

Preliminary Report of Histoplasmin and Other Antigen Sensitivity in North Carolina*

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RECENTLY, it has been noted that chest roentgenograms from the Mass X-ray Survey in North Carolina show sectional differences in the incidence of multiple calcifications such as Palmer¹ and Christie² described and related to histoplasmin sensitivity. Casual testing for histoplasmin sensitivity in this state had yielded a very low percentage of reactors and this was regarded as an area where histoplasmin sensitivity was low and of little interest. Palmer³ tested 241 student nurses from the states of North Carolina, South Carolina, Georgia, and Florida and found that only 2.8 per cent reacted to histoplasmin. Gass, *et al.*,⁴ in Tennessee have previously shown that in an area with a high rate of pulmonary calcification a large proportion of persons with such lesions have a negative tuberculin reaction and therefore the calcification is probably due to some disease other than tuberculosis. The observations made on Mass Survey films by the Tuberculosis Section of the North Carolina State Board of Health, however, suggested that in certain areas the incidence might be much higher and clarification of this issue seemed indicated.

The problem was approached by skin

testing with histoplasmin antigen of (1) the patients in the three state tuberculosis sanatoria, (2) a group of individuals previously identified in the Mass Survey as having pulmonary calcifications, and (3) an unselected group of inhabitants from a county known to have a high incidence of pulmonary calcifications. Dr. Norman Conant and Dr. D. T. Smith of Duke University suggested that the survey might be widened to include tests with coccidioidin and blastomycin.

SOURCE OF MATERIAL AND TECHNIQUE

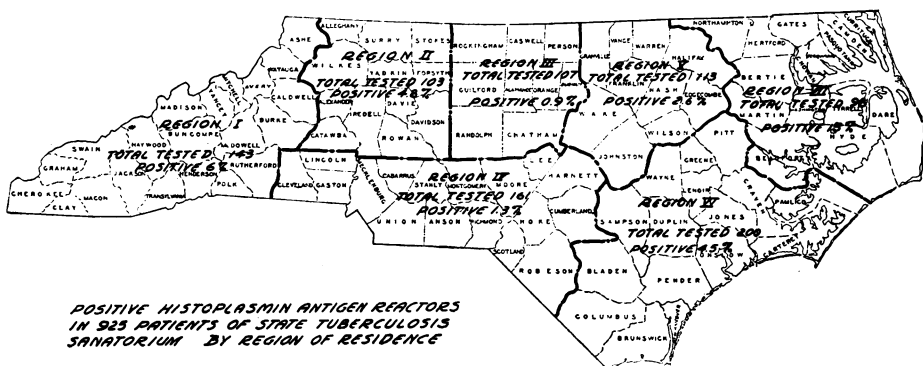
Histoplasmin (lot H-40) freshly diluted 1:1,000, and blastomycin (lot B-7) diluted 1:1,000 were obtained from Dr. Arden Howell of the U. S. Public Health Service Mycological Laboratory. Coccidioidin diluted 1:100 was obtained from Dr. Norman Conant, and the PPD was a Parke-Davis product diluted to an intermediate strength so that 0.1 ml. contained 0.0001 mg. of PPD. This material was given intradermally in the usual manner within 48 hours after it was diluted and the reaction was read in 48 hours. The induration in millimeters was measured and recorded.

FIRST SURVEY

The patients in the sanatoria were tested with histoplasmin, blastomycin, and coccidioidin. PPD was not used

* Read before the North Carolina State Tuberculosis Society, May 22, 1950.

FIGURE 1



in this survey. The majority of the sanatorium patients in this state were long residents of the counties from which they were admitted. Those patients who had spent a considerable length of time outside of North Carolina were rejected from the survey. Accordingly, we had an unusually stable group for testing. The total found suitable by virtue of their residence was 925. Of this number, 48 were found to have a positive reaction to histoplasmin antigen, or 5.1 per cent. This is somewhat higher than Palmer's³ figure of 2.8 per cent for this general area. However, when North Carolina is analyzed by sections, there are marked and significant differences in the percentage of positive reactors, and it is this regional variation that is of interest. There were, in the sanatoria, representatives from every county in the state except three, thus giving us a fairly good representation from the state as a whole. (Figure 1 shows a map of the state divided into seven sections. Samples from each of these sections consisted of 98 or more persons tested.)

The highest reactions to the histoplasmin skin tests were in the north-eastern area bounded by the western-most borders of Northampton, Bertie, Martin, and Beaufort counties. A total of 98 sanatorium patients were tested

from this area, and 15 per cent showed a positive reaction to histoplasmin. This is in contrast to other sections of the state, notably the north central and south central areas, which varied between 0.9 per cent and 1.3 per cent reactors. The section that showed the next highest percentage of reactors was in the western area, where 6 per cent of the sanatorium patients were positive to histoplasmin. This area is bounded on the east by Ashe, Watauga, Caldwell, Burke, and Rutherford counties. The Statistical Department of the North Carolina State Board of Health is of the opinion that this percentage variation is significant.

Emmons⁵ has recently shown that *Histoplasma capsulatum* has a saprophytic existence in the soil of endemic areas and he has isolated the organism from animals that live in these areas. Although the relationship of histoplasmin sensitivity in the human being to the presence of the fungus in the soil has not been proved, the evidence is suggestive. Accordingly, a geologist from North Carolina State College in Raleigh was consulted. The north-eastern sector of North Carolina and the seashore line of the southeastern section are approximately 25 feet above sea level. The soil is of a fine, silty loam and is exceedingly fertile. It is quite

retentive of moisture and there is poor drainage in this area due to the low elevation. The rainfall averages about 50 inches a year. The pH of the soil varies from 5.0 to 5.5. The majority of the population in this area live on farms and therefore have a close relationship with the soil. Due to the poor drainage and fairly high rainfall, the soil in this area is moist most of the time.

The western part of the state, wherein 6 per cent of our survey patients showed a positive reaction, also has a high rainfall and the soil is moist most of the year. By way of comparison, the mountain areas of Tennessee are similar in terrain, soil, and climatological conditions and they also have a fairly high percentage of histoplasmin reactors. The highest percentage in Tennessee, however, is in the Mississippi Valley region, which may be said to correspond to the North Carolina Coastal Plain region. Both of these areas have soil of exceedingly high fertility that is retentive of moisture. It is to be understood that the relationships involved are on a conjectural basis.

Of the sanatorium patients tested, 10 showed a positive reaction to blastomycin. Five of these patients with positive tests to blastomycin also showed

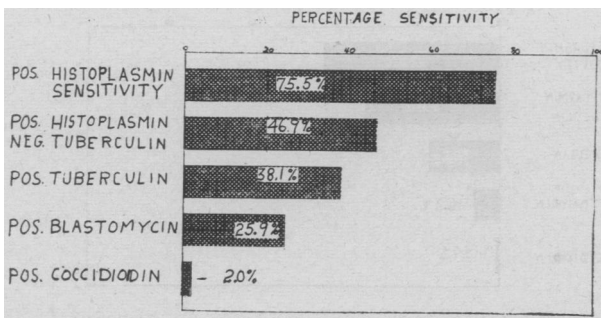
positive reaction to histoplasmin of more than 10 mm. induration. One sanatorium patient, who had never been out of the state, showed a positive reaction to coccidioidin and did not react to other antigens. This test was repeated, with similar results.

It was felt that further, more detailed studies should be made, particularly within the area of highest reaction.

SECOND SURVEY

Beaufort County, which is in the northeast coastal section, was selected for study of skin sensitivity to four antigens: histoplasmin, blastomycin, coccidioidin, and tuberculin (See Figure 2). One hundred and forty-seven patients who had shown pulmonary calcification on previous Mass Survey films were tested, and 76 per cent showed a positive reaction to histoplasmin of 5 mm. or more induration. Thirty-eight per cent showed a positive tuberculin reaction to PPD. Twenty-six per cent showed a positive reaction to blastomycin, and all of these also reacted to histoplasmin, usually with more than 10 mm. of induration. Two per cent showed positive reaction to coccidioidin. Some of the residents of Beaufort County showed a very marked reaction to histo-

FIGURE 2.- PERCENTAGE HISTOPLASMIN AND OTHER ANTIGEN⁰¹ SENSITIVITY IN 147 INDIVIDUALS TESTED WITH PULMONARY CALCIFICATION: BEAUFORT COUNTY, 1950



I. ANTIGENS: TUBERCULIN (PPD), COCCIDIODIN, AND BLASTOMYCIN

plasmin, giving as much as 26 mm. induration, with pronounced vesiculation and with erythema extending to 75 mm.

Several of these cases were persuaded to undergo retesting in order to get pictures of the reaction. It was observed that most of them showed less marked reaction on retesting. The interval between the two tests was five months and the strength of the material and the technique were the same.

THIRD SURVEY

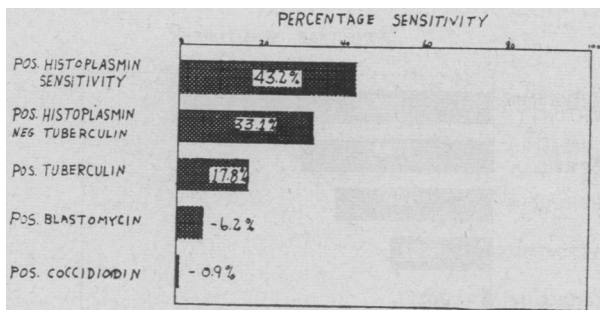
Since the survey in Beaufort County was made on patients selected on the basis of pulmonary calcifications, it was thought advisable to test an unselected group in this area of high reaction. Accordingly, Hyde County, which adjoins Beaufort, was selected. This county is on the Pamlico Sound, and its soil is extremely fertile. It is a low, flat country, poorly drained, and is predominately a farming, fishing, and hunting section. A total of 338 persons, representing both Negro and white and most age groups, was considered. The persons tested were picked at random, with no preliminary screening. The same four antigens were used. Of the 338 tested, 43 per cent showed a skin

reaction to histoplasmin of 5 mm. or more induration. The population ratio of colored persons to white in the county is about 1½:1 and the persons tested were in that ratio; however, there was no significant difference in reaction as to race (Figure 3).

There was very little sex difference, although the females had a slightly smaller percentage of reactors. Parsons and Zarafonitis,⁶ on the contrary, found a marked sex difference in their study, with 3½ times as many males as females reacting in all age groups and 7 times as many males over 10 years of age. Included in the North Carolina survey were a number of school children, and the mean age of all those tested was 17 years. Of those above 20 years, 46.8 per cent showed a positive histoplasmin test. One hundred and twelve, or 33 per cent, were found to have negative tuberculin and positive histoplasmin reactions. Four-and-seven-tenths per cent were positive to blastomycin, and the majority of these were associated with histoplasmin sensitivity of 10 mm. induration or greater. This may have represented cross-reaction. Coccidioidin tests revealed only 0.9 per cent reactors.

Subsequent chest x-rays of the posi-

FIGURE 3 - PERCENTAGE HISTOPLASMIN AND OTHER ANTIGEN⁽¹⁾ SENSITIVITY IN 338 INDIVIDUALS TESTED⁽²⁾ IN HYDE COUNTY, 1950



1. ANTIGENS: TUBERCULIN (PPD), COCCIDIODIN, AND BLASTOMYCIN.
2. 338 INDIVIDUALS SELECTED AT RANDOM FROM THE GENERAL POPULATION.

active reactors were made by Dr. W. A. Smith of the State Board of Health, but no active cases of histoplasmosis were revealed.

SUMMARY

1. North Carolina has a higher percentage of histoplasmin reactors than was formerly thought. Five per cent of 925 sanatorium patients from 97 counties reacted to histoplasmin.

2. Regional differences to histoplasmin sensitivity are marked. They varied from 0.9 per cent in the north central section to 15 per cent in the northeastern section.

3. Larger scale studies were made in counties in the northeastern section. Studies in Beaufort County revealed that 75 per cent of 147 patients with pulmonary calcification reacted to histoplasmin. Studies in Hyde County showed that 43 per cent of 338

persons chosen at random reacted to histoplasmin.

4. Pulmonary calcification among positive histoplasmin reactors in Beaufort County was similar to that described by others and related to histoplasmin sensitivity.

5. Further study and skin testing to histoplasmosis is indicated in North Carolina.

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International Neurologists' Panel

The National Multiple Sclerosis Society has taken the lead in organizing a Panel of International Corresponding Neurologists. Its purpose is "to establish liaison throughout the world with physicians and scientists interested in the problems of multiple sclerosis." A total of 56 neurologists from 26 coun-

tries comprise the present panel, whose membership will be expanded with representatives from other countries.

Headquarters of the panel are at the National Multiple Sclerosis Society, New York City. Medical director of the society and founder of the panel is Cornelius H. Traeger, M.D.