TUBERCULOID CHANGES IN LEPROSY

II. LEPRA REACTION IN TUBERCULOID LEPROSY

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INTRODUCTION

Manifestations of lepra reaction in cases of tuberculoid leprosy or in individual tuberculoid lesions have not been described as such. Evidence of its occurrence would doubtless be found in the literature if it were searched interpretively—bearing in mind the fact that tuberculoid lesions are usually not recognized for what they are. For example, the peculiar nerve abscess common in India is probably a reaction condition, as Lowe believes (1), and as is shown in another paper (2) a specimen of the condition obtained through his courtesy has proved to be tuberculoid. In South Africa a reaction condition is recognized clinically among cases of the sort that we have shown to be tuberculoid (3, 4). The writer was privileged to see several of these reaction cases, and certain others that are suspected of having been in a reaction state of less degree. The material studied is sufficiently peculiar to be discussed separately, this report supplementing that dealing with the ordinary phases of tuberculoid leprosy as seen in South Africa.

PRELIMINARY OBSERVATIONS

MANILA CASE

A probable instance of reaction in a tuberculoid lesion was seen in Manila in 1922, in a case reported in 1927 (5).

The patient, a girl of 18 years, had had a solitary, indolent, infiltrated macule on the arm for eight years, never diagnosed. Without any known reason this had suddenly become redder and more infiltrated, and several small isolated nodules had appeared elsewhere. When seen several weeks later the condition seemed clearly leprotic, but smears proved negative for bacilli.[1] A biopsy of the main

[1] Examination by Dr. L. W. Smith, at that time Professor of Pathology and Bacteriology, College of Medicine and Surgery, University of the Philippines, Manila, at whose request the case was seen.

lesion was arranged for. Sections showed the tissue to be tuberculoid, and unlike those of the usual, non-reacting lesion of that sort, they were found to contain numbers of scattered bacilli. The patient did well under chaulmoogra treatment.

In retrospect it seems quite probable that the sudden activation of the old lesion and the appearance of new ones in this case was of the nature of a reaction phenomenon. The fact that bacilli, though not found in smears, were numerous enough to be found readily in the sections is in line with observations to be reported herein.

CASES AT AMATAKULU

Of the first cases believed to be of reaction in tuberculoid leprosy that the writer saw among the patients in South Africa—all Negroes—no biopsy specimens or photographs were obtained, so they are noted merely as introductory to consideration of others. They were seen at the Amatakulu Leper Institution, in Natal,[2] where a considerable number of patients had skin changes of the type that one had diagnosed as probably tuberculoid. Among them were noted several with lesions that were suspected of undergoing transformation to the "cutaneous" (i. e., lepromatous) type. These lesions were more florid than the others, redder and of a more succulent appearance, with a distinct suggestion of translucence. In full expectation that bacilli would be obtained smears were taken from several of them by the scraped incision method, but they were all reported negative.

One of these patients was a young woman of good physique who, it was said, had been admitted to the observation station near Durban some six months before with only flat, hypopigmented macules typical of ordinary nerve leprosy, and was given potassium iodide with a view to eliciting evidence of activity of the condition. Had no such evidence appeared—reddening at the edges of the macules was especially looked for—she would have been returned to her home. Through oversight the attendant continued the drug until the patient suddenly broke out with a violent reaction which involved all of her existing lesions and brought out many new ones. When seen she was an unhappy sight, with very numerous succulent-looking infiltrated macules, some with a little scaling, and and apparent impairment of the general health. It was assumed that the lesions had become lepromatous, but the smears from this patient were negative with the rest.

[2] This institution was visited from Durban with Dr. G. A. Park-Ross, and Dr. B. Samson, senior health officer and government pathologist, respectively, of the Natal district; the later kindly made the bacteriological examinations to which reference is made.

That this was a case of general lepra reaction following the administration of potassium iodide there can be no question. That the skin lesions when seen were of tuberculoid nature cannot be asserted positively, of course, but the fact that bacilli were not found in them is very suggestive, and the clinical history and appearance leave little doubt in the light of the cases seen later at Emjanyana.

OBSERVATIONS AT EMJANYANA

Of the forty cases specially examined at the Emjanyana Leper Institution six are discussed here, in three groups of two each. Four were diagnosed as in a state of reaction by Dr. Davison, the medical officer in charge. Two (first group) were of moderate degree; they were not biopsied. The other two (second group) were of severe degree and long standing; tissue was obtained from them. The last (third group) were not diagnosed by Davison as in reaction, and tissue was taken from only one of them, but this specimen and certain other features suggest the possibility that it was or had been in that state, so it and a probably related case are included in this report.

GROUP I. MILD REACTION CASES, NOT BIOPSIED

Case 1. No. 4487.—"Reaction, early stage" (Davison). Broad-margined pale macules on the back, with markedly erythematous and infiltrated borders (Fig. 1). No biopsy specimen. Smears negative.

The notes taken refer only to the lesions of the back—macules with broad margins, only moderately infiltrated, smooth grained. In the larger of them central resolution had occurred, leaving broad margins so pale that their erythematous borders were especially conspicuous. These were about one-quarter inch wide, more infiltrated than the rest of the margin, the infiltration extending somewhat into skin that had not yet become hypopigmented, and as in ordinary lesions the erythema extending slightly beyond the infiltration. Three smears from active border zones (one from a lesion touching the midline and two from below the scapulae) were all negative.

Case 2. No. 4847.—Reaction, duration unknown, "subsiding" (Davison). Extensive recovered areas were outlined by striking linear marginal zones (Fig. 2). No biopsy specimen. Smears negative.

The patient had recently been admitted in the condition seen. The back was extensively covered with large, fusing areas that, within very narrow marginal zones, had resolved practically completely, leaving at most only slight coarsening. The margins measured only one-quarter inch or so in width and

were sharply limited and rounded—the "linear" type. They were only moderately hypopigmented, but quite markedly erythematous, the reddening extending under the normal pigment. Their surfaces were fairly smooth, as if the tissue were filled by infiltration too uniformly to form papules. Two smears from active borders (one from between the scapulae, the other from below the left one) negative.

Comment.—The condition in the first case, which would hardly have been diagnosed as reaction except by one experienced with such cases, is perhaps minimal and is of interest especially for comparison with the others. The second case, of moderate degree but perhaps of long duration, seems more clearly related to the severe conditions seen in Cases 3 and 4, though unlike them (but like Case 1) the lesions had not become bacteriologically positive. The sharp limitation of the active zone to the very borders in both of these cases is noteworthy; the narrowness of the entire infiltrated zone in the second is remarkable. A comparison of the histopathology of lesions like these with the more severe ones of the next group would be highly desirable.

GROUP II. SEVERE REACTION CASES, BIOPSIED

CASE 3. No. 2468.—Severe, protracted reaction. Extensive involvement by peculiar, double-bordered, annular macules, with considerable scaling (Figs. 3 and 4). Face supposedly lepromatous. Biopsy specimen from the back; sections show a marked grade of tuberculoid change, especially in the papillary layer (Fig. 13). Smears positive, but bacilli few and scattered.

This patient's original skin lesions had cleared up under treatment when, 22 months before the time of examination, he was given the potassium iodide test for activity with a view to discharge. After a single dose of 10 grains numerous active lesions suddenly broke out, many more than there had been originally, and these persisted in a reaction state. In spite of its severity and duration the patient was in good general condition and had not lost weight. A smear from the chest was found negative four months before.

When seen there were strikingly annular, peculiarly double-bordered macules over the back and chest and on the neck and extremities. Many were rather small and individually definable, while in places there were irregular plaques, especially on the lower back. The face was extensively involved by an irregular infiltration assumed to be a "nodular" (lepromatous) development. The double-bordered appearance was due to active reaction in both the inner and outer borders of the infiltrated zone. They were especially erythematous and infiltrated, not papulate but relatively smooth, and showed considerable scaling and even a little erosion and crusting. Hypopigmentation was rather marked.

All three of the smears taken were found positive, but the bacilli were far from abundant; from the chest and back they were few and from the forehead

very few. In sections of the biopsy specimen from the back bacilli also were found, but again they were very few in comparison with lepromatous lesions. The histopathology, though less in degree, is essentially similar to that in the next case.

CASE 4. No. 4070.—Especially severe, protracted reaction. Plaques and marginate lesions especially extensive on back, with some erosion (Fig. 5). Several lesions suspected of having undergone lepromatous change. Two biopsy specimens from the back; sections show an extreme grade of tuberculoid change (Fig. 11). Smears positive, bacilli few and scattered.

In 1926 the patient had "raised erythematous macules all over." By May, 1929, most of these had decreased but in November of that year reaction occurred, the macules all becoming very raised and very erythematous and the face "nodular." There had been no remission in the two years thereafter.

When seen much of the back was covered with extensive, somewhat erythematous and hypopigmented areas that apparently had originated at the sides and were progressing upward and inward toward the midline. The scalp was extensively involved with macules, "also reacting." The borders of those on the back were highly erythematous, abruptly raised, and smooth. In places central resolution had advanced until the border zones were practically linear, as in Case 2. In certain places, however, there was so much infiltration that lepromatous change was suspected. Over some of the rougher areas, and here and there on the margins, the surface had become denuded and small scabs had formed.

One biopsy specimen was taken from an infiltrated (supposedly lepromatous) area above the left axillary fold (Fig. 5, A) and another from an advancing margin near the midline (Fig. 5, B). Three smears from the back were all positive, but as in the preceding case the bacilli were scarce, recorded as "few", "very few" and "extremely few." In sections from both biopsy specimens a very few bacilli were found. The tissue changes in the two specimens differ only in degree among themselves and from that of the preceding case. One assumes that the one with the more marked degree of change came from the advancing margin (site B).

Comment.—These cases, examples of marked and prolonged reaction, both presented striking though dissimilar conditions with apparently unimpaired general health. The causation in Case 3 was potassium iodide; that in Case 4 was not known. In the former there were very many lesions of small average size, many new ones having appeared with the reaction, and they were remarkably double-marginate; in the latter the lesion-areas were few but extensive, even the scalp being affected. In both there was more or less scaling, and in Case 4 considerable erosion and crusting. In both the face had undergone an irregular infiltration that was assumed to be leproma-

tous transformation, and in Case 4 this was also assumed for some of the lesions on the back, but no such process was evident in the biopsy specimens. Though smears and sections from these cases showed bacilli, they were much fewer than would be expected from lepromatous infiltrations.

GROUP III. CASES WITH POSSIBLY REACTION LESIONS

Case 5. No. 4603.—Macular papulo-infiltrated lesions on arm and chest (Figs. 7 and 8); face supposedly lepromatous (Fig. 6). Two biopsy specimens, both tuberculoid, one considered suggestive of a reaction condition. Smears positive.

This patient was paraded in a group of supposedly primary neural cases, but when seen by the demonstrating physician the diagnosis was changed to "nodular." Smears from the nasal mucosa taken three and two months previously had been found positive.

There were extensive macules on the body and limbs, most of them (as in Fig. 7) with abrupt edges and pebbled infiltrated zones that shaded off gradually inside. Of special note, they were unusually and diffusely erythematous, with the peculiar suggestion of succulence or increased translucence that has been referred to earlier. On the chest (Fig. 8) was a small palish area with some deep infiltration, studded with a superficial papular (lichenoid) eruption. The face (Fig. 6) was irregularly but rather extensively infiltrated in moderate degree. A notation was made that "face clearly shows cutaneous-type infiltration; elsewhere suspicious."

Three smears were all found positive; that from the face contained numerous bacilli, those from the chest lesion and arm (sites of biopsy) contained few. The biopsy specimens show only tuberculoid changes, one (probably that from the chest) of ordinary type, the other more epithelioid than usual. Sections of the former showed extremely few bacilli, those of the latter relatively many.

Case 6. No. 4872.—Case clinically similar to the preceding, with infiltration of face suspected of being lepromatous (Fig. 9) and other lesions not suspicious (Fig. 10). Biopsy not made. Smears positive (two out of three).

There were a smooth, reddish zone of infiltration on the forehead, assumed to be lepromatous, and elsewhere on the face (Fig. 9) patches of infiltration with an apparent nodular tendency. On the back (Fig. 10) and extremities were macules, some fairly extensive, with broad, finely granular marginal zones, the border marked by hypopigmentation but not by special erythema, and not suspected of having undergone leprotic change. Some showed a tendency to form fine scales.

Smears were positive from the smooth infiltration on the forehead (bacilli "not numerous") and the edge of a lesion on the face recorded as "marginate, recurring, undergoing conversion" (bacilli "more numerous"). One from the right forearm was negative.

Comment.—These cases are presented, as stated, as possible examples of reaction conditions. Clinically the two have distinct similarities to each other and to those of the preceding group, at least as regards the appearance of the face and the positive smear-findings.

HISTOLOGICAL FEATURES

SEVERE CASES (NOS. 3 AND 4)

The two specimens obtained from Case 3 were very much alike, that from Case 4 was essentially similar though of less degree. Case 5 is considered separately since it cannot be said positively to have been in a reaction state; the lesion is intermediate between the others and the ordinary tuberculoid change as described in the preceding article (1).

To the naked eye the sections show, just under the epidermis, a solid, fairly uniform, rather deeply-staining layer 4 to 5 mm. in thickness. Microscopically this is a tuberculoid granuloma (Figs. 11, 12, etc.) separated from the epidermis by the narrow zone usual in leprosy lesions. It is not homogeneous, but more or less divided by strands of the fixed tissue in which some elastic fibers persist and round cells of simple chronic inflammation tend to concentrate. This separation is more conspicuous in the less extreme lesion from Case 3 (Fig. 13), which incidentally does not have the same extensions into the deeper layers,—or connections with lesion-foci in them—as Case 4 (Fig. 14). The epithelioid foci are often rather large and the component cells conspicuous, and sometimes they show a tendency to further subdivision and in places to a whorl arrangement (Fig. 15). Giant cells are numerous in the Case 4 lesions; many of them are large and conspicuous (Fig. 12) but others are less typical or regular (Figs. 16 and 17, the latter showing one in the epidermis). Round cells on the whole are not conspicuous; large mononuclear leucocytes are a more important feature of the lesion.

The epidermis shows evidences of the desquamative and erosive processes seen in the patients. There is decided hyperkeratosis in Case 3 (Fig. 13) and proliferation of the basal epithelium with diffusion of pigment. The Case 4 sections show in places swelling and sometimes dispersal of the cells of the basal layer, and actual cellular infiltration (Figs. 12 and 16); flattening and thinning are marked (Fig.11), in keeping with the degree of the granuloma, and in the very thin sub-epidermal zone the elastic fibers are practically absent. In the lesser lesion of Case 3, where the papillae are not yet flattened (Fig. 13), there are still a great many of the fine elastic fibers.

As usual the tissue appears well nourished, the vessels apparently more numerous than normal, certainly often enlarged and sometimes even cavernous. Necrosis, as usual, is absent from most of these lesions. However, in the Case 4 sections there is sometimes to be seen, between cells in good condition, scattered material evidently produced by necrosis of individual cells, and at one place there is a necrotic area of relatively large size (Fig. 16).

Recognizable nerve branches are conspicuously absent from the superficial tuberculoid foci, as is common, and in the Case 4 sections no nerves at all are to be found. Epithelioid whorls might sometimes be mistaken for nerve structures but the resemblance is very superficial. Whether or not the nerves of the regions occupied by the granuloma have been actually destroyed cannot be said, but if they are present they are so dispersed that they are unrecognizable even with special stains that ordinarily demonstrate them well. On the other hand, in Case 3 an occasional larger branch is seen, uninvaded and well preserved, embedded in a lesion-focus in the deeper part of the dermis. Sweat glands and hair follicles are rather badly affected in these lesions.

PROBABLE CASE (NO. 5)

Of the two pieces of tissue obtained from Case 5, one shows tuberculoid changes of ordinary degree and kind, such as would be expected of the chest lesion (Fig. 8) and need not be discussed. The more extensive granuloma in the other is in keeping with the more solid and active-appearing lesion of the arm (Fig. 7), and it is assumed to be from that location.

One end of the section is practically normal. Beyond that portion the papillary zone is abruptly filled with a rather large tuberculoid mass over which the epidermis is flattened. Unlike the chronic lesions of the other cases the granuloma is neither uniform in width nor continuous; it is rather intermediate between it and the ordinary non-reaction changes and, in fact, might not be considered peculiar were the lesion from which it came not clinically suspicious of reaction. However, in the portion shown in Fig. 18 the three tuberculoid foci, separated by two bands of uninvolved tissue, are larger, more cellular, and less circumscribed than usual, and the diffuse, irregular distribution of the epithelioid cells (Figs. 19 and 20) is more like that in the reaction lesions here described than in the ordinary ones. Of interest here (as in Case 3) is the concentration in the papillary layer, that vascular structure seeming especially favored by this condition; in Fig. 18 there are only three small foci in the expanse of reticular layer shown. As usual, there is no suggestion of necrosis, and no nerves can be found in the superficial zone.

DISCUSSION

The few cases so incompletely dealt with here are not, of course, sufficient to establish a definite picture of lepra reaction in tuberculoid leprosy, but they at least suffice to call attention to it. That interesting condition presents a number of points for consideration, most of which for the present can be discussed only in a tentative and distinctly speculative manner.

Causation.—It appears that the immediate causation of the reaction in these cases is ordinarily not evident. Potassium iodide may cause it, but this is an artificial excitant. The more usual, natural

causes are seemingly no more apparent than in other forms of leprosy.

Degree of reaction.—It is widely recognized that lepra reaction in ordinary cutaneous-type leprosy may vary from a mild "exacerbation" of one or two pre-existing lesions, or sudden appearance of one or two new ones, to an exanthematous eruption with fever that sends the patient to bed and that, persisting indefinitely, may ultimately lead to death. In other words it ranges from mild and local reactions through mild generalized ones to severe general disturbances. This range is not always appreciated where the concept of "lepra fever" is maintained, rather than that of "lepra reaction."

In the first four cases presented the severity ranged from very mild to severe, but all were generalized. In the mildest, it is understood, only pre-existing lesions were affected, while in one of the severe ones (Case 3) many new lesions appeared. There was no apparent relation between the degree of change and duration, and Davison stated that one cannot tell from appearances whether a reaction has persisted for a month or a year. Nothing was learned of temperature changes, but at all events the condition of the patients indicates that general disturbance is not serious as in a comparable state in cutaneous leprosy.

Whether in these cases there occur simple local reactions, limited to one or a few lesions, cannot be said, but it is considered highly probable. The nerve abscesses of India (1, 2) may be of such nature. A double marginate lesion (as in Case 3) was seen in only one other patient; in Case 7 of the preceding article just one of many lesions was of that kind, possibly indicating a limited local reaction. If such limited reactions do occur the milder ones may be difficult to detect. Generalized reactions are apparently easy to recognize, though in the lesser degrees of them the individual lesions show only slight increased hyperemia and infiltration. Localized reactions, if mild, may perhaps not show changes sufficiently marked or sufficiently peculiar to permit positive recognition. One suspects that reaction of intermediate degree is indicated by the reddish, peculiarly succulent, semitranslucent appearance noted in some of the cases; the assumption that they were undergoing lepromatous transformation was not borne out by the negative smears in the Amatakulu cases and the histological findings in Case 5. The "nodular" lesions are also to be considered in this connection.

Lepromatous transformation.—The lesions supposed to have undergone nodular transformation, implying replacement of the epithelioid tissue by a lepra-cell accumulation, are exemplified by the faces of Cases 3 to 6 (Figs. 3, 6, 9) and the areas of irregular infiltration in Case 4 (Fig. 5, A). These lesions were erythematous but the infiltration seemed chronic—firm, not succulent, and rough and irregular, in contrast with the diffuse smoothness typical of moderate-degree lepromatous infiltration of the face. Those that were examined bacteriologically were positive—the cases with these lesions were, with a single exception, the only ones found positive among the entire forty examined—but the bacilli were few and scattered and no globi whatever were found. For histological evidence of the nature of this type of infiltration we have only the shoulder lesion of Case 4, which was tuberculoid of extreme grade. It seems quite likely that the face lesions were of the same nature, and it is but a step further to suggest that their peculiar appearance may possibly have been due to reaction.

It would be of particular interest to follow these "nodular" cases clinically, and especially to compare them as regards appearance, course and outcome with cases of the ordinary cutaneous type of the disease. That transformation from the tuberculoid to the lepromatous type (or to a mixed type) may occur is not doubted, but further observations are required to establish this as a fact, and to elucidate the process.

Histopathology of reaction.—The tissues from the two cases of severe prolonged reaction show exuberant and diffuse, non-focalized epithelioid production that is distinctly different from the findings in the non-reaction cases. One is therefore inclined to accept this picture as characteristic of reaction of such degree and duration, and to anticipate that lesions with less severe but sufficiently prolonged reaction will show a similar condition in lesser degree, as is believed to be the case with one of the specimens from Case 5. It may very well turn out that the lesser degrees of the change will not permit the diagnosis of reaction on microscopic grounds alone, though they may suggest it, and that on the other hand the lesser degrees of clinical reaction may show nothing distinctive histologically, especially when of short duration.

On the whole, despite its apparent activity and severity, the reaction process in the lesions studied is fairly bland and one would expect that recovery might be fairly complete. The fact that they

are well vascularized probably accounts for the slight tendency to necrosis, though it is not surprising that it does sometimes occur, as seen in Case 4. The relatively poor vascularization of the nerves may explain the evident frequency of necrosis in that structure seen in India.

Location of the causative agent.—In the abrupt infiltration of the border of the typical tuberculoid macule and its usual resolution centrally is evidence that the causative agent tends to disappear from the older part of the lesion. But usually the infiltrated zone is rather broad and there is little indication as to whether or not the agent is present diffusely through it. However, though the probably complex mechanism of the local condition in lepra reaction is not understood, the usual concentration of the condition in a narrow zone of the advancing portion suggests that the agent may be concentrated there.

This is apparently departed from in Cases 3 and 4. A characteristic of the usual marginate macule is that tissue once recovered is not reinvaded. As occurs in trichophytosis (Jadassohn), it apparently acquires an immunity that is strictly local and not shared with the tissue outside of the infiltrated margin. In Case 3, however, this condition had apparently not persisted, for most of the lesions were double margined, evidently progressing both ways. Unless all of these many lesions arose as rings this indicates that retrograde invasion is going on. Whether the foci inside the margins in Case 4 represent recurrence or persistence cannot be said.

Significance of bacilli.—Several questions arise with regard to the development of bacilli in these lesions in numbers sufficient to be found in standard smears. One is whether it really is especially associated with prolonged lepra reaction, as our observations indicate. Another is with regard to prognosis, without and with treatment. As for the latter, Davison's experience is that these cases are not favorable, though there is a belief that chaulmoogra treatment is more effective with bacillus-containing than with non-bacillated lesions (6). A practical effect of this development is the change of status from "closed" to "open" under the administrative classification of the Memorial Conference, with serious inconvenience to the patient where, as in the Philippines, cases are isolated only when found bacteriologically positive. As for the question whether in type-classification they should be transferred to the cutaneous group, it is clear that the lesions do not necessarily become lepromatous.

In none of those examined had there been loss of that factor which determined that the invading macrophage cells should take on the epithelioid characteristics instead of massing as phagocytic lepra cells —to the contrary, epithelioid-cell production had evidently been increased. It is submitted that both clinically and histologically such cases differ distinctly from the true cutaneous case and should not be classified as such, any more than an ordinary neural case is called cutaneous when a nasal smear is found positive.

No evidence on the recently raised question of the nature or form of the causative agent can be adduced from the presence of bacilli in these lesions. Supporters of the so-called "virus" hypothesis might hold that the reaction itself is to the presence of a submicroscopic form of the organism, and that the appearance of the bacillary phase in the more severe and persistent reactions is a secondary occurrence due to the reduction of an inhibiting factor. Those holding the older—and more conservative—view believe that the tuberculoid lesion is due to the usual leprosy bacillus, but that because of an extraordinary reactivity of the tissue (a matter presumably tied up with resistance) it requires so few of them to induce the change that it is usually impossible to find any in specimens examined. Under that view it might be held that in lepra reaction, especially when chronic, the local conditions permit increase of bacilli; that though in the lesser degrees of reaction (as in Cases 1 and 2) they would still be too few to be found by standard methods of examination, they may in the more severe and prolonged reactions increase sufficiently to be so found, though not in the numbers usual with the common lepromata. Until more evidence is adduced than at present to support the submicroscopic hypothesis the writer must incline to the latter view.

SUMMARY AND CONCLUSIONS

1. Six cases are described of probable lepra reaction seen among the forty cases of evident tuberculoid leprosy examined at Emjanyana, in South Africa. Four were diagnosed by the clinician as in the reaction condition, two of mild grades and two severe and protracted; the last two were both found bacteriologically positive and were biopsied. The other two cases (both bacteriologically positive, one biopsied) were probably also in reaction but were not so diagnosed. Certain preliminary observations of the condition are noted.

2. As with lepra reaction in ordinary leprosy, the existing cause is usually not determinable, though potassium iodide is apt to pre-

cipitate it. Duration seems prone to be long, with no evident relation to the degree of the reaction phenomenon. In the more severe degrees the general disturbance appears less severe than in similarly extensive reactions in the cutaneous type of leprosy. As a whole the clinical features remain to be established.

3. The four definite cases all show apparent activity of the borders of the lesions, with increased erythema, infiltration, and even scaling and erosion in the more severe ones. Whether limited, localized reactions occur as in ordinary leprosy, and if so whether they can be positively recognized, is uncertain but seems probable.

4. Histologically the lesions examined show only tuberculoid changes, the more marked ones with epithelioid production of an extreme degree believed to be characteristic of prolonged severe reaction. It is considered probable that lesions with mild degrees of reaction may show nothing characteristic, or lesser degrees of epithelioid production that may suffice only to suggest, not diagnose, reaction. It is demonstrated that the presence of relatively numerous bacilli does not necessarily involve departure from the tuberculoid condition.

5. In both of the severe cases, and in both of those considered probably in reaction, "nodular" (i. e., lepromatous) transformation was assumed to have taken place, especially in the face. Smears from these cases showed bacilli, usually very few and always scattered, never in globi. Since two lesions of this category proved markedly tuberculoid it is held probable that all of them were of that nature, the change perhaps due to reaction, possibly localized, regional. This whole question requires careful investigation.

6. The reacting lesions offer evidence that the causative organism is specially localized in the advancing borders. The immunity to reinvasion ordinarily shown by the recovered tissue may evidently be broken down; one case presented annular lesions with active inner borders, apparently reinvading, and another suggested the possibility of recurrence within lesions.

7. No evidence concerning the form of the causative organism is adduced. It could be argued on the one hand that the chronic reaction condition permits bacilli which are normally present and essential though rare to multiply, or on the other hand that it leads to the evolution of the bacillary form from the hypothetical submicroscopic phase.

8. The significance of this development as regards prognosis is said to be unfavorable. It necessarily involves a change from "closed" to "open" in the so-called administrative classification. Whether it should cause change of type classification from tuberculoid-neural to cutaneous may be open to argument, but it is submitted that this should not be the case in the absence of ordinary cutaneous lepromatous transformation (lepromatous) lesions.

To Dr. A. R. Davison, medical officer in charge at Emjanyana, special indebtedness is gladly acknowledged for the demonstrations made and much of the data and material here presented. Appreciation of the many courtesies extended by other officials in the Union of South Africa in connection with the visits and observations made, expressed in the first paper of this series, is here reiterated.

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DESCRIPTION OF PLATES

PLATE 1

FIG. 1. CASE 1 (No. 4478). Reaction, of slight degree, "early stage" (Davison). Quarter-inch, moderately erythematous and infiltrated zones bordering pale, broad-zone macules. Smears negative. No biopsy.

FIG. 2. CASE 2 (No. 4847). Reaction, of moderate degree, "subsiding" (Davison). Prominent narrow linear margins, rounded by the infiltration of the reaction, the limitation of which is extraordinarily sharp. Smears negative. No biopsy.

FIGS. 3 AND 4. CASE 3 (No. 4268). Severe, protracted reaction, of two years duration, occurring after administration of potassium iodide in an apparently recovered case. The conspicuous annular, double-bordered lesions with active inner as well as outer borders are unusual. The more marked and irregular infiltration of the face was assumed (erroneously?) to signify "nodular" (lepromatous) transformation. Smears positive, bacilli few. Biopsy from back.

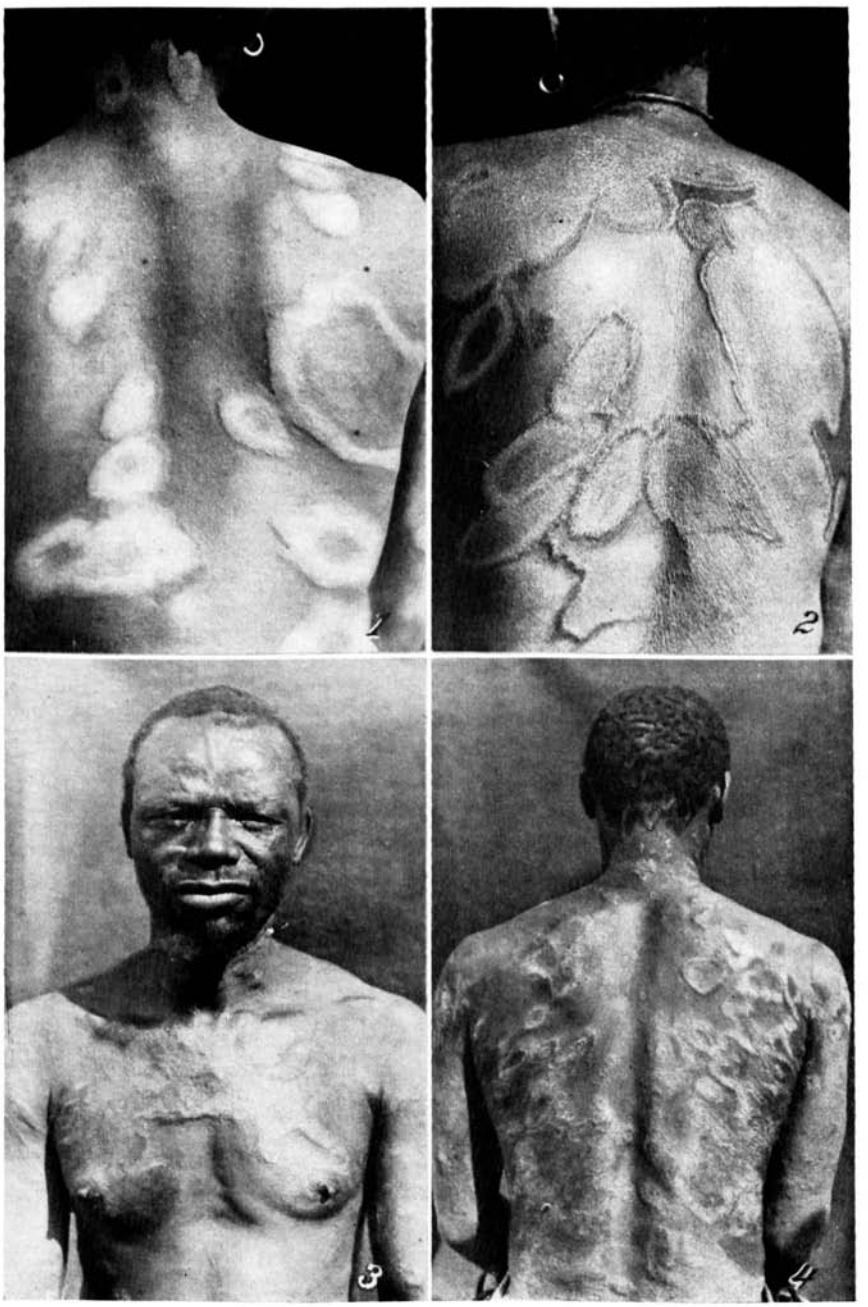


PLATE 1.

PLATE 2

FIG. 5. CASE 4 (No. 4070). Severe protracted reaction, two years duration. Erosion and crusting in places. Margins of all lesions in the reaction state. Some have partly resolved centrally, others are partly unresolved (or recurrent?). The assumption that they had undergone lepromatous transformation was proved erroneous. Biopsies from A and B. Smears from these places and from the infiltration above A were all positive, bacilli few.

FIGS. 6, 7 AND 8. CASE 5 (No. 4603). Case believed probably reaction, moderate. Face was assumed to have undergone conversion to lepromatous type. On the left chest an infiltrated macule with a superficial papular (lichenoid) eruption. Arm with erythematous, semitranslucent (apparently reacting) edge of a lesion of uncertain breadth. Smears positive from all three regions. Biopsies from arm and chest; locations shown by the scars.

FIGS. 9 AND 10. CASE 6 (No. 4872). Case possibly reaction. Face with irregular infiltration assumed to have become lepromatous, shoulder with more ordinary (tuberculoid) lesion; all with tendency to scaling. Great auricular nerve grossly enlarged. Two of three smears positive. No biopsy.

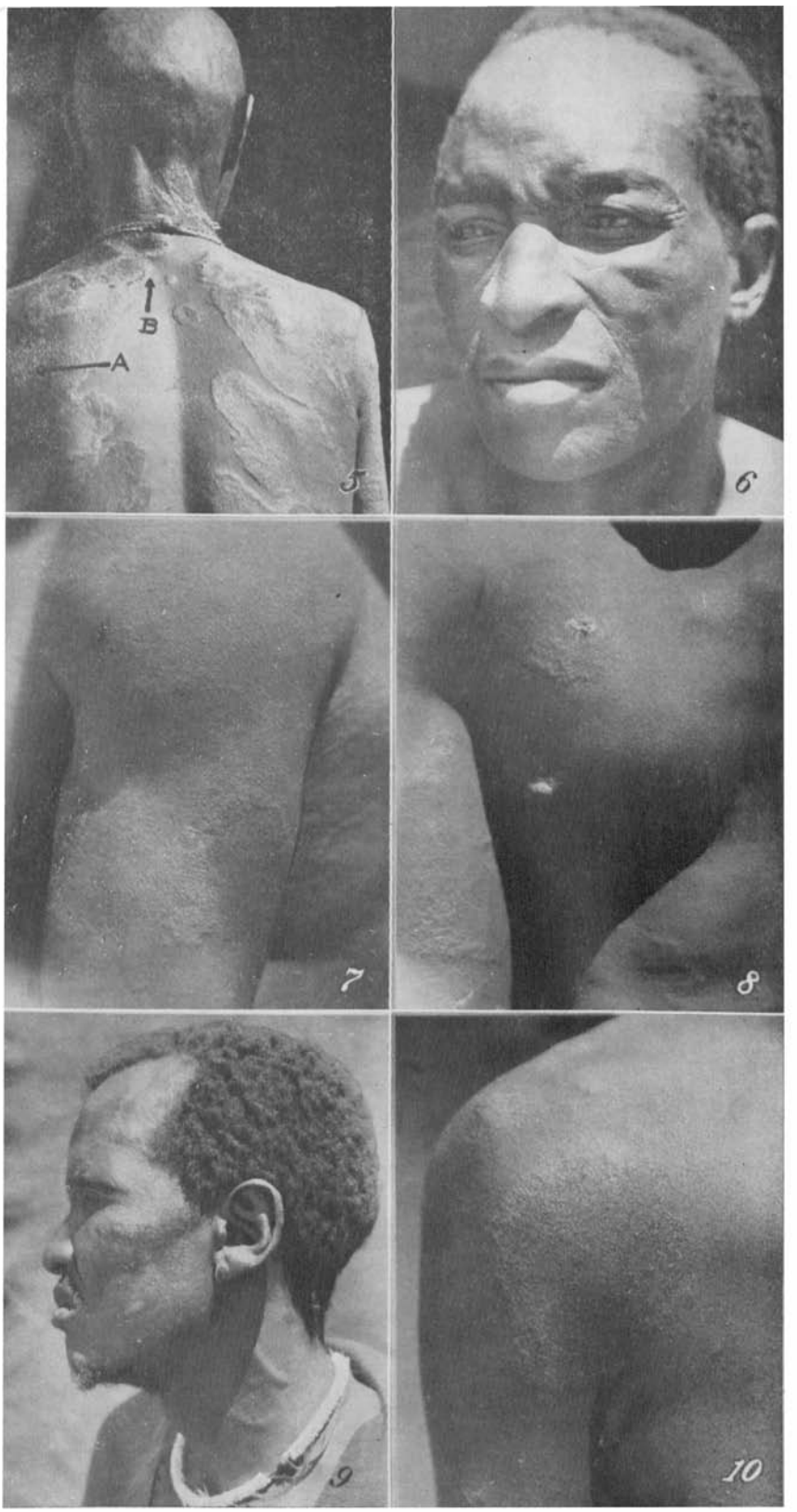


PLATE 2.

PLATE 3

FIG. 11. A medium magnification view of the extreme tuberculoid lesion from Case 4. Epidermis flattened, granuloma more or less separated into lobules by connective tissue strands, lobules composed of epithelioid masses. Giant cells are conspicuous here, and a few more or less cavernous blood spaces are seen. (Photomicrograph by W. S. Dunn, Cornell Medical School, New York City.)

FIG. 12. High magnification view of a field near the foregoing, showing details of the cellular constituents and moderate disturbance of the epidermis (left side). The subepidermal space is less well-preserved here than usual. (Photomicrograph by W. S. Dunn.)

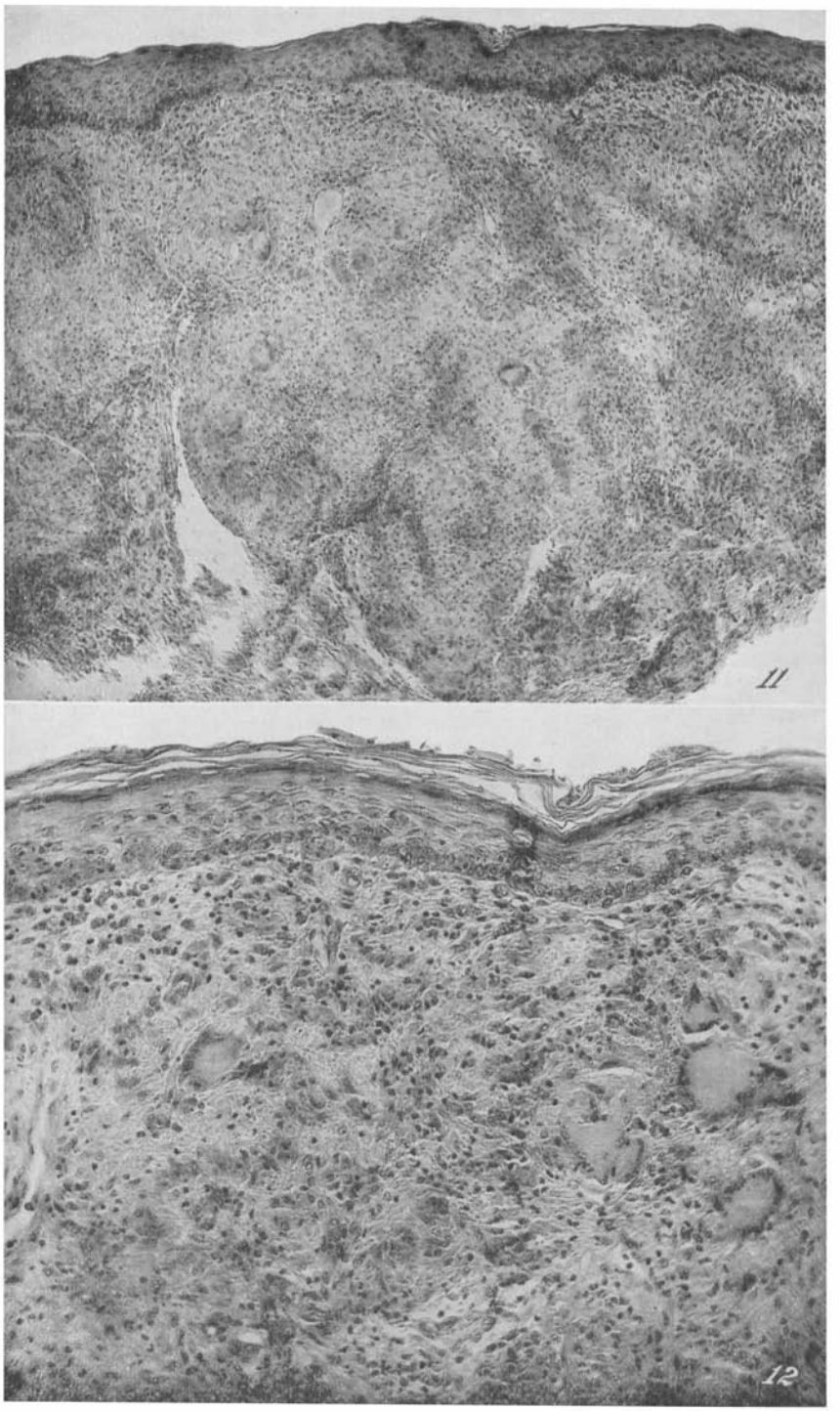


PLATE 3.

PLATE 4

FIG. 13. Low magnification view of the lesion of Case 3, from near the advancing edge. Hyperkeratinization is notable but the epidermis is not flattened and the uninvaded sub-epidermal space is broad. The granulomatous zone is still well separated into focal masses. Little involvement of the reticular layer below. ×55.

FIG. 14. Showing extensions of the Case 4 lesion into (or connections with the lesions of) the reticular layer. ×30.

FIG. 15. Rather small epithelioid whorls seen in parts of the Case 4 lesion. The tendency to form giant cells is seen, but in this region it is usually frustrated. ×150.

FIG. 16. A small area of necrosis in one of the Case 4 sections. Above it is a thin layer of apparently ordinary epithelioid tissue, with leucocytic invasion of the epidermis and the subepidermal zone. Giant-cell formation is evident, better accomplished than in the preceding figure. ×150.

FIG. 17. The epidermal thickening seen here, though moderate in degree, is unusual for tuberculoid lesions. A typical giant cell is isolated in it, and below it is a tangential section of a large giant cell showing massed nuclei. ×200.

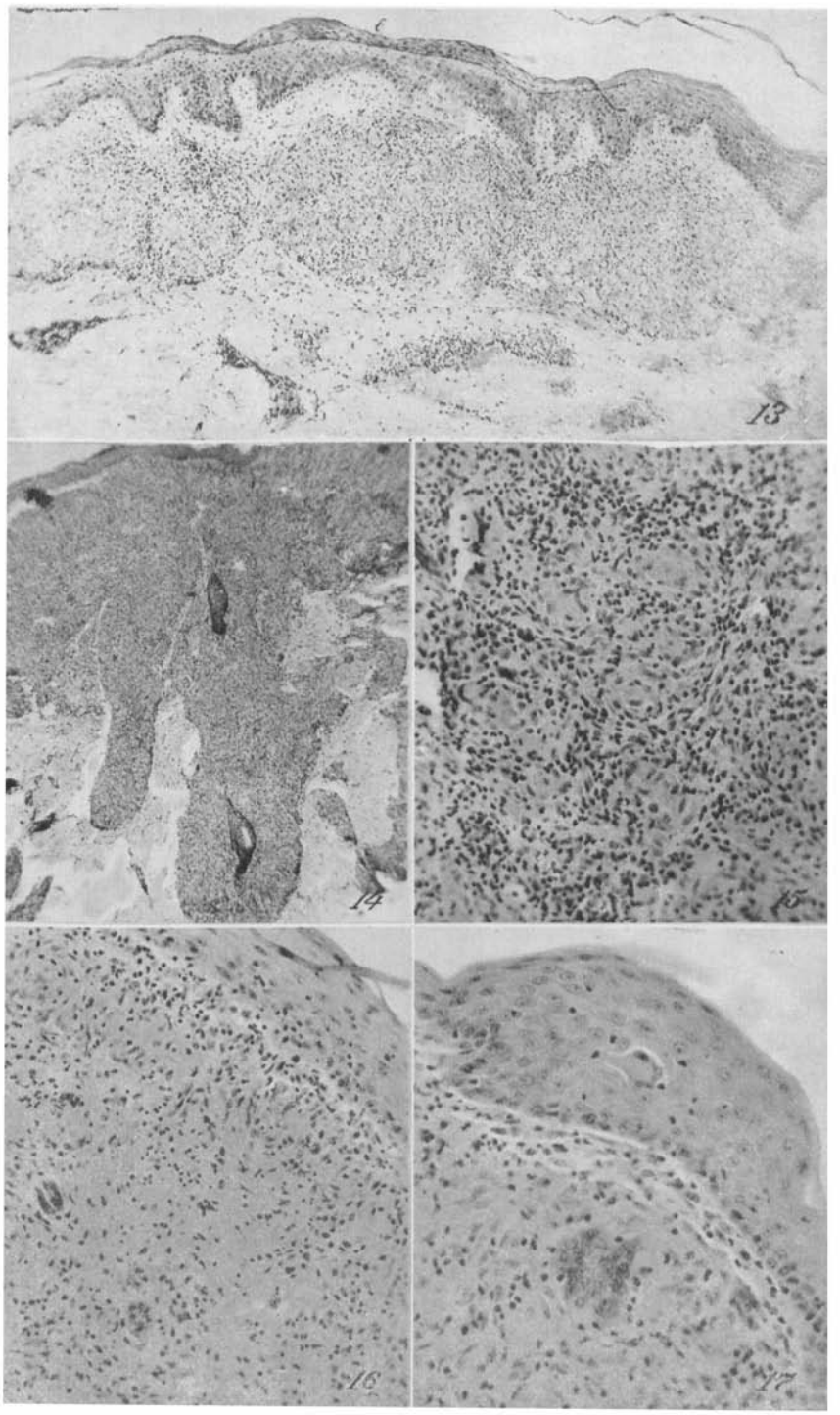
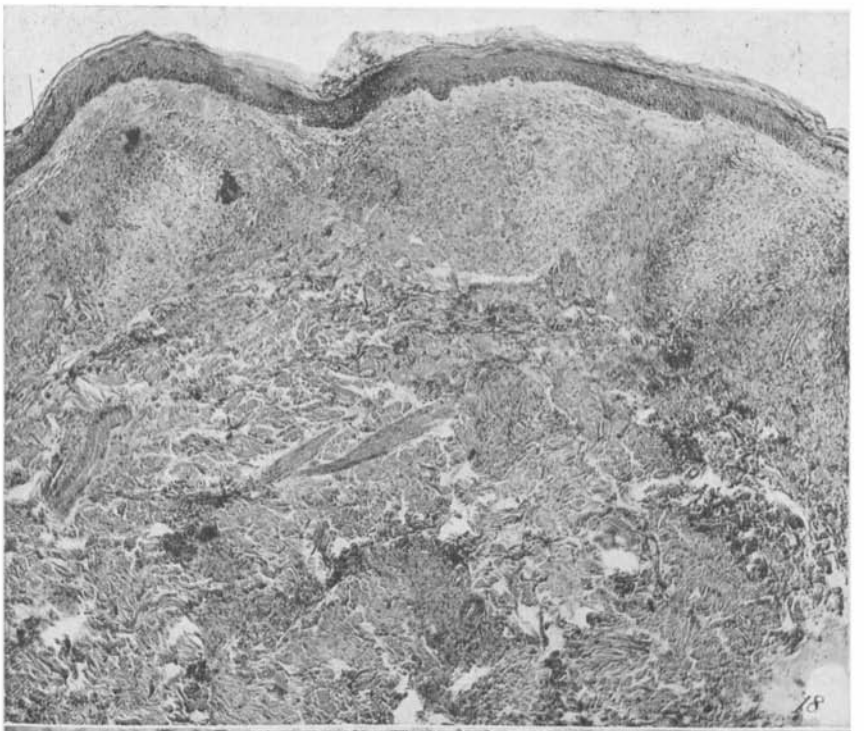


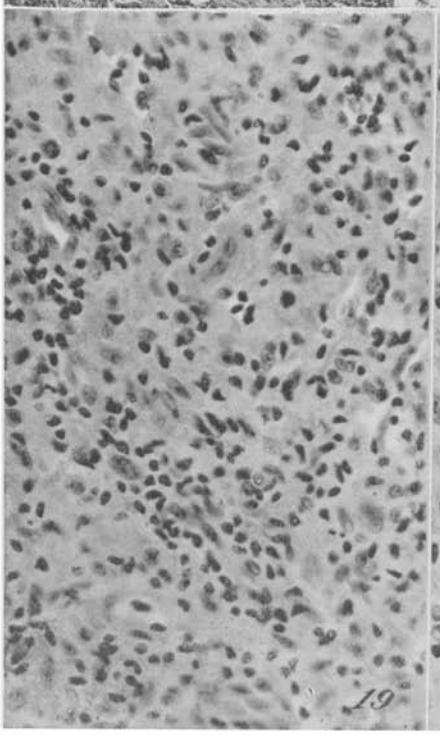
PLATE 4.

PLATE 5

FIG. 18. Low magnification view of the lesions of Case 5 suspected of being in a chronic reaction state. The massing of large foci of epithelioid cells in the papillary layer, though less extreme than in the known reaction cases, approaches that of Case 3 and is considered very suggestive. (Photomicrograph by W. S. Dunn.)

FIGS. 19 and 20. Two fields of the epithelioid foci of the Case 5 sections lesion, much more extensive and diffuse than is typical of ordinary-phase tuberculoid lesions. ×350 and ×430, respectively.





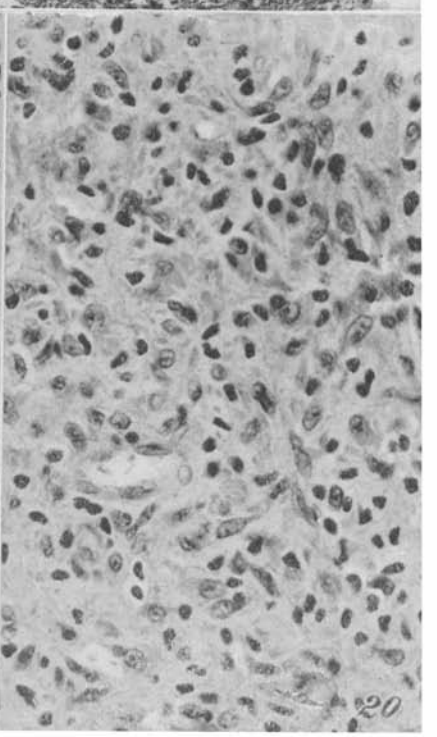


PLATE 5.