

INTERNATIONAL JOURNAL OF LEPROSY

VOL. 4

OCTOBER-DECEMBER, 1936

No. 4

ORIGINAL ARTICLES

THE SKIN LESIONS OF NEURAL LEPROSY⁶ I. GENERAL INTRODUCTION

BY H. W. WADE, M.D.

*Medical Director, Leonard Wood Memorial
(American Leprosy Foundation)
Culion, Philippine Islands*

- Introduction
 - Sources of material
 - Purposes of the study
 - Correlation of the individual studies
- Terminology and classification
 - Characteristics of the leprides
 - Primary classification of the leprides
 - Simple leprides
 - Minor tuberculoid leprides
 - Major tuberculoid leprides
 - Borderline lesions
- Activity in leprides
 - Active lesions
 - Healed or residual lesions
 - Retrogressive and quiescent lesions
- Enlargement of cutaneous nerves
- Technique
 - Surgical technique
 - Pathological technique
 - Bacteriology
 - Photography
- Nature of the histological changes
- References

INTRODUCTION

The present article introduces a series of reports, to be made in collaboration with clinical workers in several regions, that deal

chiefly with the macular skin lesions (leprides) that occur in the neural type of leprosy. The cases dealt with range from the earliest and slightest ones ("incipient" cases), up to the common neural ones with trophic changes, and to the most striking forms that are widely recognized as "tuberculoid leprosy." Some workers hesitate to class the incipient cases definitely as neural, because of insufficiency of other symptoms characteristic of that type and uncertainty as to future course; there is also a strong tendency to put the more marked tuberculoid cases aside as a peculiar group, intermediate between the neural and cutaneous types, because the principal changes are manifested in the skin rather than in the peripheral nervous system; but these cases are considered here as part of the same complex picture so long as they have not undergone essential change.

Briefly, the study is in the main one of those granulomatous changes in the leprides that have the tuberculoid structure, which is a much broader question than is generally realized. Until recently "tuberculoid leprosy" has been regarded as uncommon, limited to a relatively small number of cases whose lesions are of rather striking and peculiar appearance, so that the Leonard Wood Memorial Conference (10) did not discuss the matter particularly. Even at that time some people still believed that tuberculoid changes in leprosy were due to tuberculous infection. The view that they are unusual or peculiar was first brought seriously into question when Manalang (9) reported finding them in lesions of ordinary kinds.

Manalang examined skin specimens from 33 bacteriologically negative cases of various kinds. Of those from 15 "suspects" and "clinical lepers," 7 showed tuberculoid changes; also those from 4 of 8 cases under treatment at the Cebu Skin Dispensary, 3 of 6 children of leprosy parents at the Welfareville children's home, and 3 of 4 paroled cases that previously had been bacteriologically positive. He concluded that these lesions "precede the well-known bacilli-laden leproma." Later papers in which he refers to the matter give no further details, though in one of them he records that he had found tuberculoid changes in 50 percent of biopsy materials from 146 cases "in different clinical phases of the disease."

With reference to other writers it need only be said that, since Manalang's publications appeared, Chiyuto (2), Rodriguez (15), Lara (6), and others in the Philippines, and Ota and Sato (14) in Japan, have recorded similar findings. While the present paper was in preparation, Lowe, of Calcutta, informed the writer that he had concluded that tuberculoid changes are characteristic of all of the

leprides.¹ On the other hand Jeanselme, representative of the older view, summarized in his recent book (5) the pathology of the skin lesions of leprosy by quoting Lewandowsky to the effect that there are three main classes of changes:

(1) Inflammatory changes that are amorphous and not at all characteristic, often consisting of unorganized perivascular mantles of young cells, and generally containing only isolated and scattered bacilli, the search for which is laborious. (2) More or less well-limited neoplasms, very rich in bacilli, of granulomatous structure, made up of the typical elements of leprosy, the lepra cells. (3) Lesions which more or less recall those of the lupus of Willan, the cutaneous sarcoids of Boeck, or the subcutaneous sarcoids of Darier and Roussey; these are the tuberculoids of the skin and nerve trunks.

The first of these groups, obviously, is the ordinary macule of neural leprosy as that has been understood heretofore. The second is the leproma of cutaneous leprosy. The third, tuberculoid leprosy, is as usual classed as a thing apart.

Sources of material.—The writer has had no experience with the lesser lesions of primary neural leprosy at the Culsion Leper Colony. Except for a few neural cases that have been found bacteriologically positive, including some marked tuberculoid ones, only cutaneous-type cases are confined there. During the epidemiological survey made in Cebu by Doull, Rodriguez and others in 1933 (3), a number of biopsy specimens taken from the slighter grades of leprides in newly discovered, bacteriologically negative cases was sent to me for examination. The workers mentioned reported that of nine specimens from cases thought by them to be active, eight showed tuberculoid changes, while six of seven specimens from apparently inactive cases showed at most only "round-cell" infiltration. A year later I saw several of these cases personally, and further material was collected at the Cebu Skin Dispensary in collaboration with Dr. J. N. Rodriguez. That inquiry is the subject of the next article in the present series.

Publication of our findings was deferred until comparable material could be obtained from other regions and different races. The fact that tuberculoid changes had not been recognized in ordinary leprides by the older European students of the disease suggested that there might be racial differences in this matter. Being in an

¹Since the present article was prepared for press, Lowe's report, entitled "A study of macules in nerve leprosy with particular reference to the 'tuberculoid' macule," has appeared in *Leprosy in India*, 8 (1936) 97-112. His classification of these lesions differs from that presented herein.

especially fortunate position to do comparative work, I was able, later in 1934, to secure another lot of material in Swatow, South China, with Dr. N. D. Fraser and his associates; a few specimens were also collected in Shanghai, several persons cooperating. Early in the present year I spent several months in the India-Ceylon region, where a large amount of material was collected in collaboration mainly with Dr. Robert G. Cochrane, at the Lady Willingdon Leper Settlement, Chingleput, South India; Dr. John Lowe, at the School of Tropical Medicine, in Calcutta; and Drs. D. S. de Simon and A. C. Fernandez in Colombo.

Purposes of the study.—The primary object of this study was to ascertain whether the tuberculoid condition is characteristic of all clinical varieties of the leprides, or whether some of them regularly show only simple inflammatory changes. This question involves the general relationship of the different varieties of lesions of this large class, and the relation of tissue changes to clinical activity, progression and retrogression. There is also a question of racial variation, as has been indicated; unfortunately, though we have material from peoples of Malayan, Chinese and Indian origins, we have none from any of the European races.

The grossest form of the tuberculoid condition (here called "major" tuberculoid) offers a number of interesting special aspects. An especially important problem is its relation to the cutaneous form of the disease. Some believe that it is a transition stage between the neural and the cutaneous types, while others, to the contrary, though perhaps accepting it as an intermediate condition, believe that it is distinct from cutaneous leprosy and on the whole of good prognosis.

Another matter of interest is the nature and degree of change in the cutaneous and other nerves that are affected in neural leprosy, but it is possible to go into that only to a limited extent; it is much more difficult to procure biopsy specimens of the nerves than of the skin. It is in this matter especially that there seems to be a regional, if not racial, peculiarity. Enlargement of the cutaneous nerves supplying affected skin areas is not unusual, but as a rule little stress is laid on it. On the other hand, reports from India, especially those of Muir (11), Lowe (7), Muir and Chatterji (13) and Chatterji (1), have given much emphasis to nerve affections. The most striking of these is cold abscess. This condition is extremely rare in most other parts of the world, though it has recently been reported from South America by de Souza Campos (18) and Schujman (16).

Finally, besides the immediate study of the cases dealt with, this work was intended to establish a basis for later observations, to determine the significance of the changes existing at a given time as regards the future course of the disease. This will necessarily require follow-up studies by the clinical workers. The matter is somewhat complicated by the fact that most of the cases brought under study will receive treatment which, it is to be expected, will interfere with the natural course of events. As a matter of fact, this factor complicates the original inquiry, because many of the cases studied had undergone more or less improvement under treatment before our examinations were made.

Correlation of studies.—Obviously, there should be advantages in an investigation in which a single individual collaborates directly with the workers in several more or less widely separated regions. At the same time there are certain inherent difficulties. In visits abroad there is unavoidably a tendency to rushed work and incompleteness of observation; records of different institutions differ in nature and extent; and it is difficult to carry on follow-up work jointly.

The preparation of the individual reports of this series is not without problems. It would perhaps have been simpler had a report been made after the completion of each unit of observations, but it has seemed best to carry the several studies at least to partial completion before reporting on any of them. The entire series of reports is, naturally, written from a viewpoint resulting from the whole study. Not all of the collaborators subscribe completely to this viewpoint, and in consequence of this and other circumstances the writer must assume considerable responsibility for it. This is done with the realization that he may appear to assume an undue degree of credit—where credit is due—for all features of the matters presented. Actually, to a large degree they represent a joint product.²

TERMINOLOGY AND CLASSIFICATION

In the course of this study we have come to employ certain special terms, and have arrived at what is believed to be a logical and useful primary classification of the leprides. In the interest of simplification and coherence, these and certain other preliminary considerations are taken up in this general introduction.

²Thanks are due Drs. Rodriguez, Cochrane and Lowe for helpful criticism of the preliminary draft of the clinical parts of the present article.

CHARACTERISTICS OF THE LEPRIDES

First, though it is not new matter, it seems desirable to point out the significance of "lepride" and to summarize the principal characteristics of these lesions. The term, said to have been introduced by Arning (4), denotes the various skin lesions that are characteristic of the neural form of leprosy. It is used in contradistinction to "leproma," which applies to the bacillus-rich lepra cell granuloma which characterizes the cutaneous type of the disease.⁵ The leprides are, of course, "cutaneous" lesions in the dictionary sense of that word, but because of the special sense that it has in modern classification of leprosy it would be utterly confusing to apply it to them; it would be much better to use "dermal" as a general term in this connection.

The definition of "macule," as adopted by the Memorial Conference (10), applies to the leprides, as far as it goes, though it is a general term, since macules also occur in cutaneous leprosy.

A macule is a circumscribed area of skin showing changes in color, sometimes with slight elevation or depression. The following descriptive terms may be applied to indicate its peculiar characteristics: Hypopigmented, hyperpigmented, erythematous, circinate, marginate, zonal, raised, atrophic.

It is to be added that the leprides typically are negative for bacilli by standard clinical methods of examination. Special forms and phases of them will sometimes yield a few bacilli, and, infrequently, considerable numbers of them. It would be helpful if it could be said that they never give rise to globi, but rare cases have been encountered that yielded occasional small globi, though histologically they showed no trace of lepromatous transformation.

In spite of the usual negative findings in bacteriological smears, there are now few leprologists who doubt that these lesions are due to the presence of bacilli. As in some tuberculous lesions, the bacilli are usually so few that they can be demonstrated in sections with difficulty, if at all, but this demonstration has been made by many workers. This fact necessitated abandoning the old idea that the

*"Lepride" is not analogous to "syphilide," which dermatologists apply to syphilitic eruptions in general, but rather to "tuberculide" which, following Darier, they use to designate a group of skin lesions that occur in tuberculous subjects but are distinct from lupus vulgaris, scrofuloderma, and other frankly tuberculous conditions of the skin. The lepromata are in a sense analogous to the latter group. Lepride does not signify leprosy skin lesions in general, as Dorland's medical dictionary would have it, any more than tuberculide means "any skin eruption occurring in association with evident manifestations of tuberculosis," as the same dictionary defines that term.

leprides may be due to "toxic" substances produced by bacilli located elsewhere, or that they may result from bacillary invasion of the nerve rather than of the skin tissue itself, which led Unna to call them "neuro-leprides" (20).

The leprides may be flat (i. e., not raised), or they may be infiltrated, in part or wholly and in different degrees; the limitation imposed by the word "slight" of the definition quoted above does not cover the case. Infiltrated lesions may be called "smooth" when they are fairly uniform as to surface—that is, when the amount or distribution of the infiltration, if any, is not irregular. This applies mainly to those slightly infiltrated ones that can still be called "simple," though there are more grossly thickened ones that are smooth because of diffuseness and deep location of the granulomatous condition. On the other hand the surface is irregular, rough, "granular," pebbled, or "micropapillate" when the lesion foci are more isolated, and especially when they are located mostly in the superficial layers of the skin; the grosser, deeply seated lesions of this nature may be coarsely irregular as to surface, or even actually nodular in some degree.

In this article, as in previous ones (21), the word "edge" is applied only to the actual periphery of the lesion; "margin" signifies the outer zone when, as on a printed page, there is a distinction between it and the central portion of the affected area; "border" is often used in the same sense. "Discontinuous" lesions are those in which the infiltrated zone is broken in places; "segmental" ones are those only partly outlined by bands of infiltration. With regard to color change, "depigmentation" is avoided because it may seem to imply complete rather than the usual partial loss of pigment; "hypopigmentation" is preferred, or "hypochromia."

Typically the leprides undergo "progression," or "extension" (i. e., enlargement by spreading); they do not show reduction to decreased area, though they undergo "retrogression" in the sense of decreased activity and infiltration. Progression is centrifugal, the process extending like fire in grass—or better, because it is submerged and gradual, in a peat bog. Because the rate of progression is often very variable, both in different lesions and in different parts of the same lesion, and because adjacent lesions often merge, there are great differences as to outline (shape of the affected area), and also the nature of the periphery. Many lesions are more or less

"regular" in general outline (round, oval, etc.), especially when they are small; but marked irregularity is common.

Often, because of wave-like advancement of the active zone, the lesions are "smooth" as to edge, regardless of whether the shape as a whole is regular or not. On the other hand, irregularity of the edge is common, even in lesions that are quite regular in general contour. This irregularity is due to different rates of extension at different points, as if in places there were channels more favorable to advancement than elsewhere. Sometimes this is so marked that the projecting portions seem to have streamed forward rapidly, suggesting a little the progression of an ameba; these lesions may be described as "streaming." In the extreme of this condition small foci occur outside the periphery (extraperipheral spotting) as if the process had advanced by burrowing deeply, to come to the surface at points beyond the edge of the main mass. In due course, if progression continues, the mass catches up with these advanced foci, though in the meantime new ones may have developed farther on.

The edge in active lesions is ordinarily well demarked, whether it is smooth or irregular. Consequently the leprides are usually well differentiated from the normal skin, not diffusing or blending gradually into it in the manner typical of the lepromata. This characteristic holds most constantly for the infiltration, which aids greatly in the differential diagnosis between major tuberculoid lesions and lepromatous infiltrations and nodules. Inside the lepride, when the central portion clears up, gradual decrease of infiltration is the rule because resolution is far less abrupt than development.

Fairly definite demarkation of hypopigmentation at the edge of a macule is also common, but in this matter there are frequent exceptions, and gradual color change (diffusion) is not infrequent. Diffusion is often seen around active, so-called "lichenoid" lesions, and around older, more ordinary ones that have recently undergone sudden activation at the edge. There are also (according to certain of our collaborators) cases with multiple pale, flat, indefinitely bordered macules that are especially prone to develop into the cutaneous form of the disease. Diffusion at the edge of healed lesions, or parts of them, as repigmentation proceeds, is one of the means of distinguishing between a residual condition and one that is "quiescent" but potentially active.

The matter of sensory changes, which are an important feature of the leprides (in contrast with the lepromata) cannot be discussed

in detail. In early lesions and in the active parts of old ones, such changes are not as constant or conspicuous as is commonly believed. If tactile anesthesia is expected to be constant, or if it alone is tested for, the findings may be decidedly misleading, especially in the diagnosis of early ("incipient") cases. Thermal anesthesia frequently precedes it; analgesia is often a comparatively late development, but it frequently precedes tactile anesthesia. There is, unfortunately, no rule in the matter, which is further complicated by the fact that in some cases that come up for diagnosis no evidence whatever of this "cardinal sign" can be elicited. Some workers who recognize such cases as leprosy hesitate to classify them as belonging to the neural type, though the lesions otherwise are similar to others that are anesthetic, and certainly are not lepromatous, and though evidence of nerve change may appear sooner or later if the condition persists and progresses.

PRIMARY CLASSIFICATION OF THE LEPRIDES

The leprides present such a wide range of varieties that, if there is to be any accuracy and intelligibility of observation and conclusion in their study, it is necessary to select some particular character by which to distinguish their main types. If each variety (and several varieties, or subtypes, of each type can be set up) were designated by some features peculiar to itself, it would be necessary to define a large and confusing number. For example Tisseul (19), referring only to lesions that he recognizes as tuberculoid, distinguishes no less than nine kinds: "en medallion, en aires, rose-jaunâtres, parakératosique, granitées, rosées, en plateau, rouges, et brillantes."

In considering the clinical features that may be used for primary classification, neither erythema, nor color, nor form proves satisfactory. More than one kind of lepride may be erythematous, and lepromatous macules also show that characteristic; furthermore, the same lesion may or may not be erythematous according to its state of activity at a given time, and even the air temperature or exposure to sunlight may affect it. Form, useful as it is in describing individual lesions or varieties (subtypes), also varies greatly in the same kind of lesion, both in different cases and in the same case in different stages of development or on different parts of the body. As for actual color, since that results from the state of blood circulation and skin pigmentation combined, it is hardly more useful than erythema, especially in view of color variations in different individuals and races.

During the course of this work we have come to depend, for primary classification, chiefly upon the presence or absence of clinically evident infiltration, and its degree and character when present. Though the resulting division of the lesions is essentially clinical, there is in the main a pathological basis, and in naming the three main groups that emerge we recognize their pathology when that is unmistakable upon inspection. In doing this we have avoided departure from current practice in the naming of important kinds of lesions, and also the necessity of devising and seeking the acceptance of new names. No attempt has been made to enumerate all the different varieties of leprides, or to arrive at single descriptive terms. It seems necessary, as with animals and plants, to resort to two or more words for the designation of most of the subsidiary forms.

A large proportion of the leprides that are encountered have, if they are at all active, at least a narrow marginal zone that is infiltrated to some extent. In degree there is a wide range upward to thick lesions that may easily be mistaken for lepromata. In its lesser degrees infiltration may be difficult to see except with proper lighting (²²), though it may be perceptible on gently drawing the finger-tip across the margin of the lesion, or on pinching up a fold of the affected area.

With this feature as a basis, three main varieties of active leprides are recognized: "simple," "minor tuberculoid," and "major tuberculoid." Those that are called tuberculoid are recognizable as such by clinicians who have paid attention to this matter, and the distinction between minor and major varieties is also primarily a clinical one. The term "simple" may be misleading if it is understood to imply that the pathology of these lesions is necessarily different in its essentials from that of the others, but it may not always be without justification even from the viewpoint of pathology. There is reason to believe that some of the flat (noninfiltrated) lesions that microscopically show only perivascular "round-cell" accumulation are really active, or at least likely to become active. In any case, few clinical workers can appeal to the pathologist to determine the structure of individual lesions of a group that look more or less alike, and it is not yet certain that a differentiation can be made clinically.

There are, of course, borderline lesions between the types named, and more divisions could probably be made, but it is desirable that the classes be as few and distinctly differentiable as possible. The

difficulty of placing intermediate cases is less than would be that of distinguishing a larger number of main classes.

The question of significance and prognosis of the different kinds of leprides is not one to be discussed here. To arrive at final conclusions on that question will require clinical follow-up, over a long period of time, of many cases whose lesions have been definitely classified and carefully recorded.

Simple leprides.—The simple leprides, which comprise a considerable proportion of those encountered, include all (*a*) that are without outwardly evident infiltration, or (*b*) that have slight infiltration which is smooth as to surface. Definitely “residual” and “aborted” lesions, which are also without actual infiltration and therefore simple (though they may be thickened by scarring), may in a way be considered a distinct group, but it does not seem logical to make a separate type of them. In a simple lepride that is infiltrated this condition is really slight and usually limited to a narrow marginal zone, though it may be more general, especially on the face where the skin is not as distinctly stratified as elsewhere.

Minor tuberculoid leprides.—This group comprises the lesser lesions which are now becoming generally accepted as regularly tuberculoid histologically, and that are clinically recognizable as such with certainty. They show definite infiltration of characteristic nature, though it varies very greatly as to extent and degree. They are marked by irregularity of the surface, due to the essentially focal nature and superficial location of the tuberculoid process. The group is divisible into two subgroups that might almost be considered distinct types. They are: (*a*) discretely papulate infiltrated lesions with very little or no general infiltration, and (*b*) more infiltrated lesions in which the distribution or location of the pathological change is such that the surface is irregular, granular or pebbled rather than actually papulate.

The papulate lesions may in general be described as simple ones in which, at isolated points, the development of tuberculoid foci in the superficial (papillary) layer of the skin has produced small, abrupt elevations, usually pinhead or less in size, though there may be fusion of two or more contiguous ones. There may be only a very few such points, in which case the term “paucipapulate” is appropriate, or they may be quite numerous—“multipapulate” lesions. Distribution of the papules is usually marginal, and they seem commonly to be secondary developments in the advanced zone of retro-

gressive lesions, but they are sometimes more widely distributed, especially when they are numerous.

In the more marked lesions of this class the condition typically involves more of the deeper layers of the skin, or at least involves them more extensively, so that there is decided infiltration of the affected zone. Even when the granuloma is mostly superficial, the amount of it is such that the surface usually shows general irregularity or pebbling rather than discrete papulation. The infiltration may be limited to a narrow marginal zone or it may extend over a wide one, and when resolution is much delayed, areas of considerable size may be affected.

Major tuberculoid leprides.—These are the more striking, grossly infiltrated lesions to which recognition as tuberculoid has mainly been confined in the past. They are “major” both in the degree and the nature of the pathological process. Typically the process invades the deeper layers of the skin to a marked degree, and by further progression it may produce gross involvement of the related cutaneous nerves. There being ordinarily little or no apparent focalization in the superficial layer of the skin—much less than is typical of the minor group—and more massive deep infiltration, the surface, if not comparatively smooth, is coarsely irregular, not pebbled.

These are the lesions which are most likely to be mistaken for lepromata. This is especially the case when they are (a) small but thick, really nodular; (b) in a “reaction” condition, reddish, turgid and smooth; and (c) bacteriologically positive. One feature that helps to differentiate them is their usually sharp demarkation. Furthermore, in cases with extensive lesions, which, if the disease were of the cutaneous form, would be expected to show more or less general involvement, especially of the earlobes, the ears are often normal, and if they are affected the infiltrations are usually unilateral or confined to limited areas. Similarly, one cheek may be extensively affected with no involvement of the other one. Another feature that sometimes helps to distinguish these cases is the tendency ultimately to show marked involvement of the local cutaneous nerves, and even of the deep trunks on the affected extremity.

A point of considerable interest is the frequency with which these lesions start abruptly, as a sort of “reaction” condition, and the rapidity—and, sometimes, the completeness—with which they may

subside. This behavior will be discussed in the following and other articles of this series.

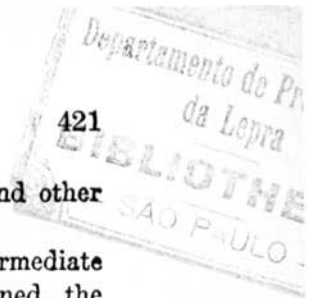
Borderline lesions.—With regard to the leprides intermediate between the simple and minor tuberculoid groups as defined, the discretely papulate ones without infiltration are not easily mistaken in a careful examination. Among lesions that have infiltration without distinct papulation, the simple may be difficult to distinguish from the slight major tuberculoid. A growing realization that all leprides that have more than the slightest degree of evident infiltration may be expected to show some degree of tuberculoid change has led to a tendency in some quarters to classify as tuberculoid even those that show little or no irregularity of surface. This is a tendency that may go too far for practical purposes of classification; unavoidably there will be much personal variation.

There is on the whole less difficulty in classifying cases intermediate between the two tuberculoid groups. For one thing, not so many of them are met with. However, the question does arise, because the most marked degree of the minor variety may be as conspicuous as the lesser degrees of the major one. Furthermore, previously major lesions that have undergone considerable retrogression may appear to be minor in degree of thickening, though without typical irregularity. In classifying all such lesions weight must be given to (a) the apparent location of the process, whether it is chiefly superficial or deep in the skin; (b) the involvement of the related cutaneous nerves, which when it is evident at all is typically greatest in the major variety; and (c) the history, to ascertain whether or not there was previously more thickening and activity, and also the nature of the onset.

ACTIVITY IN THE LEPRIDES

A question of prime importance in dealing with cases of neural leprosy is whether or not their lesions are active. This question comes up in connection with treatment particularly, and sometimes with administrative measures. In studying the pathology of the leprides it is essential to consider this factor.

By "active" is meant a lepride that is actually (not merely potentially) progressive. "Quiescent" lesions are those of which there is reason to believe that they are neither active nor strictly residual, but in which the disease process is in a state of latency; they are potentially active, and will be overcome or again become progressive according to future circumstances. In much the same



category as the quiescent lesions are the "retrogressive" ones, which show evidence of undergoing resolution. "Residual" lesions are those which, so far as can be determined, are actually healed, completely arrested, the exciting agent overcome.

It is often impossible to decide whether a lesion under scrutiny is quiescent or slowly, indolently active; prolonged observation may be required. A lesion may seem to be entirely inactive, yet the history may show that it has been spreading steadily for years with no essential change in character. In the examination, attention is focused primarily on the margin.

Active lesions.—When there is much activity in a lesion this can be recognized without difficulty. Primarily there is erythema. This may be confined to a very narrow line at the periphery, or extend over a marginal zone, or involve the whole area. Slight erythema may be difficult to detect in dark skins, especially when it is confined to a narrow peripheral band beyond the zone of frank infiltration and hypopigmentation. In some instances activity is central rather than peripheral, but this is seen chiefly in the peculiar, small, hazy lichenoid lesions that have been mentioned.

Hypopigmentation in active lesions is variable but usually distinct. The streaming and spotty lesions that have been mentioned usually show little more than loss of pigment, but they must be looked upon with suspicion.

Infiltration, if at all marked, is of full, unretrogressed appearance. Slight infiltration is not entirely incompatible with quiescence, but if it is at all pronounced, especially when there is much hypochromia, the lesion may be indolently active, although there may be no erythema whatever.

When activity is marked, it is necessary to consider the possible existence of a "reaction" condition, a form of lepra reaction. This may be slight or very conspicuous. For example, in a quiescent flat macule, reaction produced by the administration of potassium iodide may be manifested only by the reddening of a narrow zone of perhaps only a part of the periphery. On the other hand, a major tuberculoid lesion in reaction, highly erythematous and turgid, and sometimes scaling as the condition subsides, is one of the most striking features of leprosy.

Healed or residual lesions.—At the other extreme are the residual lesions, without any evidence of present or potential activity; they include those of the so-called abortive cases. They show no marginal erythema, and no infiltration aside from such as may be due to fibrosis. Some decrease of pigment may persist for a long time, but it is less than when the lesion was active or quiescent, and it diffuses off to the normal skin.

Repigmentation is one of the most definite signs of healing, and in time it may be quite complete if there is no superficial scarring with atrophy of the epidermis. There may, of course, be hyperpigmentation. Recovery may be so complete that the normal tone and grain of the skin is regained. Loss of hair and of sweat-gland function may be persistent, but on the whole the principal abnormality in a recovered area is continued hyposensitivity, which perhaps will be the only change to reveal the site of a lesion; but even that may disappear in the course of time.

It commonly happens that only a part of a lesion will heal, while in other parts activity persists. This fading out is the rule where the axillary and other "immune" areas are approached, and it is also common on the extremities, especially the forearms and legs. In such parts it may be quite impossible to tell just how far the process extended before it died out.

Abortive cases, in which the disease process is extinguished by nature at an early stage, are of peculiar importance because of the frequent difficulty of making a positive diagnosis. In this connection it is particularly important to distinguish between actually residual lesions and those that are merely quiescent.

Retrogressive and quiescent lesions.—These lesions, not essentially separable, lie between the two extremes discussed. Being capable of reactivation, they are of uncertain future. The retrogressive ones, in which a previously active condition is evidently subsiding, are of special interest in the evaluation of the effect of treatment. The quiescent ones, which may be thought to be quite arrested, are important in connection with the release of patients from treatment. A lesion cannot be looked upon as healed, or cured, if there remains any danger of reactivation; flare-up of the process is often seen after long periods of complete inactivity.

In these stages there is no active erythema. In a retrogressive lesion there may still be some marginal infiltration, and if previously this was more marked than at the time of examination there may be

shrinkage effects and atrophic changes. Hypopigmentation is usually distinct and often fairly well delimited. Beyond this, and what has been said above, no description can be attempted; only personal observation of cases over long periods of time permit decision as to the state of lesions in this category.

ENLARGEMENT OF CUTANEOUS NERVES

In the ordinary examination for enlargement of nerves in leprosy most attention is given the main peripheral trunks, the ulnars and peroneals. With the sole exception of the great auriculars, the superficial cutaneous nerves are largely ignored. Practice is quite otherwise in the leprosy clinic at the School of Tropical Medicine in Calcutta. There all cases of the neural type are carefully examined in this respect, and the examiners detect nerves on the extremities and elsewhere so small as to be palpated with difficulty by the unskilled. Frequently they are not diagnosed as actually enlarged unless the corresponding nerve on the other side is definitely smaller or not palpable at all. A diagram that shows the nerves looked for, and the places where they are sought, is given in Text-fig. 1.⁴ Except for the supraclaviculars, those on the trunk are not included because they are rarely palpable. Those on the upper arms and the thighs also can seldom be palpated, even when there are major skin lesions in those regions.

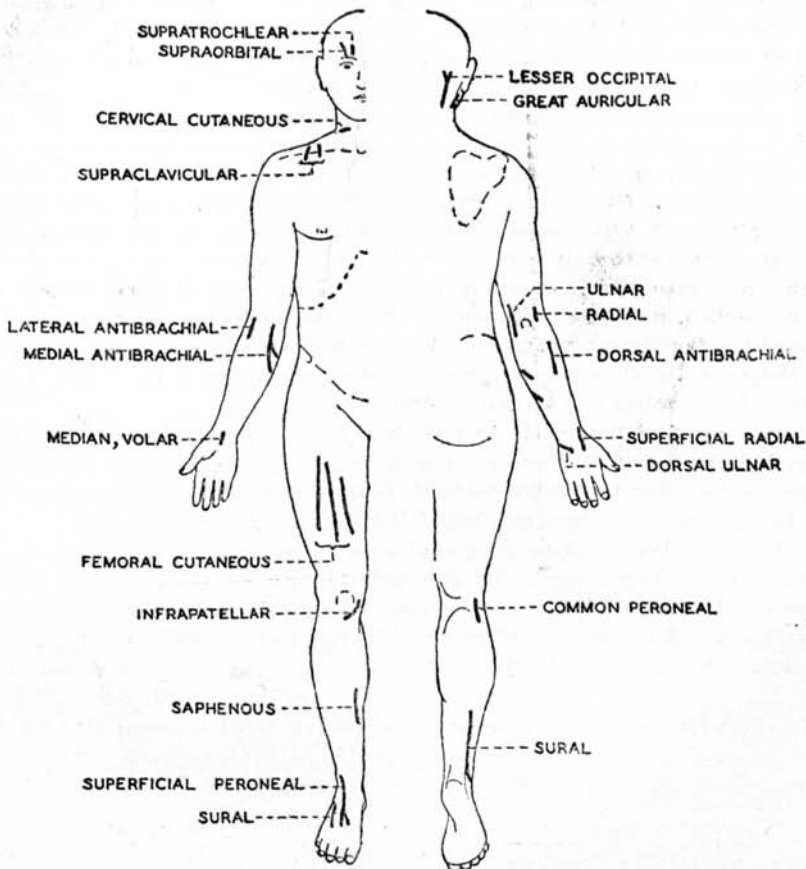
TECHNIQUE

Surgical technique.—All of the specimens examined in this study were removed by our collaborators, or by others cooperating with them. In this work there were considerable variations of technique. In this connection emphasis must be given the importance of selecting biopsy sites with care, and of removing sufficiently deep specimens.

With regard to asepsis, conditions have varied from those of the regular operating room to those of the simplest country clinic where gloves were not available and ordinary antiseptics were depended upon entirely. Carelessness is not to be condoned, of course, but it is true that the more elaborate the technique the greater is the inhibition to resorting frequently to biopsy examinations, and also that no ill effects resulted from the simplest technique used when the wounds were properly closed and dressed. The healthy skin is resistant to secondary infection, and leprosy lesions are healthy in the surgical sense.

⁴This diagram is from one supplied by Dr. S. N. Chatterji, of the Calcutta clinic.

For local anesthesia two percent novocaine with adrenalin was usually used. It has been employed by (a) encircling intradermally the area to be excised, which does not always reach the deeper layers sufficiently; (b) solid infiltration of the tissue to be removed and a zone around it, which is unnecessarily disturbing to the patient and to the tissue to be studied; and (c) rather massive subcutaneous infiltration alone. The last method was the easiest for operator and patient, and was entirely satisfactory when enough of the drug was used and sufficient time was allowed for it to take effect.



TEXT-FIG. 1. Diagram showing locations of nerves examined for enlargement. (Calcutta clinic.)

The necessity of exercising care in selecting and marking the spot to be biopsied is not always realized, and more than one case in our series has had to be dropped on that account. A specimen taken from inside the active zone may show only healed tissue; one from outside it will be normal; one cut longitudinally rather than transversely in a narrow active zone will give an exaggerated

idea of the condition. The selected area should be marked, as with a wax or indelible pencil, before the patient is turned over to the surgeon, and the latter should be careful not to obliterate the mark in preparing the operation site.

When, as is often the case, an elongate specimen is needed to examine (a) the uninvaded skin beyond the edge of the lesion, (b) the margin of the lesion, and (c) recovered skin inside the active zone, it is of course necessary to use the scalpel. When, however, only a small piece is needed to determine the condition at a given point, the skin trephine is simple and effective.⁵ With moderate pressure and a rotary motion it cuts a core that is picked up with fine rat-tooth forceps and snipped off with scissors. The operator is more likely to obtain subcutaneous tissue with this instrument than with the scalpel. Snips taken with scissors are the most unsatisfactory specimens possible.

If subcutaneous tissue is not included in the specimen, downward extension of a lesion through the dermis and in relation to the vessels and nerves immediately underlying it cannot be determined. Size of surface area is often less important than depth. Out of consideration for their patients some operators fail to go deeply enough. The common tendency is to incise the skin obliquely, so that the specimen removed is V-shaped and contains little if any of the deeper structures. When the incisions are vertical, and the piece of tissue removed of square section, it is easy to include all of the desired layers. In closing such a wound the two flat-cut surfaces are brought together neatly, and there is little if any more disturbance to the patient or scarring than with the V-shaped cut, though the operation may seem more drastic.

A word of caution should be said about the manner of handling the tissue that is being removed. Crushing it with forceps affects seriously the histological picture. The use of fine rat-tooth forceps in good condition, employed so as to injure as little tissue as possible, is strongly to be recommended.

In closing the wound, suturing is of course desirable when particularly large specimens have been removed, but ordinarily the simple, speedily applied Michel clips may be used with entire satisfaction. Exception is to be made of a surface that is under much tension, where the clips may pull out and leave the wound gaping, to heal with an excessive scar.

Pathological technique.—The technique used in such studies as the present one is of considerable importance. Only enough to guide a trained technician need be said about it here.

In our work Zenker fixation is depended upon for the histological study, because of certain inherent advantages. Formalin is extremely unsatisfactory; it is often responsible for shrinkage that makes interpretation of sections difficult, and may actually mislead the examiner by causing a false appearance of foamy-cell accumulation. Furthermore, formalin-fixed tissues are not suitable for certain very useful staining methods. On the other hand, Zenker's fluid is on

⁵The instrument referred to is a special one manufactured by the Jetter and Scheerer Company, of Tuttlingen, Germany (list No. SB12147), and is procurable in sets of four: 3, 5, 7 and 9 mm. in diameter. The two largest have been used extensively in our work, but the smaller ones may be used where it is important to minimize the size of the scar, as on the face.

the whole less satisfactory for the search for bacilli than formalin or alcohol. Consequently, in our work duplicate specimens have sometimes been taken, one to be fixed for the tissue study and the other for the search for bacilli, while at other times a single specimen has been divided.*

In dividing a single specimen, if it is elongate, it should be cut longitudinally so as to include all phases of the lesion in each part; otherwise one will have two pieces that are not comparable. It is often immaterial how a round, trephine specimen is cut. In preparing the fixed tissues for embedding, care is taken that the sections will show all layers of the skin. Trephine specimens are split open, but the two halves are not quite separated; they are opened up and embedded flat, so as to give sections of both cut surfaces; this gives a slide with two sections of known relation to each other.

Sectioning has been done exclusively by the paraffin method. The histological staining methods that have been employed regularly are: (1) the usual hematoxylin-eosin method, (2) Mallory's phosphotungstic-hematoxylin method, (3) Mallory's aniline-blue method for connective tissue, and (4) Verhoeff's method for elastic tissue(8).

Bacteriology.—In this study ordinary smear examinations were made as a matter of routine. On the other hand the question of whether or not bacilli could be found in the tissues was considered secondary to that of the histology of the lesions.

For the ordinary bacteriological examination, in some cases smears were made from the biopsy wound, but usually this was impracticable. Sometimes they were made directly from the biopsy specimens, but this is injurious to the tissue. Usually the routine bacteriological examination of the patients was depended upon, multiple smears being made from several places, including of course the lesions biopsied.

Photography.—Good photographs of lesions are not only indispensable to illustrate published reports; they are also important as records for accurate follow-up observations. In our work pictures have been taken whenever possible, under many different circumstances and with variable results.

For best results are needed (a) photographic materials that will register small variations in color and give fair contrast, and (b) lighting that will bring out fine details of the skin surface. Panchromatic material is the most desirable, and cut film or plates are far better than the ordinary films used for snapshot work since they give stronger negatives; conditions have too often prevented us from using the most favorable materials. Whenever possible direct sunlight has been used for illumination, in the hours when it is fairly oblique; in the four hours or so around noon it is too directly overhead to give the best results. Work must be rapid, as patients will move; this applies to both the time between for

* Recent improvements in technique of staining the leprosy bacillus in sections of Zenker-fixed tissues will be discussed in a future report.

focusing and exposure, and the exposure itself. With regard to the former, the reflex type of camera, like the graflex, has a great advantage, and for the latter a reasonably fast lens is needed, though a large stop reduces the depth of focus so greatly as to be often troublesome in close-up work. It is often best to take the picture from a greater distance and make an enlargement of the essential part of the negative to bring out details. The slower photographic emulsions are a handicap in this respect, though otherwise they may have advantages. Accurate focusing is often difficult when there are no strong details that show up clearly on the focusing screen; it helps greatly to have an assistant hold a slip of printed paper close against the part being focused on, for the lettering shows up clearly. Development of the negative should be for moderate contrast rather than for soft effects.

HISTOLOGICAL CHANGES

In concluding this general introduction a few salient points should be established in connection with the histological changes to be discussed. Mainly, it is to be understood that the principal characteristic of the lesions under discussion is the occurrence of tubercle-like foci the essential feature of which is a collection of epithelial cells. Giant cells and "round cells" are also in the picture, but they are secondary and more variable. Lesions with only round-cell changes are of some importance.

The term "epithelioid" applies strictly to those cells which are most familiar in the focal lesions of tuberculosis, though they are also found in other conditions and so are not pathognomonic of any. The matter is confused by the frequently indefinite use of that term by older European writers, which often makes their descriptions impossible to interpret with certainty. Nor is it always used correctly by modern writers. For example, in describing the histology of a specimen from an obviously cutaneous-type case reported by Silcock(17), Muende called the prevailing cell epithelioid, but actually it was the foamy Virchow lepra cell of the lepromata. More important, Muir(12) has used the same term in describing the skin lesion of cutaneous leprosy, stating that the cells therein are similar in type to those of the neural macules, "chiefly of the so-called epithelioid type."

Giant cells, usually of the Langhans type but sometimes of the less differentiated "foreign body" variety, are present in most well-established tuberculoid lesions. However, they are not constant or essential, and are seldom found in the small tuberculoid foci, common to the lesser leprides.

Round-cell infiltration of some degree is also commonly present. The use of the term "round cell" in leprosy work is often unfortunately loose. In ordinary pathological parlance it refers to the so-called lymphoid cells which, with or without plasma cells, are characteristic of banal chronic inflammation. In leprosy work it is necessary to consider another type of cell that may be confused with them, namely, the mononuclear wandering cells, variously called macrophages, histiocytes, etc. Lymphoid cells are often present, as a result of

the inflammatory process, but they are of minor importance. To the contrary, there is reason to believe that the accumulation of cells of the macrophage type is decidedly important, and lesions that contain them in numbers must be looked upon with some concern, no matter how simple they may appear clinically.

Finally, the examiner must bear in mind that lesions which have been treated by intradermal injection of chaulmoogra drugs will show disturbed pictures. Accumulations of macrophages that have taken up residual oily particles may simulate lepromatous infiltrations so closely as to be seriously misleading.

The several factual articles in the present series will be based upon the foregoing discussion with as little repetition or divergence as possible. Discussion of the findings recorded in each article will be limited for the most part to the particular features brought out therein. As yet little can be said of the developments in the cases under study, subsequent to the examinations recorded, except for the Cebu groups.

REFERENCES

- (1) CHATTERJI, S. N. Thickened nerves in leprosy in relation to skin lesions. *Internat. Jour. Lep.* 1 (1933) 283-292.
- (2) CHIYUTO, S. Early leprotic changes in children and their bearing on the transmission and evolution of the disease. *Month. Bull. Bu. Health (Manila)* 13 (1933) 5-48; also, *Idem*, II. *Ibid* 14 (1934) No. 12.
- (3) DOULL, J. A., RODRIGUEZ, J. N., GUINTO, A. AND PLANTILLA, F. C. A field study of leprosy in Cebu. *Internat. Jour. Lep.* 4 (1936) 141-170.
- (4) [EDITORIAL.] Arning's observations. *Internat. Jour. Lep.* 4 (1936) 100-101.
- (5) JEANSELME, ED. *La Lèpre*. G. Doin et Cie, Paris, 1934, p. 204.
- (6) LARA, C. B. AND DE VERA, B. Clinical observations with reference to leprosy of children. *Jour. Philippine Islands Med. Assoc.* 15 (1935) 115; *reprinted Internat. Jour. Lep.* 4 (1936) 349-362.
- (7) LOWE, J. Nerve abscess in leprosy. *Indian Med. Gaz.* 64 (1929) 24. A further note on nerve abscess in leprosy. *Internat. Jour. Lep.* 3 (1934) 301-304.
- (8) MALLORY, F. B. AND WRIGHT, J. H. *Pathological Technique*. W. B. Saunders Company, Philadelphia and London, 8th ed., 1924.
- (9) MANALANG, C. Significance of pathological findings in biopsy material from lepers. *Month. Bull. Philippine Health Serv.* 11 (1931) Dec., and *Rev. Filipina Med. Farmac.* 23 (1932) 43.
- (10) [MEMORIAL CONFERENCE.] Report of the Leonard Wood Memorial Conference on Leprosy. *Philippine Jour. Sci.* 44 (1931) 449-481. *Reprinted: Internat. Jour. Lep.* 2 (1934) 352.
- (11) MUIR, E. Nerve abscess in leprosy. *Indian Med. Gaz.* 59 (1924) 87.

- (12) MUIR, E. The relationship of skin and nerve leprosy. *Indian Jour. Med. Res.* 22 (1934) 383-392.
- (13) MUIR, E. AND CHATTERJI, S. N. Leprous nerve lesions of the cutis and subcutis. *Internat. Jour. Lep.* 1 (1933) 129-148.
- (14) OTA, M. AND SATO, S. Ueber die tuberculoide Veränderung der Lepra. *La Lepro* 6 (1935) 37 (abstract section; original in Japanese.)
- (15) RODRIGUEZ, J. N. Significance of the histology of bacteriologically negative lesions of leprosy. *Internat. Jour. Lep.* 4 (1936) 289-293; *also*, correspondence, p. 270.
- (16) SCHUJMAN, S. Coexistencia de abceso nervioso y lepra tuberculoide. *Rev. Leprol. S. Paulo* 2 (135) 277.
- (17) SILCOCK, F. A. E. Leprosy (mixed nodular and anaesthetic). (Case report) *Proc. Roy. Soc. Med.* 27 (1934) 1459.
- (18) DE SOUZA CAMPOS, N. Tuméfaction caséuse des nerfs cours de la lèpre. *Internat. Jour. Lep.* 4 (1936) 1-24.
- (19) TISSEUL, J. Essai de classification des tuberculoïdes de la lèpre. *Bull. Soc. Path. exot.* 29 (1936) 238-242.
- (20) UNNA, P. G. *The Histopathology of Diseases of the Skin.* English edition (translation by N. Walker), W. F. Clay, Edinburg, 1896.
- (21) WADE, H. W. Tuberculoid changes in leprosy. I. The pathology of tuberculoid leprosy in South Africa. *Internat. Jour. Lep.* 2 (1934) 7-38.
- (22) WAYSON, N. E. The lighting of the examining room. *Internat. Jour. Lep.* 4 (1936) 345-347.