OBSERVATIONS ON THE CLASSIFICATION OF LEPROSY

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I. HISTORICAL

The first generally accepted classification of leprosy was probably that of Danielssen and Boeck (1) who in 1848 proposed the terms "nodular" and "anesthetic" to indicate the two main forms. Hansen and Looft (2) later proposed the designations "tuberosa" and "maculo-anesthetica" for the same types. In 1931 at the Leonard Wood Memorial Conference held in Manila the terms were changed to "cutaneous" and "neural" with some modification in the concepts of the two types. No reference was made to the tuberculoid type in the final report of this Conference, indicating that it was not recognized at that time as a problem in classification. The sudden outburst of interest in this type occurred shortly after the close of this Conference.

It should not be inferred that the tuberculoid type had been unknown before 1931. Although other writers had previously described elements of tuberculoid histology in leprosy, the term was

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first used by Jadassohn (3) in 1898 and the credit for the recognition of this special histological feature as well as for its proper interpretation rightly belongs to him. His original article was followed by important publications by Klingmüller in 1900 (4) and by Unna, P. Sr. in 1910 (5). Kedrowsky (6) and Unna, P. Jr. (7, 8) each reported a case a few years later. With the presentation of excellent reports by Darier (9) based on 3 cases and by Pautrier and Boez (10) on one case at the Third Leprosy Conference held at Strasbourg in 1923, more interest in what had previously been considered merely a pathological curiosity resulted in the reporting of occasional cases in such widely scattered regions as Australia, the Philippines, India, South Africa, France, and Germany, by Tebbutt and Molesworth (11) in 1926, Wade and Pineda (12) in 1927, Henderson (13) in 1928, LeRoux Du Pre (14) in 1930, Mottat (15) in 1931, and Bruusgaard (16) in 1931 respectively. In spite of these isolated reports, however, tuberculoid leprosy continued to be considered merely as an interesting but rare variety.

Another line of observation slowly developing at the same time was the study of the macules. Such lesions were known to be a rather infrequent early manifestation of nodular leprosy. They were much more often associated with lesions of the nerves producing the long-known clinical picture of *lepra maculo-anesthetica.* However, the exact relationship between the macules and the nerve lesions had always been puzzling; there are many macules not associated with definite nerve changes, as well as many neural cases without associated macular lesions throughout their course. The macules of leprosy have always been difficult to classify.

As study of the disease improved in tropical countries, closer examination of the macules in the colored skin indicated that there were several varieties which had not been seen or which had been missed on the white skin. Numerous good descriptions of such macules were published in the early decades of the present century; the most frequent contributors being the workers in India (Muir, Henderson, Lowe, Cochrane), scattered workers in Africa, and a distinguished group in South America. In the Philippines, since 1918, a line of observers (Nicolas, Rodriguez, de Vera, Chiyuto, Manalang, Lara, Velasco) had been following the early lesions of children born in the Culion Colony.

In the meantime, Muir in 1924 (17) and Lowe in 1929 (18) had reported on the nerve abscess, later found to be one of the characteristic features of the tuberculoid type.

II. IMPORTANCE OF THE TUBERCULOID FORM

It was not until workers began to make biopsies of the macular lesions in a systematic manner that the importance and possible significance of tuberculoid leprosy was recognized. The first investigator to do this was Manalang in 1931 (19). His first cases were in adults seen at the Cebu Skin Dispensary; the following ones were in children born in the Culion Colony who had been separated from their parents and were being cared for at Welfareville, near Manila.

At about the same time, Wade, who was returning to America via the Cape of Good Hope after the Manila Conference, saw some cases at the Pretoria and the Emjanjana leprosy institutions with interesting macular lesions which he had seldom seen before. Biopsy specimens secured at that time and later studied by him in London in 1932 (20) were found to have definite tuberculoid architecture. Soon after, workers in India and South America also began to biopsy more of their cases.

In South America, independent early investigations on tuberculoid lesions were undertaken with vigor and enthusiasm, and the workers in these countries have assumed undisputed leadership in this field during the last decade or so.

In the opinion of the writer, the firing shot in the vigorous controversy regarding the interpretation of the tuberculoid type was the outspoken and thought-provoking articles of Manalang (19, 21). On the basis of a study of repeated biopsies and emphasizing the importance of serial sections, Manalang proposed the theory that the histogenesis of leprosy starts with peri-vascular round cell infiltration (later known as "uncharacteristic" in the South American classification), passes through the tuberculoid stage, and finally leads to the lepromatous structure. This theory did not gain general acceptance, but it did arouse much interest and discussion.

The main difficulty with Manalang's conception is his insistence that every case of leprosy must pass successively through the three stages, that infection can occur only in infancy since all adults are absolutely immune, and that once infection has taken place, it takes an inexorable and irreversible course. As he states, "Once a leper, always a leper."

These discoveries were further advanced and consolidated as a result of a memorable series of articles by Wade (22, 23, 24, 25), based on specimens obtained from different countries. There can be no doubt that his investigations served to establish the groundwork of our present knowledge regarding tuberculoid leprosy.

By the time of the Cairo Congress in 1938, therefore, good progress had been made in the study of tuberculoid leprosy in the Philippines, Brazil, Argentina, and India. In fact, Rabello Junior (26) as early as 1936 had already proposed a classification based on the two polar types of leprosy, one of them being the tuberculoid form.

The lively and prolonged discussions within the Committee on Classification at the Cairo Conference indicated the importance that the tuberculoid type of the disease had gained in the minds of investigators. The final report of the Committee was vigorously opposed by the South American delegates for the reason that the tuberculoid form was considered merely a sub-variety under the neural type. The report recognized two main types, namely, (a) lepromatous and (b) neural, with three sub-types under the latter, pure neural, simple macular, and tuberculoid. The South American delegates and some others thought that the tuberculoid form was of sufficient importance to merit consideration as a separate type.

III. THE SOUTH AMERICAN CLASSIFICATION

The South American delegates, as already mentioned, completely disagreed with this report and on their way home, some of them decided to continue their discussions and observations at São Paulo, Brazil. There, under the guidance of Prof. Aguiar Pupo, they advanced in 1938 the classification (27, 28) which is now known the world over as the South American. Shortly after the Cairo Conference, Baliña, dean of South American leprologists, and Basombrio, (29) also published an authoritative article on the new classification. Since then, much ground work has been laid and numerous articles dealing with this classification have appeared. This subject was discussed by Brazilian and Argentine leprologists at various meetings, the most important being those at Tres Coracoes and São Paulo but it was not until 1943 when Pardo Castello and Tiant presented a paper at the 93rd annual meeting of the American Medical Association (30) that the classification became extensively known in the United States.

A more general acceptance of the South American classification took place at the Second Pan-American Conference in Rio de Janeiro when papers were presented to clarify its clinical, histological, and immuno-biological bases. It was then adopted as the Pan-American classification. The final authoritative statement of the new classification is found in the Report of the Committee on Classification (31) of the Conference.

A tabular summary of the types and clinical forms which have been established is given below:

TYPE	VARIETY OF CLINICAL FORMS
Lepromatous (L)	Macular Infiltrative (in plaques or diffuse) Nodular Neural Generalized
Uncharacteristic (I) or Unidentified	Macular Neural Neuro-macular
Tuberculoid (T)	Macular Papular Neural Reactive

All those interested in the classification of leprosy should read the Report of the Committee which was published in full in the Jan.-March issue of the JOURNAL, Volume 15, pages 100-107.

The Report contains a striking modification of the original South American classification in the sense that the uncharacteristic form has been raised to the status of a fundamental type. In other words, it now occupies the same rank as the tuberculoid and the lepromatous types. On the surface, this appears to be a significant departure from the previous classifications in use during the last hundred years, all of which had maintained only two main types. It will be seen later that fundamentally, there has been no change. We have emphasized above in the historical review that in spite of the change of designations and slight modifications of the distinguishing features, the two-polar idea has persisted.

The Report further emphasizes certain features of the new classification:

(1) The types are distinguished primarily by their histo-pathological structures.

(2) The relative stability of the tuberculoid in contrast with the unstable nature of the uncharacteristic type is stressed.

(3) Two main types of the tuberculoid are recognized:
   (a) The non-reactive or torpid (minor tuberculoid) and
   (b) the reactive (major tuberculoid). The latter is further sub-divided into 2 sub-varieties: (i) those in

which the phenomena of reaction occur on a pre-existing torpid lesion and (ii) cases in which the reactive lesions appear as such from the very outset on apparently normal skin, that is, where there was no pre-existing lesion.

One of the important features of the Report is the further subdivision of the three main types into clinical sub-varieties with detailed description of their distinctive lesions, so that except for the neural cases, there should be little difficulty in applying it in the field.

IV. COMMENTS ON THE PAN-AMERICAN CLASSIFICATION

It is generally agreed that in the Report of the Rio de Janeiro Committee a practical classification with a proper histological basis and supported by clinical and immuno-biological characteristics has at last been elaborated.

Nevertheless certain important points have been left open by the Report for further study and discussion. These include two questions which are so important in understanding the classification that they will be discussed at some length.

1. Is the transformation of cases from the tuberculoid type to the lepromatous possible?
2. Can the clinical classification of the neural forms be made easier?

1. (a) Possible transformation from tuberculoid to lepromatous:

This is a point that was not definitely dealt with in the Report. Instances of definite transformation from tuberculoid to lepromatous types have been reported in the past by Lowe (32), Rodriguez, Wade, and Plantilla (33), Velasco (34), and others. But true transformations have been denied so vigorously for years by many workers that it is necessary to present additional information on the subject.

An indication of the close inter-relationship between the tuberculoid and the lepromatous forms is the occasional finding of the characteristic cells of both types, namely, epithelioid and lepra cells in the same section of skin. Such an occurrence is discussed in an article presented at the Second Pan-American Conference at Rio de Janeiro by Moacyr de Souza Lima, Jose Barba Rubio, Lauro de Souza Lima, and Paulo Rath de Souza (35) from which the following is quoted:

"Finally, we have observed exceedingly few cases (an infinite

minority) in which the phenomenon of phagocytosis, particularly the lytic function, is not present in distinctly polar extremes, but rather, whereas some cells completely destroy the bacilli, others merely engulf them or are themselves destroyed by the bacilli. The resulting structure shows a multitude of epithelioid cells, scarcely forming tubercular or nodular arrangement, accompanied by vascular dilatation, interstitial edema, with a few lymphocytes and giant cells. Some of the epithelial cells are so similar to the Virchow cells that the histologist, on a study of the structure alone, is unable to decide whether the lesion is tuberculoid or lepromatous. To complicate matters, there are found in such sections, after acid-fast staining, more bacilli than could be expected from an equivalent advancement of tuberculoid lesion and less than in a similar degree of lepromatous infiltration.

"In this stage (which we repeat is not a clinical form) should be included the limiting, intermediary, and relapsed lesions, delineated and studied by Drs. Lauro Souza Lima and de Souza Campos as well as the lepromatous lesions with a large number of epithelioid cells mixed with Virchow cells, and with a tendency to nodular formation."

The authors insist, however, that they have not observed a single instance of a definite transformation from the tuberculoid to the lepromatous type.

Even more significant were the cases reported by Souza Campos (cited by the Committee Report) which started as uncharacteristic lesions, became definitely "reactivated tuberculoid" in character, and finally were transformed into the lepromatous form.

Finally, during the visit to São Paulo by a number of the delegates to the Pan-American Leprosy Conference last November, Souza Lima demonstrated 4 lepromatous cases in which previous biopsies had shown a tuberculoid histology and in which still more pertinently, previously strongly positive Mitsuda reactions were evidenced by manifest scars. In these 4 cases at least, the postulates required for proving a true transformation from one polar form to another had been complied with, namely (1) reversal of a strong Mitsuda reaction, (2) change in the histological architecture, (3) reversal of the bacteriological findings, and (4) complete transformation of the clinical picture. Several other transformations were demonstrated differing from these 4 cases only in that they did not exhibit scars following somewhat weaker Mitsuda reactions.

The question may be raised at this point: Why is it that so many workers have failed to observe transformation from tubercu-

loid to lepromatous? The main reason is that such a transformation is much less frequent and usually proceeds at a very much slower rate than the comparatively more common and rapid change from the uncharacteristic to either the lepromatous or the tuberculoid form; this latter usually takes place within a matter of a few months or a couple of years. In the experience of the writer, the change from a tuberculoid to a lepromatous form is a process that usually takes a much longer time than this.

It has been demonstrated, therefore, that transformations do occur from the tuberculoid to the lepromatous type. The point remaining to be determined is whether such changes take place frequently enough to influence basically concepts concerning classification. Although further confirmation of this transformation is perhaps desirable, the writer considers that its occurrence has been established. Furthermore, the question is of fundamental importance for it proves that in spite of its comparative stability, the tuberculoid type is itself a mutable or evolutive form of the disease.

Portugal (36) has rightly pointed out that there are 3 groups of patients included in the uncharacteristic type: (1) those about to become tuberculoid, (2) a number progressing towards the lepromatous, and (3) a group which do not undergo any transformation and remain as uncharacteristic until their disappearance. Likewise, it may be considered that there are also three groups of cases in the tuberculoid type: (1) some that will not go beyond this stage but will retrogress to the uncharacteristic type, (2) a large group that will remain tuberculoid until the lesions have been absorbed, and (3) some that will progress to the lepromatous type. Thus, the uncharacteristic and the tuberculoid types are in effect also stages or successive steps in the pathogenesis of the infection.

Since this concept, which is neither admitted nor denied in the Pan-American classification, if accepted must necessarily lead to modifications of the classification, it is necessary to explain its basis more fully and to point out the place of the tuberculoid type in the evolution of the disease.

(b) Difficulty of clinical differentiation of "Neural" cases:

In spite of the fact that the neural manifestations of leprosy are one of the most characteristic features of the disease, they are the most difficult to explain in the present stage of our knowledge, and have always been the "bête noir" of all classifications. This is reflected by the following statements appearing in the report of the Committee on Classification of the Rio de Janeiro Conference:

"Compared to the symptoms of the cutaneous form of leprosy,

the neurological syndromes are an expression of the specificity of the disease to attack the nerves. These syndromes do not possess sufficiently distinct characteristics to be placed in either of the three principal forms." "*Amyotrophies and Trophic Phenomena:* Leprosy cases with partial or total atrophy of muscles of the extremities, mutilations, trophic ulcers, etc., with regional anesthesia, occasionally without anesthesia, are hard to classify satisfactorily."

When it is realized that in certain regions of India, for instance, at least 40 per cent of all cases show amyotrophies and trophic phenomena without cutaneous lesions (secondary neurals and burnt-out cases) the importance of this deficiency of the classification is made apparent.

These difficulties are in part due to insufficient knowledge of the pathological changes occurring in the involved nerves because of the natural disinclination of workers to biopsy nerves. A tremendous amount of work has been done in the past in determining the disturbances of cutaneous sensibility over the involved areas but we require many additional investigations of the kind which have been done by Ermakova (37, 38), Muir and Chatterjee (39), and Souza Lima and Alayon (40) if we are eventually to understand the underlying basis of the neural changes.

V. THE NATURAL EVOLUTION OF THE DISEASE IN LEPROSY

In order to indicate the position of the tuberculoid type in the developmental cycle of the disease and to show its relationship to the other types, it is necessary to follow the course of the infection, as understood at the present time, in an average case of leprosy.

It is accepted that the development of any infection is the result of an interplay between the invasive powers of the infective organisms and the defensive forces mobilized by the host. Leprosy is unique in that this conflict is unusually prolonged. Within wide limits also, the disease follows fairly well-defined patterns apparently conditioned mainly by the ebb and flow of the bodily resistance.

Based on observations somewhat similar to those found to be true in tuberculosis, it is commonly considered that adults show some degree of resistance or partial immunity to leprosy, a state which is associated in some way or other with sensitivity to the Mitsuda antigen. Since this partial immunity and accompanying reactivity to the Mitsuda test are absent in most infants and very young children, it is presumed that both are acquired and perfected as the child grows up.

When infection occurs in an adult, the resistance already present may be further built up and the appearance of the lesions of the tuberculoid type may represent its fullest development. When the infection occurs in children the uncharacteristic lesions are most likely to appear first. These may either progress to the tuberculoid stage or if sufficient resistance is not developed, they may become lepromatous. Often such lesions may disappear without progressing further. If the bacilli gain the upper hand the resistance which has been gradually built up is overcome, and whenever this happens, reactivity to the Mitsuda test is lost and transformation to the lepromatous type takes place.

When such a transformation occurs, at first the resisting powers of the host seem to be completely overwhelmed and the bacilli seem to multiply in an unrestrained fashion. Yet, in the course of years in many cases there reappears slowly and haltingly at first, a "second wind" as it were; that is, the resistance is gradually built up again, and through some means not yet even guessed at, the bacilli (both those within the lepra cells as well as those lying free in the interstitial tissue) are slowly disposed of, with gradual return of reactivity to the Mitsuda test.

Most of the cases reaching the lepromatous stage show one or more cycles of improvement which coincide with reappearance of weakly positive Mitsuda tests and retrogression of the skin lesions, alternating with periods of relapses with disappearance of the Mitsuda reactivity according to Hayashi (41). It is the existence of these periods that makes the evaluation of treatment so difficult in leprosy.

Some patients, however, fail to produce any resistance at all and remain lepromatous until the end. The bacilli continue to multiply unrestrainedly and the entire skin becomes infiltrated with lepromatous tissue made up chiefly of masses of bacilli. These individuals are presumed to have been originally negative, or at most, weakly positive to the Mitsuda reaction.

In other cases practically all the bacilli in the skin, mucous membranes, and nerves, if not in all the internal organs, are eventually lost and the cutaneous lesions gradually disappear, leaving behind wrinkled or scarred skin with underlying cicatricial tissue. Thus in all the stages a tendency to self-limitation is observed in many cases of leprosy, a fact which has been much emphasized in the past. Among the older workers, the presence of some degree of atrophy and of trophic disturbances accompanying the regression of the cutaneous lesions were considered of good import in the prognosis with regard to relapses. This has contributed to the im-

pression that, as a rule, patients with neural manifestations have a better prognosis than those with predominatingly cutaneous lesions.

Unfortunately, particularly if the infective process has passed through an advanced lepromatous stage, permanent damage to certain nerves is likely to be produced, causing the self-cured patients to become crippled and deformed for life.

As stated previously, the struggle between the *M. leprae* and the tissues of the host may go on for long periods of time in a silent and uneventful manner. Occasionally, however, it flares up in a spectacular way. In the tuberculoid stage, this acute process produces the striking "reactionary tuberculoid" lesions, while in the lepromatous stage, the acute flare-up is known as "Lepra reaction" or *Erythema nodosum leprosum.*

When the full cycle of the development of the disease is considered as above, it becomes clear that the longest, most important, and the most characteristic stage of leprosy is the lepromatous—it is the real disease. The other types, including the tuberculoid, merely represent either benign atypical cases or evolutionary forms of the earliest stages of the disease. We must not allow the novelty of their comparatively recent discovery to distort the true perspective.

Inasmuch as the Mitsuda or lepromin reaction has been frequently mentioned in the discussion and will be further referred to, it may be well to discuss it briefly; a more extended presentation would be entirely out of place here.

In endemic countries, about 60 - 80 per cent of all adults give a positive reaction to the Mitsuda test, although in about half of the cases, the reactions are not strong. Incidentally, many laboratory animals react positively to the test. In non-endemic countries, the percentage of positive reactors in the adult population varies from 25 to 75 per cent, with many weak reactions. It has not been definitely determined whether or not there is a real difference in the prevalence of positive reactors in endemic and non-endemic countries. Among infants below the age of one year, among the children of both leprous and normal parents, Chiyuto (42) found none reacting positively at birth but by the age of 2 to 3 years about 40 per cent were Mitsuda positive.

At the present time, many investigators consider that the Mitsuda reaction is in some manner associated with resistance on the part of the host to the *M. leprae,* although it will be impossible to show the nature of this relationship until a susceptible experimental animal has been found. Furthermore there is need of standard-

izing the composition of the antigen, manner of application, dosage, and interpretation of results. In tuberculoid leprosy, the percentage of Mitsuda positives is high, ranging from 75 per cent to 90 per cent with many strong reactions, but unfortunately, most workers, in interpreting their results, do not take into consideration the fact that the positive reactions may at least in part be due to the reactivity of normal adults and can not entirely be ascribed to the tuberculoid lesions. In our experience, the Mitsuda reaction remains at about the same level or is increased in persons who develop tuberculoid leprosy, but this reactivity is entirely lost if they develop the lepromatous form.

The negative result of the Mitsuda test in a high proportion of cases of the lepromatous type is the one definite finding in connection with the test which gives it some degree of specificity. Using "Stefansky leprolin" from animals heavily infected with rat leprosy, results are obtained in non-leprous persons and in patients with tuberculoid lesions which are very similar to those found with the Mitsuda antigen. As already stated, Mitsuda's test is usually negative in the lepromatous type; the Stefansky leprolin on the contrary usually gives a positive reaction in such cases. Likewise, preparations from cultures of timothy hay, smegma, and other saprophytic acid-fast organisms as well as of strains of supposed leprosy bacilli obtained by the methods of Clegg, Needham, McCoy, Duval, and Kedrowsky also usually give positive results in the lepromatous type.

In tuberculous and syphilitic adults, positive reaction to the Mitsuda test is the rule.

VI. A FOURTH FUNDAMENTAL TYPE

The establishment of a fourth fundamental type to distinguish a special neural form would tend to clarify some of the difficulties in understanding the classification of the disease, because many neural cases which do not logically fall into any of the presently recognized types will probably be found to fit into this proposed type. The pathological characteristic of this type is interstitial proliferation or simple growth of fibrous tissue which, under the Pan-American classification, is included under the uncharacteristic type. The proposal, therefore, consists in separating this histological architecture from the easily distinguishable round cell infiltration.

In many cases of leprosy, there is a period of "prolonged latency" extending over a period of many years, in which the bacilli are presumed to lie in a quiescent state in the tissues of the skin,

nerves, and perhaps other organs of the body. During this period, they retain their viability but seemingly do not multiply to any large extent and do not produce any markedly noticeable tissue change or reaction. What the histological picture of the involved tissues in the early part of this stage is, is of course not known; Wade (43) describes the earliest noticeable changes in the nerves as follows:

"Frequently in nerve sections one may see no change whatever other than the irregularly distributed increase of the connective tissue surrounding the nerve fibers themselves. This moderate fibrosis, in the absence of infiltrating cells, seems quite innocent of infection. Nevertheless, bacilli are often present, usually in groups, ordinarily not particularly abundant. In this stage they are apparently entirely in the connective tissue itself, where they cause sufficient irritation to lead to slow proliferation."

In the skin, such a picture is associated with a fairly distinguishable type of macule, quite distinctly outlined, simulating some varieties of tuberculoid macules but differing from them in being less red in color, and in showing no papulation, although the margin may be quite distinctly raised.

In spite of such distinct lesions on the skin, the tissue changes are so minimal that before the existence of bacilli was proven in such macules, P. G. Unna is said to have hypothesized that they were produced simply by "the toxins of the bacilli through the nerves," according to Lie (44). Later, after the bacilli had been demonstrated, Unna himself abandoned this theory.

In some cases of leprosy, the histological and bacteriological findings do not progress beyond this initial stage, and yet are associated with distinct clinical lesions. In tissue sections of the lesions from such cases, bacilli are seen singly or in small clumps in the interstitial spaces without producing any response beyond slight increase of the connective tissue. These are the cases which the writer proposes to place in a new fourth type to be designated as "maculo-anesthetic" *(senso stricto)*.

The basis for this separate maculo-anesthetic type of leprosy, therefore, would be as follows:

(a) histologically — interstitial proliferation
(b) bacteriologically — few scattered bacilli in the connective tissue on repeated careful examination of sections stained for acid-fast organisms. Ordinary smears are negative.
(c) clinically — macules with above histological and bacteriological characteristics followed by peripheral anesthesia with atrophies and trophic disturbances.

With regard to reactivity to the Mitsuda test, the maculo-anesthetic type in the early stages, behaves as does the round cell or uncharacteristic type, that is, the result is variable, but in the late stages with distinct trophic changes, the Mitsuda test is positive to the same extent as in tuberculoid leprosy, with a tendency to very strong reactions.

Under the Pan-American classification, this type is considered as a sub-variety of the uncharacteristic with the designation of "neuro-macular."

It should be emphasized again that this type is, like the other types, in part a stage in the development of the disease and transformation of some cases to other types is possible, although other cases persist in this stage indefinitely, as already indicated.

In order to avoid unnecessary discussions in the future, it should be pointed out that one must not expect to find many cases of maculo-anesthetic leprosy in leprosaria because only the few who happen to have been found positive in the nasal septum would be admitted to such institutions. It would be a mistake for physicians working in leprosaria to try to classify some of their secondary neural cases as maculo-anesthetic. Then again, for those who are studying the early lesions of children of leprous parents in preventoria, the writer wishes to add that of 398 Culion children whom he observed for two and one-half years, only 4 developed leprotic lesions which could be classified as of the maculo-anesthetic type. However, among similar children at the Boys and Girls Home near Honolulu, Wayson (45) seems to have found more cases belonging to this type.

By and large, most of the cases of true maculo-anesthetic leprosy would be found in surveys in which the entire population had been examined. Furthermore, more and more will be so diagnosed the longer the macular lesions of the early cases are followed.

It appears evident that there is little difficulty in providing fairly distinctive pathological and clinical bases for the proposed maculo-anesthetic type. There is nothing new or unknown about any of its characteristics, all that has been done is to give it a distinct entity and to place it in its proper place in the developmental pattern of the disease.

VII. PROPOSED MODIFICATION OF THE PAN-AMERICAN CLASSIFICATION

(a) Histological basis of proposed classification

In the opinion of the writer, the successive stages in the de-

velopmental or evolutive course of the disease with their corresponding histology are as summarized below:

	Type	*Histological structure*
1.	Maculo-anesthetic (neuro-leprid)	Interstitial proliferation
2.	Simple macular (leprid)	Round cell infiltration
3.	Tuberculoid	Tuberculoid granuloma
4.	Lepromatous	Foamy cell (lepra cell) infiltration

1. The histological features of the maculo-anesthetic which is considered as the earliest stage in the developmental cycle have already been discussed. In the ordinary case of leprosy, this stage is missed because there are no external or histological manifestations of the disease.

2. The next histological stage is that of round cell infiltration. It is supposed that the bacilli either are carried by the lymph current or are spread by direct contiguity to the cutaneous nerve endings and to the minute blood vessels, for both of which structures they seem to show a special affinity. We are not here concerned whether "the bacilli commonly occur in the endothelial cells of blood vessels" as has been stated by Cowdry (46), or are present just outside the capillaries as has been found by Fite (47). The important thing is that the collections of bacilli in these locations are frequently associated in the early stages of leprosy with a mild inflammatory reaction, accompanied by an accumulation of lymphocytes and other mononuclear cells around the affected vessels. The histological picture ranges from a hardly noticeable collection of a few small round cells to long spindle shaped cords of solid round cell infiltrate in the cutis and sub-cutis running parallel to the surface of the skin, with a small round or oval core of epithelioid cells in their thickest portions. This latter structure can be demonstrated only by serial sections.

3. The next stage is the well-known "tuberculoid" form which has been so thoroughly discussed in the literature that no attempt will be made to describe it here. It is sufficient to recall that this histological structure is considered by Sulzberger (48) to be another manifestation of the Jadassohn - Lewandowsky law which is said to state that "whenever the immune mechanisms of the host are sufficiently active to produce a diminution of micro-organisms or their virulence within the tissues of the host, tuberculoid structures may appear." The histology ranges from typical compact tuberculoid foci showing giant cells to diffuse collections of epithelioid cells mixed with some young lepra cells as described by Wade and Rodriguez (49) among their border-line cases.

4. Finally, we come to the "lepromatous" type or final stage which has been even more extensively described than all the previous stages. The lepra cell is believed by Moacyr de Souza *et al.* (35) to originate from the same type of cell (perivascular adventitious cells of the reticulo-endothelial system) as the epithelioid cells. In this type, there is incomplete phagocytosis of the bacilli (that is, there is phagocytosis without lysis), and once inside the phagocytic cells, the bacilli seem to enjoy considerable protection and proceed to multiply rapidly.

Another feature of lepromatous leprosy which is important to remember is that as soon as this stage is reached, dissemination by the blood stream is the rule and numerous foci are established in the skin, nerves, as well as in the internal organs. In some cases, for reasons yet unknown, this dissemination is not marked and is limited chiefly to the nerves.

Finally, a lipoid substance of characteristic nature has been demonstrated to exist in the vacuoles of the foamy cells, whether they contain bacilli or not. Mitsuda (50) long ago demonstrated that lepromatous lesions of the viscera which are often missed by inexperienced workers due to their minute size (less than 1 mm.) can be demonstrated with ease by staining with Sudan III which stains this lipoid substance red. It is suggested that this stain might be employed to distinguish lepromatous lesions from all the other lesions of leprosy, as has been done by Portugal (36) and others. According to Mitsuda, the fatty degeneration which sometimes occurs in tuberculous lesions always stain lightly and can thus be easily distinguished from a lepromatous condition.

The writer believes that this conception of the pathogenesis of leprosy, as he has presented here, will aid in giving a clearer understanding of the classification of the disease.

When the uncharacteristic type is split and allowed to disappear, its place is taken by two types with *characteristic* but *non-specific* histological structures, just as the tuberculoid structure itself is characteristic but non-specific. The underlying *non-specific* pathology of the three developmental types is thus more clearly perceived, as contrasted with the specific granuloma of the lepromatous stage. In other words, from the pathological point of view, the latter is the only real leprosy, hence the aptness of the term "lepromatous." The other types are imperfectly developed forms representing gradations of tissue response under varying degrees of partial immunity. If this manner of thinking were followed to its logical conclusion, it would appear then that leprosy has in reality only one main type and three minor stages.

These atypical forms or stages are in a state of unbalance; when the partial immunity becomes complete, the infection is overcome and the patient is cured; if it is totally lost, transformation to the lepromatous type follows. When the latter takes place, the long process of rebuilding the resistance has to be gone through again, this time from the very beginning.

The present and past classifications have in reality been differentiating the specific granuloma or real disease successively called tubercular, nodular, cutaneous, and lepromatous, from the developmental or atypical forms grouped together under such various designations as nervous, maculo-anesthetic, neural, and tuberculoid. Under this interpretation of the different types, re-evaluation of the South American and Cairo classifications can now be attempted.

The South American classification establishes a histological and other adequate basis for the two main types with which we are already familiar, with the added implication that since the tuberculoid is the highest-developed and most stable form in the second or atypical group, it should be considered as representative of the group. Practically every one now agrees with this concept. The only question that may be asked is, does the tuberculoid really represent this heterogeneous group?

This simple and clear basis for the classification loses its value, however, when it is insisted upon that the two polar forms are immutable, that is, no transformation can take place from one to the other as if the two were totally different diseases. This concept does not fit into the picture. In other words, failure to understand the position of the tuberculoid type in the developmental cycle of the disease prevents a good grasp of the underlying principles of the classification.

As for the Cairo classification, the actual grouping of the types is obviously the same, that is, the lepromatous is set off from the developmental forms which incidentally are sub-divided along practically the same lines as the modified classification to be presented in this paper. Some consider the selection of the term "neural" as an indication that in the minds of those who supported this classification, the common factor which binds together the non-lepromatous group is the *neural involvement.* In justice to those who favored this classification, it must be stated that this was not really quite the case.

Wade (51), in an Editorial appearing in the first number of the JOURNAL for 1936, states the following:

"In view of this, it should not be difficult to agree, in turn, that "neural" does not imply that in a case to be so designated the infec-

tion must be confined to the nerves, and that the skin must be free from any detectable change other than trophic, that it may not have active skin lesions caused by the bacillus. The distinction of the types is more fundamental. It is based less on the location than on the nature of the active process; it is based on the broad but clear differences in the whole picture, clinical, bacteriological, pathological, and also immunological so far as we know anything about that — differences that are induced by the nature of the reaction to the infection and of resistance to its progress."

This was the view adopted at Cairo with regard to the classification and the use of the term "neural." Close scrutiny of the above statement of Wade will show that so far as the basic concepts underlying the two main forms are concerned, the Cairo and the South American classifications are essentially the same. The main difference lies in the greater emphasis placed on the histological features by the latter classification and in its insistence that these features should form the main basis of the differentiation Evidently, Wade had also considered this view and had rejected it, for he states in the same Editorial: "Histopathological examinations cannot be made in most institutions which fact necessitates laying particular stress on the bacteriological examination."

The great contribution of the South American classification lies in its clarification and extension of the knowledge regarding the relationships between the two main forms along histological, immuno-physiological, clinical, and bacteriological lines, with particular emphasis on the first two.

Next the difficult question of neural leprosy must be considered. It is the impression of most leprosy workers that preponderance of nerve involvement over the cutaneous lesions generally indicates a better prognosis than the opposite condition and that in some way or other the neural manifestations are associated with benignity of the disease.

The writer is inclined to consider that there are unknown factors which complicate the issue and it may be that if and when it is possible to culture the *M. leprae* and to transmit it to laboratory animals, it will be found that there exist one or more neurotropic strains which tend to produce mild forms of the disease.

The evolution of the classification of leprosy during the last one hundred years now becomes clear. Starting with the Danielssen and Boeck classification in 1848 to the 1931 Manila one, the basis was morphological, that is, the distinction between the two main types was based on whether the skin or the nerves were chiefly involved. The Cairo classification may be said to be partly morpho-

logical (neural type) and partly pathologic (lepromatous). Finally, in the South American classification, the distinction between the two main types has been placed entirely on a histological basis.

It is desired to emphasize once more that experience has shown that only a certain proportion of cases pass through the successive stages, particularly from the tuberculoid stage to the final lepromatous type. In other words, many, perhaps most, of the cases with developmental or atypical lesions never progress to the lepromatous type and of those which actually become lepromatous, a large number skip one or more of the developmental stages, especially the tuberculoid.

Then again, it may be theorized that the patient most likely to go through all the stages would be an individual who would have a natural resistance somewhat below par at the time of exposure. Perhaps many individuals around the age of puberty might have about this degree of resistance. After infection has taken place, his lesions would show successive histological characteristics up to and including the tuberculoid form as his resistance is gradually built up from its original level. Eventually, however, his resistance is overcome and his case becomes lepromatous. Thus he passes through all the stages.

If a person has more resistance than the above theoretical individual, which perhaps would be likely to be the case if he were older at the time of exposure and onset, the progress of the infection would be impeded by the high degree of resistance present and might become arrested in any of the developmental stages, particularly in the tuberculoid stage.

On the other hand, persons with less resistance than the first individual, as would likely be the case with those with negative or weak Mitsuda reactions, would be apt to skip from the earliest stages directly to the lepromatous type.

It may be assumed further that the proportion undergoing mutation from one stage to another or from each stage directly to the lepromatous varies in different groups of patients or perhaps even in different peoples or different countries. For instance, the proportion passing from the interstitial proliferation stage (not usually recognizable clinically) or from the round cell stage directly to the lepromatous (thereby by-passing the tuberculoid stage) would be greater among those exposed at birth or early childhood than among those exposed to the disease at later ages. This is to be expected since the former have little or no resistance at the time of exposure. Likewise, the proportion passing through the tuberculoid stage would be higher among peoples who have developed a

relatively high degree of resistance through long association with leprosy or through better nutrition and tuberculoid cases would be more numerous and more conspicuous among them, than among a people who have been exposed only recently to the disease and who are undernourished.

With regard to transformations from one type to another, therefore, it is not safe to generalize too much from observations obtained in a special group (i. e. children of leprous parents) or in one particular region or country.

(b) Clinical and immuno-biological bases of proposed modified classification.

Having established a simple pathological foundation for the proposed classification, it remains to give it form and substance by fitting the four fundamental types with definite clinical syndromes.

There can be no doubt that the present Pan-American classification is a scientific one, resting as it does on an established structural or histological basis. But unfortunately, very few active leprosy workers are located near enough to laboratories that are equipped and, what is even more important, manned by histologists capable of giving expert interpretation of the biopsy findings, to render this classification a suitable one for routine application in the field. Furthermore, in clinical trials with anti-leprotic drugs which usually are limited exclusively to lepromatous cases, it is necessary that the basis of the classification be essentially clinical. It is well known, for instance, that the prognosis of an ordinary case of this type depends greatly upon such factors as the extent, degree, and duration of the lesions, predominance of the cutaneous over neural manifestations or *vice versa*, and the rapidity of clinical progress before treatment.

Furthermore, in the uncharacteristic and tuberculoid forms, it is possible to distinguish sub-types with fairly distinct clinical characteristics.

There is need, therefore, of a clinical classification, at least for the time being, to supplement an essentially pathological or laboratory one.

The following is an outline in schematic form of such a classification which may prove satisfactory to a majority of active field workers.

A PROPOSED MODIFIED CLASSIFICATION OF LEPROSY

I. Interstitial (maculo-anesthetic) (neuro-leprid) stage.
   - MA_1 (Mitsuda positive or negative in varying proportion)
   - MA_2 (Moderate atrophies) (Mitsuda positive)
   - MA_3 (Marked atrophies, paralyses, trophic ulcers) (Mitsuda strongly positive)

II. Perivascular round cell (uncharacteristic) stage (Mitsuda positive or negative in varying proportion)
   - RCpt Pre-tuberculoid (leprid) (well-defined macules with hypo- or hyper-pigmentation with or without erythema)
   - RCpl Pre-lepromatous (Ill-defined macules, common in children of leprous parents)
   - RCr Residual (Usually previously tuberculoid)

III. Tuberculoid stage (T) (Mitsuda positive)
   - T Simple (torpid or minor)
   - Tm Macular
   - Tmp Maculo-papular or papular
   - Tmn or Tmpn With nerve involvement
   - TR Reacting tuberculoid (major) (With or without secondary lesions; primary or with pre-existing macules)
   - TRn With nerve involvement
   - Tr Residual
   - Tlaz Lazarine leprosy (hyperergic)

IV. Lepromatous (foamy cell) type (Mitsuda negative)

C_1	C_1 N_1	C_1 N_2	C_1 N_3	N_1
C_2	C_2 N_1	C_2 N_2	C_2 N_3	N_2 *
C_3	C_3 N_1	C_3 N_2	C_3 N_3	N_3

* Post lepromatous, Mitsuda positive.

1. The characteristic macule of the maculo-anesthetic type is hypochromic on the dark skin and although it is frequently flat or level with surrounding skin, its edges are well-defined. The margins may occasionally be raised and reddish but in spite of these manifestations of clinical activity, the histological sections show no evidence of tissue reaction beyond slight interstitial proliferation. Detailed examination of histological sections stained for acid-fast organisms may reveal a few scattered extra-cellular bacilli.

Clinically, the most important characteristic of this macule is the early development of *complete anesthesia* either in certain portions or over the entire lesion. This indicates that there occurs early an involvement of practically all the sensory nerve endings in the involved area; i. e., the bacilli in these cases are distinctly neurotropic. In the later stages of the disease, these macules may become extensive and acquire the characteristic yellowish tinge of the typical neuro-leprid, and they may disappear completely.

Sometimes preceding, but more frequently following the appearance of the macule, an anesthesia of the acroteric type develops terminating often in atrophies and trophic disturbances, which indicate upward involvement of the affected nerves. Frequently, at the time of diagnosis, this is the only sign of the disease present. The strongest lepromin reactions the writer has ever seen occurrrd in some of these advanced neuro-macular cases.

In all cases of this type, the skin smears are invariably negative for *M. leprae*, but in a respectable percentage of them, however, smears from the nasal septum are found positive particularly when there is ulceration of the nasal septum. It is this feature, which is quite common in the maculo-anesthetic type, that has given rise to the erroneous impression (Stricker's theory) that the earliest lesions in leprosy occur in the nasal mucosa.

2. The only known lesions microscopically characterized by round cell infiltration are macular ones, and nerve lesions that are very difficult to differentiate clinically from lepromatous nerve involvement. In the pre-tuberculoid variety, the macule looks very much like the maculo-anesthetic lesion. However, the anesthesia is ordinarily not complete, at least, in the early stages, and, if present, will probably be found in the clearing center of the macule. Furthermore, if the pre-tuberculoid macule shows any indication of clinical activity such as redness, raised margins, increase in size, etc., serial sections of a biopsy specimen secured from the area showing such activity are likely to show a few nests of tuberculoid foci here and there. These represent the cores of epithelioid tissue referred to above in the discussion on the pathological findings in this type.

The pre-lepromatous variety in our experience is best observed in the children followed in preventoria, and frequently are the earliest lesions seen. The main characteristic of this macule is its vagueness, there being no distinct edges. It may be so hazy as to be indistinguishable unless the skin is examined under oblique light. Frequently, no anesthesia is found over the lesion although the young age of these patients usually renders an accu-

rate neurological examination impossible. The bacilli show no neurophilic tendency. On the other hand, they seem to show predilection for tissues about the small blood vessels with a tendency towards early dissemination through the blood stream.

The residual round cell infiltration macules are simply the hypo- or hyper-chromic patches produced by the subsidence of previous tuberculoid lesions. They are differentiated from the two sub-varieties of the small round cell type chiefly by the history.

3. The tuberculoid lesions have been so frequently described in the literature that their characteristics need not be discussed. It needs comparatively little clinical experience to distinguish the different sub-varieties from each other and from the lesions of the other types.

Some characteristics of the lesions in the nerves in tuberculoid leprosy should be mentioned. Because the process is an ascending one, the involved nerve is the regional nerve twig or branch supplying the skin area affected. The nerve feels beaded or granular, in contrast with the fusiform type of nerve swelling in lepromatous leprosy. Involvement of other nerve trunks whose corresponding areas of distribution show no involvement is suspicious of a possible transformation to the lepromatous type.

It is usually possible to diagnose a residual reactive tuberculoid lesion merely by the appearance of the characteristic atrophic and deeply anesthetic scar produced. When the "mother lesion" has occurred on the face, the underlying orbicularis oris and oculi muscles may be paralyzed. On the extremities, the typical scar is associated with atrophy of distal muscles and distortion of the digits of the affected member if there has been involvement of large superficial nerve trunks.

In reporting the first case of lazarine leprosy, an atypical case, which has occurred outside of Mexico and Cuba, Rodriguez (52) considered this type as an extremely hyperergic form of "reactive tuberculoid." Pardo-Castello and Tiant (30), who are the authorities on this form of the disease, apparently accept this view. Typical cases of lazarine leprosy have not been reported outside of these two countries mentioned.

4. In the lepromatous type, the old familiar symbols C and N indicating the extent and advancement of the cutaneous and neural lesions (with combinations of the two for the mixed cases) have been retained. This should prove convenient for the older workers. Those grouped under C_1, C_2, C_3 may be called pure cutaneous forms; those under C_2,N_1, C_3,N_1, and C_3,N_2 would be mixed forms

with predominating cutaneous lesions; those under C_1N_2, C_1N_3, C_2N_3 would be mixed forms also but with predominating neural manifestations, while those under N_1, N_2, and N_3 would be the pure lepromatous or post-lepromatous neurals. Among the latter the thickening of the nerve trunks is usually fusiform, in contrast with the nodular or beaded thickening of the superficial nerve trunks when they are involved in the tuberculoid type. Furthermore, in the lepromatous type, involvement of the superficial nerve trunks such as the ulnars, the peroneals, and the great auriculars is typically bilateral and in advanced cases all of them are thickened, although not necessarily to the same extent.

The pure cutaneous cases, particularly C_1 and C_2, need special attention. The most frequent early lesions consisting of slight and diffuse infiltration, usually on the ear-lobes, alae nasi, cheeks, chin, buttocks, and exterior surface of the extremities, should offer little difficulty. The macular lesions may be distinguished from the tuberculoid macules, aside from the biopsy, by the fact that they are bacteriologically positive, and clinically by the gradual fading of the outer border into the surrounding skin. The lepromatous macule is not usually definitely anesthetic and ordinarily shows no marked tendency to clear at the center.

From the uncharacteristic or round cell or round cell pre-lepromatous macule, the lepromatous macule is clinically recognizable by the elevation of the surface, the sensation of distinct infiltration or thickening when the skin is rolled between the thumb and the forefinger, and by its reddish or coppery color. The bacteriological examination should establish the differentiation at once.

The early pure neural varieties of the lepromatous type (N_1 and N_2) must be differentiated from the tuberculoid type with nerve involvement and the maculo-anesthetic type. In this connection, it is useful to recall that in both of these latter types, the nerve involvement starts from the sensory nerve-endings in the skin and the process spreads upwards. In lepromatous leprosy, on the other hand, the nerve trunks are initially involved higher up following embolic deposits at the portions exposed to trauma (such as above the olecranon in the case of the ulnar nerve) and from these sites, the lepromatous process extends both peripherally and centrally. Clinically, in the early stages at least, (which may be obtained from the history in some cases,) there may be no noticeable macule at the site of a well-defined area of marked anesthesia, there is no paralysis or atrophy, and there is no palpable thickening of the regional nerve or nerve trunk. Such anesthetic areas are usually accidentally discovered by the more observing patients

and in our experience are invariably followed later by leprotic macules or infiltrations either at the site of the anesthesia or elsewhere. In one case the intervening period was fifteen years.

Secondary post-lepromatous neurals should show scars or areas of atrophic skin at the sites of previous lepromatous lesions on the ear-lobes, face, and extremities, or must at least give a definite history of having had probable lepromatous lesions.

Transitional forms between one stage and the next or from each stage directly to the lepromatous type are naturally to be expected.

The modification of the South American classification here presented is not intended as a final classification. It is probable that no completely satisfactory classification will be found until we possess a great deal more accurate knowledge about the disease than what we have at present.

SUMMARY AND CONCLUSION

The Pan-American classification represents a distinct advance over all the other past ones in that for the first time, the classification of leprosy has been placed on a histological basis. There is unanimity of opinion as to the existence of the underlying histological characteristics of the different main types established; the remaining problems are (a) the question of the interpretation of the structural findings and (b) fitting them to easily recognized clinical forms, since histological studies can not be done in many parts of the world. An attempt along these two lines has been made in the present paper. In order to understand the basic problems involved, it has been found necessary to review briefly the past and present classifications and to trace the development of our knowledge regarding "tuberculoid leprosy."

Leprosy is at present classified on the basis of two main types. One is characterized by a *specific* granulomatous reaction; the other by a *non-specific* tissue response to *M. leprae*. The first is believed to be the result of a complete loss, either temporarily or permanently, of resistance on the part of the host; the second is the effect of the existence of varying degrees of partial immunity. Depending on the extent of resistance present, the second may be further sub-divided into three types or stages, each with a characteristic histological structure, namely, interstitial proliferation, round cell infiltration, and tuberculoid granuloma. These types in the second group manifest increasing degrees of clinical stability.

A proper collective designation for the second group, as distinctive of the group as the term "lepromatous" is for the first

group, still remains to be proposed. In the Cairo classification, the term used is "neural"; in the South American one, the corresponding designation is "tuberculoid." In the present paper, the terms "developmental," "evolutive," and "atypical" have been used indiscriminately to indicate the non-lepromatous group. A possible solution might be to consider that only one main type of leprosy exists, the others being mere stages of the disease. Such a classification would be in line with the views of the writer who proposes a modification of the South American classification which is intended merely to serve as one more basis for further study and discussion on the subject.

The Mitsuda test furnishes a rough measure of the degree of clinical stability and is believed to be associated with partial immunity and may even serve as a measure of the degree of resistance present. Unfortunately, the question of immunity or resistance in connection with leprosy is an entirely hypothetical matter since its existence has never been proved experimentally. The test is negative in the lepromatous type while varying degrees of positivity are obtained in the second group.

The neural forms cannot be classified on the basis of histological structure alone. The presence of such forms seems to be best explained by presuming the existence of mild neurotropic strains of *M. leprae*. Of course, this is impossible to confirm until the organism has been grown successfully in artificial media and then transmitted to laboratory animals. Until this lack of knowledge about the causative agent of the disease has been corrected, all discussions on the classification of leprosy, of necessity, must be largely theoretical in nature.

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