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PILOT HISTOPLASMOSIS SURVEY IN DELHI AREA

BY

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Clinical and epidemiological research during the past 12 years has demonstrated that histoplasmosis, caused by *Histoplasma capsulatum*, is one of the widely prevalent chronic pulmonary diseases in certain areas of the world. Before 1945 histoplasmosis was regarded as a fatal disease with widespread involvement of the reticulo-endothelial system. Now that the existence of a benign form of the disease is recognized, future epidemiological studies are bound to reveal its more extensive prevalence.

The widespread incidence of the benign primary form along the valleys of the Mississippi and Ohio rivers has been discovered by Christie and Peterson (1945) and by Palmer (1945). There is high incidence of positive reactors to histoplasmin in Mexico and Panama. It is also found to exist in Australia and in certain countries of northern Europe, but to a less extent.

Information regarding the prevalence of histoplasmosis in India is scanty. Wahi (1952, 1955) conducted a pilot survey in Agra with skin tests. He found 22 positive reactors to histoplasmin out of 1,331 people tested, giving 1.65% positives. Sen and Ghosh (1956), in a histoplasmin survey in Calcutta, found 0.67% positive reactors. Panja and Sen (1954) reported on "a unique case of histoplasmosis." Kalra *et al.* (1957) reported a case of histoplasmosis from Poona and claimed to have isolated the fungus and identified the same as *Histoplasma duboissi*. Recently Sen Gupta *et al.* (1957) have reported another case of histoplasmosis confirmed by culture.

The present pilot study was undertaken with a view to finding out the possible incidence of benign histoplasmosis in the Delhi area.

Material and Methods

Three areas were chosen for survey. One was in Alipur, a small village situated about 10 miles (16 km.) from Delhi. The second was in Nai Basti and Jumna Bazaar, which are situated on the bank of the River Jumna. The third area, which constitutes the urban area, was represented by patients attending the Municipal Tuberculosis Clinic and the Clinical Research Centre of the Chest Institute.

People tested were selected at random and belong to all age-groups above 5 years. The histoplasmin used for the survey was the one manufactured by Parke, Davis & Co. and supplied by the courtesy of the Technical Co-operation Mission of the U.S.A. 0.1 ml. of 1 in 100 dilution of the antigen was given intradermally on the forearm. All cases were simultaneously tuberculin-tested by intradermal injection of 5 T.U. of P.P.D. Readings were made 48 hours after the test. A reaction showing an induration measuring 5 by 5 mm. or greater was taken as positive.

All available histoplasmin reactors were subjected to thorough physical, radiological, and laboratory examinations, which included complement-fixation test, blood culture, bone-marrow biopsy, and culture of bronchial aspirations. Sabouraud's glucose agar incubated at 25° C. and brain-heart infusion blood-agar incubated at 37° C. were used as media for culturing the fungus. The cultures were kept under observation for three to four weeks before they were discarded as negative for fungus. Examination for acid-fast bacilli was also done simultaneously.

Results

The results of skin-testing and examination of histoplasmin-positive reactors are summarized in Tables I and II. It will be seen from Table I that the highest percentage of histoplasmin-positive reactors—namely, 12.3—was found among the population inhabiting Nai Basti and Jumna Bazaar areas. Even in the rural and urban areas our percentages for positive reactors are higher than those reported by Wahi in Agra and Sen and Ghosh in Calcutta.

TABLE I.—*Incidence of Histoplasmin-positive Reactors and Their Response to the P.P.D. Test in Different Areas*

Place	No. Tested	No. Read	No. of Histoplasmin Positives	% of Histoplasmin Positives	Response of Histoplasmin Positives to P.P.D. Test		% of P.P.D. Negatives Histoplasmin Positives
					No. of P.P.D. Positives	No. of P.P.D. Negatives	
Delhi, rural	112	103	3	2·9	3	0	
Delhi, riverine	235	162	20	12·3	18	2	10%
Delhi, urban	400	301	15	4·9	15	0	

TABLE II.—*Results of Investigations on 26 Histoplasmin Reactors*

No. with no signs	3
,, ,, multiple pulmonary calcifications	17
,, ,, pulmonary calcifications and tuberculous lesions	3
,, ,, hilar enlargement only	2
,, ,, other diseases (cancer)	1
,, ,, positive histoplasma culture	0

During the course of another study which is being conducted in this institute, out of 30,000 chest *x*-ray films examined, 29 showed multiple pulmonary calcification without any evidence of any other disease in the lungs. Seven of these 29 were positive to the histoplasmin test. In the present study 17 out of 26 histoplasmin-positive reactors had multiple pulmonary calcifications.

The diagnosis of endemic histoplasmosis in a certain area will no doubt depend upon the four criteria laid down by Grayston and Furcolow (1956): (*a*) positive histoplasmin skin test, (*b*) positive histoplasmin serology, (*c*) development of miliary pulmonary calcification, and (*d*) isolation of *Histoplasma capsulatum* from the soil. Even though all the criteria have not been satisfied in the present survey, the significantly high percentage of histoplasmin-positive reactors and the not uncommon finding of multiple pulmonary calcification without any

previous history of illness are suggestive of the presence of histoplasmosis infection, particularly in the riverine areas. Though no definite conclusions can be drawn about the extent of the incidence of histoplasmosis in Delhi and in other parts of the country from the present study, it undoubtedly emphasizes the urgent need for a more comprehensive survey which will provide further information about the epidemiology of the disease in this country.

Summary

A pilot histoplasmin survey was carried out in the Delhi area. Skin tests were performed on 747 people from different places representing rural, urban, and riverine areas of Delhi.

12.3% positive reactors were found in the riverine area, 2.9% in the rural area, and 4.9% in the urban area.

Cultural and serological examinations of histoplasmin-positive reactors were all negative.

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PUERPERAL ERYTHEMA NODOSUM AFTER LIVER EXTRACT INJECTIONS

TREATMENT WITH PREDNISONE

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In 1958 a trial was instituted by the South-East England Faculty of the College of General Practitioners into the prevention of early puerperal depression by injections of liver extract. Alternate cases were to be given two intramuscular injections of 4 ml. of "anahaemin" on successive days after confinement. The only two patients in this practice who were given these injections developed erythema nodosum within a month of confinement.

Previous Reports

It is known that some patients have an allergic tendency to react to all forms of liver injections, but such reactions are thought less likely to occur with anahaemin because of the refined nature of the product. It has not previously been reported as causing erythema nodosum.

Favour and Sosman (1947) found erythema nodosum associated with respiratory infection in 80% of their patients. Half the throat swabs taken grew haemolytic streptococci, but rheumatic fever was rare and tuberculosis was uncommon. They noted that 80% of their adult patients had accompanying arthritis and that many of those treated with penicillin or sulphonamides recovered no more rapidly than otherwise expected. Most reports of drug-induced erythema nodosum concern sulphathiazole, this being bound to serum proteins more than other sulphonamides. Doxiadis and McLean (1948) found that in children with sulphathiazole-provoked erythema nodosum it began within seven days of the start of treatment and faded within nine days. Histologically it appeared the same as spontaneous erythema nodosum. Lemaire *et al.* (1948), reporting two adult cases of active early tuberculosis, found that the erythema nodosum provoked by sulphathiazole disappeared in spite of continued use of the drug.

A detailed study by Rollof (1950) of the erythema nodosum provoked by sulphathiazole in children showed 81% associated with tuberculosis; the more recent the infection the more commonly was erythema nodosum provoked. He concluded that it is not a specific disease, but that, whether spontaneous or sulphathiazole-induced, it is a manifestation of an allergic phenomenon due to some kind of infection. Added weight is given to this theory by the remarkably prompt response to cortisone recorded in four separate cases (without active tuberculosis) treated in the U.S.A. (Allbright and Kuffel, 1951; Ureles and Kalmansohn, 1951; Farber and Mandelbaum, 1951; Schneierson, 1952). But, as in the following two cases, there is often no obvious source of infection.

Case 1

The patient, aged 42, was a gravida-6, including three abortions. Blood group A Rh+; Hb, 95%; W.R. and Kahn negative. Previous obstetric and general history without note. Her general health during pregnancy was good except for varicose veins and one day's slight vaginal loss of blood (and epistaxis) at the 27th week.

She had a normal confinement at home on July 6, 1958. Blood loss was 10 oz. (280 ml.). Ergometrine 0.5 mg. was given intramuscularly after the third stage into the outer side of one thigh. On the first two days of the puerperium anahaemin 4 ml. was given into each outer thigh. On the 10th and 19th days she developed mild superficial phlebitis of the right long saphenous vein in the calf and above the knee. Breast-feeding was established and maintained throughout the forthcoming illness.

31st Day.—She now developed "cellulitis" of the outer side of the right thigh at the site of an anahaemin or ergometrine injection. This appeared gradually over four days and was accompanied by an inguinal adenitis. Twice-daily injections of penicillin were started. During the next two days tender erythema occurred in old scars on the left knee and buttock and the right shin, and she complained of backache.

33rd Day.—Admitted to hospital with her baby as a case of septicaemia not responding to penicillin. Throat swab and high vaginal swab: no pathogens isolated. Catheter specimen of urine—nothing abnormal. E.S.R. (Westergren), 100 mm./hour, Hb 89%; W.B.C., 11,000/c.mm. (neutrophils 80%, eosinophils 5%, lymphocytes 9%, monocytes 6%). Penicillin was continued without effect on the fever or patches of erythema which remained confined to the legs. Three days later the area of cellulitis on the thigh was incised but no pus obtained. A swab gave no growth. Skin biopsy: erythema nodosum with giant cells and no caseation. Mantoux 1/1,000, negative. Chest *x*-ray film normal.