TUBERCULOID CHANGES IN LEPROSY

I. THE PATHOLOGY OF TUBERCULOID LEPROSY IN SOUTH AFRICA

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INTRODUCTION

STATUS OF TUBERCULOID LEPROSY

Until recently tuberculoid leprosy was given scant attention generally, though the last International Leprosy Conference (Strasbourg, 1923) especially called attention to it (9). It certainly was not recognized as a problem by the Memorial Conference held in Manila in 1931 (17), though it complicates the matter of classification of leprosy. However, during that year the writer was brought to a realization of its importance by things seen in Japan, India, and especially in the Union of South Africa. A preliminary report of these observations has been made (27); the present paper is based on further study of the material.

By coincidence, during the same year Manalang (16) in Manila, reported early tuberculoid lesions in children of Culion inmates, and also found changes in adult cases that supplement certain findings of Wade and Pineda (30), who had reported this condition in cases of cutaneous type that had improved under treatment. It is clear that the Calcutta workers meet the condition commonly (6, 7, 8), though heretofore they have not recognized it as at all special. Certain South American and European workers have recently written on tuberculoid changes, especially Mottat (18) and Tisseuil (23). On the whole there is ample evidence that much more interest now centers in this type of change than heretofore.

THE TERM "TUBERCULOID"

Objections having been heard to the application of the term "tuberculoid" to any form or feature of leprosy, it may be pointed out that it is not new. Jadassohn first used it definitely in 1898 (10), though others had previously described the elements of such changes in leprosy. In the quarter century between that and the Strasbourg conference there were a number of other reports of this type of condition by Klingmüller (12), Kedrowsky (11), Unna (25), and others. At the Strasbourg conference Darier (3) and Poutrier and Boez (21) presented reports of "tuberculoid leprosy", and the conference resolved that it should be studied further. Since then the matter has been written on by several authors, among them Tebbutt and Molesworth (22) and Wade and Pineda from extra-European regions. With all this the terms are certainly well established.

As for their meaning, the possibility of confusion with infection by tuberculosis itself is not of importance, though it has occurred,

nor is possible confusion with "tubercular" leprosy of concern since this term is obsolete. It is to be realized, however, that in its primary significance "tuberculoid" refers to a histological picture rather than a clinical one; that it is descriptive and not diagnostic; and that the condition is not peculiar to leprosy. So far is it from being specific to any disease that some writers call it the "lipoid reaction". It can be produced experimentally by the injection of dead tubercle and other acid-fast bacilli, and even by lipins obtained from them and from other sources. Similar though perhaps not identical lesions occur in various infections, especially in tuberculosis and in syphilis where the condition is seen usually in lesions of the skin.[1] Darier (2, 3) has pointed out that these changes of leprosy are analogous to the tuberculoids of tuberculosis and of syphilis.

The term "tuberculoid leprosy" one understands to imply a variety (not type) of leprosy that can be distinguished clinically. Tuberculoid *lesions* of leprosy may occur in cases of the cutaneous type, probably signifying special resistance. Tuberculoid *leprosy* signifies cases with skin lesions of this variety only (plus, perhaps, simple flat ones); and so far as is known such cases are always of the neural type.

CLINICAL FEATURES OF TUBERCULOID LEPROSY

It cannot be said yet whether or not cases of tuberculoid leprosy always can be recognized on clinical grounds alone—including in this category the simple microscopic examination for bacilli, without which clinical work in leprosy cannot be done properly—but there is a certain variety that can be recognized. Briefly, the cases are of neural type but with macules with marginal zones so infiltrated that they seem to be lepromatous (i. e., of cutaneous type), though normally they are bacteriologically negative by standard methods of examination, commonly show more sensory changes than do the lepromata, and typically undergo central resolution in a way and to a degree not usual in lepromata. This lesion is a variety of the group to which some leprologists apply the useful term "lepride", to distinguish them from the lepromata.

HISTOLOGICAL FEATURES OF TUBERCULOID LESIONS

Like the tubercle of tuberculosis the tuberculoid lepride is a granuloma, and its elements are familiar from that condition. (1)

[1] A fairly recent paper [MICHELSON, H. E. *Arch. Derm. and Syph.* 19 (1929) 66] describes "tuberculoid reactions" in the inguinal lymph nodes in early syphilis.

The one real essential feature consists of distinct *epithelioid foci*, which are often extremely small, containing only a very few epithelioid cells, though occasionally they may be of considerable size, especially in lesions in the state of lepra reaction. (2) Ordinarily there is more or less chronic inflammatory *round-cell infiltration*, often slight and sometimes lacking but at times forming the greater part of the granuloma. (3) *Giant cells* of the Langhans type occur frequently and are often conspicuous, but they are not an essential element.[2] (4) *Necrosis* is far from being a part of the picture. Jadassohn found some, and in one of the specimens described herein there is a little, but ordinarily there is none. On the other hand, it would appear from a recent report by Muir and Chatterji (20), and especially from descriptions of nerve abscesses by Muir (19) and Lowe (14), that it is frequently encountered in India (29). This is evidently another regional peculiarity of the disease.

OBSERVATIONS MADE

When the Memorial Conference classification was adopted early in 1931 Mitsuda and his colleagues in Japan objected to it because it does not provide especially for a variety of cases which they call "maculo-anesthetic". These have progressive macules with conspicuously infiltrated margins, because of which the Japanese workers distinguish the cases from the ordinary "nervous", though they really consider them a division of the neural type because of the general clinical picture, including the course and prognosis (4). The only difficulty with the Conference classification is that histologically these lesions are granulomatous in nature, thus coming within the letter if not the spirit of the Memorial Conference's definition of "leprotic" and therefore of "leproma"—changes which were accepted as characteristic of the cutaneous type of leprosy. However, they differ essentially from the real lepromata, being histologically tuberculoid and having clinically negative bacteriological and positive neuro-

[2] If, as is held by Sabin and Smithburn [*Science* 77 (1933) 496], giant cells are produced only in reaction to the waxlike substances that are responsible for acid-fastness, such cells should be relatively scarce in lesions like these, which contain very few or no demonstrable acid-fast bacilli, and common in the ordinary lepromata where there are vast numbers of the bacilli. Actually the reverse is the case. Their presence in syphilitic tuberculoids seems not to be explained on that ground.

logical findings, characteristic of the lesions of neural rather than of cutaneous leprosy.

In India there was opportunity to see sections of lesions that are there called "erythematous macules", and these were found to be of tuberculoid nature. How prevalent in India are clinically distinguishable lesions of this type is not certain, but recently Hayashi (5) has expressed the opinion that there is much more tuberculoid leprosy there than in the Philippines or Japan, and Santra agrees that it is common.[3]

In South Africa the same question about the Conference classsification was met as in Japan. Some of the cases seen at the Pretoria Leprosy institution presented distinctive lesions for which a diagnosis of tuberculoid was ventured, an opinion strengthened by information that a biopsy specimen from one such case had been diagnosed "tuberculosis" by a local laboratory. After numerous cases of similar type had been seen at the Amatakulu institution, in Natal, preparations were made to collect specimens and photographs at the next institution to be visited, at Emjanyana, in the Transkei.

MATERIAL STUDIED

At the Emjanyana Leprosy institution forty cases that were taken to be tuberculoid were given special attention[4], and another was examined later at East London. It was attempted to select cases representative of the varieties and degrees of the condition. Brief notes were made on all; bacteriological smears were made by the scraped-incision method from all but one, a young child; photographs of 35 were taken at the time or were received later; biopsy specimens of skin were obtained from 16 (including the East London case) and from an ordinary leproma for a control. The smears, one to three per patient, were examined for acid-fast bacilli. The biopsy specimens were taken from the advancing edges of the macules, usually including some of the uninvolved skin. Paraffin sections were obtained, first at the public health laboratory in Cape Town, later in New York, the final large lot (serial sections) in our own laboratory.

HISTOLOGICAL METHODS

The writer follows Mallory (15) in the choice of Zenker's fluid as the best fixative for all-around use because of the excellence of the resulting cell-picture, the satisfactory preservation of tissues for long periods, and their availability for certain special stains. Neither formalin (in which only the East London

[3] Dr. I. Santra, personal communication. Since this was written an article by Muir has appeared [*Leprosy in India* 5 (1933) 204] in which he recognizes the tuberculoid condition, though referring to the cases as of a "macular type".

[4] Special thanks are due Dr. R. A. Davison, Medical Officer, for demonstrating these cases, providing some of the clinical data, removing the biopsy specimens, and active coöperation in other ways.

specimen was fixed) nor alcohol is as satisfactory, though the latter is probably better for demonstrating bacilli. Sections are made by the paraffin method.

In addition to the ordinary hematoxylin and eosin stain, which is routine, Mallory's phosphotungstic-acid hematoxylin and aniline blue connective-tissue stains are used regularly for all special work. After the former the cellular areas and certain other elements, including necrotic material and fibrin, are of a rich purplish-blue color; epithelioid foci and giant cells are especially conspicuous. After the aniline-blue stain the granulomatous areas are red, in strong contrast with the bright clear blue of the connective tissue. This stain is decidedly useful in demonstrating traces of a nerve branch in a tuberculoid focus, the peculiarly delicate connective tissue showing up well when it cannot be recognized positively in ordinary sections. Voerhoff's stain for elastic tissue has proved especially useful in distinguishing between uninvaded and recovered skin in tuberculoid cases, for the latter may show no abnormality other than loss of elastic fibers in the papillary layer. Sections were stained for acid-fast bacilli by the writer's method.

REPORTS OF CASES

This is not a clinical report. It would be manifestly impossible to set up an accurately detailed and comprehensive description of tuberculoid leprosy as it occurs in South Africa on the basis of the limited data available. However, to orient the pathology seen in the specimens here dealt with, the principal features of each case so examined are noted briefly, and a general summary is then made which includes observations on the cases not biopsied.

Fourteen cases are here recorded, including the control cutaneous (lepromatous) one. The specimens of the first six cases show increasing degrees of the tuberculoid change, all predominantly in the superficial (papillary and sub-papillary) layers. In Cases 5 and 6 there is an unusual focal activity. In the next two cases the changes are predominantly in the deeper (reticular) portion of the dermis. In Cases 9 and 10 the specimens were from the face, in which the zonation of the tissue is not distinct and, therefore, the tuberculoid foci tend to be more diffusely distributed. Cases 11 and 12 exemplify lesions in the way of retrogression. In Case 13 the specimen is atypical, the cells tending to resemble those in the lesions of Case 14, which is the cutaneous control, the lepromata of which are of what one may call the "fibroblast" type in which the usual large lepra cell is in abeyance.

All cases of this group except the control proved bacteriologically negative, in both smears and sections. In all of them definite epithelioid foci were found. These are not spoken of as "tubercles", a designation which, however proper, would certainly invite confusion with tuberculosis; it seems preferable to follow

the French writers and employ "tuberculoid" as an adjectival noun. A "pretuberculoid" lesion is one so slight that it would not be diagnosed as tuberculoid at all if there were no unmistakeable lesions in the specimen, but the term may have to be applied also to a tangential section of a tuberculoid, as in Fig. 43. Reference to perivascular infiltration or accumulation signifies "round-cells". In the clinical description of the lesions "margin" is used to denote the entire infiltrated zone of a macule when there is central resolution; "border" designates the outer portion of this margin when it is made peculiar by congestion or otherwise; "edge" denotes the outer limit or actual periphery of the lesion. Referring to varieties of lesions, the terms "linear", "discontinuous", and "segmental" are explained later.

CASE 1, No. 4777.—Biopsy of a superficial, "segmental" lesion on shoulder (Fig. 20), said to be recurrent. Sections show moderate tuberculoid changes superficially, none in the deeper layers.

Clinically, there were numerous lesions, a recrudescence of one year's duration that occurred after the patient had been a year away from the institution after 14 years in it. On both the shoulders were the segmental lesions common to that location, "discontinuous", their surfaces irregular and papulate. Outlining the pelvis posteriorly was a discontinuous saddle zone (Fig. 21). The arms were irregularly involved, with moderate keloidal scarring on one side.

Sections show both ends non-granulamatous. In the middle third is a superficial, interrupted zone of infiltration with a few small tuberculoids. A very few small giant cells are found (Fig. 35). The lesion is confined to the papillary layer and is mostly perivascular, the vessels being enlarged. It begins abruptly with a tuberculoid, with practically no transition (Fig. 28). Serial sections show this tuberculoid to be solitary, though others in the specimen (Figs. 34 to 37) are not entirely so. The deeper layers have only a little infiltration here and there. The epidermis shows depigmentation over the lesions, and over the larger foci some flattening, thinning, and even loosening of the basal layer and invasion by a few mononuclear cells.

In ordinary sections the two ends show no real difference, having no definite perivascular infiltration, recognizable abnormality of the epithelium, detectable difference in the vessels, or distinction as regards the connective tissue, though in one end there is a little less pigment than in the other. However, in that end the fine elastic tissue fibers under the epidermis are decidedly fewer, especially in the papillae.

Comment.—The lesion begins abruptly, without transition; the epithelioid foci are small, most of them practically minimal; and there is almost no abnormality in the deeper layers. The epidermis shows a variety of changes typical of the mild-degree lesion. It could not be said with certainty which of the two ends was from inside the infiltrated zone were it not for the loss of elastic fibers at one end, which indicates how complete recovery may be. Obviously the

condition is progressing laterally through the papillary layer, and it neither arises from the deeper layers nor extends into it.

CASE 2, No. 4748.—Biopsy of an exceptionally superficial, finely papillate macule on the back, irregular in width and discontinuous (Fig. 6). Sections show fairly marked tuberculoid formation and infiltration, almost entirely superficial; the uninvaded tissue shows transition.

Clinically, of the several other lesions on the back one, evidently early, was merely an irregular patch of close-set superficial papules (Fig. 5). In contrast was a discontinuous, narrow ring ("linear" lesion), unusual in this location. Over the buttocks was an extensive, irregular gyrate area with only moderate marginal infiltration.

Sections include clinically uninvolved tissue in which there is (a) for a distance nothing but slight perivascular accumulation in the superficial layer, then (b) for a further distance more marked infiltration, a little of it extending slightly into the reticular layer. Beyond this is the tuberculoid lesion, where the infiltration of the papillary layer is both perivascular and diffuse and contains a few epithelioid foci. Serial sections show that the two largest of these determined discrete papules. A few giant cells are in them, some rather large. Figs. 38 to 43, inclusive, show serially a discrete epithelioid focus that produced a small papule. Deeper in the tissue there is practically no change. The epidermis is mostly normal or nearly so; flattening is seen only over the main tuberculoids, where there is also reduction of pigment and a little cellular invasion.

Comment.—The actual lesion here is entirely superficial, apparently active and recent. Extension, obviously, is primarily horizontal, in the papillary layer, though there is a beginning of downward extension. The apparent transition zone that precedes the granuloma shows only perivascular infiltration.

CASE 3, No. 4546.—Biopsy of a rough-grained, broad-zoned, irregular-edged, superficial lesion on the arm (Fig. 13). Sections show slight to moderate tuberculoid changes superficially, with some in the deeper layers. Very little transition in the uninvolved tissue.

Clinically, such areas were extensive on the back (Fig. 9) where they showed much merging, and extended around onto the chest. In these, as in the biopsied one on the arm, central resolution was irregular, in places much delayed, in others incomplete, with isolated papular areas in skin that otherwise seemed recovered.

Sections, for more than half their length, show only negligible perivascular accumulation in the papillary layer, with more at the edge of the lesion. One subpapillary vessel in the series is quite similar to that in Fig. 29, with round-cell infiltration extending outward from an epithelioid focus. Beyond this point to the other end the papillary layer is more or less filled with tuberculoid change, partly in small foci but more in larger ones that have rather few round

cells. The epithelioid cells are less of the usual soft, degenerating appearance than of the firmer type suggestive of fibroblasts, and giant cells are few and entirely inconspicuous. Connective tissue cells are apparently increased, without definite fibrosis. The epithelium shows only hypopigmentation and some mechanical flattening over the lesion-foci. In the reticular layer there is some infiltration around several blood vessels, two hair muscles, and a hair follicle area, with a few small tuberculoids at different levels, one in contact with subcutaneous fat. Both focal and continuous relation to vessels is seen in the serial sections; no relation to nerves is apparent.

Comment.—This lesion has larger epithelioid-cell foci than the preceding, and moderate extension into the depths of the skin along blood vessels. From the appearance of the epithelioid cells it seems probable that the condition is comparatively inactive. It is not known whether the papular areas within the margins are residual or recurrent.

CASE 4, No. 4851.—Biopsy of a small, narrow-zoned, discontinuous lesion, composed of large flattened papules, in the scapular region (Fig. 7). Sections show moderately extensive tuberculoid changes, both superficial and deep.

Clinically, there were conspicuous linear lesions on the face, and ordinary flat macules on the arms. In the only lesion on the back (described above) many of the component units instead of being rounded papules were relatively broad and flat.

Sections show, first, practically normal tissue, then an isolated tuberculoid close to a sweat duct near the surface, then shortly a long granulomatous zone with abundant infiltration completely surrounding several small epithelioid areas and a large striking one, with several large giant cells (Fig. 44). The epidermis is flattened and has little pigment, but is not much thinned. In the sub-papillary zone beneath the granuloma some of the vessels show considerable changes about them. In Figs. 31 to 33 are shown stages in the course of a long tuberculoid sheath about a tiny vessel. Throughout the deeper layers, under the granuloma, there is generally a little perivascular accumulation, with small epithelioid foci mostly in relation to blood vessels, especially around the sweat glands. Some nerves accompanying these vessels are not in the infiltration but only surrounded by it. At the inner end of the granulomatous zone a broad band of it containing nice epithelioid areas extends to the subcutaneous fat, along a zone of blood vessels and sweat glands.

Both ends show transition stages not seen before. In both the epidermis appears normal. In the recovered end there is considerable increase of connective tissue, broadening the papillary layer, somewhat as in Case 6 (Figs. 51 and 52). At the same time there is marked loss of the elastic tissue fibers that contact the epidermis in the normal end. In the new end a few sections of the series show a tiny pre-tuberculoid focus beside a longitudinally-cut vessel in the papillary layer near the beginning of the lesion proper, and between them rather conspicuous perivascular infiltration. In the resolved end the lesion

has cleared up less abruptly than in other specimens, and the residual foci taper off as regards size. However, only a few of the larger contain epithelioid elements. For a distance over this region the epidermis remains flattened, then returns to normal.

Comment.—Deep involvement, though still not extensive, is greater than in the preceding cases. It is mostly perivascular, either isolated or in relation to accessory structures. There is no indication that invasion was by extension from below; to the contrary, in the serial sections it seems definitely to trace from above. The distinction between the uninvaded and recovered ends is again made with reference to both the connective and elastic tissue elements. Unusual is the evidence of transition, with a tiny advanced pre-tuberculoid focus, and the gradual recovery.

Case 5, No. 4881.—Biopsy of a discontinuous ring lesion on arm, with especially prominent large papular elements (Fig. 16). Sections show correspondingly marked tuberculoid change superficially, the epithelioid foci showing apparent activity inducing hyperkeratosis, erosion, and even slight necrosis. Changes in the deeper layers moderate.

Clinically, the lesions were mostly linear, closed rings or open lines. On the left cheek was an excellent one, complete, continuous and fairly smooth, with another around the nose and a long almost straight one along the jaw (Fig. 15). Besides the biopsied ring on the left upper arm there was on the back a smaller lesion only partly encircling a small pale area. The striking characteristics were the narrow, mole-burrow band and the evident completeness of healing inside.

Sections show a long uninvolved end and a short, incompletely resolved one with considerable round-cell accumulation, some connective tissue increase, and marked diminution of elastic fibers. The uninvolved end, which indubitably extends beyond the outer erythematous zone, is entirely normal for nearly 5 mm., then shows a long intermediate or transition zone (about 4 mm.) in which the papillary vessels are dilated and have some perivascular accumulation, at first slight and simple, later more marked (Fig. 29), and sometimes with traces of epithelioid-cell development (Fig. 30).

The main superficial granuloma (over 5 mm. long) is interrupted by an uninvaded bit with normal epidermis, this interruption marking the division between one rounded papule (2 mm.) and a broader lesion which comprises a definite papule and a younger, advanced portion. The latter is composed of several smallish, close-set tuberculoids with some large giant cells and a few round cells but without epidermal flattening. The two older foci contain more round cells, and in each of them is an especially active epithelioid mass in which there is rarefaction just below the epidermis, which is specially thinned and disturbed and shows some hyperkeratosis (Fig. 46). Over the solitary

papule the epidermis is actually separated for about 0.5 mm., and there is here a little diffuse necrosis, red-cell diffusion and fibrin deposit. At two or three other points a little necrosis is seen (Figs. 49 and 50).

The involvement of the deeper layers beneath the superficial granulomatous zone is rather extensive, the epithelioid foci being unusually large (Figs. 46 to 48). They are chiefly in evident relation to vessels; sweat glands here are entirely uninvolved except as seen in Fig. 48; some nerve branches are free, others are surrounded, but none shows actual invasion. A few small epithelioid-cell groups are found in relation to vessels in the subcutaneous tissue.

Comment.—In appearance the several larger epithelioid foci are suggestive of Boeck's "sarcoid" tuberculide. The whole process here is evidently active, especially in the superficial lesions where there is a little necrosis at several points and injury of the epidermis in places. If this condition is a "reaction" condition (local lepra reaction) this was not recognized clinically. In spite of the activity evidenced, resolution has been complete and prompt and there is none of the fibrosis seen in the next case. There is a longer and more definite transition zone than in any other specimen in the lot.

CASE 6, No. 4878.—Biopsy of an interrupted shoulder lesion, narrow, very irregularly raised (Fig. 19). Sections show a fairly marked tuberculoid process, superficial, with erosive activity as in the preceding case, and also chronic changes not seen in other cases. Comparatively little change in the deeper layers.

Clinically, the principal lesions were two large, bilateral, more or less symmetrical macules on the shoulders, partly outlined by discontinuous, segmental, infiltrated zones but for the most part inactive, marked only by hypopigmentation. The raised lesion was unusually irregular. There were ring lesions on the face; lesions on the lower back and buttocks were not conspicuous.

Sections show a long superficial lesion-zone (about 11 mm.), between ends that are free from granuloma. Though the lesion is unusually marked and active, the invasion of the lower parts of the dermis is comparatively slight. The main lesion is interrupted in places, once by a short bit apparently not yet involved, and again by a zone over 3 mm. long of resolved but fibrotic tissue. The granulomatous areas are large, rather diffuse, with considerable round-cell infiltration massed between the epithelioid foci; giant cells are fairly numerous and large. The epidermis is hypopigmented as usual, flattened and sometimes stretched over the granulomatous areas, and in places there is active thinning, cellular infiltration and hyperkeratinization. In the outer portion of the largest tuberculoid focus there is a collection of loose epithelioid cells streaming outward, and over it the epidermis is thin, degenerate, loosened and actually interrupted (Fig. 45). Capillaries accompany the epithelioid cells. A few polymorphonuclears are present.

The unaffected end shows only slight perivascular infiltration. In the other, though the epidermis is fairly normal, the papillary layer is much widened;

the blood vessels are prominent, with some infiltration about a few, and there is conspicuous increase of moderately fine-grained connective tissue, while the fine elastic fibers have virtually disappeared. The same description applies to the zone between the two main granulomatous areas except that here the epidermis is still more or less flattened (Figs. 51 and 52).

Comment.—Here as in preceding case is special epithelioid activity, with erosion, in spite of which the deeper layers are not much involved. There is no necrosis, but a striking increase of connective tissue not duplicated in any other specimen. The difference in the epidermis between the inner zone and the central one—which is apparently the more recently resolved—exemplifies delay in return to normal of this structure. The loss of elastic fibers is much more prolonged, if not permanent.

Case 7, No. 4653.—Biopsy of lesion on arm, one of many widely distributed, rather small lesions with broad-zone tendency (Fig. 4). Sections show tuberculoid changes throughout, in this case the superficial changes being less than the deeper.

Clinically, most of the many small lesions on the body and extremities were well separated, their surfaces finely granular, the infiltration tending to delayed resolution (Fig. 3). On the face were plaques, and on the neck was a circinate lesion (Fig. 12).

Sections show that most of the change is deep. In the papillary layer there is a thin discontinuous zone of infiltration containing a few small tuberculoids in close contact with the epidermis which, however, shows only moderate hypopig mentation. Scattered throughout the deeper layers are rather marked and conspicuous epithelioid foci, with giant cells in moderate numbers. The epithelioid cells are mostly of the apparently inactive, fibroblast-like variety. The condition seems related chiefly to blood vessels, though some nerve branches are also surrounded; in one place a small vessel is more or less destroyed, and the fibers of a long hair muscle are separated by infiltration.

Comment.—Unlike the preceding cases most of the granulomatous change is in the deeper levels. A clinical distinction from the cases with the more superficial lesions cannot be made with certainty on the photographs, but it seems probable that in this case the surface pebbling would not be conspicuous. A suggestion arises that there may be a relation between this deep location of the process and the production of plaque formation as seen in the face of this patient.

Case 8, No. 3480—Biopsy of an active flank lesion extending around the side of the body under the axilla (Fig. 14). Sections show rather marked tuberculoid changes, mostly in the deeper layers.

Clinically, there were extensive, moderately infiltrated areas on the body, apparently spreading rapidly. The one biopsied was wide, the edge not abrupt,

papule formation not prominent, the lesion "not actually granular; epidermis shiny"—which led to a suspicion that it might be lepromatous.

Sections show the papillary layer thin, containing only a small amount of granuloma. The epidermis is flattened in one portion, and there is some elastic-fiber disturbance here but there is now no lesion present to explain this, either superficial or deep. In the actively involved part the principal changes are deep. Prominent tuberculoids of moderate size are at different levels, the largest in sweat-gland areas. In two or three instances there is more of an apparent relation to nerve than usual, though as in the preceding cases most, when affected at all, are simply surrounded by the granuloma and inwardly seem undisturbed.

Comment.—The papillary involvement is even less than in the preceding case, and in evident correlation is the less papulation of the surface. There is some indication of preferential relation with nerve branches. That the process may have extended from below outward rather than the reverse is a possibility in this case.

CASE 9, No. 4879.—Biopsy of an interrupted linear (ring) lesion of the face. Sections show beautiful tuberculoid foci in all levels.

Clinically, the striking face lesions were cord-like, continuous but irregularly infiltrated, at times almost nodular. On the right side one started on the neck, crossed the markedly thickened great auricular nerve, passed upward along the hair line and crossed the ear regardless of structural configuration (Fig. 17). A second is to be seen above the mouth. On the left side a similar lesion involved the forehead, cheek and both eyelids; the biopsy was taken from this one on the cheek.

Sections show that, as the skin of the face is not clearly divided into papillary and reticular layers, so the distribution of the lesions is without the zonation that is prominent in most cases. Both ends show some infiltration around vessels and hair structures, but in one the epidermis for a bit is flattened and elastic fibers are completely absent. Most of the section contains numerous conspicuous tuberculoids, with relatively large, fine epithelioid areas, sometimes with large giant cells. Several are in relation to hair structures; one is beside a hair muscle; several have no evident relation except to blood vessels. Changes in the upper level are much less marked than those deeper, and though the epidermis is considerably flattened and shows hypopigmentation it is otherwise not affected.

Comment.—This lesion shows lack of zonal distribution, in keeping with the structure of the skin of the face. The tuberculoids are especially fine. There is no definite indication of the mode by which the condition entered or became distributed through the tissue.

CASE 10, E. L.—Biopsy from an extensive area of irregular, linear and diffuse infiltration on the forehead (Fig. 18). Section shows marked chronic inflammatory changes throughout, with moderate tuberculoid.

Clinically, the only recognizable lesion was the infiltration of the forehead which the patient, aged 28, claimed had always been present. On the infiltrated base were prominent linear lesions. According to the demonstrating physician (Dr. R. V. S. Stevenson) the condition had increased greatly in the preceding six months. The only other abnormality found was hypoesthesia to light touch over the little fingers.

Sections were made from three portions of an elongate piece of tissue, one transverse and two longitudinal. As in Case 9 there is no definite zonation, but in this instance most of the lesion is superficial and is chiefly diffuse round-cell infiltration. Mostly in this zone but partly below it are considerable epithelioid areas, peculiarly diffuse and loose, with many small spaces between cells, probably due to edema. Most of the deeper tissue is free from involvement, but in a coil-gland area is a nice round epithelioid mass. A similar lesion, apparently encapsulated, is within or at least involves a fairly large nerve.

Comment.—The activity which had caused the condition to increase in the preceding six months perhaps explains the amount of the epithelioid tissue, but its loose, apparently edematous condition and the exceptional amount of round-cell accumulation are not explained. It is not believed that there is local lepra reaction here, and if the patient had used an irritating application he said nothing of it and there was no surface indication. The nerve involved is unique among these cases; the fact that it is a nerve is proved only by the specially stained sections.

Case 11, No. 4481.—Biopsy of a round, annular lesion high on back (Fig. 24), unlike the main lesions present. Sections show a chronic, apparently residual condition throughout their whole extent.

Clinically, extensive merging broad-zone, granular-surfaced macules virtually covered the back and in part the legs. Most of the face, the eyebrows and earlobes were covered with more marked infiltration, considered probably lepromatous. High on the back were two or three annular lesions, peculiar in that they seemed to be double-bordered, with an apparently active inner edge that suggested a centripetal advance. The largest was nearly four inches in diameter, the infiltrated margin about an inch wide, the flat center more than an inch across; the biopsy scar is barely discernible in the photograph.

Sections show, throughout, rather marked fibrosis and great diminution of the elastic fibers in the papillary layer. The superficial vessels are enlarged and most have more or less perivascular infiltration, but only here and there is a small tuberculoid found. The epidermis is little affected. (Recuperated?) In the depths are larger foci of infiltration, mostly in relation to hair or sweat-gland structures but a few to deeper vessels or to nerve branches. These foci seem residual, with a tendency to fibrosis and with little epithelioid element. No giant cells are seen.

Comment.—The condition is apparently a very chronic tuberculoid lesion that has undergone general retrogression with fibrosis.

As usual the round-cell infiltration seems to out-last the epithelioid change.

CASE 12, No. 4910.—Biopsy from an improved case, most of the macules now flat; tissue from a fairly small, pale, "inactive" lesion. Sections show little present tuberculoid change, but evidence of a more severe one pre-existing.

Clinically, these improved lesions—previously raised-edged (Davison)—were fairly extensive macules, mostly on the back and extremities. Hypopigmentation was moderate to marked; the erythematous borders, when any, were narrow. In some the edges were still moderately raised but "apparently not active". In the lumbar region and below were irregular saddle and related lesions (as in Fig. 21).

Sections show relatively slight changes. The epidermis is practically normal. The papillary layer shows at most only slight perivascular accumulation. Deeper in the tissue are limited amounts of infiltration about vessels, nerves and the accessory structures. In the series of sections are seen several groups of a few epithelioid cells ("pre-tuberculoids" and very small tuberculoids), one of which in the series follows a vessel for a considerable distance. One nerve seen is much disturbed. Though at a first glance the superficial layer seems almost normal, there is rather extensive connective-tissue increase of moderate degree, and considerable loss of elastic fibers.

Comment.—This specimen evidently exemplifies an all but healed stage of a lesion that while active caused a little fibrosis and considerable loss of elastic fibers in the papillary layer. The tuberculoid change now existing is definite but practically minimal. Small foci of infiltration are in relation to nerve branches (in one instance intraneural), but more often with blood vessels and other structures. Apparently the condition is residual.

CASE 13, No. 4004.—Biopsy of the edge of a plaque type of lesion on the back (Fig. 25). Sections show marked, atypical changes superficially, moderate deeper.

Clinically, the lesions on the back were very extensive, compound, the advancing edges abruptly and markedly raised, the marginal zones uniform and rather narrow. Resolution was so incomplete over wide areas that the appearance was of extensive, coarse-grained plaques. The body anteriorly and the extremities were extensively involved. The face in part appeared as if lepromatous. The upper lip was swollen and erythematous (neuro-edema? localized lepra reaction?).

Sections show one end normal. The first small lesions are in the reticular layer, tiny granulomatous foci about a small vessel and a small nerve branch; shortly beyond there is a definite little tuberculoid in the papillary layer and for a space occasional small lesion foci occur both here and deeper. Predominance in the papillary layer is found only in the last third or so, where there is a

rather large granuloma. Except for the tuberculoid mentioned as such, all of the lesions are atypical, without ordinary epithelioid foci or much round-cell infiltration; giant cells are absent. The granulomatous masses are mostly made up of elongate cells of more definite delimitation, less yellowish-red color after eosin, than ordinary epithelioid cells. Part are probably ordinary epithelioid, but others are more suggestive of fibroblasts. The lesions as a whole have a resemblance to those in Case 14, but have distinct histological differences and bacilli are not demonstrable in them. Aside from flattening over the larger foci the epidermis is more normal than in most cases, less hypopigmented and only a little disturbed, this being by infiltration where the main granulomatous mass contacts it.

Comment.—This case has to be set apart, for though clinically it is evidently in the same category as the others, and histologically it is tuberculoid rather than lepromatous, nevertheless it would seem to approach the "fibroblast" type of leproma of cutaneous leprosy. This very likely had to do with the plaque formation, and may possibly represent an intermediate stage between the two types of changes.

Case 14. No. 5006.—This patient had obvious cutaneous-type infiltrations of the face, and elsewhere. A diffuse infiltration on the thigh, without raised margin (Fig. 27), was biopsied to provide a lepromatous specimen for comparison with the anticipated tuberculoid changes of the other cases.

Clinically, the face was diffusely and smoothly infiltrated and smears from it contained bacilli in typical abundance. On the extremities were extensive infiltrated areas, also apparently leprotic. The biopsied one on the right thigh was slightly hypopigmented, shiny, dryish and crackled ("ichthyoid").

Sections show extensive islands of leprotic (lepromatous) tissue with practically no round-cell accumulation. The cells are mostly of the elongate ("fibroblast") type, with comparatively few foamy cells distinguishable as such, and definite globi in only an occasional focus. Special stains show many delicate connective-tissue fibrils more or less parallel, directed as are the leproma cells. The process is, as usual, associated with hair structures, infiltrates coil-gland areas, and surrounds vessels and nerves, causing perineural proliferation, but it lacks any evident tendency to invade these structures or the epidermis. There is the usual narrow intact zone immediately between the epidermis and the leproma, sometimes absent in tuberculoid lesions. Elastic fibers are much reduced over the lesion foci, though not as completely as is usual immediately over tuberculoids. Bacilli are abundant, in sections as well as in smears.

Comment.—This lesion has no apparent relation whatever with the ordinary tuberculoid granuloma. On the other hand its distinction from the atypical lesion in Case 13 is much less clear because both are composed largely of elongate cells, with little or no round-

cell infiltration. However, there is a difference in the cell types, and in some areas here globus-vacuoles are seen, though bacilli are also numerous where there are no vacuoles.

SUMMARY OF MACROSCOPIC FEATURES

Here is attempted a summarization of the gross skin changes in the cases observed. No attempt is made to deal with other features of the clinical picture, or to discuss the more common evidences of leprosy such as atrophies and mutilations, which it may be said were not common in these cases.

Basic characters.—Nothing can be said of the primary lesion except to point to Figs. 22 and 23. For the earliest of the kind studied (obviously secondary, metastatic) one might take a group of small, discrete papules as in Fig. 5 or a little, rounded, follicle-indented nodule which might be distinguishable from a leproma only on bacteriological examination (as in Fig. 1), or an infiltration newly arising at the edge of an ordinary flat, pale spot. However, apparently the earliest typical lesion is an infiltrated macule which is flat-surfaced (as also in Fig. 1), obviously because the maximum degree of the tissue change is fairly uniform throughout. If the lesion enlarges at a uniform rate the macule remains more or less circular (Fig. 3), but in most instances they soon become irregular. On the back—an especially favorable location—they may for a time be elongate, the axis parallel with the ribs (see Plate 1). If they are at all numerous or close they merge (Fig. 4) to form gyrate, serpiginous, sometimes decidedly complicated figures (Fig. 24).

The degree of elevation is ordinarily considerable, and often marked. The edge may be raised rather abruptly, or may be sloped or beveled; it is sometimes rather smooth, the invasion progressing evenly—especially smooth ones are seen in plaques on the face (Fig. 11) and in lesions in the reaction state—but usually the edge is distinctly irregular. Characteristic are the strikingly rough, pebbled, papulate surfaces, but they may be fairly smooth (as in Fig. 26), which is a more common appearance elsewhere. Though the individual papules may be decidedly irregular in size (as in Fig. 8) they are usually uniform and small. Sometimes they are broad, flattened (Fig. 7), but ordinarily they are rounded and sometimes quite lichenoid (Fig. 5), indicating the superficiality and individuality of the microscopic lesion units (tuberculoids).

Progression.—How primary lesions appear remains to be determined, but new secondary ones often appear as by metastasis, as in Fig. 3, and some cases have a history of sudden, multiple "reaction" eruptions, all of which bespeak for such cases a blood-stream distribution of the causative agent. Once established, the lesions undergo expansion, enlarging centrifugally. The invasion of the surrounding tissue does not progress smoothly, solidly; the edges are usually rough, indicating a colonial form of progression, the spaces between the advanced foci being filled secondarily, sometimes not at all ("discontinuous lesions").

Resolution.—As a rule the expanding macules sooner or later begin to return to normal centrally, so that most of them become marginate, annular. There is much variation in the promptness, uniformity, and apparent completeness of this resolution. When it is prompt relative to the rate of spread the infiltrated zone is narrow; this is seen best in the linear lesions (Fig. 15), but usually the margins are wider (Fig. 3). If resolution progresses uniformly the margin is fairly regular in width (Fig. 1), but commonly it is decidedly otherwise (Fig. 2). Ordinarily the inner border of the infiltrated zone tapers off gradually, though sometimes—apparently under special conditions—it may be as abrupt and sharply delimited as is typical of the outer borders. As for completeness of recovery, the center often returns almost if not quite to normal in color and grain (Fig. 2), but sometimes there is a considerable residual coarsening (Fig. 8). Occasionally one sees isolated patches of evidently active infiltration in the recovered area well inside the marginal zone, but whether these patches are residual or recurrent may not be evident.

Plaque formation.—It may happen that resolution does not occur, or is so delayed relative to the rate of progress of the margin that broad areas of infiltration result. These plaques reach their maximum on the back (Fig. 25), but they seem more frequent on the face where they are the antithesis of the narrow rings that occur there, sometimes in the same patient (Fig. 12). The special interest that attaches to these lesions is touched on later.

"Linear" lesions.—This term is applied to a variety of lesion, most often seen on the face and neck, which presents a conspicuous raised zone so narrow that it is rounded, appearing as if corded or as if produced by a burrowing parasite (Fig. 18). These may be closed rings, or may be open, segmental; typically they appear to

be merely expanding zone-lesions that have undergone relatively prompt resolution.

"Discontinuous" lesions.—Sometimes the progressing zone is not complete or solid, but is broken here and there (Fig. 21). This is usually seen when the infiltrated zone is narrow (Fig. 7), though it may occur in other lesions (Fig. 6).

"Segmental" lesions.—These are more or less irregular open zones, continuous or not, that only partially outline macules which otherwise are usually to be defined only by the hypopigmentation. They usually appear as if they were interrupted segments of originally annular lesions, and are common on the shoulders—where they are usually bilateral and more or less symmetrical (Fig. 19)—and on the lower back—where symmetrical, wing-shaped zones often outline the upper margin of the pelvis (Fig. 21). The open linear lesions of the face apparently are formed in the same way (Fig. 15). However, lesions may be segmental from the start, as was one seen at Durban that arose at only a part of the edge of an ordinary flat macule. At Emjanyana a young child had a slightly pale area in the margin of which was an eruption of tiny papules, mostly well separated (Fig. 22); a month or so later some of these had disappeared while others had increased and were fusing to make very small solid areas (Fig. 23). The condition pictured in Fig. 18 is unusual; the irregular bands in a diffusely infiltrated base were the only ones on that patient.

Peculiarities of location.—These lesions show much the same peculiarities of location as do the ordinary macular leprides. They are most common on the back lumbar region and buttocks, upper arms, and face. Other areas are less commonly involved (anterior surface of the body—especially the abdomen—the forearms and legs); and some are relatively immune (axilla—see Fig. 14—crural region, folds of the elbows and knees). However, established lesions sometimes progress with amazing disregard of structural peculiarities, as is the one seen about the ear in Fig. 17. It is of interest that in these African patients the scalp is often covered with flat macules; according to Davison perhaps 25 per cent are affected. This evidently does not injure the hair follicles for the condition is usually not detected unless the hair is clipped. On the other hand one sees in Africa very few cases of nodular scalp invasion with alopecia like that common in Japan and apparently nowhere else.

The form-variety of the lesion is considerably influenced by the location. Ring and segmental linear (circinate) lesions occur especially on the face and neck, and open segmental ones on the shoulders and lower back. On the other hand the face is prone to show solid plaques and also, in keeping with its histology, it most frequently undergoes an irregular, relatively extensive and deep infiltration which suggests lepromatous change.

Color of lesions.—These dark-skinned patients show considerable hypopigmentation of the infiltrated portions, and the tops of papules where the epidermis is stretched thin are often especially pale. Typically there is also some erythema, ordinarily limited to the very border and extending into the uninfiltrated skin, where it is difficult to detect. In the reaction state the erythema of the active lesions is marked and conspicuous. After resolution the color usually returns practically to normal.

Other changes.—With regard to the sensory and related neural changes, including the reaction to histamine, little can be said. However, it was striking that as a rule perception of light touch was less affected in the macules than was expected, and frequently there was no evident hypoesthesia whatever. Nevertheless, some disturbance of temperature perception seems to be the rule. In a number of cases there were, on the face and elsewhere, infiltrated lesions that were thought by the clinician to be undergoing or to have undergone conversion from the macular to the lepromatous type. In some instances bacteriological smears contained a few scattered bacilli. This matter will be discussed in another article (28).

Recurrence.—The active process may be cleared up, following which, as in the cutaneous type of the disease, there arises the problem of recurrence. Figs. 10 (back and shoulder) and 20 (shoulder) are of cases in which that had happened. Curiously, in the former case the infiltration, which was deep and relatively slight, was in the erythematous zone outside of the hypopigmented zone.

SUMMARY OF MICROSCOPIC FEATURES

BACTERIOLOGICAL FINDINGS

As has been stated, no acid-fast bacilli were found in smears from the tuberculoid cases described. Nor were they obtained from any of the others used in the summary of microscopic features except the one with plaques shown in Fig. 11, from which a single bacillus

was secured in each of two smears. Sections stained by the writer's method were likewise negative.

HISTOLOGICAL FINDINGS

With the exception of the atypical lesion of Case 13, the pathology in the specimens described departs in nó real essential from the ordinary. However, there is interest especially in the apparent differences in activity and in the indications of the processes of progression and recovery.

Essential lesion.—In some cases the epithelioid foci are very few and small, and in most of them they are not large (Plates 7 to 9); those in Case 6, which suggest Boeck's sarcoids (Figs. 46 to 48) are exceptional. Round-cell accumulation is always present, sometimes slight, usually tending to correspond in amount with the apparent activity of the lesion as a whole. Giant cells are a variable element, as usual, and occasionally are absent. Activity of the lesions seems to be indicated by abundance of *typical* epithelioid cells in the tuberculoids, and usually relative prominence of giant cells (as in Fig. 44), with or without especially marked round-cell concentration. Erosion may result from especially marked activity (Fig. 45). The small foci of necrosis in Case 5 (Figs. 49 and 50), if not due to some superimposed condition, are exceptional. On the other hand, where the sections show atypical epithelioid cells (unusually firm, discrete, fibroblast-like) and few giant cells the process seems relatively inactive.

Very early and small tuberculoids may be seen about the capillaries of the actual papillae, but this is not the rule; usually, as in Figs. 30 and 31, the lesion-foci are located in relation to the vessels in the papillary layer and those just below it ("subpapillary"). The obliteration of the individual papillae by a tuberculoid which forms a papular elevation of the surface is illustrated by the one shown serially in Plate 9. Often as in that instance the epithelioid foci are discrete, as in miliary tuberculosis, separated from each other by uninvolved tissue or by round-cell infiltration. Often, too, those found along vessels are proved by serial sections to be similarly focal, but in other instances they are more or less continuous, ensheathing the vessels as in the instance illustrated by Figs. 31 to 33. On the other hand the epithelioid masses may ramify irregularly—whether primarily by growth extension, or secondarily by fusion—as is seen on a small scale in Figs. 34 to 37. In either case it appears that the epi-

thelioid focus increases by expansion rather than by infiltration, and pushes other structures aside as it expands.

Changes in the epidermis.—This tissue is clearly more liable to disturbance over tuberculoids than over lepromata, the changes being both simple and structural. Simple flattening and thinning (Figs. 31 and 36) are accounted for by mechanical interference, pressure from the larger tuberculoids. Probably dependent more upon an active influence of tuberculoids which contact it than upon pressure, the epidermis at the points of contact may also show structural changes, separation and apparent loosening of the basal layer, occasionally actual invasion by mononuclear leucocytes (Fig. 44), and finally thinning by dissolution from below. It is doubtless this process which causes hyperkeratinization and scaling, and even erosion (Figs. 45, 46, 50). Nothing comparable to the epidermal hyperplasia so conspicuous in tuberculosis of the skin is ever seen in this condition. Hypopigmentation is naturally more noticeable clinically than microscopically, but the more severe degrees are conspicuous in the sections. Because it often occurs when there is relatively little infiltration (especially in the flat macules) it would seem to be a functional aberration rather than of mechanical causation.

Changes in other structures.—Some of the sections show rather marked disturbance of sweat-gland areas. The gland tubules are often separated by the granuloma but the actual epithelioid foci simply push them aside, the separation being due to round-cell infiltration (Fig. 48). The tubules usually appear inactive, sometimes actually compressed, but the basement membrane is seldom involved. Normal hair follicles are seen, but often the hair shaft appears abnormal or is absent. Though the process is outstandingly perivascular, seldom is a vessel wall actually invaded to any extent. The same is true of the nerve branches, which are less regularly involved. In both cases the process surrounds these structures, but as a rule invades only their outer sheaths when it is invasive at all. Outstanding in these lesions is the destruction of the elastic fibers of the papillary layer when the tuberculoid process is at all marked.

Progression of the lesion.—Indications as to the manner of progression of the condition into new tissue are to be had, some of that beyond the edge of the infiltration being included in most specimens. Evidently correlated with the zone of erythema that precedes the infiltration in an active lesion is the usual finding of vascular dilatation and a little perivascular infiltration in the papillary layer, the

invading cells being on the whole young and rather cytoplasmic. This infiltration is present in some degree in most specimens but in some it is negligible, normal skin being probably not entirely free from it.

Approaching the edge of the infiltration most specimens show no real transitional change, the granuloma starting quite abruptly (Fig. 28) in keeping with the gross appearance of many lesions. The first portion of the infiltration may be tuberculoid, perhaps with relatively few round cells, or it may be only round-cell infiltration. On the other hand, in some sections there is transition, marked by increase of the perivascular infiltration and even a tendency to diffusion of this in the tissue between. Some of these foci may then show a few large mononuclears which may resemble somewhat the epithelioid cell and are probably becoming that ("pre-tuberculoid", Fig. 30). Only a few of the specimens show this stage or the picture of direct continuity shown in Fig. 29 where a band of round-cell infiltration extends in the vascular layer from an epithelioid focus toward the normal tissue.

Concerning extension downward, none is seen beneath the extra-marginal zone of simple perivascular accumulation; as a rule the deeper layers are found affected only within the limit of the papillary-layer granuloma, even when this does not predominate. Some of the specimens show comparatively little change in the depths. It is noteworthy that, as Unna pointed out with regard to the ordinary leprides (24), the deeper lesion foci are typically in relation with organized structures and are not scattered indiscriminately throughout the reticular layer. Only rarely is a tuberculoid seen in the denser connective tissue away from some recognizable structure. There is much less tendency to follow the sweat ducts than the blood vessels.

Resolution of the lesion.—In two of the cases (Nos. 11 and 12) general resolution is evidently under way. In six of them (Nos. 1, 4, 5, 6, 7, and 9) the lesion zone was so narrow that the sections include some of the more or less recovered tissue. These specimens necessarily represent relatively prompt resolution and may differ much from the tissue well inside a broad marginal zone. In certain instances resolution is so complete that there would be no positive distinction between the outer and recovered ends were it not for the loss of elastic fibers in the latter. Where a distinction is evident on other grounds this is less because of persistence of inflammatory in-

filtration than because of increase of connective tissue, especially in the papillary layer, but in most of the specimens there is little of this and only in Case 6 (Figs. 51 and 52) and Case 12 is it at all conspicuous.

As for details of the process of resolution, most of the sections are not illuminative, the change in them being so abrupt that at one point there is a well-developed tuberculoid and somewhat beyond it only perivascular infiltration. However, it appears as if the first stage in resolution is simply degeneration and disappearance of the epithelioid element of the lesion, after which the round-cell infiltration decreases and ultimately more or less completely disappears. The epidermis that has been flattened apparently returns to normal slowly. Whether the elastic fibers that have disappeared are replaced eventually cannot be said.

DISCUSSION

Cases of the type here discussed—which represent a clinical variety of tuberculoid leprosy—have, as stated, been distinguished clinically in a manner by the South African workers. Le Roux (13) differentiates between this type of raised-edged lesions, which he calls the "primary cutaneous macule", and the ordinary flat macules, which are considered "primary neural". The former he speaks of as "bacillary active skin lesions" though he says nothing definite concerning the relation of bacilli to them. As has been said, bacilli were found in none of the group here described, which is entirely typical of tuberculoid lesions, at least in the ordinary phases. If the bacillus is present in its ordinary form in these tissues it is certainly in extremely small numbers. Beyond saying this, and pointing out that tuberculoid lesions are not necessarily always negative (28), discussion of the matter is reserved for the present.

The fact that these cases were in leprosaria illustrates differences of regulations in different countries. In the Philippines they would not have been isolated, being bacteriologically negative by the standard examination. In South Africa evidence of clinical activity leads to isolation. This should be better for the patients than to permit them to be at large where they cannot receive the benefits of treatment, but it would be decidedly interesting to know whether it is actually of value to the public at large.

Just how frequent these tuberculoid cases are in South Africa is not known. A figure heard, 15 per cent, is said to be an over-

estimate[5] but the cases are evidently rather numerous. On the other hand, tuberculoid cases are apparently not as numerous and are certainly not as distinctive farther north. None was noticed in the asylums visited in Tanganyika and Zanzibar, and at the Ngomahuru leprosarium in Southern Rhodesia the physician in charge (Dr. Bernard Moiser) pointed out only two or three cases, of the ordinary type illustrated by Fig. 26. But if one may judge from pictures, cases of that sort are not rare among Negroes both in Africa and elsewhere.[6] However, this can be said only tentatively, for the general clinical features of tuberculoid leprosy have yet to be clearly established or generally recognized. This should be done and the significance of the condition as regards treatment, prognosis, and if possible infectiousness should be determined.

An attempt is made here to summarize the macroscopic features seen in the variety of the condition studied, subject of course to amplification by the leprologists of South Africa. The outstanding peculiarities noted are the unusually rough, pebbled surface of the lesions and the tendency to build up isolated macules, and also the occasional but striking linear lesions. The surface peculiarity is clearly ascribable to the separation and especially to the superficiality of the individual tuberculoids, which in some cases (as in Fig. 6), are confined entirely to the papillary layer, but as to the reason for this condition one can only speculate concerning the possibility of some peculiarity of the skin of the people concerned. In cases without the granular surface the appearance indicates that the condition is mostly in the deeper layers, as was the fact in Cases 7 and 8.

Correlation of the histology of our specimens and the clinical aspect is handicapped by lack of history of the actual tissues studied—the duration or age of the lesions, whether they were slowly or rapidly progressive, etc. One would, obviously, expect considerable differences in the history, as there are in the histology, of the conditions shown in Figs. 6 and 14, but in this respect as in others these observations can be only suggestive for more extended study. Of some interest is the apparent variation of the histological picture with

[5] Sir Edward Thornton, Secretary of Public Health, Pretoria; personal communication.

[6] For example, photographs exhibited at the London School of Tropical Medicine, and a lot taken at the St. Croix leprosarium in the Virgin Islands by Dr. Howard Fox, whose observations were reported in the JOURNAL 1 (1933) 321, both included some of apparent tuberculoid cases of ordinary type.

activity—abundant typical, diffuse, poor-conditioned epithelioid cells in apparently active lesions (Figs. 44 to 48), often with numerous and conspicuous giant cells (Fig. 44), and on the other hand predominance of firmer, "fibroblast-like" epithelioid cells and few or no giant cells in apparently torpid, inactive, but, persistent lesions. One is not inclined to consider the special activity noted merely a marked grade of the usual process; that seems ordinarily too bland, though less so than the ordinary leproma. No record was made that applications of trichloracetic acid had been used in these cases, and the change noted is not suggestive of reaction to such treatment. From the amount of epithelioid tissue and the numerous giant cells it seems possible that they may represent a local condition of the nature of lepra reaction, but such a condition was not recognized at the time and cannot be determined from the photographs.

The very different condition that leads to plaque formation is especially interesting. Is it due simply to unusual rapidity of spread, as le Roux seems to believe, or is there an actual delay or failure of resolution? If the latter is the case, is this due to a depression or resistance on the part of the patient, or to a peculiarity on the part of the lesion? This last suggestion arises from the findings in Case 13, in which the lesion resembles closely the fibroblast variety of leproma (Case 14) and may be expected to resolve less readily than the usual condition. Is this variety of change related to the conversion of these lesions to the lepromatous type, which is supposed to occur but concerning which there seems to be nothing definitely known? It is possibly significant that, as stated, of all the cases dealt with in this report the only one found bacteriologically positive was the plaque shown in Fig. 11.

With regard to the question of the origin of the condition, little is known. Only le Roux's statement that they are sometimes the site of the primary infection has been seen. On the other hand, as stated in describing the segmental lesion, the writer saw cases in which papulate, obviously tuberculoid lesions were developing at the borders or parts of borders of ordinary flat macules (as in Figs. 22 and 23), and cases in which both kinds of lesions existed simultaneously (Case 6). Light is needed on the relationship between the frank tuberculoid and the ordinary macule. One gathers, especially from Henderson, that in India these clinically simple lesions are commonly tuberculoid in their histology, but this is not universally the fact. The descriptions of European writers indicate that such lesions seen

there are ordinarily of simple chronic inflammatory nature, and Lie[1] says that in his forty years' experience he never encountered a section of one that was tuberculoid; only one such case has ever been reported from Norway (1).

Aside from the conditions mentioned the histological features in these cases do not differ essentially from the typical. As regards the comparatively slight degree of sensory change that seems common in these cases—one of the three general points in le Roux's summary is that "macules are by no means always anesthetic"—there is an evident correlation with the comparatively slight nerve involvement in our specimens. Really few of the nerves show actual disturbance, though numbers of them are surrounded by the lesions. This is very different from the view of Muir and Chatterji (21), according to whom nerve involvement in skin lesions is of primary importance.

Correlation of the changes in the sweat glands and hair follicles with the clinical condition cannot be attempted. On the whole the degree and severity of the affection of the sweat glands seems to depend upon the severity and, perhaps, duration of the lesion. In chronic ones periglandular fibrosis may put them permanently out of commission, but usually they do not seem greatly injured, and it seems probable that fairly normal function may exist in at least the more promptly and completely resolved areas. As stated, there are indications of loss of hair. Whether this loss is temporary or permanent it would also be interesting to know.

The marked loss of superficial elastic fibers herein described doubtless results in an alteration of quality or tone of the skin, even when there is no fibrosis of account. Whether or not this loss is permanent cannot be said. Hypopigmentation and flattening of the epidermis is recovered from fairly soon after resolution of the granuloma. The connective-tissue increase is so variable that on the one hand it may be apparently negligible, while in some cases there is undoubtedly enough to cause distinct thickening and stiffening of the skin. This was undoubtedly so in Case 6, with a specially active lesion (Figs. 51 and 52) and in Case 12, a chronic subsiding one. However, in comparison with the scars of infections like tuberculosis or tertiary syphilis or yaws, the most marked degree of fibrosis in these lesions is far from important.

Observations on the processes of progression and resolution are recorded, apparently for the first time. Most of the sections include

[1] Dr. H. P. Lie, of Bergen, Norway; personal communication.

uninvaded tissue and, so narrow were some of the lesions biopsied, six of the specimens also contain recovered tissue, wherefore they are definitely instructive in this matter. In most of these specimens it is evident that centrifugal progression of the process occurs by extension of the exciting agent along the line of least resistance, namely, in the perivascular (lymphatic) spaces, especially in the vascular plexus of the papillary layer (Figs. 29 and 30). Ordinarily it does not advance as a massive, sweeping process but forms advanced colonies, so to speak, represented by discrete tuberculoids (Fig. 28; also Plate 9). How frequently and in what cases, if at all, the change originates in the lower levels cannot be said from this material. In a few of the specimens there is more of the granuloma in the deeper layers than superficially, but how this developed is not evident. In only one case did a deep origin seem at all likely and, interestingly, in that there was more involvement of nerve branches than in the others. On the other hand, the findings in several specimens leave little possibility of doubt that what invasion there is in the deeper levels of them got there by extension from above. In our material the indications are that the infection usually came from some distant locus by metastasis, lodging in the capillary system of the papillae, the deeper papillary and subpapullary plexuses, the "baskets" of the sweat glands, and the subcutaneous tissue.

As for the process of resolution there would seem to be—necessarily following the inactivation or removal of the causative influence—first degeneration and removal of the epithelioid and giant cells present, and later the more or less complete disappearance of the residual round-cell infiltration. That the products of degeneration of epithelioid cells do not ordinarily accumulate during activity, as in tuberculosis, or remain during resolution, is probably ascribable to a slow, cell-by-cell necrosis in these lesions and also to their more open, vascular nature, which makes them accessible to scavenger cells. Why this invasive skin affection ordinarily clears up in any given point, and does not persist indefinitely as is usual with most (though not all) lepromata, is not evident unless it is because of the development of a local immunity of kind or degree necessary to put a stop to the process and, presumably, to prevent its re-entry to the same ground. This question is worthy of attention, and the related one of recurrence in these lesions is also of considerable interest.

Other questions that can only be mentioned in passing include the basic reason for this type of tissue response in leprosy and especially its relation to resistance, and the position in classification of the tuberculoid variety of leprosy. In connection with the latter, it may be said simply that the cases here dealt with were essentially of the neural type, as are the tuberculoid "maculo-anesthetic" cases of the Japanese and as were most cases of *tuberculoid leprosy* recorded in the literature. The occurrence of tuberculoid *lesions* in cases of other kinds is quite another matter, which cannot be discussed here.

SUMMARY AND CONCLUSIONS

1. A variety of tuberculoid leprosy seen in South Africa, which in certain respects differs from the usual, is discussed on the basis of thirteen of the sixteen cases from which biopsy specimens were obtained for histological examination, and more than twenty-five others examined less carefully. Cases of this variety are distinguished from others by South African leprologists, but not on the basis that is indicated by their histological characteristics.

2. The well-established terms "tuberculoid", as applied to a non-specific histological picture, and "tuberculoid leprosy", signifying a distinct and clinically recognizable variety of the disease, are held to be appropriate and useful.

3. A tentative clinical picture of the lesions under discussion is set up. The outstanding peculiarity of the condition is an unusual tendency to a rough, pebbled or "granular" surface, and striking linear lesions are also seen. The relatively slight sensory disturbance common in these cases is correlated with a slight degree of nerve involvement in the sections studied.

4. The essential microscopic unit lesion, called the "tuberculoid", does not differ in these cases from the typical in material from other sources, having the essential epithelioid focus accompanied by more or less round-cell infiltration, with Langhans' giant cells present inconstantly and in varying numbers, and rarely any necrosis whatever and little tendency to scar-formation. Activity is apparently associated with abundance of epithelioid tissue and giant cells. An interesting fibroblast-like variety of epithelioid cell is apparently associated with special indolence and persistence of the lesions.

5. Bacteriological smears from the cases here dealt with in detail, and sections stained for bacilli by the author's method, showed no acid-fast bacilli, which is typical of the ordinary forms and phases

of the tuberculoid lesion. With a single exception the bacteriologically positive cases, not dealt with in the present report, showed unusual features.

6. The sections permit observation of the extension of the process into the normal skin. In the zone which clinically shows only slight erythema there is slight to moderate perivascular round-cell infiltration in the papillary layer, indicating extension of the process along the vascular plexus. Ordinarily there is little further change until the full-blown granuloma develops, though sometimes there is a transition stage. In certain evidently early lesions the deeper layers are apparently invaded by extension downward; in others, more advanced or chronic, the manner of invasion of the deeper tissue is not evident.

7. Resolution, at least where especially prompt as in certain of the specimens examined, may be very complete. Ordinarily there is comparatively little fibrosis, though it is sometimes sufficient to be clinically evident. Non-resolution, with plaque formation, and recurrence are conditions that call for special study.

8. Several questions that can be elucidated only by workers actually dealing with such cases are suggested. Certain others, especially that of lepra reaction in such lesions, will be considered in later articles of the present series.

ACKNOWLEDGMENTS

Grateful acknowledgment is made of many courtesies from many men in connection with this study: Primarily, to the late Dr. J. Alexander Mitchell, then Secretary of Public Health of the Union of South Africa, and to Sir Edward Thornton, his successor, for arranging the tour in that country and for permission to use the data obtained. To Drs. F. C. Willmot and G. A. Park-Ross, senior health officers of the Cape Province and Natal, respectively, for active coöperation. To Dr. B. Samson, government pathologist at Durban, and to the officials of the leprosaria visited; especially to those of the Emjanyana Institution, without whose generous coöperation the observations and material could not have been collected: Mr. J. A. MacDonald, superintendent, for providing facilities; Dr. A. R. Davison, medical officer, for special coöperation already mentioned; Mr. Shonland, dispenser, for notable aid in the photographic work and otherwise. For helpful demonstrations and discussions also to Dr. J. J. du Pré le Roux at Pretoria, Dr. J. M. Henderson at Calcutta, Drs. K. Mitsuda and F. Hayashi in Japan, and Professors Jadassohn, Klingmüller, and MacLeod and Drs. Lie and Unna in Europe and England. For courtesies in the way of laboratory work, to Drs. Willmot in Cape Town, MacLeod in London, and Howard Fox in New York.

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DESCRIPTION OF PLATES

Photographs of cases were taken at the Emjanyana Leper Institution, South Africa, in part by the author and in part by Mr. Schonland; Fig. 18 was taken at East London, through the courtesy of Dr. Stevenson. The cost of the extra plates used to illustrate this article has been met by the Leonard Wood Memorial.

Plate 1

Fig. 1. A very small, early lesion (rounded, follicle-indented), near the uppermost of the five keloids in the midline, and near it two larger, typically flat-surfaced early lesions. In other macules the edges are erythematous, the marginal zones fairly uniform and narrow. Resolution is fairly prompt, and in the large macule fairly complete.

Fig. 2. Two fairly early lesions and a well-established one on the back. The edges are irregular, colonial advancement conspicuous in the lower small one. The marginal zone of the largest is irregular in width, recovery delayed but complete.

Fig. 3. Early and well-established lesions on the back, the largest nearly round, the marginal zone rather broad but uniform. Case 7. (Figs. 4 and 12 from the same patient.)

Fig. 4. Merging lesions on the upper arm. Biopsy specimen, Case 7, from the edge. (Figs. 3 and 12 from the same patient.)

Fig. 5. Very early superficial lesion on the back, an irregular collection of minute papules. Case 2. (Fig. 6 from the same patient.)

Fig. 6. A discontinuous, irregular-zone macule of superficial papules on the back; almost complete resolution in places. Biopsy specimen, Case 2, from the thin upper edge. (Fig. 5 from the same patient.)

Fig. 7. A small, discontinuous, narrow-margined macule on back, made up of broad flat papules. Case 4; scar of biopsy is seen.

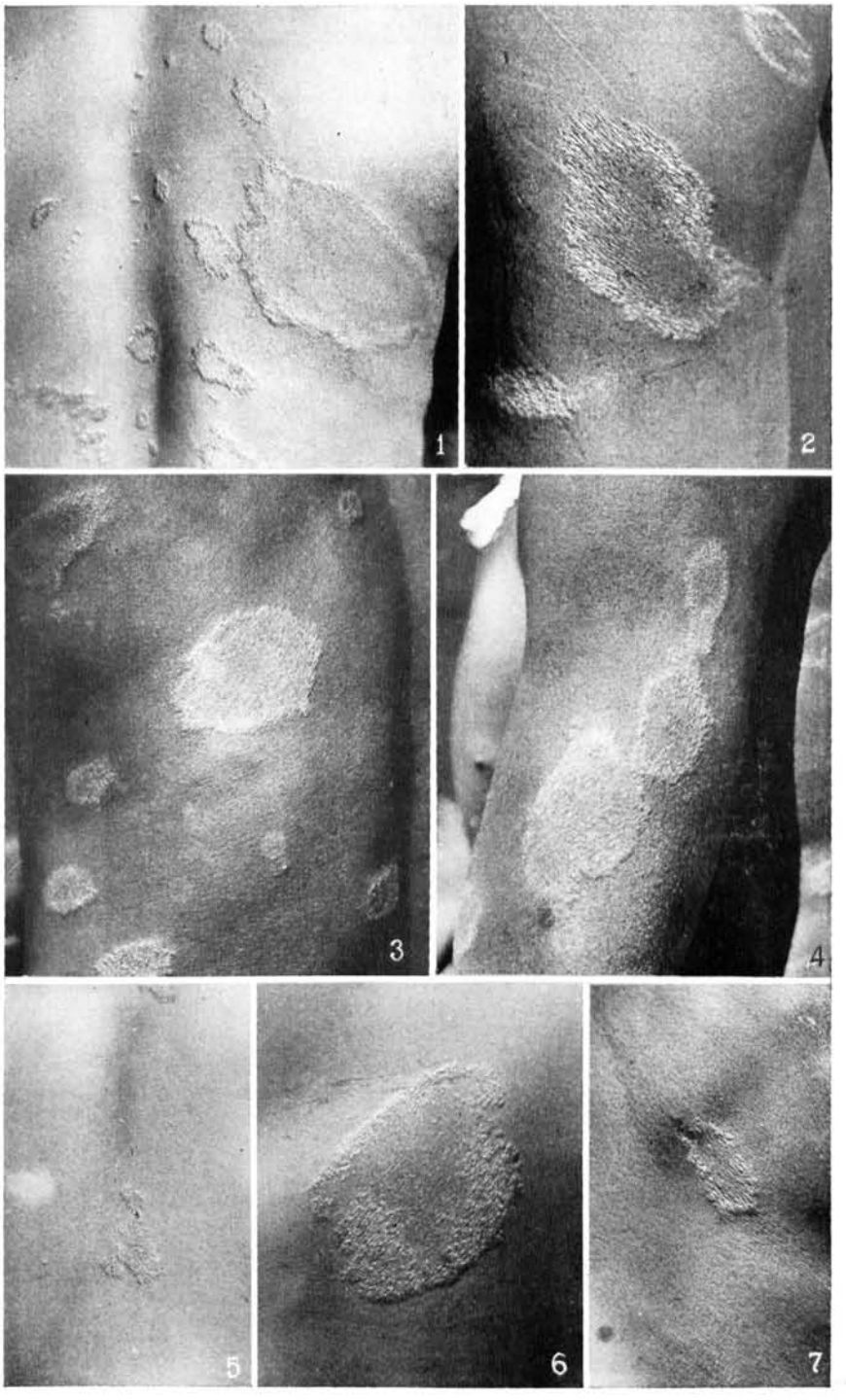


PLATE 1.

PLATE 2

FIG. 8. Extensive macules, edges very irregular, zones narrow and finely nodulate. On the neck are striking circinate lesions.

FIG. 9. Extensive compound macules, very irregular in width, markedly papillate. Case 3. (Fig. 13 from the same patient.)

FIG. 10. Relapse of supposedly healed lesions. A narrow active zone of slight infiltration and moderate erythema just outside of the border of a previous, paler area. (The scars seen are due to native treatment.)

PLATE 2.

PLATE 3

FIG. 11. Smooth and abrupt-edged plaque on cheek, and a small round area on the neck. (A single acid-fast bacillus was found in each of two smears from this plaque.)

FIG. 12. Plaque on cheek much as in Fig. 11 except that the edge is less abrupt. Other lesions over the lower jaw and on the neck (circinate). Case 7. (Figs. 3 and 4 from the same patient.)

FIG. 13. Irregular-edged, diffuse-zone lesion on arm, biopsied, Case 3; suture still in place. (Fig. 9 from the same patient.)

FIG. 14. Extensive "flank lesion" spreading over the back and chest; the axillary space was not invaded. Scar of biopsy specimen seen; Case 8; tissue was taken from the edge but the lesion extended in the month that elapsed before this photograph was taken.

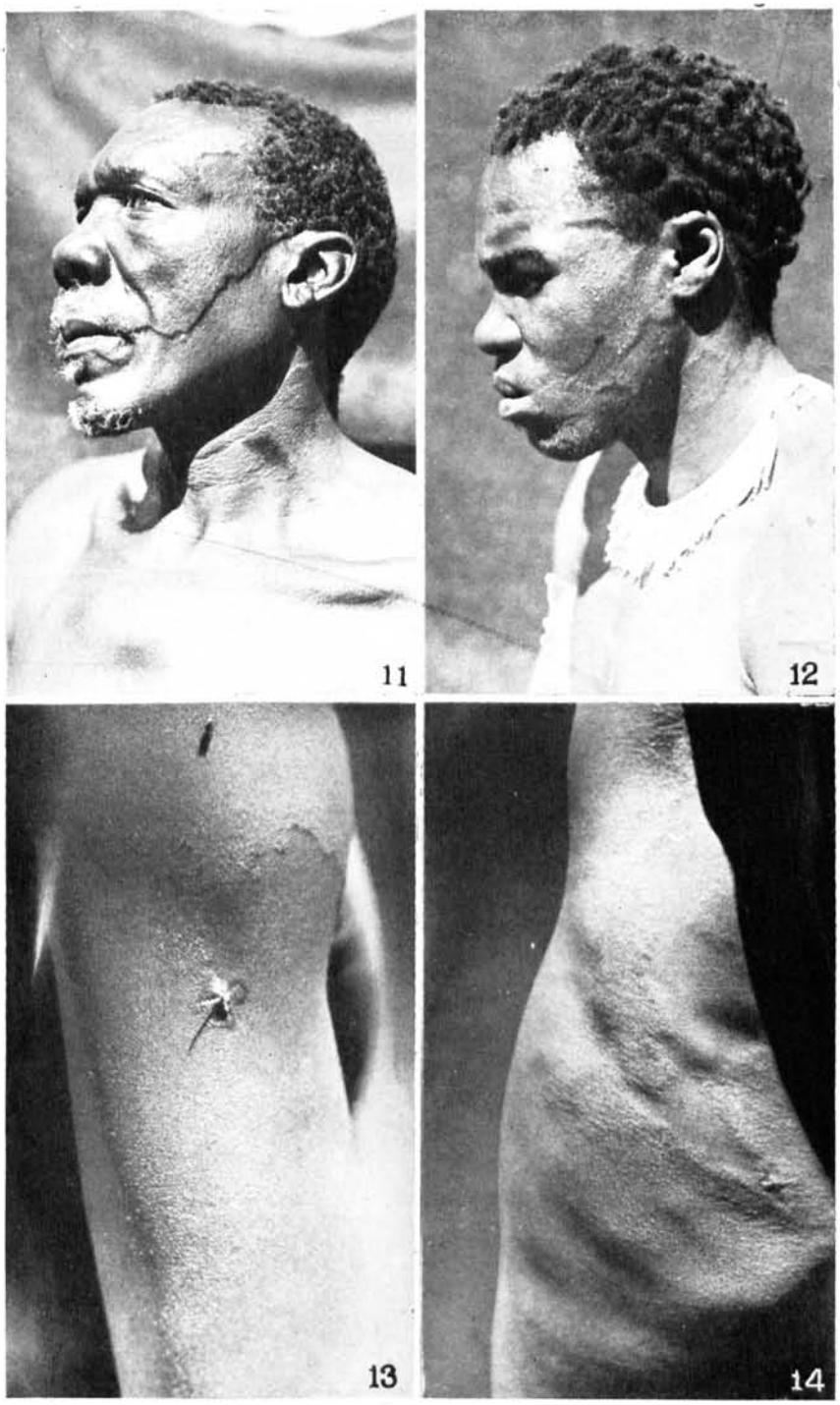


PLATE 3.

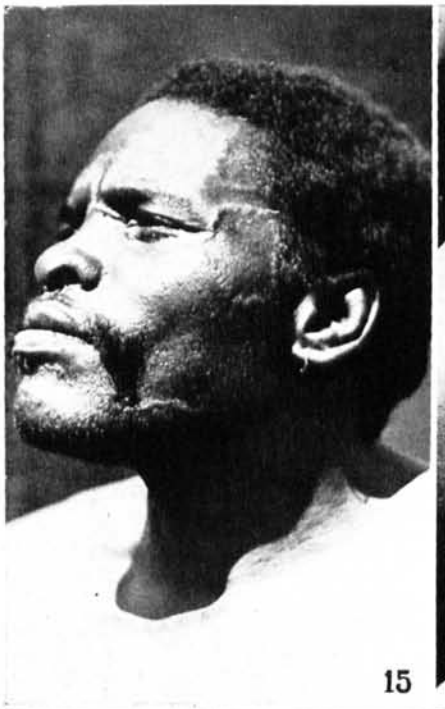
Plate 4

Fig. 15. A striking ring lesion on the upper cheek, and an open linear one running across the chin onto the cheeks on both sides. Case 5. (Fig. 16 from the same patient.)

Fig. 16. A discontinuous ring on upper arm. Biopsy specimen, Case 5, from this lesion. (Same patient as Fig. 15.)

Fig. 17. A curved, linear lesion crossing backward over the grossly enlarged great auricular nerve, up along the hair line and across the ear onto the cheek, disregarding tissue conformation. Another lesion passes upward from the corner of the mouth. Biopsy specimen, Case 9, from a third one on the other cheek.

Fig. 18. Irregular linear lesions in an infiltrated back-ground, the only lesions on the person, supposedly of 25 years' duration. Biopsy, Case 10, from this lesion.



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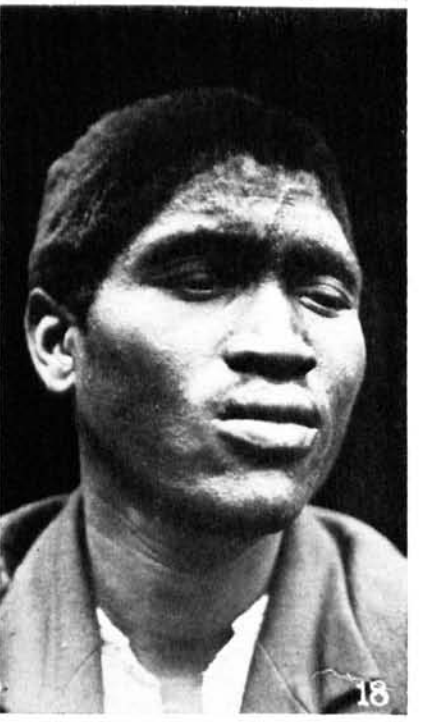

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PLATE 4.

Plate 5

Fig. 19. Bilateral segmental shoulder lesions, the most conspicuous changes in the case. Biopsy specimen, Case 6, from the left one, about the middle.

Fig. 20. Similar shoulder lesion, closer. Case 1; place of biopsy indicated by scar. (Fig. 21 from the same case.)

Fig. 21. Discontinuous, coarsely papular zone on lower back, outlining the pelvis. Residual (?) areas on the buttocks. Case 1. (Fig. 20 from the same patients).

Fig. 22. Herpetiform ring of papules, very recent, outlining a pale macular area on the left side of chest. Patient a female child. (Fig 23 from the same patient.)

Fig. 23. The same lesion about a month later. Some papules have subsided, but others have increased and are forming small solid collections. (White spots are artefacts in the negative.)

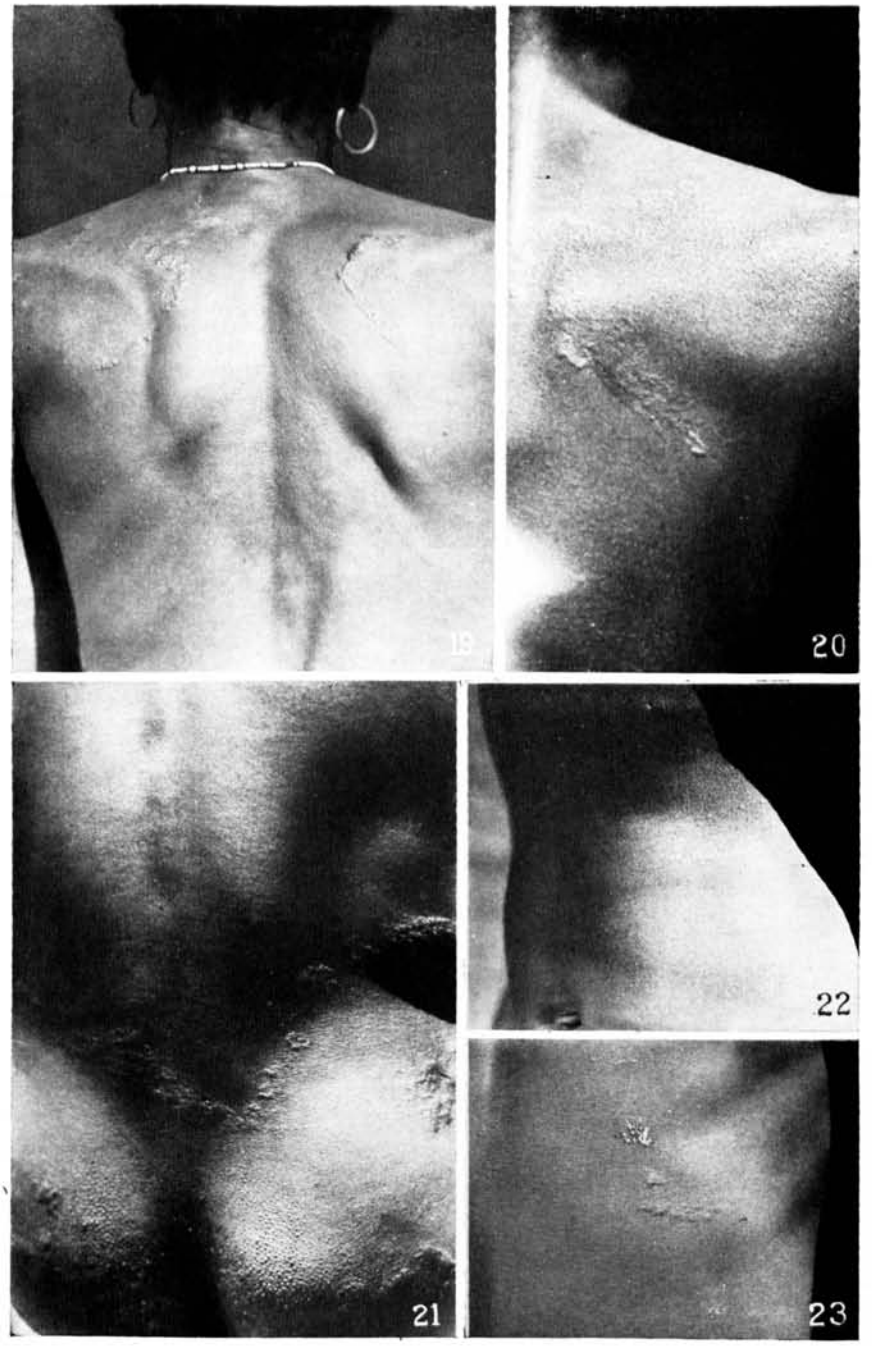

PLATE 5.

Plate 6

Fig. 24. Extensive, irregular merging, broad-margined lesions on back. High on neck (out of focus) is an unusual annular lesion. Biopsy specimen, Case 11, from the upper portion of this lesion; scar visible.

Fig. 25. Extensive, compound plaque-like lesions on back. The edges are abrupt, the margin narrow, but resolution very incomplete. Scar of biopsy specimen, Case 13, seen high on the left.

Fig. 26. Smooth-edged, smooth-surfaced, uniformly narrow marginal zones, undoubtedly tuberculoid, the lesion evidently deep-seated, the appearance more like that of the condition as met in other countries than are most of the lesions pictured here.

Fig. 27. Cutaneous-type infiltration of thigh, margin not infiltrated, surface smooth, ichthyoid, biopsied for comparison. Case 14. Bacteriological smears positive.

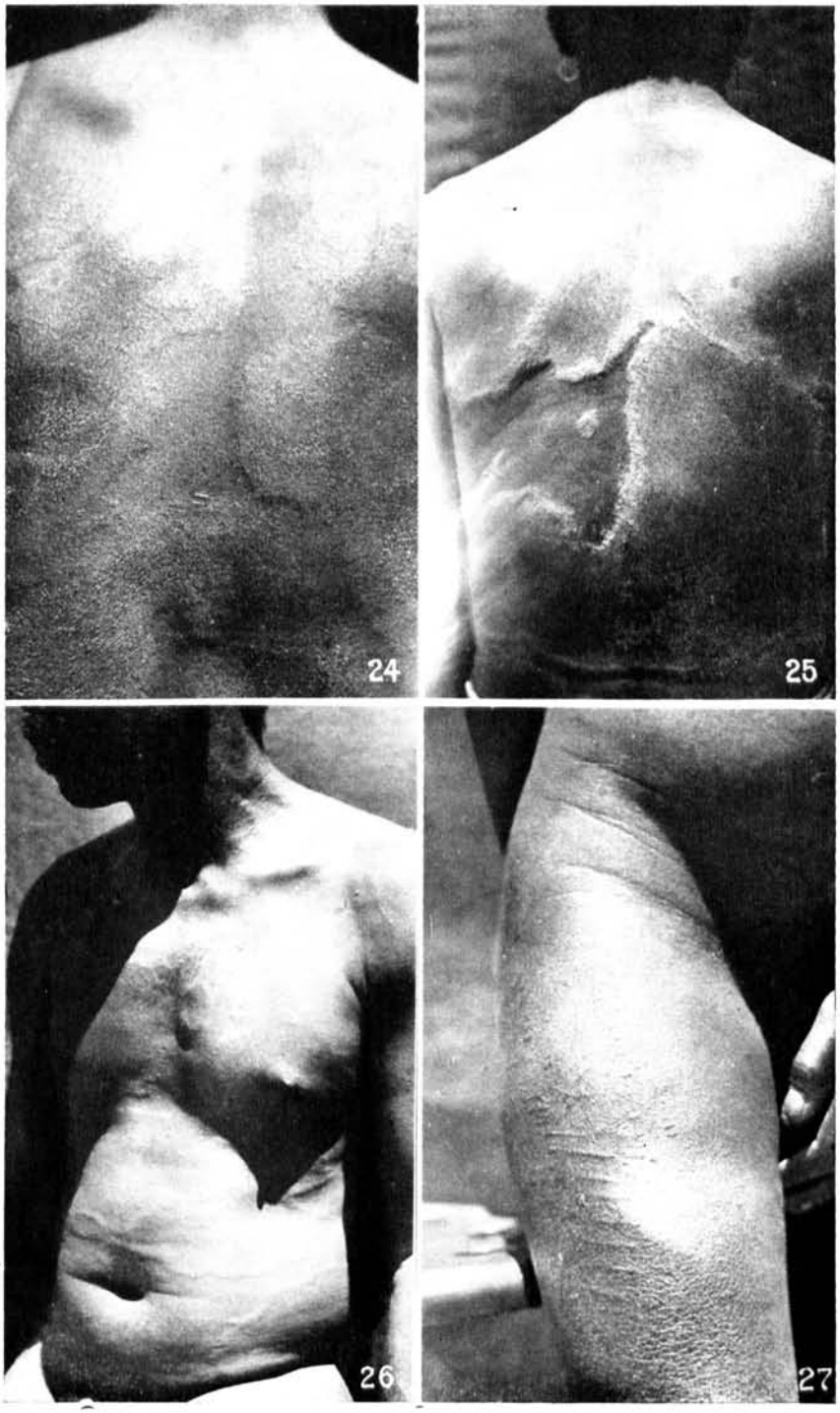

PLATE 6.

PLATE 7

FIG. 28. This lesion (a) has an abrupt, tuberculoid beginning, the uninvolved end showing no transitional condition, and (b) is confined to the papillary layers. ×50. Case 1; Figs. 34 to 37, inclusive, are from the same specimen.

FIG. 29. Showing extension of the superficial lesion into new territory, with transition from a tuberculoid focus along a subpapillary blood vessel, about which there is only round-cell infiltration, without epithelioid cells. ×100. Case 5; Figs. 30 and 46-50 from the same specimen. (The point marked X corresponds to that similarly marked inFig. 47.)

FIG. 30. A small pre-tuberculoid focus in advance of the actual lesion. Some of the cells are of the large mononuclear type, apparently about to undergo ipithelioid change. ×250. Case 5; from the same specimen as Fig. 29 but from a different level.

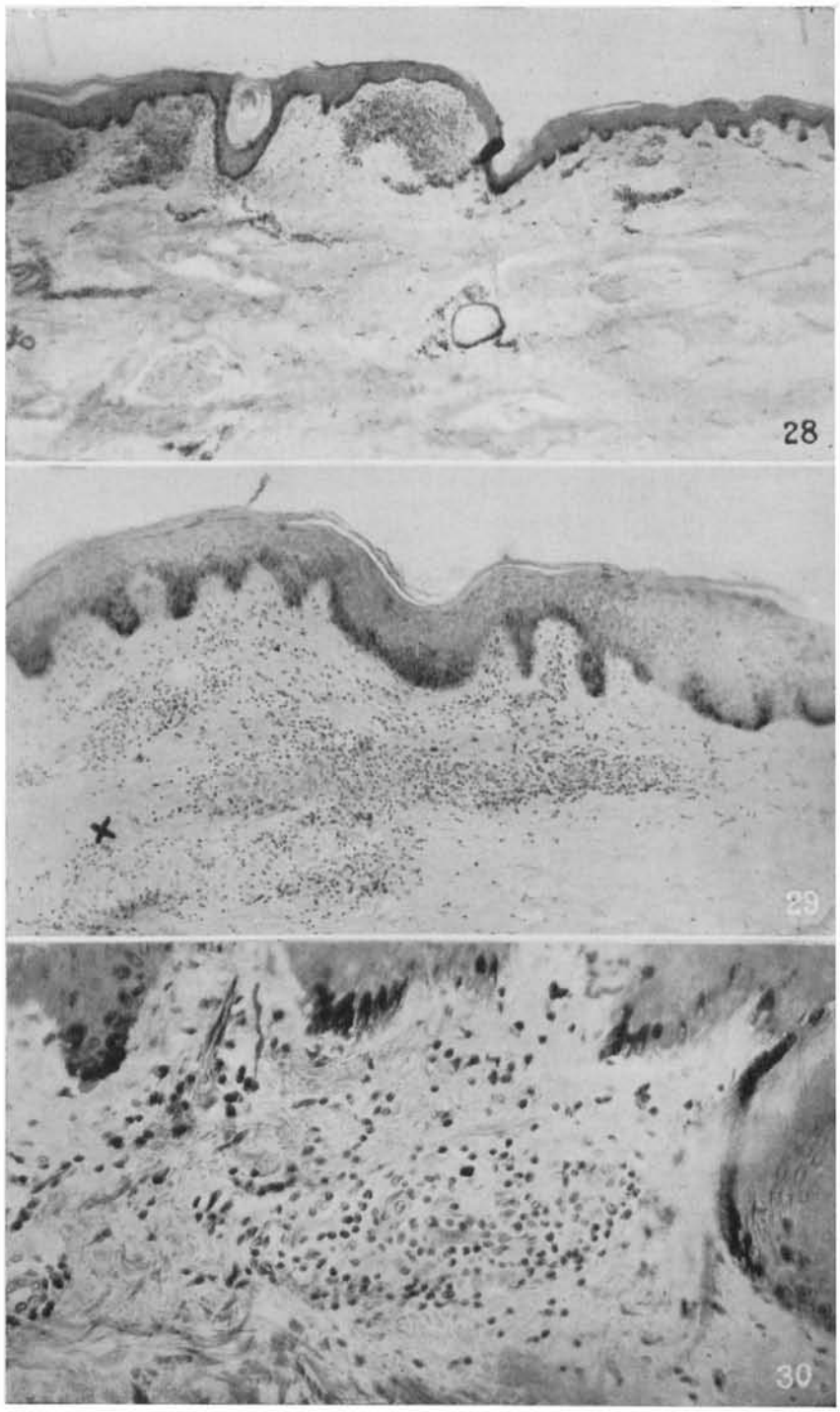

PLATE 7.

Plate 8

Figs. 31 to 33. Serial sections showing stages of a continuous perivascular tuberculoid lesion in the subpapillary (upper reticular) layer. In Fig. 31 a large focus surrounds two or more small vessels; it connects with the lesion of the papillary layer in another level of the specimen. In Fig. 32 a single vessel has separated off, surrounded by a sheath of granuloma containing a few epithelioid cells, which in Fig. 33 are more numerous and include two or three small giant cells. The vessel concerned is indicated at A. In Fig. 32, above the main lesion and coursing to the surface, is a smaller one (marked B); in Fig. 33 it has joined with the main lesion. ×100. Case 4.

Figs. 34 to 37. Serial sections of a small tuberculoid in the papillary layer, located in relation to a sweat duct. In Fig. 34, a section from high in the lesion, the epithelioid cells are few. In Fig. 35, from a few sections lower, the lesion is at its maximum and contains a couple of giant cells. In Fig. 36 it is much reduced and the sweat duct upon which it lies is in sight in the lower part of the picture. Fig. 37 is from below the level of the duct, the opening of which is in the epidermis. There remains no trace of the particular epithelioid focus which has been followed, though at the left is a focus the start of which can be traced in Figs. 35 and 36. At the right is a round-cell collection beneath which, in a lower level, is another epithelioid collection. ×125. Case 1; Fig. 28 from the same specimen.

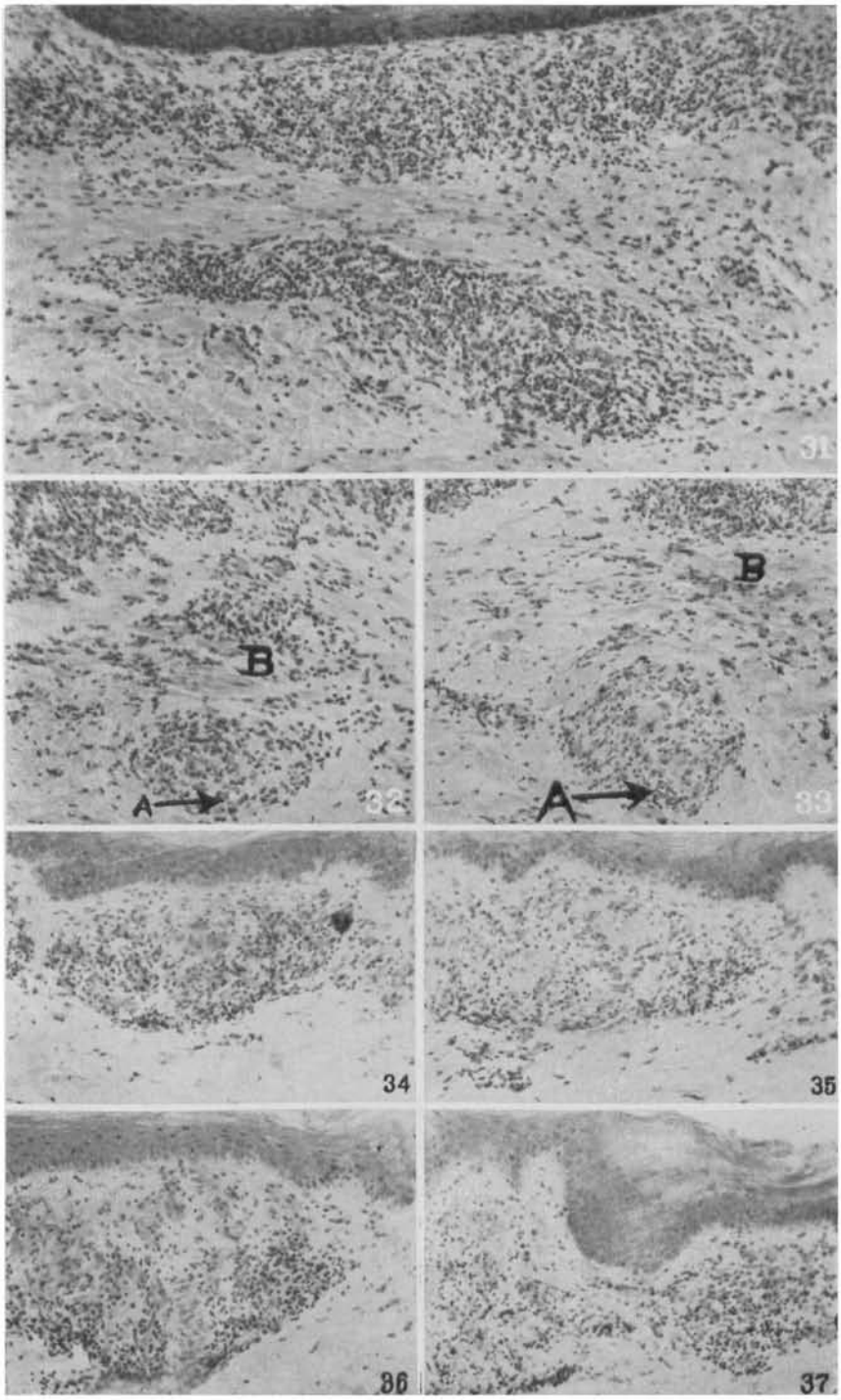

PLATE 8.

Plate 9

Figs 38 to 43. Serial sections of a solitary tuberculoid which formed a discrete papule, as is evident from the epidermis. In Fig. 38 the epithelioid cells are few but unmistakable. In Fig. 39 is a tangential section of the giant cell cut lower in Fig. 40, where separate epithelioid cells are not conspicuous. In Fig. 41 is a group of epithelioid cells which underlay the giant cell and which continues for a space (Fig. 42) but soon disappears completely. In Fig. 43 there remains only a trace which without other sections, would of necessity be called pre-tuberculoid. ×200. Case 2.

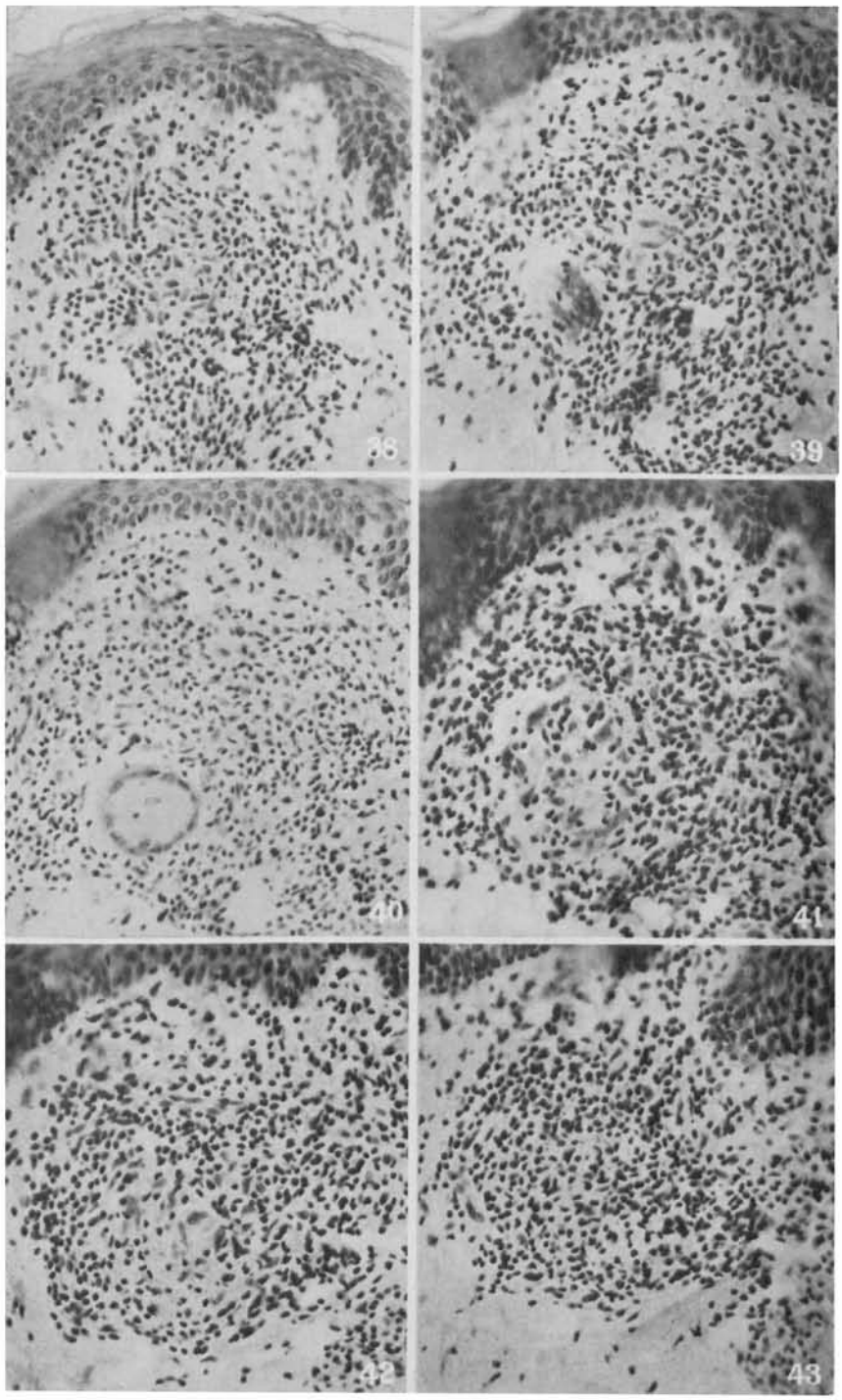

PLATE 9.

Plate 10

Fig. 44. A large tuberculoid in the papillary layer, elevating the epidermis. The abundance and appearance of the epithelioid cells and the presence of several large giant cells indicates unusual activity. ×110. Case 4.

Fig. 45. A large, very active tuberculoid with numerous small giant cells and actual erosion of the epidermis. ×35. Case 6.

Figs. 46 to 48. Large epithelioid areas unusual in size and in semblance to Boeck's "sarcoid" tuberculide. In Fig. 46 the lesion is in the papillary layer and has caused marked thinning of the epidermis, almost to the point of destruction. That in Fig. 47 is in the upper reticular layer; that in Fig. 48 is deeper, near the subcutis (not shown) and in relation with a sweat-gland area. ×70. Case 5; Figs. 29 and 30, and 49 and 50 from the same specimen.

Figs. 49 and 50. Small foci of necrosis in the specially active epithelioid lesions of Case 5 (see Figs. 46-48). In Fig. 49 it is hardly definite, with only a few cells involved, but in Fig. 50 the change is more extensive and the epidermis is much affected. ×140. Case 5.

Figs. 51 and 52. Unusual fibrosis of recovered tissue with thickening of the papillary layer. The lines drawn indicate roughly the level of the subpapillary plexus. ×55. Case 6.

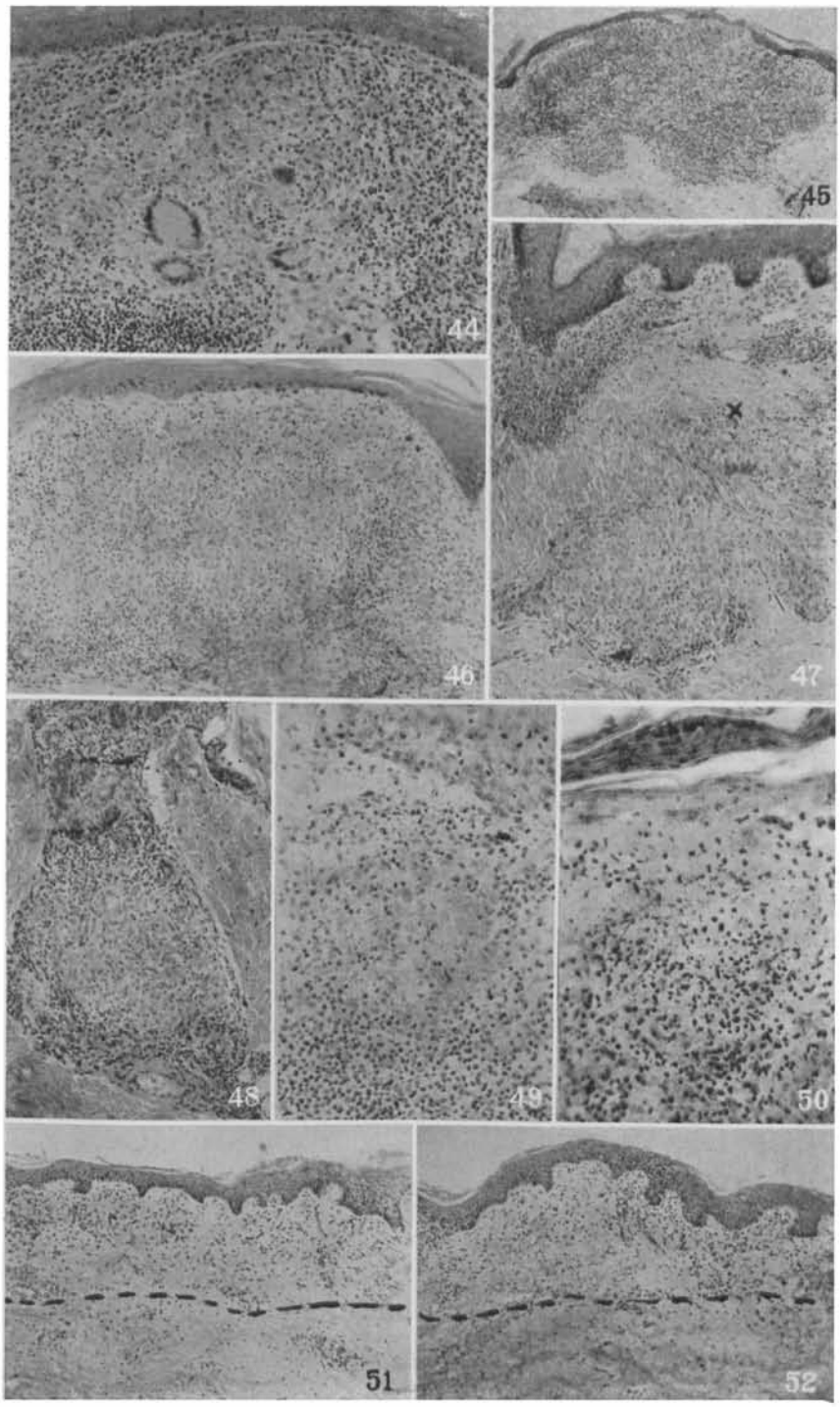

PLATE 10.