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EDITORIALS

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THE USE OF BCG IN LEPROSY

In 1939, Fernández[1] 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,[2] one by Ginés and Poletti in 1945,[3] and finally one by Azulay in 1948.[4] These authors confirmed the results of Fernández and concurred with his conclusions. Chaussinand,[5] 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. Rosemberg 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

[1] FERNANDEZ, J. M. M. Estudio comparativo de la reacción de Mitsuda con las reacciones tuberculínicas. Rev. Argentina Dermatosif. **23** (1939) 425-453.

[2] FERNANDEZ, J. M. M. Influencia del factor tuberculosis sobre la reacción a la lepromina. Rev. Argentino-Norteamericana de Cien. Méd. **1** (1943) 592-600.

[3] GINES, A. R. and POLETTI, J. G. La reacción de Mitsuda en los vacunados con BCG. (Posibilidades de la vacunación con BCG en la profilaxis de la lepra.) Hoja Tisiol. (Montevideo) **5** (1945) 284-292.

[4] AZULAY, R. D. A ação do B.C.G. sôbre a reação lepromímica. O Hosp. (Rio de Janeiro) **34** (1948) 853-856.

[5] CHAUSSINAND, R. Prémunition relative antilépreuse par la vaccination au B.C.G. Rev. Colon. Med. Chir. **21** (1949) 170.

prevention of leprosy. They are too numerous to list here, except for the first one,[6] which bears immediately on the present subject.

In the meantime the Madrid congress (1953) considered these possibilities with some degree of enthusiasm. Wade,[7] 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,[8, 9] Paula Souza, Ferraz and Bechelli,[10] Bechelli[11] 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 Fernández'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.[12] This matter was reviewed at length by Wade in 1955,[13] who called attention to the fact that Ustvedt[14] 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 Fernández'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

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[6] ROSEMBERG, J., DE SOUZA CAMPOS, N. and AUN, J. N. Da relação immunobiológica entre tuberculose e lepra. I. Ação positivante do BCG sôbre a lepromino-reação. Rev. brasileira Leprol. **18** (1950) 3-23. [The other papers in this series are included in the list of references of No. 17 of the present list.]

[7] WADE, H. W. The beginning with BCG in leprosy work. Internat. J. Leprosy **24** (1956) 191-194 (editorial).

[8] LARA, C. B. Mitsuda's skin reaction (leprolin test) in young children of leprous parents. 1. Observations on children from one to five years old. Month. Bull. Bur. Hlth. (Manila) **19** (1939) 15-47.

[9] LARA, C. B. Mitsuda's skin reaction (lepromin test) in children of leprous parents. II. Observations on newly-born to eighteen-month-old children. Internat. J. Leprosy **8** (1940) 15-28.

[10] PAULA SOUZA, R., FERRAZ, N. T. and BECHELLI, L. M. Influencia do BCG vivo e morto sôbre a reacção de Mitsuda. Rev. brasileira Leprol. **21** (1953) 43-50.

[11] BECHELLI, L. M. The influence of repeated lepromin testing on the Mitsuda reaction in healthy people. Internat. J. Leprosy **27** (1959) 228-235.

[12] FERNANDEZ, J. M. M. Reacciones provocadas por antígenos leprosos y tuberculosos en individuos sanos, infectados y enfermos. Leprología **4** (1959) 86-107.

[13] WADE, H. W. Induction of lepromin reactivity by repeated lepromin testing. Internat. J. Leprosy **23** (1955) 310-315 (editorial).

[14] USTVED, H. C. The BCG test. WHO/Exp. Vac.TBC/ **6** Nov. 1953.

the objections to Fernández's conclusions are technically valid, later work has confirmed them. Doull, Guinto and Mabalay,[15] Kinnear Brown and Stone[16] and Rosemberg and associates[17]—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 Arcuri[20] 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 Convit 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,

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[15] Doull, J. A., Guinto, R. S. and Mabalay, M. C. Effect of BCG vaccination, lepromin testing and natural causes in inducing reactivity to lepromin and to tuberculin. Internat. J. Leprosy **25** (1957) 13-37.

[16] Brown, J. A. K. and Stone, M. M. The multipuncture depot lepromin test: I. Technique and advantages. II. Application of the study of BCG-induced lepromin reactivity. Internat. J. Leprosy **29** (1961) 1-13.

[17] Rosemberg, J., de Souza Campos, N., Aun, J. N. and da Rocha Passos, M. C., Jr. Immunobiologic relation between tuberculosis and leprosy. X. Comparative study of the results of the lepromin test in subjects submitted to serial injections of Mitsuda's antigen and to oral BCG vaccination. Internat. J. Leprosy **28** (1960) 271-283.

[18] Wade, H. W. The lepromin reaction in normal dogs; preliminary report. Internat. J. Leprosy **9** (1941) 39-56.

[19] Feldman, W. H., Karlson, A. G. and Grindlay, J. H. Lepromin; Mitsuda's reaction with experimental observations in dogs. Ann. New York Acad. Sci. **54** (1951) 53-72.

[20] Olmos Castro, N. and Arcuri, P. B. Sensitization of the dog with lepromin and BCG, and evidence of cross sensitization. Internat. J. Leprosy **25** (1957) 231-237.

[21] Fernandez, J. M. M., Mercau, A. R., Fernandez Podesta, T. A., Carboni, E. and Agüero, H. Fenómenos de sensibilización cruzada provocados por antígenos derivados del M.L., M.t. y "M. lepraemurium." II. Investigaciones realizadas en perros. (In press, in Leprología.)

[22] Convit, J. Studies of leprosy in the German ethnic group of Colonia Tovar, Venezuela. V. The morbidity rates in BCG-vaccinated and unvaccinated groups during five years. Internat. J. Leprosy **24** (1956) 269-274.

all of them free from clinical signs of leprosy. Divided into two groups, 584 were inoculated with BCG and 522 were used as controls. In 1950 and 1951 all of them received a first intradermal injection of lepromin, which was repeated in 1954-1955; in cases which gave negative reactions the injection was repeated every year.

Two intradermal injections of BCG, in doses of 75 mgm. of bacilli, 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 tuberculoid leprosy occurred during the course of the first two years. Originally lepromin negative, they later responded with an intensely positive reaction. The lesions were evanescent, disappearing quickly. (2) In the nonvaccinated group, 25 developed the infection—6 lepromatous, 3 "dimorphous" (borderline?), 8 tuberculoid, 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 5.11 per cent, all tuberculoid. 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 tuberculoid and 1 indeterminate, bringing the total up to 5 cases. In the nonvaccinated group, 4 new cases had occurred, 3 tuberculoid and 1 indeterminate, bringing the total up to 29. There may be significance in the fact that in none of these late-appearing cases was the disease of severe form.

Experiment of Chatterjee and associates.—In India, during the course of 1953,[23] 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 antituberculosis 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 tuberculoid 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 Martinique[24] 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:

	NEW CASES		TYPES IN CHILDREN		
Period	*Total*	*Children*	*Lepromatous*	*Tuberculoid*	*Indeterminate*
1949-1953	591	169 (31.3%)	53 (32.5%)	28 (16.5%)	89 (50.8%)
1954-1958	813	216 (26.6%)	31 (14.3%)	41 (19.0%)	144 (66.7%)
1958	122	31 (25.4%)	3 (9.7%)	12 (38.7%)	16 (51.7%)

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

[23] CHATTERJEE, K. R., SOUCOU, P. and SAINTE-ROSE, M. Prophylactic value of B.C.G. vaccination against leprosy; a preliminary report. Bull. Calcutta Sch. Trop. Med. **6** (1958) 164-166.

[24] MONTESTRUC, E. Endemicite lépreuse et vaccination par le B.C.G. de certaines categories d'enfants (contacts et non contacts) à la Martinique. Internat. J. Leprosy **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:

1954	13	cases	out	of	196	vaccinated	— 6.6%
1955	13	"	"	"	217	"	— 6.1%
1956	4	"	"	"	130	"	— 3.1%
1957	3	"	"	"	113	"	— 2.7%
1958	2	"	"	"	122	"	— 1.6%

The three experimental observations related gave similar results, and they concur with those obtained by Fernández[25] 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 nonmalign forms of the disease, while in the nonvaccinated group there were more or less numerous cases of the malign 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 leprology, 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 solves the problem of leprosy control, they might suppress funds for ordinary control work and do no more than vaccinate contacts with BCG.

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[25] Fernandez, J. M. M. Influence of the tuberculosis factor on the clinical and immunological evolution of child contacts with leprosy patients. Internat. J. Leprosy **23** (1955) 243-258.

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 Leprosy[26] 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

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[26] World Health Organization. Expert Committee on Leprosy; Second Report. Wld. Hlth. Org. Tech. Rep. Ser. No. 189, 1960.