DEVELOPMENT OF THE LESIONS OF LEPROSY

WITH PARTICULAR REFERENCE TO TUBERCULOID LEPROSY AND THE SIGNIFICANCE OF THE LEPROMIN TEST

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After a tour of leprosy countries in 1931 during which he collected study material in South Africa, Wade (8, 9) brought to the attention of leprologists the importance of the tuberculoid form of the disease. Tuberculoid leprosy had been described by earlier workers, particularly in Europe, but little attention had been given to it elsewhere. As a result of the widespread recognition of this variety of neural-type leprosy, and of equally extensive investigation of the lepromin reaction, the whole conception of resistance in leprosy has now been changed. Therefore, before presenting the views with regard to the development of lesions in leprosy that are the subject of this paper, it is necessary to review the position of that form of the disease.

In India the histological picture of what is now recognized as tuberculoid leprosy was described in 1928 by Henderson (3), but at that time the clinical condition was not regarded as requiring special mention. The reasons for this were, first, that in Calcutta it is comparatively common, and therefore it was not considered in any way peculiar, and, second, that because the lesions are frequently positive to standard methods of bacteriological examination they were considered at that time to be "cutaneous," and no further importance was attached to them. In view of the emphasis now placed on tuberculoid leprosy it is somewhat remarkable that it received no recognition in the Manila Conference of 1931. The viewpoint of the Calcutta workers being as stated, they did not bring the subject up for special discussion, while other workers, if they were aware of the condition, considered it so rare that it was not timely to enter into a discussion of its relationship to the supposedly more common types of the disease.

The literature of the past ten years reveals the importance that tuberculoid leprosy has assumed, not only in the question

of diagnosis but also in that of immunity in this disease. It is not proposed to discuss in detail here the question of resistance and immunity in leprosy, but it is to be noted that the tuberculoid variety, especially in its more acute manifestations, is now generally accepted to be the outward evidence of sensitization of the tissues to the causative organism of leprosy or its products. The only definite method known of overcoming the disease appears to be the development of a tissue sensitization which results in focalizing the infective process and preventing its general dissemination; or, perhaps more correctly stated, in the production of an allergic condition of the tissue which is at once manifested either in skin or nerve when the bacilli begin to show activity, and which prevents their dissemination. On the other hand, when there is no such tissue sensitization the bacilli, if they become active, multiply and spread diffusely in the dermis, there being no attempt on the part of the body to focalize the infection. Thus the organism may rapidly invade the whole reticulo-endothelial system, and so give rise to the malignant or lepromatous form of the disease.

The essential cell in this process is the macrophage.[1] These wandering cells ingest the bacilli and distribute them widely. In addition, in the stage of lepra reaction the bacilli may be disseminated by the blood stream, and this spread probably occurs continually by way of the lymphatic current. Histologically this process is well seen, and is in marked contrast with that of tuberculoid leprosy, in which the infection is localized in the tuberculoid focus. Clinically the difference of response is seen in the fact that in early lepromatous leprosy the edges of the lesions are indefinite and merge imperceptibly into the surrounding skin, whereas in tuberculoid leprosy, because of the focalization of the process, the edges are well defined.

Since the original papers on major tuberculoid leprosy appeared there has been considerable discussion regarding the possibility that the tissues may lose their allergic sensitivity, and it has been held that the major tuberculoid variety may turn into the more serious lepromatous type. This question is one which is exercising the minds of leprologists. Wade (10), in a paper on reaction in tuberculoid leprosy, definitely described a histological picture which is different from that of what, for

[1] The bacilli are evidently not destroyed by the macrophages but live in a state of commensalism within the cells, sometimes multiplying rapidly, and thus the whole reticulo-endothelial system becomes invaded.

the want of a better term, might be described as frank tuberculoid leprosy. Lowe (11) refers to certain cases as "N?C," indicating a doubt as to whether they are of the neural type, or neural becoming cutaneous (now called lepromatous).

In the older records of this institution are descriptions of such cases as major tuberculoid turning lepromatous, it having been accepted as a fact that such a change did actually take place. A closer study of such cases has caused me to doubt the possibility that they are really tuberculoid ones which underwent transformation. This doubt first arose when it was found that cases of this kind were consistently negative to lepromin, apparently indicating that the tissues were not allergic but that the reactive disease condition was due to a "pseudoallergy." It is theoretically possible for a lepromin-positive case to become negative, but so far I have encountered no example of that change. Therefore I am of the opinion that these lesions which simulate tuberculoid leprosy so closely belong to an intermediate variety, which as a rule undergoes recovery but occasionally passes into the frank lepromatous form.

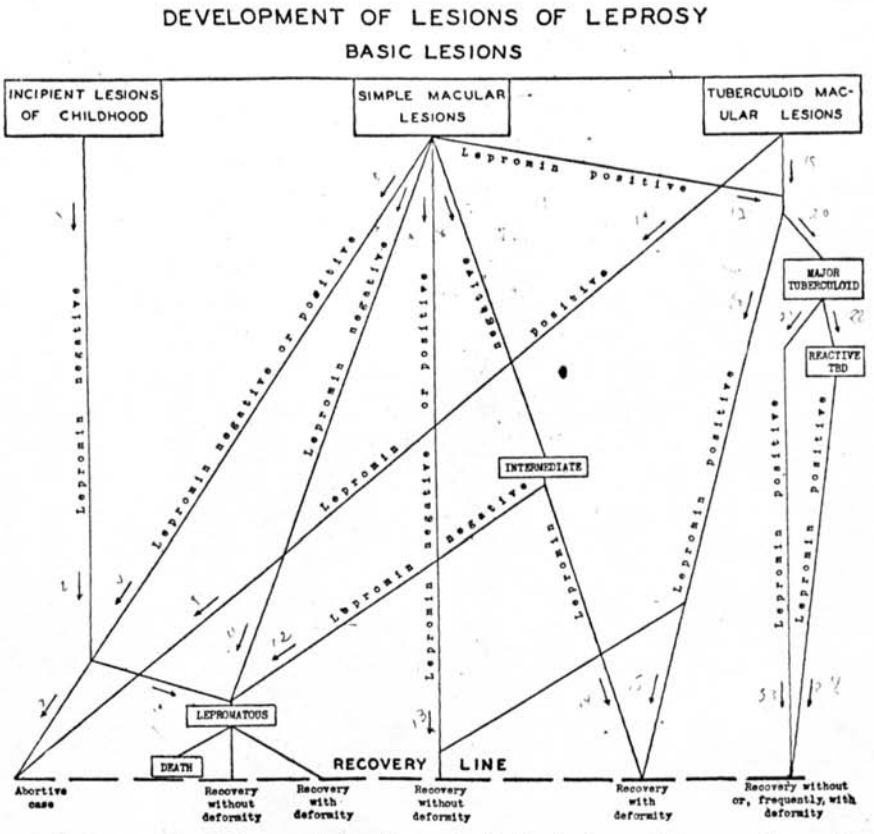
DEVELOPMENT OF LEPROSY LESIONS

If this hypothesis is correct, is there any evidence regarding the way in which these lesions arise? This raises the whole question of the development of lesions in leprosy, a question to which there have been very few references. Muir, in 1923 (5), indicated what he then considered the mode of spread of the disease throughout the body, suggesting that it spread from an original initial lesion. Text-fig. 1 illustrates diagramatically my conception of the process.

In this scheme it is suggested that there are probably three basic lesions, meaning by that term those from which all others develop. These are: (*a*) the incipient lesions of childhood, (*b*) the simple macular lesion, and (*c*) the tuberculoid macular lesion. I am aware that many writers do not consider tuberculoid leprosy a type, but a variety. Wade (10) states: ". . . . the term tuberculoid leprosy one understands to imply a variety (not type) of leprosy which can be distinguished clinically . . . . ." and goes on to say that this lesion is a variety of the group to which some writers apply the useful term "leprid," to distinguish them from the lepromata.

Certain workers on the other hand, particularly those in South America, hold that tuberculoid leprosy should be regarded

as a separate type. It is difficult to accept this contention, however, because the tuberculoid process varies so greatly in degree. The majority of simple macular lesions show the tuberculoid histology in more or less slight degree. It is evidently only when the characteristic tissue reaction is sufficiently marked that there are produced lesions which can be recognized clinically as of tuberculoid nature. Nevertheless, there is evidence to show



TEXT-FIG. 1. Scheme of development of the lesions of leprosy from the basic lesions.

that the clinically tuberculoid macule often commences as such and does not necessarily develop from the simple macule of neural leprosy; therefore it must be included under the term "basic lesion."

It will be noted that among the basic lesions are included the "incipient lesions of childhood." For some considerable time I have held that these lesions are frequently the precursors of

lepromatous leprosy, and that those cases which appear to have commenced as lepromatous would, if examined carefully, have shown lesions of the "incipient" type before they become definitely of lepromatous nature. The period between the time when visible lesions appear and that when bacilli can be found in them is very variable; it may be weeks or months or, possibly, years. In the more susceptible races, such as the Mongolian and European, this period may be so short and the lesions so slight that they are entirely overlooked, with the result that the impression is gained that lepromatous leprosy commences without any previous evidence of infection. It would be interesting to know whether this experience can be confirmed elsewhere.

THE BASIC LESIONS

A more detailed consideration of the development of these so-called basic lesions will now be presented.

INCIPIENT LESIONS OF CHILDHOOD

These lesions have been described elsewhere (6), and all that need be stressed is their similarity to lesions of lepromatous leprosy. The two main distinguishing features are (*a*) that the incipient lesions do not show erythema, nor do they have the marked shiny or glistening appearance which is a characteristic feature of lesions that have become lepromatous, and (*b*) that bacilli cannot be obtained from them by standard methods of examination. Apart from these two differences the incipient lesions have the characteristics of those of lepromatous leprosy, both as to their distribution and as to the character of their edge; in fact, the vagueness of the periphery of these lesions, and the frequent inability to recognize them except in a good light (see Plate 29, fig. 1), are reasons why they are so often overlooked. In addition, patients with these lesions seem always to be negative to lepromin.

Histologically the incipient lesion shows nothing characteristic at first. A considerable amount of round-cell infiltration can be demonstrated superficially in the dermis (Plate 33, figs. 17 and 18), and there may be some accumulation of these cells around hair follicles, but the infiltration is diffuse, with no definite evidence of focalization, and the epithelioid and giant cells characteristic of the tuberculoid condition are absent. While the actual change to the leproma has not been demonstrated histologically, the process can be easily visualized. The infiltra-

tion probably becomes more intense by an increasing invasion of round cells and macrophages, which begin to produce the picture of the leproma because of their uniform distribution and the noninvasion of the zone immediately beneath the epidermis. The bacilli begin to multiply more rapidly at this stage, and the macrophages ingest them. As the tissues are not allergic there is no attempt at focalization of the invading process, and the bacilli become disseminated widely throughout the skin and in the deeper tissues.

It is equally easy to imagine that in other cases, instead of this widespread dissemination of the bacilli, the alternative change may take place—that is, that the process becomes focalized, the round-cell infiltration becoming more intense while the characteristic tuberculoid change develops. I believe that this process does not usually occur because of the absence of tissue sensitization, the production of definite epithelioid foci with giant cell formation being evidently an indication of that condition. Clinical evidence is available that incipient lesions do pass into the lepromatous kind, but their development into clinically tuberculoid leprids has not been seen.

SIMPLE MACULAR LESIONS

It is held by some investigators that, histologically, all simple macular lesions (illustrated in Plate 29, fig. 2) are essentially tuberculoid in their histology. If by that is meant evidence of focalization of the invading process, with commencing epithelioid change, I agree. In another paper to be published shortly it is shown that lesions of simple macular leprosy (Ns of the Cairo classification) occur in patients with negative lepromin reactions and in others who are lepromin positive. It would seem, therefore, that there are two methods of development of such lesions: either they may become lepromatous, or—in lepromin-positive cases, those which are potentially allergic —they may become frankly tuberculoid. I have traced the histories of about twenty cases in this settlement which were previously of neural type, with simple macular lesions, but that subsequently developed lepromatous leprosy. The actual change has not been witnessed, although Rodriguez, Wade and Plantilla (6) have recently described that occurrence. The factor which determines whether the simple macular lesion becomes lepromatous or not lies, I believe, in whether or not the tissues show latent allergy. In other words, the more strongly posi-

tive the lepromin test the less likely are the cases to pass into that type.

As indicated in Text-fig. 1, the lesions of simple macular leprosy, as well as those of incipient leprosy, may become abortive. Whether that happens or not may depend upon the number and massiveness of previous inoculations. It has been shown elsewhere (2) that, in this region, the number of children showing multiple lesions is twice as high when the contact is intrafamilial than when it is extrafamilial. Furthermore, it appears that the number of lepromin-positive cases diminishes as the degree of contact increases.

TUBERCULOID MACULAR LESIONS

The tuberculoid macular lesions have been divided, according to the degree of clinical (and histological) change, into minor and major varieties. These lesions, which show wide variations, have become so familiar in recent years that their ordinary forms are not illustrated here. As yet I have never seen the lepromatous transformation of a frank tuberculoid lesion—meaning by that a lesion which clinically shows the characteristics of the major tuberculoid leprids—in a case strongly positive to the lepromin test. Whether the slighter degrees of minor tuberculoid leprosy become lepromatous I am not in a position to say, but as yet no one has produced evidence to show that, once the allergic condition in the disease is definitely established, it can be broken down and a previously strongly positive lepromin reaction become negative.

It is well known that a patient with major tuberculoid leprosy may show, from time to time, acute exacerbations of the lesions. Lowe (4) has shown that there may be a seasonal variation in this matter. Whatever the reason may be, the lesions suddenly flare up, becoming erythematous and angry looking (Plate 32, figs. 5-8); and in the more severe cases they frequently desquamate, the scales often being excessive and simulating psoriasis. The fact that, in such cases, the reaction-lesion resulting from the intradermal injection of lepromin breaks down and suppurates indicates an extreme sensitization of the tissues. This fact makes unacceptable the view that major tuberculoid leprosy may become lepromatous. I cannot visualize an allergic process of such intensity turning into an anergic process.

THE INTERMEDIATE LESION

Besides the basic lesions that have been discussed, there

are certain ones, neither tuberculoid nor frank lepromatous, which have puzzled leprologists from time to time. These lesions may be called "intermediate," because they fall into no particular category.

Such lesions have been recognized by various workers, particularly by Wade (10), who calls such cases "borderline," and Lowe (11), who has referred to them as "N?C." South American writers speak of them as tuberculoid cases with negative lepromin reactions. Wade mentions some of the features of this condition, particularly the more succulent nature of the lesions and the greater tendency, histologically, for the granuloma to be separated from the epidermis by a narrow zone which is usual in leproma. The clear zone between the epidermis and the granulomatous masses frequently shows numerous dilated capillaries. The nerves usually are grossly invaded, although sometimes the invasion is less marked than in massive tuberculoid leprosy.

Clinically these lesions usually appear to behave in a manner similar to the major tuberculoid ones in that they frequently recover (Plate 31, figs. 9-12), although the recovery period is very much longer. There are one or two curious features with regard to their progress. For one thing, the patients frequently pass through a stage of extreme emaciation, and one sometimes almost despairs of their life. During the stage of activity of lesions and emaciation the patients frequently become febrile, the fever sometimes lasting for months and not responding to the antimony products. The lesions are erythematous, scaly and frequently edematous, and percussion of the patches elicits acute tenderness. In the most severe cases they may break down rapidly and ulcerate (Plate 32, figs. 13 and 14). Altogether the patient is very miserable and causes the physician considerable concern. Bacilli can usually be demonstrated, and they may be found considerably longer than in tuberculoid cases in the reactive condition—that is, for more than six months and sometimes as long as 18 months. I have not actually seen one of these cases becoming frankly lepromatous, although there is now in the settlement a lepromatous case which appears to have been one of this intermediate variety (Plate 32, figs. 15 and 16). In other words, clinically these cases usually show features akin to both lepromatous and tuberculoid leprosy, but apparently they almost invariably recover. Every case that I have yet tested has given a negative lepromin reaction. It is

because the latter finding is so constant that I believe that this condition, which so closely resembles tuberculoid leprosy, is not an allergic process and, for want of a better term, I have called it a "pseudoallergy." A negative lepromin test in major tuberculoid leprosy is a contradiction; I believe that true allergy cannot occur in the presence of a negative lepromin test.

DIFFERENTIATION OF MAJOR TUBERCULOID AND INTERMEDIATE LESIONS

It is to be realized that no hard and fast lines of separation between these two classes of lesions can be maintained. Diagnosis of the intermediate type is based primarily on the clinical findings, supported by the lepromin test. The histological appearance, while fairly constant (Plate 33, figs. 22-24), frequently simulates so closely that of tuberculoid leprosy in the reactive state that it may be impossible to give a definite opinion unless the microscopic picture is correlated with the clinical condition and the lepromin reaction. In the following tabulation are given the main clinical and histological differences between cases of these two classes, so far as they can be laid down.

TUBERCULOID CASES	INTERMEDIATE CASES
Lesions: Raised, erythematous and infiltrated, with sharply defined edges which remain distinct, even when they extend.	Raised erythematous lesions with a more succulent appearance; edges, while infiltrated, tend to be less well defined.
Reactive stage: Considerable tenderness of lesions. Febrile period, if any, of short duration. Emaciation seldom marked and patient rarely so ill as to need hospitalization.	During reactive stage marked burning and tenderness of lesions, which may ulcerate. With fever, sometimes prolonged, and emaciation, patient may appear extremely ill, and often requires hospitalization.
Bacilli: Lesions positive, usually becoming negative within six months.	Positive, not becoming negative in less than 9 to 18 months.
Histology: The granuloma usually extends to the epidermis, with no subepidermal clear zone. Giant and epithelioid cells well marked. No foamy cells.	The granuloma tends to respect the subepidermal zone, where dilated capillaries are frequently seen. Tuberculoid structure not so obvious, giant cells tending to be fewer or smaller, and may be absent. Foamy cells not infrequently seen, sometimes in the same field as giant cells.
Lepromin: Reaction positive.	Reaction negative.
Nerve abscess: Common.	Abscess unusual.

It would be interesting to know if the lesions which Ryrie (7) described as ulcerating tuberculoid leprosy, and which he states may become lepromatous, are not in reality examples of pseudoallergy and come into this category. He has made no statement regarding the results of the lepromin test in these cases.

An interesting question to speculate upon is how these intermediate cases commence. Are they intermediate from the beginning—that is, can they be described as true basic lesions—or do they develop from some other type of lesion? This question cannot be answered entirely satisfactorily. I have never seen a major tuberculoid case pass into this intermediate type. The histories which have so far been obtained from patients indicate that these lesions develop from simple macular leprosy, and therefore I have indicated this possibility in Text-fig. 1.

TISSUE SENSITIVENESS

The course of leprosy seems largely to depend on whether the tissues are potentially allergic or not, as shown by the lepromin test. If the reaction to lepromin is strongly positive, then when the disease begins to show activity the characteristic cellular response is seen in the tissue (Plate 33, fig. 20) and tuberculoid leprosy develops. This results in the enclosing of the bacilli within the tuberculoid foci, and thus their general dissemination throughout the reticulo-endothelial system is prevented. Benign leprosy thus ensues. On the other hand, when the tissues are anergic and no cellular response results, the bacilli become widely disseminated in the skin and are carried by the macrophages throughout the reticulo-endothelial system. Lepromatous or malignant leprosy then results (Plate 34, fig. 21). In the intermediate lesion there is some factor which inhibits the establishment of allergy; such cases seem to progress toward the condition of skin sensitization but are unable to become allergic. The multiplying bacilli invade the macrophages much more intensely than is usually seen in tuberculoid leprosy, and lepra cells and foamy cells are formed. There must, however, be an immunological response, which may or may not be akin to allergy, as witnessed by the great majority of cases overcoming their infection, apparently spontaneously.

It seems very certain that in tissue sensitization lies the answer to many of our problems in leprosy, and that if it were possible to sensitize tissues which do not exhibit allergy we

would establish a natural cure for leprosy, for apparently it is only by this allergic process that the body can arrest the development of the disease in cases where multiplication of the bacilli is active. There is evidence of spontaneous recovery in lepromatous leprosy, although that may be exceptional, and therefore I am of the opinion that there may be established an immunity which is different from the allergic response of sensitized tissues, and consequently that allergy and immunity may bear no direct relationship to each other. If it could be determined whether the allergic response so frequently seen in sensitized tissues is hereditary or acquired, and what the nature of the immunity is in lepromatous leprosy which becomes spontaneously healed, we would be well on the way to discovering an effective method of treating the disease, and methods of prevention should then become considerably simplified. Studies are being pursued along these lines. This paper is published in the hope that the questions raised will receive the attention of other workers and pave the way to further advances in our knowledge of this perplexing disease.

Acknowledgments are due to the assistant medical officers in the Lady Willingdon Leper Settlement; and especially to Dr. Paul Raj, the research assistant under the Indian Research Fund Association, for help in collecting material for this article and for his criticisms of it.

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DESCRIPTION OF PLATES

PLATE 29

FIG. 1. Incipient lesions of childhood, showing vagueness of the affected areas. A red filter is necessary for such photographs, and even then they are almost impossible to demonstrate in photographs.

FIG. 2. Simple macule in neural type leprosy, with typically well defined margins.

FIG. 3. Lesions of early lepromatous leprosy. Areas fairly well differentiated, but margins indefinite.

FIG. 4. Lesions of generalized lepromatous leprosy. In this case the skin reaction is so slight that the condition is almost impossible to demonstrate photographically, yet smears were highly positive.

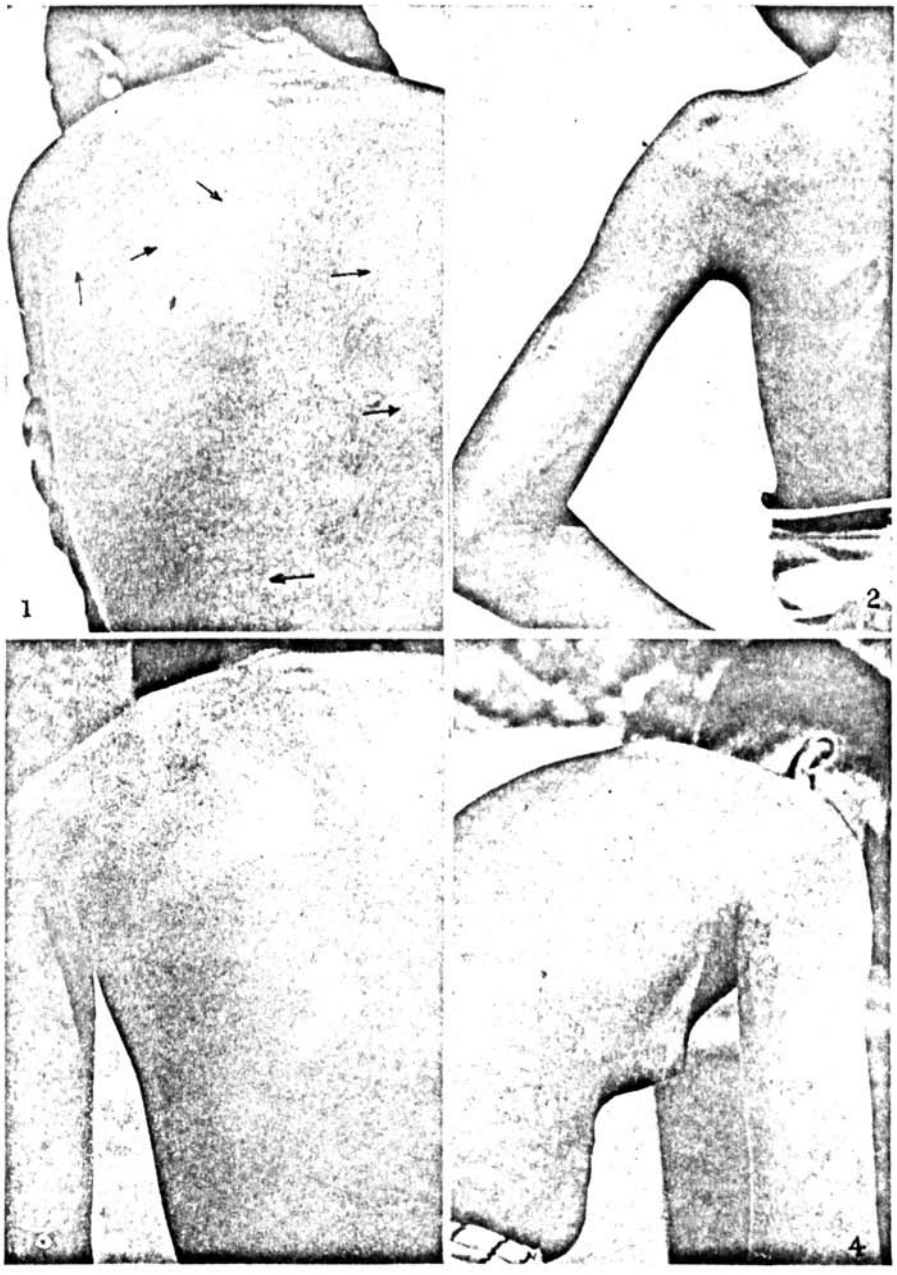

PLATE 29

PLATE 31

FIG. 9. Lesions of intermediate type on the face.

FIG. 10. The same patient as in Fig. 9, showing complete subsidence of the lesions within seven months.

FIG. 11. Intermediate lesions on the upper back. Similar lesions were present throughout the body.

FIG. 12. Same patient as in Fig. 11, showing subsidence of the lesions three months later. Bacteriological smears, however, remained positive.

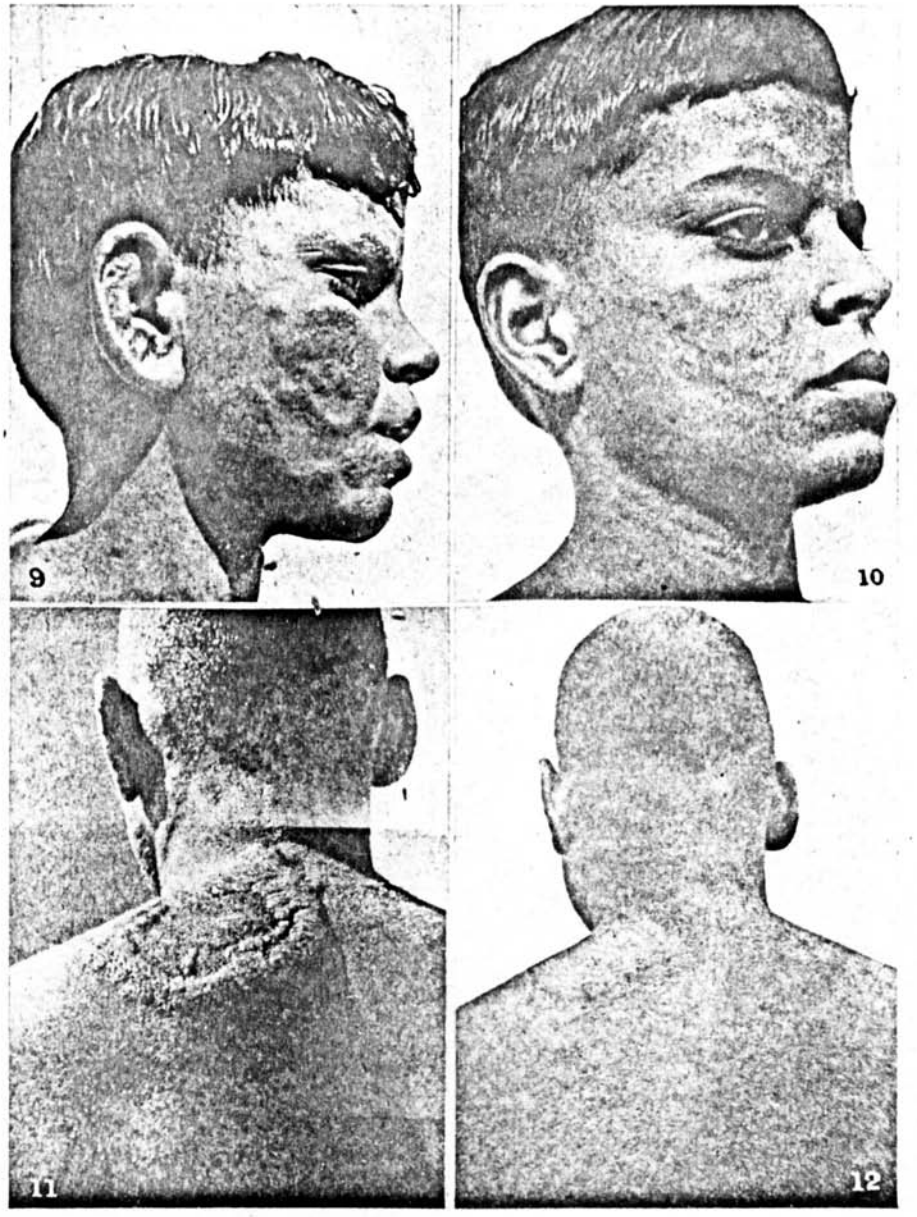

PLATE 31

PLATE 32

FIG. 13. Patient with ulcerative lesions of intermediate type, showing breaking down of one on the left cheek (see Fig. 14).

FIG. 14. The same patient as in Fig. 13, showing extensive ulcerations of lesions on the hand and arm. This patient has been in the hospital for more than four months.

FIG. 15. Intermediate lesions on the body, discrete but with tendency to diffusion of the edges (see Fig. 16).

FIG. 16. Same patient as in Fig. 15, three years later. The case has now become lepromatous.

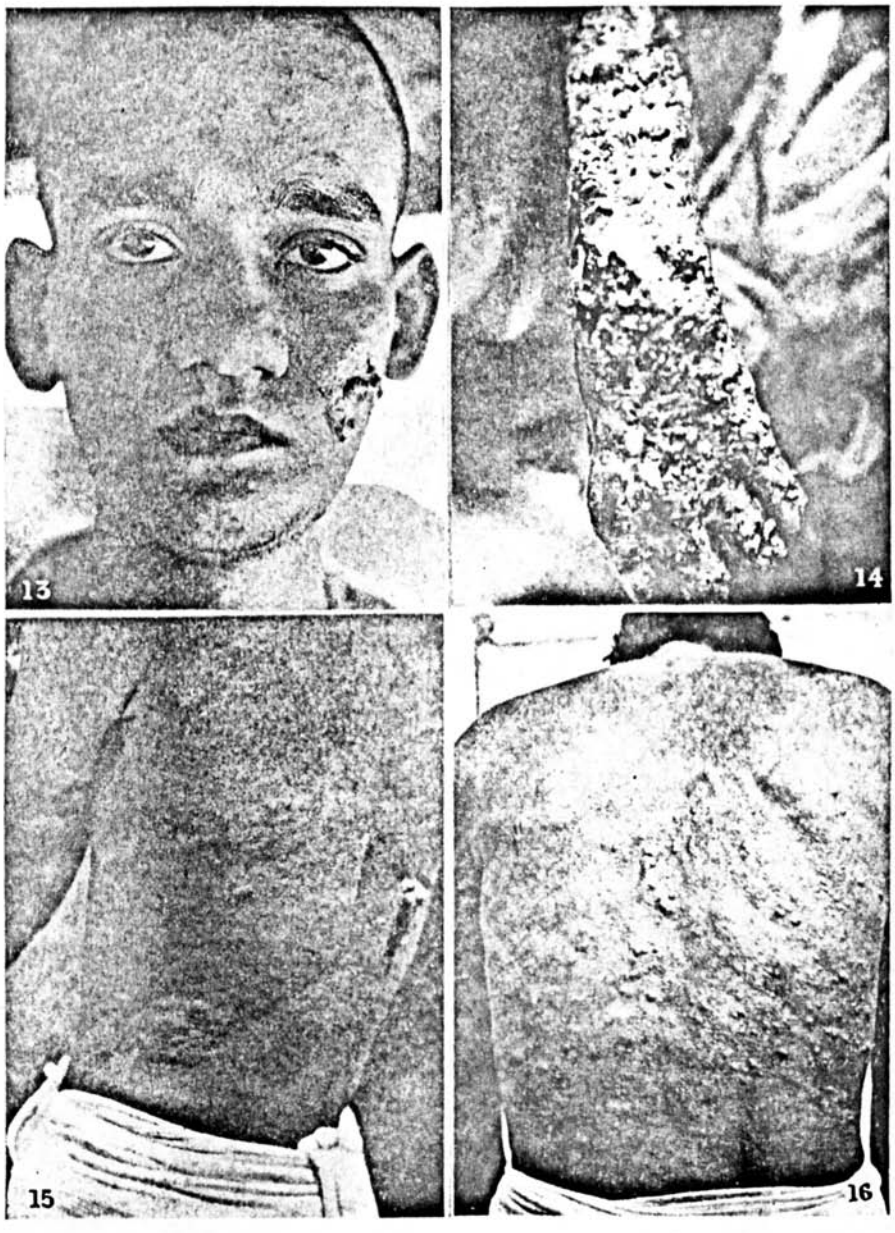

PLATE 32

PLATE 33

FIG. 17. An incipient lesion. Low power photomicrograph showing the very slight infiltration.

FIG. 18. Same lesion as in Fig. 17, as seen with the oil-immersion objective. Round cells and a few macrophages under the epidermis.

FIG. 19. Early macular leprosy (simple macular). Low power photomicrograph showing round-cell infiltration extending up to epidermis, with a tendency to focalization.

FIG. 20. Tuberculoid macular leprosy (major), showing conspicuous giant cells.

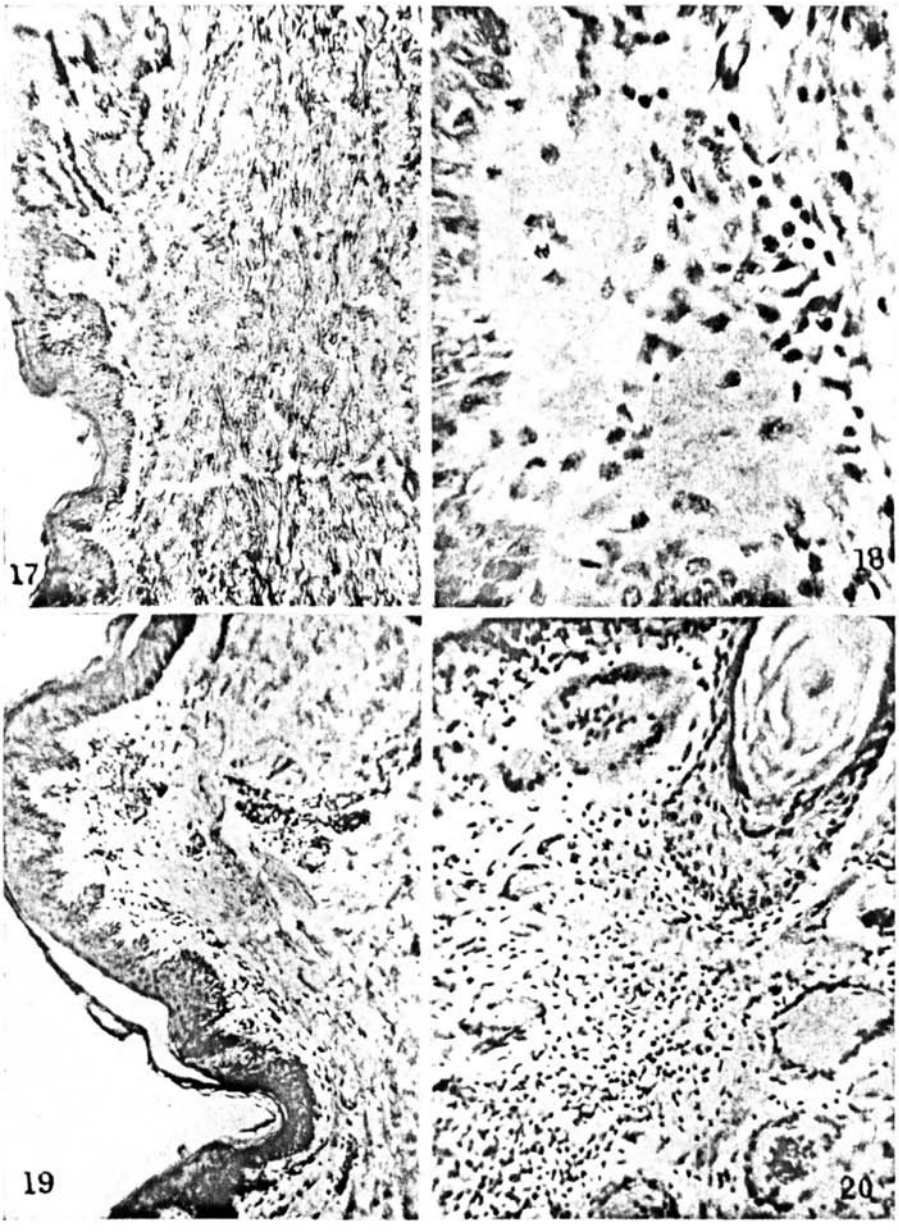

PLATE 33

PLATE 34

FIG. 21. Early lepromatous leprosy, showing diffuse infiltration in the subpapillary layers, respecting the subepidermal zone, and (at A) a small nerve in the deeper tissue uninvaded.

FIG. 22. An intermediate lesion, containing a small giant cell. This lesion illustrates the comparatively free subepidermal zone, in which there are numerous dilated capillaries.

FIG. 23. Large foamy cell (A) in the deeper tissues in a lesion of an intermediate case (see Fig. 24).

FIG. 24. Giant cell in a field adjacent to that shown in Fig. 23.

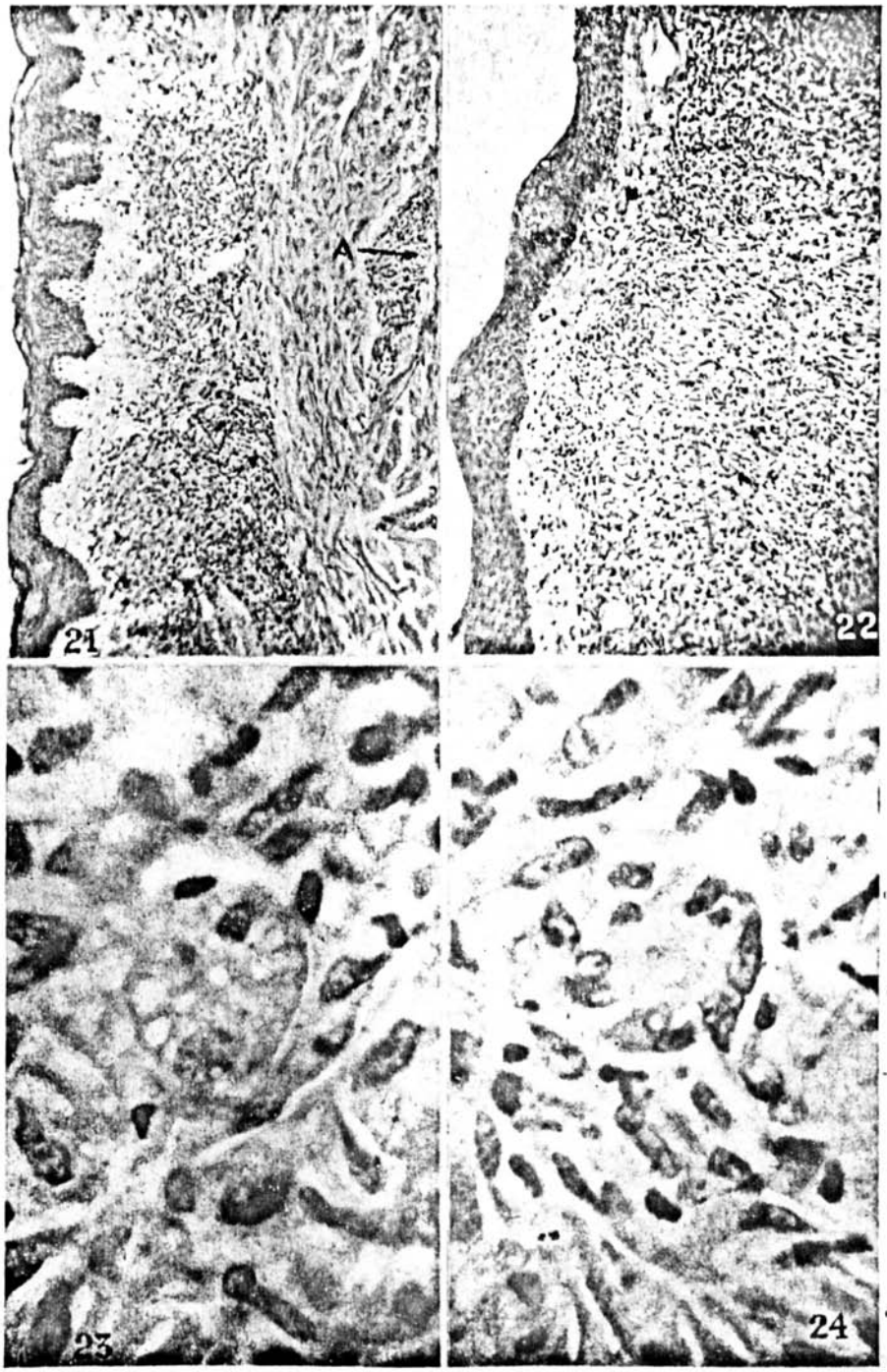

PLATE 31