

TUBERCULOID CHANGES IN LEPROSY¹

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In recent years there have appeared increasingly numerous studies of tuberculoid leprosy by various authors. Some of them, as Wade and Lowe, have directed their attention to the clinical manifestations of those forms of the disease which can be classed as tuberculoid on clinical grounds. Reviewing the pictures of such cases that have been observed in the tropics, one must agree with the views of these authors. Though some of their cases present clinical pictures similar to those of the common forms of the disease, many that have been described and documented with excellent photographs are absolutely different from the typical ones. Such are many of those dealt with in the richly illustrated reports published by Wade and his collaborators in this JOURNAL since 1934. Similar cases had previously been reported by Darier and by Pautrier and Boëz. The lesions shown in the photographs of Rabello do not differ from lupus and Boeck's sarcoid.

Little has been written of cases of the tuberculoid form of the disease in northern countries. It is therefore of interest to compare with the reports from tropical regions the observations which I have made personally in Russia. These concern three cases among those in the Krutyje Rutschji leprosarium, classified as *lepra maculo-anesthetica* under the old system. Their lesions, which need not be described in detail since the manifestations of that form of the disease are well known, were biopsied for histological examination. In them were found tuberculoid changes, not typical of such macules. In four other patients tuberculoid changes have also been found histologically.

CASE 1. Patient P. T., 50 years old, fisherman, born in the Rostov District. A brother and two sisters have leprosy. The first symptom, which appeared in 1914, was pain in the feet; nodules appeared on the face in 1920. On admission there were diffuse reddish infiltrations over the face,

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nodules on the body and extremities, and infiltrations of the tibial regions. At the time of biopsy there were non-elevated rose-colored macules in various places; dark brown ones were present on the hips, and reddish-brown ones on the legs (Fig. 1). There were extensive areas of anesthesia, and atrophy of the muscles of the hands.

Histological examination.—The epithelium is atrophic, thinned, the stratum corneum scaling, the prickle-cell layer composed of three or four rows of ordinary cells, the germinative layer missing completely or composed of flattened rectangular cells. In the papillary layer is a thick, diffuse infiltration of nonspecific nature, arranged in elongate streaks lying parallel to the epidermis and one above the other; between them are narrow bands of connective tissue. The uppermost of these infiltrations are in immediate contact with the epidermis and destroy the palisade-shaped layer of the stratum germinativum. In the deeper layers of the cutis there is a rather extensive infiltration, consisting only of lymphocytes, surrounding the nerves and blood vessels, the walls of which are thickened. This infiltration extends upward, ramifying and fusing with that in the papillary layer. In the lymphocytic infiltration in the upper and medial layers of the skin are to be found here and there limited, round, focal aggregations composed of epithelioid cells and containing giant cells of the Langhans type with eccentrically arranged nuclei (Fig. 5). No bacilli were found in appropriately stained sections.

This case presented a common clinical picture of leprosy with flat macules without peripheral elevation. Histologically there was the picture common to such macules, nonspecific banal inflammation around the nerves, extending upward and ramifying in the papillary layer. But there was also an unusual finding for such lesions—foci of tuberculoid structure, epithelioid accumulations with giant cells.

CASE 2. Patient S.M., 19 years old, laborer. The grandparents, often visited by him, had leprosy. In 1932 a spot appeared on the left upper arm, others later on the body and the extremities. In April, 1934, at the time of the biopsy (abdomen), there were macules on the upper arms, body, and over the right knee. These macules, rose-colored with discolored centers, were not elevated above the level of the skin (Fig. 2).

Histological examination.—The epithelium is of atrophic appearance, the horny layer almost completely missing, the granular layer represented by a row of cells, the prickle-cell layer composed of several layers of cells most of which are changed, with light zones around the nuclei—the “*altération cavitaire*” of Leloir. The cells of the germinative layer are flattened in many places, strikingly lower than normal, and in some places the regular palisade layer is destroyed. The intrapapillary extensions, however, are well developed and even lengthened. In the cutis are numerous rounded nodules, located in the papillary layer near the epithelium. For the most part they are discrete, not confluent, separated by unchanged connective tissue. In structure they are extraordinarily similar, composed for the most part of epithelioid cells but with a rather large number of lymphocytes. There are also giant cells, of varying numbers and sizes, of the Langhans type with eccentrically arranged nuclei (Fig. 6). Similar epithelioid foci are also found in the deeper

layers of the skin, beside the hair follicles. On staining with Sudan III no lipid element could be found. Bacilli were not demonstrated.

In this case there were well-marked clinical manifestations of leprosy: macules of typical appearance, of reddish color with discolored centers and complete loss of sensibility. Histologically there was found, instead of banal nonspecific chronic inflammation, a picture like that of lichen scrofulosus, not distinguishable from tuberculous changes.

CASE 3. Patient M. K., 46 years old, laborer. Sick since 1927, at which time a macule appeared on the thigh. Others soon appeared on the other extremities. In April, 1934, at the time of biopsy (thigh) there was found a large area covering the whole of the left thigh anteriorly. The peripheral part appeared as a zone of bluish-red color; the central part was discolored as compared with the surrounding skin. On the left ankle were areas, 3 to 9 cm. in size, composed of separate small spots the size of a millet grain and of brownish-yellow color. The grain of the skin in the macules was exaggerated. In this case the peripheral zone was a little higher than the surrounding skin (Fig. 3).

Histological examination.—The epithelium is of common appearance, with marked "altération cavitaire," the nuclei sickle-shaped. The intrapapillary plugs are oblong, some longer than normally—*akanthosis*. From the papillary layer, immediately under the epidermis, down to the subcutis there are found many epithelioid nodules. As in the second case, they consist mostly of epithelioid cells with light-staining nuclei, a rather large number of lymphocytes, and Langhans giant cells (Fig. 7). These foci are usually separated by connective tissue, but in some places they are confluent and form large accumulations. Changes of the connective tissue are to be seen in places, where it takes on a dirty reddish color with the van Gieson stain. Some bundles are difficult to separate from each other, having degenerated into short fragments and undergone necrosis (Fig. 8). Stained with Sudan III, small lipid inclusions of brownish-yellow color are found in some of the epithelioid foci, and the cytoplasm of the giant cells is of the same color. The foci of altered connective tissue are rather light yellow. No Hansen bacilli found after appropriate staining.

In this case also there were macules of typical appearance, but contrary to the preceding one there were also large ones with discolored centers and pink marginal zones that were elevated above the surrounding skin. Histologically there were foci of infiltration occupying all of the cutis and reminding one of the changes in lupus pernio. Notable is the presence of lipid particles in the epithelial cells, staining brownish-yellow like the lipoids of the Virchow cells. Lipoids were also present in the Langhans giant cells and in the necrotic foci of the connective tissue.

CASE 4. Patient A. O., 25 years old, born in Siberia. There were no cases of leprosy in the family, and the patient had never seen one. In

January, 1930, the left hand became edematous; two weeks later both feet were edematous, and after another 2 weeks pink spots appeared on the chest, back and hands, and the face became swollen. In March, 1930, the patient was admitted to the dermatological clinic of the 1st Leningrad Medical Institute. At this time he had some red plaques with sharp edges and elevated margins on the face and extremities. Face, right hand and both feet were moderately swollen. Temperature discrimination lost on the forehead; sensibility for pain and touch diminished in the plaques. Sensibility completely absent on the extremities, involving the unaffected skin. Mucous membranes not affected. Wassermann reaction and Pirquet test negative. Leprosy bacilli not found in smears of the contents of blisters (after CO₂) in the lesion areas, or in material obtained by puncture of an inguinal lymph node. Biopsy of a plaque of the face was performed, and an inguinal gland was removed. Parts of the specimens were inoculated under the skin of a guinea pig. Autopsy of the animal performed after one year revealed no tuberculous changes.

Histological examination.—(a) Skin: The epithelium is thin and of atropic appearance. The keratinized layer consists of several layers; the prickle-cell layer is represented by two or three rows of ordinary cells, around some nuclei of which is the "altération cavitaire"; the basal layer is changed, the cells being flattened, of rectangular shape, their palisade-like arrangement destroyed at many points. In the cutis are accumulations of nodules, mostly situated immediately beneath the epithelium, which consist mainly of epithelioid cells with typical nuclei, with large numbers of lymphocytes and also giant cells with marginal nuclei. The individual foci are separated from each other by connective tissue. These nodular foci are found not only in the papillary layer, but also extending far into the tissue, so that they infiltrate all of the cutis.

(b) Lymph node: The whole glandular tissue is studded with a large number of small foci consisting almost exclusively of epithelioid cells (Fig. 9). In only a few of them are giant cells of the Langhans type to be found.

In this case there were numerous clinical infiltrations with elevated margins, and rather marked disturbance of sensation. The microscopic examination revealed the presence of epithelioid foci with Langhans giant cells in the skin, the condition not distinguishable from Boeck's sarcoid. The same is to be said of the changes seen in the lymph node examined. Hansen bacilli were not found in either of the specimens, and an animal inoculation experiment was negative.

CASE 5. Patient N.B., 56 years old. No leprosy in the family or in the environment. Born in the town of Ssimbirsk, he lived for eleven years in Astrakan. In 1934, after an attack of influenza, one hand became very painful, later swollen and red. Thereafter macules appeared on the upper arm and on the face. In 1935 he was admitted to the Leningrad leprosarium with infiltrations on the forehead, cheeks, chest, back, upper arms and hands, sacral region, hips, knees, calves and feet. These lesions were round, firm and of brownish-red color, 2 to 12 cm. in diameter. Complete lack of sensibility in some of the infiltrations, in others only marked diminution. Atrophy of the interosseous muscles of the hands.

Histological examination.—The epithelium is thin, the intrapapillary cones poorly developed and missing entirely in many places. The horny layer is well developed, the granular layer consists of two rows of cells, the prickle-cell layer of three to four rows, the basal layer is of ordinary appearance. In the cutis are numerous accumulations of nodules, most of them sharply circumscribed and of different sizes, consisting of epithelioid cells, more or less numerous lymphocytes, and Langhans giant cells. Isolated foci extend from the upper layers of the cutis to the subcutaneous connective tissue (Fig. 10). After staining with Sudan III, very small lipid inclusions of a yellow color and nuclear appearance can be seen in the epithelioid cells, and the protoplasm of the Langhans giant cells is of a diffuse yellow color. Ziehl-Nielsen staining for bacilli revealed in one focus deep in the cutis, at the margin of the subcutaneous connective tissue, large accumulations of red granules and groups of short bacilli.

In this case there were cutaneous infiltrations of different sizes and of brownish-red color, strongly reminiscent of the diffuse infiltrated form of the miliary lupoids. Histologic changes typical of lupus pernio and Boeck's sarcoid were found—well-developed foci of epithelioid cells, lymphocytes and Langhans giant cells, separated by broad strands of connective tissue. In the epithelioid cells lipid bodies of small size were present, and the giant cells were colored diffusely yellow with Sudan III. Red granules were found after staining by the Ziehl-Nielsen method.

CASE 6. Patient L., 26 years old, born in the Baltic Provinces. The parents and a brother had leprosy. In 1927 there appeared in the tibial region nodules which became confluent in a short time. Infiltrations of various kinds appeared on the face and the extremities afterwards. In January, 1930, red nodules appeared on the cheeks, upper lips and chin, confluent in some places; and on the upper extremities were infiltrations that represented former nodules, and on the legs ulcers. Biopsy of a lesion on the hip was performed at this time.

Histological examination.—The epithelium is on the whole little changed. In the cutis is a massive diffuse infiltration, which reaches to the epidermis. It consists mostly of histiocytes, rather numerous lymphocytes and fixed connective tissue cells. Part of the histiocytes contain very numerous vacuoles—Virchow cells. The cutis is markedly thickened and penetrated throughout by this infiltration (Fig. 11). In the deepest layers, near the subcutis, are numerous and sharply delimited accumulations composed mostly of epithelioid cells, lymphocytes and Langhans giant cells (Fig. 12). Bacilli are found in the form of large clumps and smaller groups situated in the vacuoles of the lepra cells.

In this case there were, clinically, nodules and infiltrations of common appearance, typical of nodular leprosy. Histologically the structure was that characteristic of that form of the disease—the leprous granuloma with Virchow cells and bacilli.

On the other hand, in the deeper layers of the skin only epithelioid nodules with giant cells were found, without lepra cells.

A seventh case, observed together with Dr. A. A. Wyschnewsky, is wholly different from the preceding ones and will be reported separately. It was of neural type, without skin lesions but with nodulations of the nerves of the upper extremities. Histologically these lesions showed a caseating condition with the classical appearance of tuberculosis of the inner organs.

DISCUSSION

In none of the several cases here reported, in which tuberculoid changes were found histologically, was there the clinical picture of which Darier, Pautrier and Boez, Wade, Rabello and others have described as a special form of leprosy. Never have I been able to observe typical clinical changes which would permit one to say, without histological examination, that in a given case the lesions would show the tuberculoid structure. Never have I found lesions of the kinds observed and described in connection with patients in the tropics, with characteristic lichenification or the presence of papulate peripheral margins of purplish color. Contrary to the findings of the workers mentioned, I have seen only unusually variegated clinical pictures; with the exception of the case in which there were nodules in the nerves without skin lesions, the cases showed the common leprous macules with discolored centers and rose-tinted margins, or erythematous plaques, or typical infiltrations which were not differentiable from the ordinary ones of the nodular form of leprosy.

As is known, the tuberculoid changes are to be seen in various forms of leprosy. The majority of descriptions of such changes pertain to its neural form (Kedrowski, Klingmüller, Cochrane, Delamaire, etc.). But they are also known in the nodular form (Brutzer, Dohi, Molesworth and Tebbutt), and also in mixed leprosy (Kayser, van Houtum, Garzella and P. Unna). The tuberculoid condition which I found in Case 1 evidently represents a transition of ordinary macules to the tuberculoid form; and similar observations have been reported by others (Jadassohn, Kedrowski, Rabello). Tièche observed the contrary process, disappearance of the tuberculoid changes in a transition to the nonspecific infiltration.

In all of my cases, in which the clinical picture was so

varied, there was found a histologically particular structure in the lesions. Predominant were more or less numerous nodular cell-accumulations. In all of these the dominant element was the epithelioid cells, besides which there were larger or smaller numbers of lymphocytes and typical, peripherally nucleate Langhans giant cells.

In some of the cases there were observed changes of the epithelium which are unusual for leprosy. Though there were flattening and atrophy, the intrapapillary projections persisted. The arrangement and forms of the cells of the basal layer were disturbed, evidently because the infiltration of the cutis came into immediate contact with the epithelium. Perhaps the fact that the intrapapillary projections remain intact can be explained on the same grounds as in tuberculosis of the skin, namely, the reaction of the epithelium and its participation in the inflammatory process in the cutis, as was shown by me in connection with lupus vulgaris.

In spite of the fact that the nodular (i.e., focal) lesion-substrate was the same everywhere in the specimens studied, the general appearance of the histological changes differed in the individual cases. There was either a condition like lichen scrofulosis, with nodules in contact with the hair follicles; or pictures which were reminiscent of those of lupus; or changes that were in no way differentiated from Boeck's sarcoid or lupus pernio; or, finally (in the nerve case mentioned) nodules with caseous degeneration typical of tuberculosis of the inner organs. In one case with changes of the sarcoid type that condition was not confined to the skin, but was also found in an inguinal lymph node. Therefore, in spite of the common general tuberculoid structure in all of these cases, the picture as a whole was variegated histologically as well as clinically.

The findings were also inconstant with regard to the presence of the Hansen bacillus in this condition. In spite of many attempts to demonstrate them in the eruptions it was usually impossible to do so; but on the other hand they may be present in large numbers. Bacilli in tuberculoid lesions have been reported by Lisi and Sebastiani, Quérangel des Essarts and Lefrou, and others. Thus even in relation to the bacilli, the described findings are not of the same value.

Turning to discussions in the literature of the nature of the cells and other changes in the leprous tuberculoid struc-

ture, all investigators have found the nodular foci to be made up of epithelioid cells, lymphocytes and Langhans giant cells. Kyrle and Hamdi also observed the lepra cell of Virchow, as I did in one of my cases. The vacuoles in epithelioid cells described by me were also noted by Kedrowsky. Tuberculoid changes were found in some of my cases that showed clinically typical leprous infiltrations (*Ulpromes en nappe*) and lepromas. Kyrle and Gans also observed such changes in lepromas. In the case reported by Brutzer, with illustrations, the skin lesions are doubtless to be considered as lepromas.

Eranzquin and Seminorio noted histological features in the tuberculoid leprotic changes which they believed to permit their differentiation from those of tuberculosis, but the opinion is not confirmed by my study. They mention four characteristics, as follows:

1. The giant cells are in the centers of the lesion-foci, which do not have the appearance of tuberculous ones. In my cases there were lesions that could not be distinguished from the classical ones of tuberculosis; and in the atypical foci the giant cells were variously located, sometimes at the periphery and sometimes centrally.

2. The infiltration in leprosy is greater than in the lupoids, and less limited by the surrounding connective tissue. This feature also was not to be seen in all of my cases.

3. In leprosy the infiltration is more superficial than in the lupoids, and is separated from the epithelium by a layer of connective tissue. As can be seen from the descriptions, the infiltrations in my material occupied first the upper layers and then spread directly downward as far as the subcutaneous tissue. Most of the specimens were marked by the spread of the infiltration in the papillary layer, as noted by Darier and by Klingmüller, resulting in the enlargement of the papillae. In contrast with the typical structure of the leproma, in the tuberculoid lesion there is not a subepithelial layer of connective tissue which is free from involvement.

4. In the tuberculoid lesions of leprosy, they say, there is not seen the proliferation of the epithelium that occurs in tuberculosis. The contrary condition was found in my material.

Klingmüller emphasizes the sharp limitation of the infiltration, as in sarcoids. From the descriptions of my specimens it is to be seen that this peculiarity is not always present.

In the cases here described a general characteristic is a certain parallelism between the clinical appearance of the lesions and their histological structure. In those in which the eruption was macular, there were found isolated lesion-foci or small aggregations of them, mostly around the hair follicles, the condition resembling lichen scrofulosus. In the cases with clinically slight infiltrations the histological picture resembled that found in the flat forms of lupus—lupus planus. In the cases with more marked, thick lesions the changes observed were not distinguishable from those of lupus pernio and sarcoid.

Thus we have, clinically as well as histologically, different pictures in the tuberculoid lesions of leprosy. Clinically there are gradual transitions from macules to marked infiltrations. Histologically there are changes varying from those similar to lichen scrofulosus to those typical of the leproma. Reiss, and also Quérangel des Essarts and Lefrou, have observed tuberculoid changes in the various forms of leprosy, and also in transition forms. Lowe has recorded the transition of tuberculoid cases to the nodular form. Everything points to the conclusion that the tuberculoid condition is not characteristic of a definite form of the disease. It is known that the tissue change is not only typical for tuberculosis, but that it also occurs in syphilis (third stage), fungus infections and other diseases. In the lesions of tuberculosis the proliferative character of the process is very marked, especially in tuberculosis of the skin.

In such lesions of the infections mentioned there is evidence of an especially marked allergic state—for tuberculosis in patients with lupus, for syphilis in the gummatous stage. Such lesions in trichophytosis are accompanied by especially marked allergy. It is difficult to believe that leprosy is an exception in this respect, and many facts indicate the contrary. In it the tuberculoid changes occur as a rule in the macular forms, and my material was mostly of that kind. Now it is known that it is just such cases that are distinguished by definite specific allergy. Mitsuda, Mariani, Bargehr, Ferrari, Hayashi, Stein and Steperin and others have dealt with the reactions to specific antigens which occur clearly in the macular and neural forms of the disease. The forms with macules are characterized by the mild course of the leprous process; in them the general condition is less affected than in nodular leprosy, the inner organs are less involved, and the expectation of life is greater. Tuberculoid changes in leprosy are manifestations of

a peculiar condition that is evidently associated with high immunity. Those which I found in the nodular form of the disease are not in any way contradictory to that idea; the patient formerly was affected with the macular type and in a skin test for cutaneous allergy gave a reaction as strong as would be expected in a macular case. Wade, Lowe, Quérangel des Esarts and Lefrou, Lisi and Sebastiani and many other authors consider the tuberculoid changes as a manifestation of allergy.

In one of the cases described focal changes of the connective tissue were found, in the form of cloudy-staining fibers and necrosis (Fig. 8). Such findings are known to be significant of an allergic condition. It would be of interest to ascertain, in more abundant material, how often they occur in leprous lesions; perhaps this will serve as a new evidence of the allergic nature of these tuberculoid lesions of leprosy.

Finally it is necessary to point out the difficulty of diagnosis in some of the cases of leprosy with tuberculoid changes. One of the above cases (No. 4) was demonstrated before the Leningrad Dermatological Society for diagnosis, but unfortunately none was made. The one without skin lesions was diagnosed by distinguished neuropathologists as neurofibromatosis. In both cases, besides a careful analysis of the clinical picture, which bespoke the leprous nature of the manifestations, animal inoculations were made. These gave negative results, eliminating the possibility of tuberculosis which was suggested by the histological findings.

CONCLUSIONS

On the ground of the clinical observations and histological investigations in the cases here reported, the following conclusions can be drawn:

1. Leprotic lesions which histologically present tuberculoid changes are clinically of various kinds—macules, infiltrations and nodules of the nerves.
2. Histologically the tuberculoid lesions of leprosy are like those seen in other conditions—lichen scrofulosus, lupus, Boeck's sarcoid, and even tuberculosis of the internal organs.
3. There is a certain parallelism between the clinical picture and the histological structure.
4. The existence of gradual transition forms between one kind of lesion and another, both clinically and histologically,

is evidence against the existence of a special tuberculoid form of the disease.

5. In the tuberculoid lesions a proliferative reaction of the epidermis is observed, and sometimes focal necrosis of the connective tissue of the cutis occurs. Lipoid inclusions in the epithelioid cells may also be found.

6. With regard to the presence of the leprosy bacillus, the tuberculoid lesions are not all alike.

7. Tuberculoid changes are an expression of a peculiar allergic condition, which is apparently accompanied by a strongly developed immunity, and usually they bespeak the benignity of the case.

8. The diagnosis of some cases with tuberculoid lesions is difficult.

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DESCRIPTION OF PLATES

PLATE 4

- FIG. 1. Reddish-brown, flat macules on both legs. Case 1.
FIG. 2. Rose-colored flat macules with pale centers. Case 2.
FIG. 3. Bluish-red, somewhat elevated macules. Case 3.
FIG. 4. Small, prominent brownish-red infiltrations. Case 5.

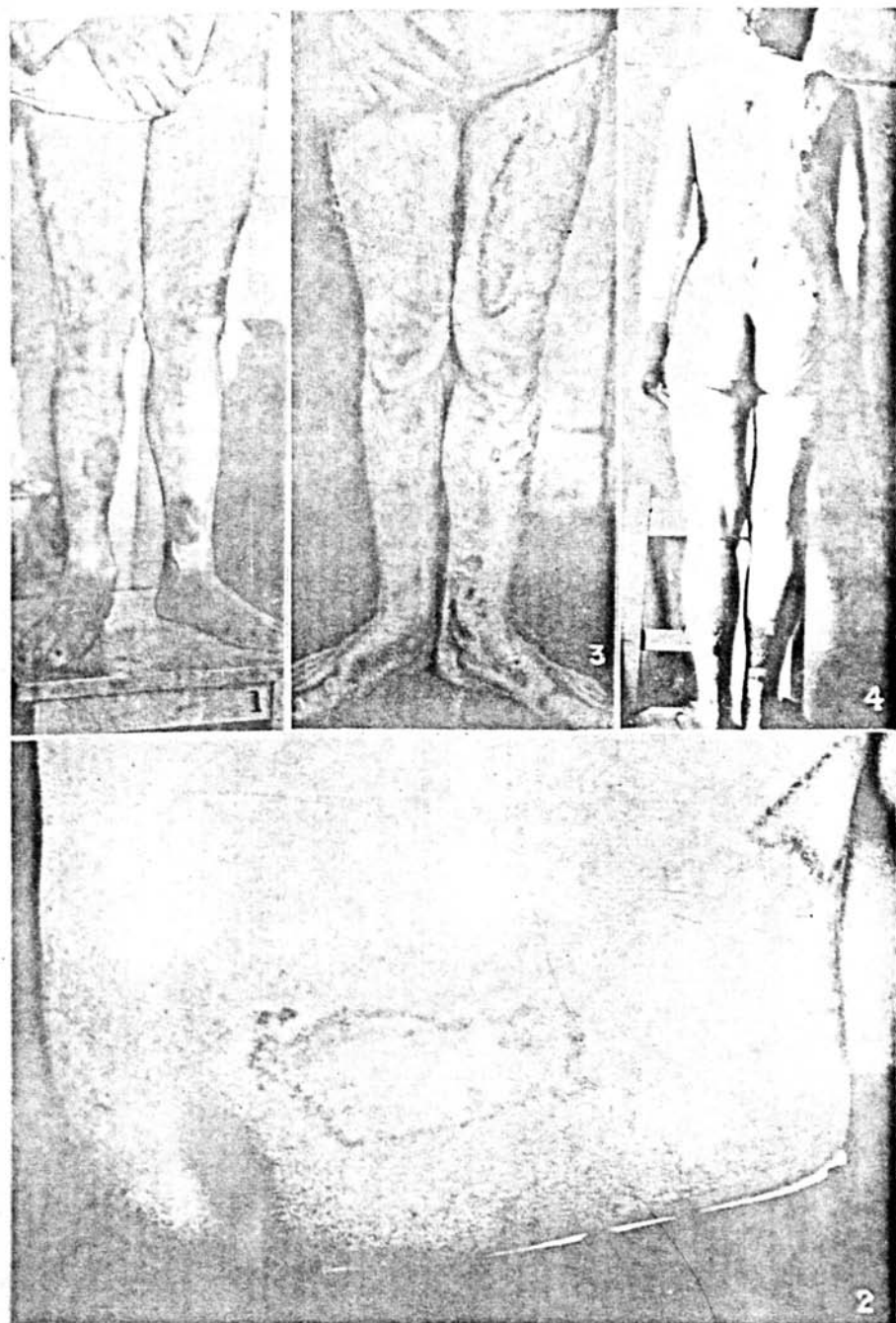


PLATE 4

PLATE 5

FIG. 5. Lymphocytic infiltrations of the cutis in which there are foci composed of epithelioid cells with Langhans giant cells. Case 1.

FIG. 6. Typical tuberculoid structure—foci of epithelioid cells and giant cells with lymphocytes. Case 2.

FIG. 7. A focus of epithelioid cells containing Langhans giant cells with marginally-located nuclei. Case 3.

FIG. 8. Two foci of connective-tissue necrosis beneath the epidermis. Case 3.

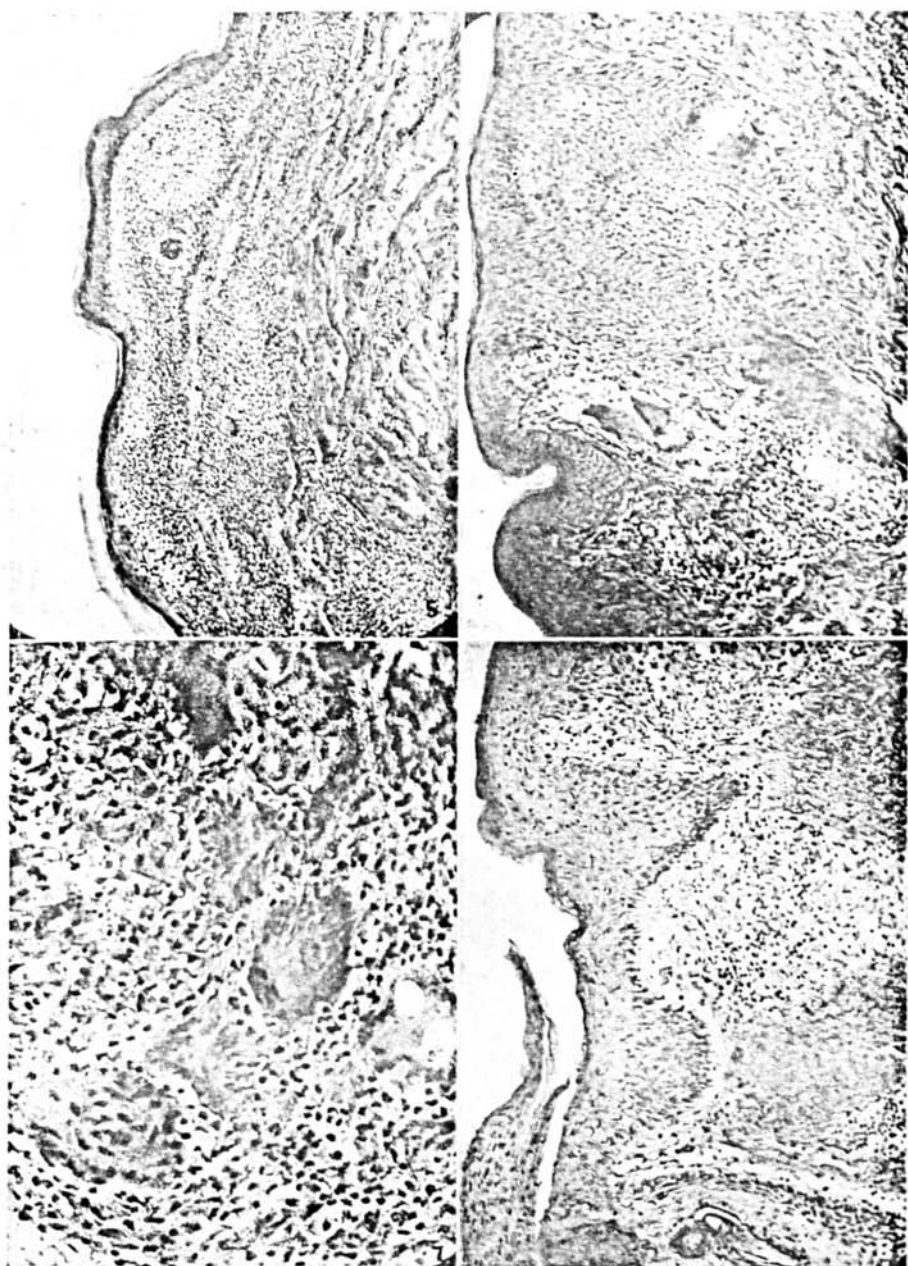


PLATE 5

PLATE 6

FIG. 9. A dense lymphocytic infiltration with small epithelioid-cell foci in the periglandular tissue. Case 4.

FIG. 10. Lesion composed of isolated foci of infiltration, microscopically not distinguishable from lupus pernio or Boeck's sarcoid. Case 5.

FIG. 11. Typical leprous granuloma.

FIG. 12. The same preparation, at the border of the subcutis. Epithelioid-cell foci with giant cells of the Langhans type.

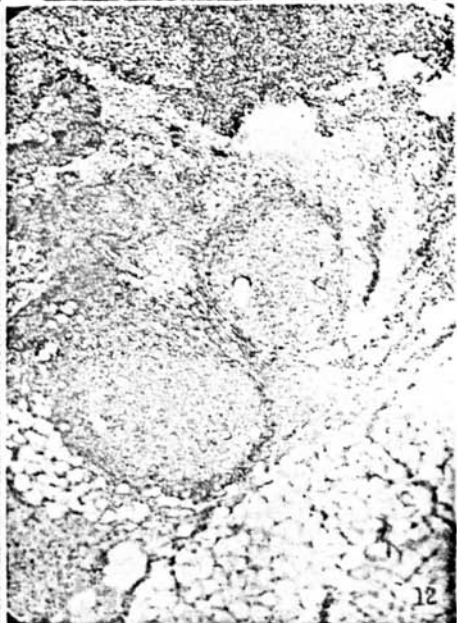
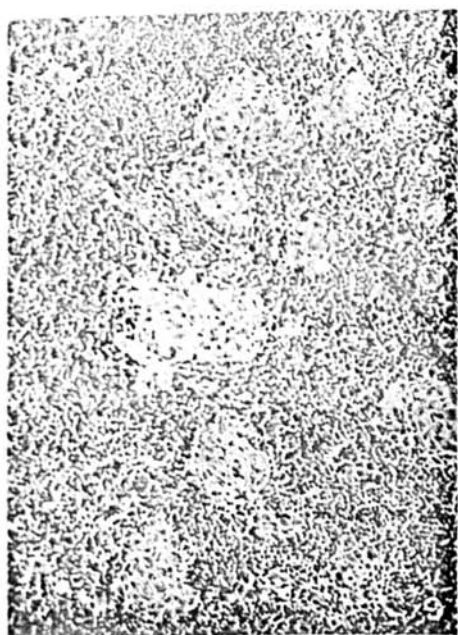


PLATE 6

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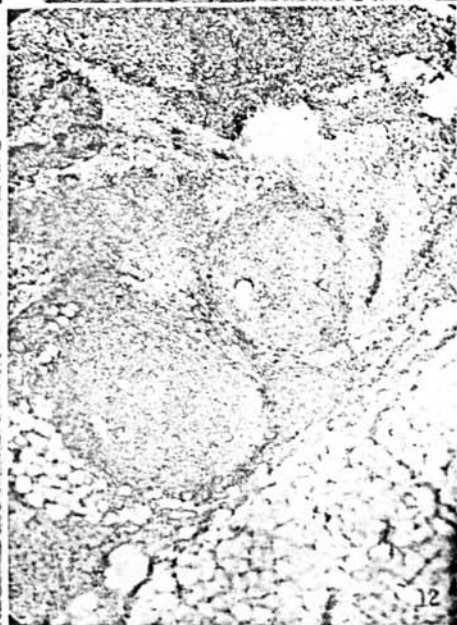
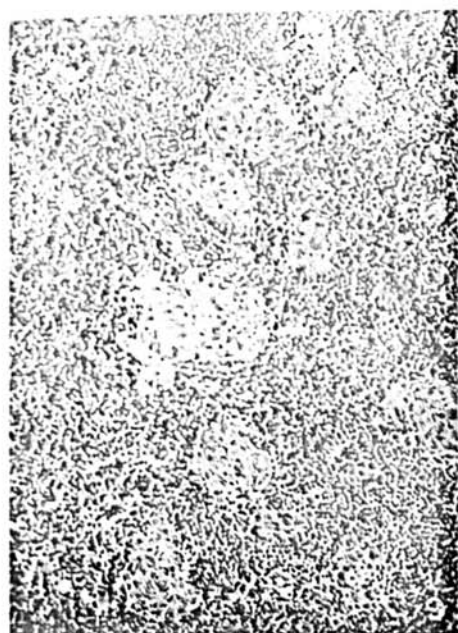


PLATE 6