

# Primary Cutaneous Coccidioidomycosis

## The Criteria for Diagnosis and a Report of a Case

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IT IS NOW ACCEPTED that coccidioidomycosis usually occurs as a pulmonary infection, resulting from the inhalation of dust containing the arthrospores of *Coccidioides immitis*. In addition, however, almost all writers on the subject have indicated their belief that in some instances the disease results from primary inoculation of the fungus directly into the skin.<sup>3, 4, 13, 18, 23, 24</sup> In many of the reports recorded in the literature the observers believed that the disease had been acquired in this manner;<sup>1, 2, 5, 6, 8, 16, 19, 27</sup> this is true even of the first case ever to be described in North America, that reported first by Rixford<sup>25</sup> in 1894 and again later by Rixford and Gilchrist<sup>26</sup> in 1896, of which it was stated that the initial lesion occurred on the "back of the neck where the collar band rubbed."

The present concept of the pathogenesis of coccidioidomycosis, however, leads to the conclusion that the skin is very rarely the portal of entry. Indeed there is but a single case recorded in the literature (that reported by Guy and Jacob<sup>15</sup> to be referred to later) in which the facts and their chronology reasonably warrant the conclusion that the infection was acquired by this route. The remainder appear almost certainly to represent instances in which a cutaneous lesion, although admittedly the first observed manifestation of the presence of the disease, actually resulted from the dissemination of the organisms to the skin from an earlier, unrecognized, primary pulmonary infection.

The determination of the manner and route of acquisition of the infection is important not only in studying epidemiologic aspects and pathogenesis of coccidioidomycosis, but also it may be of medico-legal importance. Thus, decision as to the justification for compensation of an illness as occupational may be necessary. Also, amputation of a limb or surgical removal of tissue may be wrongly advised

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• *Study was made of a case of coccidioidomycosis known to have resulted from primary inoculation of the organisms into the skin. Clinical observations and laboratory data were obtained at the time of clinical illness and for a period of five years thereafter. From the information thus obtained and correlation of it with what already was known of coccidioidomycosis, it was concluded that the disease originates very rarely as the result of primary cutaneous inoculation. In most instances lesions suspected to be of this type have actually resulted by dissemination of the organisms to the skin from a previously unrecognized pulmonary focus.*

*Primary cutaneous coccidioidomycotic lesions closely resemble the primary cutaneous lesions (chancres) in other infectious granulomata, such as syphilis, tuberculosis and sporotrichosis. Spontaneous involution should occur within three months and then there should be immunity to reinfection in all but one or two per thousand instances.*

*From these observations certain criteria were evolved by which to determine in a case of coccidioidomycosis with cutaneous manifestations whether or not the infecting organism entered through the skin.*

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in the belief that the "primary" lesion as well as all diseased tissue can thereby be eliminated, when actually the lungs and perhaps other organs are actively involved.

During the past five years the progress of a patient who undoubtedly acquired coccidioidomycosis by direct primary inoculation of the fungus into the skin has been closely observed. The subsequent course of events has strengthened the view that certain criteria can be assigned as necessary for the diagnosis of "primary cutaneous coccidioidomycosis." In the present communication these criteria will be enumerated and their significance discussed.

**TABLE 1.—Immunological tests\* in a patient with primary cutaneous coccidioidomycosis, arranged chronologically**

Duration of Infection	Reaction to Test Material in Various Dilutions					
	Intracutaneous		Precipitin		Complement Fixation	
5 weeks.....	1:100	+++	Undiluted	++++	Serial dilutions from 1:2 to 1:256, all negative	
	1:1000	++	1:10	++++		
			1:40	++++		
16 weeks.....	1:100	++++	Undiluted	++++	1:2	++++
	1:1000	+++	1:10	++++	1:4	+
			1:40	Negative	1:8 to 1:256	Negative
30 weeks.....	1:1000	++++	Negative to all dilutions		1:2	++++
					1:4	+
					1:8 to 1:256	Negative
56 weeks.....	Not done		Negative to all dilutions		1:2	++++
					1:4	++
					All others negative	
4½ years.....	1:1000	+++*	Negative to all dilutions		1:2	+++
					All others negative	

\*The authors are indebted to Dr. Clement Counter of Long Beach for the performance of some of these tests.

**REPORT OF A CASE\***

On March 20, 1948, in the course of his regular duties as an employed embalmer, a 32-year-old white man severely abraded the dorsal surface of the proximal phalanx of the right middle finger against a casket. Four days later the area appeared swollen, reddened and mildly tender. The accident was reported to the employer but medical care was not sought until the 16th day after the injury. There was then at the site of the abrasion a mildly tender, deeply indurated granulomatous lesion, 2x1 cm. in size, with a central ulcerative cavity. The hand was moderately swollen and erythematous but neither lymphangitis nor lymphadenopathy was present. The oral temperature was 99.6 degrees F. On April 9 (20th day) the temperature was 101.0 degrees F. in the afternoon. Eight scattered, poorly defined but discrete firm subcutaneous nodules were observed on the dorsal surface of the forearm extending to the elbow. During the succeeding few days the right epitrochlear and axillary glands became enlarged and tender.

Results of routine urinalysis and examination of the blood were within normal limits. The sedimentation rate was 14 mm. in one hour (Westergren method). Tularemia was suspected but smears, cultures and agglutination tests were negative for the organism. In darkfield examination no spirochetes were seen and reactions to serologic tests for syphilis were negative. A roentgenogram of the chest was interpreted as normal. Tests for typhoid and paratyphoid gave negative results. Reaction to a tuberculin patch test was moderately positive. A specimen excised from a nodule for biopsy was interpreted as "non-specific granulation tissue."

The patient first came to the attention of one of the authors (J.W.W.) on April 23 (34th day) for consultation relative to a tentative diagnosis of primary tuberculous complex, which indeed seemed acceptable clinically and was concurred in by Dr. M. E. Obermayer. However, because of the possibility of sporotrichosis (suggested principally by the chain of subcutaneous nodules along the course of the lymphatic vessels), material taken from the primary "chancre" and from one of the subcutaneous nodules was inoculated into Sabouraud's glucose agar. Growth was noted on the third day in all cultures and observed to be inconsistent with *Sporotrichum schenckii*, but not otherwise identifiable

\*Permission to study this case and utilize the experience gained thereby as the basis of this report was cordially granted by Carl Johnson, M.D., of Long Beach. The authors are also indebted to Norman E. Levan, M.D., of Bakersfield for bringing the case to their attention.

at that time. On the fifth day, however, a few arthrospores suggestive of *Coccidioides immitis* were seen on microscopic examination of fragments of the culture, and this identification was confirmed the next day. Mice were inoculated intraperitoneally with this culture material, and at autopsy ten days later sporangia (spherules) containing endospores typical of *C. immitis* were seen. Special attention was then given to a review of the histopathologic section previously referred to and endosporeulating spherules were noted.

Immunological tests for coccidioidal infection were carried out, beginning as soon as the diagnosis was suspected and at appropriate intervals thereafter during the course of the illness. The most recent was shortly before the preparation of this report. The results are given in Table 1. The sequence of events is graphically illustrated in Chart 1.

With the diagnosis thus established, further investigation disclosed that shortly after the injury to the patient's hand had occurred he had embalmed the body of a person in whom the cause of death was disseminated coccidioidomycosis. This had been recognized antemortem by those in charge of the case and was so recorded eventually on the death certificate; at autopsy† widespread lesions containing myriads of coccidioidal organisms were noted in the abdominal viscera, skin, lungs and bones. However, neither the patient in the present case nor his employer was aware of these facts at the time the embalming was done. It was also recalled that during the procedure of preparing the body, which entailed considerable handling of the visceral organs, bloody and seropurulent material had entered through a cut in the patient's right glove and had come into contact with the previously injured area.

The patient had not lived in or recently traveled through any of the areas recognized as endemic for coccidioidomycosis and had noted no recent respiratory illness.

The photographs (Figure 1) were unfortunately not obtained until May 5, the 44th day of the illness (dating from the inoculation), at which time the "chancre" had involuted approximately 80 per cent toward normal. It is important to emphasize that this beneficial change had occurred entirely spontaneously, since no specific treatment had been administered. In fact the diagnosis had been established but a few days at that time. The significance of this feature will be discussed later.

The axillary nodes became fluctant on April 26 (37th day) and were incised. From them came purulent fluid in

† Performed by Edward M. Butt, M.D., Professor of Pathology, University of Southern California School of Medicine.

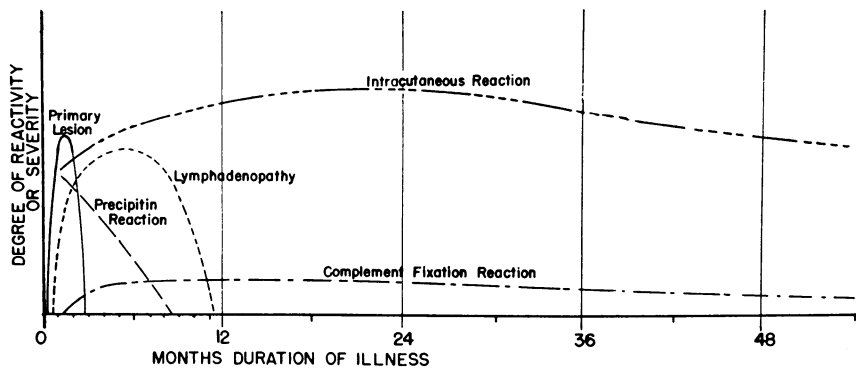


Chart 1.—Graphic representation of the sequence of events in primary cutaneous coccidioidomycosis.

which *Coccidioides* was demonstrated both by direct microscopic examination and by culture. Moderate numbers of the organism were also noted in histopathologic preparations of a specimen taken from an incised node.

By June 10 (80th day) the original primary "chancre" had entirely healed and the subcutaneous nodules of the forearm had disappeared without ulceration. The fever had subsided and the sedimentation rate was 10 mm. in one hour. As before, results of urinalysis and of routine examination of the blood were within normal limits. The axillary lymph nodes were still swollen but drainage had ceased. The patient returned to work. The residual lymphadenopathy slowly but completely subsided.

The patient has been well during the succeeding four and one-half years. At present a slight scar is visible at the site of the original inoculation and another in the axillary region.

#### COMMENT

It is noteworthy that in the case here reported the disease resulted from the inoculation of the organism when it was in the "spherule" or "tissue" stage, in contrast to the "arthrospore" or "culture" phase in which it was acquired from dust in all other heretofore reported cases of infection of humans. It may be argued that this case cannot therefore reliably be accepted as prototypical of what can be expected to result from percutaneous inoculation of natural dust containing arthrospores. However, all experience gained in animal inoculation experiments indicates conclusively that no matter which form of the organism is used for inoculation the resulting disease is always identical.

It is obvious that the skin may become involved by coccidioidal infection in two entirely different ways, either by inoculation of the organisms directly into the skin of a previously uninfected person or by dissemination of them to the skin from a primary pulmonary focus of infection acquired some time before by a person whose immunological mechanism fails to focalize the infection. It is the authors' contention that there is much variation between the two cutaneous pathologic processes which follow respectively these two routes of acquisition; they differ

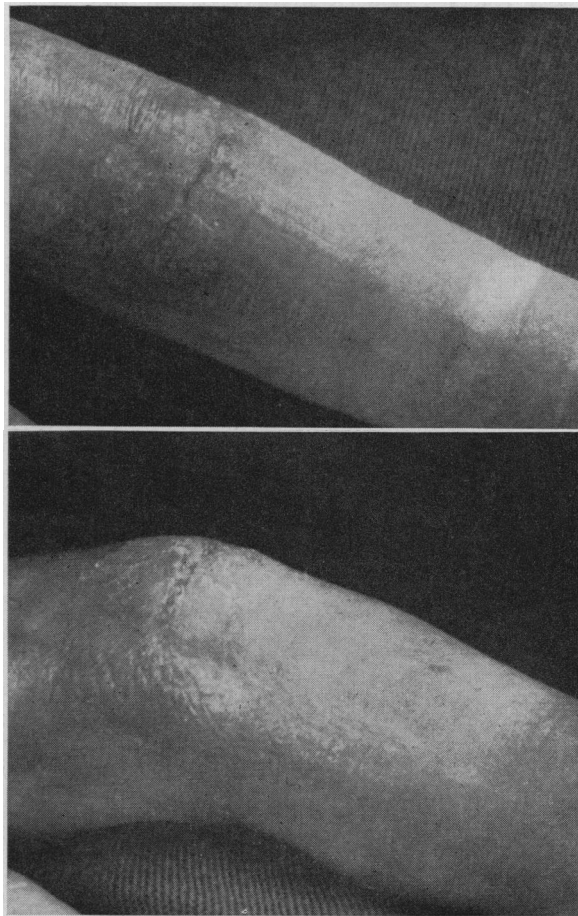


Figure 1.—Primary cutaneous coccidioidomycosis. Lesion on middle finger six weeks after inoculation. Above, dorsal view; below, lateral view.

significantly in the chronologic sequence of events, in symptoms, in the gross and microscopic pathologic changes they cause, in the manner of extension, in serologic and immunologic manifestations, and in the ultimate prognosis. Each of these subjects needs consideration if the subject is to be adequately covered.

## Chronology

In the first 42 years after the discovery of coccidioidomycosis, when only the serious, granulomatous form of the disease was recognized, it was natural to conclude that in previously "normal" persons the sudden appearance in or under the skin of a lesion provably due to this fungus indicated that it had been inoculated into the skin directly at that point. This conclusion was even more forcefully supported in cases in which there was known to have been recent trauma at the site, frequently a penetrating wound, which obviously could have been a portal of entry for the pathogenic organisms.

An explanation which more closely adheres to the facts has been available, however, since the discovery by Dickson<sup>9, 10</sup> and Dickson and Gifford in 1937<sup>11</sup> that "San Joaquin Valley Fever" is due to a primary pulmonary coccidioidal infection frequently accompanied by allergic manifestations in the skin consisting of lesions of erythema multiforme or erythema nodosum. In all patients in whom such allergic symptoms develop the prognosis is excellent. In addition, subsequent studies have demonstrated that most of the long-time residents of endemic areas have undergone pulmonary coccidioidal infections, in two-thirds of them in so mild a form as to have been completely inapparent and thus unrecognized. Even though this initial pulmonary invasion remains asymptomatic, however, dissemination to other organs may occur later, and in many cases the first such lesion to be observed will appear in or beneath the skin; indeed, it is now evident that the skin is an organ of predilection in this regard. Also, it is suspected that when dissemination is in progress or imminent, local trauma, whether or not of such a nature as to penetrate the skin, predisposes the injured area to early involvement by the infection.<sup>14, 19, 33</sup> Such cutaneous events as these have been observed repeatedly in patients who were known to have previously acquired coccidioidomycosis by the primary pulmonary route; it seems logical to attribute many less definitive cases to the same mechanism, simply postulating that the preceding pulmonary infection was too mild to have been recognized as such.

To avoid repetition the variations between the two types of infection with regard to the sequence of events will be pointed out in connection with the subject matter covered by the succeeding paragraphs.

## Symptomatology

The relative freedom from pain or tenderness in the so-called primary cutaneous "chancre" was a pronounced feature of the process in the case herein reported, as were the firm induration around it, the lymphangitis, the nodules along the lymphatic vessels draining the site, and the regional lymphadenopathy. These observations are all deemed significant.

There is a striking similarity between primary cutaneous coccidioidomycosis (as exemplified in the case reported by Guy and Jacob<sup>15\*</sup> and in the present case) and the primary "chancre" phase of several other infectious granulomatous diseases. The syndrome of the mildly painful, deeply indurated, dusky erythematous, ulcerative nodule arising at the inoculated site, followed shortly by regional lymphadenopathy and a moderate constitutional reaction, all having a tendency to subside spontaneously within a few weeks or months, is encountered with but minor variations when the skin has been inoculated with the causative organisms of syphilis, tuberculosis, espundia (American leishmaniasis), sporotrichosis and yaws. In espundia and sporotrichosis there are also commonly tumorous nodules along the regional lymph channels such as were observed in the present case. Aside from this feature, the resemblance to the primary tuberculous complex, when the portal of entry is the skin, is especially close. This is not unexpected when it is recalled how closely coccidioidomycosis mimics tuberculosis in many other phases of pathogenesis, development of symptoms and pathologic changes.<sup>7, 28, 33</sup>

However, the symptoms which result from dissemination of coccidioides to the skin from a previous pulmonary focus are entirely different. Such a lesion begins as an indurated subcutaneous nodule, which then slowly enlarges. At times it develops into a painful abscess which ruptures to the surface and remains for weeks or months as an ulcer or a draining sinus but with little surrounding induration; even more frequently the original blood-borne fungi produce a verrucous plaque with serpiginous, slowly extending borders. There is practically no tendency to spontaneous healing; rather, the skin is likely to become involved over an ever expanding area with a chronic ulcerative, purulent, crusted process. Lymphadenopathy does not ordinarily occur unless bacteria secondarily invade the area.

## Pathology

The gross pathologic changes resulting from infections occurring by the pulmonary and by the cutaneous routes have already been described in the preceding paragraphs and the variations between the two entities emphasized.

In histopathologic study of material taken from the original "chancre" in the case herein reported, reaction of mixed type was noted, varying from an acute inflammatory infiltrate in some areas in which polymorphonuclear cells predominated with some eosinophils and lymphocytes, to a chronic, granulomatous reaction in contiguous spots, in which epi-

\*It is necessary to point out that in that case secondary coccidioidal lesions developed later beyond the drainage area, suggesting dissemination. The patient recovered, however.

thelioid cells, small lymphocytes and giant cells were seen. With the exception of the eosinophils, these are the histopathologic features commonly considered to be typical of coccidioidomycosis, regardless of the location or type of infection. The coccidioidal spherules were sparsely distributed and difficult to discover. The same pattern was observed in material taken from the regional lymph nodes.

These features are at variance with those to be expected in primary "chancres" of other infectious granulomatous diseases, at least in the early phases wherein an acute reaction predominates and the causative organisms are present in large numbers. It is most important, however, to recall that the tissue examined in the present case was not obtained until five weeks after the onset of the infection, at a time when considerable involution had taken place. In comparison, a "chancre" due to syphilis would have similarly involuted during such an interval so that the original acute phase of the inflammatory process would have become more chronic and the spirochetes much reduced in number. Hence it does not seem warranted to conclude that the histopathologic studies in this case supplied evidence against an intracutaneous portal of entry, although it must be admitted that they did not assist in proving it. It is hoped that when similar cases are encountered in the future, specimens may be obtained for biopsy as early as possible so that this feature may be clarified.

#### *The Significance of the Immunological Tests for Coccidioidal Infection*

During recent years extracts prepared from cultures of *Coccidioides immitis* have been employed in an ever increasing proportion of cases of coccidioidomycosis because of their value as diagnostic and prognostic aids. Three testing procedures have been developed: The so-called "skin test,"<sup>18, 20, 29</sup> in which the reaction to the intracutaneous injection of "coccidioidin" is observed, and two serological tests, one for the demonstration of complement fixation,<sup>22, 30, 31</sup> and the other for precipitins.<sup>29, 30, 31</sup> It is necessary to mention that a single "batch" of coccidioidin seldom evokes all three of these reactions suitably; accurate standardization and selection must be carried out in each instance before reliable results can be expected.

From the statistical study of the reactions to these tests as observed in thousands of cases, certain facts concerning their chronologic relationship to the progress of the disease have been established.<sup>20, 22, 29, 30, 31, 32</sup> The application of this knowledge provides additional evidence regarding the portal of entry of the fungus. The significance of each of these tests in this regard is pointed out in the following paragraphs.

*Intracutaneous Reaction.* The reaction to the intracutaneous injection of coccidioidin is a diagnostic aid analogous to the tuberculin reaction; for this purpose 0.1 ml. of a 1:100 dilution is usually employed. In addition, it may be of value in ascertaining the prognosis<sup>29</sup> during the course of coccidioidomycosis when used in a sort of "quantitation" by ascertaining the degree of response to various dilutions (1:100, 1:10 and undiluted). Clinicians have learned to rely upon a highly positive reaction to a high dilution as indicating good immunologic resistance to the disease; in severe disseminated cases the "titre" is likely to be low or entirely negative. Jacobson,<sup>17</sup> who first applied the intracutaneous test extensively, used 0.3 ml. of undiluted coccidioidin, which indicates the low degree of sensitivity frequently encountered in the severe disseminated infections with which he was dealing exclusively. Thus, if a patient with a cutaneous lesion persistently has no reaction to the intracutaneous test in a dilution of 1:100, it is probable that the lesion is disseminated from a primary pulmonary focus rather than a primary cutaneous infection. Non-reaction to a single cutaneous test might signify only that the infection had occurred too recently for hypersensitivity to have developed.<sup>29</sup> On the other hand a positive reaction might occur if the lesion had arisen by dissemination from a pulmonary focus, provided the patient had developed resistance.

Thus, a positive intracutaneous response gives no clue as to the portal of entry, but persistent non-reaction bespeaks the pulmonary, rather than the cutaneous, route for the primary infection. In the case here reported upon, strong reactivity was noted whenever the intracutaneous test was carried out throughout the course of the disease. It is unfortunate that the test was not done earlier than the fifth week when the reaction was already positive. Undoubtedly, if testing had been started earlier, conversion from negative to positive which must have occurred would have been observed.

*Complement Fixation Test.* During the past decade the quantitative complement fixation test has proved of practical value in the diagnosis and prognosis of coccidioidomycosis.<sup>22, 30, 31, 32</sup> In general, the more severe the infection, the higher the titer of fixation. Thus, serum from patients with *extensively* disseminating infection usually fixes complement in a dilution greater than 1:16. However, serum from patients with primary pulmonary infection and a *single* extrapulmonary disseminated lesion may fix complement only in low titer. Thus, high-titered fixation of complement in serum, like cutaneous anergy, would be unlikely in a patient with a primary cutaneous infection. Serum of a patient with a primary cutaneous lesion would be expected to have a low titer or per-

haps not fix complement at all. In the present case the titer was only sufficient to be of assistance in diagnosis (Table 1).

The time sequence may supply an additional clue. The ability to react positively to the complement fixation test develops more slowly than to the precipitin test or the intracutaneous injection.<sup>29</sup> Thus, the appearance of a positive complement fixation reaction in high titer early in the course of a cutaneous lesion would constitute evidence against cutaneous primary infection and indicative that it derived by dissemination from an earlier pulmonary infection. Five weeks after the onset of the cutaneous lesion, serum from the patient in the present case did not fix complement. Even when tested at the 16th week, the titer was still very low (slightly positive in a dilution of 1:4). If the immunologic mechanisms of the patient had been sufficiently defective originally to have allowed dissemination to occur from a primary pulmonary focus to the skin, it is more likely that the resulting cutaneous disease would have continued for a longer time, accompanied by a rise in complement fixation titer. On the contrary, the titer never became high and soon began to decline.

*Precipitin Test.* Precipitins are usually demonstrable in the serum of patients undergoing coccidioidal infection.<sup>30, 31</sup> The titer is not known to have prognostic significance, its principal use being diagnostic. However, the time relationships of the appearance and disappearance of precipitins may give clues as to the recentness of the infection. Precipitins develop before complement-fixing antibodies (although after intradermal sensitivity to coccidioidin) and seldom persist longer than three or four months after infection is acquired. Thus, absence of precipitins in a patient with a recently developed cutaneous lesion proved to be coccidioidal would be likely to indicate dissemination from an earlier pulmonary infection. In the present case, precipitins were strongly present in the first specimen of serum tested (five weeks), had decreased in titer at four months, and when the next test was done at seven months they had vanished. However, precipitins do occasionally persist for a year or so in the serum of a patient with disseminated infection. Therefore, demonstration of precipitins is not conclusive proof that the infection was recently acquired.

### *Prognosis*

Almost all persons who acquire coccidioidomycosis by the primary pulmonary route recover quickly and are thereafter immune to reinfection. Only one or two per thousand, immunologically defective, subsequently have the disease in the disseminated, granulomatous form that often causes death. It would be most unlikely that the disease

caused by primary cutaneous inoculation of the organisms would pursue a different course; indeed, since the skin is so highly reactive to the products of the fungus (coccidioidin) in those persons who do acquire immunologic resistance, inoculation by the intracutaneous route theoretically should result in conferring immunity even more quickly and consistently than does pulmonary infection. Since rapid involution of the primary cutaneous chancre and its sequelae should be expected in all but one or two per thousand instances, the continuation of a cutaneous lesion for more than three months should be considered strong evidence against its having arisen by primary cutaneous inoculation.

### *Criteria for Cutaneous Portal of Entry*

Criteria to be met in determining that the skin was the portal in a case of coccidioidomycosis are, in chronological order, as follows:

1. There should be no history of significant pulmonary disease immediately preceding the appearance of the cutaneous lesion.

2. The history should be suggestive of inoculation through a break in the skin at the site of the first cutaneous lesion observed. Simple "injury" such as a bump or bruise should be considered insufficient evidence.

3. Only a short incubation period should elapse, probably between one and three weeks, before a visible cutaneous lesion develops.

4. The primary lesion should resemble a "chancre" as seen in primary syphilis or the primary cutaneous tuberculous complex, rather than an abscess or torpid cutaneous ulcer. The lesion should be a relatively painless, firmly indurated nodule or nodular plaque, with central ulceration.

5. The precipitin reaction to coccidioidin should soon become positive. It should decline somewhat more slowly than if the disease had been present in the lungs for a few antecedent weeks.

6. The response to the intracutaneous injection of coccidioidin should become positive and should increase in sensitivity (1:1000 dilution) unless immunity fails to develop.

7. The complement-fixation reaction should be negative at first, and remain so for several weeks, after which it should be present only in low titer, unless immunity fails to develop.

8. Lymphangitis and lymphadenopathy should develop, but in the region of drainage only. Development of nodules similar to those seen in sporotrichosis may be expected.

9. Spontaneous healing of the "primary" cutaneous syndrome should occur within a few weeks (unless the patient is immunologically defective: This should be anticipated in but one or two per thousand instances).

*Criteria for Cutaneous Lesions Arising by Dissemination from the Lungs*

The following findings should be regarded as indicative that a cutaneous lesion is not primary but is derived from a previously unrecognized primary pulmonary infection, although it must be emphasized that the absence of these phenomena does not gain-say the possibility:

1. History of an influenzal or other acute respiratory illness (especially if accompanied by pleural pain) a few weeks or months before the appearance of the cutaneous lesion.

2. Persistence of non-reaction to the intracutaneous coccidioidin test with a 1:100 dilution.

3. Positive reaction in high titer to the complement fixation test, especially if observed early in the course of the cutaneous lesion.

4. No precipitins demonstrable if tested between three and five weeks after the appearance of the cutaneous lesion. (This is less significant than the preceding conditions.)

5. No regional lymphadenopathy or inflammatory nodules along lymphatic channels draining the region of the cutaneous lesion, unless secondary bacterial infection is concomitant.

6. Continuance of the cutaneous lesion without involution beyond three months.

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