

## OBSERVATION OF PATIENTS WITH ATYPICAL MITSUDA REACTIONS, AFTER AN INTERVAL OF TEN YEARS

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During a period of four years, beginning in 1928, the authors applied the Mitsuda test to about one thousand leprosy patients, old and newly admitted cases, in the Zensei leprosarium in Tokyo. Those who gave doubtful reactions were tested two or more times, with daily observations for a month. When one of us (F.H.) left Zensei for Aiseien, Nagashima, and later transferred to Keiaien, Kagoshima, he took with him the cards of the more interesting cases, and from time to time made inquiry concerning these patients of the other of us (M.I.), who remained at Zensei.

It was learned with particular interest that all of three neural cases that were exceptional in that they had given completely negative reactions when tested in 1928, had become converted to the lepromatous type within a few years. This development was not unique. It is well known that the course of individual cases cannot always be predicted. A slightly affected neural case may become marked lepromatous, and on the other hand an occasional lepromatous case may unexpectedly undergo resolution. The point of immediate interest is that such changes can usually be predicted on the basis of the Mitsuda reaction. In this connection it was thought worth while to investigate the course of the disease in all of the Zensei patients referred to, whose reactions had been doubtful or atypical ten years previously. This follow-up inquiry was completed by the senior author.

Concerning the significance of this reaction, the following clinical facts were established by Mitsuda twenty years ago, and the matter attracted intense interest among leprologists generally when Hayashi published on the subject in this journal (1). Subsequently Muir, Chiyuto, Rodriguez, Fernandez, Schujman and many others have investigated the reaction, and Mitsuda's resistance theory, based on the results obtained with it, has been generally accepted. The essential features are as follows: (a) The reaction

is positive in the neural and macular (i.e., tuberculoid) forms of the disease and in nonleprosy persons; (b) it is negative in the lepromatous type, except in cases that have undergone marked resolution—the so-called secondary neural cases, which, incidentally, constitute about 10 percent of lepromatous cases in our leprosaria; and (c) cases of the neural type that give negative reactions may be expected to become lepromatous within a relatively short time.

#### PERSONAL OBSERVATIONS

The cases dealt with in this report are divided into seven groups, the first five of which comprise lepromatous cases which were in a state of resolution at the time of the original tests, the other two groups comprising originally neural cases that are of interest. These groups are: (1) resolved lepromatous cases with positive reactions that have not relapsed; (2) similar cases that have relapsed; (3) such cases with doubtful ( $\pm$ ) reactions that have not relapsed; (4) similar cases that have relapsed; and (5) such cases with negative reactions, that have relapsed. The neural-case groups are: (6) cases with negative reactions that have become lepromatous; and (7) one case with a typical positive reaction which unexpectedly has undergone that change.

1. *Resolved lepromatous cases with positive reactions, not relapsed.*—As stated, some cases of the lepromatous form, in which the Mitsuda reaction is typically negative, later show complete absorption of their lesions and then become positive to the test. This change indicates a good prognosis and, in Japan, is used in deciding the time at which such improved patients may be allowed to return to their homes.

Among our cases there were 28 of this category that have not undergone relapse since they were tested. At that time the period which had elapsed since the apparent recovery had taken place varied from 3 to 23 years, with an average of 13.6 years. Adding to that figure the further 10 years, these patients have remained in this favorable condition, on the average, for almost 24 years.

Of this group 12 individuals were males and 16 females. It is noteworthy that the sex ratio, 1:1.3, shows a reverse of predominance from the usual one of leprosy cases in general, which is 2:1 or 3:1 in favor of males. Taken together these figures show, not only that the female is less susceptible to leprosy than the male, but also that the lepromatous form of the disease is less severe in females and that they are more likely to recover.

Details of two interesting patients in this group are given.

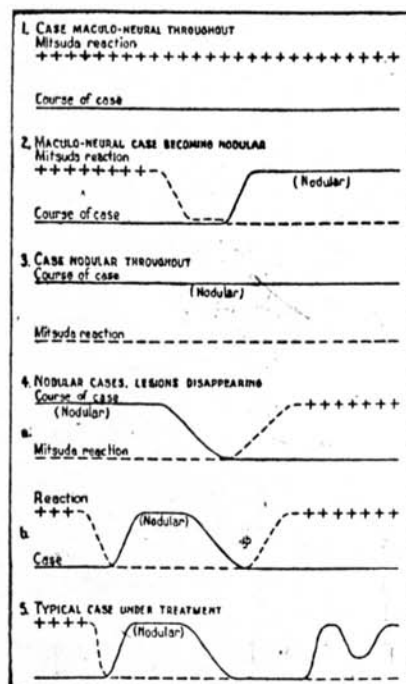
CASE 1.—I.K., male, age 38 years. Onset of the disease at the age of 19 years, admitted in 1924. Mitsuda reaction 2+ on October 28, 1928. Retested on July 14, 1939; again 2+. When tested in 1928 the case had the appearance of a neural one, but Dr. Mitsuda stated that there had been infiltration, with many bacilli, on the chin at the time of admission four years before. As a rule, when only one leproma is to be found in the skin, visceral involvement would be found at autopsy. In this case, since visceral lesions could not be observed, it would have been classified as neural had the earlier infiltrative lesion not been seen. It is now well over 10 years since the infiltration was resolved, and no further change has occurred.

CASE 2.—S.H., male, age 64 years. Onset of the disease at the age of 21 years; admitted in 1924. Mitsuda reaction 1+ on October 15, 1928. Retested on July 14, 1939; 2+. In 1928 he had the so-called chaulmoogra facies: wrinkled face, earlobes and extremities. In appearance he resembled one of the patients in Group 5 (T.N.) whose reaction was negative notwithstanding the complete resolution of his lesions, and who has relapsed, whereas the present patient has remained without further change and now shows a rather stronger reaction than ten years ago.

Two other patients in this favorable positive group (S.U. and S.K.) may be mentioned. When first tested in 1917, by Mitsuda, their reactions were, respectively, negative and doubtful. This shows that they had active lepromatous efflorescences 22 years ago.

2. *Resolved lepromatous cases with positive reactions, relapsed.*—The observations made on this group are important as they have a bearing on a question of long standing, namely, the opinion of Mitsuda's school that once a case has undergone resorption of the lesions and has acquired a positive skin reaction it will not relapse. In the graphs published in the previous article mentioned (1) and reproduced here (Text-fig. 1), No. 4a represents the course of events in such cases as it was then understood—a negatively-reacting lepromatous case undergoing resolution clinically and acquiring a positive reaction, which was not interrupted, at least within the period represented by the graph. In graph 5 is shown the course, as it was then understood, in cases that were to relapse later; in the period of recession of lesions, shown by the drop of the clinical line from the nodular zone, the Mitsuda reaction continued negative, the prognosis being therefore unfavorable. But it was not certain whether or not relapse would occur in at least some small proportion of resolved lepromatous cases with positive reactions.

In that connection we made, in 1930, repeat tests on a group of 72 cases that had been tested by Mitsuda in 1917, thirteen years before. The results, shown in Table 1, are of interest, especially in the fact that no less than 15 out of 68 originally negative cases (22 percent) had become positive; but, since all of the originally positive cases that were still living to



TEXT-FIG. 1. Curves illustrating the relation of the Mitsuda reaction to the progress of cases.

be tested (4 only) had remained positive, the point in question remained unsettled.

In the present investigation we have found seven patients who, ten years ago, reacted positively after resolution of the lepromatous condition, and who have relapsed in the subsequent period. The proportion of relapse, only 20 percent of such positively reacting cases, is of course much lower than in resolved cases with negative or doubtful reactions, but it proves that the apparently more favor-

TABLE 1. Results of Mitsuda tests made in 1930, in comparison with those of tests made by Mitsuda in 1917, on 72 patients.

Reactions 1917 : 1930	Cases tested		
	Male	Female	Total
- : - .....	38	15	53
- : + .....	10	5	15
+ : + .....	3	1	4
+ : - .....	0	0	0
TOTALS .....	51	21	72

able cases do not always escape untoward later developments. The fact that all of these cases were males serves further to show their relative instability with regard to this disease as compared with females.

CASE 1.—A.S., male. Reaction 2+ on October 15, 1928. Died of tuberculous peritonitis in 1937. Marked lepromatous infiltrations and nodules at that time.

CASE 2.—S.S., male. Reaction 1+ on June 16, 1928. Now with marked infiltrations and leprous pannus.

CASE 3.—O.M., male. Reaction 2+ on May 19, 1930. Relapsed in 1935, died in 1939.

CASE 4.—S.U., male. Reaction 1+ on May 19, 1930. Marked infiltrations now.

CASE 5.—U.S., male. Reaction 1+ on November 19, 1930. Died in 1935, with marked infiltrations.

CASE 6.—K.N., male. Reaction 2+ on July 1, 1928. Now with marked infiltrations.

CASE 7.—K.H., male. Reaction 1+ on November 13, 1930. Now with marked infiltrations.

3. *Resolved lepromatous cases with weak reactions, not relapsed.*—Weak ( $\pm$ ) reactions were given by a total of 11 resolved lepromatous cases, all of which, it happens, were females. In the 6 cases of this group that have proved to be of favorable outcome, without relapse, the lepromatous lesions had been resolved for periods of from 5 to 12 years at the time of the original tests. Comparison with the outcome in the next group indicates that a case with a reaction of this degree has approximately a 50 percent chance of remaining well, a fact which has not heretofore been expected. It has been found that in wholly resolved "burnt-out" cases the Mitsuda reaction often remains weak.

CASE 1.—F.M., female. Lesions resolved for 5 years when tested. Reaction  $\mp$  (2 mm.) on July 2, 1929.

CASE 2.—K.M., female. Lesions resolved for 5 years when first tested. Reaction negative on June 21, 1929 and 1+ on May 2, 1930. Retested on July 14, 1939;  $\pm$  (3 mm.).

CASE 3.—I.A., female. Lesions resolved for 9 years when first tested. Reaction  $\mp$  (2 mm.) on June 26, 1930. Retested on July 14, 1939;  $\pm$  (3 mm.).

CASE 4.—R.N., female. Lesions resolved for 12 years when first tested; reaction  $\mp$  (2 mm.) on June 26, 1930. Retested on July 14, 1939; + (4 $\times$ 5 mm.).

CASE 5.—H.T., female. Lesions resolved for 10 years when tested on June 26, 1930. Reaction, two successive readings:  $\mp$  (1 mm.) and negative.

CASE 6.—S.O., female. Lesions resolved for 10 years when first tested, on June 26, 1930. Reaction, three successive readings;  $\mp$ ,  $\mp$  (2 mm.) and negative. Retested, July 14, 1939;  $1+$  (7 mm.).

4. *Resolved lepromatous cases with weak reactions, relapsed.*—Five of the patients with weak reactions later relapsed, with severe lepromatous manifestations, and the three living ones all give negative reactions. In the following notes on these cases the three successive readings refer to the findings at the end of the first, second and third weeks.

CASE 1.—T.M., female. Reaction  $\mp$ ,  $\mp$  and  $\pm$ , June 25, 1930. Died in 1938, with nodules and infiltrations.

CASE 2.—T.T., female. Reaction  $\pm$ ,  $+$  and  $-$ , June 26, 1930. Now with nodules and infiltrations; blind.

CASE 3.—Y.R., female. Reaction  $-$ ,  $-$  and  $\pm$ , October 1, 1928. This patient had lepromatous infiltrations that resembled macules, and the reaction was very weak. Now with nodules and infiltrations.

CASE 4.—H.K., female. Lesions resolved for 5 years at time of test. Reaction  $\pm$ ,  $\pm$  and  $\pm$ , October 1, 1938. Died in 1937, with nodules and infiltrations.

CASE 5.—R.F., female. Lesions resolved for 15 years at time of test. Reaction  $\pm$ ,  $-$  and  $-$ , June 26, 1930. Disseminated nodules and infiltrations since 1938.

5. *Resolved lepromatous cases with negative reactions, now relapsed.*—Among many such cases, the following four are the most noteworthy.

CASE 1.—T.T., male. Onset of the disease in 1925, when he was 10 years of age; admitted in the following year. Reaction negative on October 15, 1928. At the time of the test he was a handsome boy, with no sign of this disease except slight hypoesthesia of the extremities. Now he is 24 years of age and suffering from marked, lepromatous leprosy, in miserable condition.

CASE 2.—I.S., male. Reaction negative March 15, 1929. At that time the case seemed to be of neural type, but Mitsuda had previously seen a lepromatous infiltration on the forehead. In 1930 he relapsed, again with infiltration of the face.

CASE 3.—T.N., male. Reaction negative on two occasions, on October 20, 1928 and June 7, 1929. A picture of this patient was used in Rogers and Muir's "Leprosy" to illustrate the effect of treatment with chaulmoogra oil. The Mitsuda reaction, however, was found negative on several occasions, and relapse occurred in 1930, after ten years of apparent cure.

CASE 4.—I.S., male. Admitted in 1927 with an infiltration on the buttock that resembled a tuberculoid macule but which histological examination proved to be lepromatous. Reaction negative, March 10, 1930. In 1933 (November 24), the condition seeming still to be comparatively well resolved, the reaction was  $\pm$ . Another test made in 1937 (February 9) was also  $\pm$ , though infiltration of the face had developed then. A year later (February 8, 1938), with many nodules present, a final test was negative.

6. *Neural cases with negative reactions that have become lepromatous.*—These three cases are the only neural ones with negative Mitsuda reaction found in the entire group examined in Zensei in 1928. All of them became lepromatous later. They are most important, showing as they do that a negative reaction precedes the change in clinical symptoms ("anteponieren").

CASE 1.—K.K., male. Onset of the disease at the age of 15 years. He was a handsome boy of 19 in 1928 and played female parts in Japanese dramas in Zensei; at that time there were only small anesthetic areas on the extremities. However, the Mitsuda reaction was negative on several occasions in 1928 and 1929, without any lepromatous manifestations. It was learned in 1935 that lepromatous infiltrations had begun to appear, as had been expected. The patient is now a marked lepromatous case, the Mitsuda reaction still negative.

CASE 2.—S.U., male, 38 years old. Onset of the disease 1923; admitted in 1926. Neural leprosy, but with repeated negative reactions in 1928 and 1929. In 1933 several small nodules appeared on the face. Reaction still negative.

CASE 3.—S.I., male. Onset of the disease at the age of 15; admitted in 1918. Neural leprosy, with negative reaction. A test made on May 9, 1929, gave the following readings: on May 20, negative; on June 4, negative; on June 8,  $\pm$  (4 mm.). This was a "spæet" or delayed reaction, signifying a very weakly positive one. In 1930 another test was absolutely negative, and it was in that year that a small phlebitic leproma was found on the back of the left hand. The case is now a marked lepromatous one. It is of interest that this patient had been tested by Mitsuda in 1917, that is, 13 years before appearance of nodules, and in recording the result he wrote: "Negative, observe!"

7. *Neural case, reaction positive, that became lepromatous.*—Dr. Yoshinobu Hayashi, director of the Zensei leprosarium, has brought to our attention a neural case that, unexpectedly, has recently become lepromatous, with a negative reaction. This patient's old record, made in 1929, shows that he gave a positive Mitsuda reaction then. In this instance, therefore, this reaction did not permit anticipation of the actual turn of events. However, it is to be remembered that it is ten years since that test was made; had it been repeated three or five years before the change occurred the reaction would probably have been negative.

#### CONCLUSIONS

In the study here reported, of cases which ten years ago gave atypical reactions to the Mitsuda test, the following observations have been made.

1. Of a total of 35 improved lepromatous cases the lesions of which had been resolved long before the tests were made and which

gave positive reactions, 28, or 80 percent, have remained well, without relapse.

2. The other 7 cases of this original group (20 percent) have relapsed, the Mitsuda reaction of course becoming negative. This observation answers the hitherto unsettled question of whether or not improved lepromatous cases that give positive reactions may undergo relapse.

3. Of a total of 11 similarly improved lepromatous cases that gave only weakly positive ( $\pm$ ) Mitsuda reactions, only 5 have relapsed. The other 6 have, unexpectedly, remained without further symptoms, indicating an about even chance of favorable outcome in such cases.

4. Most of the lepromatous cases with resolved lesions that gave negative Mitsuda reactions have relapsed. Such cases are regularly of poor prognosis.

5. Three neural cases whose reactions were repeatedly negative have all relapsed. It is noteworthy that this significant result of this test precedes by a considerable time the unfavorable turn of the clinical course.

6. One neural case with a typical positive reaction that has, nevertheless, become lepromatous is mentioned.

7. The element of sex appears to have influenced the outcome of these cases. (a) Among the resolved lepromatous cases with positive reactions that have not relapsed are 12 males and 16 females, a ratio of 1:1.3, which is in contrast with the usual ratio of 2:1 to 3:1 among leprosy cases in general. (b) On the other hand the 7 cases of this category that have relapsed are all males. (c) The six resolved cases with weak reactions that have not relapsed are all females, but all cases with that grade of reaction were of that sex. (d) The three neural cases that had negative reactions and that relapsed were all males. Even as males predominate numerically among leprosy cases in general, and among female cases the neural type is relatively predominant, so in the cases the subject of this study there is evidence that the prognosis is more favorable and the disease process more stable among females than among males.

#### REFERENCE

- (1) HAYASHI, F. Mitsuda's skin reaction in leprosy. *Internat. Jour. Lep.* 1 (1933) 31-38; *reprinted in Lep. Rev.* 4 (1933) 159-165.