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INFLUENCE OF THE TUBERCULOSIS FACTOR ON THE CLINICAL AND IMMUNOLOGICAL EVOLUTION OF CHILD CONTACTS WITH LEPROSY PATIENTS[1]

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The influence that a tuberculosis infection, either spontaneous or provoked, may exert on the evolution of leprosy has been the subject of interesting speculations and numerous investigations. On the basis of epidemiological data, some authorities hold that tuberculosis and leprosy are antagonistic diseases, and that where the former prevails the latter declines.

Furthermore, studies of the influence of BCG on the lepromin reaction, started by Fernandez (5) in 1939, led to the idea that attenuated tuberculosis infection might have a protective effect on an individual exposed to infection by *Mycobacterium leprae*. In my experiment the intradermal administration of BCG induced, in a group of healthy orphanage children, the conversion of over 90 per cent of lepromin nonreactors to reactors. These results led me to speculate on the use of that vaccine as a preventive measure in lepromin-negative contacts.

That experiment has been repeated by many investigators and the results have been amply confirmed, but several years elapsed before the matter was taken up seriously. In 1945 Ginez and Poletti (8), in Paraguay, reported having vaccinated a number of children of leprous parents, with results that encouraged the idea of possibly protecting them against leprosy infection, if—they added—the positive Mitsuda reaction signifies a relative immunity. Azulay (2), in Rio de Janeiro, also vaccinated a small group of preventorium children, and discussed protection by that means. Chaussinand (3), at the BCG Congress held in Paris in 1948, spoke of the advisability of employing the vaccine for prophylaxis in endemic countries. The most thorough investigation on this subject,

[1] Paper read before the Sociedad Argentina de Leprologia, May 21, 1955.

carried out according to a plan which covered all aspects of BCG vaccination in leprosy, we owe to Rosemberg, Souza Campos and Aun (14-23). In a series of studies they went into various aspects of the problem and arrived at the conclusion that this vaccine should be used in the prophylaxis of leprosy, inasmuch as the classical methods, especially segregation, have failed to solve the problem.

In the Third Pan-American Conference, at Buenos Aires in 1951; in the Second Brazilian Congress of Hygiene, at Belo Horizonte in 1953; and in the Sixth International Congress of Leprology, at Madrid in 1953, there were discussions of the proposition that BCG should be used for the prophylaxis of leprosy, with recommendations that investigation of the matter be extended in order to establish the definite value of the measure.

Noteworthy in this connection are the contribution of Neyra Ramírez and Pesce (12), and a recent article of Lowe and McNulty (10) the conclusions of which are based on ample experimental evidence. In a critical study of this subject Souza Campos (24) has presented a very complete survey of the literature.

It is now well established that BCG can provoke positive lepromin reactivity in a nonreactive healthy person. The next question, the essential one, is what influence lepromin positivity induced in this way will have when such an individual is exposed to infection. Experience in this field is as yet very limited. We know of only three articles that mention subsequent events among BCG-vaccinated contacts.

The first is a report by Montestruc and Blanche (11). They told of 7 children of lepromatous mothers, vaccinated with BCG at birth for protection against tuberculosis, who remained healthy and lepromin positive although they continued living in contact with the leprosy sources. The duration of the contact of these children ranged from 5 to 12 years. On the other hand, of 4 boys who had lived under the same conditions as the others but who had not been vaccinated with BCG, all contracted the disease, 3 of them in the lepromatous form.

The second report is that of Souza Campos (25) who reported the following results: In the Department of Leprosy Prophylaxis of São Paulo, 2,866 contacts were vaccinated with BCG (200 mgm. by mouth, weekly for 3 weeks) between February 1952 and June 1953. Out of this group, 16 individuals (0.55%) developed manifestations of the disease, all of them tuberculoid. During the same period 6,141 unvaccinated contacts were examined, and 248 (4%) were found with lesions, 62 of them lepromatous, 115 indeterminate, and 71 tuberculoid.[2]

The third report was by Convit and associates of Venezuela (4). In July 1950 these authors examined a group of 107 lepromin-negative contacts of lepromatous leprosy patients, in an area where the prevalence of leprosy was 10 per cent. All but one were vaccinated with BCG twice intradermally. Thereafter they were examined clinically and tested with lepromin once a year. In the last examination, in 1953,

[2] It is not stated in the report cited that the unvaccinated contacts referred to were all without lesions at the time they were examined and developed manifestations of the disease in the same period of time during which the vaccinated individuals were observed. It therefore seems possible that the two groups were not strictly comparable.

103 of the 106 vaccinated contacts were found clinically free from symptoms while 3 had developed tuberculoid leprosy. The one individual who had not been vaccinated had developed lepromatous leprosy. All, with that sole exception, were Mitsuda positive.

With respect to the influence of *spontaneous* tuberculosis infection on the course of leprosy, there is very little documentation. The majority of the published reports deal with limited investigations in the immuno-allergic field.

PERSONAL EXPERIENCE

Between 1939 and 1955 I had opportunity to observe the clinical and immunological evolution of 110 contacts, 83 of them associated with lepromatous cases and 27 with tuberculoid cases. The present study is especially concerned with the 83 individuals who lived with lepromatous patients, because in them the exposure to infection was indubitable, intimate and prolonged. Regarding the 27 in contact with tuberculoid cases, who were examined to serve as a control group not one has had or has developed clinical evidence of infection. In contrast, among the 83 lepromatous contacts, 32 (39%) are known to have had or developed lesions.

To permit determining the effects of the various factors involved, so far as that can be done with so limited a number of individuals, the lepromatous contacts are divided into three groups:

Group 1. Vaccinated with BCG, tuberculin reactivity immaterial; 28 individuals (Table 1).
Group 2. Not vaccinated with BCG, tuberculin positive, 32 individuals (Table 2).
Group 3. Not vaccinated with BCG, tuberculin negative; 23 individuals (Table 3).

Age, living conditions, and degree and type of exposure to infection were similar in the three groups. In many instances even brothers and first cousins were found to be distributed among different groups. Both the contacts and their sources of infection were personally examined by me, almost all of them several times.

The majority of those contacts were kept under surveillance for a sufficient length of time to permit discovery of individuals with latent infection, i.e., those without lesions at the time of the first examination but which would become overt cases later. The recommended period is five years, and that requirement was amply met in the great majority of the cases.

GROUP 1. BCG-VACCINATED CONTACTS

Method of vaccination.—The BCG was given intradermally in a single dose of 0.15 or 0.20 mgm. to 22 of the contacts.[3] The BCG strains used in these children were either one from the Bacteriological Institute of the National Department of Health (now the Instituto Malbrán), supplied by Dr. A. Arena, or one obtained from

[3] These 22 children were not vaccinated by me, but in the hospital service where they were born as a routine precaution against tuberculosis. It was not known that they were children of leprous parents, but later I inquired in every case about the method of vaccination employed and the source of the BCG.

that institute by Prof. E. Scrimaglio of the Department of Bacteriology of the School of Medicine of Rosario. Of these 22 contacts given BCG intradermally, 15 were routinely vaccinated at birth, between the 3rd and 7th days; the other 7 were vaccinated at ages varying from 2 months to 11 years. No tuberculin tests were made, and none of the children was revaccinated.

TABLE 1.—*Data of 28 children, contacts of lepromatous cases, vaccinated with BCG at various ages.*

Case and age (years)	Exposure source[a] and duration	Age, first examination	Vaccination year, age and route[b]	Subsequent development[c]	Results, last examination		
					Year	Clinical[d]	Lepromin[e]
1. W. M., 16	Gf. 10 yr.	2 yr.	'39, 1da., I	Healthy	1954	Neg.	F+, M+
2. M. L., 15	Mo. 10 yr.	3 yr.	'39, 1da., I	Healthy	1954	Neg.	F+, M+
3. H. B., 16	Mo. 14 yr.	1 yr.	'39, 1da., I	Healthy	1954	Neg.	F—, M+
4. N. P., 16	Gf. 6 yr.	6 yr.	'39, 1da., I	Healthy	1945	Neg.	F+, M+
5. E. L., 16	Fa. 3 yr.	2 mo.	'39, 3mo., I	Tbd, 2yr	1954	Neg.	F+, M+
6. H. L., 18	Fa. 3 yr.	2 yr.	'39, 2yr., I	Healthy	1955	Neg.	F—, M+
7. E. L., 22	Fa. 5 yr.	5 yr.	'39, 5yr., I	Healthy	1955	Neg.	F+, M+
8. A. F., 26	Br. 10 yr.	11 yr.	'39, 11yr., I	Healthy	1955	Neg.	F+, M+
9. J. G., 15	Mo. 10 yr.	2 mo.	'40, 1da., I	Tbd, 2yr	1954	Neg.	F+, M+[f]
10. C. M., 15	Fa. 6 yr.	3 yr.	'40, 1da., I	Ind, 12yr	1955	Ind.	F—, M—[g]
11. H. G., 14	Mo. 9 yr.	1 yr.	'41, 1da., I	Healthy	1954	Neg.	F+, M+
12. J. T., 14	Mo. 14 yr.	8 mo.	'41, 1da., I	Tbd, 12yr	1954	Regr.	F—, M+[f]
13. A. I., 15	Mo. 14 yr.	1 mo.	'42, 1da., I	Healthy	1955	Neg.	F+, M+
14. S. D., 13	Mo. 8 yr.	1 mo.	'42, 1da., I	Healthy	1954	Neg.	F±, M+
15. T. L., 13	Mo. 7 yr.	8 mo.	'42, 1da., I	Healthy	1955	Neg.	F—, M—
16. J. L., 13	Mo. 10 yr.	3 mo.	'42, 1da., I	Healthy	1954	Neg.	F+, M+
17. M. K., 12	Mo. 10 yr.	2 mo.	'43, 1da., I	Tbd, 3yr	1954	Neg.	F+, M+
18. V. I., 14	Mo. 8 yr.	2 yr.	'43, 2yr., I	Healthy	1955	Neg.	F+, M+
19. J. P., 6	Fa. 6 yr.	2 yr.	'49, 1da., I	Tbd, 5yr	1955	Regr.	F+, M+[h]
20. M. C., 4	Fa. 4 yr.	6 mo.	'51, 6mo., O	Tbd, 3yr	1955	Regr.	F+, M+[h]
21. G. B., 7	Fa. 6 yr.	3 yr.	'51, 3yr., I	Healthy	1955	Neg.	F+, M+[h]
22. B. S., 8	Mo. 4 yr.	4 yr.	'51, 4yr., O	Healthy	1955	Neg.	F+, M+[h]
23. H. I., 3	Mo. 3 yr.	20 mo.	'52, 1da., I	Healthy	1954	Neg.	F—, M+[h]
24. A. L., 4	Mo. 3 yr.	1 yr.	'52, 1yr., O	Healthy	1955	Neg.	F+, M+
25. J. G., 4	Mo. 3 yr.	2 yr.	'52, 1yr., I	Healthy	1954	Neg.	F+, M+[h]
26. A. S., 5	Mo. 18 mo.	18 mo.	'52, 2yr., O	Tbd, 4yr	1955	Regr.	F+, M+[h]
27. M. K., 3	Mo. 2 yr.	3 mo.	'53, 3mo., O	Healthy	1955	Neg.	F+, M+[h]
28. C. C., 2	Bo. 2 yr.	4 mo.	'53, 4mo., O	Tbd, 20mo	1955	Stat.	F—, M+[h]

a Sources of contagion: Fa. = father, Mo. = mother, Bo. = both parents, Br. = brother, Sr. = sister, Un. = uncle, Gf. = grandfather.

b Routes of vaccination: I = intradermal, O = oral.

c Developments: Tbd = tuberculoid, Ind = indeterminate.

d Clinical: Neg. = negative, Regr. = regressive, Stat. = stationary.

e Lepromin reactions: F = Fernandez (early), M = Mitsuda (late).

f Patients with lesions, received no treatment.

g Received BCG revaccination, oral, at 11 years, and sulfone treatment.

h Under observation.

In the other 6 vaccinated children the oral route was used, the BCG being obtained from the Liga Argentina contra la Tuberculosis, for which it was prepared under the direction of Drs. R. Vaccareza and C. Urquijo. The doses were either a single one of 100 mgm. (3 cases) or 400 mgm. in two doses (3 cases). The ages at the time of vaccination varied from 3 months to 4 years.

Number infected and type of the disease.—In Table 1 are given the results of the examinations of the 28 vaccinated contacts. It will be seen that 9 cases (32%) developed evidence of infection. The type was tuberculoid in 8 instances; the other case is put down in the table as "indeterminate," but actually it was of polyneuritic form which might have been either indeterminate or lepromatous.

In 7 cases evidence of infection appeared before or at the age of 5 years, in the other 2 at the age of 12. The youngest one was only 20 months old. Of these infected children, 6 were males and 3 were females; the 19 uninfected ones were 10 males and 9 females.

Lepromin reactions.—In all but 4, the lepromin reaction was or became positive. Of the 4 lepromin-negative cases, all females and all vaccinated intradermally shortly after birth, 2 became positive reactors at the age of 7 years, after a "preventive" course of sulfone treatment.[4] Both girls are now 13 years old, clinically free from any sign of infection and lepromin positive. The third negative case, also 13 years old now, has remained lepromin negative but has shown no suspicious clinical symptoms of any kind. The fourth negative case was also given preventive sulfone treatment for 3 months at the age of 7 years, but he did not become reactive. Two years later he was revaccinated orally (200 mgm. of BCG), still without affecting his response to lepromin. At the age of 11 he developed manifestations of the pure polyneuritic type. At present he is under treatment, still lepromin negative.

In summary, with respect to the lepromin reaction, of the 28 vaccinated children 26 are now lepromin positive, while 2 have been persistently negative. One of the latter developed leprosy in the pure polyneuritic form, while the other is clinically free from any manifestations of the disease.

Present status.—One of the vaccinated children was examined for the last time in 1945, at the age of 6 years. He had been vaccinated at birth and had always lived with his lepromatous grandmother, but he had no sign of infection at the time and was lepromin positive. The other 27 were reexamined recently (1954 and 1955), with the following findings:

Seventeen are clinically negative and lepromin positive.

One is clinically negative and lepromin negative. This one was vaccinated at birth and is now 13 years old.

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[4] This treatment consisted of the administration of Diasone, 1 tablet a day for a series of 20 days, then 10 days of rest, for a total of 4 months in one case and 10 months in another.

In this group the periods of time from vaccination to the last examination are: more than 10 years in 10 cases, 4 years in 2 cases, and 3 years in 4 cases.

TABLE 2.—*Data of 32 unvaccinated children, Contacts of lepromatous cases, with positive tuberculin reactions.*

Case	Exposure source[a] and duration[b]	First examination				Last examination		Remarks
		Year	Age	Lepromin	Clinical[c]	Year	Clinical	
1. C. F.	Fa. 1 yr.	1939	1 yr.	F±, M+	Neg.	1940	Healthy	F+, M+
2. S. L.	Mo. 4 yr.	1939	4 yr.	F+, M+	Tbd.	1955	Healthy	Untreated
3. E. L.	Fa. 4 yr.	1939	4 yr.	F+, M+	Neg.	1955	Healthy	
4. H. P.	Mo. 5 yr.	1939	5 yr.	F—, M+	Tbd.	1945	Healthy	Untreated Twins
5. A. P.	Mo. 5 yr.	1939	5 yr.	F±, M+	Tbd.	1945	Healthy	
6. H. S.	Mo. 4 yr.	1939	5 yr.	F+, M+	Tbd. R	1945	Healthy	
7. H. I.	Gf. 5 yr.	1939	5 yr.	F+, M+	Tbd.	1955	Healthy	
8. H. B.	Br. 5 yr.	1939	5 yr.	F—, M+	Neg.	1940	Healthy	F+, M+
9. E. L.	Mo. 6 yr.	1939	6 yr.	F+, M+	Tbd. R.	1955	Healthy	Untreated
10. R. N.	Fa. 6 yr.	1939	6 yr.	F+, M+	Tbd. R.	1942	Healthy	Untreated
11. L. V.	Mo. 4 yr.	1939	6 yr.	F—, M—	Indet.	1942	Healthy	BCG 1939
12. P. B.	Fa. 6 yr.	1939	8 yr.	F+, M+	Neg.	1942	Healthy	
13. A. P.	Mo. 8 yr.	1939	8 yr.	F+, M+	Neg.	1945	Healthy	F+, M+
14. A. I.	Gf. 9 yr.	1939	9 yr.	F+, M+	Tbd.	1945	Healthy	
15. N. B.	Mo. 6 yr.	1939	9 yr.	F+, M+	Neg.	—	—	
16. R. B.	Fa. 10 yr.	1939	10 yr.	F+, M+	Tbd. R.	1945	Healthy	Scrof., hld.
17. E. B.	Fa. 8 yr.	1939	10 yr.	F+, M+	Neg.	1942	Healthy	
18. M. S.	Fa. 5 yr.	1939	10 yr.	F+, M+	Neg.	1945	Healthy	
19. C. M.	Mo. 11 yr.	1939	11 yr.	F+, M+	Neg.	1945	Healthy	
20. A. M.	Fa. 3 yr.	1939	12 yr.	F+, M+	Tbd. R.	1941	Healthy	
21. O. F.	Sr. 10 yr.	1939	13 yr.	F+, M+	Neg.	1942	Healthy	
22. A. M.	Fa. 3 yr.	1939	13 yr.	F—, M+	Neg.	—	—	
23. Y. B.	Fa. 10 yr.	1939	14 yr.	F+, M+	Tbd. C.	1945	Healthy	PTB
24. S. P.	Mo. 10 yr.	1939	14 yr.	F—, M+	Neg.	1940	Healthy	M+
25. R. C.	Fa. 10 yr.	1939	15 yr.	F+, M+	Neg.	1942	Healthy	
26. J. V.	Un. 10 yr.	1939	15 yr.	F+, M+	Neg.	1944	Healthy	
27. M. P.	Mo. 10 yr.	1939	15 yr.	F+, M+	Neg.	1940	Healthy	
28. A. R.	Mo. 5 yr.	1939	16 yr.	F—, M—	Neg.	—	—	
29. A. B.	Fa. 4 yr.	1950	6 yr.	F+, M+	Neg.	1955	Healthy	
30. M. B.	Fa. 6 yr.	1950	8 yr.	F+, M+	Tbd. R.	1954	Healthy	PTB 1950
31. J. T.	Fa. 8 yr.	1955	10 yr.	F+, M+	Neg.	1955	Healthy	
32. S. C.	Mo. 6 yr.	1955	12 yr.	F+, M+	Neg.	1955	Healthy	

a Sources of contagion: See corresponding footnote, Table 1.
b Duration at time of first examination.
c Clinical: Neg. = negative. Tbd. = tuberculoid, Tbd.R. = residual tuberculoid, Tbd.C. = cicatrix of tuberculoid.

Eight cases developed tuberculoid lesions, and are lepromin positive.

In 4 of them the lesions disappeared more than ten years ago, and in 3 cases they are in full regression; in the other case they have continued stationary. None has received any treatment.

One case, as said, developed pure neural manifestations of leprosy, is lepromin negative, and is receiving sulfone treatment.

GROUP 2. TUBERCULIN-POSITIVE, UNVACCINATED CONTACTS

This group of 32 contacts consisted of 17 males and 15 females, whose ages ranged from 4 to 15 years at the time of their first examination by me (Table 2). In most of them the tuberculin test was positive at a dilution of 1:1000 OT; one was positive at 1:100, and a few at 1:10.[5]

Number infected and type of the disease.—Of this group, a total of 13 (or 41%) were found to have leprosy lesions at the time they were first seen. Of these cases, 12 were of the tuberculoid type, the other 1 indeterminate; 5 were males and 8 were females.

Lepromin reactions.—In 2 cases both reactions, early (Fernandez) and late (Mitsuda), were negative; in 6 cases the former was negative, the latter positive; and in 24 cases both were positive. The Mitsuda reaction was, therefore, positive in 30 (94%) of the cases, the Fernandez reaction in 24 (75%). In the single case of indeterminate leprosy in this group both lepromin reactions were negative, whereas the 12 tuberculoid cases gave positive reactions.

Clinical and immunological evolution.—All of the contacts that became infected were subjected to periodical follow-up examinations, clinical and immunological, until their lesions had completely disappeared. Only 2 of the 13 cases with lesions (Nos. 2 and 14) received any treatment, and that was chaulmoogra given irregularly and insufficiently because of intolerance to the drug, yet their lesions disappeared. So did those of the other tuberculoid cases, without any treatment whatever; and their lepromin reactions remained positive. In the one indeterminate case, negative to lepromin, there was other intervention: BCG vaccination was given; by 1942 the lesions had gone and the Mitsuda reaction was positive.

The children of this group without lesions were also examined periodically, with the exception of 4 who disappeared after the first examination. These 4 had had 5, 6, 8 and 10 years of contact with their lepromatous sources at the time they were seen and all were healthy, 3 positive to lepromin and 1 negative. All the others remained lepromin positive and clinically negative while under observation.

GROUP 3. TUBERCULIN-NEGATIVE, UNVACCINATED CONTACTS

In all of this group of 23 contacts, consisting of 10 males and 13 females, whose ages range from 6 months to 15 years at the time of the

[5] Crude Koch tuberculin prepared by the Malbrán Institute of Buenos Aires was used. Reactions with an erythematous, infiltrated halo not less than 10 mm. in diameter are considered positive.

first reexamination (Table 3), the tuberculin reaction was negative at 1:10 dilution.

TABLE 3.—*Data of 23 unvaccinated children, contacts of lepromatous cases, with negative tuberculin reactions.*

Case	Exposure source[a] and duration[b]	First examination				Last examination		Remarks
		Year	Age	Lepromin	Clinical[c]	Year	Clinical	
1. L. V.	Fa. 4 yr.	1939	4 yr.	F+, M+	Neg.	—	—	Unknown
2. R. C.	Fa. 5 yr.	1939	5 yr.	F+, M+	Tbd.	—	—	Unknown
3. L. B.	Fa. 5 yr.	1939	5 yr.	F—, M—	Neg.	—	—	Unknown
4. P. B.	Fa. 7 yr.	1939	7 yr.	F—, M—	Lpmts.	1955	—	Treatment
5. G. P.	Mo. 7 yr.	1939	7 yr.	F+, M+	Tbd.	1952	Healthy	
6. O. B.	Fa. 8 yr.	1939	8 yr.	F—, M—	Lpmts.	—	—	Treatment Rctn. '50
7. A. N.	Fa. 8 yr.	1939	8 yr.	F+, M+	Tbd.	1943	Healthy	F+, M+
8. J. B.	Fa. 5 yr.	1939	8 yr.	F—, M—	Neg.	—	—	Unknown
9. J. B.	Br. 7 yr.	1939	9 yr.	F±, M+	Neg.	1944	Healthy	F+, M+
10. N. N.	Fa. 9 yr.	1939	9 yr.	F—, M—	Indet.	—	—	Unknown
11. M. V.	Mo. 10 yr.	1939	10 yr.	F—, M—	Indet.	1942	Indet.	BCG 1942 Regressing
12. A. M.	Fa. 3 yr.	1939	10 yr.	F—, M—	Neg.	1942	Healthy	F—, M—
13. A. M.	Fa. 3 yr.	1939	10 yr.	F—, M+	Neg.	1942	Healthy	
14. J. S.	Mo. 5 yr.	1939	10 yr.	F—, M—	Neg.	1943	Healthy	
15. A. F.	Br. 11 yr.	1939	11 yr.	F—, M—	Neg.	1950	Healthy	BCG 1940
16. N. P.	Fa. 8 yr.	1939	11 yr.	F—, M+	Neg.	1945	Healthy	F—, M+
17. B. B.	Fa. 5 yr.	1939	11 yr.	F—, M—	Neg.	—	—	Unknown
18. E. S.	Mo. 5 yr.	1939	13 yr.	F—, M—	Neg.	—	—	Unknown
19. C. B.	Fa. 15 yr.	1939	15 yr.	F—, M—	Lpmts.	—	Lpmts.	Treatment
20. D. N.	Fa. 9 yr.	1939	15 yr.	F—, M—	Neg.	—	—	Unknown
21. G. S.	Mo. 6 mo.	1940	6 mo.	F—, M—	Neg.	1943	Tbd.	M+
22. V. I.	Gf. 10 yr.	1942	10 yr.	F+, M+	Tbd.	—	Tbd.	Regressed
23. J. C.	Mo. 5 yr.	1955	9 yr.	F±, M+	Neg.	—	Healthy	

a Sources of contagion: See corresponding footnote, Table 1.

b Duration at time of first examination.

c Clinical: Neg. = negative, Tbd. = tuberculoid, Lpmts. = lepromatous, Indet = indeterminate.

Number infected, and type of the disease.—Evidence of infection was found in 10 (or 43%) of this group. Lesions were seen at the first examination in 9 of them, and 3 years later in the other. The type of leprosy was tuberculoid in 5 cases, lepromatous in 3, and indeterminate in 2.

Lepromin reaction.—Of this group no less than 14 (61%) were completely negative to lepromin, compared with only 2 of the 32 (6%) in the tuberculin-positive group. Of the 9 (39%) that reacted positively, 5 gave the late reaction only, 4 being negative for the early one (including two recorded as ±).

Nine of this group of children, or 39%, were found with evidence of infection. There were 4 among the lepromin positives, but they were all tuberculoid. Of the 5 found among the 14 lepromin negatives, none was tuberculoid; 2 were indeterminate and 3 were lepromatous—the only lepromatous cases among all the contacts studied.

Clinical and immunological evolution.—The follow-up of the 5 tuberculoid cases was continued until the lesions had undergone complete regression, and none of them was given treatment; all were discharged clinically free from lesions and lepromin positive. Of the 2 indeterminate cases, both lepromin negative, 1 was given BCG vaccination at the age of 10 years and made favorable progress, with disappearance of his lesions in 1942; the other one stopped visiting the clinic although still with active manifestations. The 3 lepromatous cases received treatment, and 2 of them had episodes of lepra reaction some years later.

Of the 13 clinically uninfected children of this group, 2 were discharged, lepromin positive, after five years of follow up; 1 is still under observation, also lepromin positive; 2 other lepromin positives stopped visiting the clinic. Of the remaining 8, all lepromin negative, 5 were lost to sight and 3 were vaccinated with BCG; one of the latter is healthy and lepromin-positive (1955), but what happened to the other two is not known.

DISCUSSION

Comparing the findings in the small group of 23 contacts that were free from tuberculosis infection (Group 3) with those in the 60 children that were either vaccinated with BCG or were found tuberculin positive (Groups 1 and 2), all exposed to an open case of leprosy, we see that in the former, the rate of infection was the highest, 43 per cent (Table 4). More striking and important, however, is the fact that one-third of those

TABLE 4.—*Clinical and immunological evolution of the 83 contacts of lepromatous cases.*

Group	Clinical findings		Mitsuda reaction	
	Leprous	Healthy	Positive	Negative
1. BCG vaccinated (28)	9 (32%)	19	26 (93%)	2
2. Tuberculin + (32)	13 (41%)	19	30 (94%)	2
Subtotal (60)	22 (37%)	38	56 (93%)	4
3. Tuberculin — (23)	10 (43%)	13	9 (39%)	14
TOTAL (83)	32 (39%)	51	65 (78%)	18

with lesions in Group 3 were lepromatous, and that no lepromatous case was seen or developed in either of the other two groups (Table 5). In these other 60 children, taken together, the incidence of infection is 37

per cent, but all but two were of the tuberculoid type, and the two exceptions were indeterminate.

The fact that the two lots—Group 3 on the one hand, and Groups 1 and 2 on the other hand—are numerically unequal enhances the significance of the fact that all the lepromatous cases belonged to the group lacking tuberculin sensitivity—the smallest of the three. It is evident that such persons are the least protected against the infection.

From the immunological point of view there is also a difference between the tuberculin negatives on the one hand and the tuberculin positives and vaccinated contacts on the other hand (Table 4). In the

TABLE 5.—*Type of leprosy in the infected cases.*

Group	Leprosy cases, by type[a]			Total leprosy[b]
	Tuberculoid	Indeterminate	Lepromatous	
1. BCG vaccinated (28)	8 (89%)	1 (11%)	—	9 (32%)
2. Tuberculin + (32)	12 (92%)	1 (8%)	—	13 (41%)
Subtotal (60)	20 (91%)	2 (9%)	—	22 (37%)
3. Tuberculoid — (23)	5 (50%)	2 (20%)	3 (30%)	10 (43%)
TOTAL (83)	25 (78%)	4 (12%)	3 (9%)	32 (39%)

a Percentages here refer to type distribution among the total leprosy cases of each group.

b Percentages here refer to the totals of the individual groups concerned.

former the Mitsuda reaction was positive in only 9 (39%) of the 23 cases, whereas among the other 60 no less than 56 (93%) were Mitsuda positive.

The importance of the lepromin reaction as an element of prognosis among contacts is known. If a Mitsuda-positive contact becomes infected, it is very unlikely that he will develop a malign form of the disease. This assertion is supported by the present observations, for all cases of the more serious forms—indeterminate and lepromatous—were found exclusively among the lepromin negatives, whereas all cases of the benign —tuberculoid—form were among the lepromin positive contacts.

Comparing the three groups, the one vaccinated with BCG showed the lowest rate of infection. The unvaccinated, tuberculin-positive group had the largest proportion of lepromin positives and the highest rate of the benign form of the infection. The differences, however, were small.

The question arises, then, whether or not a previous tuberculosis infection, either spontaneous or provoked, exerts any protective action against aggression by *M. leprae*.

On the basis of immunological studies of various authors which have shown that the tuberculosis factor induces positivity to the lepromin test, and also on the findings of the present investigation, I believe the answer to be in the affirmative. If an individual who has a tuberculosis

infection that is under control is placed in contact with an open source of leprosy infection, I believe, he will defend himself better than one who is free from tuberculous infection. I also believe that inoculation with BCG exercises an equal protective effect. In both cases, however, the proviso must be made that the tuberculous infection must occur *before the leprosy infection has gained ground.* If the latter has already become established, there is little or no benefit to be derived from the tuberculous infection. In the same way, an individual with smallpox who is vaccinated during his illness derives no benefit. Every protective system of the preventive type must, logically, act before the beginning of the process which it aims to prevent.

Lowe and McNulty state that is has been suspected that tuberculoid leprosy might be caused by a leprosy infection in an individual with tuberculosis. This would produce a sensitization of the organism that would enable it to react allergically to the Hansen bacillus. To test the truth of this theory, they studied the tuberculin sensitivity of a group of leprosy patients and found that proportion of tuberculin positives among their tuberculoid cases was only 55 per cent, which was even lower than the proportion in their lepromatous cases, which was 59 per cent. Among the healthy inhabitants of the locality the rate of tuberculin positives was relatively higher, 75 per cent. These results, the authors concluded, are contrary to the theory that tuberculosis infection is always a causative factor of tuberculoid leprosy. But, they added, "This does not mean that [tuberculosis] is never a contributing factor, although our findings give no clear indications on this point."

I believe that, although a previous tuberculosis infection, whether spontaneous or provoked, confers a certain degree of protection against a malign (lepromatous) infection, yet this does not mean that in the absence of this tuberculosis factor the organism cannot defend itself. Experience shows, and is confirmed by this present study, that a person who is free from tuberculosis and is placed in contact with a source of leprosy may also defend himself, either not becoming infected at all or acquiring only a benign form. However, it would seem that he can defend himself better if there has been an adequate and timely tuberculosis infection.

Here is what I believe to be the explanation of these facts: In accord with Rodriguez (13) and Gonzaga and associates (9), I agree that a child is born with a certain degree of relative, nonspecific immunity, which protects him during the first months of his life from certain infections (scarlet fever, measles, etc.). If, during that time, while the protection exists, the child is placed in contact with an open source of leprosy (lepromatous mother or father, for example), he may under favorable conditions tolerate the invasion of *M. leprae* and as a result of this "specific" and "spontaneous" vaccination develop a relative immunity that will protect him against a serious leprosy infection.

If, on the other hand, the child is born in surroundings free from leprosy and his first contact with *M. leprae* occurs later, when he no longer possesses the nonspecific protection of the early months, the risk of contracting a grave form of leprosy is greater than in the former case, unless he previously has had a primary tuberculosis infection or BCG vaccination. These, then, are the cases in which previous tuberculosis sensitization may be of positive value.

Lastly, if the case be that of an adult who is exposed to infection, this person will, speaking generally, have had a primary tuberculosis infection, in which case his possibilities of defense are good.

In synthesis, the child who is exposed to *M. leprae* from birth has had an opportunity to acquire "spontaneous specific immunization"; and the adult who is exposed to contagion has probably acquired a "spontaneous nonspecific immunization" (tuberculosis infection). On the other hand, the child or adolescent who is exposed to infection late may lack both of these two protective factors, and these individuals constitute the part of the population most liable to contract malign leprosy.

In this connection I believe that it would be very useful to study the tuberculin sensitivity in those cases of leprosy in which the contact with the infective source did not occur at birth but later, as for example spouses of leprosy patients, and adult immigrants from nonendemic countries who have settled in endemic areas and contracted the disease. In those cases it is very probable that tuberculosis infection will have preceded the invasion of the leprosy bacillus, and it would be very instructive to compare the tuberculin positives and the negatives with respect to the effect of the leprosy infection.

In a study made in 1946 (6) of 190 spouses of leprosy patients, I found 38 cases of infection, of whom 33 (87%) were tuberculoid and 5 (13%) were lepromatous.[6] Unfortunately I did not make tuberculin tests on these couples, which would have given interesting information. It is significant, however, that in this group of adults, presumably for the most part tuberculin positive, the proportion of tuberculoid cases was high.

Assuming that BCG is effective in the prevention of leprosy, there are three questions that may be asked about its use: whom, when and how to vaccinate?

If we admit that vaccination by mouth is innocuous, and that the procedure is simple because it requires no previous tuberculin testing, and since it is believed that it can increase the defense of the individual exposed to leprosy infection, then I would not hesitate to advise mass oral vaccination of the people in endemic leprosy areas. Should that desideratum be impossible to accomplish for economic or other reasons, so that

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[6] The infection rate indicated by these figures, 20 per cent, is only the apparent one. The true percentage is only 10.

it would be necessary to select the cases to be vaccinated, the following would be the order of priority:

1. Contacts with open leprosy cases, lepromin negative;
2. Contacts with any case of leprosy, lepromin negative;
3. All contacts with leprosy of any form;
4. School population, lepromin negative, of an endemic area;
5. School population, without distinction, of endemic area;
6. Entire population of endemic area.

Vaccination of contacts should be done as early as possible. The ideal time would be at birth, since great significance is attached to the priority of tuberculosis infection over leprosy infection in order that the protective action of *M. tuberculosis* may be effective.

With respect to dosage, route and schedule of BCG administration, I do not have sufficient experience to make any statement. Rosemberg, Souza Campos and Aun (23) has discussed this subject thoroughly. Judging from the results obtained by Argüello Pitt and associates (1) in converting the lepromin reaction, I am inclined to favor the dual route—oral and intradermal—since it seems to provoke the highest rate of Mitsuda positives.

Special attention is merited by the fortunately small group of individuals resistant to positivization of the lepromin reaction by means of BCG. But this aspect of the matter deserves separate consideration, when justified by further experience.

It is recognized that this study suffers the defect of limited numbers of observations, preventing the drawing of definite conclusions. Nevertheless, the observations lead to appreciation of the great influence which the tuberculosis factor exercises on the fate of leprosy contacts. Furthermore, it demonstrates that, in studies of this nature, intended to evaluate the efficacy of BCG in the prevention of leprosy, it is important to differentiate in the unvaccinated control group the tuberculin positives and negatives, in order to appreciate clearly the influence of the tuberculosis factor.

This study indicates a probable protective influence of the tuberculosis factor, and particularly of BCG, on the individual exposed to leprosy contagion. Despite the fact that the BCG-treated contacts (Group 1) were vaccinated in a deficient manner—mostly for protection against tuberculosis, and not against leprosy—they have shown promising results. I hope to be able to further this investigation in the near future.

SUMMARY

Out of 110 contact children observed between 1939 and 1955, a total of 83 lived in contact with open, lepromatous cases. The clinical and immunological evolution in these 83 children, whose ages ranged from 1 month to 15 years when first seen, is the subject of this report. The children are divided into three groups: (1) those vaccinated with BCG,

28; (2) those not vaccinated with BCG but tuberculin positive, 32; and (3) those not vaccinated with BCG and tuberculin negative, 23.

In the first group, mostly vaccinated intradermally at birth, the rest orally at different ages, 9 (32%) developed leprosy, 8 of them of the tuberculoid and 1 of the indeterminate forms. All but 2 of these cases (i.e., 93%) gave positive Mitsuda reactions.

In the second group there were 13 cases of infection (41%), of which again all were tuberculoid except 1 indeterminate case. The incidence of positive Mitsuda reactions in this group was practically the same as in the first group (94%).

In the third group there were 10 cases of infection (43%), of which 5 were of the tuberculoid type, 2 were indeterminate and 3 were lepromatous. Of this group only 39 per cent were Mitsuda positive.

When the findings in the two groups of children in which there was a tuberculosis factor, induced by BCG vaccination or spontaneous, are compared with those in the tuberculin-negative group, it is found that the former were better protected against aggression by *M. leprae* than the latter, judging especially from the type of the disease. The only lepromatous cases found in the study were in that group.

ADDENDUM

Statistical conclusions.—1. The difference between the frequencies of infection in the contacts of the two types of leprosy (i.e., 32 out of 83 lepromatous contacts against 0 out of 27 tuberculoid contacts), is statistically significant: $x^2 = 12.86$; $p < 0.01$.

2. There is a very marked relationship between the positive Mitsuda and positive tuberculin reaction, with or without BCG, as shown in the subtotal of Table 4: $x^2 = 28.68$; $p < 0.01$.

3. The significance in the data of Table 5 is attributable entirely to the absence of individuals with the lepromatous type in the first two groups, i.e., the BCG-vaccinated and the tuberculin positives: $x^2 = 8.697$; $p < 0.02$. If no distinction is made between the different types of leprosy, as in Table 4, the significance disappears: $x^2 = 0.78$; $p > 0.70$.

—FRIDA BERGMANN

RESÚMEN

El A. estudia comparativamente la evolución clínica e inmunológica de 83 niños cuyas edades oscilaban entre 1 mes y 15 años, convivientes con enfermos lepromatosos, distribuidos en tres grupos: 1) 28 cases vacunados con BCG; 2) 32 casos no vacunados con BCG, tuberculino positivos; 3) 23 casos no vacunados con BCG, tuberculino negativos.

En el primer grupo, constituido por niños vacunados con BCG (en su mayoría por vía intradérmica, al nacer, y otros por vía oral a distintas edades) adquirieron la enfermedad 9 (32%), 8 casos tuberculoides y un caso indeterminado. En 26 casos (93%) la reacción de Mitsuda resultó positiva.

En el segundo grupo se observaron 13 casos de contagio (41%), de los cuales 12 tuberculoides y 1 indeterminado. El índice de positividad de la Mitsuda fue de 94 por ciento.

En el tercer grupo se comprobaron 10 casos de contagio (43%), de los cuales 5 de tipo tuberculoide, 2 de indeterminado y 3 de lepromatoso. La proporción de Mitsuda positiva fue de 39 por ciento.

Si se analizan comparativamente los resultados observados en los dos grupos en que intervino el factor tuberculosis (vacunados con BCG y tuberculino positivos) con los del grupo tuberculino negativo, se comprueba que los primeros estuvieron mejor protejigos contra la agresión del *M. leprae* que los segundos, a juzgar por el índice de contagio y la gravedad de la infección observados en uno y otro caso.

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