

HISTOPLASMIN, COCCIDIOIDIN AND TUBERCULIN SENSITIVITIES IN CUBA

A STUDY OF 195 PATIENTS^{1, 2}

BY DRs. OSVALDO A. PARDO,³ V. PARDO CASTELLO,⁴ AND HAROLD A. TUCKER⁵

At the time this study was begun no infections with *Histoplasma capsulatum* had been recognized in Cuba. It was felt that knowledge of the local prevalence of intradermal sensitivity to histoplasmin might provide evidence as to whether this absence of histoplasmosis was apparent or real. Indigenous coccidioidomycosis has not been encountered here but tuberculosis has long been highly endemic. It was thought desirable, therefore, to determine also the prevalences of sensitivity to coccidioidin and to tuberculin as well. It is the purpose of this brief report to present the results obtained by the use of these intradermal tests in 195 residents of Cuba and to discuss the implications of our findings, especially as compared to results of a similar study recently carried out on the Isthmus of Panama (1).

MATERIALS AND METHOD

Between January, 1950 and April, 1951, 195 patients admitted to the wards of the Calixto García Hospital, Habana, were studied. There were 137 males, 58 females. By race, there were 142 Cuban whites, 51 Negroes and two Chinese. Only 17 had not been born and reared in Cuba but all of these had been in continuous residence here for at least 25 years.

A complete history and physical examination, hemogram and urinalysis was done on each patient. Each was then subjected to a battery of intradermal tests by one of us (O. A. P.). Tests consisted of the injection of 0.1 cc of diluted antigen into the forearm. These were read approximately 48 hours later and a reaction characterized by induration 5 or more mm in diameter was considered positive. At this time appropriate treatment was begun for the various venereologic and dermatologic conditions presented by these patients, which fell into the following categories: syphilis, all types (36 cases), lymphogranuloma venereum (11), dermatitides (56), stasis ulcers (15), cutaneous mycoses (12), psoriasis (7), cutaneous tuberculosis (6), lupus erythematosus (5), Duhring's disease (2); the remainder was made up of a group of miscellaneous conditions.

¹ Received for publication July, 1951.

² From the Department of Dermatology and Syphilology, Calixto García Hospital, Habana, Cuba.

³ Instructor in Dermatology and Syphilology, University of Habana.

⁴ Assistant Professor of Dermatology and Syphilology, University of Habana.

⁵ Chief Medical Advisor to Venereal Disease Control Project in Burma (WHO).

Undiluted histoplasmin was obtained from Dr. C. E. Roach, Eli Lilly and Company (Lot CT-189). Dr. J. F. Kessell, University of Southern California School of Medicine, supplied the undiluted coccidioidin (Lot A-2), and the tuberculin was made available by the Hospital. Both fungous antigens were prepared by growing several strains of the particular fungus on synthetic asparagine media and had previously been shown to induce reproducible responses in sensitized individuals (1); both antigens were used in a dilution of 1:100. Tuberculin tests were done using a 1:10 dilution of second strength PPD (0.0005 mg). Solutions of antigens were kept under refrigeration when not in use. Equipment was autoclaved before use and so labeled as to prevent interchange.

RESULTS

There were four reactors to coccidioidin (2.1%), 40 reactors to histoplasmin (20.5%) and 136 who were sensitive to tuberculin (69.7%). Two coccidioidin reactors were histoplasmin-positive and all four were sensitive to tuberculin. Twelve of the histoplasmin-sensitive patients did not react to tuberculin; the remainder responded to both antigens. Analysis showed that there were no significant differences in prevalences of intradermal sensitivities associated with sex, race, geographic background or the particular illnesses represented. The data given in the Table suggest

Prevalence of Intradermal Sensitivities to Histoplasmin and Tuberculin Among 195 Residents of Cuba, by Ten-Year Age Groups

Ten-Year Age Group	Total Histo +		Histo + Tblin 0		Histo + Tblin +		Histo 0 Tblin +		Non-reactors	Total Tested
	No.	P.R.*	No.	P.R.	No.	P.R.	No.	P.R.		
10-19	1	10.0	1	10.0	—	—	6	60.0	3	10
20-29	9	22.5	4	10.0	5	12.5	23	57.5	8	40
30-39	6	18.2	3	9.1	3	9.1	21	63.7	6	33
40-49	9	27.3	1	3.0	8	24.3	18	54.6	6	33
50-59	9	22.0	1	2.4	8	19.6	23	57.0	9	41
60-69	6	15.8	2	5.3	4	10.5	17	44.7	15	38
Total....	40	20.5	12	6.2	28	14.3	108	55.4	47	195

* Each prevalence ratio (percentage of total tested in age group) in this column represents the sum of ratios in next two columns.

that age may have been an important factor in the development of sensitivity, but the small magnitude of the figures involved precluded definite demonstration of increasing prevalence ratios with increasing age. The Table shows however, that among the adults in the sample tested, over 65 and 20% reacted to tuberculin and histoplasmin, respectively. Reactors to coccidioidin were too few to justify tabulation.

DISCUSSION

The finding that approximately two-thirds of the patients tested were sensitive to tuberculin was anticipated in view of the known endemicity of tuberculosis in the population from which the sample was drawn.

The present study was designed primarily to provide insight into the status in Cuba of the fungi causing coccidioidomycosis and histoplasmosis; at the time this work was begun no cases of human infection with the causative fungi had been reported from this area. Only 2% of patients tested were sensitive to extracts of *Coccidioides immitis*. On the basis of experience with the same antigen in Panama (2) and in Honduras (3) where this fungus was also apparently absent, the reactions in these few patients were interpreted as nonspecific or cross-reactions and were believed to be compatible with the belief that the fungus was not endemic in this locale. These tests served as an adequate control series.

On the other hand, of the 40 reactors to extracts of *Histoplasma*, nearly one-third was sensitive to that antigen only, suggesting to us that specific sensitization may have occurred. This impression was born out at the April, 1951 meeting of the Sociedad de Estudios Clínicos de La Habana, when Sanguily *et al.* (4) described disseminated histoplasmosis in a 52-year-old Spanish male, a resident of Cuba for 25 years. In the discussion, Barquet Chediak (5) reported an unquestionably indigenous infection in a three-year-old Cuban boy of Spanish extraction. In both cases morphologic and cultural criteria for the identification of *H. capsulatum* were satisfied. This development was remarkably similar to recent experience on the Isthmus of Panama where, at the conclusion of a survey of 1,000 hospitalized residents of the area which disclosed an over-all prevalence of sensitization to histoplasmin of about 40%, the first human infection in nearly 45 years was recognized (6). Such experiences illustrate again the validity of the observation by Hodgson *et al.* (7) that "authenticated cases (of histoplasmosis) continue to be more numerous in the areas where interest in the condition is greatest."

SUMMARY

Between January, 1950 and April, 1951, 195 residents of Cuba were tested intradermally with histoplasmin, coccidioidin and tuberculin on the wards of Calixto García Hospital, Habana. Four reacted to coccidioidin (1:100) and these responses were interpreted as probable nonspecific reactions. The known high endemicity of tuberculosis was reflected by the demonstration of tuberculin sensitivity in 70% of the sample tested. Forty patients reacted to histoplasmin (1:100), of whom 12 were tuberculin-negative, a finding suggesting to us that specific sensitization by *Histoplasma* may have occurred in some or all patients in this group. This opinion was later substantiated by reports of the first indigenous Cuban cases of histoplasmosis by Sanguily *et al.* and by Parquet Chediak.

REFERENCES

- (1) Tucker, H. A.: Histoplasmin Sensitivity in the Panama Canal Zone: A correlated clinicopathologic study of 1,000 patients, with speculations as to the present status of *Histoplasma capsulatum* on the Isthmus of Panama, *Arch. Dermat. & Syph.*, 64:713, Dec. 1951.
- (2) ———: Coccidioidin Sensitivity on the Isthmus of Panama: Report of tests performed on 1,000 patients, *Am. Rev. Tub.*, 63:657, 1951.
- (3) Hoekenga, M. T., and Tucker, H. A.: Sensibilidad a la histoplasmina y a la coccidioidina en Honduras, *Bol. Of. San. Pan.*, 1135, Nov. 1950.
- (4) Sanguily, J.; Fernández Ferrer, O., and León Blanco, F.: Histoplasmosis in Cuba: Report of case, *Vida Nueva*; in press.
- (5) Barquet Chediak, J.: Histoplasmosis in Cuba: Report of case, *Arch. Med. Hosp. Universidad Calixto García (Habana)*; in press.
- (6) Tucker, H. A.: Histoplasmosis on the Isthmus of Panama: Summary of epidemiologic survey (1949-1950) and report of fourth local case (1951), *Am. Jour. Trop. Med.*; in press.
- (7) Hodgson, C. H.; Weed, L. A., and Clagett, O. T.: Pulmonary Histoplasmosis; Summary of data on reported cases and a report on two patients treated by lobectomy, *Jour. Am. Med. Assn.*, 145:807, 1951.

SENSIBILIDAD A LA HISTOPLASMINA, COCCIDIOIDINA Y TUBERCULINA EN CUBA (*Sumario*)

De enero 1950 a abril 1951, los autores comprobaron intradérmicamente con histoplasmina, coccidioidina y tuberculina a 195 residentes de Cuba en las salas del Hospital Calixto García de La Habana. Cuatro reaccionaron a la coccidioidina (1:100), interpretándose estas reacciones como anespecíficas probables. El descubrimiento de sensibilidad a la tuberculina en 70% de los sujetos comprobados, refleja la elevada endemicidad de la tuberculosis. De 40 enfermos que reaccionaron a la histoplasmina (1:100), 12 resultaron negativos a la tuberculina, lo cual parece indicar que algunos o todos los enfermos del grupo quizás revelaran sensibilización específica por *Histoplasma*. Los informes de Sanguily y colaboradores, y de Parquet Chediak sobre los primeros casos autóctonos de histoplasmosis en Cuba, apoyaron posteriormente esta opinión.