MEDICAL PROGRESS:

Recent Progress in Pulmonary Mycotic Infections*

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THIS discussion is limited to coccidioidal infection and certain aspects of pulmonary calcifications associated with sensitivity to histoplasmin. We do not infer that progress has been restricted to those subjects. It continues in actinomycosis, blastomycosis, sporotrichosis and moniliasis as well as in the superficial mycoses. Restriction of space necessitates focusing our attention.

For those in the West, coccidioidal infection poses the outstanding problem of pulmonary mycoses. It is the only one yet recognized as occurring significantly within this area, although we do see sporadic actinomycosis. The status of knowledge regarding coccidioidal infection prior to these recent developments was admirably summarized by Beck, Dickson and Rixford in 1931.[4] The one noteworthy advance between that monograph and our present era was the recovery of *Coccidioides* from soil near Delano, Kern County, by Stewart and Meyer.[74] Then, just ten years ago, the "renaissance period in the study of coccidioidomycosis" [54] was ushered in by the discovery of Gifford[36] and Dickson[23] that benign coccidioidal infection could occur in the form of coccidioidal erythema nodosum ("Valley Fever"). Subsequent reports[18,28,44,48,66,73,79] furthered our knowledge regarding this entity, gave significant evidence regarding the epidemiology of coccidioidal infection and confirmed the importance of the coccidioidin skin test. It was during this same period that the coccidioidal endemic area was proven to extend beyond the confines of the San Joaquin Valley and even of California. Also, the importance of pulmonary cavitation began to be appreciated.

The greatest stimulus to our knowledge, however, came with the introduction of vast numbers of susceptible military personnel into the arid southwest because of its ideal training conditions. The potential dangers were appreciated in the Surgeon General's Office and the Air Surgeon's Office by such men as Generals S. Bayne-Jones and Charles R. Glenn and Dr. Francis G. Blake, president of the Army Epidemiological Board. Their prompt action insured a pattern of study and control which added significantly to our knowledge and minimized infection and death. Moreover, moving into this picture was Army physician personnel with fresh viewpoints and great energy. Their contributions are continuing as they carry this knowledge into civilian life. In the over-all picture should be mentioned the splendid review of literature prepared by Forbus and Bestebreurtje[34] and the monograph prepared by Lee, Nixon and Jamison[49] which succinctly summarized the then current knowledge. At this point it seems desirable to indicate certain specific aspects of this newer knowledge.

One of the most important outgrowths of the war experience has been better recognition of the coccidioidal endemic area. The distribution of coccidioidal infection up to this period was critically reviewed in 1942 by Schenken and Palik[62] and in 1943 by Baker, Mrak and Smith.[2] Previously reported isolated cases or coccidioidin sensitizations originating in Texas,[10a,33,51,71a,b] Arizona[8,29,30,59,76,85] and California outside the endemic area[2,4,48] have been extended by civilian and military experiences. In Texas the area extends along most of the Mexican Border and includes a large part of western Texas.[64,10b,40,49,71c] It covers southern New Mexico and southern and central Arizona.[1,3,24,49,50,77] The southern tip of Nevada and southwest Utah also seem included. In California the most highly endemic area is the southern San Joaquin Valley. Further north at Merced[70] and Modesto[12] the incidence becomes very spotty. The endemic area along the west side of the Valley extends farther, approximately to Tracy. The endemic area spreads into and over the Coast Range.[19,65] Although the infection is seen in the vicinity of Paso Robles and through Santa Barbara and Ventura counties, the area does not reach the coast. The status of southern Californa is not well delimited. Certainly there are spotty endemic areas in San Diego County[53] and also in San Bernardino and Riverside counties.[39,82] These facts coupled with the knowledge that merely driving through an endemic area can result in infection mean that the infection must be kept in the differential diagnosis by most physicians in the Western States. With such a peregrinating public, physicians throughout the entire country may occasionally see such a patient.

The question of where the fungus multiplies in nature is not settled. The endemic areas are arid or semi-arid. The months of July through October when it is dry and dusty provide maximal incidence. Minimal incidence occurs during the wet season.[66,70] Actually, considerable reduction in infection can be accomplished on military installations by dust control measures.[70] These facts bespeak the infectivity of the minute arthrospores and chlamydospores of the mycelial phase of *Coccidioides immitis*.[2,25] Moreover the

* This review is based on continuing investigations of coccidioidomycosis conducted by the Commission on Acute Respiratory Diseases, Army Epidemiological Board, Office of The Surgeon General, U. S. Army, Washington, D. C., at the Department of Public Health and Preventive Medicine, Stanford University School of Medicine, San Francisco, California.

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fungus has been recovered from soil.[24a,69,74] Emmons[24a,b,c] has suggested that certain wild rodents, notably pocket mice, may become infected, die, and in their carcasses the mycelia develop from the "spherules" (sporangia) of the "parasitic" phase. As he indicates, this examination of wild rodents by the experienced who can avoid the tularemia and plague so frequently encountered in coccidioidal endemic areas could provide a means of delimiting coccidioidal endemic areas. However, many would consider that a high infection in rodents would be anticipated in view of the frequent infection in humans,* cows,† sheep[5] and dogs[31] of endemic areas. Thus the rodent reservoir theory is interesting and stimulating, but it would seem fair to consider the answer as not yet settled.

Military studies[38,39,72,77,82] permitted estimation of the frequencies of the different manifestations of coccidioidal infection. At one extreme is the person with completely asymptomatic or "inapparent" infection. Such an infection can be demonstrated only by the "conversion" or "changeover" from negative to positive coccidioidin. While dosage and other factors may influence this ratio, in the southern San Joaquin Valley approximately 60 per cent of "natural" infections fall in this category. Even under conditions optimal for diagnosis only one-quarter of the infections produce clinically diagnosed disease. Around 4 per cent of the infections in white males and 10 to 25 per cent of the infections in white females are accompanied by the erythema nodosum or multiforme of classical Dickson-Gifford "Valley Fever." The proportion of these manifestations of hypersensitivity in clinically diagnosed *disease* is approximately five times as high. Various authors[39,77] have not realized that these estimates agree closely with their own, viz., that approximately 20 per cent of the clinically diagnosed cases of coccidioidal infection have erythema nodosum or multiforme.

Disseminated, "secondary" or progressive coccidioidal infection are other names for the long-recognized coccidioidal granuloma. These Army studies have indicated that approximately 1 in 400 coccidioidal *infections*, or 1 in 100 cases of diagnosed *disease* in white adult males, disseminate. The Army experience[47,50,63,72,82] also confirms the belief[36b] that there is a racial susceptibility to progressive disease. Even under identical conditions of housing, nutrition and medical care, the frequency of dissemination in coccidioidal infections and diagnosed cases of Negroes is at least ten times that of the whites.[72]

Other complications of coccidioidal infection are pleural effusion and spontaneous pneumothorax. The former, while not usual is not rare; spontaneous pneumothorax is rare. However a really important complication of the primary infection which is sometimes confused with progressive disease is coccidioidal pulmonary cavitation.

Within the past six years we have come to recognize the frequency of coccidioidal pulmonary cavitation. Prior to Winn's[83a] article on 13 such patients, occasional cases[29,86] had been reported. The unique opportunities in the military service for following the pathogenesis of the cavities by serial x-rays have yielded clearer understanding of the evolution of these cavities. Colburn's[16] study of cavity formation in three cases has been extended greatly by Jamison's[47] study of 35. Sweigert, Turner and Gillespie[77] also have described their experience with the development of these cavities. It is to be hoped that Verne R. Mason's unpublished studies as Consultant in Medicine to the Ninth Service Command will be followed through.

The diagnosis of these cases is frequently difficult since they may be sensitive both to tuberculin and to coccidioidin and their coccidioidal serology is frequently negative. In this event, only recovery of the fungus can establish the etiology. All investigators have agreed that these patients have a high degree of immunity and very rarely disseminate. Most have no symptoms and rarely should anything be done to them. The usual indication for intervention is persistent hemoptysis. The experience of Denenholz and Cheney[22] in the beneficial effect of phrenic crush has been in line with our findings. In selected cases[58,84] pneumothorax may be used. However, the indication should be absolute and one should recognize that rarely hydro- or pyopneumothorax may ensue. Moreover, some cavities not only do not close but a few actually increase in size under pneumothorax. Successful lobectomies and lobe resections for coccidioidal cavities have been carried out at various military hospitals. While the accounts have not been published, they revise our previous opinion[67,58] that such procedures are contraindicated. However, not even chemotherapy and other adjuncts of the new techniques of intrathoracic surgery make it a casual undertaking. Most pulmonary cavities will close spontaneously and very few of those which remain open seriously impair health. Their danger of dissemination is negligible.

Various articles* have indicated currently accepted methods for diagnosis of coccidioidomycosis. The coccidioidin skin test continues to serve as the first step in diagnosis. In coccidioidal erythema nodosum a 1:1000 or 1:10,000 dilution is generally sufficient. In undisseminated active infections, 1:1000 coccidioidin[38,77,82] is usually adequate. For surveys, 1:100 is probably advisable.[68] While vesiculation is frequent with such a concentration, there is no danger of disseminating or reactivating an infection, although in relatively recent infections a bout of erythema nodosum may be precipitated.[48,68] As the antigenicity of coccidioidin is negligible, it should not be withheld for fear of sensitizing or of evoking humoral antibodies which would interfere with serological tests. Results of the coccidioidin test are necessary for adequate interpretation of serological findings. Negative skin tests may result when they are performed too early. In 1:1000 dilution the coc-

*References 36c, 44, 48, 66, 70.
†References 4, 5, 6, 20, 37, 75.

* References 13, 22, 38, 39, 65, 67, 68, 77, 82, 83.

cidioidin may be negative as long as six weeks,[77] although this would be very unusual. We[68] have found that during the first week of illness, one-sixth fail to react, while during the third week the non-reactors with undisseminated infections fall to 1 per cent. On the other hand, 70 per cent of those with disseminated infections fail to react to 1:100 coccidioidin. Jacobson,[45] who pioneered its diagnostic use in coccidioidal granuloma patients, advocated 0.3 ml. of *undiluted* coccidioidin. Unfortunately, the cross reactions become much more frequent with dilutions of 1:10. Strong coccidioidin sensitivity does occur in some patients who disseminate.[68] Very frequently the sensitivity then wanes. It may be reestablished with clinical improvement so the test has some prognostic value. There is difference of opinion as to the duration of sensitivity. Cheney and Denenholz[12] have presented evidence that the sensitivity is rapidly lost when people leave coccidioidal endemic areas. However, others[66,68] have reported dissimilar experience which would indicate that sensitivity is maintained at "readable" levels over many years and that duration of sensitivity is probably independent of exposure to the fungus. The studies of Butt and Hoffman[9] have demonstrated a correlation between sensitivity to coccidioidin and coccidioidal autopsy lesions analogous to that seen in tuberculosis. The undiluted coccidioidin seems stable almost indefinitely[68] and even diluted if kept uncontaminated, it is potent for months. However, contamination, subcutaneous instead of intracutaneous injection, faulty reading and biologicals adsorbed on syringes account for errors which may confuse the test. Moreover, while there is no cross reaction with tuberculin, there is rare cross reaction with some other agents[67] typified by histoplasmin.

When the coccidioidin test has been performed, if it is positive and there is clinical evidence of an active coccidioidal infection which is not disseminated, serological tests† may be useful. If dissemination is suspected, even a negative coccidioidin warrants these follow-up tests. In view of the persistence of coccidioidin sensitivity, a mere positive coccidioidin is no indication for serological tests. Moreover, unless dissemination is suspected, a negative coccidioidin should screen out the serological test. In patients who do not disseminate, the humoral antibodies are not present prior to development of coccidioidin sensitivity. With very mild infections, serology may never become positive. Generally, precipitins develop earlier and vanish sooner than do the complement fixing antibodies. The latter appear to have important prognostic value, for only very rarely are they negative in progressive disease.

Identification of the causative organism, *Coccidioides immitis*, provides conclusive diagnosis. Demonstration of the doubly refractile spherule or "sporangium" with endospores and without budding is possible in tissue sections. Unfortunately, unless one fulfills these criteria, errors do occur. Recently, DeLamater and Weed of Mayos[21] believed they demonstrated budding of *Coccidioides* in animal tissue. These confusing structures, noted by other investigators, are probably adherent fungus cells. They may result from incomplete separation of sporangia developed from injected mycelial fragments[2] or from incomplete cleavage or separation of adjacent endospores of sporangia.[26] However, the conservatism of the Mayo workers is certainly justified in demanding the identification of endosporulation in the sporangia. These observations also emphasize the hazards of diagnosis by coverslip examination of sputum or pus. While culturing is hazardous because of the frequency of laboratory infections when mycelia are handled, structures in sputum or even pus which are thought to be *Coccidioides* frequently are not. Besides the usual Sabouraud's or malt extract media, useful differential media[80,67] are now available. The suspected culture should be injected into mice or guinea pigs[67] to confirm the identity. Tager[78] has suggested intranasal instillation and in his hands the technique has appeared successful. Because of the theoretical risk of infection through expulsion of droplets containing the suspension, we have continued to inject the suspension intraperitoneally in our mice. The suggestion has been made by Wilhelm[80] that the suspending fluid be introduced by needle and luer through the cotton stopper if the fungus has been grown on test tube slant. Particularly in patients with pulmonary cavities wherein both tuberculin and coccidioidin tests are positive and complement is not fixed, the only hope of diagnosis is by demonstration of the etiological agent. In this event, there is no substitute for coccidioidal cultures. The point recently emphasized by Cherry[13] that active tuberculosis and coccidioidomycosis may coexist also should be borne in mind.

The elevation of the sedimentation rate with active coccidioidal infection has been mentioned frequently. It is useful in following the course of the infection. While not diagnostic, the eosinophilia which often accompanies coccidioidal disease may be a helpful lead. Willett and Oppenheim[81] recently emphasized that this eosinophilia may result in confusion of coccidioidomycosis with Loeffler's syndrome of transitory pulmonary infiltration associated with eosinophilia. One of their coccidioidal patients had a record breaking 89 per cent eosinophiles in a total white count of 49,650. In spinal fluid from patients with coccidioidal meningitis the cells are, as in tuberculous meningitis, predominantly lymphocytes. However, in the relatively few polymorphonuclear cells there is frequently a disproportionate number of eosinophiles. Even more useful in differentiation is the frequency of the "paretic" form of the colloidal gold curve. Allusion has already been made* to more recent contributions to our knowledge of the roentgenological aspects of coccidioidal infection. Others[7,15,60] also have added to the basic information in which Carter[11] pioneered. While not diagnostic, the roentgenogram is another aid in alerting the physician.

† References 13, 22, 38, 67, 77, 82, 83.

* References 16, 22, 30, 38, 47, 49, 58, 77, 82, 83.

As yet no specific drug is available for treatment. In turn the sulfonamides, penicillin and streptomycin have failed. Streptothricin[61] like tyrothricin may aid in superficial lesions. Both antibiotics are too toxic for systemic use. Coccidioidin in various forms continues to be used at times and in some instances possibly helps. However, it is very difficult to assess the efficacy of treatment in a condition where the fatality rate is 50 per cent. There is even on record one apparent recovery from coccidioidal meningitis. Every known therapeutic measure has been attempted in treating this condition but without success. This patient reported by Sweigert[77] had no treatment other than general supportive measures. It is fair to say that only in the hands of Jacobson[46] has a high level of cures by vaccine or coccidioidin been attained. The plan of restricting activities while the patient has fever and other signs of active infection, elevated sedimentation rate, rising titer of complement fixation or the roentgenological evidence of progressive pulmonary involvement remains the only suggestion. Even the beneficial effect of rest has been impugned by some skeptics. Nevertheless, even if dissemination has occurred, rest and the regime prescribed for the tuberculous continue to seem advisable.

The association of pulmonary calcifications with coccidioidal infections has been recognized for some years. Cox and Smith[17] presented experimental as well as autopsy material establishing its occurrence. These autopsy findings have been extended greatly and correlated with coccidioidin sensitivity by Butt and Hoffman.[9] The studies of Aronson and his associates[1] not only proved there was no cross reaction between tuberculin and coccidioidin and verified the geographic localization of coccidioidal infection but also gave strong evidence supporting frequency of pulmonary calcification due to coccidioidal infection. Our conception of complete specificity of coccidioidin was supported by the findings of others.[52] However, we received reports[55] of reactions in Ohio to stronger concentrations of coccidioidin. Moreover, Emmons[24b] discovered cross reaction between coccidioidin and haplosporangin, a comparable product from his Arizona fungus, *Haplosporangium parvum*. Then in our Army studies we began obtaining occasional "equivocal" and even rare positive reactions to 1:100 coccidioidin in soldiers immediately after they detrained. They denied ever having been in the West previously. These reactions occurred in personnel especially from the Ohio River area but also from most of the Mississippi Basin. Accordingly in 1943[67] we called attention to this fact and mentioned that it corresponded to the areas of recognized histoplasmosis and of frequent pulmonary calcification in the tuberculin negative.

Christie and Peterson undertook the preparation of histoplasmin and the careful investigation of the association of sensitivity to histoplasmin and pulmonary calcification. They also sought for a syndrome of histoplasmosis comparable to primary coccidioidomycosis. Their first paper[14a] presents an excellent review of the problem of pulmonary calcifications in non-tuberculous. In a group of 181 Tennessee children, they noted pulmonary calcifications in 44 per cent. Of these 78 children with calcifications, 62 per cent were histoplasmin positive and tuberculin negative, while only 6 per cent were tuberculin positive and histoplasmin negative. They presented other data supporting this association of histoplasmin sensitivity and pulmonary calcification. Subsequent papers[14b,c] have extended their observations and among 610 Tennesseeans with pulmonary calcifications, 71 per cent were histoplasmin positive, tuberculin negative and 3 per cent tuberculin positive, histoplasmin negative. Sixteen per cent reacted to both materials. The age distribution of pulmonary calcification followed that of histoplasmin sensitivity rather than that of tuberculin sensitivity. Their sectional distribution of histoplasmin sensitivity within Tennessee paralleled the pulmonary calcifications. Their studies of geographic distribution by states also supported an association between the histoplasmin sensitivity and pulmonary calcification. However, they have been careful to indicate that as yet conclusive proof of causal relationship between pulmonary calcifications and histoplasmosis remains lacking.

The exceedingly extensive studies of the Tuberculosis Control Division of the United States Public Health Service are bringing a tremendous volume of evidence for this association. Palmer's initial investigation[57a] included 3,105 student nurses with 294 pulmonary calcifications. In the latter, only 6.8 per cent were tuberculin positive and histoplasmin negative while 67 per cent were histoplasmin positive and tuberculin negative. Only 1.2 per cent reacted neither to tuberculin nor to histoplasmin. Thus the experiences of the two groups are in substantial agreement. Palmer's subsequent paper[57b] dealing with the geographic differences in histoplasmin sensitivity in over 8,000 nurses indicated that the highest prevalence of histoplasmin sensitivity is in the central part of the United States.

Recognizing that Kansas City is an area of very high histoplasmin sensitivity, the Tuberculosis Control Division initiated very detailed studies in that area. One must read these papers to appreciate their careful, critical and cautious presentations. However, Furcolow et al[35] showed that in Missouri as in Tennessee, the percentage of reactors to histoplasmin increases with age, with pulmonary calcifications paralleling the rise. They found that among whites the percentage of reactors increased from five at age of two years to nearly 70 at 18 years. Consistently, the percentage among males was slightly greater than among females and among whites slightly higher than among Negroes. Ferebee and Furcolow[32] recently studied histoplasmin reactions in Kansas City siblings. Within the same family they found the factor appeared to be a broad one, "less localized than one limited by family environment." High[41] has reported that splenic calcifications in Kansas City also appeared to be associated with sensitivity to histoplasmin. Eighty per cent of the school children

of that city who had pulmonary calcification reacted to histoplasmin. Seventy-nine per cent of those with splenic calcifications were histoplasmin reactors. These were twice as great as the histoplasmin reactivity of the general school population.

Roentgenographic descriptions of these calcifications are contained in various recent publications.[14a,41,42,87] Most noteworthy is the frequency with which *disseminated* (miliary or multiple bilateral) calcifications are associated with histoplasmin sensitivity. In the series of High, Zwerling and Furcolow[42] wherein 108 persons with disseminated calcifications were tested both with tuberculin and histoplasmin, 96 per cent reacted to histoplasmin, only 10 per cent reacted to tuberculin and none reacted only to tuberculin.

The other group of workers leading in the studies of histoplasmin sensitivity and pulmonary calcifications is at the National Institute of Health. It was the histoplasmin prepared by Emmons of this group which Palmer used in his studies. Neither the Christie-Peterson Vanderbilt team nor the Palmer-Furcolow Tuberculosis Control Division group is ready to commit itself to *Histoplasma capsulatum* as the sole, or even dominant etiological agent responsible for the histoplasmin sensitivity associated with pulmonary calcification. The group at the National Institute of Health is even more conservative. In their recent publication, Olson, Bell and Emmons[56] could not prove that there was statistically valid correlation in Loudoun County, Virginia, between pulmonary calcification and sensitivity to histoplasmin. Loudoun County has had a high incidence of proven histoplasmosis (four fatal human cases). Three Loudoun dogs and one mouse also were demonstrated to have been naturally infected with *Histoplasma*. While 83 per cent of the inhabitants tested reacted to histoplasmin, pulmonary calcification seemed to be more frequently associated with tuberculin sensitivity and history of contact with open tuberculosis. Moreover, Emmons, Olson and Eldridge[27] also have pointed out the cross sensitivity which exists between histoplasmin and blastomycin. Although coccidioidin shared in this to a degree, it was not sufficient to be very disturbing. Coccidioidin and haplosporangin are more apt to cross react. By studying the potency of the appropriate material, Howell[43] of the Kansas City group believes it is possible to ascertain dominant sensitivity. This has also been our experience. However, at the present stage there is danger of uncritical over-enthusiasm. This whole subject is developing rapidly, changing from month to month. Of paramount interest is ascertaining what infectious agent or agents are responsible for histoplasmin sensitivity. In all probability the etiology is mycotic and the infection or infections are so benign they are even more frequently inapparent than is coccidioidomycosis. Once the specific facts are known, there will probably be little point in attempting to pigeon hole or classify as long as one is sure that he is not dealing with tuberculosis. It is tuberculosis of which we must continue to beware. Although in many regions mycotic infections seem well-nigh universal, fortunately serious mycotic disease is rare.

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