

CORRESPONDENCE

This department is provided for the publication of informal communications which are of interest because they are informative or stimulating, and for the discussion of controversial matters.

THE LEPROMIN REACTION AND BCG

TO THE EDITOR:

J'ai lu avec beaucoup d'intérêt la note que vous avez jointe à ma lettre dans *THE JOURNAL* 20 (1952) 382-383.

Je ne connais pas d'explication satisfaisante de la réaction de Fernandez. Mais je pense que, comme moi, vous trouverez une interprétation valable de la réaction de Mitsuda positive, après vaccination par le BCG, dans les expériences de Bargehr [*Münchner med. Wochen.* 82 (1935) 56]. Cet auteur a toujours rendu positive une réaction de Mitsuda, négative, après 2 ou 3, rarement 4 injections de lépromine.

Ce n'est pas l'inoculation de BCG qui rend la deuxième injection de lépromine positive, mais c'est la première qui a sensibilisé l'organisme à la deuxième sans l'intervention du BCG.

Quelques auteurs, d'après leurs expériences, pensent que la vaccination par le BCG rend positive une réaction de Mitsuda antérieurement négative, d'autres trouvent qu'avec la répétition des injections de lépromine, seule, la réaction devient positive. Ces dernières réactions suffisent à convaincre qu'une première injection de lépromine sensibilise à une nouvelle injection sans faire intervenir une vaccination par le BCG et qu'il n'y a pas de parallergie de la tuberculose pour la lèpre.

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[Note: This letter was submitted to certain leprologists who have worked with BCG, and the replies received—translated when not in English—follow. Dr. Tisseuil's views were published, at greater length than in the letter referred to, in the *Bulletin de la Société française de Dermatologie et de Syphiligraphie* 59 (1952) 231-233, in which the conclusions are not only that the Mitsuda reaction is neither allergic nor parallergic (the latter because it may be negative in tuberculous persons), but also, "Elle n'est qu'une réaction de première infection."—EDITOR.]

From Dr. Rubem D. Azulay, Rio de Janeiro, Brazil: My opinion regarding Dr. Tisseuil's letter is the following:

There is no doubt that BCG vaccination is responsible for the positivity of the reactions to lepromin, Fernandez (early) and Mitsuda (late),

in children previously negative, in the experience of several workers including myself. That idea is supported by the following facts observed by me:

1. In my experience of 1947, reported at the Havana congress and published in Brazil in 1948, I had as a control group 8 children who continued negative to the second test, while those who had received BCG orally became positive—66 per cent Fernandez, 80 per cent Mitsuda.

2. My experiments in animals, not yet published, show that those which are given BCG react positively to the first injection of the lepromin antigen, while controls are negative.

3. I have observed that some children who were repeatedly lepromin-negative became positive as soon as they received BCG.

Examples of our observations in this last group, and certain others, are given briefly. (a) Two cases repeatedly negative to lepromin but found positive after administration of BCG: R.C.S., tested 1/26/45, 4/3/46, 4/9/47 and 7/17/47, negative throughout; given BCG on 11/14/47; retested 1/19/48 and found positive, early and late. M.C.J., tested 4/9/47 and 7/17/47, with negative results; given BCG on 11/14/47; positive early (strong) and late, to retest made 1/19/48.

(b) Two cases tested repeatedly without change of negativity: A.B., tested 4/4/46, 7/10/46 and 4/9/47; persistently negative. M.A.R., tested 1/12/42, 6/26/42 and 9/13/44; Mitsuda negative throughout, although the early (Fernandez) reaction was positive on the first two occasions.

(c) Three cases in which positive late reactions occurred after previous negative results: J.C.S., tested 1/15/44, 7/23/44, 1/24/45 (early reaction positive on this occasion), 4/3/46 (both reactions negative), and 7/10/46, both reactions then positive. A.G.S., tested 4/3/46, 7/7/46, 4/9/47 and 7/17/47; both reactions negative in the first three tests, both positive in the last one. C.S., tested 1/24/45, 4/3/46, 7/10/46 and 4/9/47; the Mitsuda reaction positive in both of the last two tests, the Fernandez reaction negative throughout.

From Dr. R. Chaussinand, Paris, France: I am not inclined to believe that the argument of Dr. Tisseuil merits a symposium, and I think that all questions concerning the Mitsuda reaction may be discussed more effectively at the Madrid congress. Nevertheless, here are my comments on the matter.

The Bargehr reaction is not identical to the Mitsuda reaction. Bargehr prepared a suspension of ground-up lepromas, boiled in a waterbath with very little water (a few drops!), and added 0.5 per cent phenol. This suspension was used in the "cutireaction," like tuberculin in the technique of von Pirquet; i.e., the bacillary suspension was applied to a scarification of the skin and left for some minutes. The reading of the reaction was done 3 to 5 days later.

The conclusions of Bargehr are, to say the least, curious. The following is a translation of the principal passage of the article cited by Dr. Tisseuil, which was headed: "Cutaneous vaccination with lepromas."

"(a) Persons who have never been in contact with a leper: *Reaction negative* (no antibody against the Hansen bacillus).

"(b) Healthy persons who have lived for a long time in contact with lepers: *Reaction positive* (the antibodies have destroyed the Hansen bacilli).

"(c) Leprous persons with positive bacteriological findings and presenting [active] symptoms: *Reaction negative* (antibodies insufficient to combat the disease).

"(d) Persons who have had leprosy for a more or less long period of time but who [actually] present neither bacilli nor symptoms of the disease: *Reaction positive* (antibodies in excess, having led to the cure of the leprosy)."

Furthermore, Bargehr claimed to have rendered positive to his reaction healthy individuals who had never been in contact with leprosy persons by "vaccinating" them by 2 to 4 consecutive cuti-reactions at intervals of 5 to 7 days. The positive results were especially observed in adults. He thought that he had thus discovered a real preventive vaccine against leprosy.

If all these statements of Bargehr were confirmed, and I seriously doubt that, his reaction might be compared with that of Fernandez, but certainly not with the Mitsuda reaction.

On the other hand, in my experiments with monkeys, and especially with guinea-pigs, inoculated with leprosy by leproma grafts, without preliminary Mitsuda testing, I observed positive Mitsuda reactions, often ulcerated, three to four months after the inoculation. (It is to be noted that in the grafted monkeys, tested later every six months, the Mitsuda reactions became progressively weaker and finally negative about two years after the inoculation.) In animals vaccinated with BCG, without preliminary lepromin testing, I obtained positive Mitsuda reactions, often ulcerated, about two months after the vaccination. Lastly, all guinea-pigs inoculated with tuberculosis gave positive Mitsuda reactions. On the contrary, no normal monkeys or guinea-pigs, uninoculated and unvaccinated, ever reacted to lepromin.

If one repeatedly injects a monkey with large doses (1-2 cc.) of Mitsuda antigen by the subcutaneous route at intervals of one or two weeks, on the face for example, one may succeed in "vaccinating" the animal against the antigen. One then observes local lesions appearing more and more early but gradually diminishing in intensity, until finally there is a total absence of local lesions after the injections. However, I have never succeeded in sensitizing monkeys or guinea-pigs by injecting them with Mitsuda antigen in 0.1 cc. dose intradermally at three-months intervals.

From Dr. J. M. M. Fernandez, Rosario, Argentina: Regarding the opinion of Dr. Tisseuil about the influence of retesting with lepromin and vaccination with BCG on the lepromin reaction, I would like to point out the following facts:

1. The early or Fernandez reaction, read after 24-48 hours, is an allergic phenomenon. Its clinical and histopathological features are similar to those of the "delayed" type of hypersensitivity reaction exemplified by that induced by tuberculin. It is positive only in individuals who have previously been in contact with *Mycobacterium leprae* or *M. tuberculosis*. A negative reactor may be converted into a positive one, on retesting, by injections of killed tubercle bacilli or by BCG vaccination. As Wade has pointed out, the retesting with lepromin itself may increase the positiveness of this reaction in positive reactors. That means that this early reaction is "seconde," "precoce," "differente."

2. The late or Mitsuda reaction, usually maximal at 3 weeks, reflects a state of resistance against the disease. This reaction is therefore positive

in the majority of benign cases and negative in lepromatous ones. Mitsuda-positive contacts are better protected against contagion than the negatives, as has been demonstrated by Souza Campos and myself.

3. In a group of 257 healthy children in an orphanage in Rosario, vaccinated with BCG (0.15 mgm. intradermally) and *not previously tested with lepromin*, I performed the lepromin test and observed 48.6 per cent of positive early reactions and 91.3 per cent of positive late reactions. In a control group of 136 healthy children in the same orphanage, not vaccinated with BCG and Mantoux negative (1:10), the lepromin test gave only 2.2 per cent positive early reactions and 6.5 per cent positive late reactions.

4. Rosemberg, Souza Campos and Aun tested with lepromin a group of 45 healthy children in an orphanage of São Paulo. Thirty of these children were simultaneously vaccinated with BCG (100 mgm. by mouth, weekly for 3 weeks), and 15 were left unvaccinated as controls. The vaccinated group showed 100 per cent Mitsuda positivity within 23 to 60 days after vaccination; the control group remained 100 per cent Mitsuda negative. One year later all 45 children were retested with lepromin; all of the vaccinated ones were still Mitsuda positive, and all of the unvaccinated ones were still negative.

5. A group of 105 contact children isolated in a preventoria, all of whom had had at least 3 repeated lepromin tests and some had had 7, and all of whom had remained negative, were vaccinated by Rosemberg, Souza Campos and Aun with BCG (200 mgm. by mouth, weekly for 4 weeks). At the end of the third week, simultaneous with the last dose of BCG, all of them were retested with lepromin. All of them gave positive Mitsuda reactions.

I agree that repeated injections of lepromin may, sometimes, convert a negative lepromin reactor to positive, as has been demonstrated by Lara, by Souza Campos and by myself. But that conversion is not always obtained with lepromin, and never in the high percentage that is observed with BCG.

From Dr. Hervé Floch, Cayenne, French Guiana: The open discussion of the letter of Dr. Tisseuil on the nature of the Mitsuda reaction which appeared in THE JOURNAL last year is interesting.

It is quite evident that if one were to indulge in theoretical discussions of allergy, one would never end. There is far from being unanimity as to exactly what allergy is. For example, should the late "serum sickness" be related to early allergy?

It is evident from the start that Dr. Tisseuil, as you point out, "forgot" the reaction of Fernandez, and that is an early reaction!

The essential point of Dr. Tisseuil's argument is that when we vaccinate a Mitsuda-negative person with BCG and he becomes Mitsuda-positive, this transformation is due to the earlier introduction of the Mitsuda antigen. This is wrong, because the modification observed is indeed due to BCG. It is wrong because:

1. When we vaccinate new-born infants with BCG, without previous lepromin test, they become Mitsuda positive. It cannot be believed that they were all Mitsuda-positive before the vaccination.

2. When we vaccinate with BCG individuals who have been tested with lepromin with negative results, they become—as a general rule—Mitsuda-positive, whereas the controls who were also tested but not vaccinated remain Mitsuda-negative.

(For confirmation of this statement see the one on BCG by the Belra Conference on Sulfone Therapy in *THE JOURNAL* 20 (1952)126. Also see my note, Discussions sur les résultats obtenus en prophylaxie antilépreuse par la vaccination B.C.G., presented at the 10th Brazilian Congress of Hygiene, at Belo Horizonte in October 1952, and published as Publication No. 279 of the Arch. Inst. Pasteur de la Guyane, March 1953).

What is certain, then, is that the BCG vaccination transforms Mitsuda-negative individuals to Mitsuda-positive. It seems evidently logical that Mitsuda-positivity is an indication of a certain resistance to leprosy. Whether or not the reactivity induced by BCG is parallergic, it is of interest from the point of view of prophylaxis to employ BCG vaccination.

From Dr. Nelson de Souza Campos, Goiânia, Brazil: The conclusions or points of view of Dr. Tisseuil do not seem to negative the concept of an interrelationship between tuberculosis and leprosy, of the correlations between the tuberculin and lepromin reactions, and much less the capability of BCG to induce change of lepromin reactivity in nonreactors.

In the first place, the workers who have observed the change of the Mitsuda reaction following repeated applications of the lepromin test have never made a comparative study with the tuberculin test.

In my first work in this field, reported in the *Revista brasileira de Leprologia* 6 (1938) 31-48, I attempted to effect this change in non-reactors, not only by repetition of the Mitsuda test but also by the use of blood and serum of Mitsuda-positive persons. The change occurred in a small percentage of the subjects, but too few to be of statistical significance. Later, in work reported at the Havana congress (*Memorias*, pp. 598-608), I studied the change of the lepromin reaction in about 50 lepromin-negative contact cases, children of leprous parents, who had been given series of 4, 5, 6 or 7 Mitsuda tests. In these studies I did not make parallel Mantoux tests. I am inclined to believe that the instances of change which occurred after repeated Mitsuda testing were due to infection of the subjects with tuberculosis during the period of experimentation.

In the more recent studies with Rosemberg we employed control cases which had one or two reinoculations of lepromin without modification of the negative results. These were changed only after BCG vaccination.

This matter is so important and revolutionary that it cannot be expected to be accepted without objections. They are even necessary, in order that the matter may be clarified.

Here in Goiânia I am now making Mitsuda tests in a reformatory where there are 50 children with no leprous relatives and without any known contact with leprosy, and who were given BCG forty days ago. Here Dr. Tisseuil cannot speak of sensitization due to a primary injection of lepromin. Dr. Rosemberg, in São Paulo, is being asked to undertake a comparative experiment in two groups of children, one group to be given the tuberculin test and the other group the lepromin test, monthly for six months to one year.

Dr. Tisseuil, I think, holds the opinion that he does because he does not believe that the lepromin reaction is a phenomenon of allergy.

ADDENDUM: I now submit two experiments showing the results of tests made here in Goiânia. The first has to do with 49 children, aged 4 to 14 years (average 10.5), without leprous parents and with no contact with leprosy patients. Without preliminary lepromin testing they were given

BCG, by mouth weekly, most of them (35) receiving 5 doses of 100 mgm. each, the others 4 doses. Five or six weeks after the last dose they were all tested with lepromin. Of the 47 recorded after 48 hours, only 9 were positive, and in only 3 of them did the early reaction reach 10 mm. in diameter. After 25 days, 47 (96%) were Mitsuda positive, 1 being \pm and 1 negative; of the positives, 20 were 2+ and of them 9 had ulcers. These very high positive results cannot be ascribed to reinoculation of the antigen, as Tisseuil would have it, for only the one test was made.

The other table shows the results obtained in 27 children of leprous parents in a preventorium here in Goiânia, of whom 22 were tested with lepromin for from 4 to 9 times (average 5.2 times), within periods ranging from 11 to 54 months (average 20.8 months), without becoming reactive to that antigen. Each was then given 3 doses of BCG, but in unusual sequence and dosage. The first dose, 200 mgm., was given in November or December 1952; the second dose, also 200 mgm., was given in March 1953; the third dose, this one of 400 or 500 mgm., was given 40 days later. The lepromin tests were made after another month. This group showed very little early reactivity—only in 2 cases, their reactions measuring 5 and 8 mm. The late reaction was now positive in 24 cases (89%), 3 remaining negative; of the positives, 7 were 2+ and of them 3 with ulceration.