

## BCG IN THE PROPHYLAXIS OF LEPROSY A PRELIMINARY REPORT<sup>1</sup>

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For some years, since Fernandez (1) showed that reactivity to lepromin can be induced by BCG vaccination, a fact soon confirmed by other workers, and especially since an intensive study of the matter was begun in São Paulo (3-11), much interest has been taken in the possibility that BCG vaccination may be of signal value in the prophylaxis. One of the questions frequently asked is whether or not artificially induced reactivity is of the same significance as "natural" reactivity, it being recognized that that signifies a material degree of resistance in actual patients and presumably in others. The answers to this basic question and others await actual experience.

In 1951, Fernandez (2) gave his views regarding the value of vaccination. Citing specifically a group of children whom he had inoculated with BCG by the intradermal method shortly after birth and had observed for several years, and among whom no case of the lepromatous form had developed, he said that although BCG vaccination is not expected to confer absolute protection against leprosy infection it is expected to establish a sufficient degree of resistance so that if the disease does develop it will be of a benign form. If these expectations should be fulfilled, he said, prophylactic BCG vaccination of all lepromin-negative persons in endemic areas would be indicated. For the purpose of eliciting definite information on the subject, he asked the following questions:

1. What is the value of the positive Mitsuda reactivity induced by BCG in a healthy individual?
2. What is the incidence of leprosy among subjects vaccinated with BCG and among those not so vaccinated?
3. Are there well-substantiated cases of lepromatous leprosy developing in individuals previously vaccinated with BCG?

At that time the use of BCG for the purpose of inducing

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<sup>1</sup> This article was submitted as a Letter to the Editor, translated from the Portuguese jointly by Dr. José M. M. Fernandez and this office. The data presented, being the first of its kind on this important subject, the contribution was set up in its present form with the consent of the author.—EDITOR.

reactivity to lepromin was being investigated by only a few workers, and the number of vaccinated contacts amounted to only a few hundreds. Consequently, there had not been sufficient material or time of observation to ascertain the value of BCG for protection against leprosy infection. Now, more than a year later, and nearing the end of the fourth year of our investigations in this field, we believe that we are in a position to express opinions on these questions. The answer to the third one will appear in the discussion of the second.

1. *The value of the BCG-induced lepromin reactivity.*—The question of the value of the positive Mitsuda reactivity induced by BCG may be put in other words: Has the lepromin-induced reactivity the same significance as the "spontaneous" or "natural" reactivity? We are convinced that it has, that in both instances the positive reaction reflects the same condition of resistance of the organism to leprosy infection. Not considering for this argument the identical clinical aspect of the positive reaction in both instances, or the identical structural aspect of the reactional lesions, or the persistency of positivity, which we have now observed for four years, we will discuss only the interpretation or meaning of the natural or spontaneous positive reaction.

The reason why certain persons with no contact with leprosy patients exhibit positivity to the lepromin test was until recently unknown. With the increase and generalization of studies of the interrelationship between tuberculosis and leprosy, the explanation of this matter has now become evident. It is, undoubtedly, primary infection with tuberculosis which conditions this positivity. In the tuberculosis dispensary, primarily infected children of tuberculous parents, less than one year of age, give positive reactions to both tuberculin and lepromin. This explains the usual concordance of the results of the two tests in countries with little or no endemic leprosy.

We do not wish to imply that only primary tuberculosis infection can condition this positivity. It is known that leprosy infection can equally condition it, and it is possible that other infections may also do so. Furthermore, in exceptional cases the lepromin reaction may be positive in the absence of any of these factors. There may be congenital conditions, intrinsic and constitutional, which can give rise to this positivity. By these same conditions, we may have the explanation of the contrary phenomenon: persons who do not react to primary infection by tuberculosis, or to leprosy, or to any other

biological or chemical stimulus, are always negative to lepromin. If the majority of the natural positive reactions to lepromin are explained on the grounds of primary tuberculosis infection it is logical to admit that BCG vaccination, which possesses the capacity of allergizing the organism by sensitizing it to tuberculin, may also possess the same capacity to make positive the reaction to lepromin by the same mechanism of sensitization.

2. *The incidence of leprosy in vaccinated and nonvaccinated individuals.*—Regarding this matter I believe there are no observations in the literature which are of statistical value. Systematic or large-scale application of BCG vaccination among leprosy contacts has only recently been undertaken in certain services. In the central dispensary of the Department of Leprosy Prophylaxis of the state of São Paulo, contacts who come for examination are being vaccinated. From February to December 1952 this was done with 1,658 contacts, the vaccine being administered by the oral route in weekly doses of 200 mgm. for 3 weeks, a total of 600 mgm. In the same period there were 3,329 contacts who were examined but not vaccinated.

In the vaccinated group, to the time this note was prepared, there had appeared 10 cases of leprosy, an incidence of 0.6 per cent, all of them of the tuberculoid type. In the nonvaccinated group during the same period leprosy had developed in 179 cases, or 5.4 per cent. These cases were classified as 47 lepromatous, 84 undifferentiated, and 48 tuberculoid.

TABLE 1.—Data on the 10 leprosy cases developing among 1,658 contacts vaccinated with BCG.

No.	Case	Sex	Age, years	Contact/a	Period of contact, years	Lesions found/b	Last dose BCG/b	Interval, weeks or months	Diagnosis, form of tuberculoid
1	1623	F.	10	Father	3	7/5	6/20	2 wk.	Nodular
2	2537	F.	32	Spouse	2	7/20	6/25	3½ wk.	Reactional
3	875	M.	14	Mother	2	8/18	6/—	±2 mo.	Circinate
4	....	M.	2	Father	2	10/7	8/28	5½ wk.	Nodular
5	2627	F.	3	Father	2	10/14	10/—	2 wk.	Nodular
6	2678	M.	21	Sister	2	11/6	10/15	3 wk.	Reactional/c
7	36832	M.	7	G'd. f.	7	11/12	9/12	2 mo.	Reactional
8	23324	F.	3	Father	2	12/5	6/20	5½ mo.	Nodular
9	2857	M.	17	Mother	4	12/15	5/—	±7 mo.	Reactional/c
10	2846	M.	25	Spouse	10	1/2	12/3	1 mo.	Reactional/c

a All contacts lepromatous. b The first numeral refers to the month, the second the day, all in 1952 except for the date of finding lesions in Case 10, which was in January 1953. c Biopsy made.

Because no report has as yet been published of cases with lesions developing after BCG vaccination, details of the 10 cases mentioned are given here, partly in Table 1 and partly in descriptions to follow.

It will be noted from the table that 6 of the 10 patients were children under 15 years of age, while 3 were adults of 21 years or more; the other one was 17. In all instances the contact cases were lepromatous. The periods of contact varied from 2 years (6 cases) to 7 years. All but one had received three doses of BCG, 200 mgm. each, at weekly intervals; the other (Case 3) received six such doses. The periods between the last dose of vaccine and the finding of lesion or lesions were: 1 month or less, 5 cases (Nos. 1, 2, 5, 6 and 10); from 1 to 2 months, 3 cases (Nos. 3, 4 and 7); and 5 to 7 months, 2 cases (Nos. 8 and 9). The condition was reactional in 5 instances—in all the three adults, in the 17-year-old youth, and in one of the younger children. The descriptions of the lesions observed, and the histological findings in the cases biopsied, are as follows:

CASE 1. Papules of lupoid aspect on the right upper eyelid and left hand. Diagnosis: Nodular tuberculoid leprosy.

CASE 2. Six reddish, erythematous infiltrated macules of various sizes. Diagnosis: Reactional tuberculoid leprosy.

CASE 3. A circinate lesion 1 cm. in diameter, with infiltrated border, in the right lumbosacral region. Diagnosis: Circinate tuberculoid leprosy.

CASE 4. Three violaceous, bean-sized nodules on the face, right and left. Diagnosis: Nodular tuberculoid leprosy.

CASE 5. Two reddish, erythematous macules a little larger than a bean, on the right face. Diagnosis: Nodular tuberculoid leprosy.

CASE 6. Infiltrated erythematous macules of the face, right ear, chin, arms and legs, with distinct borders of varied sizes. Thickened auricular nerve. Smears negative. Biopsy done. Histology (No. 27,666): Chronic inflammatory infiltration of involutive aspect in the corium, with nodular structures in several places. Negative for bacilli. Diagnosis: Reactional tuberculoid leprosy, involutive.

CASE 7. Infiltrated erythematous macules, outlines clearly limited, on the face and lower limbs. Smears positive, 2+. Diagnosis: Reactional tuberculoid leprosy.

CASE 8. Nodular lesion on the lateral aspect of the right cervical region, of translucent, yellowish color and lupoid aspect. Diagnosis: Nodular tuberculoid leprosy.

CASE 9. A small spot on the posterior aspect of the left thigh, and numular ones on the right forearm. Biopsy done. Histology (No. 27,483): Granuloma of tuberculoid structure. Very rare bacilli. Diagnosis: Reactional tuberculoid leprosy.

CASE 10. Three small numular, infiltrated plaques on the right thigh, left leg and left knee. Smears negative. Biopsy done. Histology (No. 27,719): Moderate chronic inflammatory infiltration in the corium, with

nodular structures. Very rare bacilli. Diagnosis: Reactional tuberculoid leprosy.

The inadequacy of the laboratory examinations of these cases was due mainly to the fact that most of the lesions were located on the face, and some of the patients were young children. Only three cases were biopsied (Nos. 6, 9 and 10), and that only some time after the appearance of the lesions. The diagnosis of the cases was clinical, but there was no doubt as to their tuberculoid nature.

#### CONCLUSIONS

Certain conclusions can be drawn from the foregoing observations.

1. BCG vaccination clearly has a protective effect as regards leprosy infection, as shown by the incidence of only 0.6 per cent among the vaccinated cases against 5.6 per cent among the nonvaccinated ones during the same period of time.

2. Among the vaccinated contacts only tuberculoid leprosy developed, reactional in 5 instances, the childhood nodular form in 4 instances, and circinate in 1 instance. In contrast, of the cases among the nonvaccinated contacts 26.3 per cent were of the lepromatous form, 46.9 per cent of the undifferentiated form, and only 26.8 per cent of the tuberculoid form.

These data are obviously initial ones, and subsequent observations may alter them quantitatively and qualitatively. There is no doubt, however, that they indicate clearly that BCG has a protective effect against leprosy infection.

#### CONCLUSIONES

1. La vacuna BCG tiene una acción protectora contra la infección de la lepra, como lo demuestra una frecuencia de solo 0.6% entre los vacunados contra 5.6% entre los no vacunados durante el mismo período de tiempo.

2. Entre los vacunados, solo se desarrolló lepra tipo tuberculoide reactiva en 5 casos, nodular infantil en 4, y circinata en 1. Por el contrario, entre los no vacunados, el 26.3% fueron lepromatosos, el 46.9% del tipo indeterminado, y solo el 26.8% tuberculoides.

Aunque éstos datos son de tipo provisional, y pueden ser alterados en el futuro tanto cualitativamente como cuantitativamente, no hay duda, sin embargo, que ellos indican que la vacuna BCG tiene efecto protectoro contra la infección de la lepra.

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