

STUDIES ON THE LEPROMIN TEST  
IV. INFLUENCE OF LEPROSY ON THE REACTIONS TO  
LEPROMIN, TUBERCULIN, AND THE  
"875 BACILLUS" SUSPENSION

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Lepromatous leprosy patients are usually considered to be anergic to lepromin. When testing patients at the leprosarium at Sorong, Netherlands New Guinea, with 1/20 lepromin (prepared according to Wade's method), it was found that many of them showed weak responses. No relationship was found between the size of the lepromin reactions and the duration of the disease, the progress of the disease, the period of treatment, or the bacillus count.

The patients were re-examined clinically, with particular attention to the distribution and infiltration of the lesions and the definition of their margins. Based upon these criteria the patients were divided into three groups:

(1) The first group consists of patients with symmetric or almost symmetric, very ill-defined lesions. It was often difficult to distinguish between infiltrated and apparently normal skin. Infiltration was usually not very marked. Hypopigmentation was usually absent or very vague, and atrophy of the skin only moderate. This group was called "diffuse lepromatous." Most cases were of the secondary diffuse lepromatous type, a few cases would perhaps fit the description of the primary diffuse form of lepromatous leprosy, although the Lucio phenomenon was not seen in these cases.

(2) The second group showed better-defined lesions than the former group, and the infiltrations were usually more marked. Several cases showed nodules, although the pedunculated type was not seen. There was a tendency to asymmetry. Healed lesions were often still clearly made visible by hypopigmentation and atrophy. This group was called "nondiffuse lepromatous."

(3) The third group showed even more defined and less symmetric lesions, although not as well-defined as in ordinary tuberculoid cases. In some patients an "immune area" (Wade) was seen. Usually this represented the first or one of the first lesions, which had healed. Healed lesions often showed a crinkled appearance (paper skin), or even scarred remnants of former ulcerating reactions. This group was called "borderline lepromatous."

As some cases were early, others very advanced, and probably most of them were secondary diffuse and many had already received treatment for several years, the subclassification was difficult and certainly errors were made. The lepromin reactions were only very small, and errors of 1 mm. in reading such reactions are easily made. It is there-

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fore not justified to draw conclusions from the lepromin reactions in individual cases. However, notwithstanding the unsatisfactory features of this material, statistically significant differences in the average sizes of the lepromin reaction are seen when the groups are compared (Table 1).

TABLE 1.—Lepromin reactions in 128 lepromatous patients (lepromin 1/20).

Variety of lepromatous	No. of cases	Size of reactions (mm.)						Average size of reactions
		0	1	2	3	4	5	
Diffuse	54	18	20	16	—	—	—	0.97
Nondiffuse	53	11	15	20	5	2	—	1.47
Borderline	21	—	2	6	9	3	1	2.76
Total	128	29	37	42	14	5	1	—

In lepromatous leprosy a parallel exists between the size of the lepromin reaction and the clinical symptoms. Guinto (personal communication) has experimented with a "super-lepromin," and he saw that many lepromatous patients reacted to this concentrated antigen.<sup>2</sup> It is possible that such a lepromin may be helpful in measuring the weak resistance to *M. leprae* that part of the lepromatous patients have.

The groups differ in other respects than those mentioned. In the "diffuse" group both ulnar and both peroneal nerves were often diffusely enlarged. However, even in many of the very advanced cases with very thickened nerves, irreversible contractures of the fingers, trophic ulcers and mutilations were absent. These symptoms were far more prevalent in the "nondiffuse" group, and they were common and also more asymmetric, in the "borderline" group.

Histopathologically, some differences between the groups were seen, but these are difficult to evaluate since differences in the stage of the disease, the duration of treatment, etc., have a great influence on the lesions. In the "borderline" group the granulomas of vacuolated histiocytes were usually more or less rounded. In advanced cases, when the granulomas had coalesced, the original ones were often well recognizable. Globi, if they occurred, were usually small. Nerve twigs were surrounded by infiltrate, the sheath was often thickened, and the infiltrate was often seen also within the nerve twigs.

In the lesions of the "nondiffuse" group the infiltrate of Virchow cells was usually very extensive and formed broad bands, even in rather early stages of the disease. In more advanced cases many large globi were seen. Infiltration of nerve twigs was often found, but less conspicuous than in the "borderline" group.

In the "diffuse" group the infiltrate of Virchow cells was compara-

<sup>2</sup>Guinto has written that he had been able to induce Mitsuda reactions of 4 mm. or more (but not more than 5 mm.) in about 40 per cent of lepromatous cases in Cebu by using an antigen concentrated to five or more times the ordinary strength.

tively limited, compared with the great number of bacilli to be found. The infiltrate was mainly perivascular, and star- and streak-like in appearance. Although many bacilli were found within the nerves, intraneural infiltration was very moderate or often even absent.

In a few cases only little perivascular infiltrate of lepra cells and lymphocytes was seen, although bacilli were very numerous. These cases were clinically of the pure diffuse lepromatous form, and they showed no response to lepromin.

It seems that the pure diffuse lepromatous variety is the only true anergic type of leprosy. All cases which show histologically Virchow cells are not completely anergic. Phagocytosis is the expression of a very weak resistance to *M. leprae*.

As every grade of resistance is seen, when a sufficient number of patients is examined, theoretically one may expect some cases of the pure diffuse variety in every country where leprosy is endemic, although the frequency may differ greatly.

Some authors claim that the lepromin reaction in lepromatous patients may become positive after sulfone treatment, after bacillus negativity is attained. Personally I have never seen evidence of such a transformation. If a patient classified as lepromatous showed a positive lepromin reaction, definite borderline symptoms were always found.

If the use of lepromin of different strengths and technical errors are excluded, still another explanation remains possible. In many lepromatous cases great parts of the skin contain bacilli, although infiltration is not always conspicuous. If in this apparently healthy skin the small number of dead bacilli from the lepromin is added to the greater number of living bacilli already present, one cannot expect much more reaction to the lepromin than already had been caused by the bacilli already in the skin. The lepromin reaction will therefore be negative. After treatment the bacilli and the infiltration of the skin disappear. If lepromin is injected in this stage, and if the patient is not a diffuse case, some reaction to the lepromin may now be seen. The conversion to positive is not a real one. This explains, too, why several nondiffuse cases in our series did not show any reaction at all to lepromin.

This hypothesis was supported when lepromin was injected within and outside of rather well-defined lesions in nondiffuse and borderline cases. No reaction was seen within the infiltrate, whereas a weak response was seen outside the lesion. After the infiltration had subsided, the response to lepromin was the same within and outside of the lesion.

Elsewhere I have pointed out that leprosy bacilli, other acid-fast bacilli, and normal skin have probably one or more components in common, and that lepromatous patients differ from other people in that they lack the ability to react to these components. If this is true one would expect that leprosy patients and healthy people also to differ in

their response to intradermal injections of other acid-fast bacilli or their components.

One pertinent observation that has been made is of the sizes of non-specific reactions to 5 TU of PPD tuberculin in healthy persons and in tuberculoid and lepromatous leprosy patients. The results of tests made on adults in the Wandamen and Sorong areas, shown in Table 2, reveal distinct differences in the average sizes of the reactions in the two areas.

TABLE 2.—Nonspecific reactions to 5 TU of human PPD in adult healthy persons and leprosy patients, in the Wandamen Bay and Sorong areas.

Group tested	No. of cases	Average size (mm.)	Distribution of reactions (mm.)					
			0-1	2-3	4-5	6-7	8-9	10-11
<i>Wandamen Bay</i>								
Healthy	192	7.9	7	10	23	35	42	75
Tuberculoid	21	6.8	3	2	2	4	3	7
Lepromatous	30	6.3	5	1	5	5	6	8
<i>Sorong</i>								
Healthy	220	5.2	50	36	34	33	37	36
Tuberculoid	31	4.2	8	7	4	7	3	2
Lepromatous	46	3.5	17	6	7	10	4	2

The difference may be due to a difference in prevalence of the non-specific factors that are responsible for these reactions. It is also possible that protein deficiency plays a role. The protein intake of the patients in the Sorong area is certainly less than in the Wandamen area. Therefore the tests in the two areas are not combined, although the number of leprosy patients thus becomes rather small. It is seen that in both areas the response of lepromatous patients to tuberculin is slightly weaker than of tuberculoid patients, and the response of the latter group is again weaker than that of healthy people of the same age group in the same area. The differences, however, are small.

In another experiment adult leprosy patients and healthy adults were tested with a suspension of the "875" bacillus (a strain of acid-fast bacilli morphologically similar to *M. leprae*, but easily cultured on Sabouraud agar at room temperature). Of this suspension, containing about the same number of bacilli as lepromin of the usual strength, 0.1 cc. was injected intradermally and the reactions were read after three weeks. In a former experiment it had been found that the reactions to the "875" suspension were stronger in PPD-positive than in the PPD-negative people, therefore the people tested were divided in respect to their tuberculin reactivity.

As is seen in Table 3, lepromatous patients react less strongly to the "875" suspension than tuberculoid patients, and the latter again react less strongly than healthy people of the same age group and living in the same area. The influence of tuberculin positivity is again demonstrated here. The average size of the reactions in the tuberculin-positive

TABLE 3.—Reactions to "875-bacillus" suspension in PPD-negative and PPD-positive adult healthy persons and leprosy patients.

Group tested	No. of cases	Average size (mm.)	Distribution of reactions (mm.)								
			2-	4-	6-	8-	10-	12-	14-	16-	>16
<i>PPD-negative</i>											
Healthy	52	9.3	—	4	8	15	13	3	4	5	—
Tuberculoid	23	8.3	1	2	6	5	5	2	—	2	—
Lepromatous	48	6.1	5	13	11	13	5	1	—	—	—
<i>PPD-positive</i>											
Healthy	39	14.3	—	—	1	—	4	15	6	5	8
Tuberculoid	13	12.2	—	—	2	1	2	2	4	1	1
Lepromatous	53	10.3	—	2	3	11	18	11	4	3	1

lepromatous cases was larger than that of the tuberculin-negative healthy group.

It is concluded that one or more group-specific factors play a role in the lepromin reaction. Leprosy patients and people who are susceptible to *M. leprae* differ from other people in that they are less capable or even incapable of reacting to these components.

#### SUMMARY

Not all lepromatous patients are completely anergic to lepromin, as a weak response has been seen in many such cases. A correlation between clinical symptoms and the size of the lepromin reaction was found when different groups of these patients were compared. The selection of these groups was based mainly upon the definition of the margin of the lesions, the degree of infiltration, and the degree of symmetry of distribution. Some histologic differences between the groups are also described.

It is concluded that phagocytosis of the bacilli is the expression of a very weak resistance to *M. leprae*. Only cases of the pure diffuse variety of lepromatous leprosy are completely anergic to lepromin.

When lepromin is injected in an infiltrated skin, no reaction can be expected because the skin has already reacted to the greater number of living bacilli already present. After treatment, when the bacilli have disappeared, a nondiffuse patient may show a weak response to lepromin. Then the conversion of the reaction is not a real one.

It was found that the nonspecific reactions to 5 TU of PPD tuberculin were on the average smaller in leprosy patients than in healthy people of the same age group and living in the same area, and that lepromatous leprosy patients reacted still more weakly than tuberculoid patients. The differences were small. A greater difference was found when the reactions of healthy people, tuberculoid patients, and lepromatous patients who had been injected with 0.1 cc. of a suspension of the "875" bacillus were compared.

It is concluded that one or more group-specific components play a

role in the reaction to lepromin. Leprosy patients and healthy people susceptible to *M. leprae* are incapable, or less capable, of reacting to these components.

## RESUMEN

No son todos los lepromatosos absolutamente anérgicos a la lepromina, pues en muchos de esos casos se ha observado una respuesta débil. Al comparar diversos grupos de esos enfermos, se descubrió una correlación entre los síntomas clínicos y el tamaño de la reacción a la lepromina. La selección de los grupos se basó principalmente en la definición del borde de las lesiones, el grado de infiltración y la proporción de simetría en la distribución. Además se describen algunas diferencias histológicas entre los grupos.

Considérase que la fagocitosis de los bacilos constituye la expresión de una resistencia muy débil al *M. leprae*. Sólo los casos de la variedad difusa pura de lepra lepromatosa son absolutamente anérgicos a la lepromina.

Cuando se inyecta lepromina en una piel infiltrada, no cabe esperar reacción, porque la piel ya ha reaccionado al número mayor de bacilos que ya había. Después del tratamiento, cuando los bacilos han desaparecido, un sujeto lepromatoso de la variedad no difusa tal vez revele una respuesta débil a la lepromina. En ese caso, el viraje de la reacción no es real.

Se observó que las reacciones inespecíficas a 5 UT de DPP eran en conjunto más pequeñas en los leprosos que en sujetos sanos del mismo grupo de edad que vivían en la misma zona, y que los enfermos de lepra lepromatosa reaccionaban todavía más débilmente que los tuberculoideos. Las diferencias fueron pequeñas. Se notó una diferencia mayor cuando se compararon las reacciones de sujetos sanos, tuberculoideos y lepromatosos, a quienes se había inyectado 0.1 c.c. de una suspensión del bacilo "875."

Se deduce que uno o más de los componentes específicos para grupos desempeñan un papel en la reacción a la lepromina. Los leprosos y los sujetos sanos susceptibles al *M. leprae* son incapaces, o menos capaces, de reaccionar a dichos componentes.

## RESUMÉ

Les lépromateux ne sont pas tous complètement anergiques à la lépromine, car une faible réponse a été observée dans bien des cas. Différents groupes de malades ayant été comparées, une corrélation entre les symptômes cliniques et la dimension de la réaction à la lépromine a été constatée. Le choix de ces groupes a été basé sur le caractère tranché ou non du bord des lésions, sur l'importance de l'infiltration, et sur le degré de symétrie dans la distribution des lésions. Quelques différences histologiques entre ces groupes sont également décrites.

Il en a été conclu que la phagocytose des bacilles est l'expression d'une résistance très faible au *M. leprae*. Ce ne sont que les cas atteints de lèpre lépromateuse purement diffuse qui sont complètement anergiques à la lépromine.

Quand de la lépromine est injectée dans une peau infiltrée, on ne peut s'attendre à une réaction car la peau a déjà réagi aux bacilles vivants qui y sont présents en beaucoup plus grand nombre. Après traitement, lorsque les bacilles ont disparu, un malade atteint d'une forme lépromateuse non diffuse peut manifester une faible réactivité à la lépromine. Dans ce cas, cette transformation de la réaction ne constitue pas un véritable virage.

Il a été observé que les réactions non spécifiques à 5 Unités de tuberculine PPD sont, en moyenne, plus petites chez les malades atteints de lèpre que chez les individus sains d'âge comparable et de la même région. Chez les malades lépromateux, cette réaction est plus faible encore que chez les malades atteints de la forme tuberculoïde de l'affection. Les différences sont minimes. Une différence plus marquée est constatée si l'on compare les réactions observées après injection de 0.1 cc. d'une suspension de bacilles "875" chez des sujets sains, des tuberculoïdes et des lépromateux.

En conclusion, dans la réaction à la lépromine interviennent une, ou des composantes dotées d'une spécificité de groupe. Les malades atteints de lèpre, ainsi que les sujets sains susceptibles au *M. lepre*, sont incapables, ou moins capables, de réagir à ces composantes.