

LEPROMIN AND TUBERCULIN TESTS IN VENEZUELAN  
LEPROSY FOCI, INDUCTION OF LEPROMIN  
REACTIVITY BY BCG VACCINATION

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The work reported in this paper was carried out by the Fourth Antileprosy Service of the Leprosy Division of the Ministry of Health of Venezuela. It was planned for the purpose of studying the lepromin and tuberculin reactions before and after the administration of BCG in a relatively large group of persons living in leprosy foci of rural areas. Statistics regarding the induction of the lepromin reaction by BCG would be valuable as a criterion for the extension of vaccination to all foci in the country.

MATERIALS AND METHODS

The leprosy foci chosen for this work were in the rural areas of the districts of Boconó and Niquitao of the state of Trujillo, and in the districts of Miranda, Rangel, Rivas Dávila, Campo Elías and Liberador of the state of Mérida.

As a basis for the study a dermatological examination was made of practically the entire population in these foci, and every healthy person was given the lepromin and tuberculin tests. The latter was read after 72 hours, the former in the fourth week after injection. The antigens used were PPD of 5 units strength and standard lepromin prepared at the Cabo Blanco Leprosarium by the Mitsuda-Hayashi method. The measure of the reaction accepted as positive for the Mantoux test was that recommended by the World Health Organization, and for the Mitsuda the one accepted by the Second Pan-American Leprosy Conference (Rio de Janeiro, 1946). Almost all lepromin-negative persons were vaccinated with BCG prepared in the National Institute for Tuberculosis in Caracas. The dose was 0.2 mgm. of bacilli in two simultaneous, intradermal injections of 0.1 cc. each on the upper back. The lepromin test was repeated 3 months after vaccination.

RESULTS

The examinations included a total of 8,385 persons, all of whom were given the lepromin and tuberculin tests. In total, 7,029 persons, or 83.8 per cent, were found to be lepromin positive. The data are given in Table 1. If we study the figures for positivity to lepromin in the different age groups it will be noted that 4,984, almost 60 per cent of the total number of persons, were below 24 years of age and that 74 per cent of them were lepromin positive. It will also be observed that the percentage of positivity increases with age. In the group of infants, 0 to 4 years, only 57.6 per cent were positive, while in the 45-64-years group the positives were 96.8 per cent, and in the oldest group the index of positivity was 100 per cent.

When we consider the variations in the intensity of the Mitsuda reaction, we find that there are higher percentages of 2+ and 3+ reactions in the higher age groups. In the group below 14 years of age the per-

TABLE 1.—Positive lepromin reactions in relation to age, initial tests.

Age group	No. of persons	1+	Per cent	2+	Per cent	3+	Per cent	Total positive	Per cent
0-4	900	417	46.3	91	10.1	10	1.1	518	57.6
5-14	2,732	1,164	42.6	717	26.2	211	7.7	2,092	76.6
15-24	1,432	400	27.9	650	45.4	207	14.4	1,257	87.8
25-44	2,084	408	19.6	1,074	51.5	481	23.1	1,963	94.2
45-64	1,068	182	17.0	610	57.1	242	22.6	1,034	96.8
65-74	127	30	23.6	71	55.9	22	17.3	123	96.9
75+	42	11	26.2	27	64.3	4	9.5	42	100.0
Total	8,385	2,612	31.2	3,240	38.6	1,177	14.0	7,029	83.8

centage of 1+ positivity is higher than the percentage of the 2+ and 3+ reactions combined. In general, it may be said that the percentage of positivity in the higher age groups is above 90, and that the 2+ and 3+ reactions predominate.

The Mantoux test given to the initial group of 8,385 persons gave positive reactions in 3,148 persons, or 37.5 per cent. Data showing the relation between age and the index of positivity to that test are given in Table 2. It will be observed that here the index also shows a notable rise in higher age groups, being only 5.6 per cent in the group of infants of 0 to 4 years, and reaching 76.2 per cent among the people 75

TABLE 2.—Positive tuberculin reactions in relation to age, initial tests.

Age group	No. of persons	1+	Per cent	2+	Per cent	3+	Per cent	4+	Per cent	Total	Per cent
0-4	900	29	3.2	19	2.1	1	0.1	1	0.1	50	5.6
5-14	2,732	211	7.7	205	7.5	46	1.7	9	0.3	471	17.2
15-24	1,432	216	15.1	277	19.3	47	3.3	10	0.7	550	38.4
25-44	2,084	472	22.6	636	30.5	121	5.8	13	0.6	1,242	59.6
45-64	1,068	307	28.7	341	31.9	63	5.9	14	1.3	725	67.9
65-74	127	36	28.3	38	29.9	3	2.4	1	0.8	78	61.4
75+	42	15	35.7	16	38.1	1	2.4	—	—	32	76.2
Total	8,385	1,267	15.1	1,526	18.2	280	3.3	48	0.6	3,148	37.5

years old or more. When we examine the data on intensity of these Mantoux reactions, we find that the great majority of the positive reactions were in the nature of a weak or medium-degree allergy, i.e., 1+ or 2+, and that the percentage of strong allergies (3+ and 4+) was very low.

The relationship between the two tests, Mantoux and Mitsuda, is shown in Table 3. The coefficient of correlation between the reactions was 0.44, which is comparatively low, due probably to the low incidence of tuberculosis in the areas studied in contrast with the higher index of natural protection against leprosy evidenced by the positive lepromin

TABLE 3.—Correlation between the Mantoux and the Mitsuda reactions, initial tests.

Mantoux reaction <sup>a</sup>	Mitsuda reaction <sup>a</sup>				
	—	1+	2+	3+	Total
—	1,329	2,152	1,302	454	5,237
1+	19	246	777	244	1,286
2+	6	173	982	371	1,532
3+	2	38	151	91	282
4+	—	3	28	17	48
Total	1,356	2,612	3,240	1,177	8,385

<sup>a</sup> Coefficient of correlation, 0.44.

reactions. This coefficient of correlation in rural areas is in conspicuous contrast to that which we have observed in cities, where the coefficient practically reaches unity.

TABLE 4.—The Mantoux reaction as a function of age in Mitsuda-positive and negative persons, initial tests, total both sexes.

Age group	Mitsuda positive	Mantoux positive 1+ to 4+	Per cent	Mitsuda negative	Mantoux positive 1+ to 4+	Per cent
0-4	518	46	8.9	382	4	1.0
5-14	2,092	463	22.1	640	8	1.2
15-24	1,257	545	43.4	175	5	2.8
25-44	1,963	1,233	62.8	121	6	5.0
45-64	1,034	721	69.7	34	4	11.8
65-74	123	78	63.4	4	—	—
75+	42	32	76.2	—	—	—
Total	7,029	3,118	44.4	1,356	27	3.0



In the study of the Mantoux reaction with regard to the age of the Mitsuda-positive and the Mitsuda-negative persons (Table 4), we find that the index of tuberculin positivity is roughly 45 per cent for the lepromin positives, while it is only 3 per cent for the lepromin negatives.

The reverse of the picture, i.e., the relation between lepromin reactivity and the age of the Mantoux-positive persons, is shown in Table 5. There

TABLE 5.—*The Mitsuda reaction as a function of age in Mantoux-positive and-negative persons, initial tests, total both sexes.*

Age Group	Mantoux positive	Mitsuda positive 1+ to 4+	Per cent	Mantoux negative	Mitsuda positive	Per cent
0-4	50	46	92.0	850	472	55.5
5-14	471	461	97.9	2,261	1,631	72.1
15-24	550	550	100.0	882	707	80.2
25-44	1,242	1,241	99.9	842	722	85.7
45-64	725	725	100.0	343	309	90.1
65-74	78	78	100.0	49	45	91.8
75+	32	32	100.0	10	10	100.0
Total	3,148	3,133	99.5	5,237	3,896	74.4

it will be seen that the percentages of positivity to the Mitsuda test are above 90 in all the age groups. It is also to be seen that positivity to lepromin for the Mantoux negatives increases from 55.5 per cent in the 0-4 age group to 91.8 per cent in the 64-74 group, while it reaches 100 per cent in the group of 75 or over.

The differences observed in the percentages of the two series up to the age of 64 and in the general total are highly significant. This is also true for the groups aged 65 to 75 years. Differences of this order would occur by mere chance only 1.8 times in 100 trials with samples of equal size from the same universe.

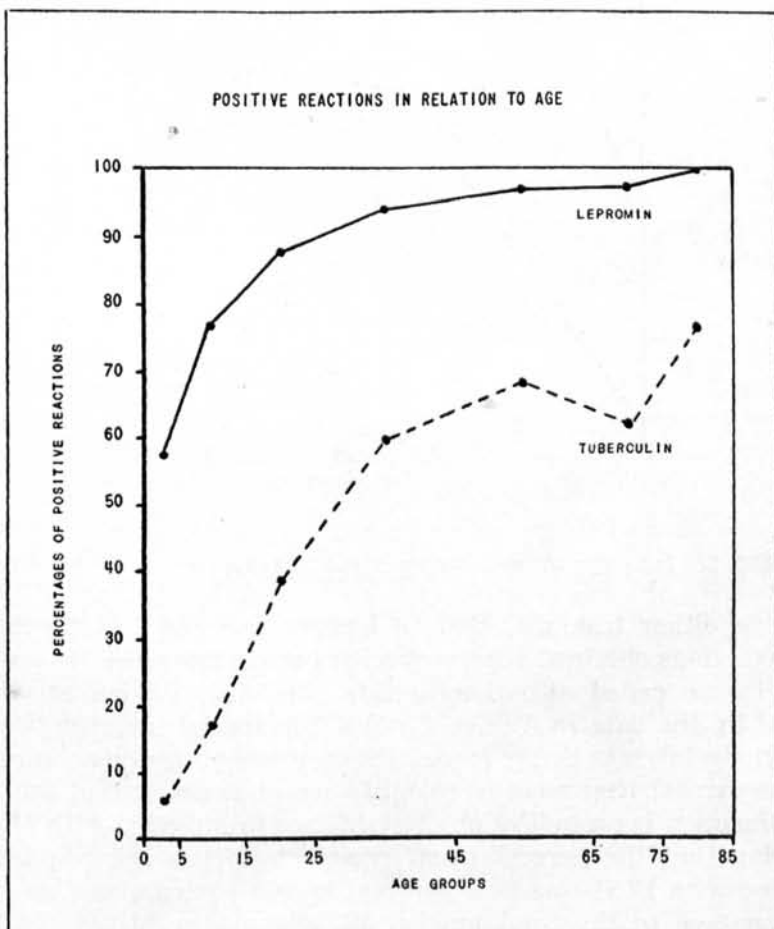
Of the 1,356 persons proved to be lepromin negative, only 960 presented themselves for vaccination with BCG and for the second lepromin test. From Table 6 it will be seen that 92.2 per cent of these individuals become lepromin reactors. There was ample evidence that the induced reactivity had the same characteristics as the phenomenon of spontaneous, natural positivity. It was similar also as regards the characteristic increase in the higher age groups, and showed the same parallelism of steadily rising percentages of strongly positive reactions (2+ and 3+). No differences worthy of mention were found between the sexes as regards the induced lepromin reaction.

## DISCUSSION

The results obtained with the lepromin test in the initial examinations reveal a relatively low index of protection, considering that 16.2 per cent of the persons at that time lacked the resistance to leprosy that is indicated by positivity to lepromin. It is a well-known fact that the great majority of lepromatous and indeterminate cases come from the Mitsuda-negative group.

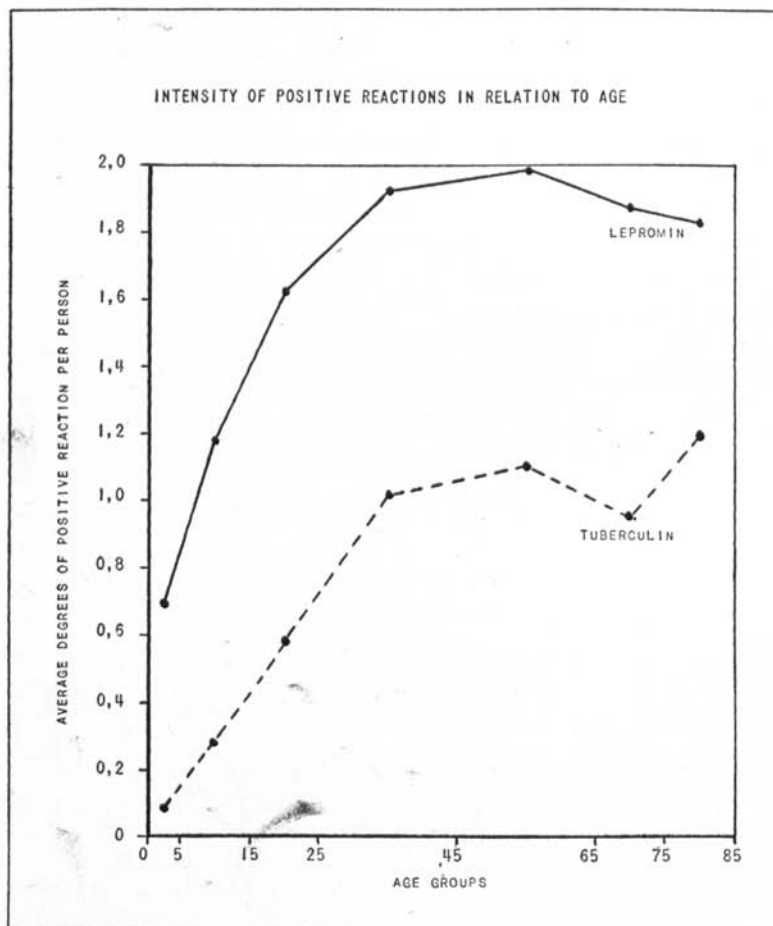
We have characterized the lepromin index of protection as being relatively low, because the zones in which the investigation was carried out are important foci of leprosy endemicity, and, moreover, because it is lower than what we have found in other active leprosy foci in this country. This line of reasoning applies more especially to the age groups ranging from birth to 24 years.

It is an observed fact that infection with *Mycobacterium tuberculosis* is capable of evoking resistance to infection with *M. leprae*, and the



TEXT-FIG. 1. Percentage of positive reactors to tuberculin and lepromin by age.

possibility exists that the biological mechanism underlying resistance is common for both diseases. The possibility also exists that the allergy that may be induced by an infection with *M. leprae* may be evidenced by a



TEXT-FIG. 2. Intensity of positive reactions to tuberculin and lepromin by age.

response to either test, and that in leprosy foci some of the Mantoux positive reactions obtained are not specific but paraspecific. In a previous report (1) we called attention to this possibility, which seems to be supported by the data in Tables 4 and 5. A special investigation which we have undertaken to throw more light on this matter is now in progress.

At the present time most leprologists accept as a fact that the positive Mitsuda reaction is an indication of resistance to infection with *M. leprae*. Considering that the percentage of positivity to the Mitsuda test after vaccination with BCG was 92.2 per cent in 960 persons, and by applying that percentage to the total number of Mitsuda negatives—i.e., to the 1,356—we can be reasonably sure that a total of 1,250 would have become

Mitsuda positive if they all had returned for vaccination and the second test. Only 106 persons would thus have remained negative to lepromin out of a total of 8,385, and this would mean that only 1.3 per cent of the inhabitants could continue without protection, as compared with the 16.2 per cent found in the initial tests.

TABLE 6.—*Induction of lepromin reactivity by BCG vaccination, in relation to age.*

Age group	No. of persons	1+	Per cent	2+	Per cent	3+	Per cent	Total	Per cent
0-4	232	109	47.0	77	33.2	4	1.7	190	81.9
5-14	478	216	45.2	201	42.0	31	6.5	448	93.7
15-24	130	35	26.9	89	68.5	4	3.1	128	98.4
25-44	94	31	33.0	53	56.4	9	9.6	93	98.9
45-64	24	7	29.2	17	70.8	—	—	24	100.0
65-74	2	1	50.0	1	50.0	—	—	2	100.0
75+	—	—	—	—	—	—	—	—	—
Total	960	399	41.6	438	45.6	48	5.0	885	92.2

#### SUMMARY

The reactions to tuberculin and lepromin were studied in 8,353 inhabitants of leprosy foci in rural areas in Venezuela. Of this general group, a total of 1,356 (16.2%) proved to be negative to the Mitsuda test, while 5,205 (62.5%) were Mantoux negative. In the group of Mitsuda-positive persons 44.8 per cent were also Mantoux positive, while in the Mitsuda-negative group only 3 per cent were Mantoux positive.

In the Mantoux-positive group 99.5 per cent were Mitsuda-positive, while in the Mantoux-negative group 74.4 per cent were Mitsuda-positive.

Considering that 16.2 per cent of the persons examined were found to be without protection against leprosy in the first tests, and taking into account that almost all lepromatous and indeterminate cases come from the lepromin negatives, which form the endemic matrix of the disease, there can be no doubt but that BCG vaccination will be an effective prophylaxis, at least in rural areas, when it can reduce the percentage of Mitsuda negative from 16.2 to 1.3 per cent.

#### RESÚMEN

Fué realizado un estudio a base de pruebas con tuberculina y lepromina en 8,353 habitantes de focos de lepra en áreas rurales de Venezuela.

Del grupo estudiado, 1,356 resultaron negativos al Mitsuda, 16.2 por ciento. La reacción de Mantoux dió resultado negativo en 5,205, 62.5 por ciento. Del grupo de Mitsuda positivo un 44.4 por ciento presentaron Mantoux positivo, en tanto que del grupo Mitsuda negativo solamente presentaron Mantoux positivo 3.0 por ciento. Del

grupo de Mantoux positivo el 99.5 por ciento presentaron Mitsuda positivo, en tanto que del grupo Mantoux negativo solamente el 74.4 por ciento presentaron Mitsuda positivo.

Si tomamos en cuenta que el 16.2 por ciento de las personal del grupo estaban sin protección frente a la lepra para el momento de la investigación por presentar un Mitsuda negativo y teniendo además en cuenta que es de los leprominosos negativos que salen la casi totalidad de los casos lepromatosos e indeterminados, matriz de la endemia, es evidente que la vacunación BCG haciendo descender el porcentaje de los Mitsuda negativos de 16.2 por ciento a 1.3 por ciento, representa un método indudable de profilaxis antileprosa, por lo menos en las áreas rurales.

#### ACKNOWLEDGMENT

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#### REFERENCE

1. CONVIT, J., GONZALES, C. L. and RASSI, E. Estudios sobre en el grupo étnico Alemán de la Colonia Tovar, Venezuela. *Internat. J. Leprosy* **20** (1952) 185-193.