

AN INVESTIGATION OF LEPROSY IN THE GERMAN ETHNIC GROUP OF COLONIA TOVAR IN VENEZUELA

IV. CLINICAL FINDINGS AND VARIATIONS IN THE MANTOUX AND MITSUDA REACTIONS OBSERVED DURING FIVE YEARS AFTER BCG VACCINATION OF MITSUDA-NEGATIVE CONTACTS

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Five years of observation of the group of originally Mitsuda-negative contacts living with sources of infection of the lepromatous type in the rural area of Colonia Tovar have now been completed. It is therefore considered proper to report now on the clinical findings and the changes in the tuberculin and lepromin reactions since they were vaccinated with BCG in 1950. The group is believed to have been exposed to great danger of contagion both before and during the period of observation.

The present communication extends a former one which was presented to the leprosy congress held in Madrid in 1953 (3), from which it differs by the longer period of observation.

MATERIALS AND METHODS

The population studied, composed of 110 individuals, varied as regards age and sex as follows:

Age	Male	Female	Total
0- 4 years	13	10	23
5- 9 years	18	11	29
10-19 years	20	21	41
20 and over	5	12	17
Totals	56	54	110

There is a difference of three persons in comparison with the previous report. These individuals were vaccinated with the others in 1950, but they evaded follow-up examinations during the next three years. However, they were examined in 1954 and 1955.

As said, all of these persons were originally Mitsuda negative, and 100 of them were Mantoux negative as well. Five of the 10 Mantoux positives belonged to the oldest age group.

The investigation was carried out in the following manner: (1) Of the total group of 110 only 109 were vaccinated with BCG, as one failed to show up. (2) The tuberculin and lepromin tests were repeated 10 weeks after the vaccination. (3) Both tests were repeated at intervals of approximately one year thereafter. (4) Every person whose Mitsuda reaction did not become positive, or was only weakly so, was revaccinated regardless of what was shown by the Mantoux test. (5) Biopsies were made of all lesions suspicious of leprosy that were found in the clinical examinations.

The lepromin used was the standard prepared by the Mitsuda-Hayashi method. In the initial tuberculin tests 1 unit of PPD was used, but nonreactors were retested with 10 units. However, in the years following 1951 all of the test doses used were

of 5 units strength. The reading of the Mitsuda test was made according to the scale adopted by the II Pan-American Leprosy Conference (1). The Mantoux test was read according to the standard accepted by the World Health Organization. The BCG used for vaccination contained 0.00075 gm. of bacilli per 0.1 cc., and two intradermal injections, each of that quantity, were used to vaccinate each person.

CLINICAL FINDINGS

The clinical examinations, which were carried out systematically during the period of observation, revealed that a total of 106 persons of the group were without clinical signs of leprosy. Among the other four, one case of macular lepromatous leprosy was found early in 1953, this being in the person who had failed to show up for vaccination and for the clinical examinations prior to that year. The other three cases were of incipient tuberculoid leprosy in persons whose lepromin reactions had become strongly positive after the vaccination. The clinical histories of these cases are summarized as follows:

M. B. This was a five-year-old boy living in contact with a lepromatous case. His lepromin and tuberculin reactions had both become 1+ positive 10 weeks after the administration of BCG. In December 1951, however, he was again negative to both tests and was revaccinated. In the 1953 examination he was still negative to tuberculin, but he was 2+ positive to lepromin. He had a spot with a hypopigmented center and papulate border, histologically of tuberculoid structure.

A. M. Another five-year-old boy living in contact with a case of lepromatous leprosy. He was negative to both tests and remained negative to tuberculin but became 1+ positive to lepromin after the vaccination. When examined in December 1951 he was 1+ positive to tuberculin and 3+ to lepromin. At the same time he showed a hypopigmented spot with papulate border and tuberculoid structure.

M. L. G. An eight-year-old girl living in contact with a case of lepromatous leprosy. Initially negative to both tests, after vaccination she remained negative to tuberculin but became 2+ lepromin positive. In December 1951 she showed several small plaques with erythematous infiltration and tuberculoid structure. At that time she was 3+ positive to lepromin and 1+ to tuberculin.

DISCUSSION

We consider the group studied to have been especially exposed to the danger of contracting or developing the disease for the following reasons: (a) They all had had close contact with infectious cases before and during the period of observation; (b) all were originally Mitsuda negative; and (c) their living conditions, especially crowding, favored contagion.

It is presumed that there were many cases either latent or in the course of incubation in this originally Mitsuda-negative group, in which children and young adults predominate. It cannot, of course, be said how many of them would have developed the disease normally during the period of observation. We are dealing here with a new situation, one which is difficult to appraise as the group is small, although the period of observation is relatively long. It would be necessary to study a much larger group during a much longer period, with suitable controls,

in order to evaluate properly the prophylactic effect of BCG in contacts who continue to live with the sources of infection.

It is important to take into consideration the absence in this study of a control group by which to appraise the clinical evolution of nonvaccinated persons exposed to the same danger of contagion as the experimental group. However, such a control group was selected from the unvaccinated persons who were found healthy in the epidemiological investigation made in 1950. In a further communication we will compare the morbidity of those controls as regards leprosy with the vaccinated group.

An outstanding fact in the present investigation is that all the persons in the group became Mitsuda positive after BCG vaccination, although it is true that some of them needed more than one vaccination to attain this result.

As for the degree of Mitsuda positivity after vaccination, it will be seen from Table 1 that in 1950 only 35 persons of the 106 read in October

TABLE 1.—*The immunological variations in the study group before and immediately after BCG vaccination (July and October 1950) and at approximately one-year intervals thereafter.*

Tuber- culin reaction	Lepromin reaction																	
	Not read	Nega- tive	1+	2+	3+	Total	Not read	Nega- tive	1+	2+	3+	Total	Not read	Nega- tive	1+	2+	3+	Total
	July 1950						October 1950						December 1951					
Not read	—	—	—	—	—	—	6	—	6	3	—	15	4	—	2	—	—	6
Negative	—	100	—	—	—	100	—	7	44	15	9	75	—	11	35	8	5	59
1+	—	9	—	—	—	9	—	—	8	3	5	16	1	1	8	11	16	37
2+	—	1	—	—	—	1	—	—	—	—	—	0	—	—	—	3	1	4
3+	—	—	—	—	—	0	—	—	—	—	—	0	—	—	—	—	—	0
Total	0	110	0	0	0	110	6	7	58	21	14	106	5	12	45	22	22	106

TABLE 1.— Continued

	March 1953						February 1954						June 1955					
	1	1	1	3	—	6	6	—	1	—	—	7	—	—	—	—	—	0
Not read	—	—	15	18	21	54	—	—	10	28	35	73	—	—	3	28	47	78
Negative	—	—	4	14	25	43	—	—	—	3	24	27	—	—	—	—	24	24
1+	—	—	1	1	1	3	—	—	—	2	—	2	—	—	1	2	4	7
2+	—	—	—	—	—	0	—	—	—	—	—	0	—	—	—	—	—	0
3+	—	—	—	—	—	0	—	—	—	—	—	0	—	—	—	—	—	0
Total	1	1	21	36	47	106	6	0	11	33	59	109	0	0	4	30	75	109

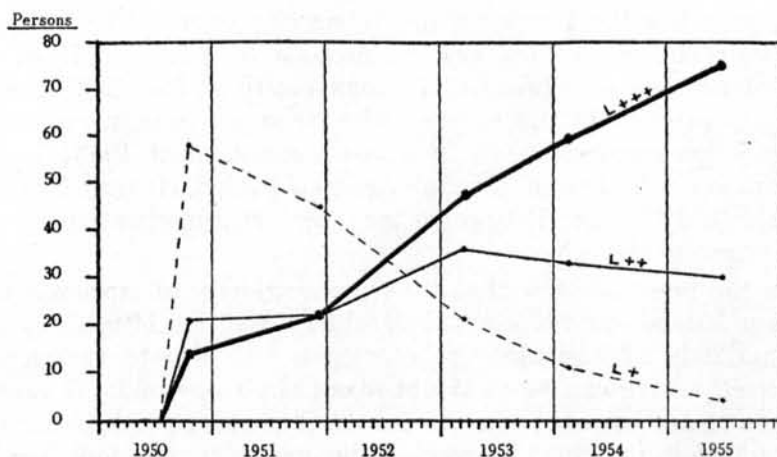
had become 2+ or 3+, but that subsequently their number increased progressively to 105 in 1955. The steady increase in the number of these stronger reactions during the five-year period can be attributed primarily to the influence of the vaccination up to and including 1953, but in the

following two years, when only one person was vaccinated, this intensification must be regarded as spontaneous—unless the repeated lepromin testing itself also had an influence in this matter.

With regard to the Mantoux test, we found only 16 persons positive after the first vaccination. This observation stands in sharp contrast to the 80 per cent positives currently obtained with vaccines from the same strain when these are given to healthy persons who have had no contact with leprosy. This peculiarity may, perhaps, be due to special immunological conditions in the group studied.

In the later tests made up to 1953, the number of Mantoux positives rose to 46, but by 1955 it had fallen to 31. This reduction was possibly due to the exhaustion of tuberculin allergin in many of them, as only one of the group was vaccinated in the last two years of the experiment.

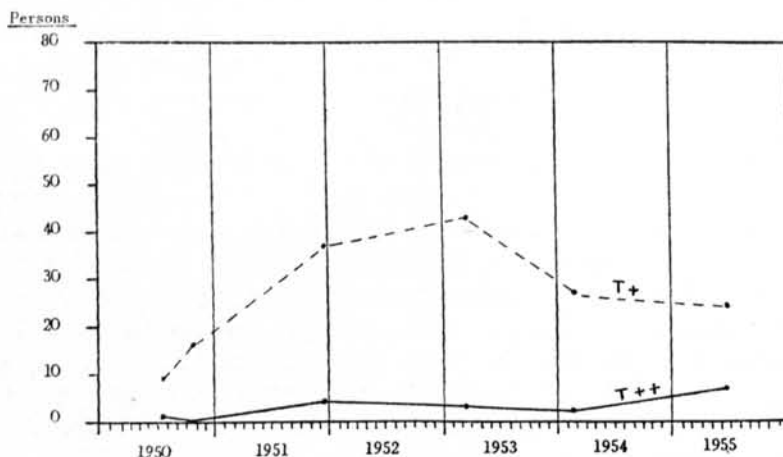
Of the 110 persons forming the total group, i. e., the 109 comprised in Table 1 and the 1 person who developed lepromatous leprosy, 10 showed at the outset discordance between the two reactions in that, while all were lepromin negative, 10 reacted to tuberculin—9 of them 1+ (between 6 and 10 mm.) and the other 2+ (12 mm.). The lepromatous case belonged to this group. Incidentally, we have observed the same discordance (positive tuberculin and negative reactions) in some other contacts that we have under observation, as well as in lepromatous patients.



TEXT-FIG. 1. Curves showing the changes of frequency and degree (1+, 2+ and 3+) of lepromin reactivity during the years 1950-1955.

The explanation of this finding may be that the tuberculin positives had been infected with *Mycobacterium tuberculosis*, especially since no paraspecific tuberculin reactivity due to infection with *M. leprae* has been conclusively demonstrated. It appears that this probable natural infection with the Koch bacillus prior to the first tests had failed to evoke lepromin reactivity, which was brought about in 9 of these 10 persons only after BCG vaccination (the remaining one being the unvaccinated

person who later developed lepromatous leprosy). Although a positive Mantoux reaction with Mitsuda negativity is rather rare in contacts, we believe that this allergic discordance is a bad prognostic sign, indicating that probably dealing with latent cases.



TEXT-FIG. 2. Curves showing the changes of frequency and degree (+ and 2+) of tuberculin reactivity during the years 1950-1955.

On comparing the lepromin and tuberculin curves (Text-figs. 1 and 2), the independence of the two phenomena becomes manifest, for the number of persons who became Mantoux positive after BCG vaccination was greatly inferior to the number who became lepromin positive. This discordance goes on, although in a less degree, until 1953; it becomes more marked at the end of the experimental period. It may be explained by a possible difference in significance, that is, sensitization to one test and resistance to the other.

From the point of view that the great majority of lepromatous cases come from Mitsuda-negative persons, while a positive Mitsuda reaction is a sign not only of resistance to contagion but also to severity of the disease itself, there can be no doubt about the value of BCG vaccination as a means of antileprosy prophylaxis. An important point, in our opinion, is the fact that the only person of the group to develop lepromatous leprosy was the one that failed to show up for vaccination.

SUMMARY

This paper deals with the fourth stage of an investigation on leprosy in the German ethnic group of the Colonia Tovar in Venezuela. The first two parts were reported at the Second Convention of Dermatologists, Venereologists and Leprologists in Caracas in March 1951 (2), and the third one was read before the VI International Congress of Leprology in Madrid in 1953 (3).

The present report covers the clinical findings and the changes in the Mantoux and Mitsuda reactions of 110 persons who were originally Mitsuda negative and without apparent clinical manifestations of leprosy, of whom 109 were vaccinated with BCG in July 1950; one of them did not appear for vaccination. They all shared quarters with lepromatous cases, and it is to be presumed that this more or less close contact placed them in great danger of contagion before and during the period of observation. Up to and including 1953 the record covers 107 of them, because 3 evaded follow-up through 1953; they were examined however, in 1954 and 1955, thus bringing the total to the original 110.

In the examination made 10 weeks after the vaccination, of the 106 retested 93 gave positive Mitsuda reactions, 7 remained negative, and 6 did not show up for the reading of the tests. Of the 93 Mitsuda positives, 58 gave 1+ reactions, 21 were 2+, and 14 were 3+. The negatives and weak (1+) reactors were revaccinated, some even twice, and at the end of the experimental period in June 1955 all were Mitsuda positive. At that time 105 were 2+ or 3+, only 4 being 1+.

In the clinical examinations, in 1953 one case of macular lepromatous leprosy was found, this being in the individual who had failed to show up for vaccination in 1950 and had remained unvaccinated. Also, three persons were found with incipient lesions of tuberculoid structure; in all of them the lepromin reaction had become strongly positive. Since 1953 no new case has been found in this group.

RESÚMEN

Este trabajo se refiere a la cuarta etapa de una investigación sobre el grupo étnico alemán de la Colonia Tovar en Venezuela. Las dos primeras fueron presentadas ante las II Jornadas Venezolanas de Dermatología, Venerología y Leprología en Caracas celebradas en Marzo de 1951 (2), y la tercera leída ante el VI Congreso Internacional de Leprología en Madrid en 1953 (3).

La presente comunicación se refiere a los hallazgos clínicos así como a las modificaciones en las reacciones de Mantoux y Mitsuda practicadas a ciento diez personas, que fueron inicialmente Mitsuda negativas y sin manifestaciones clínicas aparentes de la enfermedad.

Para cada una de ellas se llevó un record, que cubrió 107 personas hasta 1953 y tres mas, es decir, 110 durante los años 1954 y 1955. Todas ellas son contactos mas o menos directos de casos infectantes con los cuales conviven y podemos presumir que estaban sometidas a riesgo grande de contagio antes y durante el período de observación.

En julio de 1950 un total de 109 personas fueron vacunadas con BCG, porque una no concurrió a dicha vacunación. En el examen hecho diez semanas después, de las 106 testadas 93 dieron reacción de Mitsuda positiva, 7 permanecieron negativas y 6 no asistieron a la lectura. De las 93 positivas al Mitsuda, 58 lo hicieron con 1+, 21 con 2+ y 14 con 3+.

Los negativos y los positivos con 1+ a la lepromina fueron revacunados, algunos de ellos hasta dos veces y al finalizar la experiencia en junio de 1955 todos mostraron positivización del Mitsuda, 4 de 1+ y 105 entre 2+ y 3+.

El resultado de los exámenes clínicos fué el siguiente: En 1953 se encontró un caso lepromatoso macular, que resultó ser la persona no calmetizada. Además se

encontraron tres casos con lesiones incipientes de estructura tuberculoide en quienes la prueba lepromínica se había transformado en fuertemente positiva. Desde 1953 no se ha presentado un nuevo caso de lepra en el grupo motivo de esta comunicación.

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