The Distribution of Coccidioidomycosis in Southern California

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SUMMARY

In coccidioidin skin test surveys among persons of high school age in Saugus, Canoga Park, Banning and Palm Springs areas the average incidence of positive reaction was 15 per cent. Although considerably less than the 68 per cent incidence reported among high school students of Kern County, it is high enough to indicate pockets of relatively high endemicity in Southern California below the San Joaquin Valley.

Histoplasmin tests were performed on most of the persons tested with coccidioidin in this survey. The over-all incidence of positive reaction in the group was 7.6 per cent. Most of the subjects with positive reaction to histoplasmin gave a history of having previously lived in some area in the central United States where histoplasmosis is known to be endemic.

A few subjects who had positive reaction to coccidioidin tests and who had lived in areas known to be endemic for coccidioidomycosis but not for histoplasmosis, also had positive reaction to histoplasmin. However, the induration produced was always smaller than that caused by the coccidioidin reaction, and there was minimal confusion in interpreting the tests.

FOR years it was assumed that coccidioidomycosis was acquired almost exclusively in the San Joaquin Valley of California; hence the use of its common colloquial name, "San Joaquin Valley Fever." Other parts of the Pacific Southwest of the United States[1, 3, 6, 9, 10] eventually were recognized to be endemic areas and in 1943 the Office of the Surgeon General, U. S. Army, prepared a distribution map of the known and suspected areas of coccidioidomycosis. In that map, the region of California south of the San Joaquin Valley was depicted only as an "area of suspected endemicity." Subsequent reports of infection of armed forces personnel[18, 20, 22] showed that coccidioidomycosis occurred in several widely distributed areas of that region.

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Aided by a grant from the Research Fund, Los Angeles County Hospital Attending Staff Association and by a contribution to the Bacteriology Research Fund, University of Southern California, by Mr. Lewis S. Rosenstiel.

During the Second World War the microbiology laboratory of the Los Angeles County General Hospital was requested to cooperate with certain of the military units in laboratory and epidemiologic studies on coccidioidomycosis. Reports of certain of these were made available through the courtesy of Dr. George A. Young, Jr., then with the California-Arizona Maneuver Area, and those data which apply to the southern part of California are included in the distribution map of this report.

After Willett and Weiss[22] reported that 83 cases of coccidioidomycosis developed near Banning, California, the laboratory subsequently performed coccidioidin test surveys in the high schools of Banning and Palm Springs in order to determine whether there was an unusually high incidence of positive reaction among the young adults of these related areas.

Los Angeles County General Hospital records showed that a few patients with coccidioidomycosis had been admitted to the hospital from surrounding counties. These led to a study of the records of coccidioidomycosis in county hospitals of those counties in order to determine whether such cases had without doubt originated in the counties. Reports of cases from Santa Barbara, Ventura, Los Angeles, Orange, Riverside, San Bernardino, and San Diego counties were verified and are included in this study.

Los Angeles County General Hospital records also indicated that cases had originated near Canoga Park in the San Fernando Valley and suggested this region as an endemic focus. Seven patients with coccidioidomycosis[11] were subsequently admitted to the Los Angeles County General Hospital in the fall of 1948 from a Los Angeles County probation camp near Saugus, which is 12 miles north of San Fernando.

These observations led to the organization of serial skin test and serial complement fixation test surveys in three probation camps within the county, and also to coccidioidin test surveys in Canoga Park and Newhall high schools. A similar survey in Los Angeles High School, located within the city of Los Angeles, was organized as a control.

This report, therefore, includes information on coccidioidomycosis derived from the following sources: (1) Certain reports among the armed forces stationed in southern California during the Second World War; (2) reports of cases from county hospital records in Southern California or from

physicians within the area, these reports having been checked to determine whether or not the patient was a permanent resident of the area; (3) an outbreak of coccidioidomycosis in a Los Angeles County probation camp near Saugus, together with serial skin test surveys made in this camp and in two other camps within the county; (4) skin test surveys in five different high schools within the area (see map and Table 1).

Recent reports in the medical literature[2,5,16,17,21] on the distribution of histoplasmosis as based on histoplasmin surveys and questions relating to the specificity of the coccidioidin and histoplasmin reactions suggested the desirability of performing histoplasmin tests. These were performed on 984 of the individuals tested in the course of this study (see Table 2).

The histoplasmin used was from Lot H3 prepared by Dr. C. W. Emmons of the National Institutes of Health, and was furnished through the courtesy of Dr. C. E. Palmer. It was used in a dilution of 1:1,000.

The coccidioidin was from Lot A1 prepared in the Los Angeles County Hospital Laboratory by methods described by Kessel and co-workers.[10] It was used in a dilution of 1:100.

One-tenth cubic centimeter of each antigen was injected intracutaneously into the flexor surface of the forearm, and the results were observed 48 hours after injection. The results were scaled as follows:

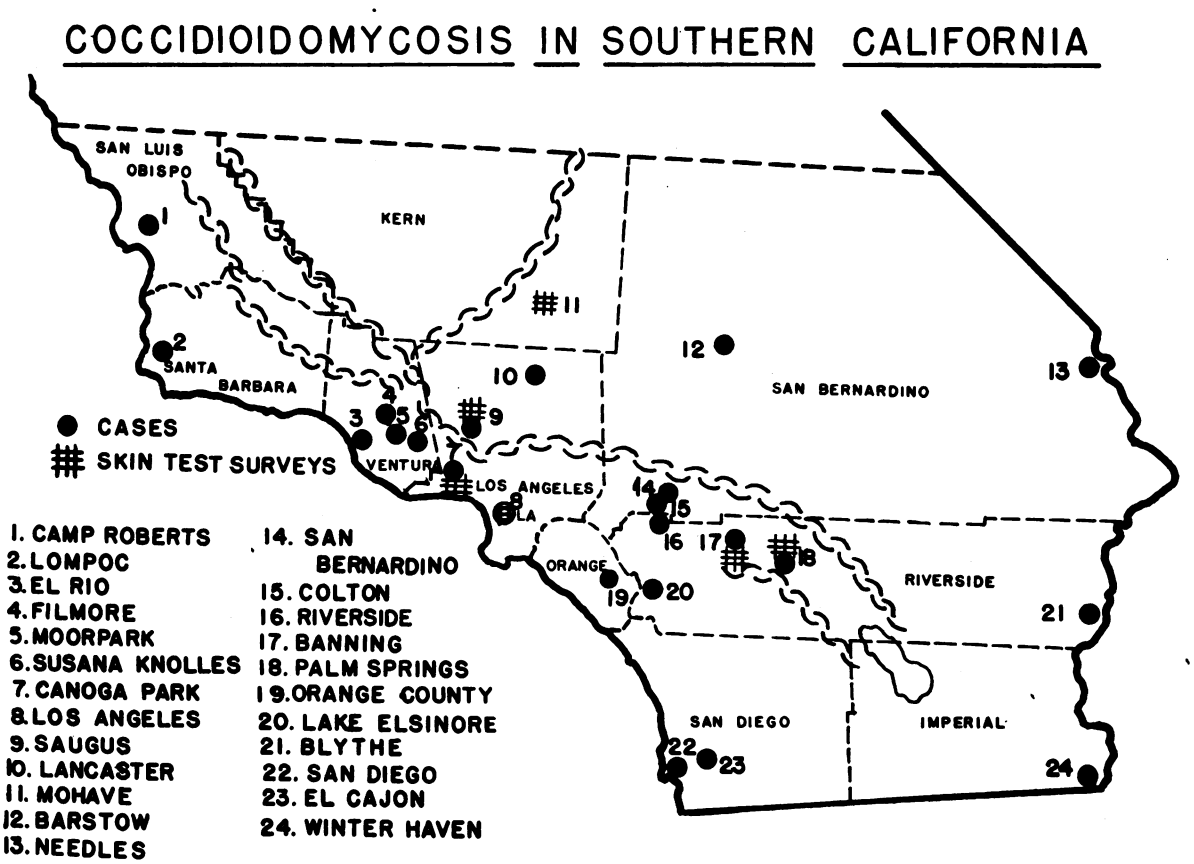
1+, = 5 to 9 mm. induration
2+, = 10 to 14 mm. induration
3+, = 15 or more mm. induration
4+, = 15 or more mm. induration plus necrosis.
Erythema alone was not regarded as a positive reaction.

RESULTS AND DISCUSSION

Coccidioidomycosis

The results of the coccidioidin surveys are summarized in Table 1. Of the 1,058 persons tested, 122 (11.5 per cent) had positive reaction. The range for the groups tested varied from 4 per cent in the Los Angeles High School to 20 per cent in the Banning and Palm Springs high schools. Since it was desired to determine the incidence of coccidioidin reactors who had acquired sensitivity in each area studied, careful histories of past and current residence in areas previously established for either coccidioidomycosis or histoplasmosis were taken from each one tested.

The persons tested were separated into two groups (Table 1), one group comprising those with previous residence in an area in which coccidioidomycosis was endemic, the other comprising those who had not resided in a known endemic area. "Residence," in this presentation, indicates residence of more than one month in a known endemic area. A majority of the reactors had resided at some time in areas previously recognized to be endemic; in this



group, the lowest percentage of positive reactors in any of the seven areas in which tests were conducted was 16 (probation camp, Azusa) and the highest was 30 (Newhall High School). In the other group, the range was from no positive reactors in one of the seven areas to 17 per cent in another.

It is assumed that there is little or no endemic coccidioidomycosis in the areas in which there was low incidence of positive reaction to coccidioidin tests. On the other hand, the three areas in which the highest incidence of positive reaction was recorded—the average for the three was 15 per cent —may be considered as newly recognized endemic areas. These are the Banning-Palm Springs area in which Willett and Weiss[22] reported 83 cases of coccidioidomycosis; Camp 4 near Saugus, from which seven patients with the disease were admitted to the Los Angeles County General Hospital in October 1948;[11] and Canoga Park, in the San Fernando Valley where several patients were suspected to have become infected. The average incidence of positive reactions (15 per cent) in the three newly recognized areas of endemicity in Southern California compares with an incidence of 68 per cent reported by Gifford[8] in similar age groups in Kern County high schools.

It is of particular interest to compare the low percentage found in the Los Angeles High School students with the higher percentages in the other high school groups. For the entire group of Los Angeles High School students tested, the incidence of positive reactions was 4 per cent, and it was only 1.6 per cent for those who were not aware of having lived in areas known to be endemic for coccidioidomycosis. The Los Angeles High School is in the center of the City of Los Angeles, and the students may be cited as a satisfactory control group, since they have a minimum opportunity for exposure to dust containing arthrospores of Coccidioides immitis. Such opportunity would be afforded only by occasional trips to known endemic areas or by exposure to arthrospores brought to Los Angeles from known endemic areas in dust, in cars, clothing or other objects. Reports in the past have shown that coccidioides may be transferred in this manner.

Distribution Map

In the past, the tendency in reporting mycotic diseases has often been to indicate the area where an infection was diagnosed or where the sensitivity of a patient was observed, without regard to his past residential history. This may lead to an entirely erroneous impression regarding geographical distribution of a disease, since the infection may have been acquired in a region quite remote from the one where the case was reported. In the accompanying map the cases of the disease and the sensitivity causing positive reaction to skin test were verified to have been acquired in the areas marked.

Evidence from these sources, together with reports of cases in military personnel stationed in the same geographic areas during and since the Second World War, shows that infections may be acquired in the following Southern California counties: Kern, southeast of Tehachapi,[18] San Luis Obispo,[20] Santa Barbara,[19] Ventura, Los Angeles,[11] Orange, Riverside,*[22] San Bernardino,* San Diego,[13-15] and Imperial.* These data point to a wide distribution of Coccidioides immitis in the southern part of California, and the map is not presumed to be complete. The cases reported to date also indicate that isolated pockets or areas of high infection rate may exist interspersed with areas of low endemicity.

Histoplasmin Surveys

The histoplasmin tests made in this study are summarized in Table 2. Of 984 persons tested, 75 (7.6 per cent) had positive reactions. These reactors were divided into two groups—those in Group 1 having previously resided in a known histoplasmosis area as judged by the map prepared by Smith and co-workers,[21] and those in Group 2 never having resided in an area in which histoplasmosis is known to occur. There was pronounced difference in incidence of reactions between the two groups. In Group 1 the percentage of positive reactors ranged from 14 per cent in the Los Angeles High School group to 45 per cent in Camp 5. In Group 2 there were few who had positive reaction to histoplasmin,

*Endemicity in Areas 13, 21 and 24 (on the map) was reported by the California-Arizona Maneuver Area.

TABLE 1.—*Coccidioidin Surveys in Southern California Areas*

Area	Total No. Tested	Total No. Positive	Per Cent Positive	Prev. Residence in Coccid. Area		No Residence in Known Coccid. Area	
				No.	Per Cent+	No.	Per Cent+
Probation Camps:							
No. 4 Saugus	100	14	14	31	20	69	12
No. 3 Calabasas	78	6	8	25	25	53	0
No. 5 Azusa	60	4	7	27	14	33	3
High Schools:							
Banning and Palm Springs	74	15	20	21	21	53	17
Canoga Park	441	65	15	82	24	359	13
Newhall	85	9	11	20	30	65	5
Los Angeles	220	9	4	38	16	182	1.6
Total	1,058	122	11.5				

with the range from zero to 4 per cent. Most of those tested in this Southern California survey who had positive reaction to histoplasmin, had previously lived in areas reported to be endemic for histoplasmosis. A related observation is that in the three clinical cases of histoplasmosis reported in the literature as occurring in California, the patients had previously lived in Louisiana,[4] Tennessee,[12] and Nebraska,[14] respectively.

Such observations further illustrate the importance, in epidemiologic studies, of ascertaining the previous residences of patients before the geographic origin of a given case is assigned.

Double Reactions

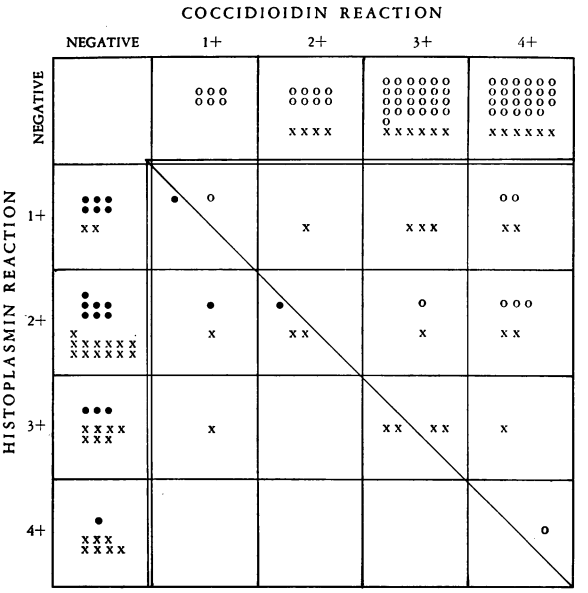
Chart 1 shows the intensity of reaction to coccidioidin and histoplasmin in 153 cases in relation to the residence history of the subjects tested.

In the chart it may be noted that: (1) The 78 cases in which there was positive reaction to coccidioidin alone are distributed in the top squares—six with 1+ reaction, eight with 2+, 25 with 3+ and 23 with 4+. (2) The 46 cases in which there was positive reaction to histoplasmin alone are distributed in the left hand squares. (3) The 29 cases in which there was positive reaction to both tests are scattered among the remaining 16 squares of the table.

Of the 29 persons with reaction to both coccidioidin and histoplasmin, 18 had lived in both coccidioidomycosis and histoplasmosis areas, three had lived in histoplasmosis areas and eight had lived only in coccidioidomycosis areas. The three who had previously lived solely in histoplasmosis areas but now live in Southern California are likely to have passed through an area in which coccidioidomycosis is prevalent—Arizona or the San Joaquin Valley—in order to reach the southern part of California. Therefore, possibility of sensitization to coccidioides en route to Southern California cannot be excluded. For this reason, no attempt is made to evaluate the cross-reactions in this group of persons. Cross-reactions in persons from histoplasmosis areas can best be studied in subjects who have never travelled in an area in which coccidioides is known to be present.

With regard to the eight persons who had lived only in coccidioidomycosis areas, yet had positive reaction to histoplasmin as well as to coccidioidin,

Chart 1.—Graph Showing Residence Histories of Coccidioidin and Histoplasmin Reactors and Relative Severity of Reactions



O Residence in coccidioidomycosis areas only.

X Residence in both coccidioidomycosis and histoplasmosis areas.

● Residence in histoplasmosis areas and travelled through coccidioidomycosis areas.

this should be noted: In six of the eight cases, the reaction to histoplasmin was of different degree than the reaction to coccidioidin; and even in the two cases in which the degree of reaction for the two tests was nominally the same (at 1+ in one instance and 4+ in the other) actually the exact size of the area of induration caused by histoplasmin was smaller than that caused by coccidioidin. There were, therefore, no cases in this series in which identical intensity of the reaction might have led to confusion in reading test results.

Question arises as to why cross-reactions between coccidioidin and histoplasmin occur. Three explanations may be considered. One possibility is that a common sensitivity occurs. (Assuming that is true, it was demonstrable in eight cases in the series reviewed.) Another possibility is that *histoplasma capsulatum* exists to a limited extent in the areas in question and some persons become sensitized to

TABLE 2.—*Histoplasmin Surveys in Southern California Areas*

Area	Total No. Tested	Total No. Positive	Per Cent Positive	Prev. Residence in Histo. Area		No Residence in Known Histo. Area	
				No.	Per Cent +	No.	Per Cent +
Camp No. 4	100	9	9	21	25	79	2.5
Camp No. 3	78	8	10	24	25	54	4.0
Camp No. 5	60	5	8	11	45	49	0.0
Canoga Park	441	30	7	164	17	277	0.7
Newhall	85	11	13.0	28	32	57	4.0
Los Angeles	220	12	6	86	14	124	0.0
Total	984	75	7.6				

this specific antigen. A third possibility is that some other fungus in the area induces intradermal sensitivity to histoplasmin. The latter two possibilities can be determined only by future investigation, and at present only the first suggestion will be reviewed.

Emmons[7] in animal experiments observed that two out of seven guinea pigs infected with Coccidioides immitis gave positive reactions when tested with histoplasmin. Of ten animals inoculated with Coccidioides immitis in a study by the authors, two had slight histoplasmin reaction. Since the cross-reactions both in experimental animals and in man observed in these studies are consistently less severe than the reaction with the specific or homologous antigen, there is little danger of confusion in reading the test. Smith and co-workers also drew this conclusion, although they left the impression that cross-reactions between coccidioidin and histoplasmin occur in a considerably higher percentage of persons than was observed in this study. They did not, however, give the previous residential histories of the persons tested. In fact, they stated, "Of course, one asks if these reactions to histoplasmin might not have been the results of independently acquired sensitivity to histoplasmin. In most instances this possibility could not be excluded." They did, however, cite 31 cases of coccidioidomycosis in which, prior to the onset of symptoms, the patients had negative reaction to both coccidioidin and histoplasmin. In this group, all patients subsequently had positive reaction to both coccidioidin and histoplasmin. In correspondence concerning the differences in incidence observed in the two different surveys, Dr. Smith suggested that the variable results may lie in differences in the histoplasmin used.

In the Los Angeles County Hospital 15 patients with proven active coccidioidomycosis recently were tested with both coccidioidin and histoplasmin. Five were tested with Lot H3 histoplasmin used in the survey herein reported, and ten with Lot H40 procured from Dr. E. S. Weiss and used in a dilution of 1:500. None of the 15 patients had previously lived in a known histoplasmosis area. All had positive reaction to coccidioidin and none had a positive reaction to histoplasmin. This observation further supports the thesis that minimal confusion occurs in the differentiation of coccidioidin and histoplasmin reactions.

The authors wish to express their appreciation to the following for their cooperation in procuring data used in this report: Dr. H. A. Ball, pathologist, San Diego County Hospital; Dr. J. P. Blanchard, pathologist, Santa Barbara County Hospital; Mr. Lester C. Dalbey, principal, Wm. S. Hart Union High School at Newhall; Dr. Warren Fox, health officer, Riverside County, and cooperating staff members of Banning and Palm Springs high schools; Dr. Roy O. Gilbert, director, Los Angeles County Health Department, and staff of the Division of Epidemiology and of the San Fernando District; Dr. J. D. Kirshbaum, pathologist, San Bernardino County Hospital; Dr. J. J. Montanus, pathologist, Orange County Hospital; Dr. G. Wendell Olson, Fullerton; Dr. C. M. Sellery, director, Health Services Branch, Los Angeles City Schools, and the cooperating staff members of the Los Angeles and Canoga Park high schools; Dr. H. D. Stailey, superintendent, Riverside County Hospital; Dr. C. T. Steggal, resident, Ventura County Hospital; Mr. John Zuck, director, Los Angeles County Probation Department, and his staff.

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