THE USE OF BCG IN LEPROSY

In 1939, Fernández injected BCG intradermally into 123 healthy children who had been found negative to the tuberculin and lepromin tests. When they were tested after the BCG inoculation, however, over 90 per cent of them gave positive responses to both tests. He concluded that BCG might be efficacious in the prevention of leprosy, and suggested its use for this purpose.

During the next 10 years only three papers were published on this subject: a second one by Fernández in 1943; one by Gines and Polettì in 1945; and finally one by Azulay in 1948. These authors confirmed the results of Fernández and concurred with his conclusions. CHaussinand, quite independently, also proposed at the International Congress on BCG which met in Paris in 1948 the use of BCG in the prophylaxis of leprosy.

In 1950 there was formed in São Paulo, Brazil, a team composed of a leprologist (Nelson de Souza Campos) and two tuberculosis experts (J. Rosenberg and J. Aun), who brought the subject of BCG up to date by a series of well-planned experiments. Their results were published in a series of papers between 1950 and 1961. These were valuable contributions towards the solution of the problem, and drew the attention of leprologists to the possibilities of BCG as an agent for the

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prevention of leprosy. They are too numerous to list here, except for the first one, which bears immediately on the present subject.

In the meantime the Madrid congress (1953) considered these possibilities with some degree of enthusiasm. Wade, commenting on the subject in a Journal editorial in 1956, pointed out the increasing interest that had been awakened in the matter, judging by the number of papers that had been published by that time.

On examining the possibilities offered by BCG as an agent for the prevention of leprosy, two questions arise: (1) Does BCG play a special role in provoking the appearance of lepromin positivity in healthy individuals previously negative to that antigen? (2) Does the reactivity artificially induced by BCG have the same value as a sign of resistance to infection as is attributed to the natural or spontaneous positivity?

The first question is justified because, although Fernández’s first observations appeared to be conclusive, later work by Lara, Souza, Ferraz and Bechelli, and others cast doubt on the special value of BCG because they found that retesting with lepromin could also convert a negative into a positive response. In Fernandez’s observations a control group composed of children who had not been inoculated with BCG, but simply retested with lepromin, embodied a deficiency that was recognized later. This matter was reviewed at length by Wade in 1956, who called attention to the fact that Ustvedt called such injections of mycobacteria “microvaccinations.”

This effect of repeated injections of lepromin was not observed until BCG as a prophylactic agent in leprosy had been the subject of important studies. This was fortunate because, if it had been observed immediately after the publication of Fernandez’s first paper, all interest in this problem might have been lost and these studies might not have been made. This would have been regrettable because, although

6 Roodenberg, J. De Sousa Campos, X. and Ant, J. N. Do relacion eunmunadiológica entre tuberculose e lepra. I. Ação positivizante do BCG sobre o lepromin reactivo. Rev. brasileira Leprofi, 18 (1956) 2-5. [The other papers in this series are included in the list of references of No. 17 of the present list.]
the objections to Fernández’s conclusions are technically valid, later work has confirmed them. Doull, Günter and Mabalay,15 Kineer Brown and Stone16 and Rosenberg and associates17—to mention only the most recent publications—have proved that BCG provokes, in a large proportion of healthy individuals, a change from a negative to a positive with the lepromin test.

As the work of Bechelli and others mentioned has definitely proved that retesting with lepromin can also induce reactivity to lepromin in man, the controversy about BCG versus lepromin may be concluded by accepting as valid the following statement: “The inoculation of suspensions of acid-fast bacilli into healthy individuals can modify their state of immunity, converting them from negative into positive reactors.”

This phenomenon, first established in animals by Wade,18 and later by Feldman and associates,19 Olmos Castro and Arcuri20 and Fernández and associates,21 have confirmed this statement in dogs, guinea pigs and man, not only with lepromin and BCG, but also with an antigen of lepromin type prepared from rat-leprosy lesions and with suspensions of the tubercle bacillus.

The second question can be stated as follows: Does vaccination with BCG, correctly performed, give any protection against leprosy? Few publications contribute information about this question, in spite of the fact that the vaccine is regularly used in many countries. Only three experiments will be considered here.

Experiment of Covis and associates.—In a rural district of Venezuela which had a high incidence of leprosy, 100 per thousand, a group of healthy persons who lived in close contact with patients were selected for observation.22 The experiment was started in 1950 with 1,106 subjects whose ages varied from 4 to over 50 years.
all of them free from clinical signs of leprosy. Divided into two groups, 384 were
inoculated with BCG and 522 were used as controls. In 1956 and 1957, all of them
received a first intradermal injection of lepromin, which was repeated in 1954-1956;
in cases which gave negative reactions the injection was repeated every year.

Two intradermal injections of BCG, in doses of 75 mgm, at intervals, were made. The
group used as a control had 24 lepromin-negative cases; the vaccinated group had 111
lepromin negatives. All the subjects were observed periodically.

In 1955, five years after the beginning of the experiment, the results were
evaluated as follows: (1) In the vaccinated group, three cases of tuberculosis leprosy
occurred during the course of the first two years. Originally lepromin negative,
they later responded with an intensely positive reaction. The lesions were exogenous,
disappearing quickly. (2) In the nonvaccinated group, 25 developed the infection—
6 lepromatous, 3 “dusky phosphous” (borderline?), 8 tuberculosis, and 8 indeterminate.
Originally, 57 per cent of them had been lepromin negative. In 18, the symptoms
appeared between the third and fourth years of observation.

In summary: In the vaccinated group the morbidity rate was 3.11 per cent,
all tuberculosis. In the nonvaccinated group the morbidity rate was 46 per cent, and
9 of the 25 cases were “open” ones with severe forms of the disease.

A second evaluation of results was made in 1958, 8 years after vaccination. In
the vaccinated group 2 more cases had appeared, 1 tuberculosis and 1 indeterminate,
bringing the total up to 5 cases. In the nonvaccinated group, 4 new cases had occurred,
3 tuberculosis and 1 indeterminate, bringing the total up to 29. There may be significance
in the fact that in some of these late-appearing cases was the disease of severe form.

Experiment of Chatterjee and associates.—In India, during the course of 1953,25
children of different ages (newly born, 1 to 5 years old, and of school age), resident
in urban and rural areas of the state of Pondicherry, were vaccinated with BCG by
WHO teams in an antileprosy campaign. Five years later the authors investigated
the incidence of leprosy in the high-prevalence rural districts of the State, comparing
contacts which had been vaccinated with those which had not. They found that out of
678 children vaccinated 5 years before, 5 (0.7%) were infected, all cases being of the
tuberculous type, while out of 1,651 nonvaccinated children, 283 (17%) were infected,
15 of them of the lepromatous type.

Experiment of Montestruc and associates.—Since 1954 it has been the practice in
Martinique26 to vaccinate with BCG all newborn infants whose parents suffer from
leprosy, and also all healthy contacts under the age of 20 who are tuberculin negative.
In the same year a law was put into force making vaccination with BCG compulsory
for all children of school age. In an evaluation of the effect of this procedure on the
incidence of leprosy, children up to 15 years of age were examined with the following
results:

<table>
<thead>
<tr>
<th>Period</th>
<th>Total</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>1949-1953</td>
<td>391</td>
<td>169 (33.3%)</td>
</tr>
<tr>
<td>1954-1956</td>
<td>833</td>
<td>216 (26.0%)</td>
</tr>
<tr>
<td>1957-1958</td>
<td>122</td>
<td>31 (25.4%)</td>
</tr>
</tbody>
</table>

Since 1954, the first year in which children of parents with leprosy were vaccinated
at birth, the proportion of children among the new cases had decreased to a moderate

25 Chatterjee, K. R., SOUCOC, P. and SAINT-JOSE, M. Prophylactic value of BCG vac-
166.

26 Montestruc, R. Endémie léprous et vaccination par le B.C.G. de certaines catego-
ries d'enfants (contacts et non contacts) à la Martinique. Internat. J. Leprocy 27 (1959)
97-102.
degree in 1958, while the proportion of lepromatous cases among them had decreased in a striking manner. In the same period, data on the incidence of leprosy in these vaccinated children up to the age of 5 years showed a striking decrease, as follows:

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases out of</th>
<th></th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1954</td>
<td>13</td>
<td>196 vaccinated</td>
<td>6.6%</td>
</tr>
<tr>
<td>1955</td>
<td>13</td>
<td>217</td>
<td>6.1%</td>
</tr>
<tr>
<td>1956</td>
<td>4</td>
<td>130</td>
<td>3.1%</td>
</tr>
<tr>
<td>1957</td>
<td>3</td>
<td>113</td>
<td>2.7%</td>
</tr>
<tr>
<td>1958</td>
<td>2</td>
<td>122</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

The three experimental observations related gave similar results, and they concur with those obtained by Fernández and Yanagisawa in two fundamental aspects: (1) The rates of infection were lower in the vaccinated than in the control groups. (2) The infected cases in the vaccinated groups had nonmalignant forms of the disease, while in the nonvaccinated group there were more or less numerous cases of the malignant forms.

What conclusions can be deduced from the experience obtained so far, with regard to the value of BCG in leprosy? The following facts should be considered: (1) The preventive action of BCG against leprosy has not been proved conclusively. (2) There are, however, observations which suggest strongly that vaccination is beneficial to individuals exposed to infection. (3) Correct vaccination with BCG does not involve any risk. (4) The protective effect against tuberculosis of BCG vaccination has been definitely proved, and is a definite benefit to the people vaccinated regardless of the effect on leprosy. (5) BCG can be used in the prophylaxis of leprosy without interfering with other aspects of a sanitary campaign against that disease.

Why is the use of an agent which offers possibilities of giving protection against leprosy, which is innocuous and which has been proved to give protection against tuberculosis, not officially recommended? What explanation is there for the reserve, vacillation, and even contradictory conclusions arrived at by congresses, conferences and seminars on leprosy, which have sometimes advised its use (III Pan-American Conference on Leprology, Buenos Aires, 1951; VI International Congress of Leprology, Madrid, 1953), while others have not (Pan-American Seminar on Leprology, Belo Horizonte, 1958; VII International Congress of Leprology, Tokyo, 1958)?

This attitude has a reasonable explanation in the fear that recommendation of its application would interfere with or disturb the development of the regular campaign against leprosy. The governments of many countries in which leprosy is endemic resist the appropriation of funds for antileprosy campaigns. If it were suggested that BCG solved the problem of leprosy control, they might suppress funds for ordinary control work and do no more than vaccinate contacts with BCG.

The most effective argument against the use of BCG is that its preventive action against leprosy has not been conclusively demonstrated statistically, therefore its use cannot be recommended until exhaustive research has given a final answer to the question.

It must be accepted that the efficiency of BCG as a preventive agent against leprosy has not been conclusively demonstrated, and it is evident that exhaustive research is needed to prove its value. There is, however, no reason to postpone its use until the results of this research are available, and there are good reasons for not postponing its use. Such research has been planned by experts of WHO, on the initiative of Gay Prieto, and funds for it would be available so that it could be started on short notice. Its results naturally would not be known for 5 to 10 years after its commencement.

Meanwhile, as said, there are no valid reasons, sanitary, moral or economic, for not recommending vaccination with BCG, as long as it does not interfere with the usual measures against leprosy and is considered only as an auxiliary to, not as a substitute for, these measures. The second report of the WHO Committee of Experts on Leprosy26 does not recommend the use of BCG, but maintains that there is no objection to its application as long as it does not disturb the other antileprosy measures.

The VIII International Congress of Leprology, which will meet in Rio de Janeiro next year, will again discuss this question. A recommendation along the lines of the sensible and cautious declaration of the WHO Committee of Experts would give an equitable solution to this prolonged controversy, and would allow the recovery of some of the time lost. Meanwhile, research under way will be continued until the results obtained permit a definitive conclusion.

—José M. M. Fernández


BORDERLINE LESIONS FOR ANIMAL INOCULATION

The article by Convit and associates on experimental inoculation, in this issue, merits special attention. It reports success in producing, in hamsters only, transferable bacillus-rich lesions from leprosy-bacillus suspensions. Success appears to have been dependent primarily on two original ideas, one about the choice of animals and the other about the selection of material for the inoculum.

The reason for choosing the hamster especially was that it is persistently lepromin negative, even after BCG vaccination or repeated lepromin testing. Thus there does not occur, at the site of the inoculation the Mitsuda phenomenon which would create a particularly hostile