

A STUDY OF THE LEPROMIN AND TUBERCULIN REACTIONS
THE CORRELATION BETWEEN THE TWO REACTIONS AND THE
INFLUENCE OF BCG VACCINATION ON NONREACTORS IN
HEALTHY LEPROSY CONTACT CHILDREN IN DJAKARTA

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Leprosy still appears to be increasing ⁽¹²⁾. Notwithstanding modern therapy and other measures, we have not as yet been able to stop the spread of the disease. Chaussinand ^{(1(a))} assumed the existence of cross sensitivity and cross immunity between tuberculosis and leprosy. He was able to show that persons in a country free from leprosy but highly infected with tuberculosis, who were positive to tuberculin were also in a high percentage of cases positive to lepromin ⁽⁹⁾; and in countries where tuberculosis and leprosy are both endemic, he found the same correlation between the two reactions ⁽²⁾.

Chaussinand holds the opinion that an increase in tuberculosis would carry with it immunization to leprosy. He gives this as one of the possible reasons for the decline of leprosy in Europe in the Middle Ages ^{(1(b))}. From a medical point of view this would be of purely academic interest, because it means the expulsion of one disease by another much more infectious one.

However, it is generally held that a positive lepromin reaction signifies a certain degree of resistance to leprosy infection. Since the effective application of BCG vaccination in the prophylaxis of tuberculosis, and since the discovery of Fernandez that lepromin negativity can be transformed to positivity by means of BCG, there exists the hope that both diseases may be controlled by the same prophylactic measure.

In recent years investigations have been carried out in this field in countries where leprosy, and usually tuberculosis as well, are endemic. The results are not always in agreement, and there have been many controversies with regard to the significance of a positive lepromin reaction and even of the tuberculin reaction, and with regard to the success and significance of BCG vaccination. In spite of this, it seems to be advisable to carry out these investigations in order to collect more detailed data.

As yet no reports on this subject have been available from Indonesia, a country where leprosy and tuberculosis are both highly endemic. Beginning in 1955 I have carried out investigations in this field with the aim of investigating (1) a group of healthy children in contact with leprosy cases, (2) a group of leprosy patients, and (3) a group of healthy persons, and of comparing the results with regard to the questions mentioned. At the time of writing I am able to give the results of a part of a group of healthy contact

children who have been tested with lepromin and tuberculin, and of whom a small number have been examined after BCG vaccination.

MATERIALS AND METHODS

The work here reported was carried out with 901 healthy contact children of leprosy patients between the ages of 1 and 15 years. The majority of them came from Djakarta, a city where both leprosy and tuberculosis are common. A small number came from a rural area near Djakarta. Because the results obtained showed only slight differences, the two groups are treated together as one.

The tuberculin used, of the PPD type, came from Manila and was received from the Public Health Department of Djakarta. The dose used was 5 TU in 0.1 cc. of solution.

The lepromin used was prepared in our laboratory and differs only insignificantly from the Hayashi-Mitsuda lepromin. Before using it we injected 300 leprosy patients simultaneously with it and with lepromin from the Philippines. The results obtained were practically the same.

The BCG used also came from Manila through the Public Health Department. It contained 1 mgm. in 1 cc., and 0.1 cc. of this suspension was given intradermally on the extensor surface of the left upper arm.

All of the children were given lepromin and tuberculin simultaneously, the tuberculin on the extensor surface of the right forearm, the lepromin on the flexor surface of the left upper arm. The tuberculin and Fernandez reactions were read after 48 hours, and the Mitsuda reaction after 21 days.

As a criterion of positivity we took an infiltration of 6 mm. and more for the tuberculin and Fernandez reactions, and for the Mitsuda reaction a nodule of 3 mm. and more in diameter. All doubtful reactions below those sizes were counted as negative.

The intensity of the different reactions was not studied. The great majority of the positive Mitsuda reactions consisted of nodules between 3 and 6 mm. in diameter, without conspicuous differences in the corresponding age groups. In the tuberculin and Fernandez reactions we seldom saw an induration larger than 10 mm. in diameter. We therefore did not think it necessary to pay particular attention to the intensity of the reactions.

Ninety-seven of the children, nonreactors to both lepromin and tuberculin, received BCG vaccination and appeared two months later for repetition of the lepromin and tuberculin tests.

Our work was planned for the purpose of studying:

1. The frequency of positive Mitsuda and tuberculin reactions in healthy contact children.
2. The relationship between those reactions.
3. The relationship between the Fernandez and Mitsuda reactions.
4. The effect of BCG vaccination on the nonreactors to both tests.

RESULTS AND DISCUSSION

Frequency of positive Mitsuda and tuberculin reactions.—Of the 901 children tested 553, or 61 per cent, gave positive late lepromin reactions, and 277, or 30 per cent, gave positive tuberculin reactions (Table 1). Thus the number of lepromin reactors was much greater than that of the tuberculin

reactors. As found by other investigators (^{3, 4}), the frequency of reactors among children to both tests increases markedly with increasing age.

TABLE 1.—*Frequency of positive Mitsuda and tuberculin reactions in 901 healthy leprosy contact children.*

Age group	No. of cases	Mitsuda positive	Tuberculin positive
1-5	378	172 (45%)	55 (14%)
6-10	381	264 (70%)	143 (37%)
11-15	142	117 (82%)	79 (69%)
Total	901	553 (61%)	277 (30%)

It is held by some workers (⁷) that there is little evidence that reactivity to lepromin is necessarily caused by prior contact or infection with the Hansen bacillus. As an example is given the reactivity to lepromin of persons living in countries practically free from leprosy. In such cases lepromin positivity has been attributed to prior infection with other acid-fast bacilli, particularly the tubercle bacillus.

In our cases, especially if we look at the first age group, the positive reactions cannot be entirely attributed to prior infection with tuberculosis because of the much lower number of tuberculin reactors. And if we admit that the contacts of children in the first years of life are normally confined to their homes, and because we are dealing here only with healthy contact children, there seems to be no other explanation in this case than that the majority of the positive reactions were due to contact with leprosy. If sensitization by tuberculosis plays a part, it must be confined only to a small proportion in such children.

If we look at the increase with age of reactors to both tests, it is noteworthy that in the third age group the percentage of tuberculin reactors had increased much more markedly than that of the lepromin reactors, compared with the corresponding increases in the previous groups. This may be explained as being the result of greater contact with the outer world in schools and playgrounds between the ages of 11 and 15 years, and the greater chance of meeting tuberculous infection.

Relationship between the tuberculin and Mitsuda reactions.—By simple addition of the numbers of children who were either positive or negative to both of the tests, we get an agreement of 59 per cent, the double positives being about 25 per cent. Among those with nonagreeing reactions, the Mitsuda-positive, tuberculin-negative group is the largest one of all, about 36 per cent of the total.

Comparing these results with the figures of others (¹¹), there is the difficulty that most of the investigations were carried out with other than healthy contact children, or with only limited numbers of them, and that the materials used—lepromin as well as tuberculin—were often so different

that they are not comparable. However, taking into account the results of Rosenberg *et al.* (10) and of Convit and Rassi (3), our results are quite similar as regards the frequency of the reactors to the two tests and the correlation between them.

TABLE 2.—*Relationship between the tuberculin and Mitsuda reactions in 901 contacts.*

T+ M+	T- M-	T+ M-	T- M+
229 (25%)	300 (33%)	48 (5%)	324 (36%)
Agreement 529 out of 901 = 59%		No agreement 372 out of 901 = 41%	

Positive tuberculin reactions and the results of the Mitsuda test.—There is still the question whether the leprosy bacillus is able to produce reactivity to tuberculin (3, 6), or whether the correlation between the two reactions is incidental and due to simultaneous exposure to leprosy and tuberculosis. Both possibilities could only properly be studied, as Lowe and McFadzean (8) said, in areas where tuberculosis occurs but not leprosy or *vice versa*, or in areas with neither tuberculosis nor leprosy.

If we correlate the positive tuberculin reactions with the positive and negative Mitsuda reactions, it is seen that in the respective age groups there is a positive association of 25 to 47 to 52 per cent, in total 41 per cent, whereas the positive tuberculin reaction was associated with lepromin negativity in, respectively, 6, 15 and 72 per cent, in total only 14 per cent.

TABLE 3.—*The tuberculin reaction in correlation with the positive and negative Mitsuda reactions.*

Age group	M+	T+	%	M-	T+	%
1- 5	172	43	25	206	12	6
6-10	264	125	47	117	18	15
11-15	117	61	52	25	18	72
Total	553	229	41	348	48	14

According to these figures there may be an influence of leprosy on the tuberculin reaction in the first two age groups. In that case a considerable proportion of these tuberculin reactions would not be specific. However, considering the figures of the third age group (72% tuberculin reactors associated with negative lepromin reactions) and the marked increase of tuberculin positivity in the third age group of Table 1, it seems much more probable that these positive tuberculin reactions are actually due to infection with tuberculosis.

Positive Mitsuda reactions and the results of the tuberculin test.—The opinion of the majority of workers concerned with the study of these tests is that tuberculosis infection, as indicated by the positive tuberculin reaction, usually makes the lepromin reaction positive. If the positive tuberculin reaction is a specific one, due to previous or present infection with tuberculosis, and if we place the positive Mitsuda reactions in relation to the positive and negative tuberculin reactions, as is done in Table 4, the figures show that in 80 per cent or more of all age groups, in total 83 per cent, tuberculin positivity is associated with reactivity to lepromin. These results would confirm the reports of the majority of previous workers.

TABLE 4.—*The Mitsuda reaction in correlation with the positive and negative tuberculin reactions.*

Age group	T+	M+	%	T-	M+	%
1-5	55	43	80	323	129	40
6-10	143	125	87	238	139	58
11-15	79	61	80	63	56	90
Total	277	229	83	624	324	52

On the other hand, there still remains the total of 52 per cent (40, 58 and 90% in the respective age groups), of lepromin reactors who are negative to tuberculin, which cannot be explained by previous tuberculous infection. That means there must be, besides tuberculous infection, still other ways by which lepromin reactivity may be induced. As already mentioned in respect to our healthy contact children, the only logical reason for these positive lepromin reactions would be contact with leprosy itself.

Relationship between the Fernandez and Mitsuda reactions.—Since we are mainly concerned with the late or Mitsuda reaction, the only criterion for lepromin reactivity, we have not made a detailed analysis of the early, or Fernandez reaction. According to the figures in Table 5, the statement

TABLE 5.—*The relationship between the Fernandez and Mitsuda reactions.*

F+ M+	F- M-	F+ M-	F- M+
195 (22%)	304 (33%)	44 (5%)	358 (40%)
Agreement 499 out of 901 = 55%		No agreement 402 out of 901 = 45%	

of Fernandez (5) about a positive association between the early and the late reactions is not confirmed. This association was observed in only 22 per cent, whereas in about 40 per cent a positive Mitsuda reaction was preceded by a negative Fernandez one.

Influence of BCG vaccination.—Before looking more closely at Table 6 it should be mentioned that of the 97 children vaccinated with BCG, all were lepromin negative before vaccination but only 87 were tuberculin negative, i.e., 10 children were tuberculin positive previously and remained so afterwards. They were given BCG because of their negativity to lepromin. For this reason the percentages of tuberculin reactors in Table 6 have been reckoned, not from the total number of 97, but from a total of 87.

TABLE 6.—*Influence of BCG vaccination on the lepromin and tuberculin reactions.*

Age group	Mitsuda negative		Tuberculin negative	
	No. of cases	Changed to positive	No. of cases	Changed to positive
1-5	60	37 (61%)	58	16 (19%)
6-10	31	20 (65%)	25	1 (4%)
11-15	6	6 (100%)	4	3 (75%)
Total	97	63 (65%)	87	20 (23%)

In total there was a conversion of lepromin negativity in 65 per cent (61, 65 and 100% in the respective age groups), while only a total of 23 per cent of the tuberculin negatives were changed to tuberculin reactors (19, 4 and 75% respectively). For the low percentage of tuberculin conversion no explanation is evident.

The total of 65 per cent lepromin reactors after BCG is lower than the results published by some other investigators⁽¹¹⁾. It was observed in a great many cases that the initial negative lepromin reaction became positive following the BCG vaccination, but it was always smaller in size than the second lepromin reaction.

For technical reasons it was not possible to check up on the skin reactions to BCG when active. The children did not appear again until two months after vaccination. Those with clearly defined scars were regarded as positive; 68 of the 97 had scars of this description. If this is a correct criterion of positivity to BCG, then of the 68 BCG positives 48 (i.e., 70%) remained Mitsuda negative, and of the 29 BCG negatives 15 (i.e., 50%) showed positive Mitsuda reactions.

SUMMARY AND CONCLUSIONS

1. Lepromin and tuberculin tests have been made on 901 healthy leprosy-contact children between the ages of 1 and 15 years. They showed in total a much lower Mantoux than Mitsuda rate, 30 vs 61 per cent.

With growing age the number of reactors to both tests increased markedly, but in the third age group (11-15 years) the number of tuberculin reactors increased much more markedly than that of the Mitsuda reactors. This finding is attributed to the fact that the younger children had had almost exclusively contact with their leprous environment, whereas the older children

had wider contact with the normal population in schools and playgrounds, where they had greater chances of meeting tuberculosis infection.

2. In the correlation between the tuberculin and lepromin reactions, there was agreement between the two reactions (simultaneously positive or negative) of 59 per cent. The positive association was 25 per cent. Among the nonagreeing reactions the tuberculin-negative, Mitsuda-positive group was the largest, about 36 per cent.

Assuming that the tuberculin positivity was induced by previous contact with leprosy, there was found a positive association of the two tests in 41 per cent (in 25, 47 and 52% in the respective age groups), and a positive tuberculin reaction associated with lepromin negativity in 14 per cent (6, 15 and 72% respectively). These figures show little evidence of tuberculin positivity having been induced by contact with the Hansen bacillus.

Assuming induction of Mitsuda positivity by previous contact with tuberculosis, there was found a positive association of the two reactions in 83 per cent (40, 58 and 90% in the respective age groups). A certain degree of influence on the Mitsuda reaction by tuberculosis cannot be denied, since of 277 tuberculin reactors 83 per cent are also lepromin positive. At the same time, however, it was found that positive Mitsuda reactions occurred in 52 per cent independently of the tuberculin reaction, probably through contact with leprosy itself.

3. In the correlation between the Fernandez and Mitsuda reactions there was a positive association in 195 cases (22%), whereas in 358 cases (about 40%) positive Mitsuda reactions occurred when the Fernandez reaction was negative. These figures do not support the view that a positive Mitsuda reaction is commonly preceded by a positive Fernandez reaction.

4. By means of BCG vaccination, 65 per cent of 97 previously Mitsuda-negative children were made positive reactors, whereas of 87 tuberculin-negative children only 23 per cent became reactive to tuberculin. For this low rate there is no evident explanation.

From so small a number of vaccinated children it is not possible to draw general conclusions. However, if lepromin positivity induced by BCG has the same significance as a naturally acquired one is supposed to have (which is still an open question which only time can resolve), then the findings of 65 per cent lepromin conversion, although below the results of some other investigators, would nevertheless be of enormous practical value in connection with the prophylaxis of leprosy.

RESUMEN

En 901 niños sanos, en contacto con leprosos, de 1 a 15 años de edad, se ejecutaron en Djakarta, Indonesia, pruebas con lepromina y tuberculina. En conjunto, 30 por ciento fueron Mantoux-positivos y 61 por ciento Mitsuda-positivos.

La frecuencia de ambas reacciones aumentó de acuerdo con la edad, subiendo en particular la positividad a la tuberculina en el grupo de mayor edad (11-15 años),

probablemente debido a mayor exposición a la infección en las escuelas y los patios de recreo. Ambas reacciones fueron positivas en 25 por ciento de los sujetos y negativas en 33 por ciento; la Mitsuda sola fué positiva en 36 por ciento, mientras que 5 por ciento fueron positivos a la tuberculina, pero no reaccionaron a la Mitsuda.

El análisis de los datos de los tuberculino-positivos con respecto a la reactividad a la lepromina arroja pocas pruebas de que la positividad a la tuberculina hubiera podido ser inducida por el contacto con el bacilo de Hansen. El análisis opuesto, de los positivos a la lepromina con respecto a positividad a la tuberculina, muestra un influjo bien definido de la infección tuberculosa sobre la reacción de Mitsuda.

Las reacciones de Fernández y de Mitsuda fueron ambas positivas en 22 por ciento del total de casos, pero 40 por ciento de éstos sólo reaccionaron a la Mitsuda, lo cual no armoniza con la idea de que la reacción tardía va comúnmente precedida de la temprana.

De 97 sujetos Mitsuda-negativos que recibieron la vacunación BCG, 65 por ciento viraron a positivos; pero de 87 tuberculino-negativos que fueron vacunados, solamente 23 por ciento viraron a positivos, coeficiente muy bajo este que no tiene explicación evidente. Si la positividad a la lepromina inducida por el BCG posee el mismo significado que se supone posee la reactividad adquirida naturalmente, la vacunación con el BCG debería ser de mucho valor en la profilaxia antileprosa.

ACKNOWLEDGMENT

My particular thanks are due to the medical assistants, Kamino (with his laboratory staff) and Santosa, who were of great help in the carrying out of this study.

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