, the physician and patient can both relax. The difficulty is the exclusion of other diagnoses, especially tumor, since asymptomatic lesions detected by mass surveys usually cannot be proved to be coccidioidal unless they are found at a site previously known to have been involved in coccidioidal pneumonitis.

RESIDENCE HISTORY

While the clinical history mainly serves to alert the physician to the possibility that a pulmonary lesion is coccidioidal, a careful residence history frequently provides extremely significant evidence. Of course, persons residing in known endemic areas always are suspect, and for those living outside such areas a history of transient exposure as in touring by automobile or train is a very valuable clue. The author has records of three persons who were infected merely as tourists on trains and of 13 others who were exposed only in riding through an endemic area by automobile or bus. With the knowledge that the incubation period is seven to 28 days, generally 10 to 16 days, it is often possible to fix the time of coccidioidal infection quite firmly by careful interrogation. Of course, the more exotic exposures to dusty products, even human fomites, must not be overlooked and rare cases are encountered in which no residence exposure can be traced. Especially should one be on the lookout for the laboratory-acquired infection.[20, 34] It is axiomatic that unless the most extraordinary facilities are available, whenever Coccidioides is handled on solid media not only the laboratory technician wielding the loop but also those in the environment may become infected. However, as the endemic area is not often thus brought to the patient, it is well to be familiar with the known geographical distribution of Coccidioides.

Several reviews[1, 22, 23, 29] have indicated the endemic areas. Outside North America, Coccidioides has long been recognized in Argentina. Recently Venezuela[3] and the Paraguayan Chaco[9] have been added. While cases have been attributed to Italy, the Balkans and Hawaii, none have been consistently reported from those areas. Those odd cases reported from China and Canada are erroneous. Certainly, the northern states of Mexico are endemic areas. Within the United States of America (Figure 1) beginning at Mission, Texas, the entire Rio Grande Valley westward is involved. The area extends northward spottily around San Antonio but certainly surrounds San Angelo. It stops south of Wichita Falls. The area extends westerly past El Paso into New Mexico. The southern part of New Mexico is involved, but Albuquerque, Santa Fe and all northern New Mexico are spared. Southern and Central Arizona are highly endemic, including both Tucson and Phoenix. At Florence 50 per cent of susceptibles are infected within six months. Northern Arizona is nonendemic, but the regions around St. George in Utah and Las Vegas in Nevada seem to be mildly endemic.

ENDEMIC AREAS IN CALIFORNIA

In California the most famous area is the San Joaquin Valley. In its southern reaches, 25 per cent of susceptibles may be infected annually.[28] The endemicity, as gauged by the incidence of the disease, diminishes from there northward. Near Hanford the incidence is one-half the Bakersfield rate. While as far north as Chowchilla there is a considerable incidence, Merced, only 20 miles farther north on Highway 99, has very few cases. Along the eastern side of the valley the incidence is very spotty in Merced and Stanislaus counties. However, along the west side it extends through Vernalis nearly to Tracy. One or two isolated cases have been noted in Yolo and Contra Costa counties, but there is no really proven endemicity in the Sacramento Valley. The area does extend over the Coast Range into San Benito, Monterey and San Luis Obispo counties. The region around San Miguel (Camp Roberts[24]) and Paso Robles is endemic but the city of San Luis Obispo is not. The westerly portions of Santa Barbara and Ventura counties (to Fillmore) are endemic, as is the northern part of Los Angeles county, apparently including at least the upper portion of the San Fernando Valley. There is spotty endemicity[38] in Riverside and San Bernardino counties as well as San Diego County.[29] More than a year ago Kessel reported on the endemicity of Southern California,[18] and additional delimitation of the area will be important. However, this sketch should recall the clues arising from geographical association. Epidemiological assistance also can come from data with respect to seasonal exposure to the dusty summer and fall or to dust storms. It should be borne in mind, moreover, that even soon after a winter rainstorm, dust frequently blows. Thus, some infections also occur during the rainy season.[25, 28]

Figure 1.—Known coccidioidal endemic areas in the United States of America. (Permission to reproduce outline map by University of Chicago Press.)

ESSENTIAL LABORATORY PROOF

While clinical and epidemiological histories may arouse suspicion and provide supporting evidence, proof that a pulmonary lesion is coccidioidal depends upon laboratory evidence.

Coccidioidin Skin Test

The first procedure should be the coccidioidin skin test. The history of the development of the coccidioidin test has been given in detail.[30] Suffice it to say that Cummings,[6] Davis,[7] Hirsch, Benson and D'Andrea,[10-11] Jacobsen,[13] Beck,[2] Eddie,[12] Kessel[16] and Stewart[35] are some of those to whom great credit is due for developing this very useful test. Now available commercially,* coccidioidin is generally used in 1:100 dilution of a Berkefeld filtrate of multiple cultures of Coccidioides grown on asparagine synthetic medium.

It does not activate old, quiescent infection, nor is the currently provided material antigenic.[30] Therefore, unlike brucellergin, it does not sensitize. Neither does coccidioidin evoke humoral antibodies and interfere with coccidioidal serological tests. While a severe reaction may cause local discomfort and occasionally evoke fever and malaise, there is no focal reaction. The only significant systemic complication which may occur is exacerbation or precipitation of erythema nodosum or erythema multiforme in association with a primary infection.

The result of an intradermal coccidioidin test should be observed at 24 and 48 hours. Induration greater than 5 mm. in diameter should be considered a positive reaction. As the active principle of coccidioidin is mainly carbohydrate, it is quite stable, which probably also accounts for its lack of antigenicity. Kept refrigerated and uncontaminated, even in 1:100 dilution it remains potent at least two years. Care must be taken not to use syringes which have contained other biologic materials unless the equipment is soaked overnight or boiled in dichromate cleaning solution.

The significance of the results of the coccidioidin test are comparable to those of the tuberculin test. The test is diagnostic only when an initial negative result early in infection is followed by a positive reaction upon repeat of the test later — so-called "conversion." In one-sixth of uncomplicated primary infections, 1:100 coccidioidin evokes no reaction during the first week of infection (Chart 1); but unless there is dissemination, there is invariably positive reaction by the fourth week. Thus "conversion" may be diagnostic. Moreover, in endemic areas if tests are repeated every six months, the test provides the most sensitive index of infection.[27, 28] Generally, it can only serve as a screen. However, if the subject tested has merely traveled through or resided a short time in an endemic area, logically a positive reaction can be considered very significant. Moreover, when erythema nodosum is suspected to

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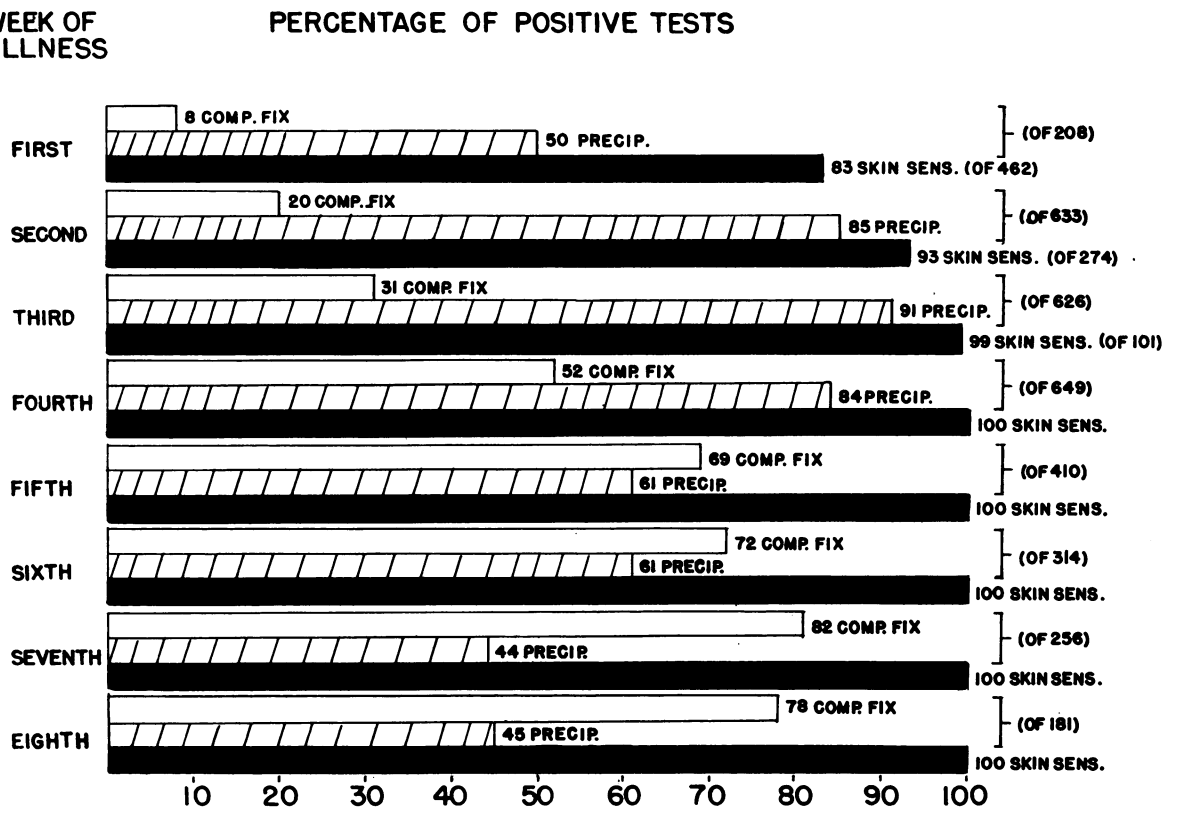
Chart 1.—Percentage distribution of positive precipitin and complement-fixation tests in sera and 1:100 coccidioidin tests in skin of patients with primary non-disseminating coccidioidomycosis (by weeks of illness).



be coccidioidal, a negative result eliminates that diagnosis since the skin lesions are themselves manifestations of hypersensitivity.[25]

Skin tests may differentiate between tuberculous and coccidioidal pulmonary lesions. Not infrequently pulmonary cavities or residuals have been established as coccidioidal when the result of a tuberculin test proved negative.

However, when a patient's infection is disseminated or an extrapulmonary lesion already has developed, there may be no reaction even to undiluted coccidioidin.[31] Moreover, there is association between sensitivity and favorable prognosis of disseminated infection, between anergy and poor outlook.

Dermal sensitivity generally persists for many years. However, sometimes it wanes and occasionally persons with coccidioidal cavities may have no reaction to coccidioidin more dilute than 1:10, and very rarely may not react to material even in that concentration.[30] That this is not the result of failure of antigenic "coverage" has been noted in several instances, when results of skin tests were negative but coccidioidin from the same strains fixed complement in the sera of the same patients. Coccidioidin in concentration of 1:10 or more must be used cautiously, for non-specific reactions may occur.[32] Coccidioidin does not cross-react with bacterial, viral or rickettsial infections; occasionally there have been cross-reactions noted with other mycotic antigens, notably haplosporangin, histoplasmin and blastomycin.[8, 26, 29, 32] Histoplasmin is more apt to cross-react in coccidioidal infections than coccidioidin in those dominantly sensitive to histoplasmin. However, when the antigens are used in balance, there is rarely difficulty in ascertaining which infection is dominant.[17, 18, 19, 32] Moreover, history of residence in the Mississippi Valley or the tropics can usually aid in fixing dominant histoplasmin sensitivity.

Serological Tests

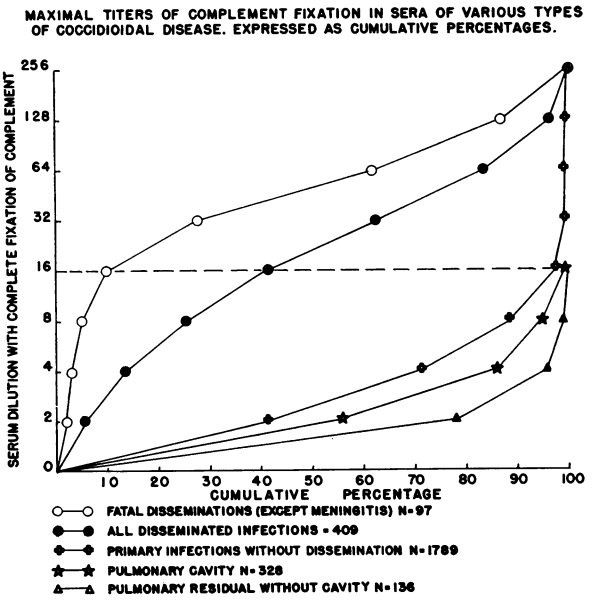
If coccidioidin sensitivity has been demonstrated, or if the test result is negative but the patient is suspected to be undergoing coccidioidal dissemination or has a very thin-walled, "nonreactive" cavity and an accusative residence history, serological tests come next.[33] If a patient is merely undergoing a respiratory illness suspected to be coccidioidal, serological tests should be deferred until "conversion" of the coccidioidin test to positive takes place. The diagnostic humoral antibodies develop more slowly than dermal sensitivity (Chart 1). Thus, while only one-sixth of the patients with uncomplicated primary infections have no reaction to 1:100 coccidioidin in the first week of the disease, fully one-half of those who ultimately will become serologically positive do not have precipitins and nine-tenths do not have complement-fixing antibodies so early. If

the skin test reaction becomes positive, serological tests may be requested. If combined precipitin and complement fixation tests are done repeatedly in patients with coccidioidal disease so severe as to require hospitalization, the results will be diagnostic in over nine-tenths of cases. If dissemination occurs, the reaction to these tests is positive in over 99 per cent of cases. The tests are diagnostic in approximately three-fifths of cases in which there is coccidioidal cavitation. They are seldom positive in patients with asymptomatic pulmonary residuals, but qualify as appropriate "long shots."

The methods of carrying out these serological tests and interpreting them have been described in detail.[33] In precipitin tests, made with a constant quantity of serum and increasing dilutions of appropriate antigen, the results are indicated by buttons which develop over a period of five days. In a series of over 3,200 positive serological tests in patients with non-disseminating primary infection, precipitins alone were positive in 44 per cent. Thus, the test is important where the acute phase of infection is suspected. It must be reiterated that serological tests should be withheld until the skin tests convert. The precipitin antibodies begin reverting in the third week of the disease and seldom persist longer than four months. The complement fixation test is done with serial dilutions of serum as in any quantitative Kolmer test.[17, 33] Positive reaction may continue into the third month (Chart 1) but in some cases reversion begins in the second month. Complement fixation may persist for several years, even with uncomplicated infections. When dissemination has occurred, even after recovery it may continue indefinitely. However, even when there is a residual pulmonary lesion or cavity formation, after several years the results of serologic tests are frequently entirely negative or equivocal. Thus when an acute, pneumonic-type illness is suspected as coccidioidal, both precipitin and complement fixation tests are appropriate. With more long-standing infections, especially for the diagnosis of old asymptomatic pulmonary residuals or cavities, only complement fixation tests need be done.

The titer of complement fixation correlates with the severity of the coccidioidal infection (Chart 2). Thus two-fifths of nearly 1,800 patients with uncomplicated primary infections whose sera fixed complement had titers no higher than the first dilution (1:2) while only one-fortieth had titers exceeding 1:16. Over half of 328 patients with coccidioidal cavities whose sera fixed complement had a titer of only 1:2 while only one in a hundred exceeded 1:16. In contrast three-fifths of over 400 patients with disseminating infections had titer over 1:16 and nine-tenths of approximately 100 patients with extensive, fatal disseminating infections exceeded that level. Negative results of serologic tests do not eliminate Coccidioides as the cause of a residual pulmonary lesion with or without cavitation. However, progressive coccidioidal pulmonary disease can usually be excluded if results are negative. The author has records of many cases of patients with primary or

CHART 2



metastatic pulmonary malignant disease or with tuberculosis in which suspicion of coccidioidomycosis could be eliminated because of negative results of serologic tests. Of course, diseases may coexist, so positive reaction to tests for coccidioidal infection does not necessarily eliminate concomitant tuberculosis or cancer from consideration. However, serial tests have given clues. When pulmonary lesions increase depite stable or falling serological titers, an additional non-coccidioidal cause is virtually certain.

Commercial provision, in the near future, of antigens for precipitin and complement fixation tests and the positive control serum requisite for the latter is probable.

Culture; Isolation of Coccidioides

Demonstration of Coccidioides is irrefutable proof of coccidioidal infection. Even during the acute primary infection a patient may not raise sputum. Unfortunately, with asymptomatic coccidioidal pulmonary residuals, results of sputum and gastric cultures are characteristically negative. The most damning objection to sputum cultures is the hazard of laboratory infections.[34] As was mentioned previously, handling of cultures on solid media almost inevitably results in laboratory infections. Coverslip examinations of sputum are safe but notoriously uncertain. The "spherules" (sporangia) with endospores may be missed or artifacts may be "identified" as Coccidioides. Culture on malt, Sabouraud's agar, or differential media[26] with inoculation of material from suspicious cultures intraperitoneally into white mice or intraperitoneally or intratesticularly into guinea pigs is necessary to complete identification as Coccidioides.

It must be admitted that in certain instances there is no substitute for culturing. For instance, in pa-

tients with pulmonary cavitation when results of both tuberculin and coccidioidin tests are positive and of serologic tests negative or equivocal, only recovery of the etiological agent will establish the diagnosis. In such circumstances the best procedure is to make cultures and, if suspicious growth occurs, to send the specimen to a place where subcultures can be made with safety.

Hematological Studies

Of accessory aid in the evaluation of pulmonary lesions are counts of leukocytes in the blood and determination of the erythrocyte sedimentation rate. During the acute illness eosinophilia can rise as high as 89 per cent.[39] Polymorphonuclear leukocytosis in the region of 10,000 to 14,000 with a high proportion of banded forms is frequent early in the illness, and this phenomenon is usually succeeded by lymphocytosis. In patients with coccidioidal cavities or pulmonary residuals the leukocyte count is normal.

The sedimentation rate usually is accelerated during "active" infection. Slowing of the rate is an index of recovery. A normal sedimentation rate in nearly three-fourths of 150 cases of coccidioidal cavitation has been reported[31]—further evidence that in most of such cases the infection is quiescent.

ROENTGENOGRAMS

Roentgenographic evidence may cause suspicion of a coccidioidal pulmonary lesion. Extensive descriptions[4, 5, 14, 15, 21, 31, 36, 40] of the various coccidioidal lesions in the lungs have been presented. However, roentgenograms can never establish the diagnosis. Radiologists with long experience may be correct nine times out of ten, and with thin-walled coccidioidal cavities may score even higher. However, as with a well-nigh indicting residence history, the diagnosis still depends upon other laboratory means.

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