MARKED INCREASE IN MITSUDA POSITIVITY IN LEPROMATOUS CASES

WITH REFERENCE TO CLINICAL FEATURES

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In two earlier papers ([16, 17]) our group reported on the results of lepromin tests made in 1954 on some 1,400 leprosy patients, stating that there was found a striking increase in the frequency of positive Mitsuda reactions in lepromatous leprosy—85.2 per cent in 1,041 cases under the Madrid criterion 14 days after injection. It was therefore suggested that the Mitsuda test was no longer applicable for the discrimination of leprosy types so long as the current criteria are employed.[1] Our observed positivity rate was so high that we were naturally disturbed by it. It appeared that the recent progress in chemotherapy might be the main cause of this change of situation with regard to the Mitsuda test.

More recently, in the autumn of 1957, we carried out another series of lepromin tests in nearly 200 cases, most of which had been in the former survey. The results were quite in accordance with the previous findings—an astonishing 84.2 per cent positive in 139 lepromatous cases with the 3 mm. limit 14 days after inoculation.

It has long been well established that the Mitsuda reaction is typically negative in lepromatous leprosy. Exception is to be made of some completely resorbed, "secondary neural" cases. Also of the condition called "acute infiltration" by Tajiri ([22]), "pseudo-exacerbation" by de Souza Lima ([20]), and "reversal reaction" by Wade ([24]); but in such exceptional cases the reactions are rather weak. On the other hand, certain South American workers—e.g., Basombrio *et al.* ([1]), Fiol *et al.* ([7]), Mom ([11]) and Schujman ([19])—have considered possible conversion of the reaction under sulfone therapy, but none has reported such striking results as ours. Recently, Mitsuda ([10]) seems to have noticed the phenomenon to some extent, stating that 104 out of 674 lepromatous cases converted to Mitsuda positive after four years of treatment with promin.

Needless to say, detailed clinical analyses of the individual cases is highly important in considering the results of the lepromin test, in the

[1]The Madrid congress ([9]) approved the 3 mm. lower limit of positivity (following Hayashi and the Second Pan-American Conference), whereas the WHO Expert Committee ([27]) recommended that positivity should start with measurements over 4 mm.

changed situation we have encountered. This is why we present this paper, in which are given the results of clinical analyses of the cases, particularly the lepromatous ones, concerned in our observations.

MATERIALS AND METHODS

Subjects.—Group 1: Clinical analyses were made of 840 out of some 1,400 patients surveyed in 1954. These cases had been accurately classified as 682 lepromatous and 158 nonlepromatous on the basis of history and the clinical picture; a majority of them had been examined bacteriologically, and histologic examinations had been made of some of them as the occasion demanded.

Group 2: Of the Group 1 cases, 177 were retested in 1957 and again analyzed clinically. These 177 cases comprised 139 lepromatous and 38 nonlepromatous ones. None of them showed conversion of type, from lepromatous to nonlepromatous or vice versa, after the lapse of these three years.

Classification of the cases.—To avoid complications and possible errors in the matter, we analyzed only the cases classifiable as lepromatous and nonlepromatous, purposely avoiding borderline, indeterminate, and doubtful cases.

Test antigen.—The Hayashi-Mitsuda lepromin was used entirely, but unavoidably not a single batch. The lot used in 1954 was prepared from pooled lepromas from several patients, while the lot used in 1957 was made of lepromas from a single patient.

Time of reading the reactions.—Because one of us (Fukuda [8]), had found that the Mitsuda reaction could be read at any time between 2 and 4 weeks after inoculation, the readings in both studies were all made after 14 days.

Clinical analyses.—We were most cautious in observing the skin lesions and the bacteriologic findings, carefully discriminating between lepromatous and nonlepromatous cases. The state or condition of the disease at the time were recorded carefully, including the bacteriologic findings. It would serve no particular purpose to go into details here, apart from indicating the grading of smears: (−), no bacilli; (±), a few hardly distinguishable acid-fast rods or granules; (1+), a very few bacilli in the whole specimen; (2+), a few bacilli in many fields; (3+), many bacilli with globi.

In designating the state of a case we employed the following three terms, which are usually used although there exists uncertainty and ambiguity in their meanings, as Wade [25] has pointed out. 1. Active or progressive: the disease vigorous, advancing; bacteriologically positive. 2. Stationary or arrested: neither active nor regressive, there still remaining more or less distinct skin lesions; sometimes bacteriologically positive, sometimes negative. 3. Resorbed or regressive: the disease process clearly regressive and residual, the lesions well resorbed; mostly bacteriologically negative, but sometimes weakly positive.

Erythema nodosum leprosum (ENL): It is widely recognized—e.g., Fernandez [6], Tachikawa [21]—that the Mitsuda reaction remains negative during ENL episodes, although there are a few authors—Carvalho [3], Nolasco [14]—who have seen conversion to positive in reactions. We did not exclude ENL cases from the analytical study, but they were not numerous. In the table + means manifest symptoms, and ± signifies cases with suggestive symptoms.

RESULTS

To avoid undue complexity in considering the clinical features with relation to the results of the Mitsuda test, the only features we employ

—as seen in the tables—are the skin lesions, the bacteriologic findings, and the condition with respect to ENL.

The new situation we have encountered may call for new criteria of positivity. We therefore give in the tables the results based on (*a*) the "Madrid criterion" of 3 mm., (*b*) the "WHO criterion" of more than 4 mm., and (*c*) the criterion of more than 7 mm. which was tentatively proposed in our previous report ([17]).

I. CLINICAL ANALYSES OF GROUP 1 CASES

1. *Lepromatous cases.*—Of the 682 lepromatous cases only 80, or 11.7 per cent, were negative by the Madrid criterion, while 602, or 88.3 per cent gave positive Mitsuda reactions. By the WHO criterion the positives were 542 or 70.6 per cent, and by our proposed criterion they were 104, or 15.3 per cent. These figures are shown in the last line of Table 1.

TABLE 1.—*Some clinical findings and the results of the Mitsuda reaction in 682 lepromatous cases examined in the 1954 survey.*

Clinical findings (graded)		No. of cases	Negative cases, Madrid criterion	Positive cases		
				Madrid criterion	WHO criterion	Proposed criterion[a]
Skin nodule	3+	7	3 (3.7%)	4 (0.7%)	4 (0.7%)	0 (0.0%)
	2+	23	0 (0.0%)	23 (3.8%)	19 (3.5%)	2 (1.9%)
	1+	73	7 (8.7%)	66 (11.0%)	61 (11.3%)	7 (6.7%)
	−	579	70 (87.5%)	509 (84.5%)	458 (84.5%)	95 (91.4%)
Infiltrated lesion	3+	42	4 (5.0%)	38 (6.3%)	22 (4.1%)	2 (1.9%)
	2+	179	26 (32.5%)	153 (25.4%)	140 (25.8%)	23 (22.1%)
	1+	376	48 (60.0%)	328 (54.5%)	300 (55.3%)	59 (56.8%)
	−	85	2 (2.5%)	83 (13.8%)	80 (14.8%)	20 (19.2%)
Leprosy bacilli in lesions	3+	35	8 (12.3%)	27 (4.9%)	27 (5.0%)	5 (4.8%)
	2+	96	11 (16.9%)	85 (15.4%)	81 (14.9%)	10 (9.6%)
	1+	292	28 (43.0%)	264 (47.8%)	260 (48.0%)	44 (42.3%)
	±	9	1 (1.5%)	8 (1.5%)	8 (1.5%)	4 (4.8%)
	−	185	17 (26.1%)	168 (30.4%)	166 (30.6%)	40 (38.5%)
	?[b]	65	15 —	50 —	0 —	0 —
Erythema nodosum leprosum	+	38	8 (10.0%)	30 (5.0%)	23 (4.2%)	3 (2.9%)
	±	11	4 (5.0%)	7 (1.2%)	5 (0.9%)	1 (1.0%)
	—	633	68 (85.0%)	565 (93.8%)	514 (94.9%)	100 (96.1%)
Total		682	80 (11.7%)	602 (88.3%)	542 (79.6%)	104 (15.3%)

a More than 7 mm. for positive reading.
b Query signifies examination not made.

It was striking that in one-third of the cases whose reactions were positive under either the Madrid or the WHO criterion the disease process was more or less marked, and that one-fifth of those cases were 2+ or 3+ bacteriologically positive (Table 1). It was also noteworthy that more than one-third of the Madrid-positive cases were of the so-called regressive group, and one-twentieth were in the active state of the disease,

as shown in Table 2. On the other hand, the negative cases were not necessarily active ones, and one-third were bacteriologically negative.

TABLE 2.—*Clinical and bacteriological status and the results of the Mitsuda reaction in 682 lepromatous cases examined in the 1954 survey.*

Clinical condition	Bacilli lesions	No. of cases	Negative cases, Madrid criterion	Positive cases		
				Madrid criterion	WHO criterion	Proposed criterion[a]
Resorbed or regressive	1+	78	3 (23.1%)	75 (34.3%)	75 (34.6%)	22 (34.9%)
	±	6	0 (0.0%)	6 (2.7%)	6 (2.8%)	5 (8.0%)
	—	148	10 (76.9%)	138 (63.0%)	136 (62.6%)	36 (57.1%)
	−/+	232	13 (100%)	219 (100%)	217 (100%)	63 (100%)
	?[b]	18	1 —	17 (0.0%)	0 (0.0%)	0 (0.0%)
Stationary or arrested	1+/2+	297	29 (78.4%)	268 (89.4%)	266 (89.2%)	35 (89.7%)
	±	3	1 (2.7%)	2 (0.6%)	2 (0.7%)	0 (0.0%)
	• −	37	7 (18.9%)	30 (10.0%)	30 (10.1%)	4 (10.3%)
	−/+	337	37 (100%)	300 (100%)	298 (100%)	39 (100%)
	?[b]	47	14 (0.0%)	33 (0.0%)	0 (0.0%)	0 (0.0%)
Active or progressive	1+/3+	48	15	33	27	2
Total		682	80	602	542	104

[a] More than 7 mm. for positive reading.
[b] Query means not examined.

The frequency distribution of the reaction sizes in the bacteriologically negative and bacteriologically positive cases is shown in Table 3. The number of cases is 608, after deducting the 65 that were not examined

TABLE 3.—*Frequency distribution of reaction sizes in the bacillus-positive and negative cases surveyed in 1954.*

Reaction size, (mm.)	Bacillus-negative cases	Bacillus-positive cases	Total
0	17 (9.1%)	42 (9.9%)	59 (9.7%)
2	— —	5 (1.1%)	5 (0.8%)
3	2 (1.0%)	8 (1.8%)	10 (1.6%)
4	33 (17.8%)	97 (22.9%)	130 (21.3%)
5	52 (28.1%)	130 (30.7%)	182 (29.9%)
6	41 (22.1%)	82 (19.3%)	123 (20.2%)
7	18 (9.7%)	36 (8.5%)	54 (8.8%)
8	12 (6.4%)	16 (3.7%)	28 (4.6%)
9	3 (1.6%)	3 (0.7%)	6 (0.9%)
10	3 (1.6%)	1 (0.2%)	4 (0.6%)
11	2 (1.0%)	3 (0.7%)	5 (0.8%)
14	1 (0.5%)	—	1 (0.16%)
15	1 (0.5%)	—	1 (0.16%)
Total	185 (100%) (30.5%)	423 (100%) (69.5%)	608 (100%) (0.16%)

and the 9 dubious (±) ones. The differences between the two groups are not great, although among the bacillus-positive cases there were, proportionately, somewhat more small reactions and fewer large ones.

2. *Nonlepromatous cases.*—All of the 158 nonlepromatous cases gave positive Mitsuda reactions under either the Madrid or the WHO criterion. Clinically, 11 of these cases were tuberculoid, 60 had hypo- or dyschromic or other residual macules, and the remaining 87 were of the so-called "pure neural" form without skin lesions. Bacilli were demonstrated in none of the macular lesions.

II. CLINICAL ANALYSES OF GROUP 2 CASES

The 177 cases re-examined in the 1957 inquiry have been studied with respect to changes in the results of the lepromin test and in the clinical pictures occurring during the three-year interval.

1. *Lepromatous cases.*—The results of the clinical analyses of the 139 lepromatous cases, with the results of the lepromin tests by the three criteria under consideration, are shown in Table 4.

TABLE 4.—*Some clinical findings in the Mitsuda positive cases among 139 lepromatous patients, tested twice in 1954 and 1957.*

Clinical findings (graded)		Results obtained in 1954 survey — Number of positive cases			Results obtained in 1957 survey — Number of positive cases		
		Madrid criterion	WHO criterion	Proposed criterion	Madrid criterion	WHO criterion	Proposed criterion
Skin nodule	3+	2 (1.7%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	2+	4 (3.4%)	4 (3.7%)	1 (6.3%)	2 (1.7%)	2 (2.2%)	0 (0.0%)
	1+	7 (5.9%)	6 (5.5%)	0 (0.0%)	3 (2.5%)	0 (0.0%)	0 (0.0%)
	−	105 (89.0%)	97 (89.0%)	15 (93.7%)	115 (95.8%)	88 (97.8%)	10 (100%)
Infiltrated lesion	3+	7 (5.9%)	7 (6.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	2+	21 (17.8%)	20 (18.4%)	3 (18.7%)	16 (13.3%)	10 (11.1%)	0 (0.0%)
	1+	80 (67.8%)	72 (66.0%)	11 (68.8%)	83 (69.2%)	62 (68.9%)	3 (30.0%)
	−	10 (8.5%)	10 (9.2%)	2 (12.5%)	21 (17.5%)	18 (20.0%)	7 (70.0%)
Leprosy bacilli in lesions	3+	8 (6.8%)	8 (7.3%)	1 (6.3%)	6 (5.0%)	5 (5.6%)	0 (0.0%)
	2+	9 (7.6%)	8 (7.3%)	0 (0.0%)	7 (5.8%)	3 (3.3%)	0 (0.0%)
	1+	59 (50.0%)	54 (49.6%)	9 (56.2%)	38 (31.7%)	26 (28.9%)	2 (20.0%)
	±	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.7%)	2 (2.2%)	0 (0.0%)
	−	42 (35.6%)	39 (35.8%)	6 (37.5%)	67 (55.8%)	54 (60.0%)	8 (80.0%)
Erythema nodosum leprosum	+	12 (10.2%)	11 (10.1%)	0 (0.0%)	5 (4.2%)	3 (3.3%)	0 (0.0%)
	±	2 (1.7%)	1 (0.9%)	0 (0.0%)	5 (4.2%)	4 (4.4%)	0 (0.0%)
	−	104 (88.1%)	97 (89.0%)	16 (100%)	110 (91.6%)	83 (92.3%)	10 (100%)
Total		118 (84.9%)	109 (78.4%)	16 (15.1%)	120 (86.3%)	90 (64.7%)	10 (7.2%)

The positive rates by the Madrid criterion were strikingly high on both occasions and practically the same, 84.9 and 86.3 per cent; on the WHO criterion the corresponding figures were 78.4 and 64.7 per cent. It is evident that not a few positive Mitsuda reactions were found among manifest and active cases, and bacteriologically positive ones. It is also

evident that on the whole the sizes of the reactions had decreased in the interval, not only from the WHO figures cited but because the positives based on our proposed 7 mm. minimum decreased a full one-half.[2]

Needless to say, the readings of the Mitsuda reaction in the two surveys did not necessarily accord with one another, even in the same individuals. On the basis of the Madrid criterion, 7 cases were negative and 106 cases were positive on both occasions, while 14 cases showed conversion from negative to positive and 12 from positive to negative. Thus, no less than four-fifths of the cases were found qualitatively unchanged in their reactivity after three years. Clinical analyses showed that there had been more or less improvement of the disease processes of the patients.

2. *Nonlepromatous cases.*—All of the 38 nonlepromatous cases were Mitsuda positive with both the Madrid and WHO criteria, in both surveys. There had been more or less marked improvement during these years. Thus, in 1954 there were 4 manifest tuberculoid cases, 14 residual tuberculoid cases, and 20 pure neural cases, whereas in 1957 there were 15 cases with residual lesions, 23 pure neural cases, and no active tuberculoid case.

III. RELATION OF SULFONE TREATMENT AND THE MITSUDA REACTION

The relationship between lepromin positivity (Madrid criterion) and treatment has been examined in detail, with respect to both the total amount of the drug received and the duration of the treatment, for 376 lepromatous cases. Treatment had been almost exclusively by injections of promin in 30 per cent solution. Only a small group of 15 cases which had received no treatment was available to serve as a control. In neither of these analyses were the findings at all striking.

Regarding total dosage, the original tabulation shows the following percentages of Mitsuda positives: 80.0, 82.3, 81.0, 80.7, 84.0, 93.1, 86.4, and 93.7, respectively, for the following dosage groups: none (15 cases), under 250 cc. (34 cases), 250-500 cc. (37 cases), 500-1000 cc. (52 cases), 1000-2000 cc. (113 cases), 2000-3000 cc. (87 cases), 3000-4000 cc. (37 cases) and over 4000 cc. (16 cases). Because of the fluctuations, which are presumably ascribable to the small sizes of the dosage groups, the three groups on each side of the largest (i.e., 1000-2000 cc.) one are consolidated in Table 5. Thus, the patients who had received less than 1000 cc. of promin solution were 81.3 per cent positive, while those who had received more than 2000 cc. were 91.4 per cent positive. The results in the untreated control group will be referred to in the discussion.

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[2]Whether or not this difference between the degrees of reactions on the two occasions may have been due, wholly or in part, to a difference in the two lots of lepromin (the first one pooled, the second one not) it is of course impossible to say.

The data obtained by an equally detailed analysis by duration of treatment were no more instructive. For example, the 1-2 years group had exactly the same proportion of Mitsuda positives as the 3-4 years group. With some consolidation, the percentages are: no treatment, 15 cases,

TABLE 5.—*Relationship between the results of the Mitsuda reaction (Madrid criterion) and total dosage of 30 per cent promin solution.*

Mitsuda reaction	Clinical status	Total dosage (cc. of 30% solution)				Total
		None	Less than 1000	1000-2000	More than 2000	
Positive	Progressive	2 (10.5%)	8 (42.1%)	5 (26.3%)	4 (21.1%)	19 (100%)
	Stationary	1 (0.5%)	49 (26.8%)	61 (33.3%)	72 (39.4%)	183 (100%)
	Regressive	9 (6.8%)	43 (32.3%)	29 (21.8%)	52 (39.2%)	133 (100%)
		12 (3.6%)	100 (29.8%)	95 (28.4%)	128 (38.2%)	335 (100%)
Negative	Progressive	0 (0.0%)	6 (50.0%)	4 (33.3%)	2 (16.7%)	12 (100%)
	Stationary	2 (6.1%)	14 (42.4%)	10 (30.3%)	7 (21.2%)	33 (100%)
	Regressive	1 (9.1%)	3 (27.3%)	4 (36.4%)	3 (27.3%)	11 (100%)
		3 (5.4%)	23 (41.1%)	18 (32.1%)	12 (21.4%)	56 (100%)
	Total	15 (3.8%)	123 (31.5%)	113 (28.9%)	140 (35.8%)	391 (100%)
Rate of positive cases separated		(80.0%)	(81.3%)	(84.0%)	(91.4%)	(85.6%)

80.0; less than 6 months, 44 cases, 79.5; 6 months to 2 years, 69 cases, 86.9; 2-4 years, 105 cases, 88.7; more than 4 years, 158 cases, 85.5. An influence, although not a striking one, of duration of treatment is suggested.

DISCUSSION

Since F. Hayashi established the Mitsuda test, it has become widely used as one of the most helpful measures for distinguishing the forms of leprosy. The essential feature of the test is that it usually, and typically, gives negative results in distinctly lepromatous leprosy,—and that is often spoken of as its sole specific feature. Consequently, our findings in recent surveys in Japan which for the first time demonstrated an astonishingly large proportion of Mitsuda-positive lepromatous cases—about 85 per cent under either the Madrid or the WHO criterion—caused us great confusion and disturbance. The findings of our first survey, in 1954, seemed hardly acceptable. Because no leprosy workers in any part of the world except Japan had reported such results, we hesitated to publish our findings. However, we obtained almost the same results in 1957 on retesting—with a different batch of the Hayashi-Mitsuda lepromin—a group of the 1954 patients. Hence the present report.

In the meantime Moriya, who once ([12]) recorded positive Mitsuda reactions to regular lepromin in typical lepromatous patients, has recently ([13]) reported the following results: Of 640 lepromatous cases, 32.2 per

cent showed no reaction, in 35.8 per cent the reactions measured 1-4 mm., in 18.4 per cent 5-6 mm., and in 13.6 per cent more than 7 mm. Practically one-third of these cases were therefore positive by the WHO criterion. According to the 1955 survey of 6,981 cases headed up by Yanagisawa ([28, 29]), the positive late reactions with the Hayashi-Mitsuda antigen were: in lepromatous leprosy, 15 per cent; neural leprosy, 69 per cent; and macular leprosy, 76 per cent. In both instances, however, the method of reading the reactions deviated far from the ordinary method established internationally. They measured the size of the redness, not of the infiltration, as seen after 14 days, calling 0-4 mm. negative, 5-6 mm. doubtful, and more than 7 mm. positive.[3]

This method of measuring was similar to our so-called "spot method" ([16]), which we once suggested in place of the ordinary method of measuring the infiltration. We had found that the easily visualized brownish-red spot almost always coincides well with the infiltration in lepromatous cases. In one-quarter of the nonlepromatous cases tested the "spot" was larger than the infiltration.

After our first amazing findings we scrutinized the tested cases clinically, and confirmed the finding that many distinctly lepromatous cases with bacillus-positive skin lesions, and many in the regressive state of the disease, had given positive Mitsuda reactions. Some of the interesting findings are to be seen in Table 1. Only one-tenth of the 30 cases with the larger (2+ and 3+) skin nodules were Mitsuda negative, and only one-eighth of the 579 cases without nodules. Equally low negative rates were found in the "infiltrated lesion" group. Negative results were obtained in only one-sixth of the 131 more strongly bacillus-positive cases, and one-tenth of the 185 bacillus-negative ones.

Comparing the frequency distribution of reaction sizes of the bacteriologically positive and negative lepromatous cases (Table 3), no conspicuous difference between the two groups was found, but the bacteriologically positive cases had, proportionately, somewhat more small reactions and fewer large ones. The figures tabulated average 5.3 mm. for the bacteriologically positive cases, and 5.8 mm. for the negatives, not a very great difference.

As to the relationship between the status of the disease process and the results of the test, the following were the main items: 68.7 per cent of the 48 progressive cases, 86.8 per cent of the 384 stationary cases, and 94.3 per cent of the 250 regressive cases were Mitsuda positive (Table 2). Nearly the same could be said of the results obtained in 1957 (Table 4). In short, even among the cases with manifest lesions, bacillus-positive and active, the Mitsuda positives were much more numerous than the negatives.

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[3]0-4 mm. signifies 0-4.9 mm; 5-6 mm. signifies 5-6.9 mm; and more than 7 means the lower limit of positivity.

Because of these results it must be emphasized that the number or severity of the skin lesions, or the bacteriologic findings, or the status of the disease process, did not influence the results as much as was expected. Nevertheless, there was a tendency for the reactions to be weaker in the more active cases, and stronger in the more regressive ones. Furthermore, 79.1 per cent of the cases showing the ENL reaction were Mitsuda positive by the Madrid criterion, contrary to the existing opinion that the Mitsuda reaction is negative during the episode.

As is generally known, the negative Mitsuda reaction in lepromatous leprosy may often convert to positive when the disease process is completely suppressed and the lesions are fully resorbed (i.e., in the so-called "secondary neural" cases). Another condition in which the reaction may convert is Tajiri's "acute infiltration," or de Souza Lima's "pseudoexacerbation," a "tuberculoid-like reaction in lepromatous leprosy" for which Wade has proposed the term "reversal reaction." The phenomenon is very interesting, but it is complicated and not yet fully made clear; it appears to be closely associated with treatment, particularly sulfone treatment. Tajiri found that in his cases the Mitsuda reaction was likely to convert to weak positive, whereas de Souza Lima reported that in his cases it remained negative. The case of Davey ([4]) became strongly positive when it changed from lepromatous to tuberculoid.

It is not always so easy to discriminate reversal reaction cases from borderline cases ([23, 26]), in which the Mitsuda reaction is said to be generally negative. Rodriguez ([15]) has said that in his experience it is the borderline case which, under sulfone treatment, is most likely to undergo the reversal reaction ("pseudoexacerbation").

In addition, it must be taken into account that the indeterminate variety of cases, in which the Mitsuda reaction is often doubtful or weekly positive, can be one of the sources of obscurity with respect to the Mitsuda reaction. Accurate discrimination of the indeterminate cases from regressed and residual lepromatous or nonlepromatous cases is sometimes not simple.

Thus it is that we should be most prudent and careful in selecting cases for the study of the lepromin reaction. It was for this reason that in our surveys we confined ourselves to cases that were distinctly lepromatous on the one hand and nonlepromatous leprosy on the other hand, not excluding lepromatous cases in ENL reaction. In certain dubious cases histologic examinations were made, for it has often been found—e.g., by S. N. Chatterjee ([2]) and Sato ([18])—that in borderline cases both lepromatous and tuberculoid changes may be found sometimes even in the same section. Since the situation is so, it would be ideal to make histologic examinations of all cases to be tested, but that would hardly be possible in such a survey as ours.

What is the reason for the phenomenally high positive rates in lepromatous cases found in our survey? We are strongly inclined to ascribe

it to the sulfone therapy, which has been so brilliantly successful that it has become difficult to find patients with the highly advanced and destructive processes that used to be so frequent in leprosaria, or to obtain sufficient florid lepromas for the preparation of lepromin and other purposes. On the other hand, clinical varieties or reactional cases with unusual features, such as the coexistence of lepromatous and tuberculoid lesions in the same case, have now become numerous. These confusing features of the disease process are nothing but expressions of unstable states of immunity, or power of resistance against the leprosy infection, namely, partially balanced or discordant states of various grades between resistance and the bacillary invasion derived from effects of the new drugs.

Lepromatous leprosy is the condition in which the power of resistance is suppressed by the bacillary invasion, and tuberculoid leprosy is the one in which the former dominates over the latter; these two are in an immunologically balanced state at the extreme ends of the "spectrum" (polar positions). From this point of view, borderline and indeterminate cases, together with clinical varieties such as reversal reaction cases in lepromatous leprosy, are in various states of unbalance and different from one another qualitatively and quantitatively.

It is certain that considerable changes have been brought about in the immunobiologic state of lepromatous patients with the decrease of the disease processes. The power of resistance of the individuals has been more or less strongly enhanced, ultimately resulting in dubious or persistent conversion of the Mitsuda reaction from negative to positive. Fukuda [8] studied the histology of the infiltration at the site of lepromin injection in 8 cases, finding that tuberculoid structure may occur in the Mitsuda reaction in lepromatous leprosy, even in bacillus-positive cases, as is generally supposed to occur only in nonlepromatous leprosy.

Conversion can be seen before the disappearance of skin lesions in many cases, and also sometimes even in cases that show more or less active, bacillus-positive lesions. On the other hand, there are found not a few individuals in whom it is difficult to raise the power of resistance despite treatment, even when the disease is regressive. This persistent negativity may be based simply on a constitutional difficulty of producing immunity.

The correlation of the results of the lepromin test with the amount of the drug given, and with the duration of treatment, tends to support this view to a certain extent, although the differences were not striking. A disconcerting problem is presented by the fact that of the control group of 15 untreated cases, no less than 12 (2 of them incipient cases) gave positive reactions, the reaction lesions varying from 3 to 10 mm. in size. This phase of the inquiry should be extended to a much larger number of such cases to permit conclusions to be reached.

According to Doull's report [5] of drug evaluation studies on a large

scale, 154 lepromatous patients of the Aisei-en leprosarium at Nagashima, who before treatment had given negative or doubtful Mitsuda reactions (WHO criterion), 25 were positive after 32 weeks of treatment. On the other hand, 13 cases that were 1+ positive before treatment 10 became negative. Similar changes were seen, in both directions, in a few cases without treatment during the 32-week period.

It has been generally accepted until lately that the negative Mitsuda reaction in lepromatous leprosy is not readily converted to positive, unless the lesions are almost completely resorbed and cleared up. Nowadays, however, we often meet with such cases. The reaction is not only convertible from negative to positive, but also from positive to negative. In our 139 retested lepromatous cases, conversion to positive in three years occurred in 14, or 10 per cent, while the opposite conversion, from positive to negative, occurred in 12 cases, or 8.6 per cent. This suggests that instability of reaction is nothing but an expression of the unsettledness in the immunobiologic state of a patient and must be associated with state of the disease process, and therefore with treatment.

Be the explanation what it may, there is no room for doubt about the finding of high rates of Mitsuda positivity in the cases that we have surveyed. Besides the striking effects of modern chemotherapeutics, a factor that also has to be considered is the improved living conditions since World War II; and, too, ethnologic and geographic factors should not be ignored. World-wide surveys of this matter of lepromin reactivity of lepromatous cases should be made.

The Mitsuda test has hitherto been one of the most useful procedures for discriminating leprosy forms, but now it would seem to have become nearly useless for the purpose so long as the Madrid or the WHO criterion is employed. We have therefore proposed that more than 7 mm. in the size of the reaction infiltration be used as the basis of positive readings. On that basis, as shown in Table 1, the positive rate in the 682 lepromatous cases of the 1954 survey decreases sharply from 88.3 (Madrid) or 72.4 (WHO) to 15.2 per cent, while in the 158 nonlepromatous cases—all positive by the usual criteria—the decrease is only to 86.7 per cent. Other conspicuous differences between the rates in lepromatous cases with the ordinary criteria and the proposed one are to be seen in Tables 1 and 2.

Judging from these results, the proposed criterion would seem to be applicable to the classification of cases, although this is not a matter to be decided hastily. No matter how suitable a criterion may be, there will come a time when it is necessary to correct it again in accordance with changes in the situation, because reactivity to lepromin may be more and more enhanced with further progress in chemotherapeutics. The real value of the Mitsuda test lies in the fact that intensity of the reaction reveals the grade of the power of resistance to the leprosy infection in the individual, as things actually are. If we make good use of this value

in the study of leprosy, the usefulness of the Mitsuda reaction must increase still more.

SUMMARY

1. The nominally high positive rates of the Mitsuda reaction in cases of lepromatous leprosy, 80 per cent and more, were observed in two surveys, made in 1954 and 1957. Clinical analyses have been made of 840 out of some 1,400 cases surveyed in 1954, and of 177 cases that were examined on both occasions.

2. The main cause of the phenomenon is believed to be marked enhancement of the power of resistance against the leprosy infection resulting from modern chemotherapy.

3. It has now become difficult to apply the Mitsuda reaction in the classification of leprosy, so long as either the Madrid or the WHO criterion of positivity is employed. In view of the findings reported, it is proposed that over 7 mm. be made the limit for positive readings.

4. The position of the Mitsuda test in the study of leprosy may be said to be ever more important, because the reaction expresses the state of resistance of the organism against the infection under existing conditions.

RESUMEN

1. Las tasas nominalmente altas en positividad de la reacción de Mitsuda en casos de lepra lepromatosa, 80 por ciento y más, fueron observadas en dos encuestas, verificadas en 1954 y 1957. Se han llevado a cabo análisis de 840 casos tomados de unos 1,400 considerados en 1954 y de 177 que fueron estudiados en ambas ocasiones.

2. La principal causa del fenómeno parece ser el acentuado aumento de la facultad de resistencia a la infección leprosa, proveniente de la quimioterapia moderna.

3. Ya se ha vuelto difícil aplicar la reacción de Mitsuda a la clasificación de la lepra, mientras se emplee la pauta de positividad de Madrid o de la OMS. A la luz de los hallazgos presentados, se propone tomar una cifra de más de 7 mm. como límite de las lecturas positivas.

4. Cabe decir que el puesto de la reacción de Mitsuda en el estudio de la lepra es cada vez más importante, porque expresa el estado de la resistencia del organismo contra la infección en las condiciones existentes.

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REFERENCES

1. Basombrio, G., Gatti, J. C., Cardama, J. E. and Colombo, C. V. Modificaciones de la lepromino reacción. Internat. J. Leprosy **18** (1950) 481-486.
2. Chatterjee, S. N. Persistent problems of classification. Internat. J. Leprosy **23** (1955) 451-454 (correspondence).
3. De Carvalho, J. Correa. Reacção leprotica e allergia. Rev. brasileira Leprol. **4** (1936) Spec. No. pp. 27-35.

4. DAVEY, T. F. The treatment of leprosy with sulphetrone. Leprosy Rev. **19** (1948) 55-61 (cited).
5. DOULL, J. A. Clinical evaluation studies in lepromatous leprosy. First series: Diasone (Diamidin), 4,4′-diaminodiphenyl sulfone, dihydrostreptomycin. Internat. J. Leprosy **22** (1954) 377-402.
6. FERNANDEZ, J. M. M. La réaction lépreuse et l'érythème noueux. Bull. Soc. française Derm. et Syph. **45** (1938) 1271-1274.
7. FIOL, H., JONQUIERES, E. D. L., BRUSCO, C., MELAMED, A. and FIRPO, C. Tratamiento de la lepra con promin (promanida). Rev. argentina Dermatosif. **31** (1947) 531-537.
8. FUKUDA, M. Contribution to the study of the lepromin reaction. Rescrutinizing of the method and the time for reading of the late reaction. Sci. Rep. Res. Inst. Tohoku Univ., Series C, **8** (1958) (to be published).
9. [MADRID CONGRESS] Technical resolutions. Committee on Immunology. Internat. J. Leprosy **21** (1953) 527-535; *also* Mem. VI Congr. Internac. Leprol. 1953; Madrid, 1954, pp. 96-104.
10. MITSUDA, K. Discussion of "Reexamination of the lepromin (Mitsuda) reaction," symposium at the 29th General Meeting of the Japanese Leprosy Association, Sendai, May, 1956. La Lepro **25** (1956) 208 (in Japanese).
11. MOM, A. M. Quimioterapia de la lepra con promin. Prensa Méd. argentina **33** (1946) 2390-2404.
12. MORIYA, M. Studies on the Mitsuda reaction. La Lepro **21** (1952) 75; **22** (1953) 196; **23** (1954) 233 (abstracts, in Japanese).
13. MORIYA, M. Reexamination of lepromin (Mitsuda) reaction. IV. Relationship between the lepromin reaction and clinical aspects. La Lepro **25** (1956) 207 (abstract, in Japanese).
14. NOLASCO, J. O. The lepromin test in lepra reaction. Internat. J. Leprosy **8** (1940) 151-158.
15. RODRIGUEZ, J. N. "Pseudoexacerbation" and "borderline" cases. Internat. J. Leprosy **18** (1950) 95 (correspondence).
16. SATO, S., FUKUDA, M., KAMIKAWA, Y., MAJIMA, S., ABE, H. and TAKEDA, M. Relationship between the sizes of the brownish red spot and infiltrated area at the site of inoculation in the late lepromin reaction; observation in some 1,400 patients. Sci. Rep. Res. Inst. Tohoku Univ., Series C, **8** (1957) 83-90.
17. SATO, S., FUKUDA, M., KAMIKAWA, Y., MAJIMA, S., ABE, H. and TAKEDA, M. Rescrutinizing of lepromin reaction, in particular, of Mitsuda's reaction. Sci. Rep. Res. Inst. Tohoku Univ., Series C, **7** (1957) 335-349.
18. SATO, S. Classification of leprosy. Symposium at the 28th General Meeting of the Japanese Leprosy Association, Kyoto, April, 1955 (abstract, in Japanese).
19. SCHUJMAN, S. Estudio evolutivo del estado inmunológico en los casos lepromatosos beneficiados con diversos medicamentos antileprosos (chaulmoogra y sulfonas). Bol. Soc. cubana Derm. y Sif. **9** (1952) 43-48; *also* Mem. III Conf. Panamericana Leprol., Buenos Aires 1951, Vol. 1, 1953, pp. 195-198.
20. DE SOUZA LIMA, L. Estados reacionais da lepra "pseudo exacerbação." Mem. III Conf. Panamericana Leprol., Buenos Aires 1951, Vol. 1, 1953, pp. 184-188; *reprinted in translation,* Internat. J. Leprosy **23** (1955) 423-434.
21. TACHIKAWA, N. On erythema nodosum leprosum. The first report. La Lepro **13** (1942) 251-270 (in Japanese; English abstract, suppl. p. 19).
22. TAJIRI, I. The "acute infiltration" reaction of lepromatous leprosy. Internat. J. Leprosy **23** (1955) 370-384.

23. WADE, H. W. Relapsed and borderline cases of tuberculoid leprosy. Leprosy Rev. **12** (1941) 3-17.

24. WADE, H. W. A tuberculoid-like reaction in lepromatous leprosy; a reactional reversal phenomenon. Internat. J. Leprosy **23** (1955) 443-446 (editorial).

25. WADE, H. W. What is an "active" case of leprosy? Internat. J. Leprosy **25** (1957) 52-53 (editorial).

26. WADE, H. W. and RODRIGUEZ, J. N. Borderline tuberculoid leprosy. Internat. J. Leprosy **8** (1940) 307-332.

27. WORLD HEALTH ORGANIZATION. Expert Committee on Leprosy; First Report. World Hlth. Org. Tech. Rep. Ser. No. 71, 1953, 28 pp.

28. YANAGISAWA, K. Fundamental aspect on the classification of leprosy 2. The immunological aspect. Symposium at the 30th General Meeting of the Japanese Leprosy Association, Nagoya, March, 1957. La Lepro **26** (1957) 194-195 (abstract, in Japanese).

29. YANAGISAWA, K., ASAMI, N., MAEDA, M., SAITO, T., SONE, M., HAYASHI, Y., YOSHIE, Y., TAJIRI, I., INABA, T., TACHIKAWA, N., TAKASHIMA, S., ISHIWARA, S., BABA, S., NAKAMURA, Y., KOJO, H., YAJIMA, R., GOTO, S., KOBAYASHI, S., HONJO, K., TERAKADO, S., NOGAMI, H., MITSUDA, K., MIYATA, T., SAKURAI, H., SHIONUMA, E., ITO, M., NAWA, C., NAGATA, M., YOKOTA, T., SAIKAWA, K., SUZUKI, M., HIBI, H., JINGU, R., NAMBA, M., and TODA, E. Studies on the lepromin test. (The second report.) Basic observations for the settlement of criteria for reading the reactions. La Lepro **24** (1955) Selected Articles Suppl. pp. 35-46.