Coccidioidal Pericarditis

By Roger Larson, M.D., and Robert E. Scherb, M.D.

In endemic areas where coccidioidomycosis is encountered, pericarditis of an occult etiology warrants a careful search for coccidioidomycosis. A coccidioidin skin test is helpful. The established diagnosis, however, depends upon positive coccidioidal complement fixation and precipitin tests, or recovery of the organism from the sputum or the pericardial fluid.

Coccidioidomycosis is a disease that occurs endemically in the San Joaquin Valley, although it is found also in arid regions of Arizona, New Mexico and Western Texas. The causative organism is a fungus, Coccidioides immitis (Rixford and Gilchrist, 1896). Before World War II it was generally conceded that a physician residing outside such endemic areas needed only a “reading acquaintance” with this disease. At the present time this concession is no longer tenable, since 6,000 to 8,000 new cases have been shown to have existed in clinically recognizable forms in transient military personnel from various military installations in these endemic areas. An increased number of cases have also been found throughout other supposedly coccidioidal-free areas, the only past history of exposure being that the subject has passed through endemic areas either by bus, automobile or train.

Excellent reviews have been presented by Forbus from material collected from the Armed Forces Institute of Pathology and by Schwarz and Muth, each with their attendant bibliographies. It is sufficient to note that the reported cases of cardiac and/or pericardial involvement were limited to those of disseminated coccidioidal involvement.

Briefly, to aid in following the data presented, it is of interest to note that disseminated coccidioides is much more prevalent in Negroes and Filipinos than in members of the white race.

Erythema nodosum occurs approximately about 8 to 15 days after onset of the disease in 5 per cent of all cases and in 20 per cent of all symptomatic cases.

Skin testing by coccidioidin (made from cultures of Coccidioides immitis) shows that 60 per cent of the positive skin reactors have had no history of clinical symptoms due to the disease. Skin testing will not cause future sensitization to skin testing nor produce positive precipitin or complement fixation reactions. However, it will often precipitate or exacerbate erythema nodosum or multiforme. Skin sensitivity lasts from 1 to 10 years, the latter being the most usual. The most important skin sensitivity reaction is the “change-over” reaction, symbolizing recent infection. The appearance of such sensitivity may occur 10 to 45 days after exposure or 2 to 21 days after onset of the disease.

The disseminated type is four times more frequent in Negros and 18 times more frequent in Filipinos than in the white subjects, while incidence being approximately 1:500 in the white race. In acute disseminated coccidioides 70 per cent will fail to react to any dilution, whether it is 1:100, 1:10 or undiluted coccidioidin. Cross reaction may be found to histoplasmosis or blastomycosis.

Diagnosis by culture and direct smears is not so efficacious as by tissue biopsy.

Complement fixation and precipitin tests are the most reliable tests for diagnosis and prognosis. The precipitin test becomes positive in low-grade primary infection, and persisting through, becomes negative before the complement fixation test; the latter remains positive much longer. The complement fixation test may never become positive with mild infection of primary type but is prognostic when positive in the disseminated form. Oddly enough, it is oftentimes negative with cavitation.

From the Internal Medicine Department, Kern General Hospital, Bakersfield, Calif.
Thus we may present the following chart:

<table>
<thead>
<tr>
<th>Disease</th>
<th>Skin Test</th>
<th>Precipitin Test</th>
<th>Complement Fixation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute benign infection</td>
<td>+</td>
<td>- or +</td>
<td>-</td>
</tr>
<tr>
<td>Acute severe, focal, not disseminated</td>
<td>+</td>
<td>+</td>
<td>- or +</td>
</tr>
<tr>
<td>Disseminated</td>
<td>(70%)</td>
<td>+ or -</td>
<td>+</td>
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</tbody>
</table>

The sedimentation rate has been found elevated by all observers. In patients with cavitation, the sedimentation rate is normal in at least 70 per cent. A fall in the sedimentation rate is a good prognostic sign.

X-ray review shows that the areas of par enchymatous lung involvement are most often in the midlung region, followed by lower lobe involvement, the least affected being the apical region.

<table>
<thead>
<tr>
<th>Date</th>
<th>Precipitin Test</th>
<th>Complement Fixation</th>
</tr>
</thead>
<tbody>
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<td>0  26  0  0 0  0  0</td>
<td>0</td>
</tr>
<tr>
<td>3/12/51</td>
<td>0  28  0  0 0  0  0</td>
<td>0</td>
</tr>
<tr>
<td>3/21/51</td>
<td>0  28  4+  4+ 4+ 3+ 0</td>
<td>0</td>
</tr>
<tr>
<td>4/3/51</td>
<td>0  36  0  0 0  0  0</td>
<td>0</td>
</tr>
<tr>
<td>4/20/51</td>
<td>0  29  4+  4+ 0  0  0</td>
<td>0</td>
</tr>
<tr>
<td>7/24/51</td>
<td>0  3   0  0 0  0  0</td>
<td>0</td>
</tr>
</tbody>
</table>

The literature is replete on the pathologic findings on the various forms of coccidioides. Microscopically, it is known that a specific tissue reaction accompanies the different developmental stages of the spherule and that the coccidioidal granuloma is rather pleomorphic, though sufficiently characteristic to lead to a suspicion of a specific granuloma and to a search for the offending pathognomonic spherules.

Case Reports

Case 1. C. W., a 49 year old Negro man, was admitted to the hospital on Feb. 20, 1951, with the chief complaint of chest pain. This involved the lower end of the sternum with radiation to the left shoulder and felt like a "great pressure" in the sternal region. The patient had experienced some dyspnea and cough since the onset of his present illness. The past and family history were of no additional value.

Physical examination revealed a well-developed, well-nourished Negro man who was in severe pain. The temperature was 37.5 C., pulse 84, respirations 18, and blood pressure 110/70. Examination of the lung fields revealed no abnormal findings.

A loud, harsh precordial friction rub was heard in the third and fourth intercostal spaces, just to the left of the sternum. The heart tones were somewhat faint. No murmurs were heard. The cardiac rhythm was regular.

The following day the friction rub had completely disappeared. The patient ran a febrile course from 37.5 to 38 C. for the first week of hospitalization and remained afebrile thereafter. For two weeks he continued to have exacerbations and remissions of his substernal pain. The total period of hospitalization was six weeks. He was last seen in the outpatient clinic on Dec. 21, 1951, at which time he was asymptomatic and doing hard agricultural labor. Physical examination at that time was entirely normal.

Laboratory Data: The while blood cell count was 6,700, with 78 per cent polymorphonuclear leukocytes, 17 per cent lymphocytes and 5 per cent monocytes. The sedimentation rate was 26 mm. in one hour. The Kahn test was negative. A chart of the serologic reactions is presented in table 1. The skin test with coccidioidin was positive and the Mantoux test was negative at 1:100.

An x-ray film made on Feb. 20, 1951 (fig. 1) showed an infiltrative process in the lower portion of the right lung field compatible with an acute pneumonitis. On March 20 (fig. 2) there was almost complete clearing of the infiltration.

The features of the electrocardiogram made on Feb. 21, 1951 are shown in fig. 3. The total picture was that of a diffuse subepicardial injury, which is characteristic of pericarditis. The electrocardiogram had returned to normal by December 21.

In summary, this 49 year old Negro man was admitted to the hospital because of severe substernal pain. The findings of a pericardial friction rub on physical examination and the characteristic changes in the electrocardiogram established the diagnosis of pericarditis. The etiology was established by the findings of pneumonitis on x-ray study, a positive coccidioidal pericarditis.
iodin skin test and a positive complement fixation test for coccidioidomycosis. The eventual course over a nine-month period of follow-up was one of complete recovery without dissemination.

Case 2. W. T., a 26 year old Negro man, was admitted to the hospital on Aug. 20, 1950 because of fever and substernal pain for two days. The pain was dull and constant in character and was aggravated by respiration. The patient also complained of fever, chills, headache and nausea.

Physical examination revealed a well developed, well nourished Negro man who was acutely ill. The blood pressure was 120/70, pulse 130, respirations 30, and temperature 40.6 C.

On examination of the lungs a few scattered post-tussive rales were heard posteriorly in both lower lung fields. There was no impairment of resonance and the breath sounds were normal. The cardiac rate was 130 and the rhythm was regular. No murmurs or friction rubs were heard.

The patient remained febrile for 11 days with a gradual subsidence of the temperature to normal. He continued to complain of some precordial and substernal pain until a few days before discharge on Sept. 19, 1950.

Laboratory data: The hemoglobin was 11.3 Gm. The white blood cell count was 9,200 with 76 per cent polymorphonuclear leukocytes and 24 per cent lymphocytes. The sedimentation rate was 30 mm. in one hour. The coccidioidin skin test was positive and the Mantoux test negative. Coccidioidal serologic reactions are summarized in table 2. Three concentrated sputum specimens were negative for tubercle bacilli on smear and one on culture.

X-ray films of the chest made on Aug. 24, 1950 showed a definite infiltrative process extending from the left hilar area to the left first anterior intercostal space with prominence of the left hilar area, suggestive of hilar adenopathy.

An electrocardiogram made on Aug. 31, 1950 (fig. 4) showed findings compatible with the diagnosis of pericarditis.

Second admission: The patient was readmitted on Oct. 12, 1950 for left precordial pain. Because of the severity of the pain the admission diagnosis was said to be possible myocardial infarction. At this time physical examination was entirely negative, except for a temperature of 37.5 C.

The coccidioidal serologic findings are shown in table 2. Seven concentrated sputum specimens were negative for tubercle bacilli on smear and three cultures were negative for *Mycobacterium tuberculosis* and *Coccidioides immitis*.

Subsequent admissions: The patient was admitted on three more occasions with the same complaint of precordial or substernal pain. On each occasion the coccidioidal serology was elevated and the electrocardiogram showed similar abnormalities. A summary of some of the laboratory work is presented in table 2.

![Fig. 1. C. W. Case 1. Posterior-anterior teleoentgenogram of the lungs taken Feb. 26, 1951 showing infiltration in right lung compatible with coccidioidomycosis.](image1)

![Fig. 2. C. W. Case 1. Posterior-anterior teleroentgenogram of the lungs taken March 20, 1951 showing partial clearing of infiltration in right lung. Infiltration compatible with coccidioidomycosis.](image2)
friction rub was ever heard, but the electrocardiograms presented sufficient abnormality. The patient was lost to follow-up after a year.

FIG. 3. C. W. Case 1. Electrocardiogram taken Feb. 21, 1951. Findings of elevation of S-T segment noted in all limb leads and in V leads. Elevation most marked in the V leads and compatible with pericarditis.

In the S-T and T segments to be compatible with a diagnosis of pericarditis. The coccidoidal etiology was established by skin sensitiv-

TABLE 2.—Serologic Studies in Case 2

<table>
<thead>
<tr>
<th>Date</th>
<th>Precipitin Test Un-</th>
<th></th>
<th>Complement Fixation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sed. Rate</td>
<td>1 10</td>
<td>1 40</td>
<td>1 100</td>
</tr>
<tr>
<td>----------</td>
<td>---------------------</td>
<td>----------</td>
<td>---------------------</td>
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<tr>
<td>8/21/50</td>
<td>30</td>
<td>4+ 4+</td>
<td>4+ 0 0 0</td>
<td>0 0 1+</td>
</tr>
<tr>
<td>10/4/50</td>
<td>32</td>
<td>4+ 4+</td>
<td>4+ 0 0 0</td>
<td>0 0 1+</td>
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<tr>
<td>10/30/50</td>
<td>4+</td>
<td>4+ 4+</td>
<td>4+ 0 0 0</td>
<td>0 0 1+</td>
</tr>
<tr>
<td>2/7/51</td>
<td>23</td>
<td>0</td>
<td>0 0 0 0</td>
<td>0 0 1+</td>
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<td>0</td>
<td>0</td>
<td>0 0 0 0</td>
<td>0 0 1+</td>
</tr>
</tbody>
</table>

At that time he had showed no evidence of dissemination, but his serology remained elevated.
Case 3. W. W., a 60 year old white man, first came to the outpatient clinic of Kern General Hospital on Dec. 20, 1949 with the complaint of cough and weight loss. An x-ray film of the chest revealed a lesion in the left apex. Skin test for tuberculosis (Mantoux) was negative but the coccidioidin skin test was positive. Two concentrated sputum specimens were negative for acid-fast bacilli, and one gastric washing was negative on direct smear and guinea pig inoculation. The patient refused hospitalization for further study and was not seen again until Jan. 22, 1951 at which time he was in a state of congestive failure.

Physical examination revealed a well developed, poorly nourished white male who was slightly dyspneic at rest. The chest was typically emphysematous. No rales were heard. The heart tones were somewhat soft and the second aortic and pulmonic sounds were equal. Blood pressure was 110/70. The abdomen was scaphoid in contour. Liver dullness could be percussed 5 cm. below the costal margin at the right midclavicular line. There was a plus 2 pitting edema of the ankles.

The patient did not respond to treatment with salt-free diet, digitalis and mercurial diuretics. He became progressively worse and he expired on Feb. 2, 1951 approximately 11 days after admission.

Laboratory data: The hemoglobin was 9.9 Gm. The red blood cells numbered 3,620,000 and white blood cells 20,050. A differential count revealed 76 per cent polymorphonuclear leukocytes with 7 per cent stab forms, 20 per cent lymphocytes and 7 per cent eosinophiles. The nonprotein nitrogen was 56 and creatine 1.5 mg. per 100 cc. The Kahn test was negative. The coccidioidin skin test was positive and the Mantoux negative.

X-ray films of the chest read on Jan. 25, 1951 (fig. 5) showed a marked pulmonary emphysema. In the central and upper lung fields the markings were dense and increased, suggesting old fibrosis.

The electrocardiographic pattern is shown in figure 6 (patient on digitalis).

Autopsy: Only the gross and microscopic findings of the heart and lungs are given with a list of final anatomic diagnoses.

The heart weighed 640 Gm. The parietal pericardium was densely adherent to the epicardium...
over the entire heart. In a few areas over the anterior portion of the heart the pericardium could be separated with difficulty from the epicardium. The myocardium was reddish brown and showed no evidence of scarring or fibrosis.

The lungs were large, voluminous and very crepitant to palpation. There were numerous emphysematous bullae on the surface of the lung, especially marked at the left base. In the region of the left apex the lung showed dense adhesions. On cutting through this area a section was discovered with little lung tissue but made up primarily of granulomatous or fibrous tissue and containing numerous smooth-lined spaces, presumably dilated bronchioles. This was thought to be an area of bronchiectasis.

Microscopically the myocardial fibres were well preserved. Several distinct small granulomas were seen in the thickened pericardium. These consisted of centers of necrosis, surrounded by epithelioid cells. Several giant cells of the Langhans type were seen in the granuloma. One of these giant cells contained a clear spherical body with a definite wall or capsule. This was interpreted as a spherule of Coccidioides immitis. Acid-fast stains of the pericardium failed to reveal any acid-fast bacilli. A slide stained by the Hotchkiss-McManus technic for fungi revealed one spherical body, which took a light red stain.

Sections through the lesion in the left apex revealed many granulomas, consisting of necrotic centers surrounded by epithelioid cells and lymphocytes. Giant cells of the Langhans type were again seen in these granulomas. Acid-fast stains failed to reveal any acid-fast bacilli. Slides stained by the Hotchkiss-McManus technic for fungi revealed several spherules of Coccidioides immitis.

In summary, this 60 year old white man was admitted to the hospital in congestive heart failure and expired 11 days later. X-ray films of the chest showed fibrosis in the upper lung fields and marked pulmonary emphysema. The coccidioidin skin test was positive and the Mantoux test negative. Previous sputum specimens had been negative for tubercle bacilli on smear, culture and guinea pig inoculation. The clinical diagnoses were pulmonary fibrosis and emphysema with cor pulmonale. These diagnoses were substantiated at autopsy, but in addition a totally unsuspected chronic adhesive pericarditis was discovered. A clue to the etiology was found in some granulomatous lesions in the apex of the left lung which microscopically revealed small granulomas containing spherules of Coccidioides immitis. Granulomas of the same microscopic structure were found in the pericardium. Special stains of the pericardium and lung failed to reveal any acid-fast bacilli. One probable spherule was seen in a giant cell in the pericardium.

In view of both the positive and negative findings it was felt justified to make the diagnosis of chronic adhesive pericarditis, due to coccidioidomycosis.

**Discussion and Summary**

Pericarditis is a well-known complication of pulmonary tuberculosis. This is generally considered to be the result of retrograde lymphatic extension or contiguous spread from a pulmonary source. It would be strange, therefore, if coccidioidomycosis, which so characteristically involves the hilar lymph nodes, did not occasionally produce pericarditis without generalized dissemination. Yet a search of the...
medical literature failed to reveal any completely documented case reports of this complication. Three cases which the authors feel justify the recognition of such an entity have been presented in this report.

The first patient showed a complete recovery both clinically and serologically. The second patient still evidenced continued activity after a year. The third patient had a chronic adhesive pericarditis, at necropsy. The microscopic appearance was that of a granulomatous process indistinguishable morphologically from tuberculosis. The diagnosis rested on the identification of spherules in the lung and in a giant cell in the pericardium, as well as the exclusion of tuberculosis by a negative skin test, negative sputum studies, and negative stains of the pathologic material.

All three patients had negative tuberculin skin tests and positive coccidioidin sensitivity. The coccidioidal serology was positive in two cases and was not determined in the third, because the diagnosis was not recognized until after necropsy. In the two patients who had sputum studies no tubercle bacilli were recovered on smear, culture or guinea pig inoculation.

All three showed roentgenologic evidence of pulmonary disease. This ranged from a frank pneumonitis with rapid clearing in the first to a chronic pulmonary fibrosis in the third.

The electrocardiographic findings were classical for pericarditis in one, compatible with pericarditis in a second and entirely nonspecific in the third. No marked pericardial effusion, so often seen in tuberculosis, was observed in any of these three patients. The necropsy findings on one make it clear that structural changes can be produced in the pericardium which might ultimately embarrass cardiac function and lead to a Pick's syndrome. Two of the patients were mistakenly diagnosed at some time in their course as myocardial infarction.

It is believed that coccidioidal pericarditis must be considered in the differential diagnosis of any patient living in or having visited an endemic area who presents the picture of pericarditis or myocardial infarction. This diagnosis may be strengthened by the finding of a coincident pneumonitis on x-ray study and a positive coccidioidin skin test. The ultimate diagnosis rests on positive coccidioidal complement fixation and precipitin tests or recovery of the organism from the sputum.

**SUMARIO ESPAÑOL**

En áreas endémicas donde la coccidioidomicosis se encuentra, pericarditis de etiología obscura merece una investigación para coccidioidomicosis. Una prueba de piel para coccidioidomicosis es de valor. Para establecer el diagnóstico, sin embargo, se depende de una prueba de fijación de complemento y una prueba de precipitación, o recogido del organismo del esputo o el fluido pericardico.

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ROGER LARSON and ROBERT E. SCHERB

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