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## EDITORIALS

*Editorials are written by members of the Editorial Board, and opinions expressed are those of the writers.*

### INDUCTION OF LEPROMIN REACTIVITY BY REPEATED LEPROMIN TESTING

There are marked discrepancies, amounting to anomalies, in the reports from different centers about the effects of repeated lepromin testing of originally negative individuals. With some workers the induction of reactivity in non-reactors, and intensification in weak reactors, by that means is the usual experience, and a few have expectations regarding the protective value of that effect. Others have found it to be unusual, to say the least, and some seem to believe that it does not happen. In connection with the report by Ignacio and associates which appears in this issue, the material at hand that bears on the subject is here reviewed summarily.

Mitsuda<sup>1</sup> mentioned the possibility of protective vaccination by his "emulsion," but there is no evidence that he pursued the matter.<sup>2</sup> Bargehr,<sup>3</sup> in Java, who concocted the term "lepromin" for his preparation, undertook to immunize nonreactive persons by repeated inoculations. He induced reactivity in most of them (noting also flare-ups in previously nonresponsive sites), with more success among adults than

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<sup>1</sup> MITSUDA, K. Les lépreux maculo-nerveux, d'une part, les tubéreux, d'autre part, se comportent différemment à la suite d'une inoculation d'émulsion de tubercle lépreux. III<sup>e</sup> Conf. Internat. Lèpre, Strasbourg, 1923, Commun. et Débats. Paris: Baillière et Fils, 1924, pp. 219-220.

<sup>2</sup> Fumio Hayashi, Mitsuda's assistant who put the test on the map, once said (personal communication) that Mitsuda had used vaccination mainly for persons with leprophobia.

<sup>3</sup> BARGEHR, P. Spezifische Hautreaktionen bei Lepra. Ztschr. Immun. u. Therap. 47 (1926) 529-531. Künstliche lepraspezifische Allergie und aktive Immunisierung gegen Lepra. *Ibid.* 49 (1926) 346-353.

among young children. De Langen<sup>4</sup> repeated Bargehr's work and results in a few cases.

The first known report of repeated intradermal testing is that of Negro Vasquez,<sup>5</sup> in Spain, who on the second test saw augmentation in a majority of cases, while some of the negatives became positive. Five years later Burnet,<sup>6</sup> in Tunisia, reported negative results, but only 11 cases were tested more than once, and 8 of them were lepromatous. A report by Radna<sup>7</sup> will be passed up because of uncertainties involved. His work included the use, for therapy, of a vaccine of the supposed leprosy bacillus of Loewenstein.<sup>8</sup>

In one of three reports from Culion, Lagrosa<sup>9</sup> reported the findings in four tests made at three-month intervals in a group of 111 patients who had become bacteriologically negative. In the first test the positive results were 61 per cent for the 41 (ex)lepromatous cases, 84 per cent for the 38 (ex)tuberculoid cases and 94 per cent for the 32 (ex)neural cases; at the end, all were positive. There was, however, only slight augmentation of reactivity. At the same time Ignacio<sup>10</sup> told of his results in a group of active, bacteriologically positive cases under treatment, 87 of them classed as lepromatous, who were given the lepromin test four times at intervals of 6 months. He got an increase of positives from 21 per cent to 84 per cent, although almost all of the reactions were only 1+ degree. This result was not ascribed to the effects of the (chaumoogra) treatment, for positivity appeared in many cases that had not improved.

In view of the innate anergy of lepromatous cases to lepromin, these reports by Lagrosa and Ignacio may well have been regarded with incredulity, where they became known. However, apart from the possibility that many of the cases may have been borderline, there was a complicating factor in that at the time of the first lepromin tests they also injected as a sort of control a dose of heat-killed tubercle bacilli, to which the reactions were so severe that that preparation was not used again.<sup>11</sup>

Relatively recently, Wade and Nolasco<sup>12</sup> injected several laboratory-staff members with a single dose of lepromin every two weeks for 6 doses, and saw in some of them

<sup>4</sup> DE LANGEN, C. D. Specifieke huidreacties bij Lepra. Med. Dienst Volksg. Nederlandsch-Indie **18** (1929) 113-119; Geneesk. Tijdschr. Nederlandsch-Indie **69** (1929) 156-164.

<sup>5</sup> NEGRO VASQUEZ, E. Alergia e inmunidad en la lepra. Arch. Med. Cir. y Esp. **36** (1933) 185.

<sup>6</sup> BURNET, E. La réaction à la léproline chez un groupe lépreux en Tunisie. Arch. Inst. Pasteur Tunis **27** (1938) 341-359.

<sup>7</sup> RADNA, R. Note sur la réaction de Mitsuda chez des sujets indemnes de lèpre. De l'influence du traitement de la lèpre sur la bacillémie lépreuse et sur les résultats de la réaction de Mitsuda. Ann. Soc. belge Med. trop. **18** (1938) 63-72.

<sup>8</sup> LOWENSTEIN, E. The cultivation of the leprosy bacillus; preliminary communication. Internat. J. Leprosy **3** (1935) 43-47.

<sup>9</sup> LAGROSA, M. The leprolin (Mitsuda) reaction in "negative" lepers. 1. Observations over a period of one year. Mo. Bull. Bur. Hlth. (Manila) **19** (1939) 83-93.

<sup>10</sup> IGNACIO, J. L. Observations on the leprolin test in clinically active, bacteriologically positive lepers. Mo. Bull. Bur. Hlth. (Manila) **19** (1939) 95-105.

<sup>11</sup> This was not the first time that the tubercle bacillus had been used for testing, along with lepromin, but it is the first time it was used when there was serial testing in which it might have influenced the results.

<sup>12</sup> Observations yet unpublished.

marked changes as the series progressed. The results in different persons emphasized the factor of individual variability of response, affecting not only the intensity of the reactions but also their nature. In certain of the subjects the early, sensitivity reaction became spectacularly enhanced. In one the size and depth of the ulcers of the late reaction increased greatly. Contrarily, one or two who reacted strongly at the beginning gave less and less marked responses, evidencing an immunization to the antigen rather than increased sensitization. Finally, in two or three others, not strong reactors, there was no essential change of response through the series.

Special interest attaches to work with children in the matter of repeated lepromin testing. Because of the entry of BCG into the picture, children have for years been the main subjects of attempts to induce or enhance lepromin reactivity by artificial means.

The first such study of children was made by Lara, in the Culion series.<sup>13</sup> One group recently separated from their leprous parents, mostly in their second year (average age, 20 months), received four injections at intervals of 3 months. The reactors increased from 50 to 89 per cent, and the average degree of the reactions increased from 1.4+ to 2.6+. Most of the increase of numbers occurred at the second test, when 81 per cent reacted; after that most of the increase was in intensity of the reactions. A younger group, 6 to 18 months old (average about 8 months), still with their parents in the colony, received three injections at intervals of four months. Of them, 73 per cent were positive at the first test 97 per cent at the second one, and 99 per cent at the end, and there was also marked augmentation. These results are remarkable for children so young, but they are authentic beyond question.

The other outstanding investigator in this field is Nelson de Souza Campos, whose experience with the children in preventoria of São Paulo does not parallel that of Lara. In 1938<sup>14</sup> he reported attempts to induce positivity in 14 nonreactive children of leprous parents by repeated testing at 3-month intervals. Only 2 of them were positive at the first retest, but nine responded to the fourth test. Another 15 children were tested only twice; again only 2 became positive.

Continuing this study, he reported in 1946<sup>15</sup> on the results of tests made at two-year intervals from 1936 to 1945, and considered the possibility that the procedure might be significant in prophylaxis. One table shows a total of 325 cases that had had two to five tests without change of reactivity (26% negative or doubtful, 74% positive). Another table concerns 219 cases with two to five tests that had changed from negative to  $\pm$  or stronger, or had shown increase of the original positivity. Of 109 children separated from their parents at birth, only 12 were positive when first tested and 9 others were doubtful. Of 59 negatives tested two or more times, 31 changed while 28 remained negative. It was remarked that in such children a factor which conditions reactivity may be evident at the first test, although it is more often revealed by repetition of the test.

<sup>13</sup> 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. *Mo. Bull. Bur. Hlth. (Manila)* **19** (1939) 15-47. *Idem*. 2. Observations on newly-born to eighteen-month-old children. *Internat. J. Leprosy* **8** (1940) 15-28.

<sup>14</sup> DE SOUZA CAMPOS, N. Resultado do "leprolin-test" nos preventorios de filhos de leprosos. (Estudo realizado nos Preventorios de Jacarehy e Asylo Sta. Therezinha.) *Rev. brasileira Leprol.* **6** (1938) 31-48.

<sup>15</sup> DE SOUZA CAMPOS, N. Da importancia da lepromino-reação no contrôlo das crianças recolhidas nos preventorios. *Rev. brasileira Leprol.* **14** (1946) 3-20.

At the Havana congress de Souza Campos<sup>16</sup> added observations on 31 children who had been tested at two-year intervals to February 1947, always with negative or at most doubtful ( $\pm$ ) results, and who were then put on Diasone treatment. Subsequently they were tested twice more, after shorter intervals. Most of them then turned positive, only 2 remaining entirely negative. This change was ascribed to the treatment.

Although de Souza Campos believed that the sulfone treatment was responsible for the changes in reactivity observed, it is possible—if not probable—that it was due to the testing. This view calls for an explanation of why in the earlier period, beginning in 1936 for some of them, these children—an obviously special group—had been continuously negative to tests made at two-year intervals. It is readily conceivable, (a) that on each of those occasions there may have been produced a conditioning by the injection which, had the subjects been retested shortly afterward, would have resulted in positive reactions, but (b) that that induced condition had subsided before the next test made after a lapse of two years.<sup>17</sup> When tests finally were made at relatively short intervals, most of these seemingly refractory children gave positive responses.

Since that time attention has been focused on BCG, and in most circles there is no interest in any other factor that might serve artificially to induce lepromin reactivity. In fact, one might think no such other factor existed. When in 1953 Tisseuil<sup>18</sup> stated flatly that it is not BCG that induces the lepromin reactivity, but the repeated testing with lepromin (. . . c'est la première [injection of lepromin] qui a sensibilisé l'organisme à la deuxième sans l'intervention de BCG), the comments in a symposium<sup>19</sup> were tinged with shock and outrage. From them it would seem that controls used in BCG experiments always remain negative on the second testing. Only Fernandez frankly agreed that repeated lepromin testing may sometimes induce positivity. Souza Campos, speaking of his 1936 observations cited above, said that change of reactivity was induced ". . . in a small percentage of the subjects, but too few to be of statistical significance." He was now inclined to believe that the changes he reported at Havana might really have been due to infection with tuberculosis during the experiment period (rather than the sulfone treatment). In the more recent BCG work with Rosemberg, he said, the controls were given "one

<sup>16</sup> DE SOUZA CAMPOS, N. Ação das sulfonas nos comunicantes Mitsuda-negativos; interpretação imuno-biológica dos efeitos positivantes. (Estudo do Preventorio Santa Terezinha.) Mem. V. Congr. Internac. Lepra, Havana, 1948; Havana, 1949, pp. 598-608.

<sup>17</sup> Sensitivity to tuberculin in natural infection disappears after the focus of infection is eliminated. Tuberculin sensitivity after BCG vaccination is in general transitory, because no permanent focus of infection is established. In our own work with animals, induced sensitivity to the Hansen or Stefansky bacillus has subsided with the lapse of time.

<sup>18</sup> TISSEUIL, J. The lepromin reaction and BCG. Internat. J. Leprosy **21** (1953) 365 (correspondence).

<sup>19</sup> [SYMPOSIUM] The lepromin reaction and BCG. Internat. J. Leprosy **21** (1953) 365-370 (correspondence; five contributors).

or two reinoculations of lepromin without modification of the negative results." It is clear that—at least at this time—this worker gave no weight to an activating or conditioning effect of previous injections of lepromin. Shortly afterward he appeared less certain.

A report by Rath de Souza and associates<sup>20</sup> told of high percentages of positives on second tests of 91 originally negative persons, mostly young. Nearly two-thirds of them turned positive, a change which they ascribed to "spontaneous conversion." Souza Campos<sup>21</sup> pointed out how unlikely is that explanation; the positive results on the second test were more probably due to sensitization by the first one, he said, although he remained dubious about that effect. Rosemberg, de Souza Campos and others<sup>22</sup> similarly paid their compliments to that work.

At Culion, studies on young children under Lara's direction were resumed when new nursery facilities permitted the successful removal of a limited number of babies at birth, and a report by Ignacio and associates<sup>23</sup> on the findings in 50 of them appears in this issue.

At first only 11 (22%) were positive, and only one of them was 2+. No less than 37 (74%) reacted to the second test, and 11 were 2+—one of them under 3 months of age. Of the 39 who were negative to the first test, exactly two-thirds had become reactive. It was not until the third test that any child attained the 3+ grade, but on the fourth test—when none remained nonreactive—one-third gave reactions of that degree. There were a few who could not be brought above the 2+ level by still further tests, and—an especially interesting observation—BCG was also ineffective in increasing reactivity.

It is obvious that if BCG had been given to the originally negative children of this group, and if the "positivization" shown by the second test had been ascribed entirely to the vaccination, there would have been gross error. About the extent to which that factor has been involved in the results of those who have used BCG to induce positivity one can only speculate.

Another question is why some workers get no positives in their controls on second testing. Granted that maximal results require several test injections at not too long intervals, nevertheless, with some workers a single retest shows much evidence of changed reactivity. Why is that not so in other centers?

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<sup>20</sup> DE PAULA SOUZA, R., DE TOLEDO FERRAZ, N. and BECHELLI, L. M. Influencia do BCG vivo e morto sobre a reação de Mitsuda. (Observações preliminares.) *Rev. brasileira Leprol.* **21** (1953) 43-50. [See abstract in this issue.]

<sup>21</sup> SOUZA CAMPOS, N. O B. C. G. na profilaxia da lepra. (Revisão bibliográfica.) *Rev. brasileira Leprol.* **21** (1953) 292-314. [See abstract in this issue.]

<sup>22</sup> ROSEMBERG, J., DE SOUZA CAMPOS, N., AUN, J. N. and BRANDINI, R. Vitalidade da vacina BCG e capacidade de induzir a reação de Mitsuda. *Mem. VI Congr. Internac. Leprol.*, Madrid, 1953; Madrid, 1954, pp. 588-603. [See abstract in this issue.]

<sup>23</sup> IGNACIO, J. L., PALAFOX, C. A. and JOSÉ, F. A. Mitsuda reactions induced by repeated lepromin testing in children removed at birth from their leprous parents. Failure of BCG to induce strong reactivity in persistently moderate reactors. *THE JOURNAL* **23** (1955) 259-269.

An intriguing question for speculation—and, if possible, investigation—is whether children born of leprous mothers and removed from them at birth are more responsive to repeated lepromin testing, because of some element received in the blood stream while *in utero*, than would be babies born of normal mothers. Be that as it may, the former appear to be highly responsive, and that is contrary to what would be expected of children such as those born in the Culion colony both of whose parents are leprous and supposedly lepromatous, if there existed the familial susceptibility of which not a little was heard in the past. —H. W. WADE