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## EDITORIALS

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#### CLASSIFICATION OF LEPROSY

In view of the fact that at the next international leprosy congress in 1953 the subject of the classification of leprosy will be one of the most important items under discussion, it is not too soon to begin seriously to consider the reasons for disagreement on this topic and why the classification placed before the International Congress at Cuba<sup>1,2</sup> did not receive general approval. It would be well, therefore, for those who believe that a clear classification is the basis of a sound knowledge of leprosy to endeavour to discover the causes of disagreement in this matter, so that an international classification of the clinical types of leprosy based on an adequate knowledge of histopathological changes may be forthcoming and acceptable.

Let it be said at the outset that to date the most logical classification is that put forward by the South American group of leprologists.<sup>3</sup> Unfortunately, to some they appear to confuse

<sup>3</sup> Classification of Leprosy. Report of Sub-committee on Classification, Second Pan-American Conference. Internat. J. Leprosy 15 (1947) 100.

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<sup>&</sup>lt;sup>1</sup>Classification of Leprosy. Resolution of the Fifth International Leprosy Congress on Classification and Nomenclature. Internat. J. Leprosy 16 (1948) 20.

<sup>&</sup>lt;sup>2</sup> Classification of Leprosy at the Havana Congress. Internat. J. Leprosy 16 (1948) 391.

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the issue by (a) introducing a term such as "uncharacteristic" and (b) giving too broad an interpretation to the word "tuberculoid." In the use of the word "uncharacteristic" no differentiation is made between the resolved lesions-be they lepromatous, tuberculoid, or belonging to the so-called "atypical" group-and the early macule which has not become differentiated into one of the two main immunological types. Further, the word "tuberculoid" appears to be used in a somewhat general fashion, apparently signifying any lesion in which epithelioid cells or giant cells are mobilised. The lack of clear recognition that epithelioid foci and giant cell systems are not the sole hallmarks of a tuberculoid case is brought forth in a recent article by Schujman,<sup>4</sup> on the transformation of reactional tuberculoid leprosy to the lepromatous form. This excellent article, with a well documented clinical record, demands careful study by all who are interested in the need for a clear classification of leprosy. Schujman himself, however, casts doubt on the true value of this immunological change when he concludes, "That the prognosis of tuberculoid leprosy in reaction does not depend on the severity of the reaction or on the number of lesions, but rather on the specific organic resistance indicated by the intensity of the Mitsuda reaction; and that only those reactional tuberculoid cases with weakly positive or negative Mitsuda reactions may evolve to the lepromatous form." Further, in the description of the histopathology of the lesion in the "tuberculoid" stage, a point is made that, "The sub-epidermal band is for the most part respected." This, to my mind, takes the whole case out of the "tuberculoid" category and places it in the "atypical," "intermediate" or "dimorphous" group of lesions.

In order to clear our minds on this most important subject of classification, I would refer to some basic histopathological work undertaken during the past five years by Khanolkar<sup>5</sup> at the Tata Memorial Hospital, Bombay. A paper recently presented—but not yet published—throws new light on this allimportant subject and may well mean the final elucidation of this complicated question. In this paper is set forth evidence indicating that the use of such terms as "neural" and "tuberculoid" only gives rise to greater confusion if the reader has

<sup>&</sup>lt;sup>4</sup> SCHUJMAN, S. Transformation of a case of tuberculoid leprosy in reaction to the lepromatous form. Internat. J. Leprosy **18** (1950) 11.

<sup>&</sup>lt;sup>5</sup> KHANOLKAR, V. R. Studies in the histology of early lesions. Paper presented at the Indian Association of Pathologists, 1950. (Not yet published.)

not a true grasp of the essential histopathological picture in the various types of leprosy. In this paper read at the recent Conference of the Indian Association of Pathologists, Khanolkar refers to the earlier work of Woit.6 Gerlach 7 and Dehio 8 demonstrating, as he says, "The centripetal spread of leprosy along nerve fibres," and therefore ruling out any hypothetical initial spread through blood and lymph stream. The work recently undertaken in Bombay clearly indicates that all leprosy is neural in its inception and that the subsequent development of the disease depends on the ability of the tissues to develop an effective cellular and humoral response leading to the "tuberculoid" histological picture, or an inability of the tissue to show an effective humoral or cellular response leading to lepromatous leprosy. It is unfortunate that the word "tuberculoid" has become generally accepted as a term in the classification of leprosy; the immunological character of the response is much more clearly indicated by the word "lepride."

With the above introduction I shall now consider the classification of leprosy in the light of the South American proposals at Havana which received more general support than those put forward by the Indian group of leprologists.

At the Cuba conference there was no general disagreement on the two main divisions of leprosy-lepromatous and tuberculoid. Some of us would prefer the word "lepride" substituted for the latter term. The general description of these two main types is acceptable to all. The word "indeterminate," however, appears to be open to serious objection. The recent work of Khanolkar suggests that from the histopathological point of view there are no such lesions as "indeterminate," but that even the earliest changes in the skin indicate that the lesion is potentially a lepride or potentially leproma. To include lesions not frankly declared to be tuberculoid or leproma in one or the other of these types appears to be logical. The nomenclature of the Cuba classification is, however, confusing and difficult to understand for those who are not familiar with the histological picture. Generally speaking, all lesions of leprosy are in a state of activity, quiescence or resolution; and histologically the end result of the lesions, be they tuberculoid or leproma, if they have resolved or are resolving, would be classified as "uncharacteristic." It would seem, therefore, that the whole group termed

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<sup>&</sup>lt;sup>6</sup> WOIT, O. Lepra 1 (1900) 50, 103, 179.

<sup>&</sup>lt;sup>7</sup> GERLACH, W. Virchows Arch. 125 (1891) 126.

<sup>&</sup>lt;sup>8</sup> DEHIO, D. Conf. Int. Lepra, Berlin 2 (1897) 85.

"indeterminate" at the Cuba conference should be renamed and the lesions placed in one of the following categories:

(a) Lepride (tuberculoid)

(b) Leproma

(c) Atypical

In the light of this discussion I shall review the various clinical manifestations in leprosy and indicate into what type they seem to fall.

It has long been suspected that early macules in leprosy can be divided into two groups: one belonging essentially to the tuberculoid or leprides, and the other to leproma. The Cuba classification indicates this very clearly when it places the simple macular lesion of the Cairo classification in the main tuberculoid type and all other indefinite macules which are generally negative to standard methods of examination in the indeterminate group. A similar recognition is given to the separation into these two groups in the polyneuritic lesions.

As far as macules are concerned, the work of Khanolkar fully corroborates the findings of the South American leprologists, indicating that these fall into two categories, one of which is closely allied to tuberculoid leprosy or the leprides (the Cuba conference report classified these as "maculo-anaesthetic" (Tm), and the other group which is essentially leproma (the indeterminate macule (Im) of the Cuba conference).

It would seem more logical, then, to include the early macule with vague edges and a histological picture essentially of a lepromatous nature under the lepromatous classification, and the early macule with definite edges under the leprides. The histological characteristics of the early prelepromatous macule are as follows:

Slight, but diffuse round celled infiltration. With Fite's <sup>o</sup> method bacilli can only be seen in the nerves and often in the finest twigs, no bacilli being demonstrated in the perineural tissue, in bundles of collagen fibres or the adjoining subcutaneous tissue (Khanolkar).

On the other hand in the simple macule (maculo-anesthetic lesion) the following is the histological picture:

Foci of cellular accumulation largely composed of histiocytes and lymphocytes. In the more advanced stages these consist mainly of epithelioid and giant cells, which in cases examined in

<sup>&</sup>lt;sup>9</sup> FITE, G. L., CAMBRE, P. J. and TURNER, A. S. Procedure for demonstrating lepra bacilli in paraffin sections. Internat. J. Leprosy 16 (1947) 381 (reprinted).

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detail by Khanolkar were shown to contain fragmented nerve fibres embedded in the granuloma. It was not possible to demonstrate bacilli in the majority of these sections except rarely where stray organisms were seen in the exudate.

With reference to the development of these lesions Khanolkar states, "The clinical course and manifestations of leprosy depend on the ability of the tissues to restrain the growth and spread of bacilli leading to a tuberculoid histological picture, or on the other hand an inability of the tissues to put up an effective humoral, or cellular response leading to lepromatous leprosy." It seems, therefore, that it would be more acceptable if the indeterminate type of lesion ("uncharacteristic" of the South American classification) were divided into two groups: (1) leproma and (2) tuberculoid or leprides. The Cuba classification would then, as far as these lesions are concerned, be modified thus:

Lepromatous leprosy Pre-leproma (pl) Macular leproma (Lm) Diffuse leproma (Ld) Infiltrative leproma (Li) Nodular leproma (Ln) Tuberculoid (lepride) Maculo-anaesthetic (Tm) Minor lepride (Te) Major lepride (TE)

In the discussion so far only the macular group has been considered. There are two further groups which should be included in any adequate classification. In one of these polyneuritic signs alone are seen. Again the Cuba conference suggested that this group consisted essentially of three divisions, and they therefore classified polyneuritic leprosy into:

- (a) Polyneuritic tuberculoid (Tp)
- (b) Polyneuritic leproma (Lp)
- (c) Polyneuritic indeterminate (Ip)

As has been mentioned, Khanolkar's recent work indicates that all leprosy is neural in its inception and bacilli, apart from those discovered in sections from contacts of positive cases,<sup>10</sup> migrate towards the superficial nerve plexus in the skin and are first seen in the nerves and not in the surrounding cellular infiltrate. Khanolkar has demonstrated the presence of blebs or saccules in the perineural sheath through which the bacilli

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<sup>&</sup>lt;sup>10</sup> FIGUEREDO, N. and DESAI, S. D. Positive bacillary findings in the skin of contacts of leprosy patients. Internat. J. Leprosy 18 (1949) 59 (reprinted).

escape into the dermis. The polyneuritic case, therefore, may represent those individuals in which the bacilli are confined to the nerves. Recently we have had clinical evidence of one such case in which bacilli were found in the nerve (section of ulnar) and not in the skin, and the histology of the nerve was essentially lepromatous, the lepromin being negative. It seems reasonable to conclude that there is another group which show polyneuritic signs in which the lepromin is positive and the tissue reaction is essentially that of a lepride. If this interpretation is accepted then the polyneuritic group would be divided between the leproma and the tuberculoid types. The indeterminate polyneuritic lesions would probably represent the resolved lesions in which the tissue had satisfactorily dealt with the bacillary invasion and the cellular reaction-whether lepromatous or that of a lepride-would disappear leaving residual fibrosis depending on the degree of reaction.

It was a disappointment to some that the Cuba conference took no note of the so-called "intermediate," "atypical" or "borderline" cases. This group of cases has been further elucidated. Schujman, in his recent article, clearly states that he has never seen a strongly positive Mitsuda reaction become negative. The case he quotes as changing to leproma shows the two main features of the atypical group: (a) weakly positive Mitsuda and (b) relatively clear zone at the junction of the dermis with the epidermis. In fact, Schujman himself states that only those reactional tuberculoid cases with weakly positive or negative Mitsuda reactions may evolve into lepromatous leprosy. Velasco<sup>11</sup> reports two cases of the transformation of tuberculoid leprosy to the lepromatous type. In the first case reported by this worker unfortunately the Mitsuda test was not done in the initial stage and the photomicrograph indicates that the lesion was more of the nature of a maculo-anaesthetic macule rather than clinically a major lepride. It is known that a small proportion of these show negative or slightly positive Mitsuda reactions and are liable to become lepromatous. The photomicrograph of the second case shows, when in the "tuberculoid" phase, a relatively clear sub-epidermal zone which is, according to some workers, an indication that it belongs to that group which Schujman refers to as "hypo-allergy." From the study of these articles and from our own experience, the tuberculoid group fall into two divisions:

<sup>&</sup>lt;sup>11</sup> VELASCO, F. Tuberculoid leprosy; its transformation to the lepromatous type. Internat. J. Leprosy 9 (1940) 91 (reprinted).

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(a) With a strongly positive Mitsuda reaction and with a tuberculoid histology, the granuloma extending up to the epidermis. Schujman himself in this connection states, "I have never seen a strongly positive Mitsuda reaction become negative."

(b) With a weakly positive or negative Mitsuda, clinically the lesions are less prominent than in the former group, the edges tending to be less distinct than in the clear-cut margins of established tuberculoid leprosy, and the histology showing the relatively free band between the epidermis and the granulomatous masses in the dermis. With regard to this group I quote Schujman again: "Patients giving weakly positive (Mitsuda) reactions may either change to strongly positive or remain with reactivity unchanged for years, or show a decrease until the reaction is frankly negative, the patient anergic."

I believe this evidence taken from the South American workers' contributions to literature is sufficient to make a plea for sub-dividing the "tuberculoid" group into two:

(i) Truly polar with strongly positive Mitsuda reaction and characteristic histological and clinical features.

(ii) Weakly positive or negative Mitsuda reaction with a characteristic histological and clinical picture and a strong tendency to transform into lepromatous leprosy.

It is this latter group which has been called by various writers "intermediate," "atypical," "borderline"; and Khanolkar<sup>12</sup> has recently coined the term "dimorphous." It is suggested, therefore, that workers study their histological and clinical material in the light of the above remarks and judge whether there is justification for giving a place in a classification, between the lepromatous and tuberculoid groups, to these cases and naming them "dimorphous," dividing this group into those which still show predominantly a tuberculoid feature (DT) and those which show a predominantly lepromatous feature (DL).

I have not discussed the question of the uncharacteristic lesion. Personally I am of the opinion that this term should be dropped, but if thought necessary it should be replaced by "resolved lesions." The uncharacteristic group of the South American workers appears to be altogether too confusing. It apparently includes (1) resolved tuberculoid lesions, (2) resolved leproma, (3) early maculo-anaesthetic lesions, (4) the pre-lepromatous macule, and (5) resolved atypical or dimorphous lesions.

<sup>12</sup> COCHRANE, R. G. Some brief comments on the classification of leprosy. Lep. in India 21 (1949) 86.

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This gives rise to considerable misunderstanding, for on histological bases alone a case could change from an early maculoanaesthetic to tuberculoid and then back again, or become a dimorphous lesion—this would have to be included in the tuberculoid group according to the present Cuba classification—reverting to uncharacteristic again and finally becoming leproma. If the word "dimorphous" is not acceptable, could not the intermediate group (I) of the Cuba classification refer to the dimorphous lesions? These are truly indeterminate and may change.

It is hoped that this review of the classification of leprosy will serve to stimulate workers to consider a more logical and acceptable nomenclature for the various types and sub-types of leprosy, and will lead to a more generally accepted international classification, which will not offend accepted dermatological and immunological concepts.

For references Nos. 6 to 8 I am indebted to Dr. V. R. Khanolkar. —R. G. COCHRANE, M. D., F. R. C. P.

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