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HYPERSENSITIVITY OF VACCINATION AND OF INFECTION DUE TO *MYCOBACTERIUM LEPRAE*

(PRELIMINARY REPORT) [1]

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In a communication presented to the Sociedad Argentina de Leprología in December 1955 ([3]) we reported confirmation of the investigations of Wade ([7]) on the sensitization of the dog to *M. leprae* by intradermal injection of integral (Hayashi-Mitsuda) lepromin. In that work we found that the second intradermal injection of lepromin in the dog previously injected with that antigen produced in 48 hours an erythematous infiltration similar to the tuberculin reaction, and by the 5th day that infiltration was transformed into a nodule which became ulcerated in 14 days and healed in 40 days. Previously this same dog had presented, 14 days after the first injection of the lepromin, a papule which transformed into a nodule one week later, became ulcerated in 30 days and healed in 56 days.

We concluded then that, as it is with BCG, a first injection of lepromin causes in the dog an alteration of the normal state of reactivity, provoking a state of hypersensitivity. In other words, lepromin is capable of sensitizing the dog in the same way as BCG does. What was striking after the second injection was, besides the tuberculin-type early reaction, the accelerated formation of the nodule or tubercle, in comparison with the developments after the first injection.

Recently we presented to the Asociación Médica Argentina a further communication ([6]) which showed that live *Mycobacterium leprae*—an unheated aqueous suspension of lepromatous tissue—will likewise produce in the dog the state of hypersensitivity to the injection of integral

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lepromin, in the same way as does heat-killed *M. leprae*. In that instance also, we wish to stress, the effect of the reinjection was characterized by an inflammatory early reaction in the form of an erythematous infiltration which was particularly marked after 48 hours, and which rapidly transformed into an erythematous nodule by the 7th day.

Fernandez and Olmos Castro ([2]), Fernandez ([1]), and Olmos Castro and Arcuri ([4]) have demonstrated that an intradermal injection of integral lepromin is capable of sensitizing adult healthy persons to *M. leprae* in a high percentage of cases.

We believe it of interest now to describe our observations on the macroscopic and evolutive characteristics of the cutaneous reaction which occurs at the site of a new injection of integral lepromin in persons previously sensitized with heat-killed leprosy bacilli (vaccination hypersensitivity) and also to compare that reaction with the one which occurs in hypersensitive tuberculoid leprosy cases (infection hypersensitivity), referring particularly to the accelerated formation of the reaction nodule.

METHODS AND OBSERVATIONS

I. HYPERSENSITIVITY INDUCED IN HEALTHY PERSONS BY LEPROMIN INJECTION

There were selected 6 patients with mental disturbance, without known contact with leprosy, who were negative for the early (Fernandez) reaction when first tested with integral lepromin (right scapular region). The inflammatory reaction at the site of the injection was measured (average of two diameters) after 2, 7, 14 and 21 days. On the 21st day after the first injection, a second one of integral lepromin was made, and the results were observed similarly.

Simultaneously with the second lepromin injection, there was made an intradermal injection of total protein leprolin (left forearm)[3]. The results are recorded as were those of the lepromin injections.

1. *The lepromin reaction.*—The results are shown in Table 1 and Text-fig. 1. It is to be seen that, in general, after the first injection the extent of the inflammatory reaction increased with time, so that the greatest degree was observed on the 21st day. After the second injection, on the contrary, the averages show that the greatest intensity occurred after 2 days, gradually decreasing to the 21st day when the observation was terminated. Fig. 1 is very demonstrative in this respect.

[3] At the suggestion of Wade we apply the term *leprolin* to the total protein antigen ([5]) in which there are no bacillary bodies and which has no sensitizing capability, to differentiate it from *lepromin*, of which bacillary bodies are the essential element and which is sensitizing. Thus we call the reactions they respectively provoke the leprolin reaction and the lepromin reaction.

TABLE 1.—*Results of the first and second lepromin tests in healthy persons, the second one made 21 days after the first one, demonstrating sensitization to heat-killed* M. leprae.

Case No.	Lepromin injection	Readings, days after the test			
		2	7	14	21
1	First	3.0	4.0	6.0	6.0
	Second	15.5	6.5	5.5	7.0
2	First	4.0	2.0	6.5	8.0
	Second	27.5	25.0	30.0	11.0
3	First	2.5	4.0	5.0	7.0
	Second	10.5	8.0	6.0	6.5
4	First	3.0	7.5	7.0	7.5
	Second	23.0	10.0	6.5	—
5	First	3.0	6.0	9.5	10.5
	Second	10.0	7.0	9.0	9.0
6	First	5.0	2.0	5.5	6.0
	Second	9.5	5.0	10.0	9.5
Average	First	3.4	4.2	6.5	7.5
	Second	15.3	10.2	11.1	8.6

Even more important than the size of the inflammatory reaction, are the morphologic and evolutive characteristics. (a) The first injection provokes an inflammatory reaction consisting of a local, slightly infiltrated inflammatory erythema which generally persists during the first week. This reaction may be attributed to a traumatic foreign body effect provoked by the injection, without immunologic significance. By the 14th day, however, one can see in most cases a small, circumscribed elevation of the skin, of inflammatory character, which has the aspect of a small tubercle or nodule. This lesion generally increases in intensity of its inflammatory characteristics so that by the third week (21 days) it presents the aspect of an inflammatory nodule.

(b) The second injection, made 21 days after the first one, provokes a different reaction with respect to its morphologic and evolutive aspects. After 48 hours there is seen an infiltrated erythema which is very similar to the tuberculin reaction. This infiltrated erythema continues until the 4th day when, although it has decreased in size, it has become more elevated and firm to the touch and the color has changed from bright red to purplish red. By the 7th day this infiltrated erythema has usually assumed a nodular aspect, although when the 48-hour reaction is very strong it may present the appearance of an infiltration, firm to the touch, of erythemato-purple color. Subsequently

it may maintain the nodular character and undergo resorption, or it may become ulcerated early (by the 14th day) and heal by cicatrization. If we observe this second injection on the 21st day, we find that it has assumed the aspect of an inflammatory nodule, sometimes ulcerated.

The notable feature of this reaction to the second injection, in comparison with the first one, is the 48-hour tuberculin-type reaction, and the accelerated formation of the tubercle or nodule by the 7th day. This is similar to what occurs in the dog hypersensitized to the leprosy bacillus.

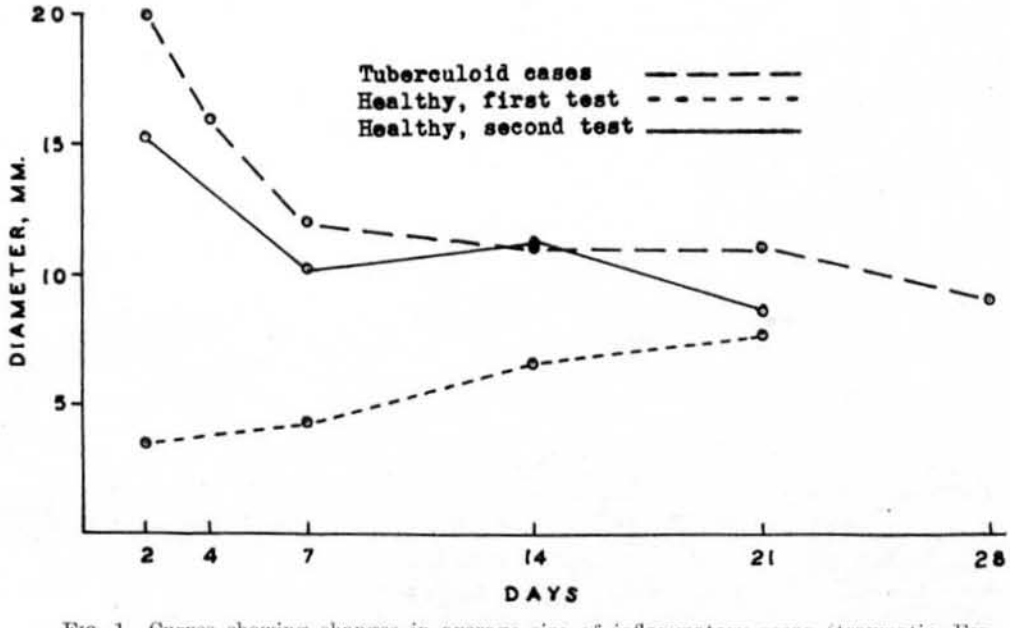

FIG. 1. Curves showing changes in average size of inflammatory areas (traumatic, Fernandez infiltrative, or Mitsuda nodular) with the passage of time after intradermal injection of lepromin in, (*a*) healthy persons previously untested (short-dash line, bottom), (*b*) the same individuals after reinjection (solid line, middle), and (*c*) patients with tuberculoid leprosy (long-dash line, top).

2. *The leprolin reaction.*—The leprolin test, made with the total protein leprolin,[3] 21 days after the first injection of lepromin, provoked in all cases severe local reactions of the tuberculin type.

II. HYPERSENSITIVITY TO *M. leprae* IN TUBERCULOID LEPROSY

Eleven hypersensitive tuberculoid patients were given injections of integral lepromin, and of total protein leprolin, as in the work with normal persons. The reactions provoked by these injections were read and recorded as before.

1. *The lepromin reaction.*—The results are shown in Table 2 and Fig. 1. It is to be seen, particularly in the averages of the different

observation days, that the greatest intensity of the reaction occurred at 48 hours, gradually decreasing with time.

TABLE 2.—*Results of the lepromin test in hypersensitive tuberculoid leprosy patients.*

Case No.	Readings, days after the test [a]					
	2	4	7	14	21	28
516	IE 17	IE 21	EN 13	UN 15 (4)	UN 12	U 3
507	IE 25	IE 25	EN 3	U 5	U 4	H
425	IE 17	IE 12	EN 5	UN 7 (3)	UN 6 (4)	H
490	IE 14	IE 16	IE 13	EN 12	EN 12	EN 13
241	IE 17	IE 14	EN 5	EN 6	EN 5	EN 6
498	IE 20	IE 21	EN 8	—	—	UN 11
326	IE 30	IE 30	IE 30	IEU 27 (10)	IEU 17 (5)	UN 12 (4)
514	IE 32	—	IE 30	IEU 25 (5)	IEU 30 (5)	UN 10 (5)
284	IE 17	—	EN 5	—	EN 8	—
350	IE 15	EN 4	EN 7	EN 6	EN 7	EN 7
449	IE 15	IE 17	IE 13	EN 6	EN 8	UN 8 (3)
Average	20	16	12	11	11	9

[a] IE = infiltrated erythema. EN = erythematous nodule. UN = ulcerated nodule. IEU = infiltrated erythema with central ulcer. U = ulcer. H = healed. The figures in parentheses refer to the size of the ulceration. For considerations of space, decimal fractions are eliminated.

As a general fact we should note that the reactions do not always change fundamentally in their morphology with the passing of time. Thus, at 48 hours they have the aspect of a flat infiltrated erythema. This infiltration continues up to the 4th day, although in smaller size but more elevated and firm to the touch. By the 7th day it has usually acquired the form of an erythematous tubercle or nodule, but when the reaction is very strong it maintains the characteristics of an infiltrated erythema and assumes a purplish-erythematous color. When ulceration occurs it is early, generally occurring by the end of the second week. The conspicuous feature of this reaction is the erythematous infiltration at 48 hours, which is very similar to the tuberculin reaction, and the accelerated formation of the tubercle or nodule, which in most cases has developed by the end of the first week.

2. *The leprolin reaction.*—When this reaction is positive, its acme is established in 48 hours, and it has the aspect of the tuberculin reaction. By the 4th day it has diminished appreciably in size and is of an erythematous-violaceous color, or else it has transformed into a residual macule. By the 7th day the erythema and infiltration have usually disappeared.

DISCUSSION

Hypersensitivity to *M. leprae* provoked by lepromin in healthy persons surely results from a mechanism similar to that which occurs in the sensitization of the dog by the leprosy bacillus, live or heat-killed. It must be emphasized that in man, as well as the dog, the first injection of lepromin produces, after a period of latency, a local inflammatory reaction of frankly nodular aspect between the second and third weeks. The second injection provokes, as in sensitized dogs, a 48-hour inflammatory reaction of the tuberculin type which rapidly transforms into a nodule or tubercle by the end of the first week. The leprolin test, made with the total protein leprolin, provokes a local inflammatory reaction of the tuberculin type which disappears between the 4th and 7th days.

Hypersensitive patients with tuberculoid leprosy respond to the intradermal injection of integral lepromin very much as do dogs and healthy persons who are hypersensitized. Thus they show a tuberculin type reaction at 48 hours, an infiltrated erythema which persists to the 4th day after which it decreases in size but becomes more elevated and firm to the touch; and, generally, by the 7th day, assumes the aspect of an erythematous nodule or tubercle. If we observe the lesion on the 21st and 28th days, we find it to have the characteristics of an erythematous nodule, sometimes ulcerated. The conspicuous feature of the reaction in such cases is the tuberculin-type inflammation at 48 hours, and the accelerated formation of the tubercle or nodule by the 7th day. As in healthy people with induced hypersensitivity, the leprolin test provokes a reaction of the tuberculin type, very similar to the Mantoux reaction.

It seems that the state of hypersensitivity to *M. leprae* provoked by lepromin in healthy persons and dogs (vaccination hypersensitivity) results from a mechanism similar to that of hypersensitivity produced in patients with tuberculoid leprosy (infection hypersensitivity). The striking things about the reaction of hypersensitivity to *M. leprae* are: (*a*) the 48-hour tuberculin-type inflammatory reaction, and (*b*) the accelerated formation of the tubercle or nodule by the end of the first week.

The early or Fernandez reaction, in healthy persons and dogs sensitized with *M. leprae* and in tuberculoid leprosy, is indubitably the manifestation of a specific, monovalent state of hypersensitivity. In this sense, it has a diagnostic value of hypersensitivity due to *M. leprae,* and it may resemble the value of the Mantoux reaction in tuberculosis.

The Mitsuda reaction, or phenomenon, provoked by the intradermal injection of lepromin has a mechanism of formation, and therefore a significance, entirely different in (*a*) the healthy man and the healthy dog from (*b*) those hypersensitized with *M. leprae.* In the healthy

man, as demonstrated by Wade in the dog, the "late nodular reaction," or Mitsuda reaction, or Mitsuda phenomenon, expresses a state of hypersensitivity created by the leprosy bacilli present in the lepromin injected. It does not indicate a pre-existent state of sensitivity, but is the manifestation of a new state created after, and because of, the injection of *M. leprae*. In the healthy man hypersensitized by heat-killed *M. leprae* (vaccination hypersensitivity), as well as in the hypersensitive patient with tuberculoid leprosy (infection hypersensitivity), the late nodular reaction, or Mitsuda reaction, or Mitsuda phenomenon, expresses nothing but the final part of the evolution, and sometimes the termination, of the tuberculin-type inflammatory reaction of hypersensitivity, the acme of which was produced some weeks before.

Although it is certain that frequently the morphologic aspect of the Mitsuda reaction (erythematous nodule, ulcerated or not) is apparently similar in the healthy man and in the man hypersensitized by *M. leprae*, yet its mechanism and significance are completely different. We cannot admit that the Fernandez reaction and the Mitsuda reaction in persons hypersensitive to *M. leprae* have a different significance, and much less that they are provoked by different mechanisms. It is much more logical to think, because of known experimental investigations and comparative study of vaccination hypersensitivity and infection hypersensitivity in man, that the inflammatory process provoked by the Fernandez reaction and by the Mitsuda reaction have a similar mechanism of formation and a similar significance. In this sense it would be arbitrary to give the nodular late reaction a different significance (reaction of resistance) from the early reaction (reaction of hypersensitivity). Their gross appearance and evolution, and their histopathology, show that they are only different stages of the same process.

To accept the view that the late nodular reaction (Mitsuda reaction) signifies a state of resistance or immunity, we would also be obliged to accept that the Fernandez reaction, in the dog and in man sensitized to *M. leprae*, not only indicates a state of hypersensitivity but also a state of resistance or immunity. But as yet we are not aware that it has been demonstrated categorically in leprosy that hypersensitivity is synonymous with resistance or immunity. On the contrary, most of the evidence indicates that hypersensitivity is independent, and that its mechanism and nature are different from those of immunity.

We have always maintained that it would be advantageous in leprosy to consider independently the phenomena of hypersensitivity and of resistance. It is not opportune here to enter into a full discussion of this topic, which will be the subject of other communications.

SUMMARY

The authors have made a comparative study of the reactions provoked by intradermal injection of lepromin in healthy persons and dogs

which are sensitized with *M. leprae* (designated vaccination hypersensitivity), and those provoked under the same conditions in patients with tuberculoid leprosy (infection hypersensitivity). It is concluded that the mechanism of development of hypersensitivity appears to be similar in all instances, and that the striking thing connected with intradermal injection of lepromin in them is the early, 48-hour, tuberculin-type reaction and the accelerated formation of the tubercle or nodule by the end of the first week. The opinion is held that the early reaction of Fernandez in these cases indubitably indicates a state of hypersensitivity to *M. leprae*, and has the same value as the Mantoux reaction in tuberculosis. The Mitsuda reaction is interpreted as the final or terminal stage of the inflammation of the tuberculin-type hypersensitivity, occurring weeks before. It is held that the early and late reactions are different stages of the same process, and that it is not permissible to give them different significances. It is emphasized that in the immunology of leprosy one should study the phenomena of hypersensitivity independently of the phenomena of resistance or immunity, and that there are many reasons for believing that they are different states and that they obey different pathogenic mechanisms.

RESUMEN

Los autores hacen un estudio comparativo sobre las reacciones que provocan la intradermo inyección de lepromina en personas sanas y perros, sensibilizados con *M. leprae* (que denominan hipersensibilidad de vacunación) con aquellas reacciones que se provocan en las mismas condiciones en lepra tuberculoide (hipersensibilidad de infección). Concluyen que el mecanismo de desarrollo de la hipersensibilidad, parece ser semajante en todos los casos y que lo conspicuo de la intradermo inyección de lepromina en éllos, es la reacción precoz de 48 horas, tipo tuberculinica y la formación acelerada del tubérculo o nódulo a fines de la primer semana. Opinan que la reacción precoz de Fernandez, en estos casos, indudablemente expresan el estado de hipersensibilidad al *M. leprae* y tendría el valor de la reacción de Mantoux en tuberculosis. La reacción de Mitsuda, la interpretan como la etapa final o terminal de la inflamación de hipersensibilidad, tipo tuberculínica, ocurrida semanas antes. Sostienen que la reacción precoz de Fernandez y tardía de Mitsuda, son diferentes etapas de un mismo proceso y que es inadmisible, atribuirles signicados diferentes. Insisten en que en inmunología de lepra, deberíase estudiar los fenómenos de hipersensibilidad en forma independiente a los fenómenos de resistencia o inmunidad y, que hay muchos argumentos para pensar que sean estados distintos y que obedecen a mecanismos patogénicos diferentes.

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