

## IMMUNO-BIOLOGIC ANOMALIES IN LEPROSY

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South American leprologists in general consider that the Mitsuda test is of great prognostic value in leprosy. This test, now commonly called the lepromin reaction, has been shown to produce two reactions. The first of these, known as the Fernandez phenomenon, is a reaction occurring within forty-eight hours, often referred to erroneously as the early reaction. The second is the original Mitsuda phenomenon. The relationship between these two reactions is not yet clear. In general, the first is considered as demonstrating an allergic condition of the patient and the second as indicating his immunity status.

The present study deals only with the Mitsuda phenomenon. In general, it is assumed that in a patient with a negative reaction to this test the prognosis is poor and in one with a positive reaction the prognosis is good. The various factors influencing prognosis, however, have not been established with sufficient clarity to substantiate fully the latter statement. Knowledge of evolution in leprosy is still limited. The majority of leprologists even now base the prognosis of a case upon the clinical appearance of the patient. This practice has led to two opinions, namely: that the prognosis is good in the tuberculoid form of leprosy but poor in the lepromatous form. These opinions have been further qualified as a result of the Mitsuda test so that at present it is believed that the prognosis is good in a tuberculoid case with a positive Mitsuda reaction and poor in a lepromatous case with a negative reaction.

The prognosis of cases classified according to the Pan-American classification as uncharacteristic (simple macular according to the Cairo classification) depends upon their later evolution to one of the polar forms, tuberculoid or lepromatous. This evolution is predicted by the result of the Mitsuda test. For uncharacteristic cases with a positive reaction the prognosis is good, with evolution to the tuberculoid form or regression of the disease. For uncharacteristic cases with a negative reaction the prognosis is poor, with evolution to the lepromatous form.

In general these are the conceptions generally accepted as to the prognostic value of the Mitsuda phenomenon. Some ex-

ceptions have been noted, attributable mainly to a faulty technic in performing the test. If this conception be accepted, certain anomalous findings appear in patients who have been observed in the Sanatorio Padre Bento for a minimum of ten years. The present study deals with a series of such cases.

#### UNCHARACTERISTIC FORM (SIMPLE MACULAR SUBTYPE)

In 1941, in collaboration with Lecheren Alayon (1), one of the authors published an extensive study of lesions of the uncharacteristic type (simple macular subtype of the neural form of the Cairo classification). In this study the result of the Mitsuda test in 216 patients was included. The present condition of these patients will be analyzed in the light of the Mitsuda reaction and of the clinical examination made in 1941. The clinical diagnosis made in 1941 as well as at the present time was confirmed by histopathologic examination. The Mitsuda test has also been repeated using the same standards for positivity as in 1941.

In table 1, the cases are classified according to the Mitsuda reactions and the clinical findings in 1941. Prior to this date, they had been under observation for five years. Of the 216 cases, 139 or 64.3 per cent had a positive Mitsuda reaction; 60 or 27.8 per cent had a negative reaction, and 17 or 7.9 per cent were doubtful.

TABLE 1.—*Clinical findings and Mitsuda reactions in 216 patients with uncharacteristic form of leprosy.*

Clinical aspect of lesion	Mitsuda reaction in 1941					Total
	3-plus	2-plus	1-plus	Plus-minus	Negative	
Achromic	13	31	20	7	20	91
Erythematohypochromic	12	21	12	6	25	76
Simple erythematous	7	11	12	4	15	49
TOTAL	32	63	44	17	60	216

#### EVOLUTION OF CASES WITH NEGATIVE MITSUDA REACTION

The 60 cases with a negative Mitsuda reaction in 1941 may be divided into two groups. The first of these, 35 in number, had undergone no change during the five years of observation prior to the negative reaction in 1941. The second group of 25 patients had on the contrary shown changes during this period.

The relationship between the clinical condition of the patient in 1941 and in 1946 for the first group of 35 Mitsuda-negative patients is shown in table 2.

TABLE 2.—*Comparison between clinical condition in 1941 and 1946 for 35 patients who had undergone no change in condition during five years prior to 1941.*

Clinical condition of lesion in 1941	Clinical Condition in 1946					Total
	Clinically cured	Residual achromic lesion	Uncharacteristic form	Tuberculoïd form	Lepromatous form	
Primary achromic	.....	.....	.....	.....	6	6
Residual achromic	1	1	.....	.....	2	4
Erythematous hypochromic	5(3*)	1	.....	1*	7	14
Erythematous	1*	.....	.....	.....	1	2
Erythematous-residual	4(1*)	.....	.....	.....	4	8
Erythematous hypochromic	.....	.....	1	.....	.....	1
TOTAL	11(4*) (31.4%)	2 (5.7%)	1 (2.9%)	1* (2.9%)	20 (57.1%)	35 (100.0)%

\* Bacteriologically negative at all times.

In this group of patients with a negative Mitsuda reaction who, prior to 1941, had undergone no change in clinical condition, in 1946 after five years of observation, approximately 57 per cent have followed the usual poor prognosis. In 43 per cent of the cases the patients have undergone a benign evolution; for these patients the prognosis was good.

The second group of patients with a negative Mitsuda reaction had already undergone changes in the five years prior to 1941. Details of these changes are shown in table 3, together with the clinical condition of the patient in 1946.

TABLE 3.—*Transformations prior to 1941 for 25 patients with negative Mitsuda reaction, with clinical condition of patients in 1946.*

Initial transformation	Present condition, lepromatous Number of patients
Achromic → lepromatous	7
Achromic → tuberculoid → uncharacteristic	2
Erythematous hypochromic → tuberculoid re- active → uncharacteristic	1
Erythematous hypochromic → lepromatous	9
Elevated erythematous → lepromatous	1
Erythematous → tuberculoid → uncharacteristic	1
Erythematous → tuberculoid → lepromatous	4
TOTAL	25

In this group of 25 patients there were 21 patients who by 1941 had fulfilled the conception of a poor prognosis in that they became lepromatous. In 4 patients, however, an interesting evolution was shown. In these patients the disease first developed into the tuberculoid form, as shown by clinical and histological findings, in spite of the poor prognosis of the negative test. This change was followed between 1941 and 1946 by a second phase in which the disease retrogressed to the uncharacteristic form and then later to the lepromatous. This shows a double anomaly; initial conversion to the tuberculoid in spite of the negative Mitsuda reaction and the later evolution of the tuberculoid to the lepromatous form.

Another interesting group consists of 7 patients whose initial negative tests had become positive by 1941. The results of their evolution are listed in table 4.



TABLE 4.—*Evolution of 7 cases with initial negative Mitsuda but who reacted positively in 1941.*

Case number	Mitsuda reaction in 1941	Evolution by 1941	Clinical condition in 1946
1	3 plus	Erythematous hypochromic	Clinically cured*
2	3 plus	Erythematous hypochromic → tuberculoid	Clinically cured*
3	3 plus	Erythematous hypochromic → tuberculoid	Clinically cured*
4	2 plus	Erythematous hypochromic → tuberculoid → uncharacteristic	Lepromatous
5	2 plus	Achromic	Lepromatous
6	1 plus	Erythematous hypochromic → tuberculoid	Clinically cured*
7	1 plus	Achromic → tuberculoid reactive → uncharacteristic	Lepromatous

\* Bacteriologically negative at all times.

In all 7 of these cases the transformation of the negative reaction to a positive one was accompanied by the clinical evolution of the uncharacteristic form to the tuberculoid form. In 3, there was a later retrogression to the uncharacteristic with a second change, in spite of the positive Mitsuda, to lepromatous. In another 3, the transformation from negative to positive was followed by a benign evolution, indicated by conversion to tuberculoid with a later disappearance of the lesion. These 3 patients are now considered clinically cured. In case number 5 a conversion to the lepromatous form occurred in spite of the transformation of the negative test to positive during the uncharacteristic phase.

## EVOLUTION OF CASES WITH POSITIVE MITSUDA TESTS

Patients with a positive Mitsuda reaction have been classified according to the degree of positivity to the test and will be considered separately. They will be further subdivided according to whether there had been any evolution of the disease prior to 1941.

There were 44 patients who were recorded as having a 1 plus reaction to the Mitsuda test in 1941. Of these, 33 had not undergone changes prior to 1941. Data for these are shown in table 5.

TABLE 5.—*Relationships between clinical condition in 1941 and 1946 in 33 patients with a 1 plus Mitsuda reaction without evolution of the disease prior to 1941.*

Initial clinical condition of lesion	Clinically cured	Achromic lesions	Circinate achromic lesions	Lepromatous	Unknown	Total
Achromic	6 (3*)	1	.....	6	.....	13
Erythematous hypochromic	4 (1*)	.....	.....	4	.....	8
Residual achromic	2*	.....	1	.....	.....	3
Erythematous, flat	2*	.....	.....	6	1	9
TOTAL	14 (43.5%)	1 (3.0%)	1 (3.0%)	16 (48.5%)	1 (3.0%)	33 (100.0%)

\* Bacteriologically negative at all times.

In this group 16 or nearly half of the patients retrogressed to the lepromatous form in spite of the 1 plus Mitsuda reaction.

The evolution of the disease in the 11 patients who had undergone changes prior to 1941 is shown in table 6.

TABLE 6.—*Evolution of disease in 11 patients with a 1 plus Mitsuda reaction who had undergone changes prior to 1941.*

Case number	Initial condition and transformation before 1941	Clinical condition in 1946
1, 2, 3	Achromic → tuberculoid → achromic	Lepromatous
4	Achromic → tuberculoid → achromic	Achromic lesion
5	Achromic → clinically cured	Lepromatous
6	Erythematous hypochromic → tuberculoid → achromic	Clinically cured
7, 8	Erythematous hypochromic → tuberculoid → clinically cured	Lepromatous
9, 11	Erythematous hypochromic → tuberculoid → clinically cured	Clinically cured*
10	Erythematous hypochromic → tuberculoid → erythematous hypochromic	Lepromatous

\* Bacteriologically negative at all times.

In this group of 11 patients anomalous results are found. In 7, there was a first phase with benign evolution either to the tuberculoid form or to complete disappearance of symptoms.

The second phase was a reversion to a negative Mitsuda with evolution to the lepromatous form. In only 3 patients has the expectation of the improvement as prognosticated by the positive Mitsuda been justified by clinical cure. In 1 patient there was a retrogression to the uncharacteristic form after a transformation to the tuberculoid form.

The largest number of patients were found among those recorded as having a 2 plus Mitsuda reaction, 63 in all. Of these, 51 had shown no changes prior to 1941. Data comparing the initial clinical condition with their condition in 1946 are shown in table 7.

TABLE 7.—*Relationship between clinical condition in 1941 and in 1946, in 51 patients with a 2 plus Mitsuda reaction, without changes prior to 1941.*

Initial condition of lesions	Clinically cured	Achromic lesion	Residual erythematous hypochromic lesion	Lepromatous	Unknown	Total
Achromic	10 (4*)	1	.....	2	.....	13
Residual achromic	13 (2*)	.....	.....	.....	1	14
Erythematous hypochromic	13 (1*)	.....	1	.....	.....	14
Residual erythematous hypochromic	1	.....	.....	.....	.....	1
Flat erythematous	3 (1*)	.....	.....	1	.....	4
Residual flat erythematous	5	.....	.....	.....	.....	5
<b>TOTAL</b>	<b>45</b> (88.2%)	<b>1</b> (2.0%)	<b>1</b> (2.0%)	<b>3</b> (5.8%)	<b>1</b> (2.0%)	<b>51</b> (100.0%)

\* Bacteriologically negative at all times.

In 45 patients of this group the evolution proceeded according to the concept of a good prognosis. In only 3 patients did the disease become lepromatous; in 2, the disease remained stationary and in 1, it was not possible to trace the patient.

The data for 12 patients with a 2 plus Mitsuda reaction who had undergone changes prior to 1941 are given in table 8.

TABLE 8.—*Evolution of disease in 12 patients with a 2 plus Mitsuda reaction who had undergone changes prior to 1941.*

Case number	Initial clinical condition and transformation prior to 1941	Clinical condition in 1946
1	Achromic → tuberculoid → achromic	Achromic
2	Achromic → tuberculoid → achromic	Circinate tuberculoid
3	Achromic → tuberculoid → achromic	Clinically cured*
4	Achromic → tuberculoid → achromic	Lepromatous
5	Erythematous hypochromic → tuberculoid → erythematous hypochromic	Erythematous hypochromic
6	Erythematous hypochromic → tuberculoid → erythematous hypochromic	Clinically cured
7, 8	Erythematous hypochromic → tuberculoid → clinically cured	Clinically cured
9	Erythematous hypochromic → tuberculoid → erythematous hypochromic	Lepromatous
10, 11	Erythematous hypochromic → tuberculoid → erythematous hypochromic	Lepromatous
12	Achromic → erythematous hypochromic	Lepromatous

\*Bacteriologically negative at all times.

This group shows many anomalies. In 4 cases the evolution proceeded in two phases, one benign and the other malignant:

1st phase	2nd phase
Uncharacteristic → tuberculoid Mitsuda 2-plus	Uncharacteristic → lepromatus Mitsuda negative

In one of these cases (number 12, case 4 in table 4) the malignant change proceeded in spite of a positive Mitsuda test. The positive reaction with benign evolution is found in 4 patients who are classified clinically cured in 1946. In 1 patient the disease had returned to its initial condition of uncharacteristic form (simple macular subtype).

Of the 32 patients who had a 3 plus Mitsuda reaction, 26 of them had undergone no reaction prior to 1941. Data for these are given in table 9.



TABLE 9.—*Relationship between clinical condition in 1941 and in 1946 for 26 patients with a 3 plus Mitsuda reaction, who had undergone no changes prior to 1941.*

Initial condition of lesions	Clinically cured	Lepromatous	Total
Achromic	8(2*)	1	9
Residual achromic	3	.....	3
Erythematous hypochromic	6(1*)	1	7
Residual erythematous hypochromic	1	.....	1
Erythematous flat	3	.....	3
Residual erythematous flat	3	.....	3
TOTAL	24 (92.3%)	2 (7.7%)	26 (100%)

\* Bacteriologically negative at all times.

In 24 of the 26 patients with a strong positive Mitsuda reaction there was complete regression of symptoms. Two, however, reacted in a wholly unexpected manner and developed lepromatous leprosy.

Data for the 6 strongly positive reactors with changes prior to 1941 are given in table 10.

TABLE 10.—*Evolution of disease in 6 patients with a 3 plus Mitsuda reaction who had undergone changes prior to 1941.*

Initial condition and transformation prior to 1941	Clinical condition in 1946	Number of cases
Erythematous hypochromic → tuberculoid → erythematous hypochromic	Clinically cured	3
Erythematous hypochromic → tuberculoid → erythematous hypochromic	Tuberculoid	1
Erythematous hypochromic → tuberculoid → achromic	Tuberculoid	1
Erythematous hypochromic → tuberculoid → achromic	Achromic	1

This small group does not depart from the general evolution expected of strongly positive Mitsuda reactors. Three progressed to a clinical cure, 2 remained tuberculoid, and 1 had only residual lesions.

## EVOLUTION OF CASES WITH DOUBTFUL MITSUDA REACTIONS

There were 17 patients in whom the Mitsuda reaction was doubtful. Their condition prior to 1941 and in 1946 are given in table 11.

TABLE 11.—Initial condition with transformations prior to 1941 and clinical conditions in 1946 for 17 patients with a doubtful Mitsuda reaction.

Initial condition and transformation prior to 1941	Clinical condition in 1946	Number of cases
Achromic	Clinically cured	2(1*)
Achromic	Lepromatous	4
Achromic → erythematous hypochromic	Lepromatous	1
Erythematous hypochromic	Lepromatous	4
Erythematous hypochromic	Clinically cured	1*
Erythematous hypochromic → tuberculoid	Lepromatous	1
Simple erythematous	Lepromatous	1
Simple erythematous	Clinically cured	2(1*)
Simple erythematous	Unknown	1
TOTAL		17

\* Bacteriologically negative at all times.

In table 12 a summary is given of the present condition of all patients classified according to their Mitsuda reaction in 1941.

TABLE 12.—Present condition of 216 patients studied prior to 1941, classified according to their Mitsuda reactions.

Present condition	Mitsuda Reaction					Total
	3-plus	2-plus	1-plus	Plus-minus	Negative	
Clinical cure	27	49	17	5	11	109
Residual uncharacteristic	1	4	3	....	7	15
Tuberculoid	2	1	....	....	1	4
Lepromatous	2	8	23	11	41	85
Unknown	....	1	1	1	....	3
TOTAL	32	63	44	17	60	216

These figures show that of 128 patients with a benign evolution 19, or 15 per cent, had a negative Mitsuda reaction. The evolution in these patients was therefore contrary to expectation. Of 85 cases of malignant evolution 33, or 39 per cent, had a positive Mitsuda reaction and therefore evolved contrary to the usual expectation.

#### TUBERCULOID FORM

The opinions of both South American and Anglo-Saxon leprologists differ in regard to the tuberculoid form of the disease. In the first study of this form of the disease, South American workers believed that in this form the reaction to the Mitsuda test was uniformly positive. Continued observations have demonstrated that in this benign form, however, frequent negative reactions occur. Some authors consider that these negative reactions are due to the reactive stage of the disease and that if such patients are excluded, the usual proportion of positive reactions will be found. For certain Anglo-Saxon workers the occurrence of the negative reaction in the "major" tuberculoid form, which corresponds to the reactive tuberculoid, is a real contradiction.

While carrying on another study the authors had the opportunity of performing the Mitsuda test in 685 patients with the tuberculoid form of leprosy. Results of these tests are given in table 13.

TABLE 13.—*Reactions to the Mitsuda-Hayashi test in 685 patients with tuberculoid leprosy, classified as to type of tuberculoid disease.*

Variety of tuberculoid form		Mitsuda-Hayashi reaction					Total
		3-plus	2-plus	1-plus	Plus-minus	Negative	
Cutaneous and cutaneo-nervous	Circinate leprides	88	127	44	2	15	276
	Reactional leprides	51	85	60	9	59	264
	Nodular	27	22	6	.....	.....	55
	Atypical	13	21	21	3	5	63
Tuberculoid of the nerve		14	11	2	.....	.....	27
TOTAL		193	266	133	14	79	685

Of the 675 tests 592 or 86.4 per cent were positive, 79 or 11.5 per cent negative, and 14 or 2.0 per cent doubtful. In justification of the prognosis of benignity in the tuberculoid



form, the great majority of these 685 patients showed a spontaneous cure of the cutaneous symptoms. Only 47 underwent an anomalous evolution to the lepromatous form. Details for these patients are shown in table 14.

TABLE 14.—*Type of tuberculoid cases with Mitsuda reaction for 47 patients with evolution to lepromatous form.*

Type	Mitsuda reaction					Total
	3-plus	2-plus	1-plus	Plus-minus	Negative	
Circinate	.....	1	2	.....	2	5
Nodular	.....	.....	.....	.....	.....	.....
Reactional	.....	3	9	1	24	37
Atypical	.....	.....	2	.....	3	5
TOTAL	.....	4	13	1	29	47

Of these 47 patients, 17 or 36 per cent not only were originally tuberculoid but also had positive Mitsuda reactions.

#### INVERSION OF MITSUDA TEST RESULTS

The inversion from positive to negative has already been noted in a relatively high percentage of patients in whom there was a transformation from the uncharacteristic or tuberculoid to the lepromatous form. In some patients this inversion was preceded by increased positivity. This, at times, was shown by a reactivation of an old Mitsuda nodule and at times appeared following a repetition of the test. The patients with increased reactivity preceding inversion are shown in table 15 together with the clinical changes.

TABLE 15.—*Increase in intensity of the positive reaction which preceded inversion to negative, together with clinical change.*

Mitsuda reaction			Clinical changes	Number of cases
1st	2nd	3rd		
1 plus	3 plus	Neg.	Uncharacteristic → lepromatous	1
1 plus	2 plus	Neg.	Uncharacteristic → lepromatous	1
1 plus	2 plus	Neg.	Uncharacteristic → tuberculoid → lepromatous	2
1 plus	2 plus	Neg.	Uncharacteristic → tuberculoid	1
1 plus	2 plus	Neg.	Uncharacteristic → tuberculoid → uncharacteristic → lepromatous	2





Among these 12 patients, there are 3 only that are anomalous, because of their transformation into the malignant form in spite of the inversion of the negative to the positive reaction.

#### SUMMARY

In general, it is assumed that in patients reacting to the Mitsuda test the prognosis is good while in those giving a negative result the prognosis is poor. The present paper records the actual findings in the patients observed over a period of years.

In 1941, of 216 patients with the uncharacteristic type of leprosy, 60 were negative to the Mitsuda test. Forty-one, or 68.3 per cent, of these developed lepromatous leprosy prior to examination in 1946. Of 139 with a positive reaction 33, or 23.7 per cent, developed lepromatous leprosy within this period. It should be noted, however, that of those with a strong (3 plus) reaction a much smaller proportion developed lepromatous leprosy than of those with weak (1 plus) reactions. Nevertheless these findings demonstrate that the general assumption regarding the prognostic value of the test is by no means universally true.

Among 685 patients with tuberculoid leprosy tested, 592, or 86.4 per cent, had a positive Mitsuda, 79, or 11.5 per cent, a negative and 14, or 2 per cent, a doubtful reaction. Of the positives, 17, or 2.9 per cent, developed lepromatous leprosy; of the negatives 29, or 36.7 per cent, and of those with a doubtful reaction, only 1.

In some cases in both the uncharacteristic and tuberculoid types a change from a positive to a negative Mitsuda was observed, as well as a change from a negative to a positive. Among the former, transformation to the lepromatous type occurred in all except 1 patient. Of 12 changing from negative to positive there were 3 who developed lepromatous leprosy in spite of the change of the Mitsuda reaction to positive.

#### REFERENCES

1. DE SOUZA LIMA, LAURO and ALAYON, LECHEREN. On the pathologic significance of the noncharacteristic lesions (simple macular subtype). 5th Monograph in the Archives of Sanatorio Padre Bento.