

Prognostic considerations based on a study of 38 hanseniasis patients submitted to Mitsuda tests 23 to 35 years previously

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ABSTRACT — Out of 2.775 hanseniasis patients Mitsuda tested by one of the authors (R) from 1933 to 1947, 38 were re-examined in 1970/1971. 28 had been treated regularly, 6 did not receive sulfones. Improvement or disappearance of dermatological lesions occurred in 31 (81.5%), independently of reactivity. All eleven bacteriologically positive out of 19 Mitsuda negative patients became bacteriologically negative, which is partly attributed to sulfones. One treated bacillary negative patient became positive. **28 (76,3%) were neurologically aggravated, independently of reactivity but more evidently among the stronger reactors.** As regards classification, all initially "tuberculoid", "Virchowian" and "dimorphous" patients continued in their types or group, but only 7 (41.2%) out of the 17 initially "indetermined" remained so. Four (23.5%) two Mitsuda+ +, two+ changed to reactional tuberculoid, 6 (35,3%) (3 Mitsuda — 2+ and 1+ +) changed to the Virchowian type. These developments according to reactivity confirm the pathogenetic theory postulated in 1937 by one of the authors (R). Mitsuda reactivity remained generally unchanged, rarely increased or decreased. **The good prognostic value of the strong Mitsuda test is generally confirmed, but only as regards classification, bacillation and dermatological lesions — not from the neurological and social viewpoints.**

Key words: Hanseniasis. Mitsuda test. Prognosis. Immunology in hanseniasis.

From the year 1933 to 1947, 2.775 hanseniasis patients were skin tested with Mitsuda's antigen by one of the authors (R). It was thought that a study of the development of the disease and reactivity many years after the tests were made, would

contribute to a better knowledge of their prognostic value.

In the years 1970-1971, forty-one of those patients were located at out-patients clinics of the city of S. Paulo, Brazil, but only 38 were willing to cooperate.

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MATERIAL AND METHODS

All of the 38 patients were Caucasoid, their ages, in 1970-1971, varying between 36 to 85 years (median: 57,5). 24 were males, 14 females. The approximate duration of the disease was between 23 and 51 years (median: 28). The antigen was prepared especially for this study, according to the classic Mitsuda-Hayashi's technique, as used in the first tests, and the readings were made in accordance with the system used in the first tests, which practically does not differ from the recommendations of the 7th. International Leprosy Congress (Tokyo, 1958). The interval between the first and last tests varied from 23 to 35 years, the longest period of observation of this kind.

Pathological examinations, to be discussed in a second article, were made of all new tests.

The clinical and bacteriological situation at the time of the first tests were appraised both by the contemporaneous records of the hospital or clinic, and by the personal records of one of the authors (R). The data collected were sufficient to replace the former classification of types of disease with the current one. Information about sulfone treatment was also collected from those records.

For tabulation and appraisal of the development of the clinical signals a system of pluses, from + to + + +, was devised according to their number and severity. Only the initial (1933-1947) and the last (1970-1971) situations were tabulated. Reactions and fluctuations of the clinical and bacteriological aspects in the interval were not taken into account in this work. Due to the scarcity of observations, statistical methods were not applied.

RESULTS AND COMMENTS

In Table I all the data of the initial and last situations are registered. Patients were placed in column A according to growing grade of Mitsuda reactivity, from negative (n.° 1 to n° 19), through + (n.° 20 to

n.° 28) to + + and + + + (n.° 29 to n.° 38).

Bacteriological development. The antagonism between Mitsuda positivity and bacillation is already seen from the first tests (columns B, C, D). Only once (n.° 21) a slight degree of bacillation was seen in a weakly positive (+) Mitsuda test. All other bacillary cases were Mitsuda negative and, with one exception (n.° 4), all became negative at the end of the period (cols. I and J). This favorable evolution may be credited to sulfone therapy, even if irregularly administered (n.°s 7, 13 and 19). However, one Mitsuda negative indiffer-entiated (indetermined) patient (n.° 4) became Virchowian despite regular treatment. All other bacteriologically negative patients remained so, whether Mitsuda positive or negative.

Mitsuda reactivity. a) Out of 19 patients originally Mitsuda-negative, 17 (89,5%) remained so. The other 2 (10,5%) became weakly positive (+). Considering the variety of stimuli occurred during the long period, the relatively fixed Mitsuda-negativity is an argument favorable to the theory of the "Anergic Margin" (18, 19, 20, 22), now also known as "constitutional incapacity to form granuloma", "defect of cell-mediated immunity", etc. Out of the 17 Mitsuda-negative patients who remained so, 15 (88,2%) had received sulfone regularly, a fact that does not confirm the Mitsuda positivation by sulfone therapy advocated by some authors (1, 2, 6, 10, 12, 24, 25).

b) Out of 9 weak (+) Mitsuda-reactors, 4 remained so, 4 turned to strong-reactors (3 ++ and 1 +++). One patient became Mitsuda negative.

c) Out of the 8 Mitsuda ++ tests, one remained so, 3 became + + +, 2 decreased to + and 2 to Mitsuda negative. The absolute stability of the strong Mitsuda reactivity was not confirmed in this small group.

d) Out of the 2 Mitsuda +++ patients, 1 remained so, the other had his reactivity decreased to + +.

Dermatological lesions. The general dermatological improvement is seen comparing columns E and K. In 31 out of the 38 patients (81,5%) the lesions improved or clinically disappeared. The improvement is more evident among the Mitsuda-positive patients (n.° 20 to n.° 38). A comparison between columns C-D-E, on one side, I-J-K on the other (n.° 1 to n.° 21) shows that the dermatological improvement was much less evident than the bacillary. This improvement of Mitsuda negative patients might be attributed to sulfone therapy, even if irregularly administered (n.° 13 and n.° 19). Dermatological improvement also occurred in a non-treated reactional tuberculoid patient (n.° 20).

Neurological lesions. A serious situation is seen comparing columns F and L, i.e., the initial and last signals of neurological involvement. 29 out of the 38 patients (76,3%) developed neurological signals or had their initial ones worsened. The neurological aggravation occurred with all grades of Mitsuda reactivity, but seemed more apparent among the strong reactors. The greater majority of the neurologically aggravated patients have regularly received sulfone therapy.

Only 7 patients (5 Mitsuda negative, one ±, one + +) did not develop nerve lesions. Except for the Mitsuda + patient, all had been regularly treated.

Two neurological improvements were recorded. Nerve thickenings initially observed in a Mitsuda negative, regularly treated patient (n.° 5) were not seen at the last observation. A non-treated reactional tuberculoid Mitsuda + patient (n.° 20) had been recorded with thickened ulnar nerves and amyotrophic changes of the right hand — not seen in the last examination.

Classification of types and groups. Checking columns G and M it can be seen that all patients belonging to the Virchowian and tuberculoid poles (including the reactional variety) and to the dimorphous group continued within their classes, in

many cases with residual lesions at the last examination.

Only in the indifferiated (indetermined) group changes were noticed, which, proves its instability. Out of the 17 of this group only 7 (41,2%) remained as indifferiated. Four (23,5%), all Mitsuda positive, developed reactional tuberculoid lesions.

More numerous were the changes to the Virchowian type. Out of the 6 (35,3%) who changed, 3 were initially Mitsuda negative, 2 Mitsuda +, one + +. These facts agree with the general evolutionary hypothesis according to Mitsuda reactivity (19, 22) now generally accepted. However, the Mitsuda indifferiated patient changed to the Virchowian pole, while his positive Mitsuda reaction became negative. This fact already reported above, conflicts with the "N-factor" theory and with the absolute good prognosis of a strong Mitsuda-test.

DISCUSSION

After the initial work of Hayashi (7), other authors who have followed their patients for various lengths of time have confirmed the prognostic value of the Mitsuda- test (3, 4, 5, 8, 9, 11, 14, 16, 17, 23, 26). The longest periods of observation are found in the works of Hayashi (7) — 13 years — and Igarashi & Hayashi (8) — 10 years.

In general, these papers report the favorable evolution of the Mitsuda positive patients (especially ++ and + + +), whose skin lesions, free from demonstrable acid-fast bacilli, disappear, remain stationary or develop into the tuberculoid type ("neural" or "neuro-macular" in the ancient classifications). Moderate degree of positivity (-i-) indicates a somewhat poorer prognosis, whereas Mitsuda-negativity points to a frequent development into the Virchowian ("nodular" or "lepromatous") type, unless checked by therapy.

Our observations a very long time after the tests (23 to 35 years) confirm the reports of earlier workers and of what is generally accepted, but other comments may be added.

The general pathogenetic theory of Hanseniasis postulated in 1937-1939 (19, 22) — and criticized for some years (A') — stating that the indifferntiated group is the matrix from which either the Virchowian or the tuberculoid aspects develop, according to the patients inability or capacity to react, is again confirmed by our results. 35,3% of the indifferntiated patients — all of them Mitsuda negative and weakly positive (+) — changed to the Virchowian type, whereas 23,5% of the same group — all of them Mitsuda strongly positive (++), weakly or strongly Mitsuda positive (+ and ++) — became reactional tuberculoid. Out of the 5 indifferntiated (indetermined) who were weakly Mitsuda positive (+) only 1 remained in the group. Two became reactional tuberculoid and two Virchowian, a fact that confirms the relative low prognostic value of the weak reactions, as reported in an earlier work (21). However, from the classificative viewpoint, the totally anergic patients are in an ever worse state, as none of the 19 Mitsuda negative patients changed to the tuberculoid pole (4 of them became reactional dimorphous).

The relative stability of the Mitsuda tests, both in positivity and negativity after such a long period of observation favors the hypothesis of a constitutional "natural" factor of resistance ("N-factor") on one side, and an "Anergic Margin" on the other, as postulated in 1937-1939 (19, 20, 22).

Small variations of that reactivity in either direction might be attributed to differences in the quality and quantity of the material employed, technique of intradermal injections and criteria of reading. However, in a non-treated reactional tuberculoid pa-

tient (n.º 28) a weak Mitsuda test (+) gave place to a + + + reaction, which might be interpreted as a demonstration that slight grades of the Mitsuda type reactivity can be enhanced.

Changes in the opposite direction were observed in two of the 8 patients who were initially Mitsuda + +. In patient n.º 29 the present Mitsuda-negativity was not accompanied by a change of his reactional tuberculoid classification, although his lesions were considered residual at the end of the observation. However, in patient n.º 31 the initial indifferntiated macules developed into Virchowian lesions (bacteriologically negative in the last few months, a possible sign of future clinical regression).

Such facts are not isolated. In one of his articles Rotberg (23) reports in a footnote that a patient was referred to him by a colleague (Gandra) with typical Virchowian lesion despite the presence of scars of previous strongly positive Mitsuda-tests. Mercklen *et al* (13) report the case of a tuberculoid patient with a "distinctly" clinically and histologically (tuberculoid) positive Mitsuda reaction, whose lesions disappeared under treatment; sometime later the patient relapsed showing erythematous bacteriologically negative macular lesions, infiltrated ear lobes and superciliar madarosis. The Mitsuda test was now negative.

If it is confirmed that strong Mitsuda tests may turn to negative and that Virchowian aspects may appear, the "N-factor" theory and all of its later correspondents ("cell mediated immunity", "constitutional reactivity", "inherited capacity to form granuloma", etc.) may have to be readapted.

Despite these doubts, Table I in general confirms *the good prognostic value of the Mitsuda test, as regards bacillation and dermatologic lesions*. The frequently observed bacillary negativation of formerly bacillary

(*) An editorial of the International Journal of Leprosy (6:371-376, 1938) qualified the theory as <<sweeping>>. The Committee of Classification of the International Leprosy Congress (Havana, 1948) considered it <<premature>> against the vote of Rebello (15), a member of the Committee.

TABLE I
Immunological, Bacilloscopic and Clinical Developments (Initial and Present Conditions)

Patient's Numbers	Initial conditions										Present conditions									
	Mitsuda		Bacilli		Clinical		Classification	Mitsuda	Bacilli		Clinical		Classification	Mitsuda		Bacilli		Clinical		
	B	A	Mucus	Skin lesion	Dermatological	Neurological			F	G	H	I		J	K	L	M			
1	—	—	—	—	+	—	RD	—	—	—	—	—	—	—	—	—	—	—	—	RD(r)
2	—	—	—	++	+	—	RD	—	—	—	—	—	—	—	—	—	—	—	—	RD
3	—	—	—	—	+	—	I	—	—	—	—	—	—	—	—	—	—	—	—	I(r)
4	—	—	—	—	+	—	I	—	—	—	—	—	—	—	—	—	—	—	—	I
5	—	—	—	—	+	—	I	—	—	—	—	—	—	—	—	—	—	—	—	I
6	—	—	—	—	+	—	I	—	—	—	—	—	—	—	—	—	—	—	—	I
7*	—	—	—	—	+	—	I	—	—	—	—	—	—	—	—	—	—	—	—	I
8	—	—	—	—	+	—	I	—	—	—	—	—	—	—	—	—	—	—	—	I
9	—	—	—	—	+	—	V	—	—	—	—	—	—	—	—	—	—	—	—	V
10	—	—	—	—	+	—	RD	—	—	—	—	—	—	—	—	—	—	—	—	RD(r)
11	—	—	—	++	+	—	V	—	—	—	—	—	—	—	—	—	—	—	—	V(r)
12	—	—	—	++	+	—	V	—	—	—	—	—	—	—	—	—	—	—	—	V(r)
13*	—	—	—	++	+	—	V	—	—	—	—	—	—	—	—	—	—	—	—	V(r)
14	—	—	—	+	+	—	I	—	—	—	—	—	—	—	—	—	—	—	—	I(r)
15	—	—	—	+	+	—	V	—	—	—	—	—	—	—	—	—	—	—	—	V(r)
16	—	—	—	++	+	—	V	—	—	—	—	—	—	—	—	—	—	—	—	V(r)
17	—	—	—	++	+	—	V	—	—	—	—	—	—	—	—	—	—	—	—	V(r)
18	—	—	—	+	+	—	V	—	—	—	—	—	—	—	—	—	—	—	—	V(r)
19*	—	—	—	+	+	—	I	—	—	—	—	—	—	—	—	—	—	—	—	I
20**	—	—	—	—	+	—	D	—	—	—	—	—	—	—	—	—	—	—	—	D(r)
21	+	—	—	—	+	—	RT	—	—	—	—	—	—	—	—	—	—	—	—	RT(r)
22	+	—	—	—	+	—	V	—	—	—	—	—	—	—	—	—	—	—	—	RT(r)
23	+	—	—	—	+	—	I	—	—	—	—	—	—	—	—	—	—	—	—	V(r)
24	+	—	—	—	+	—	I	—	—	—	—	—	—	—	—	—	—	—	—	RT(r)
25	+	—	—	—	+	—	I	—	—	—	—	—	—	—	—	—	—	—	—	RT(r)
26	+	—	—	—	+	—	I	—	—	—	—	—	—	—	—	—	—	—	—	V(r)
27**	+	—	—	—	+	—	I	—	—	—	—	—	—	—	—	—	—	—	—	RT
28**	+	—	—	—	+	—	I	—	—	—	—	—	—	—	—	—	—	—	—	I
29	+	—	—	—	+	—	I	—	—	—	—	—	—	—	—	—	—	—	—	V(r)
30**	+	—	—	—	+	—	I	—	—	—	—	—	—	—	—	—	—	—	—	RT
31	+	—	—	—	+	—	I	—	—	—	—	—	—	—	—	—	—	—	—	RT
32	+	—	—	—	+	—	I	—	—	—	—	—	—	—	—	—	—	—	—	RT
33*	+	—	—	—	+	—	I	—	—	—	—	—	—	—	—	—	—	—	—	RT
34	+	—	—	—	+	—	I	—	—	—	—	—	—	—	—	—	—	—	—	RT
35**	+	—	—	—	+	—	I	—	—	—	—	—	—	—	—	—	—	—	—	RT
36	+	—	—	—	+	—	I	—	—	—	—	—	—	—	—	—	—	—	—	RT
37**	+	—	—	—	+	—	I	—	—	—	—	—	—	—	—	—	—	—	—	I(r)
38	+	—	—	—	+	—	RT	—	—	—	—	—	—	—	—	—	—	—	—	RT

* irregularly treated
 ** not treated
 D = dimorphous
 RD = reactional dimorphous
 RD(r) = residual reactional dimorphous
 I = indetermined
 I(r) = residual indetermined
 T = tuberculoid
 RT = reactional tuberculoid
 RT(r) = residual reactional tuberculoid
 V = Virchowian
 V(r) = residual Virchowian

positive Mitsuda negative patients might be attributed, partially at least, to sulfone therapy.

As stated, *the neurological development was far from good, despite treatment and whatever the degree of Mitsuda reactivity.*

As a rule, after 23-35 years neural complications appeared during the observation period and preexistent lesions of the nerve trunks aggravated.

Therefore, *the concept of the "good prognosis" of a strong Mitsuda test must*

be qualified. The prognosis continues "good" from the dermatobacteriologic-pathologic and preventive viewpoints, assuming that tuberculoid or indifferntiated lesions are better than deforming nodules and heavily bacillary mucosae. It is "not good" from the "neuro-social" angle, if our results are confirmed that the majority of the Mitsuda-positive patients develop within two or three decades, handicapping deformities, which, in addition, reveal its "leprous" etiology to a still fearful and hostile world.

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Prognosis and Mitsuda tests

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