

THE HISTOPLASMIN REACTION IN LEPROSY PATIENTS

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INTRODUCTION

In Surinam a rather high percentage of the population shows hypersensitiveness to histoplasmin, as has been recorded by Collier and de la Fuente (2). They applied the test for the greater part to patients who were under medical treatment in the government hospital or in the lunatic asylum "Wolffebuttel." Only a small part of these latter were outpatients. None of the persons submitted to the test was in perfectly good health.

Because a relatively large number of the inhabitants of Surinam are suffering from leprosy, it is not without interest to examine a number of such patients with regard to their hypersensitivity to histoplasmin. Nothing of this matter has as yet appeared in the literature. There are no indications that any other infectious disease should in any way influence the outcome of this test. On the contrary, it has been definitely proved that there is no correlation whatever between the outcome of the tuberculin and histoplasmin tests.

MATERIAL AND METHOD

The histoplasmin test was applied to 675 leprosy patients during the month of July 1952, toward the end of the long rainy season. These patients were in the three "Hansen's Sanatoria" of Surinam. In the leprosarium "Majella," close to the government hospital in Paramaribo city, 216 of the 226 patients were tested. The leprosarium "Bethesda" is at a distance of nearly 7 km. from the center of the town; here 164 of the 169 patients were tested. The leprosarium "Groot Chatillon," which is nearly 30 km. from Paramaribo, has 342 patients of whom 295 were included in this study. In total, the test was applied to nearly 92 per cent of all the leprosy patients in the three hospitals.

The test has also been applied, toward the end of the rainy season, to a total of 932 nonleprosy persons. Most of these latter were patients included in the report of Collier and de la Fuente, but the number has been increased.

The histoplasmin preparation used was kindly placed at our disposal by the Eli Lilly Company. In each case 0.1 cc. of a 1:1000 dilution was injected intracutaneously.

The reactions were read after 48 hours. The reaction was considered positive if there was notable induration more than 4-5 mm. in diameter.

TABLE 1.—*Histoplasmin reactions in leprosy patients in the different sanatoria, and in nonleprosy controls, by sex and age groups.*

Reaction	Groot Chatillon	Bethesda	Majella	Total leprosy	Other patients
<i>Male adults</i>					
+	56	20	19	95 25.3%	239 55.5%
±	39	14	17	70 18.6%	76 17.6%
0	122	39	50	211 56.1%	116 26.9%
Total	217	73	86	376	431
<i>Female adults</i>					
+	15	18	16	49 25.1%	171 41.7%
±	10	5	9	24 12.3%	78 19.0%
0	48	30	44	122 62.6%	161 39.3%
Total	73	53	69	195	410
<i>Male children</i>					
+	0	3	5	8 13.5%	8 16.0%
±	0	4	5	9 15.3%	8 16.0%
0	2	19	21	42 71.2%	34 68.0%
Total	2	26	31	59	50
<i>Female children</i>					
+	1	4	3	8 17.8%	5 12.2%
±	0	0	3	3 6.7%	10 24.4%
0	2	8	24	34 75.5%	26 63.4%
Total	3	12	30	45	41
<i>Total patients</i>					
+	72 24.4%	45 27.4%	43 19.9%	160 23.7%	423 45.4%
±	49 16.6%	23 14.0%	34 15.7%	106 15.7%	172 18.4%
0	174 59.0%	96 58.6%	139 64.4%	409 60.6%	337 36.2%
Total	295	164	216	675	932

A softer, edematous swelling, regardless of its size, was recorded as doubtful (\pm), as well as an occasional nodule 1-2 mm. in diameter. Reactions of this \pm grade are included in this report in order to determine minor differences, if any, between leprosy and other patients. On comparing these statistics with others these \pm cases must be regarded as negative.

RESULTS

Since the three leprosaria in which these tests were made are rather far from each other, the data are first examined, in Table 1, to determine whether the patients in the different institutions gave materially different results. From the data in the last section of the table it will be seen that there were no essential differences in the frequency of definitely positive reactions in the three groups, with 24.4 per cent in Groot Chatillon, 27.4 per cent in Bethesda, and 19.9 per cent in Majella. The range of the percentages of completely negative reactions is smaller, because those for doubtful reactions are very much alike.

Also shown in Table 1 are the data by sex and age. Only two large age groups are considered, the adults including all persons above fifteen years of age, the children being all under that age. The percentages for positive reactions among the men and women are virtually identical, 25.3 and 25.1, respectively; and those for the boys and girls, 13.5 and 17.8, respectively, do not differ very much. These figures are materially smaller than in the case of the adults. The small difference between them may perhaps be attributed to the small number of persons examined.

An analysis of the data to determine whether the three ethnic groups involved in this study differ in the frequency of hypersensitivity to histoplasmin is shown in Table 2. Among the leprosy patients the percentages of definitely positive reactions for the Creoles, the Hindustani and the Indonesians are 23.3, 24.5 and 25.0, respectively, the differences entirely negligible. The range of the corresponding percentages among the nonleprosy patients, 48.2, 39.8 and 43.4, is considerably greater but of doubtful significance.

A matter of some importance, however, is the comparison of the frequency of positive histoplasmin reactions in the leprosy patients and the persons suffering from other diseases, shown in Tables 1 and 2. In total (Table 2), the nonleprosy group gave almost twice as many definitely positive reactions as the leprosy patients, 45.4 per cent as against 23.7 per cent, a ratio of 1.92:1.00. Comparing the figures for adults of both

TABLE 2.—*Histoplasmin reactions in leprosy and nonleprosy patients, by ethnic groups.*

Reaction	Creoles	Hindustani	Indonesians	Total
<i>Leprosy patients, total</i>				
+	114 23.3%	27 24.5%	19 25.0%	160 23.7%
±	79 16.2%	14 12.7%	13 17.1%	106 15.7%
0	296 60.5%	69 62.7%	44 57.9%	409 60.6%
Total	489	110	76	675
<i>Other patients, total.</i>				
+	278 48.2%	99 39.8%	46 43.4%	423 45.4%
±	98 17.0%	54 21.7%	20 18.9%	172 18.4%
0	201 34.8%	96 38.5%	40 37.7%	337 36.2%
Total	577	249	106	932

groups (Table 1), it is seen that among the males this ratio is nearly 2.2 to 1.0. Materially fewer females among the non-leprosy group gave positive reactions than the males, so the total percentages for adults are 48.8 per cent for that group and 25.2 per cent for the leprosy patients, or a ratio of 1.94:1.00. In the case of the children this difference does not exist. Of the children in the leprosaria, 15.4 per cent reacted positively, while of those in the other group 14.3 per cent were positive.

Finally, to establish whether the different forms and degrees of advancement of leprosy showed any differences regarding hypersensitiveness, Table 3 has been prepared. The cases of the lepromatous type have been divided into the usual three grades, L_1 , L_2 and L_3 .

The findings are interesting in that the persons suffering from the least degree of advancement of lepromatous leprosy (L_1) show in total the lowest percentage of positive reactions to histoplasmin, 15.9. Then follows the L_2 group, with 25.5 per cent, while the L_3 and tuberculoid groups show almost the same rate, 33.0 and 31.1 per cent, respectively.

TABLE 3.—*Histoplasmin reactions in leprosy patients, by type and degree of the disease.*

Reaction	Lepromatous leprosy			Tuberculoid leprosy
	L ₁	L ₂	L ₃	
+	38 15.9%	70 25.5%	33 33.0%	19 31.1%
±	40 16.7%	39 14.2%	18 18.0%	9 14.8%
0	161 67.4%	166 60.3%	49 49.0%	33 54.1%
Total	239	275	100	61

These data have also been analyzed with respect to the age and sex groups, but nothing of significance emerged. With regard to the ethnic groups, a point of some interest is that among the Creoles the lepromatous cases tend to be somewhat the most severe, and the tuberculoid cases are fewest, whereas the opposite condition is indicated by the figures for the Hindustani.

DISCUSSION

First to be mentioned is the fact that the men and the women in the leprosaria show the same percentage of positive reactions, 25.3 and 25.1, respectively, while in the case of other patients the men show a higher percentage than the women, 55.5 as against 41.7. Possibly the reason for this difference is that in the leprosaria men and women live permanently in the same environment, while in the other cases the differences in the percentages of reactions may be due to the occupations of the men. This is purely a matter of hypothesis, so little is known about the manner of infection with histoplasmosis.

Of most interest are the figures which clearly indicate that patients suffering from leprosy are hypersensitive to histoplasmin in a much lower degree than patients suffering from other diseases. The explanation of this phenomenon is a matter of uncertainty.

With Christie (1), we may take it as certain that hypersensitivity to histoplasmin is caused exclusively by infection with histoplasma, although in many areas cross reactions may occur with other mycotic infections.¹ Furthermore, it seems

¹ We do not consider here the question whether the symptoms of histoplasmosis are to be attributed exclusively to histoplasma, or whether in this

impossible that, in an endemic area such as Surinam undoubtedly is, leprosy patients should be less exposed to histoplasma infection than other persons.

The frequency of positive reactions among the patients of the Majella leprosarium does not differ from those of the patients of the two other leprosaria, which are situated outside the town. An attempt to explain the difference between the leprosy and other patients on the ground that those at Bethesda and Groot Chatillon are, because they live in the country, less exposed to infection than those in the town does not hold good for the Majella patients, who have lived in the town of Paramaribo for years and are certainly not less exposed than are the other inhabitants of the town. It is therefore not likely that the lower histoplasmin hypersensitivity in leprosy patients is due to less exposure.

Seasonal influences must likewise be ignored in this case, because all of the patients, in both groups, were tested at the same time. Nor are there differences in altitude, for the two leprosaria outside the town are situated at about the same altitude as Paramaribo.

Perhaps a diminution of the normal resistance of the organism may act as a check upon hypersensitivity. From that point of view, however, it might be assumed that, as the process of leprosy develops, the frequency of a positive histoplasmin reaction would decrease. The very contrary is shown by our data: the lowest percentage of positivity is seen in the L₁ group, whereas twice as many reactions were obtained in the L₃ cases.

Finally, it must be pointed out that the leprosy patients were under treatment with the modern sulfones (DDS, promacetin, promin, etc.). Whether these drugs can influence the infection with histoplasma or the physical condition in such a way as to become sensitive to histoplasma is unknown.

None of the above-mentioned possibilities can be considered very probable. It is a fact, however, that two infections occurring at the same time may occasionally influence each other, either in the sense of cooperation (synergism) or in the sense of antagonism. In this connection it may suffice to refer to the antagonism of the malaria parasite or of the *Treponema recurrentis* to *T. pallidum* and to the various trypanosomes, and that of the dysentery bacilli to the intestinal flora. The most

matter a synergistically-acting mixed infection with another agent may not play an essential part, in analogy with the relationship between the synergism between the influenza virus and the influenza bacterium.

logical explanation of the low figures of histoplasmin hypersensitivity in leprosy patients may therefore perhaps be that there is a kind of antagonism of the leprosy bacillus and the histoplasma.

SUMMARY

On testing 675 patients of the three leprosaria in Surinam it was found that 23.7 per cent gave a positive histoplasmin reaction, while of 932 patients suffering from other diseases 45.4 per cent reacted positively. Among the leprosy patients the lowest frequency (15.9%) was found in the L_1 group, and the highest frequency in the L_3 group and the tuberculoid type (33.0% and 31.1% respectively). A kind of antagonism of the leprosy agent as to histoplasma is considered to be the determining factor.

Among the leprosy patients the positive rates for adult males and females were virtually identical, whereas among the other patients the adult males gave a materially higher rate than did the females. The children all gave much lower rates, with no material differences between the sexes or the two source groups. No significant differences were found between the three racial groups involved as regards histamin hypersensitivity, although there are some differences with regard to the severity of leprosy, it being highest among the Creoles, intermediate in the Indonesians, and lowest among the Hindustani.

RESÚMEN

Se determinó el porcentaje de positividad a la histoplasmina en 675 pacientes de tres leprosarios en Surinam. Se encontró que el 23.7% reaccionaron positivamente, en contraste con 45.4% de 932 pacientes con otras varias enfermedades. Entre los leprosos, la frecuencia mas baja (15.9%) fué en el grupo L_1 , y la mas alta en los grupos L_3 y tuberculoide (33.0% y 31.3%) respectivamente. Se considera que hay cierto antagonismo entre el histoplasma y la lepra.

Entre los leprosos hubo tantos positivos varones como hembras, pero en los otros pacientes hubo preponderancia de positivos en varones. Los niños tuvieron una incidencia baja sin diferencia entre sexos ni entre los dos grupos. No hubo diferencias entre los 3 grupos raciales representados, con relación a sensibilidad a la histoplasmina, aunque si hubo diferencias con relación a la severidad de la lepra, mayor en los criollos intermedio en los indoneses y menor en los hindostanes.

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