

## THE BEGINNINGS WITH BCG IN LEPROSY WORK

It is perhaps a little early for a historical review of the use of BCG to make lepromin-negative individuals reactive, since it is only a little over fifteen years since the first experiment was reported. It may be, however, that not all leprosy workers today are aware of the beginnings of the movement that has led to the great expectations that exist and to large-scale trials of BCG for the prophylaxis of leprosy. A part of the record is somewhat obscure, and there was an independent approach in this field by Chaussinand which has not received recognition.

The beginning is unquestionably due to Fernandez, in Argentina, the time 1939.<sup>1</sup> As part of a study of the correlation of the Mitsuda and tuberculin reactions, he told—without introductory explanation—about vaccinating with BCG a lot of orphanage children, they in no way concerned with leprosy, who had been proved negative to both tuberculin and lepromin. Retested a month later, only 10 (8%) of the 123 were negative to lepromin, 87 (71%) were definitely positive, and the other 26 (21%) were weakly so—a total of 113 (92%) reactive to some extent. It is not said when the previous lepromin tests had been made, but the conversion rate was doubtless higher than could be expected from a simple repetition of the test, especially in tuberculin-negative children never with any leprosy contact. He discussed Bieling's hypothesis that a previous infection with tuberculosis may influence the course of other infections, especially leprosy, and he regarded the "allergizing" effect of BCG vaccination as in favor of that hypothesis. Two separate passages are quoted:

Based on these concepts of Bieling and my experience at the asylum, it occurred to me to vaccinate with BCG the contact children of leprosy parents who show a negative Mitsuda reaction, in the hope of producing in them a resistance that perhaps would protect them from leprosy infection.<sup>2</sup>

[One of the practical consequences of the work here reported] is the possibility that there can be produced, in a nonleprosy individual, resistance against the Hansen bacillus by means of BCG vaccination. This hypothetical possibility deserves investigation, especially among contacts, because if it is confirmed we will have a prophylactic measure of great value.

Four years passed, and then Fernandez<sup>3</sup> told of observations which "definitely confirmed the suspicion" that BCG vaccination sensitizes to

<sup>1</sup> FERNANDEZ, J. M. M. Estudio comparativo de la reacción de Mitsuda con las reacciones tuberculinicas. *Rev. argentina dermatosif.* **23** (1939) 425-453.

<sup>2</sup> Thus he enunciated the idea of vaccinating contacts in 1939, but there is no report—of that period—to show what he did about it. There is a recent report [*THE JOURNAL* **23** (1955) 243-258], which tells of subsequent developments in a number of contact children who had been vaccinated at birth in 1939. He explains (personal communication) that that was done as a matter of routine in the hospital where they were born, and he traced them out later; but that he actually had vaccinated some contacts in 1939, before this work was interrupted by changed circumstances.

<sup>3</sup> FERNANDEZ, J. M. M. Influencia del factor tuberculosis sobre la reacción a la lepromina. *Rev. argentina-norteamericano Cien. Med.* **1** (1943) 592-600.

the Hansen bacillus. These were reactions seen in four dermatology patients to whom other physicians had given, several months before he saw them, repeated intradermal injections of BCG (6 to each of two, 27 and 30 to the other two). Fernandez' main interest was in the obviously allergic early reaction (in one case the halo measured 40 x 50 mm.), but the late reactions also were exceptionally strong, all with ulcers. There is no indication that the Mitsuda reactions were *accelerated*; the readings were all made after three weeks.

The situation after that is reminiscent of the one with Mitsuda and his skin test. After his original publication in 1919 Mitsuda wrote no more on the subject except a note for the Strasbourg conference in 1923, and the brevity of that suggests that he himself was not greatly impressed. It was one of his assistants, Fumio Hayashi, who took up the matter several years later and brought it to the attention of the world outside Japan.<sup>4</sup> Twenty years later Fernandez also hit upon something of great immunological interest and practical importance. He, also, seems not to have been greatly excited. Both of these men were like prospectors sitting, serenely unaware, on undeveloped gold mines.

In 1945, Ginez and Poletti<sup>5</sup> took up the matter in the preventorium at Asuncion, Paraguay. Referring only to an unpublished lecture by Fernandez, they nevertheless gave a long quotation that ended: "Attenuated tuberculosis infection, or BCG, may have a protective effect with respect to infection by *Mycobacterium leprae*."

Ginez and Poletti vaccinated by the Rosenthal multipuncture method 20 healthy children of leprous parents who had been found negative to lepromin tests made some months before. In a retest made 26 days after vaccination, 15 (75%) of them had reacted positively within 21 days. Another 11 children were vaccinated without preliminary lepromin testing, and later 9 of them (82%) were found reactive.

These findings, it was thought, suggested the possibility of preventing leprosy by BCG, if it be accepted that a positive Mitsuda reaction implies a relative immunity. This little-known contribution, mentioned in an exhausted review of de Souza Campos,<sup>6</sup> has the distinction of being the first report of the application of this measure to contacts.

The matter was brought more widely to attention shortly afterward. Chaussinand, in a summary report of experiments on cross-reactions pub-

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<sup>4</sup> Nothing came of Mariano's limited work in 1924, which has a suggestive time relationship to Mitsuda's 1923 report although that was not mentioned. How far we would have come from Bargehr's work in 1926—also reported without mention of Mitsuda—is a matter of speculation, although it was given much more attention than was that of Mitsuda until Hayashi made his world tour in 1932, under the auspices of the League of Nations.

<sup>5</sup> GINEZ, A. R. and POLETTI, J. G. La reacción de Mitsuda en los vacunados con BCG. (Posibilidades de la vacunación BCG en la prophylaxia de la lepra.) Hoja Tisiol. (Montevideo) 5 (1945) 284-292; Bol. Of. San. Panamericana 25 (1946) 884-888. This article also appeared in two other periodicals in 1945 and 1946.

<sup>6</sup> DE SOUZA CAMPOS, N. O B. C. G. na profilaxia da lepra. Rev. brasileira Leprol. 21 (1953) 292-314 (81 references).

lished in Europe in 1947 stated (without giving further information, and without mention of earlier observations) that in man or in guinea-pig infected with tuberculosis or vaccinated with BCG the lepromin reaction is positive, contrary to findings with normals.<sup>7</sup> This difference he ascribed to parallergy. Again in 1948, at the First International BCG Congress (and again without details or reference to other work), he told of vaccinating 30 children in that city.<sup>8</sup> The following is the entire statement of what had been done (*italics omitted*):

En outre, 30 enfants ne réagissant ni à la tuberculine, ni à la réaction de Mitsuda, sont devenus sensibles à la lépromine après vaccination par le B. C. G.

It was suggested that BCG vaccination should be extensively employed in tropical regions where antileprosy prophylaxis is difficult.<sup>9</sup>

At about the same time Floch<sup>10</sup> also contributed to the matter, although only conversationally. All that the publication referred to has is a statement at the very end that he had suggested at a recent official meeting that,

. . . la vaccination antituberculeuse par la B. C. G. est susceptible de nous permettre de réaliser la transformation (au mois dans l'organisme neur) de réactions de Mitsuda négatives en réactions de Mitsuda parallergiques positives, ce qui peut être intéressant dans les pays de forte endémie lépreuse.

Nothing is said of any actual work of that kind by himself—or, for that matter, by anyone else. (Floch indicated that Calmette had started the hypothesis of cross immunity between tuberculosis and leprosy.)

In the meantime, in Brazil, Azulay<sup>11</sup> reported widely the results in 15 infants given the vaccine by mouth—the first time this route was used in this connection, that being the method which Arlindo de Assis had exploited in Brazil for antituberculosis work. Twelve of those children (80%) became positive.

Then Rosemberg, de Souza Campos and Aun entered the field in a big way. Two of the three articles, of what became a long series, which they published in 1950 deal with the effects of oral BCG vaccination on

<sup>7</sup> CHAUSSINAND, R. Para-allergies bactériennes dans la tuberculose. *Ann. Inst. Pasteur* **73** (1947) 814-815.

<sup>8</sup> CHAUSSINAND, R. Prémunition relative antilépreuse par la vaccination au BCG. *Rev. colon. Méd. et Chir.* **21** (1949) 170.

<sup>9</sup> The 1947 article referred to was one of several that had been first published in Indo-China during the war, and therefore not accessible. By request, Dr. Chausinand has contributed the Letter to the Editor in this issue which tells of his earlier experiences in this general field.

<sup>10</sup> FLOCH, H. and CAMIN, R. Réaction de Mitsuda, immunité anti-lépreuse et vaccination par le B. C. G. *Inst. Pasteur Guyane et Terr. Inini, Publication No. 172, 1948 (May)*, 4 pp; *abst. Internat. J. Leprosy* **17** (1949) 363.

<sup>11</sup> AZULAY, R. D. A ação do B. C. G. sobre a reação lepromínica. *O Hosp. (Rio de Janeiro)* **34** (1948) 853-856; *Arq. Serv. Nac. Lep.* **6** (1948) 81-86; *Mem. V Congr. Internac. Lepra, Havana, 1948; Havana, 1949, pp. 1142-1145.*

the lepromin reaction.<sup>12</sup> Their work, too extensive to be detailed here, is doubtless familiar to everyone concerned with this subject.

After that came the deluge. De Souza Campos' list referred to contains five reports on the subject in 1950, seven in 1951, two in 1952, and fifteen in 1953, the year his review was written. That, however, is recent history, not ancient. —H. W. W.

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<sup>12</sup> ROSEMBERG, J., AUN, J. N. and SOUZA CAMPOS, N. Da relação imunobiológica entre tuberculose e lepra. I. Ação positivante do BCG sobre a lepromino-reação. *Rev. brasileira Leprol.* **18** (1950) 3-23; *abst. Internat. J. Leprosy* **18** (1950) 555. *Idem.* III. A lepromino-reação em crianças de descendência não leprosa vacinadas com BCG por via oral. Dissociação entre alergia tuberculínica e reação de Mitsuda. *Ibid.* **18** (1950) 138-143; *abst. Internat. J. Leprosy* **19** (1951) 386.