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### EDITORIALS

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

#### THE MITSUDA PHENOMENON

The skin reaction of leprosy introduced by Mitsuda exemplifies in a way the gulf that separates the study of leprosy generally from other fields of human medicine. Just as the disease itself presents problems that are unique, so is this reaction unique among immunological skin tests; and just as those problems are severely avoided by medical science in general, so are the phenomena of this reaction overlooked by others than leprosy workers. This is true though it is actually representative of a more general phenomenon which seems worthy of the attention of the immunologist. That phenomenon, it may be noted, has never been given a specific designation, though often observed in other connections. It therefore seems useful and appropriate to apply to it the name of the originator of the test in leprosy, as the "Mitsuda-type reaction" or the "Mitsuda phenomenon."

With respect to the peculiarities of the lepromin reaction, nowhere else do we find so crude a skin-test antigen as this one—a *brei* of the cooked leproma with all its tissue elements and whatever concentration of bacilli it may have. Much has been said, first and last, of purifying and standardizing this material, as would certainly be necessary—and would have been done long since—were it of the nature of the solutions used in all tests for sensitization in other diseases. But that has not been

accomplished as yet, and some workers evidently consider the matter of little importance since they regard the reaction as one of "all-or-nothing" character.<sup>1</sup> Experimental evidence to be published later tends to support that view, within reasonable limits.

Another outstanding peculiarity is that it is necessary to wait for a week or longer to see even the beginning of a positive response, and three weeks or more to see its acme. These features of preliminary latency and slow culmination set it far apart from all known skin sensitivity tests, in which the 24- to 48-hour tuberculin-type reaction is spoken of as "delayed." They are so conspicuous that it would be reasonable to expect that the utmost emphasis would be laid on them in discussions of the nature of the reaction, yet by and large that is not done. One author (Rotberg) has gone so far as to insist that positive reactions in nonlepers signify sensitization due to general dissemination of the infection in the community, and to question the validity of the few reports of positive findings in nonleprous regions. On the other hand one worker experienced in the immunology of tuberculosis<sup>2</sup> has said that he had not been convinced, from the literature, that the reaction is of allergic nature at all, as recently acquired experimental evidence has shown conclusively that it is.

The feature to which the term "latent period" is applied here must be regarded as especially significant. It is just the period that in experimental work with other infections, including tuberculosis, is required for the first manifestations of the allergic state in animals capable of developing that condition in response to the antigen administered. It has been shown by Rodriguez, though heretofore completely overlooked, that certain animals—dogs, rabbits, goats—are capable of reacting positively to lepromin, the course of the reaction being essentially the same as in the human being; other animals, no less completely refractory to infection by leprosy, he found to be negative.

More could be said on the point, but the evidence is regarded as conclusive that the positive reaction to lepromin is, as it is generally held to be, one of allergic nature, whether or not other immunological elements may be involved coincidentally and secondarily. That, however, is far from saying that the test is one for the demonstration of existing allergic sensitiza-

<sup>1</sup>See H. Kitano and T. Inoué, this issue, pp. 29-38.

<sup>2</sup>Dr. John H. Hanks, bacteriologist of the Leonard Wood Memorial, at Culion; personal communication.

tion. There are, of course, peculiarities in certain features of it. Various writers, from Mitsuda in 1923 to Fernández last year,<sup>3</sup> have described erythematous reactions evidently of the tuberculin type in cases that were to give positive lepromin reactions later, but the two phenomena are entirely different and apart. Various writers, furthermore, from Mitsuda on, have reported stronger reactions in nonleprosy persons long in contact with leprosy than in noncontacts; but if there is acceleration of the reaction with respect to the time of onset the fact has escaped notice. Workers at Culion (Lara, Ignacio, Lagrosa<sup>4</sup>) have recently reported that in children of lepers, positive cases and "negatives" submitted to repeated tests at intervals of several months there have been induced positive reactions in previously negative reactors, and reactions of increased strength in previously weak reactors—without, it is said, evidence of beneficial effects. But even so, the latent period was not abolished; if it was shortened the fact was not noted. There remains the most significant fact of all, the existence of the latent period in the actual, positively-reacting cases of leprosy, the principal difference between different kinds of them being the ultimate degree of the reaction.

From these considerations the conclusion seems obvious that the test is not one for existing allergic sensitization as that is understood in other diseases—though evidently under some conditions there may be increased reactivity—but that it is one of *capability of reacting* to the presence of this antigen through the production of allergy. Thus is explained logically the positive reactions in animals, and made acceptable the reports of positive findings in normal persons never exposed to leprosy. Thus is emphasized, first, the recognized difference between those kinds of cases that do and do not react positively (the natural lesions of the former of which are in general fundamentally similar in nature to those of the lepromin lesion itself), and, second, the negative specificity of nonreactivity of lepromatous cases.

The peculiarities of this reaction and the fundamental questions connected with it that cannot as yet be answered might be expected to attract the attention of specialists in immunology. This is the more true because, as said, the phenomenon is a general one; witness the findings with rat lepromin and heat-killed suspensions of other acid-fast microorganisms, to say

<sup>3</sup>See THE JOURNAL 8 (1940) 1-14.

<sup>4</sup>See abstracts in this issue, p. 143.

nothing of phenomena such as the induction of positive lepromin reactivity by previous inoculations with heterologous antigens such as BCG. Much work has been done with antigens consisting of whole killed tubercle bacilli, in connection with both the serological changes after their introduction by the subcutaneous or other routes and the reactions to intradermal injection. But with respect to other acid-fast species, which would seem to elicit more or less different responses, the field is all but untouched.

Limited as seems to be the practical applicability of this test in leprosy, steadily increasing interest in it is being taken by investigators concerned with that disease. The numbers of references in *THE JOURNAL* to this and immediately related subjects are, by years of original publication: 1932, 6; 1933, 3; 1934, 5; 1935, 6; 1936, 6; 1937, 12; 1938, 18; 1939, 14; 1940 (partial) 6; total, 76. Most work on the subject has been done in Japan, and much in the Philippines, India, Brazil and Argentina. Very few reports, and none of any extensive study, have come from regions where leprosy is not endemic.

Büngeler and Fernández<sup>5</sup> have recently studied the reaction with special reference to its pathology. More or less intensive studies are now under way in two other places. Very recent is a summary review of the literature by Lowe and Dharmendra,<sup>6</sup> preliminary to a series of reports of a systematic clinical study, the objectives of which are outlined. Elsewhere in this issue is the first of a series of reports by the writer of this note on the phenomena of this and related reactions in dogs, a possible field of experimentation that, as stated, has heretofore been neglected. However much our understanding of this matter may be furthered by these investigations, it is still to be hoped that the interest of general immunologists in this phenomenon may be aroused, for there are involved in it features that for their elucidation demand special familiarity with that field of biological science.

—H. W. W.