

THE VALUE OF LEPROMIN REACTION IN THE DIAGNOSIS OF THE CLINICAL FORMS OF LEPROSY

SALOMON SCHUJMAN, M.D.

Chief, "E. P. Fidanza" Leprosy Service (Men's Section)

"I. Carrasco" Hospital

Rosario, Argentina

Although the present classification of leprosy, approved by the Havana leprosy congress in 1948, has a terminology which is predominantly histopathological, it is nevertheless based on clinical, bacteriological, histopathological and immunological criteria. In other words, in order to classify the leprosy patient today we take into consideration the clinical, bacteriological and histopathological features presented by his cutaneous lesions, and his immunological state as revealed by the lepromin reaction.

Clinically, we take into account especially the appearance and morphology of the skin lesions (form, border, color, etc.), and also the type and degree of the neural changes. Bacteriologically we consider whether the case is negative or positive, information which may guide us to one or the other polar form, and the degree of positivity. Histologically, the structure of the lesions permits us, in a large percentage of cases, to classify them correctly. Immunologically, we are interested in the response of the patient to the lepromin test, since the positivity or negativity of the reaction will orient us in classifying the case in one or the other form of leprosy.

The majority of leprologists—and I among them—believe that none of these criteria when taken alone is of absolute value in classification, that they all complement each other, and that only by considering them together can the leprosy patient be classified with certainty.

I wish to say, however, and this is the main purpose of the present article, that I ascribe to the immunological criterion a preponderant value in the matter of classification, since I believe that of the four features upon which the classification of leprosy is based it is the most constant and least mutable one (1). This preponderant value of the immunological state is outstanding in cases which present no cutaneous lesions, in which event it is the only decisive evidence for orientation. We will therefore consider the value of the lepromin reaction in leprosy cases with and without skin manifestations.

My views result from twenty-four years of experience in the leprosy service of the Carrasco Hospital, in both the section for interned patients and the dispensary annex, where all of the clinical forms of leprosy are seen. During this time I have had the opportunity for long-period observation—in some cases as long as twenty years—of the clinical, bacteriological and immunological evolution of the disease in patients of diverse clinical types. It is on the basis of such long observations that I can maintain that as a general rule—admitting a small percentage of exceptions—the immunological factor is the least mutable of the criteria of classification.

I. THE LEPROMIN REACTION IN CASES WITH SKIN MANIFESTATIONS

Let us consider comparatively the evolution of the clinical, histological and bacteriological characteristics of the different clinical forms of leprosy.

1. *The lepromatous form.*—The lepromatous process may continue to progress, in untreated cases or in those with insufficient treatment, or it may undergo regressive changes in those who respond well to treatment. In both events manifest clinical, bacteriological and histological modifications can be seen on prolonged observation, whereas the immunological condition remains unchanged, the lepromin reaction is persistently negative.

Clinically, when the disease progresses we see the erythematous macules change in form, size and color; they become confluent to form larger areas, and later they become infiltrated and elevated to form plaques. In the regressive phases, on the other hand, the macules become paler and diminish until they disappear, while the elevated and infiltrated elements become flattened and disinfiltated until they regress to leave only residual changes.

Bacteriologically, in the period of progression, especially of a slight (L1) case, the bacilli increase in numbers and tend to form cigar-pack groups and globi. Changes are more evident during regression under treatment: in the slight cases the bacilli disappear completely, while in the more advanced ones they first show modification of morphology (fragmentation) and of staining (loss of acid-fastness) and later diminish in numbers and in some cases disappear.

The histopathological picture also varies as the disease advances or regresses. The lepromatous infiltrate, at the beginning scattered in discrete, small foci, increases with the evolu-

tion of the disease and invades the entire middle and deep levels of the dermis, while in the regressive phases it decreases until it is quite gone, or there remain only small residual foci.

The immunological picture, on the other hand, is always the same; we have seen the lepromin reaction remain persistently negative for 20 years, the same in the initial period, in the advanced stages, and after all of the lesions have regressed.

It is in lepromatous leprosy that one sees most clearly the contrast between the successive modifications of the clinical, bacteriological and histological characteristics of the lesions and the stability or immutability of the immunology, the persistence of negativity to lepromin.

2. *The tuberculoid form.*—Here the cases of torpid or chronic evolution are considered. Although the lesions are more stable than those of the lepromatous form, one may see in their long years of evolution some modifications of the clinical aspects, with increase of infiltration or of size and number in the progressive phases, or on the contrary lessening of the infiltration or total resorption in the regressive period to leave only residual atrophic and achromic lesions, or no trace at all.

The clinical modifications are accompanied by corresponding histological changes. The very discrete tuberculoid structures of the initial periods of the lesions change with progression to marked infiltrates with large follicular formations, while in the regressive phases the follicular infiltration decreases until at the end the tuberculoid structure becomes indistinguishable.

Although the immunological factor in torpid tuberculoid leprosy does not possess the stability that it has in lepromatous leprosy, it can be said as a general statement that, especially in the frankly positive cases, it is immutable whatever clinical and histological changes occur in the lesions because the lepromin reaction always remains positive, with slight oscillations of the degree of intensity but without becoming negative. Such changes have been observed most frequently in weakly positive cases, the tendency being to increase the degree of positivity, much less frequently to become negative.

3. *The indeterminate group.*—This group, as is known, comprises the cases which, owing to their clinical and histological aspects, cannot be placed in either of the two polar forms. There are cases which appear clinically to be indeterminate but which if examined histologically can be classified, because of the structure of the lesions, as lepromatous or tuberculoid, so that where cases are examined thoroughly the numbers of indeter-

minate ones decrease while those of the polar forms increase. In our service at the Carrasco Hospital the percentage of indeterminate cases is much lower than is those of the polar forms, but we have a nucleus of patients who have been followed up for many years and we have found, as others have found, that they evolve toward one or the other of the polar forms.

It would be most important if we could determine which indeterminate cases will evolve toward the lepromatous form and which toward the tuberculoid form. There are cases, especially immunopositive ones, which will remain as such for many years. We have a certain degree of assurance regarding the significance and prognosis of these cases since the great majority of them are clearly and sometimes strongly positive to lepromin and therefore have no tendency to evolve toward the lepromatous form.

Some authors (2) hold that the immunological findings cannot always orientate us regarding the evolution of the indeterminate cases, since there are Mitsuda-negative cases which later become positive or, while remaining negative, do not evolve to the lepromatous form. Our experience shows that in the majority of instances the evolution is conditioned by the immunological status.

(a) Indeterminate cases with strongly positive Mitsuda reactions have either remained without clinical or histological change or have become tuberculoid. Never have we seen them transform to lepromatous, even if untreated or insufficiently treated.

(b) Indeterminate cases with negative Mitsuda reactions, especially if bacteriologically positive (bacilli rare) and insufficiently treated, have been seen on prolonged observation to transform to lepromatous in all respects. Only Mitsuda-negative cases have been seen to undergo this transformation.

(c) The indeterminate cases with weakly positive Mitsuda reactions are the most difficult with respect to immunological instability. The most frequently observed change has been intensification of the reaction. In other cases we have observed temporary change to negative, later becoming weakly positive again. Lastly, there have been such cases, especially those with a few bacilli in smears or sections and without sufficient treatment, in which the Mitsuda reaction has become permanently negative and evolution to the lepromatous form has occurred.

It is to be said, however, that the number of indeterminate

cases which we have been able to follow up for long periods is relatively small, and for final conclusions in the matter it is important to know the experience of other workers in this matter, and that such observations be made in different leprosy centers.

IMPORTANCE OF THE IMMUNOLOGICAL CURVE
IN INDETERMINATE CASES

Study of the immunology, and especially of the immunological curve, although necessary in all forms of leprosy, is essentially important in the indeterminate group in order to enable us to establish the significance of this form from the points of view of pathology, prognosis and future place in classification. Some authors maintain that 50 per cent of the indeterminate cases are Mitsuda positive and the other 50 per cent are negative, and that the evolution is variable since some may retain the indeterminate aspect indefinitely while the majority evolve toward one or the other polar form; but it has not been established what cases, and in what percentages and under what circumstances, such transformations occur.

I have said, speaking generally from my experience, what indeterminate cases do transform to lepromatous and what cases do not, but I wish to emphasize that it would be premature to draw firm conclusions from the limited number of cases observed, and that investigations should be made elsewhere of the evolution of the immunology of such cases, establishing immunological curves for them. If it can be verified that the Mitsuda positive cases do not evolve to lepromatous while the Mitsuda negative cases usually do, then we may consider the former as pretuberculoid or potentially tuberculoid (or ex-tuberculoid), and the latter as prelepromatous or potentially lepromatous.

To coordinate the study of the immunological curve the following is suggested:

1. Use a standard antigen and a standard amount of it. I use the Dharmendra lepromin, 1:2000 suspension, in 0.2 cc. dose, making readings after 2 and 21 days. Most importance is given the 21-day reading (the Mitsuda phenomenon), for I have seen negative early results (Fernandez reaction) with positive late ones, but not the contrary condition.
2. Determine the percentage of cases with positive and negative Mitsuda reactions, and the intensity of the positivity.
3. Pay special attention to the evolution of immunology in the negative and weakly positive cases, repeating the test every three months.

4. In the strongly positive cases it is sufficient to check the immunological state once a year.

II. THE LEPROMIN REACTION IN CASES WITHOUT SKIN MANIFESTATIONS

In leprosy cases without skin lesions the immunological criterion is of even greater importance, because in the absence of the clinical, bacteriological and histological characteristics of such lesions, and because of the difficulties involved in nerve biopsy, the lepromin reaction acquires its full value. It is a simple procedure, and it will guide us in the classification of the clinical form in the great majority of cases.

Patients may present no cutaneous manifestations under the following conditions:

(a) In the primary pure neural cases (primary polyneuritic of Wade). The patient cannot recall having previously had cutaneous lesions, and the only symptoms which he presents are the sensory, motor and trophic disturbances due to leprosy neuritis of the peripheral trunk nerves.

(b) In the secondary neural cases (secondary polyneuritic of Wade), which previously had been of the lepromatous, tuberculoid or indeterminate form. The patient tells of having had for a long time cutaneous lesions which have regressed leaving only the nerve lesions.

(c) Patients with cutaneous lesions temporarily fading or disappearing. The only thing they can say about this is that they have had some skin lesions, generally erythematous, which have disappeared under treatment leaving no traces.

In all these eventualities, and especially when the patient comes or is sent without history or record of a previous examination, classification of the case becomes very difficult. If, however, the lepromin reaction is found to be definitely and repeatedly negative it will indicate that the condition is lepromatous, while on the contrary if it is positive it will suggest the tuberculoid form. The following cases are demonstrative.

CASE 1.—Camilo Al., male, 59 years old. This patient, complaining of severe pain in the left arm, was sent to us for confirmation of the diagnosis of leprosy. There were no skin lesions and he could not recall having had any. Examination revealed two tumors on the inner aspect of the left arm and elbow larger than a nut, red and intensely painful, which were adherent to the very painful and enlarged cubital nerve (Fig. 1). There were sensory disturbances and atrophy of the thenar eminences of both hands, and of the interossei especially of the left hand with contracture of the small finger.

Because of the nodules of the cubital nerve we believed the condition

to be tuberculoid with nerve localization. It was with great surprise that we found the reactions to lepromin, both early and late, to be frankly negative. The test was repeated twice at intervals of one month, with the same negative results.

Because the pain persisted the patient was operated on surgically for transposition of the cubital nerve, and advantage was taken of the opportunity to extirpate a fragment of it for histological study. Sections revealed a frankly lepromatous structure with Virchow cells and very abundant bacilli (Fig. 2).

Two years later, in 1943, lepromatous skin lesions appeared.

In summary, a case without skin lesions which because of nodules of the cubital nerves was thought to be tuberculoid leprosy but in which the lepromin reaction was persistently negative. This indicated lepromatous leprosy with nerve localization, a diagnosis which was later confirmed by nerve biopsy.

CASE 2.—Juan A., male, 53 years old. According to the patient his trouble began 13 years ago with numbness and weakness of the fingers of the left hand, and later of both hands and the lower limbs. Five years ago he was examined by a colleague who noted several flat erythematous macules, besides marked neural changes (anesthesia and macular atrophies of the extremities), and he classified the case as incharacteristic (indeterminate).

The patient recently returned to our service to be interned because of aggravation of his neural disturbances. He showed no cutaneous manifestations of leprosy, but there were marked neural changes—extensive areas of anesthesia, muscular atrophy and trophic disturbances, and ulcerations and mutilations of several digits of the upper and lower extremities.

There being no cutaneous lesions to guide us in the classification of the case, the lepromin test was made. The early reaction was doubtful, but the late one at 21 days was positive, a 5 mm. nodule (Fig. 3). The positive Mitsuda reaction led us to believe the case to be one of neural leprosy secondary to an earlier tuberculoid condition. This diagnosis was later confirmed by means of biopsy of the cubital nerve (Fig. 4).

In summary, a case which 5 years ago was classified by a colleague as indeterminate leprosy because of the presence of macules, returned with no cutaneous lesions. On the basis of a positive Mitsuda reaction we classified the case as tuberculoid, and this diagnosis was confirmed by biopsy of the cubital nerve.

SUMMARY AND CONCLUSIONS

Although the international classification of leprosy is based on the clinical, bacteriological, histological and immunological criteria, the opinion is expressed that the immunological one as revealed by the late reaction to the lepromin test (Mitsuda phenomenon) is the most important and dependable one because it is the least subject to change. In the prolonged evolution of the disease the clinical, bacteriological and histological elements not only undergo modification but may eventually dis-

appear entirely, whereas the immunological one—as a rule, with a small percentage of exceptions—remains constant, positive in the tuberculoid form and negative in the lepromatous form.

With respect to the indeterminate group, the author has never seen a strongly positive case change to negative or evolve to the lepromatous form. On the other hand, lepromin-negative cases, especially those which are bacteriologically positive and insufficiently treated, usually transform to lepromatous. However, the number of cases observed is relatively small, and to permit definite conclusions to be drawn indeterminate cases should be studied thoroughly at other centers, establishing immunological curves by testing every three months to demonstrate immunological evolution. If it is proved that the lepromin-negative cases do eventually transform to lepromatous, they should be regarded as prelepromatous or potentially lepromatous.

The lepromin reaction assumes its full value in classification in the cases without skin lesions, in which the guidance of their clinical, bacteriological and histological aspects is lacking. Where the Mitsuda reaction is frankly negative, it may be concluded that the case is a lepromatous one with nerve localization if the patient has never had skin lesions, or a neural case secondary to a previously lepromatous one when there were skin lesions which have disappeared. When the reaction is frankly positive the case can generally be regarded as tuberculoid leprosy of the nerve where there have been no skin lesions, or neural, secondary to previously tuberculoid leprosy, when skin lesions have disappeared. Two cases are related to illustrate how the immunological findings alone permitted diagnosis of the clinical form, the diagnoses confirmed by biopsy of the cubital nerve.

The following conclusions are arrived at:

1. The lepromin reaction, especially the late, 21-day one (i.e., the Mitsuda phenomenon), has the greatest value of the four criteria of classification—clinical, bacteriological, histological and immunological—because it is the least mutable one.
2. The lepromin reaction is of still greater value in the classification of cases without cutaneous manifestations, in which the other criteria are absent. In such cases the results of the Mitsuda test orient us toward one or the other polar form of leprosy with preferential localization in the nerves.

CONCLUSIONES

1. La leprominorreacción y especialmente la reacción tardía de 21 días (Fenómeno Mitsuda) es de los 4 elementos que sirven para orientarse en el diagnóstico de forma clínica de lepra (clínico, bacteriológico, histológico é inmunológico) el que tiene el mayor valor, porque es el menos mutable de todos ellos.

2. La leprominorreacción adquiere mucho más valor aún en la orientación diagnóstico de forma clínica de los casos de lepra sin manifestaciones cutaneas donde faltan los otros elementos de juicio. Es entonces cuando la positividad o negatividad de la Mitsuda nos orientará hacia una ú otra forma polar de lepra de localización preferente en los nervios.

REFERENCES

1. SCHUJMAN, S. A propósito de una nueva clasificación de lepra. *Rev. brasileira Leprol.* 8 (1940) 111-118.
2. DE SOUZA LIMA, L. and ALAYON, F. L. Sobre a significação patológica das lesões incaracterísticas (maculares simples). 5a. Monografia dos Arquivos do Sanatorio "Padre Bento." Empresa Gráfica da "Revista dos Tribunais" Ltda. São Paulo, 1941, 302 pp. Illus.

DESCRIPTION OF PLATE

PLATE (5)

FIG. 1. Nodules of the cubital nerve (indicated by arrows) in a lepromatous case with no skin manifestations. Lepromin reaction repeatedly negative.

FIG. 2. Histological section of one of the nerve lesions shown in Fig. 1. Frank lepromatous structure, confirming the diagnosis of lepromatous form which was based on the negative results of the lepromin test. Bacilli were abundant in this lesion.

FIG. 3. Lepromin reaction in a patient without skin lesions, previously classified as indeterminate when macules were present. The early, 2-day reaction (upper) is weakly positive (\pm), the late, 21-day reaction (lower) is definitely positive (1+). These findings indicate the diagnosis of neural tuberculoid leprosy, which was confirmed by nerve biopsy.

FIG. 4. Low-magnification of a section of the cubital nerve of the case referred to in Fig 3, showing tuberculoid follicles.

(Note: A high-magnification photomicrograph of this lesion, not reproduced for lack of space, shows clearly the tuberculoid nature of this lesion.—EDITOR.)

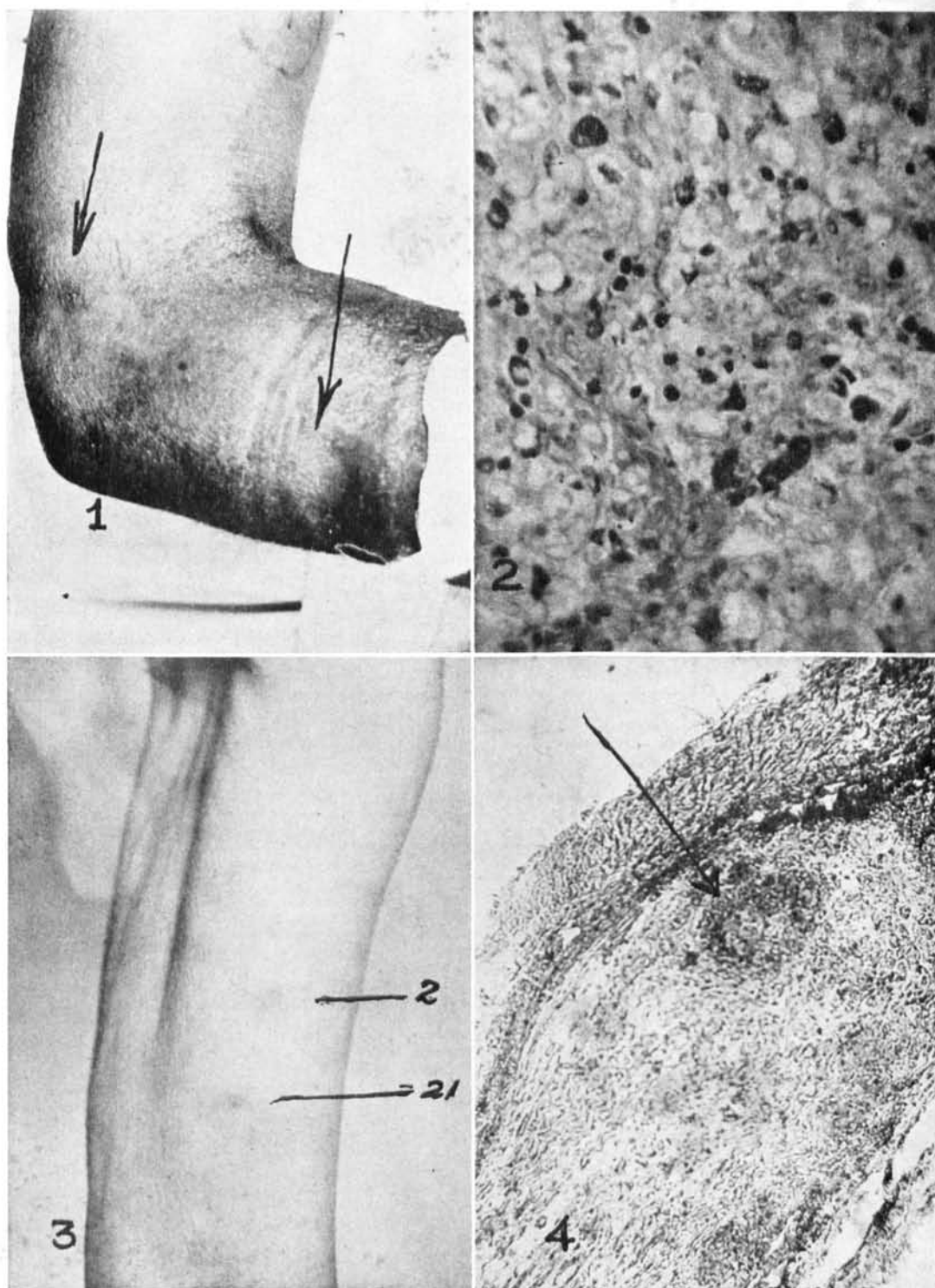


PLATE 5.