

CONTRIBUTION TO THE STUDY OF THE CLASSIFICATION
OF LEPROSY: ASPECT OF LESIONS, ANTIGENIC
RESPONSE, AND PRESENCE OF MICRO-
ORGANISMS IN HISTOLOGIC STRUCTURE*

by

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The pretentious title of this report was suggested by an important publication of Jadassohn (1), with a similar title, in which he demonstrated the value of data with reference to the number of germs, the degree of allergy, and to the structural type in determining the clinical forms of dermatoses caused by micro-organisms. At the time at which Jadassohn wrote, the antigen of Mitsuda had not entered into the leprosy picture. Nor had the histology of leprotic lesions reached its present status.

The proponents of the South American classification should be given credit for assembling the data, the value of which was previously underestimated, and for creating new criteria. They offer a better solution for the problem of classification than has previously been found.

In this paper, testimony is given as to the practical application of the classification. The 70 cases that came to our hands were referred by leprologists from the different Sanitary Districts. Some are expert dermatologists and all have had wide experience in leprosy. The specimens were presented for histological examination, either for the purpose of diagnosis or for classification as to type. For the majority it was possible to give an immediate solution. For others, it was not possible to reach a decision until the progress of the disease had been observed for some time. Time always permitted a clear solution. This latter group of difficult cases constituted an excellent test, especially since the diagnosis was made by persons in no way responsible for the new classification. The cases have been divided into three groups according to the classification; they will be discussed in ascending order of difficulty of diagnosis.

LEPROMATOUS CASES

It may be surprising that we mention here the lepromatous type, perhaps the only one which, at first sight, would seem to offer no difficulty for the classification. The truth is, however, that we received from experienced colleagues 13 patients of this type for classification. Most of them had skin lesions similar to those

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of the uncharacteristic form or tuberculoid, one case even simulating hard tuberculoid lesions. The majority were of short duration and nine had negative smears from the nasal mucosa.

The biopsied lesions were of various types: Erythematous infiltration (5 cases), hypochromic infiltrated macule (3 cases), solitary nodules (2 cases), hardened lesion of the malleolar region (1 case), papular lesions (1 case), and area of anesthesia, corresponding to a compressed nerve (1 case). Acid-fast bacteria were demonstrated in all. Also, in all the cases, the Mitsuda reaction was negative. Because of technical difficulties, search for the lipids could be made in only 9 cases, of which 6 were positive. The 3 cases with lipid-negative lesions were of recent date (four to six months), 2 being of the infiltrated erythematous type and 1 having a hypochromic patch. In other recent cases, however, the lipid test was positive.

Although the lepromatous type is the most individualized and easily identified we found a case not included in the above which caused us no little perplexity.

Mme. M., white, Brazilian, 40 years of age—erythematous infiltration of the forearm of six months' duration with the appearance of the lepromatous type. The lesion was negative for acid-fast bacilli. Histopathological examination: Acute edema of the epidermis. Many nodules of cellular infiltration in the dermis, composed of vacuolated cells, fusiform cells, lymphocytes and plasma cells. Absence of giant cells. Negative for acid-fast bacilli by the method of Ziehl-Klingmueller but numerous gram-positive bacilli by the method of Gram-Weigert.

Particularly valuable in this difficulty was the work done by Rodriguez, Mabalay, and Tolentino (2). We have made repeated search for cyanophilic bacilli in lepromatous and tuberculoid lesions; in the latter lesions, cyanophilic forms were never found in the absence of acid-fast bacilli; in the lepromatous lesions, the proportion of cyanophilic bacilli is always more than that of acid-fast ones.

TUBERCULOID CASES

We may distinguish in this form an acute or reactional group and a quiescent group with "figured" lesions. The reactional group may be further subdivided into (1) those in which the reactional lesions appeared as such at the outset (primary or "*ab initio*") and (2) those in which the phenomena of reaction involved pre-existing lesions.

(A) *Initial reaction lesions.* There were 3 cases in which the first manifestations of the disease as perceived by the patient were of the primary or "*ab initio*" form:

(1) *N. B.*, White, Russian, 46 years of age. Generalized papular eruption. Histopathological examination of biopsy from lesion on hip, February 3, 1944: Marked infiltration of epithelioid cells, edema, with occasional scattered lymphocytes in the dermis and sub-cutaneous tissue, acid-fast bacilli, no lipids. Histopathological examination of second biopsy after a new reaction showing the same clinical symptoms, August 30, 1945: Infiltrated nodules in the dermis and subcutaneous tissues composed of vacuolated cells and rare lymphocytes, many acid-fast bacilli and lipids. At this time, the patient was interned in the leprosarium.

(2) *M. A. M.*, White, Brazilian, 38 years of age. Papular erythema of two months' duration. Histopathological examination of biopsy of forearm, November 19, 1945: Nodular infiltration in the dermis, with epithelioid cells and some vacuolated giant cells and lymphocytes. No acid-fast bacilli. Fernandez reaction ++, Mantoux reaction +. No further observations have been made on this case.

(3) *F. L. V.*, White, Brazilian, 44 years of age. On August 14, 1945, nodular infiltration with edema and congestion of the frontal, temporal, and zygomatic regions, involving the upper eyelid on the right side. Histopathological examination: Marked cellular infiltration of the dermis separated from the epidermis by an edematous layer of connective tissue. The infiltration is composed of epithelioid cells, many vacuolated, and lymphocytes. Many acid-fast bacilli. Fernandez reaction, negative; Mitsuda reaction ++. On October 8, 1946, congestion of the facial lesions increased on the right side, after intradermal injection of chaulmoogra; similar lesions, less prominent and in smaller number began to appear in the same region on the left side. At the same time edematous papules appeared in the posterior cervical region. Histopathological examination of the nodular lesion of the left frontal region: Epidermis thin, beneath it extends a layer of markedly edematous connective tissue, with a few areas of edema and vascular hyperemia. Underlying cellular infiltration continues, occupying the central part of the dermis and passing the deeper part and the subcutaneous tissue. The infiltration is composed of epithelioid cells, almost without vacuole formation and with some lymphocytes, these being more numerous in the deeper layers. Many acid-fast bacilli, waxy granulations and lipid globi. The bacilli were encountered as frequently in the infiltration as in the surrounding tissue. Mitsuda reaction, forty-five days ++. Few acid-fast bacilli in the serum taken after the scarification of the nodule.

The three cases observed underwent varied evolution. The first passed from reactional tuberculoid to lepromatous during eighteen months, judging from the presence of lipids in the last examination in contrast to their absence in the first. Unfortunately, the Mitsuda test was done only at the time of the last examination and was negative.

The second case, as yet not re-examined, showed indications of establishing itself as the tuberculoid type (Mitsuda positive, lesion bacteriologically negative).

The third, more recently observed and still under observation presented a paradoxical appearance. On the one hand, the structure

remains tuberculoid in character, if anything becoming more definitely so, and the Mitsuda remains positive after forty-five days. On the other hand, the bacteriology of the lesions continues markedly positive; and to demonstrate that the cutaneous reactivity is indivisible in the presence of a specific antigen, the nodule of the Mitsuda reaction contains some bacilli. We consider the evolution of this case still uncertain.

(B) *Reactions in pre-existing lesions.* In 4 cases, the bacteriological examination of the lesions was negative. The reaction to lepromin was positive (Fernandez and Mitsuda) in 3; and negative in 1.

(C) *Quiescent tuberculoids.* This was the most numerous group, 32 cases in all, clinically represented by hypochromic patches, with configurated infiltrated borders (17 cases), erythematous spots (11 cases), and hypochromic spots, without visible infiltration (4 cases). The majority were of one to six months duration (17 cases), followed by those with a duration of one year (7), two years (3), eight years (2), and twenty years (1). In all, the structure was uniformly tuberculoid without signs of acute hyperemia, exudation, or necrosis. The bacteriological examination of the lesions in all the cases, by the routine method and by staining of sections (Ziehl-Klingmueller) was negative.

The Mitsuda reaction (read after twenty-one days) was strongly positive (+++) in 17 cases, positive (++) in 10, doubtful in 1, and negative in 1. As the last two cases differ from the classic conceptions, a summary of them is given:

Quiescent tuberculoid with doubtful Mitsuda reaction.

E. M. S., White, Brazilian, 55 years of age. Hypochromic spot with infiltrated border in the knee for one year. Nasal mucosa and cutaneous smears negative for acid-fast bacilli. Reaction to lepromin: Fernandez +, Mitsuda, twenty-one days, doubtful. Mantoux reaction ++ on November 11, 1945.

Quiescent tuberculoid with negative Mitsuda reaction.

B. M., White, Brazilian, 14 years of age. Hypochromic spot with infiltrated border on the face for two months. Bacteriological examination of nasal mucosa and cutaneous lymph negative. Fernandez reaction +, Mitsuda reaction negative, Mantoux reaction ++ July 24, 1946.

For all the cases time was lacking for a reexamination that would permit determination of the constancy or the instability of the characteristics of each case, and judgment as to the stability of the tuberculoid type. With these two exceptions noted above of the cutaneous reactivity to lepromin, the other 32 quiescent cases conformed to the usual pattern with respect to these basic requirements of diagnosis.

UNCHARACTERISTIC CASES

The cases registered as uncharacteristic were 18 in number, of which the majority had achromic or hypochromic spots (11 cases), others erythematous spots (1 case), or merely an anesthetic area (2 cases). The bacteriological examination of the lesion was positive in 2 cases and negative in 16. The Mitsuda reaction was positive in 9 and negative in 9.

The 2 bacteriologically positive cases were in the Mitsuda negative group. In all, the histology of the lesion was uniformly represented by small lymphocytic infiltrations around the small vessels. Rarely did we observe plasmocytes in these infiltrations; such cells seem to be more common in lepromatous lesions. Also we did not see nodular or circumscribed massing of the infiltrations. Thus, the histology has a certain invariability, both qualitative and quantitative. All the patients, at the time of examination, had lesions of an uncharacteristic structure, although formerly some of these had been of the tuberculoid type. Of the latter variety, 2 cases are presented. There were 2 brothers, in 1 of whom, with the evolution toward the uncharacteristic form, the Mitsuda reaction became negative.

(1) *Jo. F. da S.*, White, Brazilian, 12 years of age. Hypochromic spot on the hip. Bacteriology of nasal mucosa and lesion negative. Son of a lepromatous father. Interned in the Educandario de Santa Maria on October 14, 1943. Mitsuda positive (++) May 22, 1943. On August 14, 1943, erythematous plaque with circinated borders observed on left hip. On May 18, 1944, the lesion was shown to be anesthetic. The histopathological examination on this date revealed tuberculoid structure. At this time he was interned in the leprosarium at Curupaiti, from which he was discharged after three months as arrested. A return examination on January 10, 1946, showed a residual hypochromic spot. Mitsuda reaction positive (++) , structure of lesion uncharacteristic. Readmitted to the Educandario.

(2) *Ju. F. da S.*, White, Brazilian, 11 years of age. Brother of the preceding patient and with the same history. Was admitted to the Educandario Santa Maria, April 10, 1943. At this date, the Mitsuda reaction was weakly positive (+). On January 1, 1944 he had 4 small achromic patches on the right leg, left hip, and on the left arm. The histopathological examination on March 16, 1944 showed granulomatous structure. He was admitted to the leprosarium at Curupaiti where he remained three months. On January 10, 1946, return examination showed a residual hypochromic patch. Histopathological examination: Uncharacteristic structure, Mitsuda reaction, negative. On August 10, 1946, Mitsuda reaction negative.

In these 2 cases there was the same evolution: cutaneous spots, tuberculoid structure, and consequent admittance to the leprosarium for treatment, and transformation to the uncharacteristic type.

In the first, however, the Mitsuda reaction remained positive, and even increased in intensity. In the second, the reaction was negative, and continued negative without symptoms of activity of the disease. The hypothesis of super-infection in the leprosarium is not noted, since in one, the cutaneous reactivity was not changed.

Lack of time has not permitted the reexamination necessary for decision regarding the evolutionary possibilities of uncharacteristic lesions. The São Paulo experience is, however, sufficient: variations in the bacteriological findings, and allergic state, with evolution toward the two polar or fixed forms in structure and clinical appearance. Some remain unchanged and can be considered as the true uncharacteristic type, the others are merely initial and final stages in the leprotic infection. It is not possible, however, to distinguish one from the other. At present, there is no means of predicting the ultimate diagnosis.

"In fact, with a patient of this type, well characterized by cutaneous lesions, with a typical structure, who can foretell the evolution? Nobody, not even the most experienced leprologist; since, neither the morphological aspects of the lesion, nor the bacteriological results, much less the Mitsuda reaction, give evidence to affirm that this lesion will be transformed into tuberculoid or into lepromatous or will regress" (3).

While the uncharacteristic lesion exists in the patient, there is a possibility of evolution to one of the two polar forms: in case there has been no evolution only after a cure, can the diagnosis of the uncharacteristic type be made. This diagnosis, however, is as we see, retrospective.

The only invariable element of uncharacteristic lesions is the histological structure, which, as we know, is not specific due to the frequency with which the same structure is found in other inflammatory processes. It is sufficient to mention that it is observed as a consequence of traumatism produced when the investigator is testing for sensibility. Also the structure is associated with lepromatous and tuberculoid lesions without distinction. The histological diagnosis is based on the absence of either or both lepromatous or tuberculoid structure, particularly the latter.

The histological examination is so important that, without it, a diagnosis is almost impossible. In the true "Nevrite" (the lesion supposed to be produced by nerve involvement), differentiation may not be possible between the uncharacteristic and the tuberculoid type unless caseation is present. The reaction to lepromin will not solve the difficulty.

The uncharacteristic cases do not react in a distinctive manner to the specific antigen (Mitsuda or Fernandez test). The result of this test in uncharacteristic cases sometimes gives the same result as in the tuberculoid type; sometimes it simulates that in the lepromatous type.

In the uncharacteristic type the histology of the papule produced at the site of a positive Mitsuda reaction does not have an "uncharacteristic" histological structure; in one instance where such a papule was biopsied, the structure was tuberculoid in spite of the fact that the case belonged to the uncharacteristic type. Similarly, when an acute reaction occurs, the resulting lesions do not show an uncharacteristic histological structure; they show either one of the polar types.

As we see it, the uncharacteristic type is a heterogeneous group, so far as the future evolution is concerned. It has three distinct potentialities: (a) evolution towards the tuberculoid type, (b) evolution toward the lepromatous type, and (c) remains uncharacteristic.

To class the uncharacteristic in the same category as the lepromatous and the tuberculoid types cannot properly be done, inasmuch as these latter two are well defined, with a high degree of stability and with practically invariable characteristics. But to reduce cases belonging to this group to mere stages in the development of the disease would ignore the existence of cases which remain uncharacteristic and regress without undergoing mutation.

Faced with the dilemma of the uncharacteristic cases, we suggest that they be provisionally classified as such until we have new resources for diagnosis.

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