THE LEPROMIN TEST IN LEPRA REACTION

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The lepromin test, when positive in lepers, is generally interpreted to be a manifestation of allergy. Watanabe (17) concluded from animal experiments that repeated injections with emulsions of leprous nodules produced a certain degree of allergy for the later injections. De Langen (9), by repeated and extensive inoculations, succeeded in turning the negative reaction into a positive one in a certain number of healthy persons. Bargehr (1) and Pereira (13), from lepromin tests made on lepers, concluded that repeated inoculations transform the negative reactor to a positive one and that this change is proportional to the number of inoculations. Muir (11) considers the relative increase and diminution of reactions in cases of neural and lepromatous leprosy to indicate the presence of a specific factor connected with immunity or allergy. Hayashi (5) claims that in no case does a negative reaction occur in normal, tuberculous or syphilitic individuals. The interpretation of the positive lepromin reaction as a manifestation of resistance to leprosy is apparently based on the similarity of the test to tuberculin as that test is used in the detection of tuberculous infection, although the time required for a positive lepromin reaction to develop is such that its maximum is not reached until the end of the second, or even the third week, as pointed out by Wade (16) and Rodriguez (14).

Lepra reaction, which is characterized by the outbreak of papular eruptions with fever and chills, the eruptions at times progressing to suppuration and accompanied at times by neuritis, iritis, or orchitis, has also been considered by many workers, among them Jadassohn, Wade, Lowe, Muir, and Green (4), to be a manifestation of allergy. Cruz (3), in attempting to elucidate the nature of lepra reaction, injected large numbers of lepra bacilli intravenously, intramuscularly and subcutaneously in lepers with entirely negative results. Green reported that in patients in the state of lepra reaction the intradermal injection of fresh, unboiled leprotic tissue was followed by a reac-

tion at the site of injection. Correa de Carvalho (2) performed lepromin tests on 46 patients with lepra reaction and concluded that that condition is an allergic phase of the disease. In his observations of the test the skin reactions were read after 48 hours and subsequently observed only up to the eighth day. Rodriguez (14) tested 72 patients in varying grades of lepra reaction and found that the proportion of positive results was about the same as in bacteriologically positive nonreacting cases, and that there was no relation between the result of the test and the severity of the lepra reaction.

Because of the conflicting reports noted, and with the hope of further verifying the probable allergic nature of lepra reaction, the lepromin tests that I have made in reaction cases are presented here.

PROCEDURE

Forty-eight patients in various states of lepra reaction in the hospital wards at Culion were tested with lepromin on the antero-medial aspect of the arm or forearm, in apparently normal skin. The advancement of leprosy in these cases varied from L1-N1 to L3-N3, as follows: L1-N1, ten; L2-N1, fifteen; L3-N1, eight; L1-N2, three; L2-N2, five; L3-N2, three; and L3-N3, four cases. Six patients not in lepra reaction, all residents of the female invalids' dormitory (four of neural type and two lepromatous) were tested as controls. The lepromin employed was prepared following the technique described by Hayashi (5), and smears of the finished preparation were always made to make sure that the material was rich in bacilli. The manner of grading the reactions suggested by him was also followed. One group of 34 patients was tested in July, 1937, and another group of 14 patients in September. Readings were made at weekly intervals, the measurements being made with a metallic vernier caliper. In all cases the readings of the fourth week were the ones recorded as final. Biopsy specimens of the injected sites were taken from 35 of the 48 patients, at periods varying from 20 to 34 days after the injections, and from the control cases between the 42nd and 49th days, for the purpose of studying and correlating the histological changes in the different grades of positive and negative reactions. The findings in these specimens will be reported later (12).

For convenience, and to aid in evaluating the significance of the tests, the 48 cases have been classified arbitrarily into

five groups according to the status of the lepra reaction condition, as follows: (1) mild, brief, 2 to 6 weeks in duration (12 cases); (2) mild, recurrent, 2 months to 3 years duration (24 cases); (3) severe, brief, 6 weeks duration (1 case); (4) severe, recurrent, 11 months to 3 years duration (9 cases); and (5) severe, protracted, 2½ to 4 months duration (2 cases). The mild, brief, and mild recurrent cases were characterized by the appearance of local or general reaction lesions with moderate or little fever, and the patients did not appear to be very ill. In the severe brief, severe recurrent and severe protracted cases the patients appeared acutely ill, with moderate or very high fever, with or without suppuration of the local or general reaction lesions accompanied by severe neuritis.

After an interval varying from two to four months from the last test, 42 of the 48 patients were retested. Twenty-two were then still in the hospitals in the reaction state, while the remaining twenty had been released to their homes, apparently recovered from their reactions. Six of the patients were not retested; four of them had died during the interval while two refused the second test. No biopsies were made of the retests. The same six cases not in lepra reaction that were used as controls in the first test were again used in the same way in the retests.

RESULTS AND COMMENTS

In Table 1 it is shown that of the 48 cases in lepra reaction, 23, or 48 percent, gave negative results; 21, or 44 percent, gave one-plus (1+) reactions; 3, or 6 percent, gave 2+ reactions; only 1, or 2 percent, was graded as 3+, that because of suppuration of the reaction lesion though the maximum measurements were 8.5 by 7.9 mm. on the fourth week. Of the four neural nonreaction controls, one had a 3+ reaction lesion which suppurated, and three were 2+, while the two lepromatous-type controls were both negative. If the 1+ reactions were to be considered not significant, only four cases (three of them 2+ and one 3+) gave definitely positive reactions out of 36 patients in the mild brief and mild recurrent groups, or 8.3% of the whole group. Of the 12 patients in the severe brief, severe recurrent and severe protracted groups none gave a 2+ or stronger reaction. Concerning the significance of the 1+ reactions, Rotberg (15) accords them little importance. This point will be further discussed in the succeeding report already mentioned.

TABLE 1. *Results of first lepromin tests made during lepra reaction in 48 patients.*

Degree of lepra reaction	Results of lepromin tests				
	Neg.	1+	2+	3+	Totals
Mild, brief	4[a]	5[b]	2[c]	1	12
Mild, recurrent	10[d]	13	1	0	24
Severe, brief	1	0	0	0	1
Severe, recurrent	7[e]	2	0	0	9
Severe, protracted	1	1	0	0	2
TOTALS	23 (47.9%)	21 (43.7%)	3 (6.2%)	1 (2.1%)	48 (100%)

[a] One patient not retested.
[b] One patient not retested.
[c] One patient not retested.
[d] Two patients not retested.
[e] One patient not retested.

Retests: (a), *cases without lepra reaction.*—The results of the second tests made on the 20 patients that were without lepra reaction at the time of retesting are given in Table 2, in comparison with those of the first tests. The cases are again grouped according to the severity of the reaction at the time of the first tests, data being given regarding the duration of the lepra reactions at that time and the length of time that the condition had been quiescent when the second tests were made. It is to be seen that only four cases gave weaker reactions in the retests than at first. These are Case 5, originally 3+, later 2+; Cases 1 and 6, originally 2+, later only 1+; and Case 2, originally 1+, later negative. Five cases (Nos. 4, 7, 11, 12 and 13), all 1+ at first, gave the same reading on retesting. The remaining 11 cases showed from slightly to moderately stronger reactions in the retests: two (Nos. 3 and 16) that were originally 1+ became 2+; eight (Nos. 8, 9, 14, 15, 17, 18, 19 and 20) that had been negative became 1+; and a ninth negative case (No. 10) became 2+.

From the varying results of these retests in patients no longer in the state of lepra reaction, compared with those of the first tests when they were in reaction, there can be seen no apparent relation in the intensity of the lepromin reaction to the presence of lepra reaction. On the contrary, in a majority of the cases the retests tended to show slightly stronger reactions. This tendency was also manifested in the control group, in which one case (No. 2), previously 2+, became 3+, and one lepromatous case (No. 5), previously negative, became 1+. These results seem to support the findings of de Langen, Bargehr and Pereira, already mentioned, and those recently ob-

TABLE 2. *Results of repeated tests in 20 cases recovered from lepra reaction at the time of the second tests, including nonreaction controls.*

Lepra reaction, patient and disease				First test		Second test	
Case	Sex	Age	Class	Duration of lepra reaction[a]	Result of test	Time since subsidence of reaction	Result of test
Mild or mild, brief (10 cases)							
1. P.F.	M.	46	L2-N1	5 wk.	2+	3 mo.	1+
2. F.U.	M.	22	L2-N1	14 da.	1+	4 mo.	—
3. I.B.	M.	12	L1-N1	9 da.	1+	2 mo.	2+
4. C.C.	M.	45	L2-N1	8 da.	1+	3 mo.	1+
5. V.T.	M.	25	L2-N2	20 da.	3+	3 mo.	2+
6. T.A.	M.	35	L1-N1	21 da.	2+	3 mo.	1+
7. T.C.	F.	31	L3-N1	5 da.	1+	3 mo.	1+
8. C.C.	F.	25	L1-N1	9 da.	—	3 da.	1+
9. M.V.	F.	64	L1-N1	14 da.	—	3 mo.	1+
10. R.I.	F.	16	L1-N1	5 da.	—	1½ mo.	2+
Mild, recurrent (7 cases)							
11. E.F.	M.	42	L1-N2	12 mo.	1+	2 mo.	1+
12. J.I.	M.	23	L1-N2	7 mo.	1+	1 mo.	1+
13. R.L.	M.	20	L2-N2	2 mo.	1+	1 wk.	1+
14. A.P.	M.	49	L2-N2	2½ yr.	—	1 mo.	1+
15. M.H.	M.	62	L2-N1	2 yr.	—	3 wk.	1+
16. E.B.	F.	28	L2-N1	4 mo.	1+	1 wk.	2+
17. G.C.	F.	39	L3-N1	17 mo.	—	2 mo.	1+
Severe, brief (1 case)							
18. J.S.	M.	24	L3-N1	4 da.	—	2½ mo.	1+
Severe, recurrent (1 case)							
19. M.B.	M.	10	L3-N1	13 mo.	—	1 mo.	1+
Severe, protracted (1 case)							
20. A.L.	M.	13	L2-N1	5 da.[b]	—	1 wk.	1+
Controls, nonreaction (6 cases)							
1. E.S.	F.	66	N3	—	3+	—	3+
2. B.T.	F.	47	N3	—	2+	—	3+
3. A.C.	F.	60	N3	—	2+	—	2+
4. F.M.	F.	31	N3	—	2+	—	2+
5. F.J.	F.	28	L3-N1	—	—	—	1+
6. E.S.	F.	62	L3-N2	—	—	—	—

[a] Duration at time of first test.
[b] Reaction lasted 2½ months.

served in Culion by Lara (10), Lagrosa (8), and Ignacio (6) that the lepromin reaction, with very few exceptions, tends to become or remain positive, or to be intensified, with repeated testing. This tendency was observed in the present study, although only one previous test has been made, with intervals varying from two to four months between the two tests.

Retests: (*b*), *cases with lepra reaction.*—The results of retests of the 22 patients which were in lepra reaction at the time of the second tests—either because of continuation of the original reaction or recurrence of the condition—are shown in Table 3, the data being arranged essentially as before. It is to be seen that only two of these cases (Nos. 7 and 15) gave weaker reactions in the retests than at first; both had been 1+ and became negative. Nine cases showed no changes in the retests: five (Nos. 5, 6, 9, 13 and 16) were 1+, and four (Nos. 17, 18, 19 and 20) were negative on both occasions. The remaining 11 cases showed from slightly to moderately stronger reactions, two (Nos. 1 and 14) changing from negative to 2+, four

TABLE 3. *Results of repeated tests in 22 cases with lepra reaction, continuous or recurrent, at time of second tests.*

Lepra reaction, patient and disease				First test		Second test	
Case	Sex	Age	Class	Duration of lepra reaction[a]	Result of test	Reaction then present	Result of test
Mild, recurrent (14 cases)							
1. D.N.	M.	21	L3-N1	9 da.	—	3 wk.	2+
2. F.G.	M.	33	L2-N2	25 da.	1+	1 da.	2+
3. J.C.	M.	32	L1-N1	40 da.	1+	2 wk.	2+
4. J.C.	F.	22	L1-N2	23 da.	—	2 wk.[b]	1+
5. M.A.	F.	27	L1-N1	24 da.	1+	2 wk.	1+
6. J.L.	M.	41	L1-N1	11 mo.	1+	3 wk.	1+
7. V.C.	M.	29	L1-N1	2½ mo.	1+	Contin.	—
8. A.I.	M.	35	L2-N1	3 yr.[c]	1+	Contin.	2+
9. J.D.	F.	25	L2-N1	5 mo.	1+	Contin.	1+
10. A.B.	F.	38	L3-N1	2 mo.	1+	Contin.	2+
11. A.A.	F.	27	L2-N1	2 mo.	—	Contin.	1+
12. R.L.	M.	53	L3-N3	4½ mo.	—	(−1 da.)[d]	1+
13. F.A.	M.	37	L2-N2	18 da.	1+	Contin.	1+
14. C.C.	M.	39	L3-N2	6 da.	—	Contin.	2+
Severe, recurrent (7 cases)							
15. A.R.	F.	15	L2-N1	3 yr.	1+	3 da.	—
16. G.S.	F.	40	L3-N2	2 mo.	1+	Contin.	1+
17. F.O.	M.	39	L3-N1	2½ yr.	—	Contin.	—
18. L.B.	M.	60	L3-N2	11 mo.	—	Contin.	—
19. V.O.	F.	19	L2-N1	5 wk.	—	Contin.	—
20. S.S.	F.	39	L3-N1	2½ yr.	—	Contin.	—
21. S.A.	M.	21	L3-N1	11 mo.	—	Contin.	1+
Severe, protracted (1 case)							
22. D.J.	M.	10	L2-N1	4 mo.	1+	25 da.[e]	2+

[a] Duration at time of first test.
[b] Patient in puerperium.
[c] Patient cachectic.
[d] Reaction one day after the test injection.
[e] Period between reactions 2½ months.

(Nos. 4, 11, 12 and 21) from negative to 1+, and five (Nos. 2, 3, 8, 10 and 22) from 1+ to 2+.

These varying results of the retests obtained in patients still (or again) in reaction, compared with the first tests when they were also in reaction, again shows that there is no apparent relation in the intensity of the test to the presence of lepra reaction. In these cases, as in those whose lepra reactions had subsided at the time of the retest, there seemed to be a tendency for weak or negative reactions to become slightly or moderately stronger. An interesting group of patients in Table 3 is the severe recurrent one; 4 of the 7 cases continued to be negative in the retests.

Concerning the intensity of the lepromin test in relation to the time of the injection after the onset of the lepra reaction, which relationship is also indicated in Tables 2 and 3, no deductions can be made.

SUMMARY AND CONCLUSIONS

1. Of forty-eight hospital patients with lepromatous leprosy in various states of lepra reaction that were tested with lepromin, only four, or 8.3 percent, gave clear-cut positive reactions—one 3+ and three 2+. The 1+ reactions are considered not significant, a point to be discussed in a subsequent paper.

2. Irrespective of whether the patients were in the reaction state or not, retests made from two to four months after the original ones tended to give from slightly to moderately stronger lepromin reactions in twenty-four out of forty-eight patients (including the controls) that were retested.

3. No apparent relation in the intensity of the lepromin test to the presence of lepra reaction can be shown in the different groups into which the cases had been arbitrarily classified.

4. Similarly, no deductions can be made concerning the intensity of the lepromin test in relation to the time of the injection after the onset of lepra reaction in the mild, or mild brief and mild recurrent cases.

5. From the results of these studies, no apparent conclusion can be drawn to support the hypothesis that lepra reaction is a manifestation of allergy. Lepra reaction remains an obscure condition.

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