ORIGINAL ARTICLES

"VALLEY FEVER" OF THE SAN JOAQUIN VALLEY AND FUNGUS COCCIDIOIDES*

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DISCUSSION *by K. F. Meyer, M.D., Ph.D., San Francisco; Hiram E. Miller, M.D., San Francisco; Roland B. Tupper, M.D., Fresno.*

A FEBRILE disease which has been recognized in the San Joaquin Valley for many years has occurred so frequently that it is known locally as "valley fever." It is characterized by a cold or bronchopneumonia, often with a relatively high fever—up to 103 or 104 degrees Fahrenheit—the appearance of very painful erythema nodosum, with lesions particularly over the shins, although they may appear elsewhere, and usually rather prompt recovery. The etiology has been unknown, and has been the basis of much conjecture among the physicians of the Valley. Nearly twenty years ago an epidemiologist of the State Board of Health made a visit to Bakersfield at the request of several local physicians, but failed to identify the cause of the malady. It is curious that, although cases of the disease appear to have been very numerous, they do not seem to have been described in the literature, probably because valley fever rarely, if ever, has been considered to be a cause of death.

The following cases have been seen by me in consultation at the Stanford Medical School and, I believe, offer complete proof that the disease is a primary acute manifestation of infection with the coccidioides fungus. It is interesting that, among fourteen consecutive patients with advanced coccidioidal granuloma who were admitted to Kern County Hospital in 1935, three gave histories of having had valley fever.

REPORT OF CASES

CASE 1.—H. D. C., age 26. Medical student. Seen with Dr. P. H. Pierson.

The family history and record of previous illnesses were unimportant, in so far as the current illness was concerned.

On the morning of August 28, 1929, he commenced work on a research problem on the life cycle of fungus coccidioides, and inadvertently opened a petri dish culture of the fungus which was several months old and dried out. When the cover of the petri dish was lifted, he noticed a light-brownish cloud arising from the dish. Undoubtedly, this was a cloud of chlamydospores which were well developed in the fungus at that time. In so far as is known, this was his only direct exposure.

On September 6, nine days later, he noticed pains in the chest, resembling pleurisy pains, which increased in severity during the day. In the evening he was examined by a physician, who found no signs of disease in the chest but who strapped the chest to restrict movement. The temperature was 99 degrees Fahrenheit. For the next nine days he was far from well; he said he was tired by 10 a. m. His cough was more severe and was painful, and on several occasions he was forced to leave his work and go home to bed. In the mornings there was much purulent sputum, which sometimes was streaked with blood. He had nearly constant headache, backache, and aching in the legs. He had the feeling that he had fever, but did not take his temperature. On September 19 he found that he had lost fifteen pounds in weight in two weeks.

On September 19, an x-ray of the chest was taken and Doctor Chamberlain summarized his report as follows:

"From the x-ray standpoint there seems to be a massive involvement of the right upper lobe with tuberculosis; lobar pneumonia is, of course, a possibility from the x-ray standpoint, but my impression is that the patient's clinical picture rules out pneumonia and makes tuberculosis the much more likely as an explanation."

The patient was put to bed, and his temperature was found to range between 99 and 101 degrees Fahrenheit.

On September 25, a painful red nodule developed on one of the shins, and the next day there were several similar nodules over both shins. These were red, hot, and tender, and measured about 1.5 centimeter in diameter. They began to subside by September 30, and by October 3 were practically gone.

On October 17, 1929, Doctor Chamberlain reported: "The abnormal densities in the left lung have entirely disappeared. The abnormal densities in the right upper lobe are considerably more than half-gone in the present examination. There remains just a trace of the former mottling and consolidation in the caudal portion of the right upper lobe."

On November 14, a second eruption of erythema nodosum appeared, which reached its maximum in about three days and then disappeared.

On November 25, Doctor Pierson made a note: "Progressively better. No cough or other pulmonary symptoms."

The patient spent about five months in Arizona and then returned to work. He has had no indication of further trouble and repeated x-ray examinations of the chest have been reported normal.

Laboratory Tests

On September 29, 1929, there were 10.800 leukocytes, of which 57 per cent were polymorphonuclear and 7 per cent were eosinophils. The eosinophils dropped to 2 per cent of 5,650 polymorphonuclear forms until November 21, when they were again 5 per cent of 5,500 polymorphonuclear cells. This was at the time of the second eruption of erythema nodosum.

The first sputum for examination was received on September 24, 1929, and the last on September 27. The production of sputum ceased at that time and no further samples could be obtained.

Sputum report: First specimen of sputum was received September 24, 1929.

Smears show moderate numbers of pus cells and a few lymphocytes. There are many Gram-positive cocci occurring in pairs and chains. No acid-fast bacilli were seen in direct and antiforminized specimens.

Cultures show growth in forty-eight hours of white fungus.

The third specimen was received September 26, 1929: Smear showed no acid-fast bacilli. Direct cover-slip preparations showed moderate numbers of spherules with double-contoured capsules, the majority nonsporulating, but a few showing endospores, and a few collapsed capsules. Guinea pig 78 was injected. The animal was killed November 1, and showed moderate enlargement of inguinal and axillary glands which, on histologic examination, showed typical lesions and spherules of coccidioides infection.

Subcultures of the culture of fungus were injected into guinea pigs on November 6. All developed typical lesions of coccidioides with many sporulating and nonsporulating spherules.

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CASE 2.—G. S., age 26. Field geologist for an oil company. Patient of Dr. P. H. Pierson.

The family history and previous illnesses are unimportant.

He had been well and strong before the current illness. In December, 1929, he was working near Bakersfield in Kern County. On the 28th he did not feel well, and two days later had nausea, vomiting, and diarrhea for one day.

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On January 1, he had stabbing pains in the upper left chest on breathing, but this soon subsided. Temperature was 101.5 degrees Fahrenheit. He felt bad, was constipated, and was able to work only part time. On January 9 and 10, he had aching and pains in the ankles and wrists, and began to cough and raise sputum. He was admitted to Mount Zion Hospital in San Francisco on January 14, 1930. with the complaint of pain, fever, malaise, cough, and expectoration. He was highly irritable at the time.

The detailed hospital history is not available, but the temperature chart indicates that the acute illness had almost subsided. The temperature was 103.2 degrees Fahrenheit on the day of admission, but reached normal on the fourth day. It did not go up again thereafter.

On January 14, an x-ray examination of the chest was made by Dr. Lloyd Bryan, who reported as follows: "Chest, anteroposterior and lateral. Rather marked hilar gland enlargement with slight, coarse mottling throughout the upper half of the left lung. Conclusion: Tuberculosis."

On January 28, Doctor Bryan reported: "Chest: (The chest) markings are slightly less prominent than on the previous examination," and on March 24, 1930, his report read, "The lung fields are clear."

The first specimen of sputum for bacteriologic examination was received by me on January 27, 1930.

In part, my report was as follows (T-1813): "No acid-fast bacilli or spherules of oidia were seen. On Sabouraud medium there is a fungus growth which strongly resembles oidium coccidioides."

On January 29, the report was made (T-1904): "No acid-fast bacilli or oidia were seen, in spite of prolonged search. Culture on Sabouraud medium shows growth of fungus type which resembles oidium coccidioides."

On February 1, the cultures of Specimens 1 and 2 were injected into guinea pigs. On February 21, T-1813 A: "Guinea pig 152, which was injected with culture of sputum, shows generalized infection of coccidioidal granuloma." On March 10, T-1840 A, was reported: "Guinea pigs 149 and 150, which were injected with cultures from the third specimen of sputum, were killed and both found positive for coccidioidal granuloma." It is to be noted that the first sputum was received on January 27, ten days after the patient's temperature had become normal and no spherules were to be seen, although cultures were still positive. Neither spherules nor growth of fungus was found in December, 1930.

On January 7 and January 13, it was noted that there were 4 and 6 per cent eosinophils, respectively, just before and after the patient complained of pain in the ankles and wrists. There is no note that there was erythema nodosum at this time.

The patient made an uninterrupted recovery from the acute illness, although severe nervous manifestations developed for which no organic cause attributable to coccidioides infection could be determined. He was still under Doctor Pierson's care in March, 1936, at which time it was noted that nothing abnormal was found in the chest on physical examination and by fluoroscopy.

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CASE 3.—A. H. Engineering student. Seen with Drs. Bloomfield and Lee.

In the Christmas vacation, 1935, the patient worked in the oil fields near Coalinga, Fresno County. About two weeks later he developed a severe cold, with accompanying symptoms which he thought to be the "flu." He had fever up to 102 to 103 degrees Fahrenheit. He then had an eruption of tender, red spots on the legs, mostly below the knees, which cleared up in a few days. Some time later a pimple developed in the skin of the neck, which the patient squeezed. It then developed to resemble a boil, and cultures of the pus showed growth of fungus coccidioides. The lesion dried up once and then a series of small pustular lesions developed around it. The area was excised, but the process recurred in the scar. The skin lesions finally disappeared after treatment with 25 per cent thymol in olive oil, applied locally and per os in one-half-gram capsules three times daily.

A lump developed in the neck, which proved to be an enlarged cervical lymph gland. At first this was tender, but did not fluctuate. It has decreased in size, but is still palpable, although the patient feels well and has had no active recurrence. No detailed clinical record could be obtained.

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CASE 4.—A woman, age 53. Seen in the Medical Clinic, Lane Hospital.

The patient, a practical nurse of San Francisco, visited her daughter in Porterville, Tulare County, in December, 1935. She had been in general good health until December 26, when she contracted a "severe cold in the chest." This cold came on without any preliminary rhinitis or coryza. She remained in bed two days and then returned to San Francisco, where she was confined to her bed most of the time for the next three weeks. On January 18, she was constipated and drank a canful of sauerkraut juice, after which she vomited twice and had a large, dark-colored, liquid stool. The next morning she noticed several red, tender spots over her knees, shins, and buttocks, and a few small red spots on the chest. These were exquisitely tender; she described them as "sore as a boil." The small spots on the chest soon disappeared, but the larger ones on the legs remained practically unchanged until January 23, when she entered Lane Hospital. Her complaint on admission was: "Cough, which has lasted one month, a tired feeling, and red spots on the legs for five days."

The family history and previous illnesses were unimportant in so far as the immediate illness was concerned. The story of the present illness is as outlined above. The essential findings on physical examination were the lesions on the lower extremities, which were described by Doctor Bloomfield as follows: "Over the legs up to just above the knees there is an exquisite crop of erythema nodosum. Individual patches vary in size up to 10 centimeters in diameter, are purplish and very hot, with a clear spot around them. There are a few small lesions on the thighs, but none elsewhere. The lungs are not remarkable." There were also some signs of cardiac involvement which suggested a congenital lesion.

X-ray examination of the chest was made on January 24. Doctor Newell reported: "Hilar and bronchial markings are much increased. The lower lobes might be accounted for by chronic passive congestion, but there is more density of a somewhat fibrous nature in the right upper lobe than there is in the left. This difference on the two sides is enough to make me suspect that some of the right upper lobe density is due to tuberculosis."

On January 31, x-ray examination of the chest was repeated. Doctor Leef reported that "The amount of density throughout the lungs is not so great as it was at the previous examination. This is particularly true of the density at the right base. It is the congestion that has disappeared. I am not so suspicious of any present tuberculosis now."

On January 31, a specimen of sputum was examined. No acid-fast bacilli or fungi were seen in smear, and routine culture on Sabouraud's medium showed no growth of fungi.

On January 23, there were 11,080 leukocytes with 70 per cent polymorphonuclears and 3 per cent eosinophils. On the 29th there were 12,100 leukocytes, with 43 per cent polymorphonuclear and 6 per cent eosinophils. The sedimentation was 32 millimeters in 60 minutes.

The Wassermann test was negative, and tuberculin O. T., 1:2000, showed erythema in forty-eight hours.

Other laboratory tests, including blood culture, showed nothing remarkable.

The temperature was about 103 degrees Fahrenheit when the patient was admitted to hospital, and the fever was irregular, reaching as high as 104 degrees Fahrenheit (rectal) for several days. On the eighth day it became normal and remained so.

On February 6, the patient was dismissed. The red spots had faded, but the induration of the lesions was still palpable. The temperature was normal. Diagnosis: Erythema nodosum.

On May 9, after considerable urging, the patient returned to the clinic and was given 0.1 cubic centimeter of coccidioidin* intracutaneously. On May 11, there was a pro-

* The coccidioidin used on the patients here described was obtained from Dr. K. F. Meyer.

nounced positive reaction, with a central, indurated, dark red, slightly vesicular area 10 by 15 millimeters in diameter, surrounded by a hyperemic zone of about 6 by 9 centimeters. There was no constitutional disturbance.

The patient said she was well and was working. There was no sputum for further culture. On January 16, 1937, she reported by telephone that she has been working regularly and was "feeling fine."

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CASE 5.—W. S., male, age three and one-half years, of Ducor, Tulare County. Seen with Dr. H. K. Faber.

The patient was brought to Stanford Hospital on April 13, 1937. His mother stated that he had had a fever for two weeks, and painful red nodules on the shins for two days.

The child had been in good health, had had none of the diseases of childhood, and no glandular swelling. In December, 1936, had had nausea and vomiting for one day. On March 27 last, the child became irritable and complained of sore throat, which was not severe enough to prevent swallowing. His temperature was found to be about 100 degrees Fahrenheit, and he was thought to have a cold. The fever has continued until the time of admission, reaching from 100 to 104 degrees Fahrenheit in the afternoon, with normal morning temperature. For a few days there was rumbling in the bowels and the child had cramps without any association to meals, and was constipated. There was no vomiting. Following the administration of milk of magnesia, there were soft to watery stools about every second day.

For the past week the child has been free from gastrointestinal symptoms, but beginning nine days before admission the temperature reached 103 or 104 degrees, and a "heat rash" appeared for one day on the trunk and neck. He remained quite active until four days before admission, but since has been apathetic and has slept poorly, with night cries.

Two days before admission, painful, bright-red nodules appeared on the shins, lower thighs, and buttocks, which reached their maximum intensity within forty-eight hours and then began to fade. A diagnosis of "valley fever" was made by a physician at Porterville.

On physical examination, nothing unusual was detected except the lesions on the lower extremities and buttocks. Over the shins were many discrete and confluent nodules which were warm, red and purplish-red, indurated and tender, but not painful. They measured up to 3 centimeters in diameter. Similar but smaller nodules, not more than 1½ centimeter in diameter, were seen on the anterior surface of the thighs, above the knees, on the buttocks, on the extensor surface of the right forearm, and just above the left elbow. There was no glandular enlargement and the spleen was not palpable.

The tuberculin test was negative.

Coccidioidin test, 0.1 cubic centimeter, was strongly positive and so severe that necrosis was feared. The central, indurated, red and slightly vesicular papule was 1½ by 2 centimeters, surrounded by a hyperemic zone.

The blood count showed 8,200 leukocytes, of which polymorphonuclear were 53 per cent and eosinophils 3 per cent. The sedimentation test was rapid—31 millimeters in 60 minutes.

Because there was no expectorated sputum, the stomach contents were removed. The washings contained a considerable amount of mucopurulent sputum in which were moderate numbers of the typical spherules of coccidioides. No acid-fast bacilli were seen. Cultures on Sabouraud medium showed pure growth of Fungus coccidioides, which was proved virulent by guinea-pig inoculation.

An x-ray examination of the chest was made by Doctor Leef on April 14, 1937. The report is as follows: "The lung roots are very heavy, particularly on the left side. There is also some parenchymal infiltration on the left side at the level of the seventh and eighth ribs posteriorly. The pleura between the upper and lower lobes is quite thick. Conclusion: The appearance is compatible with tuberculosis."

On April 27, a second examination was made and reported: "There is still quite a bit of density in the upper posterior part of the left lower lobe. The left lung root also remains about as heavy as it did before. I do not see any new areas of involvement."*

COMMENT

Four of our five patients were exposed to infection in the San Joaquin Valley; the fifth in our laboratory when he was working with Fungus coccidioides. In all the onset of illness was characterized by pulmonary involvement with fever, cough and sputum. In Case 1, where the time of exposure to the infecting organism is accurately known, symptoms of pulmonary involvement began just nine days later. In four cases in which we have record of roentgenological examination of the chest, the x-ray diagnosis on first examination was tuberculosis. It was only after the shadows in the films cleared so rapidly that the radiologists questioned their diagnoses. All but one of our patients had erythema nodosum. In three patients the nodules appeared from thirteen to twenty-five days after the onset of illness, and were accompanied by from 3 to 7 per cent eosinophilia in the blood. One patient had two attacks with an interval of six weeks. In two cases the sedimentation rate was taken at the height of the disease and showed, respectively, 31 and 32 millimeters in one hour.

As is the rule with valley fever, none of our patients has succumbed. Two of them are apparently free from active coccidioides infection after an interval of seven years. One of the two who had the acute illness fifteen months ago is apparently well; the other developed secondary lesions in the skin of the neck, which healed under treatment, and in the cervical lymph glands. The fifth patient is recovering and is now ready for the Convalescent Home.

These cases prove conclusively that Fungus coccidioides is sometimes the cause of a symptom complex of acute illness which, in so far as I can learn, has hitherto not been reported. I believe that it is identical with what has been known locally in the San Joaquin Valley as "valley fever."

DIAGNOSIS

Diagnosis of the condition is not difficult if one but remembers that it may occur. In all of our cases there was cough with sputum during the febrile period. In the case of W. S., who was too small to bring up the sputum, samples were obtained by gastric lavage, which delivered mucopurulent sputum mixed with the stomach contents. When this method is used, the washings from the stomach should be promptly neutralized with soda, as the spherules are soon digested in the acid gastric juice. Typical sporulating and nonsporulating spherules are easily seen in sputum if one examines the sputum in fresh cover-slip preparations under the microscope.

The fungus grows readily on the routine culture media, but we have had best results with Sabouraud's glucose-agar, which is prepared for the cultivation of fungi. One must remember, how-

* In describing the films from a third examination made June 23, 1937, Doctor Newell reported: "Density in the left lower lobe has cleared out very remarkably, leaving only the very faintest perceptible granularity in that region."

ever, that although the colonies may appear on the second day of incubation, they may not be recognizable until the third or fourth day, so that the plates should be incubated at least a week before they are declared negative. Conclusive identification of the fungus can be made only by animal inoculation. Our routine diagnostic method for the fungus culture is to permit it to grow for about eight to ten days, until the chlamydospores are well developed, and then inject it in saline suspension into a guinea-pig testicle. Enlargement or induration of the testicle may be observed within twenty-four to thirty-six hours, and pus containing the typical spherules may be obtained in from ninety-six to one hundred and twenty hours. If female guinea pigs are injected intraperitoneally, it may be four to six weeks before the animal is ready to be sacrificed for diagnosis, but if a male guinea pig is used, the testicles may enlarge and contain pus within two or three weeks.

The intracutaneous skin test was the method of diagnosis of coccidioides infection in one of our cases where sputum was no longer available for intensive study. It was also strongly positive in our most recent case. In my opinion, a positive reaction indicates sensitization to the Fungus coccidioides, which may or may not be active at the time, but I am not sure whether specificity would persist if the body which had been previously infected with the fungus had become entirely free of the organism. On one occasion I had an opportunity of skin-testing a patient who had had valley fever at Coalinga ten years earlier. She had made prompt recovery and had suffered no indications of infection in the interval, but the skin test was still strongly positive. Stereoscopic x-ray showed that the lungs and visible adjoining lymph glands were entirely normal. I have not seen any patient in which the coccidioidin test was negative who had demonstrable signs of coccidioides infection, or who gave a history of having been infected. I, therefore, consider the test to be specific and of diagnostic value.

COMMENT

This acute disease appears to be the immediate result of initial infection with Fungus coccidioides, the organism which long has been associated with coccidioidal granuloma. I have suspected for some time that coccidioidal granuloma is a secondary manifestation, which results when organisms which have lain dormant within the body for variable lengths of time eventually gain access to the blood stream and are disseminated to outlying local areas or throughout the body, thereby causing local lesions such as coccidioidal lesions in the skin, joints, or elsewhere, on the one hand, or generalized coccidioidal infection on the other. It was reported by Ophüls, years ago, that at autopsy of generalized coccidioidal granuloma one frequently finds a lymph gland or glands at the root of the lungs which is decidedly of an older type of tissue reaction than the lesions elsewhere, and I have seen a case of coccidioidal meningitis where the only coccidioidal lesion, other than those in the meninges, was an old, fibrous lesion in a peribronchial lymph gland. It has been suspected that initial infection is primarily through the respiratory tract in the majority of cases, but, hitherto, no clinical evidence of primary infection of the lungs has been collected. (See also Addendum.)

WHAT NAME?

To obtain a name for this symptom complex which identifies it with the etiologic agent, and at the same time differentiates it from coccidioidal granuloma, presents some difficulty. Obviously, it cannot be called coccidioidal granuloma, because it is not a granuloma. It cannot be differentiated in terms of fever, of pneumonia, or of being acute, because there may be fever and pneumonia in coccidioidal granuloma, and cases of coccidioidal granuloma have been classed as acute, subacute, or chronic, depending chiefly upon the duration of the illness. The term "coccidioides infection primary" is not completely satisfactory because, while we believe that the majority of cases become infected through the respiratory tract, we know that some cases are infected through the broken skin.

The word "coccidioidomycosis" might be used to include all cases of infection with the Fungus coccidioides, regardless of the clinical manifestations, and modified in some way to define each type of the disease. Thus, such cases as are here described could be classified as coccidioidomycosis primary inspiratory; cases which are infected through the skin as coccidioidomycosis primary cutaneous; and cases of coccidioidal granuloma as coccidioidomycosis secondary or late. Such a nomenclature is cumbersome, it is true, but it does include all cases in which the illness is caused by infection with the Fungus coccidioides, and it permits of differentiation between the type of case which is here described and coccidioidal granuloma.

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ADDENDUM

Since this paper was presented, my attention has been called to an item, under the heading "San Joaquin Fever," by the County Health Officer of Kern County, Dr. Joe Smith of Bakersfield, in the annual report of the Kern County Health Department for the fiscal year 1935-1936, page 22:

> Incomplete reports showed more than a score of cases of a hitherto unpublished disease popularly called "San Joaquin" or "Desert Fever," which is characterized by early symptoms of bronchopneumonia followed in a week or ten days by raised, reddened, tender "bumps" or nodules on the legs, arms, and sometimes on the chest, neck and face; this rash is sometimes diagnosed as "erythema nodosum." An x-ray of the lungs in these cases usually reveals parenchymal and hilar lymph node involvement and sometimes pleurisy or pleurisy with effusion or interlobar empyema. An x-ray diagnosis of the chest findings in these cases is frequently "tuberculosis." However, there is usually complete recovery, as shown by the x-ray a few months later.
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> The coccidioidin test in all cases of "San Joaquin fever" so far tested with the Kessel coccidioidin preparation have been so strongly positive that it has been found necessary to use it in one-tenth dilution with normal saline to avoid temperatures and severe local reactions. To date, the typical double-walled capsules characteristic of coccidioides have been recovered by direct examination of sputum smears, cultures, and by animal inoculations from six cases diagnosed as San Joaquin fever or erythema nodosum.

This item is of particular interest in that it shows that cases similar to those reported are not

infrequent in the San Joaquin Valley. In January, 1936, I discussed the problem with Doctor Smith and asked for the coöperation of the Kern County Health Department. It is a pleasure, therefore, to acknowledge this preliminary notice of the work which is being done in Kern County.

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DISCUSSION

K. F. MEYER, M.D., Ph.D. (Hooper Foundation, San Francisco).—The discovery by Dr. E. C. Dickson that the fungus coccidioides is responsible for a nonfatal, relatively common disease known as "valley fever," is of far-reaching, general epidemiologic significance, and deserves the widest possible recognition. That the fatal coccidioides granuloma might be masquerading as erythema nodosium, or as a benign pulmonary involvement, was certainly not suspected by the early investigators of this interesting malady. In fact, the medically oriented observers could not appreciate until recently the biologically well-known fact that the clinically manifest parasitism is invariably accompanied by silent subclinical and latent infections. For the microbian and virus diseases, which maintain themselves through the agency of host or infection chains, this phenomenon is well known and supported by a rapidly increasing mass of evidence. As a rule the infective agent, whether transmitted directly or indirectly, is transferred from the infected "spender" to the noninfected "receiver." There are, however, some exceptions to this rule. For example, tetanus and botulism are not spread along infection chains, but appear as strictly isolated cases. When a person contracts tetanus, it is impossible to prove that he or she contracted the microbe from an equally infected human being or animal. Furthermore, transmission from man to man never occurs. The causative agents of these diseases are not parasites, but "pathogenic saprophytes." The infectiousness, a characteristic of every true parasite, is absent or only slightly manifest. The ability to exist and to multiply in the inanimate world is, however, fully developed; although the fungus coccidioides, which may be found in the soil of the regions in which the disease has been recognized, is more likely a "pathogenic saprophyte" with tendencies, however, to strict parasitism. In this biologic category has been placed the actinomyces, a fungus which in exceptional instances passes from an infected animal to man. It enters the body on foreign bodies on which it leads a saprophytic existence. When once introduced, the ray fungus behaves like a true parasite; it multiplies rapidly within the tissues of the host. The pathogenic effect is not conditioned by specific toxins; in fact not even febrigenic substances are formed, since the uncomplicated actinomycosis usually shows an afebrile course. Does the fungus coccidioides belong to this group? The biologist is very eager to know.

Aside from the purely academic questions, a great many others suggest themselves when reading this splendid study. Why is it that newcomers to the San Joaquin Valley are more liable to clinically recognizable coccidioides disease? Is the apparent refractoriness of the residents real, and if so is it conditioned by a previous, in all likelihood subclinical, immunizing infection by the saprophyte? Immediately the next question arises, can this acquired resistance be demonstrated? Can it be measured? Some efforts along these lines have been made; thus far merely the existence of a cutaneous allergy has been recognized. However, the distribution and the significance of the allergies in the communities in which the disease occurs remains to be determined. Would it not be advantageous to supplement the tuberculin-testing campaigns now in progress in many rural schools with coccidioidin tests? There may be some hesitancy on the part of those responsible for such a program, since the reagents frequently used cause severe and painful local, and even general reactions. Some procedure of standardization should, however, yield a uniform testing reagent which induces reactions of the same intensity and specificity as the tuberculin.

The pathogenesis of the coccidioidal granuloma, as sketched by Doctor Dickson, raises additional questions concerning the mechanism which confines the primary infection to the lung and its regional lymph nodes. Should one assume that the process remains local because fortuitous circumstances fail to corrode a blood vessel and thus allow the fungoidal spores to be transported in the blood stream to outlying areas? Just as in tuberculosis the ability to focalize the primary childhood tubercle is conditioned by genetic factors, so the resistance to generalization of the fungus coccidioides is perhaps influenced by similar factors. Some of these ideas are open to experimental approach on monkeys. In this species both local and general infections may be produced with ease. The Renaissance period in the study of coccidioidomysis, thanks to the work of Doctor Dickson, is at hand.

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HIRAM E. MILLER, M.D. (384 Post Street, San Francisco).—This is the first publication in a number of years that has given any new ideas on the clinical course of coccidioides immitis infections. Some of us have believed that a number of the inhabitants of the San Joaquin Valley acquired the disease in childhood, recovered from it and developed an immunity that remained with them throughout life. It is of interest in this regard that a large number of the patients reported had been in the San Joaquin Valley for only a few days or weeks. The disease, as reported to the State Board of Public Health, was not often observed in the old inhabitants of the Valley. It will be most interesting if it can be established that so-called "valley fever" is of frequent occurrence, and is due to an infection with coccidioides immitis. A term of this type is often a symptom-complex and not an entity.

The extent of the associated skin eruption and its rapid involution in some of these patients suggest that it would be better to classify it as a toxic eruption, and not as erythema nodosum. Erythema nodosum is always a nodular eruption. It generally occurs only on the lower legs, seldom recurs, and generally remains for two or four weeks. It would be of value to obtain a biopsy from one of these skin lesions.

The suggestion that the general term of "coccidioidomycosis," be used in place of coccidioidal granuloma, is well founded. This would be in keeping with the terminology of other deep mycosis—that is, actinomycosis and blastomycosis.

It has also been our experience that the coccidioidin test is a specific one. It would be of considerable interest if this test could be done on a large number of inhabitants of the San Joaquin Valley.

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ROLAND B. TUPPER, M.D. (2607 Fresno Street, Fresno). The author has discovered a new manifestation for coccidioides. The term "valley fever," however, must be localized to the southern part of the San Joaquin Valley, as I have inquired of several old practitioners in this locality and none had ever heard "valley fever" applied to erythema nodosum. I personally have never come in contact with the term "valley fever." However, coccidioides, as we know it here, is called "San Joaquin valley disease."

Whether or not all of the cases of erythema nodosum are caused by the fungus coccidioides, is yet to be determined. It is my opinion that the fungus coccidioides is one of many causes. Within the last month, a patient with an atypical case of erythema nodosum entered the General Hospital of Fresno County. I suggested an examination of the sputum for the coccidioides fungus, and the report came back positive. This patient had no evidence of granulomata on his body. One of the nodules was excised, but it was not a true granuloma. There are always cases of coccidioidal granuloma in the General Hospital of Fresno County, but there are comparatively few of erythema nodosum. The coccidioidal granuloma that we see here is found in persons who are in close contact with the soil, whereas the erythema nodosum is usually found among those of a better class.

For several years I have been examining fresh specimens of sputum in cases of long-continued fever with pulmonary involvement. I have been suspicious of coccidioides in these patients, but I have not found the fungus, due, no doubt, to the fact that few cultures were made. It is with interest that I shall continue to search for coccidioides in our cases of erythema nodosum, those of long-continued fever with lung involvement, with or without nodules on the shins.