

# The Isopathic Phenomenon in Infiltrated Tuberculoid and Macular Tuberculoid Leprosy

## A Comparative Histologic Study of the Tissue Response Produced by Cotton Pellet Implantation and Lepromin Injection<sup>1</sup>

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In a number of papers since 1952 Sagher and associates (18, 27, 29-35) have called attention to a specific tissue response of the noninvolved skin of lepromatous leprosy on intradermal injection with various agents. Tuberculin, leishmanin, milk, peptone and living leishmanial leptomonads elicited a prelepromatous or lepromatous infiltration, usually without bacilli, at the site of the injection. This capacity of the skin to react to various agents with a histologic pattern characteristic of the host's tissue response was called an "isopathic phenomenon." (35)

Later studies on a smaller scale conformed with Sagher's findings in lepromatous leprosy. Richter (25) used the inanimate material India ink to provoke the phenomenon. Waaler (41) studied the tuberculin response in two patients with lepromatous leprosy and in two others with maculoanesthetic<sup>3</sup> leprosy. Reyes-Javier (24) recently reported on the tissue response provoked, among others, in lepromatous patients by the injection of lepromin and various other materials.

Muir (21), abstracting one of the publications of Sagher (35), pointed to the absence of control biopsies from the nonin-

involved skin of patients near the site of the injection. A year later Muir abstracted one of the earlier publications of Sagher (33). Here his criticism was silenced because in this publication Sagher had paid attention to the need to study control biopsies. In the latter study 10 lepromatous patients were injected with different agents (leishmanin and milk) and the reactive granulomas were studied two to four days later. As a control 41 biopsies were taken from the normal appearing skin of 34 leprosy patients in varying stages of the disease (comprising the 10 patients studied). In two-thirds of the control biopsies no pathologic changes were seen. In the rest foamy cell collections, graded 1+ to 3+, were found, and in nine cases bacilli or acid-fast granules were seen.

Later, the existence of an isopathic phenomenon in lepromatous leprosy was challenged by Kooij and Pepler (16). In all specimens excised 23-65 days after the injection of BCG an epithelioid reaction only was seen. In 12 out of 15 cases in which specimens were excised 30 hours to nine days after the injection, a lepromatous infiltrate was found. In all except five cases bacilli, occasionally up to 3+, were found. In three-quarters of controls taken from the noninvolved skin lepromatous structures with bacilli were reported. Therefore Kooij (11) suggested that preexistent lepromatous structures in inapparent clinical lesions had wrongly been attributed by Sagher to an artificial tissue reaction provoked by the injection of various substances.

Sagher (28), commenting on the findings of Kooij and Pepler, remarked that differ-

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<sup>3</sup> Present diagnosis might have been borderline, or dimorphous leprosy.

ences in skin color between the dark-skinned patients of Kooij and the white-skinned patients studied by Sagher, accounted partly at least for the differences observed, since inapparent lesions are more difficult to recognize in dark-skinned patients. In addition he pointed to a discrepancy in Kooij's article between the high positivity of controls (75%) and the fact that no lepromatous background was found in 23 out of 35 biopsies taken after the injection of BCG. The fact that Kooij and Gerritsen<sup>(15)</sup> actually had invoked tuberculoid reactions by injecting normal tissue suspensions into patients with tuberculoid leprosy was welcomed by Sagher<sup>(29)</sup> as further proof of his conclusion that in leprosy there is a peculiar tissue reactivity to injected foreign material characteristic of the host's altered tissue response.

Since most of the work on the isopathic phenomenon in leprosy was confined to the study of lepromatous patients, Skinsnes<sup>(39)</sup> recently made the remark that the near absence of studies of the isopathic phenomenon in different immunologic types of leprosy, e.g., in tuberculoid leprosy, made it impossible to reach any conclusions as to the significance and practical applications of the phenomenon.

#### ISOPATHIC PHENOMENON IN TUBERCULOID LEPROSY

Study of the isopathic phenomenon in tuberculoid leprosy has lagged. Sagher<sup>(30)</sup> raised the possibility of its study, without actually pursuing the subject. At the same time, like Skinsnes<sup>(39)</sup>, he was unable to predict the outcome of it.

Histologic studies of the tissue response provoked by lepromin injection into the healthy skin of patients with tuberculoid leprosy are of course well known. In 1932 Manalang<sup>(19)</sup> reported on the histology of the Mitsuda reaction caused by lepromin in tuberculoid leprosy. Rodriguez<sup>(26)</sup> gave a detailed description of the tubercles said to be formed at the end of the second week. Recently Cochrane<sup>(1)</sup> suggested classifying neuritic cases of leprosy by submitting them to a lepromin test, biopsying the tissue response after three weeks, and judging the immunologic status of the patient from the histopathologic reaction.

Kooij and Gerritsen<sup>(14,15)</sup> reported results obtained in tuberculoid patients by the injection of suspensions and concentrates of normal skin and liver. In tuberculoid leprosy positive "lepromin" reactions were found, and in lepromatous cases reactions were negative. These findings led to a new concept of the nature of the lepromin reaction<sup>(14,15)</sup>, which differs from the opinion common to most leprologists that the lepromin reaction (Mitsuda reaction) is dependent on allergic hypersensitivity occurring in sensitized individuals in whom the injected bacilli in the lepromin act as a specific antigen. The tentative explanation adopted by Kooij and Gerritsen suggests that in the Mitsuda reaction we are dealing with a kind of foreign body reaction. The fact that, after concentration and centrifugation of the tissue fluid, the strength and specificity of the reaction decreased, led to the assumption that the size of the particles is important in eliciting this foreign body reaction<sup>(15)</sup>. Reyes-Javier<sup>(24)</sup> obtained similar results in infiltrated tuberculoid and macular tuberculoid leprosy three to four weeks after the injection of lepromin, distilled water, milk, and peptone. He remarked that further studies of the isopathic phenomenon should be undertaken in view of its possible bearing on the immunology of leprosy.

Another approach to this problem is made by the widening concept of a sarcoid reaction pattern common to different etiologic agents, such as *M. tuberculosis*, *M. leprae*, *Treponema pallidum* and substances like silica<sup>(37)</sup>, beryllium<sup>(40)</sup> and zirconium<sup>(36)</sup>. Positive reactions to the Kveim antigen—rare in diseases other than sarcoidosis—were reported in a number of cases of tuberculoid leprosy by Kooij<sup>(13)</sup>, Siltzbach<sup>(38)</sup>, and Hirako<sup>(10)</sup>, giving support to the concept of a "syndrome-sarcoidosis" of which infiltrated tuberculoid leprosy forms part<sup>(12)</sup>. The injection of a suspension of normal tissue, e.g., spleen, produced, as in tuberculoid leprosy, in patients with sarcoidosis a typical sarcoid-like infiltrate<sup>(22,23)</sup>. The suspension was prepared in the same way as the Kveim antigen to which these patients had reacted positively.

It thus appears that in tuberculoid lepro-

sy, and in other diseases like sarcoidosis, various agents are capable of eliciting an isopathic phenomenon.

Our study aims to elucidate the following objectives:

1. To determine if the hypothesis of Kooij and Gerritsen that the Mitsuda reaction is essentially a kind of foreign body reaction is correct or not. If this assumption is correct, the implantation of a crude substance like cotton pellets, introduced in pharmacologic research by Meier *et al.* (<sup>20</sup>), should be capable of stimulating a tissue response similar to that obtained by lepromin. In this respect the remark of Wade (<sup>42</sup>) is recalled that the most useful excitant to elicit the isopathic phenomenon has still to be determined.

2. To contribute to a general agreement on the position of macular tuberculoid leprosy in the international system of classification of leprosy. The inclusion of macular tuberculoid leprosy, since its final adoption at the VIth International Congress of Leprosy in Madrid (<sup>4</sup>), has been the target of notes of dissent voiced by Indian leprologists at subsequent international congresses. The insistence that maculoanesthetic leprosy represents a separate form of leprosy, inconsistent with tuberculoid leprosy, has led to the framing of the Indian classification of leprosy (<sup>6</sup>). Similarly, the concept of Davey (<sup>5</sup>) of a continuous series of macular leprosy, and the immunologic status of low-resistant tuberculoid leprosy (<sup>2,3,17</sup>), need confirmation.

Wade (<sup>42</sup>) recommended study of the isopathic phenomenon for the proper classification of cases of leprosy of uncertain diagnosis. In this respect our study may contribute to the elucidation of macular tuberculoid leprosy in general and that of maculoanesthetic and low-resistant tuberculoid leprosy in particular.

In view of these objectives a comparison was made between the tissue response provoked by the implantation of cotton pellets and by the injection of lepromin in patients with infiltrated tuberculoid leprosy and in three groups of patients with macular tuberculoid leprosy. In addition seven patients with infiltrated tuberculoid leprosy were tested with a suspension of normal tissue.

## MATERIALS AND METHODS

Forty-five Indian patients of both sexes (ages 10-25) were studied. These were distributed in four groups as follows: I. infiltrated tuberculoid leprosy (12 cases); II. macular tuberculoid leprosy with a single (established) macule (9 cases); III. disseminated macular tuberculoid leprosy with two to four macules (10 cases); IV. disseminated macular tuberculoid leprosy with more than four macules (14 cases). In groups I to III, patients were examined within one year after the indicated onset of the disease. In group IV the duration of the disease ranged from one to two years.

Bacillary lepromin (0.1 ml.), prepared according to Dharmendra's method, was injected intradermally into the noninvolved skin. The site of injection was examined after three to five weeks, and in case of a positive tissue response the papule was excised and its histology studied.

Cotton pellets were implanted into the noninvolved skin of the abdomen. A trocar 4 mm. in diameter was introduced through an incision in the skin and after withdrawal of the inner rod a sterile cotton pellet, 3 mm. in diameter, was passed through the cannula and placed under the skin as near as possible to the dermal layer. After withdrawal of the trocar the incision was closed. After approximately one month (in a number of cases after two weeks only) the site of the implantation was excised and subsequently the histology of the reactive granuloma was studied.

Bacteriologic examination by the slit-smear method was made routinely in all patients at eight different sites. Histologic examination was made of a skin lesion from all patients. Repeated deeper sections were made in the majority of cases. Biopsy specimens were fixed in 10 per cent neutral formalin. Paraffin-embedded sections were stained with hematoxylin and eosin and with acid-fast stain according to the Fite-Faraco technic.

Seven patients with infiltrated tuberculoid leprosy were injected with a tissue suspension prepared from normal tissue (spleen) according to Dharmendra's method for lepromin.

The histologic findings of skin lesions

were graded (grades 1-4) according to the size and extension of epithelioid cell foci, the presence of Langhans' giant cells and endoneural infiltration. The findings in granulomas obtained by cotton pellet implantation and lepromin injection were graded differently (grades 1-3), partly because of the absence of endoneural involvement in artificially provoked granulomas. Means were calculated for each type of leprosy studied by determining the average of grades recorded for each group, and for each excitant used, in order to obtain comparable data to judge the degree of tuberculoid infiltration for each group of patients. As grades differed in skin lesions and in cotton pellet- and lepromin-induced granulomas, no comparison could be made between grades in these two groups.

In the histologic records we adhered to the definition of the epithelioid cell given by Epstein (8). Langhans' giant cells were sometimes noted among foreign body giant cells produced by cotton pellet implantation. If unaccompanied by epithelioid cell foci the presence of these cells was disregarded.

## RESULTS

**Infiltrated tuberculoid leprosy (Table 1a).** Five patients were chosen with single lesions of minor tuberculoid leprosy. The histology of their skin showed typical tuberculoid granuloma of moderate extension. In all except one, endoneural infiltration was found. Granulomas provoked with lepromin and cotton pellets in decreasing degree showed a similar tuberculoid tissue response. Both in skin smears and in tissue sections examined histologically bacilli were absent.

**Macular tuberculoid leprosy with a single macule (Table 1b).** Nine patients were studied. The clinical appearance conformed to Cochrane's description of "established" macular tuberculoid leprosy (3). No signs of past or present infiltration were seen. The distinctly hypopigmented macule was sharply defined and there was no central hyperpigmentation. No atrophy or wrinkling of the skin was seen. There was always loss of sensation for stimuli of light touch and temperature perception. In half of the cases the sense of pain by pinprick

was lost as well. Corresponding nerves were not found enlarged.

The histology of skin lesions, in comparison with that of infiltrated lesions, showed less dense aggregates of cellular infiltration, with smaller foci of epithelioid cells. In five out of eight positive cases repeated deeper sections were needed to establish the diagnosis. Endoneural infiltration was seen only occasionally.

In six and seven patients respectively granulomas provoked by lepromin and cotton pellet showed a tuberculoid response. Multiple epithelioid foci with Langhans' giant cells were seen in two out of six and in three out of seven positive cases respectively. Means calculated for cotton pellet and lepromin granulomas were respectively 1.3 and 1.9. Both in skin smears and in sections examined histologically bacilli were absent.

**Disseminated macular tuberculoid leprosy (2-4 macules) (Table 1c).** Ten patients were studied. Clinically patients were chosen to conform with Dharmendras' description of maculoanesthetic leprosy (7), except that cutaneous nerves supplying the area were not enlarged. In two cases only (Nos. 47 and 52) some satellites were present.

The histology of skin lesions in six out of 10 cases showed a tuberculoid granuloma of lesser degree (mean 0.8) than that found in single macular lesions (mean 1.9). In five out of the six positive cases numerous deeper sections were needed to detect the typical histology. In three cases slight perineural infiltration and slight linear-shaped mononuclear infiltration was seen in the dermis, permitting only the diagnosis of indeterminate leprosy (in one case no diagnosis of leprosy could be made).

The cotton pellet granulomas showed a tuberculoid response of lesser degree (mean 0.8) than in the case of single macular lesions (mean 1.3). The tissue response produced by lepromin (mean 1.8) was similar to the host-parasite reaction seen in the skin lesion itself (mean 1.9). Multiple epithelioid foci with Langhans' giant cells were seen only in lepromin granuloma (four out of seven positive cases). The tissue response provoked by cotton pellets was of lesser degree. Both in

skin smears and in sections examined histologically bacilli were absent.

**Disseminated macular tuberculoid leprosy (> 4 macules)** (Table 1d). Fourteen patients were chosen whose clinical appearance conformed to Leiker's description of low-resistant tuberculoid leprosy in the progressing phase<sup>(17)</sup>. As patients were not taken in an exacerbated stage, lesions were purely macular, with only occasional slight tendency to slow central healing. The presence of satellites was conspicuous in nearly all cases (10 out of 14). Nerves commonly affected in leprosy were thickened in a minority of cases (6 out of 14). In two only, out of six cases, this had resulted in severe contractures (Nos. 1 and 18).

The histology of skin lesions in 10 out of 14 cases showed a tuberculoid granuloma of low degree (mean 0.9) comparable to that in patients of group III (mean 0.8). In all 10 positive cases numerous deeper sections were needed. Occasional linear and star-shaped infiltrates of mononuclear cells and histiocytes were seen, with a single, sometimes multiple, small epithelioid focus. In four cases the diagnosis of indeterminate leprosy was made.

The cotton pellet and lepromin granulomas showed a tuberculoid response in six out of 14 cases in each. The cotton pellet and lepromin granulomas showed a tuberculoid response of lesser degree (means 0.5 and 1.1 respectively) than that seen in patients of group III (means 0.8 and 1.8 respectively). Multiple epithelioid foci with Langhans' giant cells were seen in lepromin granulomas in only four out of 14 cases. The tissue response provoked by cotton pellets in this group of patients reached the lowest average of the series (mean 0.5). In skin smears bacilli were absent in all cases. In two cases only (Nos. 39 and 49) histologic examination revealed a few scattered bacilli localized exclusively in a nerve twig.

**Tissue response to normal tissue in infiltrated leprosy** (Table 2). Seven patients with infiltrated leprosy (4 with major tuberculoid leprosy, 3 with minor tuberculoid) were tested with a suspension of tissue prepared from a normal spleen injected intradermally into the noninvolved skin (Table 2). In three out of four patients

with major tuberculoid leprosy, and in one out of three patients with minor tuberculoid, a papule (diameter 2-4 mm.) was observed at the end of 30-50 days after the injection. In three out of four positive cases an epithelioid cell granuloma was seen. This response was most marked in patient No. 1708G, who showed, clinically, disseminating small infiltrated lesions of sarcoid-like appearance. Bacteriologic examination of patients was negative in all cases. Histologic examination of skin lesions was not carried out. Lepromin injections were not made in these patients.

## DISCUSSION

Our findings demonstrate that the isopathic phenomenon in tuberculoid leprosy does exist and that it can be elicited by the subcutaneous implantation of cotton pellets into the healthy skin of a number of patients ranging from infiltrated tuberculoid to macular disseminated tuberculoid leprosy. In infiltrated tuberculoid leprosy in three out of seven cases the injection of a tissue suspension prepared from a normal spleen did provoke an epithelioid granuloma.

The fact that the isopathic phenomenon in tuberculoid leprosy could be elicited with a crude substance like cotton pellets, and in a small number of cases with normal tissue, corresponds with results obtained by Kooij and Gerritsen<sup>(14,15)</sup> in tuberculoid leprosy with the injection of an extract of normal tissue. Our data confirm the assumption of Kooij and Gerritsen that in the Mitsuda reaction provoked by lepromin we are dealing with a kind of foreign body reaction. Our findings for each group of tuberculoid leprosy studied show (Table 1 a,b,c,d) that the introduction of cotton pellets produced a tuberculoid granulomatous tissue response presenting a sliding scale of weaker and less frequently occurring response in patients ranging, on the one hand, from infiltrated tuberculoid leprosy (yielding the most distinct response) to macular disseminated tuberculoid leprosy with numerous macules (low-resistant tuberculoid leprosy, yielding the least impressive response), on the other.

More marked results, as compared to

TABLE 1. Comparative histology of skin lesion and granuloma provoked by cotton pellet implantation and lepromin injection in tuberculoid leprosy.

Patient No.	Skin lesion <sup>a</sup>	Granuloma <sup>b, c</sup>		Size of lepromin papule (mm.)
		Cotton pellet	Lepromin	
<b>a. Infiltrated tuberculoid leprosy</b>				
36	4+	3+ (24)	2+ (30)	8
43	3+	3+ (30)	3+ (30)	5
44	4+	1+ (30)	3+ (21)	6
48	4+	1+ (21)	2+ (21)	6
50	3+	3+ (25)	3+ (25)	8
Mean	3.6	2.2	2.6	
<b>b. Macular tuberculoid leprosy (single macule)</b>				
8	2+	— (14)	3+ (28)	5
27	2+	1+ (28)	2+ (28)	5
29	2+	3+ (35)	2+ (35)	6
30	—	— (28)	— (28)	—
34	2+	— (34)	— (34)	—
35	2+	1+ (40)	3+ (21)	5
41	2+	2+ (35)	2+ (30)	6
45	2+	3+ (45)	3+ (21)	5
46	3+	2+ (28)	2+ (28)	4
Mean	1.9	1.3	1.9	
<b>c. Macular tuberculoid leprosy (2-4 macules)</b>				
5	1+	— (15)	no biopsy (21)	—
7	— <sup>d</sup>	— (14)	" " (14)	—
14	1+	1+ (21)	2+ (28)	5
17	— <sup>d</sup>	1+ (14)	no biopsy (28)	—
20	—	1+ (22)	3+ (22)	18
26	1+	no biopsy	2+ (21)	3
31	2+	— (28)	3+ (21)	8
42	— <sup>d</sup>	1+ (47)	3+ (22)	6
47	1+	2+ (40)	3+ (30)	6
52	2+	1+ (42)	2+ (21)	4
Mean	0.8	0.8	1.8	

those elicited with cotton pellets, were obtained by the injection of lepromin in all groups of patients (Table 1 a,b,c,d). The qualitative difference between both excitants was found in the more pronounced tuberculoid tissue response provoked by lepromin, which was maintained even in patients of group IV. It is important to note that the histology of lepromin-provoked granulomas in patients of groups III and IV

gives evidence more clearly of the exact host's tissue response than mere histologic examination of the skin lesions of corresponding groups of patients (Table 1c,1d).

In one patient (Table 1d, No. 18) the histology of a skin lesions was low-grade tuberculoid (1+), but both lepromin and cotton pellet failed to show the host's exact tissue response. The introduction of both excitants into a macule, however, led to a

TABLE 1. Continued.

Patient No.	Skin lesion <sup>a</sup>	Granuloma <sup>b, c</sup>		Size of lepromin papule (mm.)
		Cotton pellet	Lepromin	
d. Macular tuberculoid leprosy (4 macules)				
1	2+	—	(8) no biopsy	(28) —
3	— <sup>d</sup>	—	(12) 3+	(28) 5
4	1+	—	(15) —	(21) 2
6	— <sup>d</sup>	—	(15) no biopsy	(28) —
9	— <sup>d</sup>	1+	(21) 2+	(21) 5
11	1+	1+	(16) 3+	(25) 6
15	— <sup>d</sup>	1+	(14) no biopsy	(28) —
16	1+	—	(14) " "	(30) 1
18	1+	—	(14) —	(21) —
18 <sup>e</sup>	1+	2+	(21) 3+	(21) 3
19	1+	1+	(14) no biopsy	(28) —
23	1+	— <sup>f</sup>	(75) " "	(75) —
39	1+ <sup>g</sup>	—	(42) 2+	(28) 4
49	2+ <sup>g</sup>	2+	(42) 3+	(21) 3
54	1+	1+	(42) 2+	(21) 4
Mean	0.9	0.5	1.1	

<sup>a</sup> Tissue response (graded 1-4): 1+ = few epithelioid foci or endoneural infiltration

2+ = multiple epithelioid foci

3+ = multiple epithelioid foci plus Langhans' giant cells

4+ = multiple epithelioid foci, Langhans' giant cells, and endoneural infiltration

<sup>b</sup> Tissue response (graded 1-3): 1+ = few epithelioid foci

2+ = few epithelioid foci plus Langhans' giant cells or multiple epithelioid foci only

3+ = multiple epithelioid foci plus Langhans' giant cells

<sup>c</sup> The figure within parentheses indicates the number of days after introduction.

<sup>d</sup> Histologically indeterminate leprosy.

<sup>e</sup> Control biopsy of macule and histology of cotton pellet and lepromin granuloma produced inside macule near site of control biopsy of macule.

<sup>f</sup> Expulsion of cotton pellet before reexamination prevented biopsy.

<sup>g</sup> Few scattered bacilli found.

distinct tuberculoid granuloma after 21 days (2+ for the cotton pellet and 3+ for lepromin). This confirms earlier observations of Hayashi (<sup>9</sup>) and Davey (<sup>5</sup>) that the result of lepromin injection was more marked in macules than in normal skin. The study of the tissue response on injecting lepromin into the macule at the site of a preceding control biopsy of the lesion therefore should be included in future studies on the isopathic phenomenon.

Histologic study of the lepromin reaction papule should not be confined to cases of neural leprosy, (see Cochrane (<sup>1</sup>)), but should be applied, for example, to all cases of macular tuberculoid leprosy in case prior histologic examination of the skin lesion

had caused doubt as to the right classification of the disease. Histologic examination of a skin lesion should not be reported as negative unless repeated deeper sections of the same tissue confirmed this finding.

Our data indicate that cotton pellets, as compared to lepromin, are a less strong excitant in eliciting the isopathic phenomenon. However, it must be pointed out that in patients of group IV in 10 out of 14 cases cotton pellet granulomas were excised after 8-21 days. In the same patients excision of the lepromin granuloma was made between 21 and 28 days. Premature excision may be responsible partly for the less conspicuous results obtained with cotton pellets in group IV. Results obtained in

TABLE 2. *Tissue response to suspension of a normal tissue (spleen).*

Patient No.	Clinical diagnosis	Histology of reactive granuloma <sup>a</sup>		Size of papule (mm.)
<i>Infiltrated tuberculoid leprosy</i>				
308131	Major tuberculoid	Tuberculoid	(35)	3
1708 G	" "	Multiple tuberculoid	(45)	4
1695 G	" "	Tuberculoid	(50)	2
1769 G	" "			
	(regressing)	No biopsy	(40)	—
1186 G	Minor tuberculoid	Nonspecific infiltration	(30)	2
1683 G	" "	No biopsy	(50)	—
1739 G	" "	" "	(40)	—

<sup>a</sup> The figure within parentheses indicates the number of days after introduction.

other groups suggest that excision of the granulomatous reaction five to six weeks after the implantation of the cotton pellet may yield a more distinct response in the tissue.

The sliding scale of decreasing grade of tuberculoid response to lepromin and cotton pellets (Table 1b to 1d) confirmed the concept of Davey (5) of a continuous "macular series" representing a descending degree of effectiveness in dealing with the bacillary invasion. Whereas Davey's concept included the whole spectrum of leprosy, our data indicate that the same "continuous macular series" exists within the tuberculoid group.

Macular tuberculoid leprosy is a distinct entity at the tuberculoid side of the spectrum of leprosy. If histologic examination of the skin lesion, even after repeated sections, failed to provide the right classification, the histology of the immunologic response to lepromin in most instances proved the tuberculoid host-parasite response. In macular tuberculoid leprosy a sliding scale of decreasing resistance, and of increasing dissemination, was found, ranging from cases with a single macule (group II) to patients with numerous macules (group IV).

Maculoanesthetic leprosy in this "continuous series" takes an intermediary position between "established" (single) macular tuberculoid leprosy, on the one hand, and low-resistant macular tuberculoid leprosy on the other. Our findings fail to give

support to the Indian classification of leprosy providing a separate place for maculoanesthetic leprosy.

#### SUMMARY

Forty-five patients with tuberculoid leprosy were examined. These were distributed in four groups: I, infiltrated tuberculoid, 12; II, macular tuberculoid with a single macule, 9; III, maculoanesthetic, 10; and IV, low-resistant tuberculoid, 14. In 38 patients bacteriologic and histologic examination was carried out of skin lesions and reactive granulomas produced by cotton pellet implantation and lepromin injection. In seven patients (included in group I) a suspension of normal tissue was injected.

This study demonstrated the existence of an isopathic phenomenon in tuberculoid leprosy. In the majority of patients a tuberculoid tissue response was obtained. Both cotton pellets and normal tissue provoked granulomas reflecting the same pattern of immunologic response, which was of lower grade compared to that produced by lepromin. The outcome supports the hypothesis that the Mitsuda reaction produced by lepromin is a kind of foreign body reaction.

A sliding scale of decreasing tuberculoid response was seen in patients ranging from group I, the highest mean grade, to group IV, the lowest mean grade. Macular tuberculoid leprosy (groups II-IV) proved to be a distinct variety of leprosy of tuberculoid immunologic status.

The histology of lepromin-provoked granulomas in patients with disseminated macules (groups III and IV) gave evidence more clearly of the host's exact tissue response than mere histologic examination of skin lesions.

### RESUMEN

Se examinaron cuarenta y cinco enfermos con lepra tipo tuberculoide. Fueron distribuidos en cuatro grupos: (1) tuberculoide infiltrado, 12; (2) tuberculoide macular con una sola mácula, 9; (3) maculoanestésica, 10; y (4) tuberculoide de baja resistencia, 14. En 38 enfermos exámenes bacteriológicos e histológicos fueron llevados a cabo en lesiones de la piel y granulomas reactivos producidos por la implantación de pelletes de algodón e inyecciones de lepromina. En siete pacientes (incluidos en el grupo 1) se inyectó una suspensión de tejido normal.

Este estudio demostró la existencia de un fenómeno isopático en la lepra de tipo tuberculoide. En la mayoría de los enfermos se obtuvo una respuesta del tejido tuberculoide. Tanto los pelletes de algodón como el tejido normal provocaron granulomas reflejando el mismo modelo de respuesta inmunológica, el cual fué de menor grado comparado al que produjo la lepromina. El resultado apoya la hipótesis que la reacción de Mitsuda producida por la lepromina es un tipo de reacción semejante al producido por un cuerpo extraño.

Una escala decreciente de respuesta tuberculoide se observó en pacientes extendiéndose desde el grupo 1, con la mediana mas alta, al grupo 4, con la mediana mas baja. Lepra tuberculoide macular (grupos 2-4) demostró ser una variedad distinta de estado inmunológico de lepra tuberculoide.

La histología de los granulomas producidos por la lepromina en enfermos con lepra diseminada (grupos 3 y 4) puso en evidencia con mas claridad la respuesta exacta de los tejidos del huésped que el simple estudio histológico de las lesiones de la piel.

### RÉSUMÉ

Quarante-cinq malades atteints de lèpre tuberculoide ont été examinés. Ces malades étaient distribués en 4 groupes: (1) tuberculoïdes infiltrés, 12; (2) tuberculoïdes maculaires avec une macule unique, 9; (3) maculoanesthésiques, 10; (4) tuberculoïdes de faible

résistance, 14. Chez 38 malades, on a procédé à un examen bactériologique et histologique des lésions cutanées; des granulomes de réaction ont été produits par l'implantation de particules de coton et par injections de lépromine. Chez 7 malades, appartenant au premier groupe, on a injecté une suspension de tissu normal.

Cette étude a démontré l'existence d'un phénomène isopathique dans la lèpre tuberculoïde. Une réponse, consistant en la formation de tissu tuberculoïde, a été obtenue chez la plupart des malades. Tant les particules de coton que les injections de tissu sain ont provoqué des granulomes qui témoignent du même aspect de réponse immunologique; le degré de cette réponse était plus faible que celui enregistré après lépromine. Les résultats observés témoignent en faveur de l'hypothèse qui veut que la réaction de Mitsuda produite par la lépromine soit en quelque sorte une réaction à corps étranger.

D'après les groupes selon lesquels ils avaient été classés, on a enregistré chez les malades une décroissance progressive de la réponse tuberculoïde, la réponse moyenne la plus élevée ayant été trouvée dans le groupe 1, et la réponse moyenne la plus faible dans le groupe 4. La lèpre tuberculoïde maculaire (groupes 2 et 4) s'est révélée constituer une variété distincte de la lèpre avec statut immunologique tuberculoïde.

L'histologie des granulomes provoqués par la lépromine chez des malades présentant des macules disséminées (groupes 3 et 4) fournit des informations beaucoup plus nettes sur la réponse tissulaire exacte de l'hôte, que ne le fait le simple examen histologique des lésions cutanées.

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