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THE SKIN LESIONS OF NEURAL LEPROSY II. OBSERVATIONS IN CEBU

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INTRODUCTION

The initiation of the present study, during the epidemiological leprosy survey of Cordova, Cebu, by Doull, Rodriguez, et als, in 1933 (1), was mentioned in the introductory article of this series (5). At that time biopsy specimens were removed from skin lesions of a number of newly-discovered, bacteriologically closed cases. A year later (1934) the present writers re-examined as many of these cases as were accessible, and extended the inquiry to the outpatient leprosy cases at the Cebu Skin Dispensary. A considerable number of them were called up, to select for study representatives of all the varieties of lesions found; we did not choose merely those of special interest to us, but with a view to giving a complete picture of the leprides as they are seen in this region. As was stated in the article referred to, publication of the findings of this study was deferred until comparable material could be obtained from other regions and different races (H.W.W.), which has now been done.

The Cordova group comprises 18 cases of leprosy, the Dispensary group 34, the latter including one active case of the major tuberculoid type that has been added recently to round out the series. Two other

cases, one from each source, have been dropped because the biopsy specimens were unsatisfactory. On the other hand, five cases not diagnosed as leprosy are also mentioned; they were biopsied partly for diagnostic purposes and partly to serve as controls for the leprosy lesions.

The two groups of leprosy cases will be discussed together, though they differ in certain respects. Those from Cordova (designated "C") represented the results of an exceptionally intensive survey of the town to detect all cases presenting evidences of the disease, past or present, and they were practically untreated. The Dispensary cases (designated "D") had been under observation for varying lengths of time, some for as long as seven years, and most of them had taken more or less treatment. All but two were "closed" (i.e., bacteriologically negative); the exceptions were both frank tuberculoid. The group included (a) "incipient" cases, which one of us (J.R.) hesitates to designate positively as neural because of their incomplete development and uncertain future course; (b) "abortive" cases, incipients that had healed spontaneously before the disease became well established; (c) ordinary well-established neural cases, with manifestations of nerve-trunk involvement (i.e., more than local anesthesia of macules); and (d) a few that were obviously "tuberculoid" as that condition is generally recognized, a kind that many writers are still inclined to put in a class apart.

The lesions studied ranged from small areas that showed no change other than localized anesthesia, or obviously healed macules with or without scarring (in the latter case sometimes very indefinite), to the most striking major tuberculoid leprides in a state of acute reaction. With regard to their classification, from our records and a recent re-examination of the patients it has not been difficult to determine, fairly accurately we believe, the classes to which they belonged at the time they were biopsied. The primary classification into simple, minor tuberculoid and major tuberculoid (5), and the subclassification used in this report, were not employed then.

Our purpose being to ascertain the relations of the pathology to the variety and state of the lesion, little attention has been given to certain features that would be important in a more essentially clinical study. Treatment need not be considered particularly, for as far as we know retrogressive changes in the leprides are similar whether they are entirely spontaneous or aided by treatment—except, of course, when that is by direct injection into the lesions ("plancha" method), which affects the histological picture profoundly. The sensory changes

in the lesions were not gone into in much detail, and at the time little attention was paid the question of enlarged cutaneous nerves in the regions of the skin lesions. Contrary to the experience in Calcutta, marked nerve enlargement among patients of this general class in Cebu is unusual, to say the least, except in the case of the great auriculars in an occasional instance. Recently one of us (J.R.) has carefully examined most of these patients for this condition, and also many others at the dispensary, both new and old, and a number of nonlepers. The findings will be discussed in a later article, dealing with later developments in the cases dealt with here, but it may be said that they serve merely to emphasize the fact that most, though not all, of the varieties of macular lesions observed in Cebu are not accompanied by palpable thickening of the regional cutaneous nerves.

The bacteriological examination has always received due attention. It had been made, usually repeatedly, by the technician of the Cebu Skin Dispensary, as a routine matter in all cases under previous observation, and was repeated by us at the time of biopsy. Furthermore, sections of all specimens were examined for bacilli, this work being entrusted largely to the technician of the Leonard Wood Memorial laboratory at Culion. With most of the Dispensary cases a piece of each specimen was fixed in alcohol solely for that purpose.

The biopsy specimens, one per case except in one instance when two were taken, were mostly removed by the incision method, though a few were taken with the skin trephine. A considerable number of them included little or no subcutaneous tissue, but otherwise they were adequate. It was, of course, the intention that the surgeons should take them from the most recent or active parts of the lesions when there was any evident distinction,¹ but it proved difficult always to insure inclusion of small elements that should be examined, especially minute, isolated papules. Of the two cases that were biopsied but not included in this report, the specimen from one was taken accidentally from outside the lesion and was therefore negative, and that from the other was from a healed center and not significant.

For the histological examination all specimens were fixed in Zenker's fluid and embedded in paraffin. In all instances from four to twelve slides, each with two or three sections, all cut serially, were stained by various methods. Because these sections proved to be negative for tuberculoid changes, or for other reasons, more than one-half of the blocks (30) were later sectioned completely. In no less

¹The considerations that apply to the selection and removal of specimens for histological examination have been discussed in the introductory article of the present series.

than four instances (Cases 4, 5, 12 and 41) tuberculoid changes were found on this re-examination, naturally in very slight degree.

REPORTS OF CASES

The fifty-two cases here dealt with have been classified as shown below. The grouping is based on the clinical features of the lesion studied, but it cannot be claimed that later observations showed that the assignment of cases was correct in all instances, particularly with regard to the distinction between quiescence and indolent activity. The grouping here indicated is not expected to be a definitive, final classification of the leprides, but the main classes and at least the principal subgroups are certainly definite varieties. They are arranged, in general, in ascending order of severity and activity.

GROUPING OF LESIONS DISCUSSED

- A. Anesthetic patches, nonmacular.
- B. Residual macular leprides. (Healed lesions, usually nontuberculoid.)
 1. Nonatrophic.
 2. Atrophic.
- C. Simple macular leprides. (Not elevated or only slightly so, surface smooth or only coarsened in texture.)
 1. Quiescent. (Nonerythematous, flat or practically so. Frequently slight tuberculoid histologically.)
 2. Active. (Almost always tuberculoid histologically. Divisible into two main groups according to elevation, each further divisible.
 - a. Flat. (Not elevated; erythematous: (1) marginally, and (2) diffusely throughout.)
 - b. Raised. (Slightly elevated; divisible into (1) erythematous, usually only marginally, and (2) nonerythematous.)
- D. Minor tuberculoid leprides. (Frank tuberculoid, recognizable clinically, elevation more than slight, surface characteristically irregular.)
 1. Papulate. (Discrete papulations, usually marginal in a flat, often quiescent or residual base.)
 - a. Paucipapulate. (Papulations typically marginal, except in case of "lichenoid" subgroup. Active or retrogressive.)
 - b. Multipapulate. (Divisible into (1) diffuse, papulations scattered throughout, (2) marginal, papulations scattered over a broad marginal zone, and (3) circinate, papulations peripheral, often in hazy spots, isolated or agglomerated.)
 2. Diffuse. (Tuberculoid thickening diffuse in affected parts, whether lesion solid, annular or otherwise. Surface typically irregular or pebbled not actually papulate, but sometimes quite smooth.)
- E. Major tuberculoid leprides. (Maximum degree of the leprides, often resembling lepromatous lesions.)
- F. Cases with nonleprotic lesions ("controls").

All of the cases are mentioned individually, the data being presented as briefly as possible. Precise dates are avoided as of little consequence. The first clinical notes given are as of the time of biopsy, 1933 for the Cordova (C) cases and 1934 for the Dispensary (D) cases. Ages, sometimes only approximately accurate, are also given as for those years. Patients' statements regarding time of onset and other features of the histories are given without qualification, though we cannot vouch for their accuracy. Dimensions of lesions, important in current case-records, are unimportant here and when given are often only approximate. Notes on sensory changes are usually eliminated, as are those on treatment. Bacteriological findings are mentioned only when they were positive. With regard to the histological findings, attention is concentrated for the most part on the infiltrative changes, and particularly the presence or absence of the tuberculoid condition. Minor and residual conditions, including connective-tissue increase, loss of elastic fibers, and affection of the epidermis and hair structures, are usually ignored except in connection with some of the lesions classed as residual.

A. ANESTHETIC, NONMACULAR PATCHES

Limited areas of anesthesia, without macules or any other changes that could be demonstrated photographically, were presented by three cases. Two had never had a macule, but in the third case the anesthesia was residual.

CASE 1. (D-28) male, aged 25. Anesthetic area on wrist, 10 cm. long, of normal appearance. Five years previously (1929, age 20) this area and the small finger noticed to be insensitive, but when first seen (1930) only the wrist area was affected. Condition remained stationary. *Histology*: specimen (trephine) showed normal epidermis, no infiltration, no distinct abnormality of the elastic tissue, and no definite fibrosis except some in the nerve branches, which made identification of the small, superficial ones difficult.

The lack of abnormality in the skin as a whole is in keeping with the history that there had never been an active macule. How the connective-tissue increase in the nerve branches had been brought about was not evident.

CASE 2. (D-1) female, aged 18. Anesthetic area on forearm where a macule had appeared eight years previously. This was present when the case was first seen two years later (1928, age 12), but disappeared within another two years. When examined (1934) there was atrophy of the corresponding hand. *Histology*: practically identical with that of Case 1.

To find no more abnormality in an area that had once been macular was unexpected, but it was in keeping with the absolutely normal appearance of the skin.

CASE 3. (D-20) male, aged 28. Anesthetic area on one elbow, two years duration, and another recently noticed on the other. Surface of the older area (biopsied) departed vaguely from normal. *Histology*: much as in Case 1, except for a very little perivascular infiltration in the superficial plexus and, in three or four places in the series, larger collections of mononuclear cells some of which were of epithelioid appearance (here called "subtubercloid"). A small subcutaneous nerve appeared normal.

The vague change of appearance of the surface, much too slight to be called a macule, is undoubtedly to be correlated with the slight, apparently very early infiltrative changes found. This specimen is of particular interest because the area became macular later.

B. RESIDUAL MACULAR LEPRIDES

Apparently healed macular areas, in which the leprotic process had subsided so completely that they did not even have the persistent hypopigmentation that is a characteristic of the "quiescent" ones, were the only evident lesions in quite a number of the cases. They are of so much interest in diagnosis that, though they offered little in the way of pathology, several were included in the series. One-half of them showed no evidence of atrophy or "scarring," slight diffuse hypopigmentation being the principal abnormality, but in the others the disease process in subsiding had left changes of atrophic nature.

1. NONATROPHIC RESIDUAL MACULES

Seven cases were of this category, though perhaps one more (Case 39) could have been put here, while another one (Case 52), residual of the major tubercloid condition, is included in that group. Only two seemed worth trying to record photographically. The specimen from one of these, and one other, showed very slight, evidently residual tubercloid changes; the conditions found in the others are noted in some detail, because they are usually ignored.

CASE 4. (D-16) female, aged 8. A small, faint macule on hip (Plate 1, Fig. 3). History not recorded. *Histology*: several very small tubercloid foci, clearly inactive (residual), besides some fibrosis.

CASE 5. (D-3) female, aged 19. Two active lesions when first seen six years before. A year later one had disappeared; the other was quiescent, and after another year ill-defined, residual. *Histology*: four or five very small, inactive (residual) tubercloid foci found by serial sectioning. Less fibrotic changes but rather more superficial perivascular infiltration than in Cases 7 and 8.

CASE 6. (D-13) male, aged 10. A small, slightly hypochromic macule on flank, quite flat except for a few tiny pale spots, some of which appeared to be ill-defined papules (Plate 1, Fig. 4). Lesion of four years duration; when first seen

(1933, aged 9) border well defined. *Biopsy*: a considerable part of the lesion removed. *Histology*: Slight fibrosis. A single focus of round-cell infiltration that showed a suggestion of, but not definitely, tuberculoid ("subtuberculoid," probably residual from a tuberculoid focus).

CASE 7. (D-27) male, aged 20. Near wrist a small, hardly distinguishable, hypopigmented area. Started six years before (1928, age 14); when first seen (1932) slightly erythematous, border slightly raised; a year later it showed only irregular hypochromia. *Histology*: residual changes, mostly fibrotic, in papillary layer and around a few of the deeper structures. A little small-round-cell infiltration about some vessels of the superficial plexus, which were abnormally conspicuous, and in one of two subcutaneous nerves, both of which showed increase of the perineurium and endoneurium. Small superficial nerve branches not readily defined.

CASE 8. (C-19) male, aged 14. An indefinite healed area over elbow, and a more definite but ill-defined macule on buttock (biopsied). *Histology*: essentially as in Case 7, except that no subcutaneous nerve was present, and small superficial vessels were more numerous than normal.

CASE 9. (D-33) male, aged 19. Typical neural case with trophic changes of one hand and multiple, extensive old macules, many atrophic, none active when first seen a year previously. *Biopsy*: an old, small, hazy area on buttock. Almost negative. Only a part of the specimen showed any fibrosis superficially, where there was a very little perivascular infiltration. Nerve branches readily distinguished throughout.

CASE 10. (D-4) male, aged 16. Several moderate-sized, diffuse macules, inactive when first seen (1930, age 12), never anesthetic. *Histology*: essentially as in Case 6, almost negative. However, one or two acid-fast bacilli were found in the first section examined for them; other sections examined later showed none, but they did contain a very few nonacid-fast bacillary forms.

The fact that a few tuberculoid foci were found in the specimen from Case 5 at least four years after the lesion had become apparently residual, indicates how long that histological condition may persist. It is not believed that the findings in that case and Case 4 negative the clinical classification of the lesions as residual, though it cannot be said that they were completely recovered. The other ones described were apparently quite healed.

The principal feature of most of the specimens was increase of connective tissue in the regions where the pathological changes characteristic of the ordinary, milder leprides is typically located—in the papillary zone, and in relation to the neuro-vascular tracts and the accessory structures in the deeper layers. Superficial fibrosis of slight degree was the most constant feature, though clinically these cases showed no outward evidence of it. Sometimes the superficial nerve twigs were obscured, if not obliterated. In one specimen there were two small subcutaneous nerves that showed evidence of disturbance, obviously residual of a more severe condition.

2. ATROPHIC RESIDUAL MACULES

Six of the residual lesions examined showed superficial atrophy in varying degrees and of different kinds. The common "crumpled surface" effect can only be illustrated photographically (Plate 1, Fig. 1), as no specimen was taken from such an area. However, from other cases examined it can be said that the principal microscopic changes are similar to those seen in the preceding group, but with more destruction of the network of fine elastic fibers in the papillary layer which maintains the normal tone of the epidermal layer and consequently more stretching of that layer.

The following two cases presented somewhat unusual features:

CASE 11. (C-6) female, age 35. Among other lesions, mostly residual, was an atrophic, scar-like area on arm, 5 by 7.5 cm., completely anesthetic even to deep pain. The lower portion bulged, suggesting considerable infiltration, but actually it was soft and yielding. *Histology*: principal changes in the reticular layer—marked thinning and fibrillation of the connective tissue and great diminution in number and size of the elastic fibers. Epidermis rather thin and flattened. In the papillary layer marked loss of elastic fibers, a little perivascular infiltration, and conspicuous dilatation of lymph spaces.

Bulging like that seen in this lesion (Plate 1, Fig. 2) might easily be mistaken for gross infiltration of the tissue if palpation were neglected. The reason for the rarefied condition of the connective tissue and the marked diminution of elastic tissue in the reticular layer is not evident.

CASE 12. (C-7) female, age 18. An area on the thigh, nonanesthetic, resulting from a lesion that had appeared ten years before, was dotted with small, apparently depressed, pigmented spots that were gaping hair follicles. *Histology*: little abnormality, but one hair structure contained a small, residual tuberculoid focus.

Though the pathology in the specimen removed was slight, there is reason to believe that the follicular condition observed was a sequel of a special concentration of the pathological process around the hair structures, and perhaps also in them, as indicated by the unusual finding of a tuberculoid focus actually within one of them. (See also Case 40.)

The other cases present little of interest. CASE 13 (C-10, female, aged 22) had on the leg two small, hypoesthetic, scar-like areas close together, surrounded by a diffuse halo of slight hypopigmentation. CASE 14 (C-21, female, age 20) had on the forearm a slightly wrinkled, hyposensitive, atrophic area a trifle paler than normal, resulting from a macule first seen six years before. In CASE 15 (D-5, female, 56) an area on the leg, completely anesthetic, faintly hypochromic, was the site of a lesion that started more than ten years before. CASE 16 (C-22, male) was no more interesting. In all of these lesions little was found other than variable degrees of fibrotic change and at most a little cellular infiltration, in addition to the usual diminution or loss of elastic fibers.

C. SIMPLE MACULAR LEPRIDES

1. QUIESCENT SIMPLE MACULES

Eight of the lesions studied were placed in this group, which comprises the smooth-surfaced ones that show no erythema and are flat or, if raised at all, only to an insignificant degree, but that in appearance—chiefly in degree of hypopigmentation—are not sufficiently retrogressed to be called residual.

Lesions found nontuberculoid.—In three of the eight specimens in this group no tuberculoid changes were found, even after serial sectioning of the entire blocks.

CASE 17. (D-22) male, age 14. Of four very simple macules, the largest was on the buttock, 7.5 by 2.5 to 4 cm. Smooth, rather pale, especially marginally; sharply demarked, but edge finely irregular, with numerous little outshoots (finely "streaming"). Upper and outer portions of marginal zone very slightly raised. First noticed four years before (1930, age 10); little change since first examination (1933). *Biopsy*: upper margin, supposedly raised slightly. Almost negative except for considerable superficial fibrosis; a single small focus of mononuclear accumulation (subtuberculoid).

Though the edge of the lesion in this case (Plate 1, Fig. 5) was quite irregular, with fine "streaming," it was considered quiescent because of its other characteristics. The slight elevation of the surface that was noted was probably due to fibrotic changes, since there was not enough cellular infiltration to cause it.

CASE 18. (D-29) female, age 14. A single small, flat, irregularly outlined, moderately hypopigmented but distinct macule on the arm. Surface in part showed coarsening of texture; center recovering. Started two years before (1932, age 12); slightly thickened when first seen (1933). *Histology*: most of the sections practically negative, though some showed a little round-cell accumulation.

From its appearance (Plate 1, Fig. 6) this lesion might have been considered residual but for the degree of hypochromia and the slight coarsening of the grain of the skin. The slight histological abnormality indicates that it was residual. It is unusual because of its discontinuity, which presumably relates it to the "spotty" micro-papillate lesions to be discussed later.

CASE 19. (D-34) male, age 36. An old lesion on knee, reddish-brown but not erythematous, and marginally hyper- rather than hypochromic. *Histology*: no trace of tuberculoid change; almost negative except for pseudo-lepromatous changes caused by intradermal injections.

Because of the disturbances, clinical (hyperchromia) and histological (pseudo-leproma) due to "plancha" treatment, this case might have been dropped from the list. It is included only to call attention to the fact that intradermal injection of chaulmoogra drugs gives rise to a microscopic picture that may be very misleading to the unwary.

Lesions found tuberculoid.—Five specimens out of the eight classed as quiescent showed tuberculoid changes in some degree, slight or very slight except in one instance.

CASE 20. (D-23) female, age 20. Extensive, irregular, rather pale, nonelevated, confluent multiple areas on back and extremities, fairly smooth-edged, usually clearly demarked. The largest extends from right loin down onto thigh and across to cover most of left buttock. On first examination (1933) anesthesia of small finger of right hand, and feet and lower parts of legs; beginning claimed only one year previously (1932, age 18) with numbness of right foot; later a pale macule appeared, followed by others. *Biopsy:* uppermost edge of lesion, lumbar region. A very few tuberculoid foci, inactive, evidently residual, with points of scarring that indicated where others had been.

This case departs sharply from the foregoing ones in the extent of the lesions (Plate 2, Fig. 7). If their size was attained in the time claimed (two years) the spread was more rapid than in most cases. It may be noted that these lesions were subject to periodical flushing, which clinically is characteristic of lesions of very superficial nature. The slight degree of histological change was in agreement with the clinical appearance at the time of biopsy. The presence of peripheral anesthesia before the appearance of a skin lesion is not usual, but neither is it rare.

Of the following three cases, CASE 21 (C-20, male, age 10) had one lesion probably of this class, besides others more completely healed. Several tuberculoid foci in the deeper levels. Four bacilli found in one focus. CASE 22 (C-9, female, age 13) had on the buttock a single lesion with a slightly raised border. A photograph taken a year later shows only discontinuous traces of it (Plate 4, Fig. 22) with marked "follicular hypertrophy." Slight tuberculoid. CASE 23 (D-15, male, age 33) had two lesions rather similar in appearance to that of Case 17, though larger (Plate 2, Fig. 8). A very few small tuberculoid foci in the entire specimen. (The later developments in this case were particularly interesting.)

All of the preceding cases had only slight tuberculoid changes, one of them so little that many of the sections showed none. The following one presents a problem in classification.

CASE 24. (D-35) male, age 10. On the back a very small oval macule that in 1932 was 2 cm. long, pinkish, raised, of coarsened grain. When biopsied it had not increased perceptibly in size, but was still slightly elevated and finely irregular of surface. *Biopsy:* entire lesion removed. Slight to moderate tuberculoid change, not residual in appearance, involving a subcutaneous nerve as well as the skin itself; also rather marked round-cell infiltration (mostly small) around the tuberculoid foci and elsewhere.

This lesion was classed as quiescent because it had retrogressed, becoming nonerythematous and apparently with less definite elevation than at first, and also because it had remained stationary in size for two years. However, the sections showed much more, and more

active-looking, tuberculoid changes than did those from other lesions of this class examined. Without the history of nonprogression it would probably have been considered indolently active (see Case 35).

2. ACTIVE SIMPLE MACULES

These cases represent that group of lesions that lack the degree of elevation or thickening and the characters of surface that distinguish the readily recognizable, *clinically* "tuberculoid" lesions, but which show evidence of activity in consequence of which they may be expected to progress as regards size of the area affected or severity of the condition. Only eleven of our cases fall into this group, so they cannot represent all of the variations that such lesions may present; even these few are divisible into four varieties.

Flat, marginally erythematous lesions.—The first case following is the simplest one of the three of this variety; in the second the condition is on a large scale.

CASE 25. (C-1) female, age 10. On thigh, above knee, an irregularly outlined macule of four years duration which in its upper part was well defined and slightly pinkish. *Histology*: slight tuberculoid. (This lesion as seen a year later is mentioned again in connection with the minor tuberculoid condition.)

CASE 26. (D-26) male, age 24. An ordinary neural-type case, first seen seven years previously (1927, age 17). Atrophy and contracture of one hand and atrophy of one foot, with chronic ulcer. Extensive macular areas covered much of the posterior surfaces of thighs and involved the legs; a separate one on right lower buttock (biopsied). Borders in places diffused, especially low down, but above there were broad, pale zones, irregular in width and outline, with streaming edges, in part faintly reddish. *Histology*: tuberculoid, slight.

These lesions (Plate 2, Fig. 9) are of a thoroughly familiar kind, unquestionably similar in nature to some of the smaller ones observed in cases that show no evidence of affection of the peripheral nerves.

CASE 27. (D-9) female, age 9. A single region involved, right hip and buttock, extending to left natal fold. Lesion extremely irregular, broken up, patchy; some areas merging, others quite separate. Edges coarsely irregular, often streaming, but in many places ill-defined. Moderately hypopigmented, surface smooth, slightly shiny, and slightly erythematous in the more clearly-defined portions. *Biopsy*: a small, almost separate area, upper portion of lesion near midline of back, apparently active. Tuberculoid, moderate, numerous small foci, mostly deep; largely residual, but a few foci apparently active.

This lesion is decidedly peculiar in its broken-up, "patchy" character (Plate 2, Fig. 10). If the condition started as numerous independent areas, they are individually less distinct and more irregular than is usual when multiple lesions undergo fusion. It would be remarkable that so many foci should arise separately in so limited an area

with none elsewhere on the body. It seems more likely that they all arose by local extension from a single focus, the extension that produced the separate areas being, so to speak, subterranean—"colonial" development on a large scale.

Flat, diffusely erythematous lesions.—Two cases had lesions of this kind, in which the erythema is diffuse rather than marginal and which do not have the usual degree of hypopigmentation.

CASE 28. (D-19) male, age 13. An extensive macule on right leg, slightly but diffusely erythematous, not hypopigmented, "the simplest possible lesion." Discovered a month before the first examination (1933); very slightly paler than normal, hardly visible, borders ill-defined. *Biopsy*: trephine specimen; no choice as to site. Little change other than superficial fibrosis and flattening of epidermis; a little perivascular mononuclear accumulation in only a few sections.

CASE 29. (D-24) male, age 22. Large, reddish areas on arms, appearance as in Case 28. *Histology*: the skin itself showed almost negligible changes, but in the subcutis there was a nice tuberculoid focus, included quite accidentally.

Whether the very slight abnormalities found in the skin in these specimens, with no tuberculoid change except in the subcutis in one instance, is representative of the lesions as a whole cannot be said. However, the clinical features, and the fact that the first of these cases later became bacteriologically positive and was hospitalized (the other has been lost to sight) set these cases apart from the others in this series.

Raised, erythematous lesions.—None of the five cases placed here illustrates very well, both clinically and histologically, the familiar lesions of comparatively regular outline, with distinct though still slight elevation, and erythema of the margins. The surfaces of both of those that were photographed when biopsied had been disturbed by local applications, and the specimen from the best one (detailed below) was apparently not removed from the most infiltrated part.

CASE 30. (D-8) male, age 28. New case. On abdomen a slightly hypopigmented macule of 3 years duration, border in places, especially above, definite, slightly but distinctly raised and erythematous (Plate 2, Fig. 11). Surface fairly smooth, with at most coarsening of texture. A small (secondary?) area just below. *Biopsy*: upper margin of larger macule. Tuberculoid, very slight; only two or three small deep foci, insufficient to account for the infiltration noted. A few bacilli found in both parts (Zenker and alcohol fixed) of the specimen.

CASE 31. (D-12) male, age 9. A single macule on lower forearm, with marginal erythema and slight infiltration near the wrist (Plate 2, Fig. 12). *Histology*: deep in the skin small-round-cell infiltration and tuberculoid change, evidently old, of rather marked degree.

CASE 32 (D-6, male, age 8). Multiple, widely distributed macules, most of them relatively recent and many of them rather small. Smears from left cheek

positive (+); elsewhere, including biopsied lesion on buttock, negative. *Histology*: moderate tuberculoid changes, with rather marked round-cell infiltration, the latter mostly superficial.

Of the two other cases, CASE 33 (C-8, female, age 25) had on the hip a small pale macule with a slightly raised, slightly erythematous border. CASE 34 (C-13, male, age 13) had on the back a slightly raised, pinkish macule so small that most of it was removed. The specimens from both cases showed slight tuberculoid change, confined to the papillary layer.

These lesions all showed some degree of the tuberculoid condition. The visible thickening of the skin was slight, and the amount of histological change was also slight in three instances, but in Cases 31 and 32 it was more marked than was expected from the clinical appearance; its deep location undoubtedly explains the smoothness of surface. In the two lesions in which it was superficial, it was too slight to cause irregularity. The finding of a few bacilli in the sections of Case 30 was surprising in view of the degree of abnormality found; there has been no untoward development in the case.

Raised, nonerythematous lesions.—Only one case is put in this class, though it may be that one of these already discussed (Case 24) should have been placed here.

CASE 35. (D-7) male, age 19. Several fairly large lesions in different stages of progress. One (a), buttock, recent, was pale, fairly smooth, distinctly raised, with retrogression beginning in a small central area (Plate 3, Fig. 13). Another (b), leg, was large, oval, recovered centrally, with a broad, pale, very slightly thickened marginal zone (Plate 3, Fig. 14). Nine years previously (1925, age 10) a lesion appeared on arm, followed by numbness and weakness of the member. Since first seen (1927) the lesions have enlarged slowly, with periods of inactivity, and new ones have appeared. *Biopsies*: (a) buttock lesion; considerable superficial perivascular infiltration in places, with a few small tuberculoid foci in every section. (b) Leg lesion; slight perivascular infiltration, with a very few small tuberculoid foci in the deeper levels.

The recent lesion on the buttock was clinically too distinctly elevated to be considered inactive, though it showed no erythema. The amount of tuberculoid change found was surprisingly small. The leg lesion might easily have been considered quiescent, clinically and histologically, at the time the biopsy was performed, but subsequent developments have shown that that would have been erroneous.

D. MINOR TUBERCULOID LEPRIDES

This group of leprides, some of which leprologists are coming more and more to recognize as of tuberculoid nature, has to be expanded to include the following subclass.

1. PAPULATE TUBERCULOID MACULES

In the papulate lesions, of which there are several varieties, the characteristic surface irregularities have the form of papules

that are entirely superficial, usually sparse, discrete and well separated, but often numerous and tending to agglomerate into groups. This tendency, if it goes far enough, may produce an actual diffuse minor tuberculoid lesion, as in one of the cases to be described. Ordinarily the papules are located marginally in an otherwise flat base—a quiescent or residual macule—though sometimes such papulation occurs independently of pre-existing macules (“lichenoid” lesions). A considerable number of our cases had one form or another of these lesions, which are divisible into two main subgroups, “paucipapulate” and “multipapulate.”

Paucipapulate lesions, active.—Of the four lesions placed in this group, the few papulations present in three of them were relatively large and conspicuous—full and evidently active—and occurred in otherwise apparently healed macules.

CASE 36. (C-23) male, age 19. A single, roughly oval area on arm, not hypochromic, border indefinite, with slight atrophy but normal hair growth; duration about three years. At the margin, lowest portion, were three pinkish papules, each \pm 2 mm., and two others in the upper part. *Biopsy:* the group of three papules removed. Two very superficial, apparently active tuberculoid foci found; considerable subepidermal fibrosis in the space between them.

This lesion is typical of the active group. When the photograph was taken a year later a few new papules had appeared around the biopsy scar (Plate 3, Fig. 15), and those not removed (upper part) had increased in number, four or five of them being agglomerated (“lichenoid” effect). The microscopic picture confirmed the obviously superficial location and apparent activity of the papules.

CASE 37 (C-5, female, age 13) had on the shoulder a lesion very similar, clinically and histologically, to that of Case 36 except that the original macular area was not atrophic, hardly distinguishable. A photograph taken three years later (Plate 3, Fig. 16) showed a few small papules still persisting around the biopsy scar, and a new cluster (lichenoid) well apart from the macule. CASE 38 (C-18, male, age 24) was also essentially similar, though the original lesion area (arm) was larger and the papulations more numerous, making rather prominent, highly discontinuous segments in two parts of the margin. A rather striking lesion of this kind, found in still another patient (Case 45) is shown in Plate 3, Fig. 17; two years previously it was an ordinary simple macule.

“Lichenoid” lesions.—Isolated groups of papules arising *de novo*, independently of previous lesions (as in Case 37, Plate 3, Fig. 16) are sometimes called lichenoid. A similar cluster developed in Case 36 (Plate 3, Fig. 15). Frequently there is hazy hypopigmentation about them, as exemplified by a lesion of uncertain nature found recently in one of the cases already discussed (Plate 3, Fig. 18). One of the “control” cases to be mentioned presented a definitely non-

leprotic condition (Plate 3, Fig. 19) that could be mistaken for this manifestation of leprosy.

Paucipapulate lesions, retrogressive.—A few of the macules seen had scattered papules that were very small and for the most part clearly retrogressive; in one or two of the lesions classed as residual there were only traces of such papules, minute atrophic scars. The case mentioned below would be classed as quiescent, if not residual, but for the desirability of calling attention to the condition.

CASE 39. (D-31) female, age 10. On and below elbow, anteriorly, a rather indistinct macule with a few pinhead spots, "probably isolated tuberculoids." *Histology:* in two levels of the specimen there were found remnants of previously tuberculoid foci.

The lesion in this case was not photographed, but a picture from another case (Plate 4, Fig. 20) is illustrative of the condition.

Multipapulate lesions, follicular.—In one of the five cases that had lesions with papulations too numerous to be called paucipapulate, the papular elements were generalized and evidently related to the hair follicles.

CASE 40. (D-10) male, age 11. A single macule on buttock, outline very irregular, coarsely streaming, border in places well marked, slightly raised and erythematous. Surface flushed and irregularly studded with pinpoint to pinhead micropapules. (Plate 4, Fig. 21.) When first seen (1932, age 9) it was of ordinary appearance, border pinkish. *Histology:* Slight to moderate tuberculoid change, superficial and deep, retrogressive. No actual papule found, but at one place a condition (loosening of the subepithelial layer, with scattered mononuclear infiltration) that probably represents a previous papule. An unusual concentration of pathological change around the hair follicles.

So far as can be told, the micropapulation observed was due to an unusual concentration of the pathological condition around the hair follicles rather than to the usual subepithelial location of the tuberculoid foci. This probably relates this lesion to the atrophic one showing patency of the follicles (Case 12).

"Follicular hypertrophy."—In this connection note may be made of the peculiar follicular enlargement that is frequently seen in association with leprosy lesions. An example was seen in Case 37 (Plate 3, Fig. 16). In Case 22 the condition was more striking, with prominent follicles inside and widely around a discontinuous lepride of the buttock, and also on the other buttock (Plate 4, Fig. 22). This condition is often seen in nonlepers, especially in children.

Multipapulate, circinate lesions.—In four cases this interesting "spotty" variety of lesion was the principal or sole abnormality, and it also occurred in one or two others. Of the four that were

biopsied, three lesions were retrogressive to residual, but the fourth was decidedly active, at least in parts. The former will be considered first.

CASE 41. (D-14) male, age 13. Several lesions, varied in appearance. One (a) on forearm consisted of numbers of hazy pale spots, isolated and grouped, some apparently containing tiny papules. Though usually widely separated, they roughly outlined two apparently normal areas (Plate 4, Fig. 23). One of these areas represented a macule that had appeared six years before (1928, age 7), the other a later one. Another (b) on loin was a fairly recent, pale, small, roughly oval macule, edge irregular, in places streaming, with a few fine papules at or near the border and "colonial" spots outside it (Plate 4, Fig. 20). At first examination (1932) the arm lesion was composed of two "patchy marginal zones," the loin area was of about the same size as in 1934. Smears recorded as positive at the first examination, but negative a few months later, and repeatedly thereafter. *Biopsy*: a group of spots on forearm near elbow. Only three very small tuberculoid foci found in the entire specimen, none superficial.

CASE 42. (D-32) female, age 20. On arm two ill-defined areas, limits indicated in places by occasional pale spots, isolated or grouped, that appeared to represent tuberculoid points, though in few could any population be seen. At first examination (1932) these areas were ordinary pale macules. *Histology*: mononuclear infiltration in places, chiefly in the papillary layer, rather marked in degree; in a few spots a suggestion of tuberculoid change, probably residual.

CASE 43. (D-11) male, age 13. On buttock a spotty circinate lesion, the spots in upper part numerous and merging; actual population doubtful. Two years previously the lesion was a centrally healed macule with an erythematous, finely papulate border zone. *Histology*: slight, deep, tuberculoid change (rather numerous foci); also at two points under the epidermis rarefaction and round-cell infiltration (as in Case 40) with, just below one of these points, a nice tuberculoid. In places, disturbance suggestive of intradermal medication.

The two sketchily outlined lesions on the arm of Case 41 (Plate 4, Fig. 23), with only very slight changes in the specimen removed, clearly represent a late, retrogressed stage of the spotty papulate condition. That of Case 42 was very similar, but it had more histological change which, however, was not tuberculoid, though probably of that nature originally. The lesion of Case 43 was much more marked; in its clinical appearance it was more like the buttock lesion of the next case to be discussed (Plate 5, Fig. 26), and histologically it was tuberculoid, apparently not wholly inactive. In this general category is another lesion, from Case 46, that was not biopsied (Plate 4, Fig. 25). In the picture, just above the ring, is a spotty area that evidently represents an early stage of the condition in a very small macule, and that resembles the discontinuous residual lesion of Case 18 (Plate 1, Fig. 6). The paucipapulate lesion on the loin of Case 41 (Plate 4, Fig. 20) may also have been on the way to becoming a spotty circinate one. An extensive, broad-margined lesion that had gone

far in that direction was seen on the leg of another patient (Plate 4, Fig. 24).

CASE 44. (D-21) female, age 15. Spotty circinate lesions on cheek and buttock, both 5 by 8 cm. Hazy spots, both isolated and grouped, many containing pale papules or atrophic spots. In the buttock lesion where the spots fused the papulations still remained discrete (Plate 5, Fig. 26), but in a part of the cheek lesion the process formed a pale, finely pebbled, conspicuously raised segment (Plate 5, Fig. 27). On the buttock a few spots occurred outside the marginal zone, while on the cheek several were inside it. Onset eight years before (1926, age 7) with a reddish macule on cheek; buttock lesion developed a year later. When first seen (1929) both were much smaller than when biopsied; that on the face was pinkish. *Biopsy*: buttock lesion, upper margin. Tuberculoid, an excellent moderate-degree lesion, with numerous foci in all levels, even subcutaneous, but mostly deep; foci usually fairly small but none apparently retrogressive.

This is the only case in which this condition was obviously active. The existence of isolated spots outside the marginal zone of the lesion on the buttock (Plate 5, Fig. 26) indicates progression beyond and independently of the main macular area (colonial development). Whether the spotting in the otherwise healed central area of the cheek lesion (Plate 5, Fig. 27) developed secondarily or not we cannot say. The degree of pathological change in the specimen removed (buttock) was not inconsiderable. The cheek lesion would undoubtedly have shown the same condition in much more marked degree; actually it was, in part, of the diffuse minor tuberculoid type.

2. DIFFUSE MINOR TUBERCULOID LEPRIDES

Only four of our cases had lesions of the ordinary diffuse minor tuberculoid variety—that is, frankly tuberculoid but of neither the papulate form nor the massive major type—and they do not illustrate the condition particularly well.

CASE 45. (C-14) male, age 20. Among other lesions (paucipapulate and circinate spotted ones have been referred to; see Plate 3, Fig. 17 and Plate 4, Fig. 25) were a few rather small, incompletely differentiated ones on the buttocks, moderately raised, irregular of surface. Those photographed a year later (Plate 5, Fig. 29) were pebbled in part only, actually hardly more than micropapillate. *Biopsy*: small lesion on gluteal fold. Slight to moderate tuberculoid changes, mostly located rather deep.

CASE 46. (C-2) male, age 13. A large lesion extending well above and below the knee, the margin in part, especially on thigh, having a narrow, active, thickened zone. Here and there, both in the marginal zone and inside it, were scattered coarse, reddish papulations. *Histology*: fairly marked tuberculoid change, confined to the upper half of the dermis, apparently not very active.

The marginal elevation had subsided somewhat a year later, so the photograph (Plate 5, Fig. 31) does not show the original condition.

The most striking feature then was the conspicuous coarse papulation, mostly well inside the edge.

CASE 47. (C-12) female, age 50. An extensive area encircling leg and thigh, centering over knee, upper border raised, irregular of surface, erythematous. Healed area superficially atrophic, "crumpled"; it reddened diffusely on exposure to the sun. *Histology*: tuberculoid fairly marked, in all levels, with fairly large, well separated foci in the papillary layer.

The tuberculoid foci found in the papillary layer obviously caused the surface irregularity, the deep foci contributing to the diffuse thickening. The photograph, used to illustrate the "crumpled" atrophy of the recovered part (Plate 1, Fig. 1), shows the marginal raised zone very poorly, though it was still active and recorded as of the same condition as when biopsied the year before.

CASE 48. (C-17) male, age 20. On buttocks and thighs were three extensive macules, partly outlined by much-infiltrated, erythematous borders. Smears strongly positive (++ and +++). *Histology*: tuberculoid changes, chiefly in the papillary layer but of marked degree and peculiarly active appearance. Bacilli present in some numbers.

This case was unique in the series as regards the bacteriological findings, and also in the immediate group as regards the degree of the tuberculoid change. The patient was hospitalized shortly afterward.

Two cases that in 1933 had active simple lesions had, in 1934, become minor tuberculoid, and their photographs are included here. In one (Case 25) the lesion had become borderline between the multipapulate and the pebbled diffuse forms (Plate 5, Fig. 28). The other (Case 34) showed a rather deep-seated, irregular-surfaced thickening around the biopsy scar (Plate 5, Fig. 30).

E. MAJOR TUBERCULOID LEPRIDES

Examples of the major tuberculoid leprides, by far the most marked of this general class of lesions and ranking among the most striking and interesting manifestations of leprosy, were encountered only in the Dispensary group. Though all of the most interesting cases on the list had been called up for this study, they included only three of this kind, in different stages; a fourth one, more recently seen, has been added to illustrate the acute phase of the condition.

CASE 49. (L-1) male, age 10. New case, 1936. Numerous lesions on face, extremities and body, varying from small papules, barely 3 mm., to large confluent areas, all raised abruptly about 2 mm. The surfaces of the smallest were smooth; the larger ones were rough, granular, and showed some scaling very similar to that of acute psoriasis. Patches anesthetic, the papules only hypoesthetic. No enlarged superficial cutaneous nerves found; ulnars and peroneals also normal. Condition said to have started three months previously as a widespread eruption of red papules.

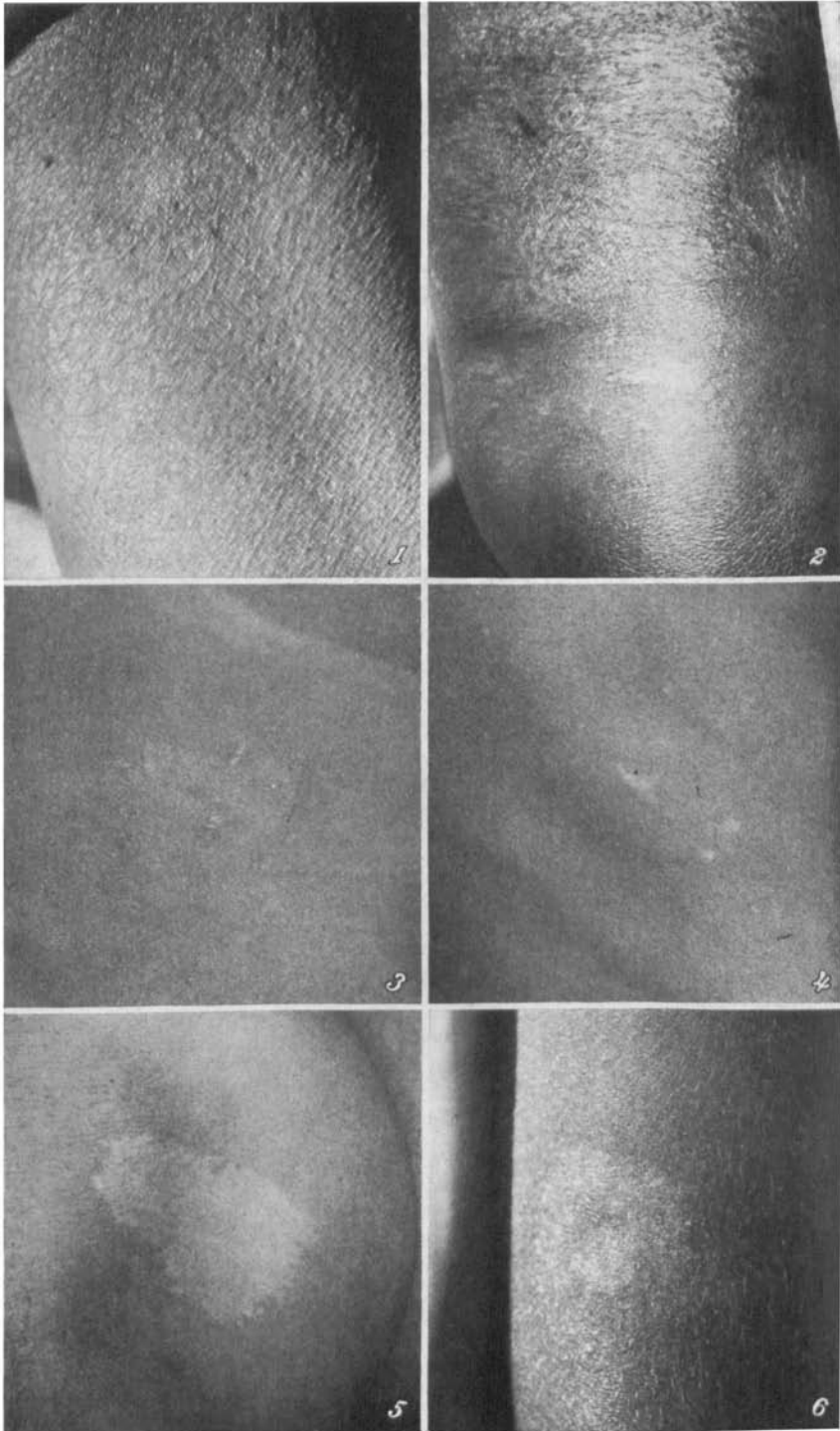


PLATE 1

PLATE 2

FIG. 7. Quiescent lesion, extensive, coarsely irregular. Histology: very slight tuberculoid, residual. Buttocks, etc., Case 20.

FIG. 8. Quiescent lesion, fairly large, extremely irregular, with extraperipheral spotting ("colonial" development). Histology: very slight tuberculoid, residual. Arm, Case 23.

FIG. 9. Active lesions, extensive, broad margined, irregular edged, with slight peripheral erythema in some places, in a well-established neural-type case. Histology: slight tuberculoid. Thighs and buttocks, Case 26.

FIG. 10. Active lesion, in some respects similar to that of Case 20 (Fig. 7), but greatly broken up, or "patchy." Histology: moderate tuberculoid, apparently not inactive. Buttocks, etc., Case 27.

FIG. 11. Single active macule, distinctly infiltrated and erythematous at margin, especially above. Surface scarring due to home medication. Histology: very slight tuberculoid, but bacilli found. Abdomen, Case 30.

FIG. 12. Active macule, much affected by home medication. Margin in part erythematous and slightly raised, especially to the right. (Elevation not well shown in photograph.) Histology: moderate degree tuberculoid, deep. Lower forearm, Case 31.



PLATE 2

PLATE 3

FIG. 13. Active, distinctly raised but nonerythematous macule, with beginning central resolution and atrophy. Histology: slight tuberculoid, with moderate perivascular infiltration. Buttock, Case 35.

FIG. 14. Essentially similar but much larger lesion on leg of same patient as Fig. 13. Large central healed area, with almost complete resolution and interruption of marginal zone in upper part. Histology: very slight tuberculoid.

FIG. 15. Active paucipapillate lesion. An otherwise healed macule with one small ("lichenoid") group of active papules in upper inner portion, and others around biopsy scar. (Photograph taken one year after biopsy.) Histology: tuberculoid, active. Arm, Case 36.

FIG. 16. Active paucipapillate lesion, with a few papules around scar of biopsy (made three years previously), and a new (lichenoid) group to the left that has appeared recently outside of the area of the original macule, which is completely healed except for the papules. Histology: tuberculoid, active. (General follicular enlargement in this area.) Shoulder, Case 37.

FIG. 17. Active paucipapillate lesion which originally was an ordinary flat macule. Abdomen, Case 45. (Not biopsied; see also Figs. 25 and 29.)

FIG. 18. A lesion of "lichenoid" appearance but uncertain nature, recently appeared in a supposedly recovered case. Posterior axillary fold, Case 10.

FIG. 19. A papulate lesion of "Cebu dermatitis," (lichen trichophyticus?) superficially resembling lichenoid lesions of leprosy. Histology: chronic inflammatory only. Control Case C-489.

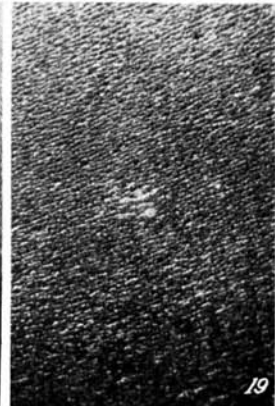


PLATE 3

PLATE 4

FIG. 20. An irregular, quiescent macule with paucipapulation, of much slighter degree than in preceding cases. Papulations very small, scattered, inconspicuous, retrogressive or residual. (Not biopsied.) Abdomen, Case 41. (See also Fig. 23.)

FIG. 21. Multipapulate macule, papulations small, irregular, generally distributed, probably due to special concentration of the (tuberculoid) pathological condition around hair follicles. Buttock, Case 40.

FIG. 22. Follicular "hypertrophy" often seen in the region of leprides, especially on buttocks (but see Fig. 16); also independently of lesions and in nonlepers. In this case the condition is around and inside a discontinuous quiescent lesion, and also on the other buttock. Case 22.

FIG. 23. "Spotty" multipapulate circinate lesion. The spots very sketchily outline two previous macules; the papules, where present, are mostly if not entirely residual. *Histology*: very slight tuberculoid. Arm, Case 41.

FIG. 24. Illustrating the development of the spotty condition, in an extensive, broad marginal but markedly retrogressed lesion on leg. (Case not biopsied.)

FIG. 25. A spotty circinate lesion, less retrogressed than in Fig. 23, the spots merging in places. Above it a small area resembling the macule of Case 18 (Fig. 6), evidently an early stage of the spotty condition. (Not biopsied.) Upper thigh, Case 45. (See also Figs. 17 and 29.)

(The larger lesions presumably developed *in toto*, but further information could not be obtained as the child's relatives could not be located.) Smear from buttock positive ++). *Biopsy*: upper edge of large lesion, forearm, including an underlying structure suspected to be an enlarged nerve but found to be a vein. Extreme tuberculoid, typical of the most marked and active lesions. Bacilli present. The piece of vein removed also showed some tuberculoid involvement.

This is a striking example of the active major tuberculoid condition in full bloom (Plate 6, Fig. 32), in an unusually young person. That the large lesions on the extremities started as papules is doubtful, but it is probable that, as claimed, the condition was of abrupt onset. Bacilli were fairly numerous in smears, but much fewer than would be expected from a leproma of similar degree of thickening. The pathological change was typical in its extreme degree and evident activity. The involvement of the vein that underlay the lesion is perhaps unique.

CASE 50. (D-30) male, age 25. New case. Two striking tuberculoid lesions, both anesthetic; one, over knee, was 5 cm. in diameter; the other, forearm, extended from elbow to wrist. Both reddish, with little loss of pigment, much raised but not as sharply demarked as usual; surfaces unusually irregular, pebbled, with nonerythematous central areas smoother and less thickened than the marginal zones. History of anesthetic, nonmacular area on site of arm lesion, beginning seven years before (1927, age 18); two months before examination it became red, especially at the borders. Patch on knee first noted then. No fever, pain or secondary symptom. *Biopsy*: margin of knee lesion. Tuberculoid, fairly marked, but comparatively little in papillary layer.

The interesting history of a large, nonmacular numb area of seven years duration that suddenly flared up and became a typical major tuberculoid lesion cannot, unfortunately, be verified from actual observation. The statement that the present condition was of abrupt onset can be accepted as probably true. Clinically, the lesions were definitely of the major tuberculoid type, though of moderate grade and more like the minor variety as regards the surface irregularity (Plate 6, Figs. 33 and 34). The microscopic change was fairly marked, but the appearance suggested that the condition had begun to subside.

CASE 51. (D-17) male, age 73. New case. An extensive, much thickened, reddish area involved right cheek from below mouth up to beneath eye and around to above eyebrow, also ear and lip on same side; some face-drop. Four months duration claimed. *Biopsy*: forehead, just above inner end of eyebrow. Tuberculoid, rather marked, in part at least retrogressive.

This lesion, like the previous one, was conspicuous (Plate 6, Fig. 35) though no longer at its maximum. It was less erythematous than at first, and histologically it seemed retrogressive. On re-examination two years later, when the skin lesion had almost completely

subsided, we found under the area that had been involved a considerably enlarged supraorbital nerve that proved to be caseous tuberculoid.

CASE 52. (D-18) male, age 72. Posteriorly on left side of neck was a markedly hypochromic area, not raised, sharply demarked only near the midline. (Other areas where lesions had existed were not studied.) One month before patient was first seen (1932) pinkish to reddish areas appeared on several parts of the body. That on the neck was the largest, in appearance like that of Case 51. The condition subsided completely, though treatment was irregular. *Biopsy*: lower margin of pale area on neck. Slight round-cell infiltration only, mostly deep. Some fibrosis, epidermis thin and flattened.

The lesions of this case were so completely healed (Plate 6, Fig. 36) that it could be identified as having belonged to the major group only by the fact that when they were first seen they were in an acute stage and clinically similar to those of Case 51. From the microscopic findings it had evidently healed completely. It is noteworthy that this patient and the preceding one were of somewhat advanced age.

F. CASES WITH NONLEPROTIC LESIONS

The five nonleprous cases that were biopsied, in part for diagnostic aid and in part for comparison with more or less similar leprous lesions, will be mentioned only briefly.

CASE C-489. Many pinkish papules with a tendency to oval grouping. The old ones itchy, with fine desquamation. *Diagnosis*: papular dermatitis (lichen trichophyticus?). *Biopsy*: a group of papules; chronic inflammatory, moderate. A year later the old lesions were gone but new ones had appeared which were somewhat suggestive of lichenoid lesions of leprosy (Plate 3, Fig. 19). Ten months afterward they, too, had disappeared.

CASE C-4361. A group of a dozen flat papules on the thigh, irregular in size and shape, some angular, most rounded or irregular, some violaceous, skin folds exaggerated. Similar but smaller ones nearby. *Diagnosis*: lichen planus? *Biopsy*: one of the papules; chronic inflammatory only. All lesions disappeared some weeks later.

CASE C-3182. A single tiny (4 or 5 mm.) pale macule of suspicious appearance on buttock. *Diagnosis*: undetermined. *Biopsy*: entire lesion removed; slight chronic inflammatory. Subsequent history negative; probably not leprosy.

CASE C-4412. Multiple macules on buttock. The largest, 4 by 7.5 cm., hypopigmented, dry, shiny, skin ridges exaggerated; border in parts distinct, elsewhere diffused. No sensory disturbance. Said to be of more than twenty years duration. *Diagnosis*: undetermined; leprosy doubtful. *Biopsy*: border of lesion; rather marked round-cell infiltration. Nothing suggestive of leprosy observed in subsequent examinations.

CASE D-P1572. Numerous very small, palish areas, said to be small-pox scars but not wholly unsuspecting in appearance. *Histology*: practically negative.

Indicative of the difficulty if not impossibility of describing the lesser skin lesions of leprosy so that they can be distinguished from other conditions is the fact that some of the lesions, as they are described above, might very well have been manifestations of that disease.

DISCUSSION

The primary object of this study being to determine the essential pathology of the lesser forms of the nonlepromatous lesions of leprosy, we will discuss first the group classed as simple, active.

Active simple leprides.—Though we endeavored to include, from among the cases from which our series was selected, all those that had lesions of this kind, there are only eleven of them (Nos. 25 to 35), and none of them was very recent. Three of the four varieties into which this group is divided are fairly common and typical; these are the flat ones with marginal erythema, and the raised ones with and without erythema. Of the nine cases of these varieties, all were histologically tuberculoid in some degree. For the most part the lesion-foci (the "tuberculoids") were small and deeply located, so that they could cause no surface irregularity. In five cases it was only slight, meaning that a few tuberculoids were found in all sections. In a sixth one it was very slight, not all of the sections of the serially-cut specimen containing tuberculoids. On the other hand in three cases the pathological changes were more marked than would be expected from the outward appearance.

Decidedly in contrast, neither specimen from the two cases with the less typical flat, diffusely erythematous macules revealed any tuberculoid changes in the skin itself. However, in the subcutaneous tissue of the latter specimen, included quite accidentally, was a nice, comparatively large focus of that nature, so even these lesions were not entirely free from that condition. One of these cases later became bacteriologically positive and was hospitalized; the other, perhaps significantly, has moved away. There is reason to believe that lesions of this kind are especially liable to untoward developments.

Quiescent simple leprides.—Further evidence as to the condition in the active macules was expected from those that appeared to have become quiescent (Cases 17 to 24). The specimens from five of the eight so classified showed tuberculoid changes; in all but one it was slight to very slight, and inactive or residual in appearance. In the other one (Case 24) there was more of it, and it did not have the same appearance of complete inactivity; even clinically the lesion might have been classed as a nonerythematous, indolently active one had

it not failed to increase in size during the two years it had been under observation at the clinic. We cannot discuss here the question of liability to reactivation of such lesions. With regard to the three nontuberculoid lesions, it seems reasonable to assume, not that they had never been of that nature, but rather that they had recovered more completely than the others and were actually residual, in spite of their persistent hypochromia. The lesion of Case 52 further indicates that recovery of color does not necessarily run parallel to resolution of the original pathological condition.

Residual leprides.—As was expected, the group of lesions classed as residual (Cases 4 to 16) showed relatively little pathology. Ten of the thirteen specimens proved negative for the tuberculoid condition, in spite of serial sectioning, though one had a single "subtuberculoid" focus. On the other hand, the other three had a little of it, residual in appearance, which shows that sometimes a lesion may go far toward recovery in appearance without complete histological recovery. In one of these specimens only one tuberculoid was found (interestingly enough, inside a hair follicle); in another there were four or five; in the third there were several, though that lesion had remained apparently residual for four years.

The purpose of examining so many lesions of this kind was mainly to ascertain the condition in which the tissue is left after the active process has been overcome. Seven lesions that showed no "atrophy" or "scarring" were examined, and six with such changes. In the regions in which the tuberculoid process is ordinarily found, some connective-tissue increase was the rule, even when not evident clinically. The outward changes called "atrophy" seem due less to fibrosis than to diminution or loss of the delicate subepidermal network of elastic-tissue, with consequent relaxation and thinning of the epidermis. In only one case were the coarser fibers of the reticular layer perceptibly affected; this, together with a peculiar fibrillation of the coarse connective tissue, had led to conspicuous, soft bulging of the area. How these changes had been brought about was not evident. In one of the atrophic lesions the most conspicuous feature was patency of the hair follicles, apparently resulting from an unusual perifollicular concentration of the lesion-process. Without detailed study of cases before and after atrophy appears, we can only suggest that that condition is indicative of a relatively severe original process.

Anesthetic nonmacular areas.—The development of a macule on an anesthetic area is not uncommon, but we know of no information concerning the pathological condition preceding the appearance

of surface changes. One of our three specimens (Case 3) was from such an area that showed only a vague departure from the normal and that became macular within a few months. Histologically there was a little perivascular infiltration, and three or four collections of mononuclear cells (subtuberculoid?) were found. Another specimen (Case 1), from an anesthetic area of five years duration, was practically negative except for some connective tissue increase in the small, superficial nerve branches, which made identification of them difficult. Whatever the process was that had affected the nerves, it had undoubtedly been overcome long since. Unexpectedly, the specimen (Case 2) from an area that had long remained anesthetic after the complete disappearance of a macule showed essentially no more abnormality.

"Elevation," "activity" and "infiltration."—At this point it may be remarked that slight elevation, which may be difficult to detect, may or may not denote the presence of actual or potential activity. It may be due to cellular infiltration, diffuse or focal, with, perhaps, increase in size or number of blood and lymph channels. On the other hand a lesion may be quiescent, in the sense of the word as it is used here, or even residual, even though it is in some part slightly raised. That condition may be due entirely to connective-tissue and other changes consequent on a process that has been completely overcome. In the absence of distinct erythema it is sometimes difficult to decide whether slight elevation is due to cellular infiltration or not, and mistakes may be expected by even the most experienced workers in distinguishing between quiescent lesions and indolently active ones on the one hand and residual ones on the other.

In this connection it should be said that the histological distinction between lesion-foci that appear "active" and "residual," a distinction frequently made in this article, cannot be discussed here. It is also desired to point out that the use, in the first article of this series, of the term "infiltration" in a clinical as well as a pathological sense has proved to be confusing. In the present article, at least, it will as a rule be applied only to the histological changes.

Papulate minor tuberculoid leprides.—To turn now to the papulate lesions (Cases 36 to 44), which are the least form of those that can be recognized definitely and readily as tuberculoid, is not as abrupt as it may seem, because of the frequently quiescent or residual nature of the macular base in which the populations develop. In this and other respects these lesions as a whole differ widely from the others that are frankly tuberculoid, and they are not generally included in that group. It would seem that in many places they are not as common

as in Cebu; that they are frequent there is indicated by the fact that no less than seven of our fifty-two cases had only such lesions, and they were also present in several others.

A relationship of at least the variety here called "spotty multipapulate" to the ordinary diffuse minor tuberculoid lesion is shown by Case 44, in one of the lesions of which active papulate spots merged to the point of forming a typical pebbled tuberculoid segment. At the same time a relationship of the active paucipapulate variety to the so-called "lichenoid" condition is indicated by Cases 36 and 37. In the three cases mentioned the condition was definitely active, but in most of the others the population was secondary, associated with retrogression. All of the lesions dealt with, including the active ones referred to, had previously been of more ordinary, simple macular nature; but when examined those areas, aside from the papules and hazy papulated spot, were either quiescent, residual or had completely cleared up. Furthermore, many of the hazy spots themselves showed only minute scars that indicated where papules had once been. Histologically the active lesions showed an active tuberculoid condition; the more retrogressed ones showed at most only traces of it, and some of the specimens were free from it.

The papules arise, as a rule, at the periphery of a macule, though sometimes a marginal zone of some width may be papulate. The multipapulate lesion with diffuse population (Case 40), in which the papules were apparently follicular, was really of another class, probably related to the follicular atrophic lesion mentioned above. Altogether, the papulate condition suggests that, here and there in parts of lesions undergoing resolution, a few or many discrete foci undergo some change that leads to a relatively high degree of tissue reaction to the presence of remnants of the infecting agent. On the whole this occurrence seems to be of good prognostic significance.

Diffuse minor tuberculoid lesions.—Only four cases (Nos. 45 to 48) presented lesions of this more ordinarily recognized kind. A year after the biopsies were made two other lesions, previously simple though active, had advanced to become minor tuberculoid, but the six together do not represent the class very well, at least photographically.² Under the circumstances little can be said here about the clinical features of this condition, but it may be noted that in our few cases the lesions seem as a rule to have developed slowly from more

²Better examples of minor tuberculoid lesions are pictured in the article by one of us (H.W.W.) on tuberculoid leprosy in South Africa (3), and others will appear in other articles of this series.

simple ones. That the variations in clinical appearance of the lesions is determined by the variations in degree and location of the tuberculoid changes is well illustrated by these cases. In one specimen the abnormality was of moderate degree, mostly deep. In two cases it was fairly marked, but in one of these it was confined largely to the upper half of the dermis and in the other the tuberculoid changes were distributed in all levels. In the fourth case (Case 48), the abnormality was marked, but mostly superficial, this being the only one to illustrate the predominantly (not exclusively) superficial location, or at least concentration, of the pathology in this variety of the leprides. This lesion, also, was by far the most active of the lot, and the sections contained numerous bacilli, as had the clinical smears. In its microscopic picture it cannot be said to differ materially from the major form or phase of the tuberculoid condition, except perhaps for its predominantly superficial location. The recorded description of the lesions does not permit classifying it as major, but from the later developments it may have been an atypical case of that kind.

Major tuberculoid lesions.—Only two actual cases of this sort—the only kind that is generally recognized as tuberculoid—were included in the original series, though another had a healed lesion that had been of that nature. However, the two, together with a third one recently added (Case 49), are fairly illustrative. So much attention has been given this condition of late that there is no need to discuss it in detail. Our pathological material adds nothing special to existing information; tuberculoid changes of the usual marked degrees were found. Case 52 is interesting, in a way, because we know of no report of examination of a healed lesion of this kind. The absence of any trace of tuberculoid change—which must unquestionably have been present when the condition was active—indicates the completeness, and also the relative rapidity, with which the condition may clear up, and also that the persistence of marked hypochromia is not a certain indication of persistence of the essential lesion.

The most interesting feature of these cases is that, in all four instances, it was claimed that the condition had developed abruptly and was of short duration (from one to four months) when the patients appeared at the clinic. In view of the massiveness of the lesions the claims regarding duration might seem unreasonable, but their uniformity is impressive. The abrupt onset is undoubtedly significant; the development, apparently, was always of "reaction" nature, far different from the ordinarily slow, uneventful progress of other forms of leprides. This point deserves particular attention; it should

be ascertained whether or not this form of leprosy ever develops by simple nonreactional progression from the minor tuberculoid stage. Another question of interest is that of the previous existence of changes of simpler nature at the sites of major lesions. In Case 50 the principal lesion developed on an area that, it was claimed, had been anesthetic for a long time, but not macular.

Frequency of frank tuberculoid cases.—In discussions of regional variations of leprosy it has been stated that the tuberculoid form is not very common in the Philippines (4). This really refers to the major form, but so far as these observations show it also applies to the diffuse minor one. Our series is not suitable for statistical analysis, because it is so small and because the cases were selected, but the relatively small numbers of frank tuberculoid cases that were included is significant because patients with such lesions are especially apt to be discovered or to appear for diagnosis, and also to continue under treatment, which would tend to load the series with such cases.

Cases of the major type in the Philippines are rather frequently found bacteriologically positive and consequently are hospitalized, as was Case 49. Lara, at the Culion Leper Colony (2) has recently collected a number of such cases that had been sent there over a period of years; we ourselves pictured one of them, then not recognized for what it was, in a booklet prepared ten years ago (6). Recently, in connection with another report in preparation, we surveyed the cases of this kind at the Cebu regional leprosarium and found that they constituted roughly one percent of the inmates. We are not prepared to cite actual statistics, but it is probable that much less than one percent of all new cases of leprosy discovered in the Cebu region are major tuberculoid. This fact, certainly, is in striking contrast to experience at the diagnostic clinic at Calcutta, where more than 25 percent of all new cases seen are of this type, and even that at the treatment clinic at Purulia, where it apparently comprises at least 10 percent of the cases (4).

Distribution of cases.—Another point of some interest is that the relative frequency of certain varieties of the lesions in the Cordova and Dispensary groups differed more than can be ascribed to the accidents of sampling. With regard to the major tuberculoid type it can only be said that, though the Cordova cases from which our group was selected comprised all that could be found in a complete, intensive survey of the town, there was no example of this form among them. On the other hand all of our four diffuse minor tuberculoid

cases were from Cordova, and two others from there advanced toward or to that form in another year; furthermore, the three active paucipapulate cases were from there. This brings up the question of influence of treatment, of which the Cordova cases had had very little if any. It seems significant that there was no example of either of these minor varieties among the Dispensary cases. On the other hand, the four circinate ("spotty") multipapulate cases were all of the Dispensary group. Also of interest is the fact that six of the seven cases with nonatrophic residual lesions were from the Dispensary, while to the contrary five of the six with atrophy were from Cordova, which at least suggests that treatment tends to limit the damage caused by a lesion before it heals.

Bacteriological findings.—It may be noted that while the lesions from both cases that were found positive clinically by the smear method (Cases 48 and 49) were also positive in sections, some of the specimens from clinically negative lesions were positive as well. A very few or several bacilli were found in those from two other cases (Nos. 21 and 30), and probably more would have proved positive had the search been more intensive. In Case 10, the first section examined was reported positive, but on repeating the examination with further sections we found only a few nonacid-fast rods, the significance of which is uncertain to say the least.

Universality of the tuberculoid condition.—Taken together, the findings here reported support very strongly the view that tuberculoid changes are characteristic of all varieties of leprides, or at least all typical ones. The only exceptions in our series were the atypical, flat, diffusely erythematous lesions. The subtuberculoid condition found in the nonmacular anesthetic area of Case 2 that became macular later suggests that tuberculoid changes may be present as soon as definite macules appear. It is difficult to reconcile our findings, and those of a few other recent workers, with the prevalent opinion that the lesser leprides are not tuberculoid, and that those which are recognized to be of tuberculoid nature (major tuberculoid) are in a class apart, "tuberculoid leprosy." There is, of course, a great difference between the conditions found in the extremes of this large group—the "simple" and the "major tuberculoid" lesions—but we submit that if enough specimens from a sufficient variety of active leprides are examined all possible variations and gradations will be seen, and it will be recognized that the pathological basis of these lesions affords no grounds for setting any of them apart as a separate form or type of the disease.

SUMMARY AND CONCLUSIONS

1. To determine (a) whether or not active leprides that do not exhibit clear outward signs of being tuberculoid are of that nature, (b) the pathological relationships of the different varieties of this large group of lesions, and (c) the relation of their pathology to clinical activity, histological examinations have been made of biopsy specimens from 52 cases of leprosy not of the cutaneous type (i.e., incipient, ordinary neural, etc.), selected from among newly-discovered patients in Cordova, Cebu (1933), and from those on the list of the Cebu Skin Dispensary (1934). Clinically the lesions examined varied from the slightest possible (nonmacular anesthetic patches) and the most completely healed (faint residual and atrophic macules) to the active major tuberculoid leprides.

2. Specimens from nine active "simple" leprides of familiar kinds all showed tuberculoid changes, usually of slight degree, as the principal pathological feature. Those from two atypical (diffusely erythematous) ones showed none in the skin proper, though one had a little in the subcutis. It is concluded that active leprides of the ordinary simpler kinds are always tuberculoid in some degree, at least in Filipino subjects. There is reason to believe that the atypical, erythematous lesions are of comparatively unfavorable prognosis.

3. "Quiescent" lesions, retrogressed from active ones, afford further evidence on the subject. Of eight that were examined, five showed tuberculoid changes, mostly slight or very slight. The three that were found nontuberculoid were evidently healed.

4. Of thirteen lesions considered "residual," with or without "atrophic" changes, only three showed any tuberculoid foci; in them the condition was very slight and apparently residual, but persistent. The changes found in the nontuberculoid lesions of this class are detailed briefly.

5. Two specimens from nonmacular anesthetic patches were practically negative. Infiltrative changes, not tuberculoid but perhaps pretuberculoid, were found in the third one, taken from a lesion that became macular shortly afterward.

6. The papulate minor tuberculoid leprides, the least form of those that exhibit unquestionable outward evidence of their structure, are as a class retrogressive. Typically the isolated papulations, whether few or many (paucipapulate or multipapulate lesions) occur secondarily in the peripheral zones of quiescent or healed macules, representing very superficially located tuberculoid foci. An excep-

tional generalized multipapulate lesion was due to special involvement of the hair follicles. In some specimens, especially from the spotty multipapulate variety, no tuberculoid changes were found; these lesions were evidently residual. This group shows relationships to the more familiar diffuse minor tuberculoid condition, and also to the so-called lichenoid lesions.

7. The four more ordinary, diffuse minor tuberculoid lesions available did not depart from the usual except in one active case (bacteriologically positive and later hospitalized) in which the pathology approached that of the major-type lesions in kind and degree. The question is raised whether such a case, left untreated, may progress to the typical marked major form.

8. Three major tuberculoid cases are presented; also one healed one, the specimen from which showed no remnant of the tuberculoid condition. The active lesions presented no unusual histological features. Clinically, particular interest attaches to the uniform histories of abrupt onset of "reaction" type, which is of interest in connection with the question noted above.

9. A few of the cases seen (including the generalized multipapulate one mentioned and a residual one with gaping follicles) indicate that occasionally the pathological process affects the hair follicles especially. In connection with this, mention is made of "follicular hypertrophy" often seen associated with leprosy lesions, and also independently of them and in nonlepers.

10. The small numbers of cases with the more familiar forms of the tuberculoid leprides among those from which our series was selected indicates their relative infrequency in the Philippines.

11. The differences of distribution, between the untreated Cordova group and the treated Dispensary group, of certain forms of lesions studied suggests a retarding influence of antileprosy medication upon the development of the leprides.

12. The findings as a whole indicate strongly the constancy of tuberculoid changes in all typical active leprides of whatever clinical variety. They emphasize the great variations in the degree, and to some extent in the histological details, of that condition, but also the lack of any clear pathological distinction of any one variety of these lesions from others. The common belief that the simpler leprides are not tuberculoid may be due to failure in the past to recognize the lesser degrees of the tuberculoid picture.

ACKNOWLEDGMENTS

In this study we have used freely the previous clinical records of the Cebu Dispensary cases, many of which were made by Dr. F. C. Plantilla, physician in charge of treatment at the clinic. Most of the original notes on the Cordova cases were made by him or Dr. Ricardo Guinto, assistant epidemiologist, Leonard Wood Memorial, who was engaged in the leprosy survey of that municipality. Dr. Plantilla and Dr. José Tolentino, resident physician at the Eversley Childs Treatment Station, did all of the surgical work of procuring the specimens.

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DESCRIPTION OF PLATES

PLATE I

FIG. 1. Superficial atrophy (crumpled surface effect) following moderate degree minor tuberculoid involvement. Thigh, Case 47. (In upper part of the picture is a somewhat raised minor tuberculoid marginal zone, not conspicuous but still active.)

FIG. 2. Superficial and deep atrophy, with bulging (conspicuous in the lower left part of the affected area) due to degenerative changes in the reticular layer. Arm, Case 11.

FIG. 3. Small residual macule, with only slight hypopigmentation. (Two scratches, above and below, from bacteriological examination.) Histology: very slight residual tuberculoid. Hip, Case 4.

FIG. 4. Residual macule, with indistinct suggestion of retrogressed "spotty" condition. Histology: very slight subtuberculoid. Loin, Case 6.

FIG. 5. Quiescent macule, rather markedly hypopigmented, sharply outlined. Edge irregular, finely "streaming." At three or four places are apparent indications of previous papulations. Histology: slight subtuberculoid. Buttock, Case 17.

FIG. 6. Quiescent (or residual?) macule, only moderately hypopigmented but rather clearly demarked. Extremely irregular, discontinuous (finely "patchy" or coarsely "spotty"); center healed. Histology: practically negative for infiltrative changes. Arm, Case 18.

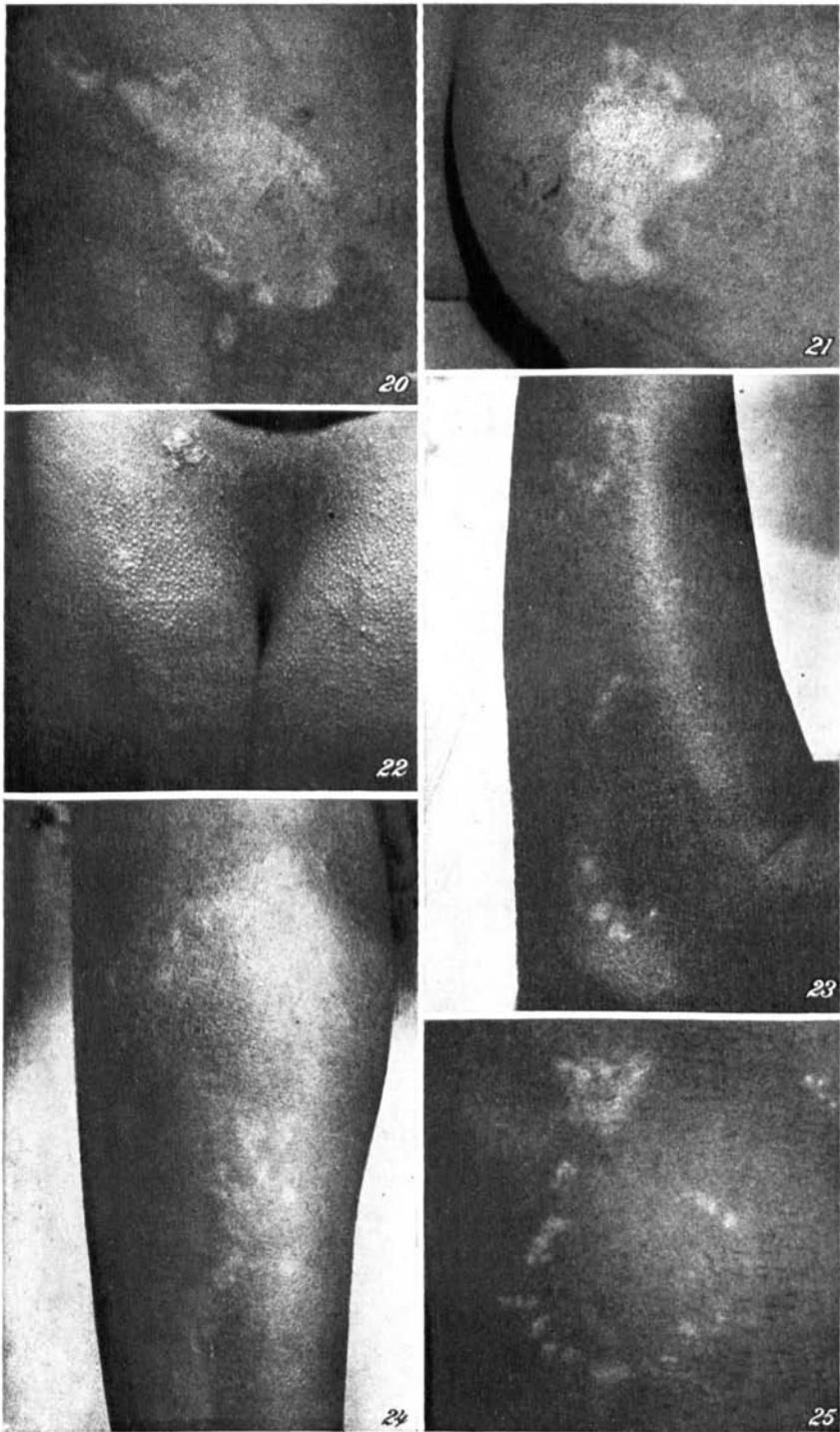


PLATE 4

PLATE 5

FIG. 26. An active spotty circinate lesion, many spots containing full, small papules, though others are retrogressive. Spots fused in several parts, and in a few places even the papulations tend to become aggregated. Extraperipheral extension at several points. *Histology:* tuberculoid, moderate degree, active. Buttock, Case 44. (See also Fig. 27.)

FIG. 27. Spotty and segmental circinate lesions on face of Case 44 (see also Fig. 26). Some spotting inside the marginal zone. The lower portion of the margin is solid, moderately and irregularly elevated, with "pebbled" surface—actually a frank minor tuberculoid condition. (Not biopsied.)

FIG. 28. An intermediate or borderline lesion, marginally multipapulate with some deeper thickening, approaching the ordinary pebbled minor tuberculoid condition. Biopsied a year before the photograph was taken, when the lesion appeared active but not definitely raised; histologically slight tuberculoid. Thigh, Case 25.

FIG. 29. Small, rather recent lesions approaching the minor tuberculoid, only slightly raised and surface pebbled only in part, still hardly more than multipapulate. Buttock, Case 45.

FIG. 30. Small, indolently progressive minor tuberculoid lesion, around scar of biopsy performed a year previously. Moderately elevated, surface coarsely irregular rather than pebbled (i.e., condition not the most superficial). Lesion when biopsied was simple; histologically slight tuberculoid. Back, Case 34.

FIG. 31. A retrogressive minor tuberculoid lesion, marginal condition largely subsided (lesion no longer spreading), but with unusual prominent foci, actually small nodulations, inside the margin. When biopsied a year previously, fairly marked tuberculoid. Thigh, Case 46.

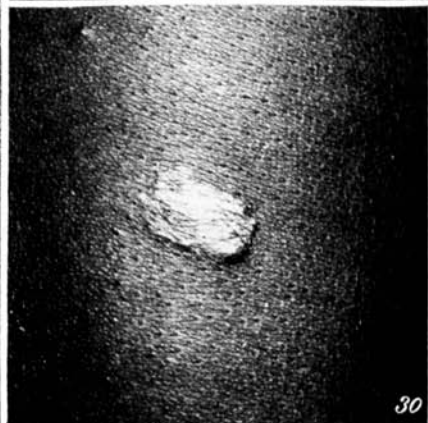
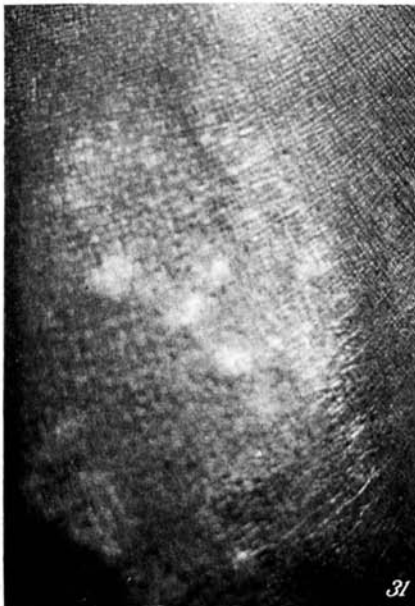
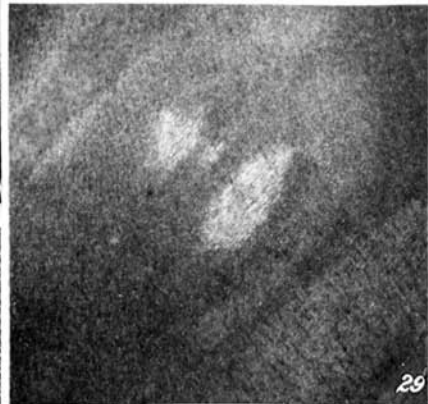
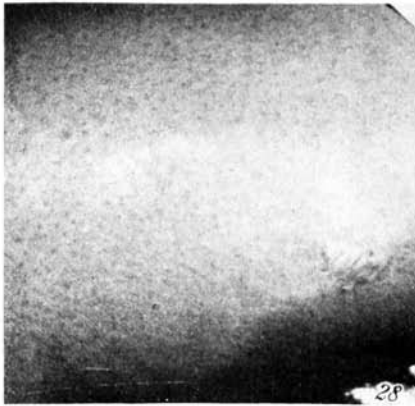
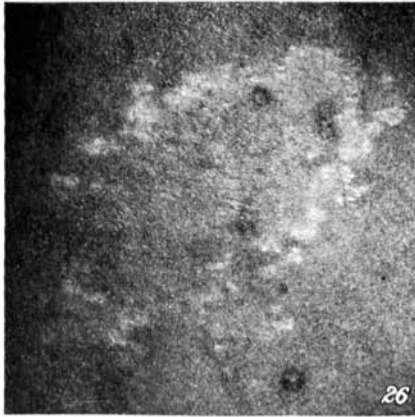


PLATE 5

PLATE 6

FIG. 32. Marked major tuberculoid lesions, recent and in reaction stage. Two large scaling areas (bacteriologically positive, bacilli few), and several small papular ones, with others of intermediate grade. Histology: very marked tuberculoid. Arm, Case 49.

FIG. 33. A rather small, discrete, major tuberculoid lesion of moderate degree, undergoing retrogression—outline more sloping and less sharp than usual, and central resolution evident. Surface more irregular (coarsely pebbled) than usual, more as in some marked minor tuberculoid lesions. Histology: marked tuberculoid. Knee, Case 50. (See also Fig. 34.)

FIG. 34. An extensive lesion on arm of Case 50 (see Fig. 33). Edge not well-defined, infiltration only moderate, surface very irregular. (On the basis of this lesion alone the case might have been classified as diffuse minor rather than major tuberculoid.)

FIG. 35. Typical but definitely retrogressive major tuberculoid lesion involving much of right side of face, with some paralysis. Limit of lesion well marked low on cheek, fairly distinct on lip and temple, less so elsewhere on face and above eyebrows. Histology: tuberculoid fairly marked, apparently retrogressive. Case 51.

FIG. 36. Residual hyperpigmentation over site of previous major tuberculoid lesion, back of neck. No other change of note, clinically or microscopically, except for the numerous areas of tinea flava (extensive on right shoulder) which in photograph are hardly distinguishable from the other lesion. Histology: completely healed. Case 52.

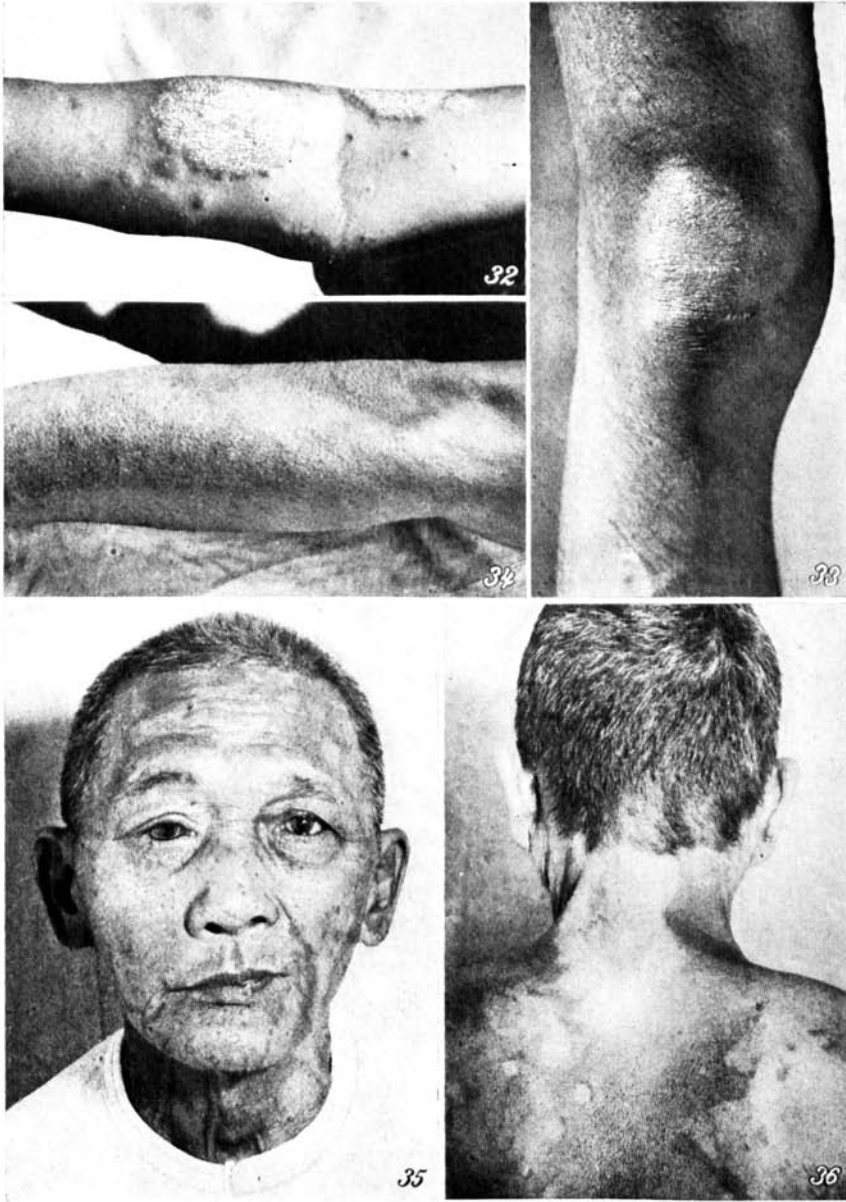


PLATE 6