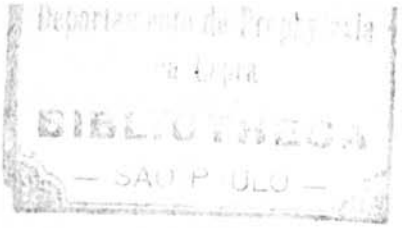

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TUBERCULOID LEPRA REACTION[1]

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In cutaneous leprosy there are observed with certain frequency instances of acute development of lepra reaction, the causes of which are not always easy to establish. Similarly in tuberculoid leprosy, a variety of the disease which daily is acquiring greater importance, there may occur periodical reactional changes in the lesions, but these present clinical, bacteriological and histological manifestations that are very distinct from the condition in cutaneous leprosy. Though common lepra reaction is well known, the tuberculoid reaction has not been observed, or, better, has not been interpreted or described as such.

Wade has recently made an excellent clinical and histopathologic study of lepra reaction in tuberculoid lesions based on several cases observed by him recently in South Africa (6, 7). Six cases were observed in the Emjayana Leper Institution, of which three were confirmed histologically. The rest were bacteriologically negative and presented a clinical picture similar to that of tuberculoid reaction. In some cases the condition appeared after the ingestion of potassium iodide, while in others it was spontaneous. Clinically the predominant lesions were annular ones with elevated, smooth, infiltrated violaceous borders; there were also nodular elements of the same color. In these *M. leprae* was not encountered, or only in small numbers. Wade described two cases with intense reaction and others of moderate degree, called attention to the good general condition of the patients and to the histological picture, which is frankly tuberculoid of marked degree, with great proliferation of epithelioid and giant cells.

PERSONAL OBSERVATIONS

Among the cases that were collected for my study of tuberculoid leprosy (4), seven were in a state of reaction. Of a majority of them (five) it was possible to make a clinical, bacteriologic and

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histopathologic study, which is summarized in the histories in the last portion of the present report. At this point are presented certain considerations which emerge from the study of these cases.

ETIOLOGY

The cause of the tuberculoid reaction is almost always difficult to establish. In two of the cases reported by Wade it resulted from the ingestion of potassium iodide, but in others the cause was not apparent. In three of our patients (including Cases 1 and 2) it appeared spontaneously, without their having received medication; in one (Case 3) it followed the administration of a series of injections of aniline drugs; the remaining three were under full chaulmoogra treatment. It should be noted, however, that many patients with the tuberculoid form of the disease have not undergone reaction in spite of having taken large quantities of potassium iodide.

All of these reaction patients were adults about forty years of age, the proportions among males and females being equal.

CLINICAL STUDY OF THE PROCESS

Onset.—The reaction almost always begins in a benign and insidious manner. The patient does not suffer any general disturbance, and attention is called only to the congestion of some or all the lesions, or to the appearance of new ones, depending upon the intensity of the condition. The eruption increases and spreads slowly, and may take from a week to a month or more to become fully established.

General condition.—A striking feature of the reaction state is the excellent general condition of the patient. There is no fever and no muscular or articular pains, so frequent in the common lepra reaction, appetite is maintained, there is not even slight wasting, and the patient continues with his habitual occupation.

Character of the lesions.—The character of the eruption varies according to its intensity. It may be limited to a few lesions, or it may be generalized, affecting all of them; it may be moderate in degree or very intense, and new, much-infiltrated lesions may appear and ulceration may occur.

In local reactions there may be, at the periphery of nonreacting lesions (which, as is known, are characterized by margins of coffee or caramel color, rough to papular, the central portions being normal in appearance or achromic), other lesions that are in reaction, distinguished by greater infiltration and elevation of the borders, which are very much wider than the others and usually smooth, congested and violaceous.

In generalized reactions one may see, besides the annular plaques described, papular to nodular elements of various sizes which are raised above the surrounding

skin level, with smooth shiny surfaces, and pinkish, coffee-colored, or more commonly wine- or ham-colored. The consistency is succulent, and gives a rubbery impression to the touch. Sometimes the lesions in reaction are covered by scales, presenting in some cases a frank psoriasiform aspect.

In intense reaction the congestion and infiltration reach a maximum. Nodules predominate, the borders of annular lesions are wide, and completely infiltrated plaques are conspicuous. Some of the lesions may be elevated more than 1 cm. above the skin, and some may become ulcerated.

The disturbances of sensibility, in the nodular lesions as well as in the plaques, are much more marked than in cutaneous leprosy.

Regression.—The eruption may persist from a month to a year or more, and I share with Davidson the opinion that there is no direct relation between the intensity of the condition and its duration. Regression may also be very slow. The nodules and the infiltrated borders lose their infiltration and become level, contracted and decongested, leaving manifestly atrophic residual marks of violaceous, coffee-like color.

BACTERIOLOGICAL EXAMINATION

A fact that attracts attention is that the reactive lesions, in spite of their activity, infiltration, and often frankly nodular aspect, usually give negative bacteriological findings. In the majority of my cases *M. leprae* was not found, either in the lesions or in the nasal mucosa. In some cases one or a few isolated bacilli were encountered, but they were very far from being as frequent or abundant as they are observed to be in cutaneous leprosy. Wade, in two of the cases with intense reaction, confirmed histologically, encountered a very few isolated bacilli.

HISTOPATHOLOGY

Histologically it is usual to encounter a frank tuberculoid structure in the lesions with reaction, but the process is more exuberant, more active, more productive than ordinarily. The lesions of the epidermis are not characteristic; there may be acanthosis, parakeratosis, atrophy and even erosion. The basal layer generally is respected, but it is not rare to encounter invasion of the epidermis by the infiltration, and at times even the presence of giant cells.

The dermis is the principal seat of the infiltration. However, instead of being in small foci that are more or less disseminated follicles, as in tuberculoid leprosy without reaction, the process is much more diffused. It generally invades the entire dermis and consists of typical follicles in which the epithelioid and giant cells are typical and peculiarly abundant. These follicles are generally separated by con-

nective tissue, but in the very intense processes they coalesce, and occupy large areas. The surrounding dermal tissue is proliferated and swollen. Polynuclear leucocytes are also abundant, and there is dilatation of the capillaries and evident tumefaction of its endothelial cells.

ERYTHROCYTE SEDIMENTATION AND LEPROLIN TEST

It is worth while to digress here to consider the interesting results that were obtained with the leprolin and erythrocyte sedimentation tests in the patients with acute tuberculoid reaction. They appear to be of a great value in differential diagnosis and as regards prognosis. Their study may afford us interesting suggestions in the field of the epidemiology and pathogenesis of leprosy.

In brief, while in nodular cutaneous leprosy and in common lepra reaction the erythrocyte sedimentation is high, and the leprolin reaction is almost always negative, all the patients with tuberculoid lepra reaction that were tested gave oppositive results. In no case was sedimentation more than of moderate degree, and in all of them the leprolin test was frankly, and even intensely, positive. The results are summarized in Table 1.

TABLE 1.—*Leprolin test and erythrocyte sedimentation index in tuberculoid lepra reaction.*

Case	Leprolin test	Erythrocyte sedimentation index
No. 1	++	28 - 4
No. 2	+++	42 - 30 - 22
No. 3	++++	29 - 48 - 32 - 49 - 22
No. 4	+++	36
No. 5	++++	37

In Cases 1 and 2 the sedimentation index was taken both during and at the end of the tuberculoid reaction. It can be seen that the sedimentation index descended to the medium range when the reaction regressed.

The reactions obtained with the intradermal leprolin test varied from a papule to a nodule, very similar clinically to the nodules of the reaction itself. Histological examination of these little leprotic nodules showed them to be of frank tuberculoid histology, the same as that of the tuberculoid lesions in reaction.

These results—strongly positive leprolin test and low erythrocyte sedimentation index—indicate an intense defensive reaction on the part of the organism. This evidence inclines me to believe that the

process probably depends upon the presence of *M. leprae* and a sensitization to it, and that if the bacilli are not found it is because the defensive reaction has overcome them and caused them to disappear. Also in favor of this view is the favorable evolution of the process, whether spontaneously or under treatment. Particularly significant is the observation in Case 4. Five months previously, when the patient was without reaction, a few bacilli were found, but during the state of reaction all of the smears were negative.

DIFFERENTIAL DIAGNOSIS

The polymorphism of the lesions with tuberculoid lepra reaction may at times simulate or be confused with certain dermatosis, as psoriasis, tricophytosis, erythema migrans, mycosis fungoides, lupus, etc. I shall not undertake to make a differential diagnosis in each particular case, but only to differentiate the condition as a whole, by its evolution, histology, and above all by the disturbances of sensation which are almost never lacking. The most important conditions to be differentiated are tuberculoid leprosy without reaction, cutaneous leprosy, and especially common lepra reaction.

Tuberculoid leprosy without reaction.—In this condition are found annular lesions with clear centers, narrow borders, infiltrated but with rough or papular surfaces of coffee or caramel color; while in the reaction state the predominant lesions are infiltrated plaques, nodules, and also annular elements in which the borders are wide, congested and smooth-surfaced, and the centers are also congested and violaceous in color. As already stated the histological changes, though they may be follicular in both cases, are much more intense in the reaction lesions.

Nodular cutaneous leprosy.—In this form of the disease are seen lepromata of all sizes, generally coffee-colored. Their evolution differs from the elements of tuberculoid lepra reaction in that the annular plaques and the congestion so common in that condition are lacking. Most distinctive are the bacteriological findings, lepromata yielding abundant bacilli and even globi, while the nodules of tuberculoid lepra reaction are generally negative. Moreover, the leprolin test is generally negative with patients that have lepromata, but intensely positive in tuberculoid lepra reaction. The sedimentation index is greatly increased (from 70 to 120) in the nodular form of the disease, while it is not much increased (less than 50) in tuberculoid lepra reaction.

Common lepra reaction.—Though in this condition there is reactivation of old lesions and new ones appear, they differ fundamentally because the process is an acute infectious, febrile one which is

generally grave; the other is a subacute, afebrile condition which does not affect the general condition of the patient and is of benign prognosis. There are a number of differential characteristics from the clinical, bacteriological, histopathologic and immunologic viewpoints which distinguish them fundamentally. These are summarized in the following tabulation:

COMMON LEPRA REACTION	TUBERCULOID LEPRA REACTION
Clinical features	
Abrupt development.	Mild and insidious onset.
General condition poor, often with fever and wasting.	General condition excellent, without fever or wasting.
Neuralgias and myalgias occur.	Pains never observed.
Typical polymorphic eruptions, with elements painful on pressure.	Annular plaques with wide borders, tubercles, nodules, painless.
Condition usually persists from several days to a month.	Usually persists from some months to more than a year.
Majority of the elements do not leave residual lesions.	Elements usually leave violaceous marks.
Bacteriological features	
Abundant bacilli always found, mostly granular.	Almost always negative; exceptionally a few bacilli.
Histopathology	
Lepromatous structure, marked congestion, polynuclears in and around vessels.	Tuberculoid structure, more accentuated than in the non-reacting tuberculoid forms.
Erythrocyte sedimentation	
Much increased, greater than 90 mm.	Slightly or moderately increased, not greater than 50.
Leprolin test	
Always negative.	Always positive.

CLINICAL HISTORIES

CASE 1. Bautista B., Italian, age 48 years. First lesion noticed on neck one year ago; rounded, with erythematous border and clear center. A similar one appeared in right groin. Eight months later the groin lesion became congested, border infiltrated; that on neck was wholly infiltrated.

Examination (January, 1935): (*a*) On neck a small elevated, infiltrated plaque (nodular), violaceous, smooth-surfaced, rubbery in consistence. (*b*) In groin a larger oval lesion, violaceous centrally, with border wide (1 cm.), elevated, infiltrated, smooth, violet-maroon in color. (Plate 7, Fig. 1.) (*c*) Superficial auricular nerve enlarged (thickness of a pencil). *Leprolin*: ++. *Erythrocyte sedimentation*: 28-4. *Bacteriology:* Isolated bacilli found.

Histology: Superficial part of dermis occupied by typical tuberculoid follicles, separated into zones by dermal tissues or confluent with other foci, with halos of lymphocyte infiltration, localized especially around hair follicles and sweat glands. Capillary endothelium swollen. In some places the infiltration reaches the deeper part of dermis (Plate 9, Figs. 11 and 12).

Progress: Under treatment (chaulmoogra, etc.), the lesions became less congested and infiltrated, and in July, 1935, they had disappeared, even the enlargement of the auricular nerve, leaving only quite flat, pigmented border zones, with normal centers (Plate 1, Fig. 2).

Comment.—This is a case of a typical tuberculoid lepra reaction which has now almost totally regressed.

CASE 2. Isabel B., Spaniard, married, age 50 years. Late in 1933 a small lesion with slightly infiltrated, erythematous border and pale center appeared on middle third of left forearm, externally. In May, 1934, the first reaction appeared, with infiltrated, slightly erythematous lesions on face and extremities. Larger ones appeared within a month on back, buttock and right knee internally. Later all lesions became congested and more infiltrated.

Examination (January, 1935): In left superciliary region an annular lesion with much-infiltrated, elevated, erythematous border. Similar but more infiltrated lesions in right infrahyoid region, on lower lip and chin. On arms, forearms and shoulders other annular lesions, borders entirely infiltrated; centers in some slightly desquamating, in others smooth, normal in appearance. Also tubercles and nodules, most numerous on face, back and thighs; congested, infiltrated, smooth or slightly scaly (Plate 7, Figs. 3 and 5). *Leprolin:* +++. *Erythrocyte sedimentation:* 40-30-22. *Bacteriology:* Bacilli not found.

Histology: Epidermis normal except for atrophy of papillary layer in places. In papillary and subpapillary layers a complete confluent band of giant cells, lymphocytes and some leucocytes and fibroblasts; in some portions infiltration reaches to basal membrane, but usually it is separated by a band of connective tissue. Intermediate and deeper layers of dermis occupied almost throughout by typical follicles with epithelioid centers, usually with giant cells and halos of lymphocytes. Some isolated, but most confluent, forming nodules which embrace from 5 to 30 follicles. Localization mainly around the blood vessels and sweat glands, not altering their structure. Surrounding dermal tissue swollen, in parts seen as layers which separate the nodules. Capillaries dilated and vascular endothelium markedly swollen (Plate 9, Figs. 13 and 14).

Progress: After two months treatment with calcium chloride and ethyl esters the lesions began to subside and the congestion to disappear, especially on face and back. In June, 1935, there were only residual marks, of violaceous coffee color, with atrophy of the skin (Plate 7, Figs. 4 and 6).

Comment.—This is a typical case of tuberculoid lepra reaction which regressed (probably spontaneously) in about five months.

CASE 3. Ana B., Argentina, age 51 years. Admitted about two years ago with annular lesions, having infiltrated, papular, coffee-colored borders and clear centers, clinically and histologically tuberculoid, on arms, back, abdomen and buttocks. Treated for one year with chaulmoogra ethyl esters, without much change. Fluorescein injections begun but after two months the condition became worse; old lesions congested and numerous new ones over most of the body surface.

Examination: Two varieties of lesions. (*a*) Some, on back on admission. (Plate 8, Fig. 7). (*b*) Others, much more numerous, more diffuse, on face, upper extremities, etc.; these also annular but more erythematous, larger, with well infiltrated borders, smooth but usually congested. *Leprolin:* ++++. *Erythrocyte sedimentation:* 29-48-32-49-22. *Bacteriology:* Lesions with and without reaction negative.

Histology: The two varieties of lesions are distinct. Both are tuberculoid; but in the nonreacting lesions the process is much more attenuated and localized than in the others, where it is productive and exuberant. Dermis occupied by abundant, confluent follicles rich in epithelioid and giant cells. Dilatation of capillaries, with swelling of endothelium.

Progress: Treatment having been suspended, the reaction condition has slowly regressed, and at present the lesions are stationary, flat, and show a tendency to atrophy, like the nonreacting ones seen in Fig. 10 (Plate 8, Fig. 7).

Comment.—In this case of tuberculoid leprosy, proven clinically and histologically (3), a reaction occurred after a liberal treatment with fluorescein though we cannot assert that that treatment was the inciting cause. The condition was a typical tuberculoid lepra reaction, both clinically and histologically, but it affected only a part of the lesions, others remaining without reaction.

CASE 4. Rosa P., Argentina, age 41 years. *Examination* (January, 1935): On arms, rounded lesions with erythematous, infiltrated borders. On right leg, several plaques infiltrated throughout, color rose-maroon, with surfaces scaly. *Leprolin:* ++++. *Erythrocyte sedimentation:* 36. *Bacteriology:* Positive, bacilli found in every four or five fields.

Histology: Perivascular foci consisting predominantly of histiolymphocytic cells of reticular appearance. This, with the finding of bacilli, led us to suspect that the lesions were undergoing evolution to the lepromatous condition.

Progress: Patient was put under treatment, but for two months there was increase in size and degree of infiltration of the old lesions and new ones appeared. Plaques on legs became more infiltrated and eroded, while lesions on arms acquired a tricophytoid aspect. At present the leg lesions have tripled in size, centers ulcerated and borders elevated (Plate 8, Fig. 8). Arm lesions now large plaques of psoriasiform aspect, with wide, infiltrated borders and flat centers, of coffee-violet color and very scaly (Plate 8, Fig. 9). On thighs and buttocks similar lesions, and violaceous, infiltrated scaly nodules and plaques simulating psoriasis. [Compare Figs. 8 and 9 with that in an earlier report (4). *Bacteriology:* Despite the clinical changes, no bacilli found since the first examination.

Histology: Most of dermis occupied by multiple nodular foci localized around hair follicles and sweat glands. Some foci are constituted by vacuolated cells of reticular appearance, but the predominant ones have clear centers of epithelioid and giant cells and are surrounded by lymphocytic halos, characteristic of tuberculoid leprosy. Swelling of connective tissue and capillary endothelium (Plate 10, Figs. 15 and 16).

Comment.—The finding of a few bacilli at the first examination, and the histological finding of perivascular foci consisting predominantly of histolymphocytes of reticular appearance, suggested that we

were dealing with a case evolving into one with lepromatous lesions. However, the whole picture is one of tuberculoid leprosy which by its intensity, acuteness and histology, must be classed as tuberculoid lepra reaction.

CASE 5. Joaquin S., Italian, age 60 years. First lesions noticed four years ago on arm, face, and thighs; annular, of various sizes, with very infiltrated coffee-colored borders. Treated irregularly (elsewhere) with chaulmoogra ethyl esters without benefit. Eight months ago patient noticed progression, congestion, and especially infiltration of lesion on left brow. All others also increased and became congested, with new ones, erythematous or violaceous, with prominent, smooth, infiltrated borders, and nodular and tubercular elements on face, arms and thighs. Two months later still more infiltration and ulceration of lesion on forehead.

Examination (June, 1935): On right brow a large plaque of red, ham color, completely infiltrated, elevated almost 1 cm., with central irregular, seropurulent ulceration (Plate 8, Fig. 10). Elsewhere on face violaceous tubercles and nodules from corn-grain to almond in size. On upper and lower extremities and buttocks polymorphic elements, completely infiltrated, violet and maroon plaques and annular lesions with infiltrated smooth borders and clear centers. Similar, isolated, ones on back and abdomen. Alteration of pain sensibility in some, and of thermal sense in a majority. General condition good. *Leprolin:* ++++. *Erythrocyte sedimentation:* 37. *Bacteriology:* Negative.

Histology: Epidermis shows discrete hyperkeratosis. Most of dermis occupied by an infiltration, in parts appearing as typical tuberculoid follicles; peripheral lymphocytic halo slight; elsewhere confluent, forming large nodules of epithelioid cells, lymphocytes, leucocytes and giant cells. These nodules mostly around the blood vessels, hair follicles and sebaceous glands not altering their structure. Conspicuous swelling of dermal tissue, dilatation of blood vessels, and tumefaction of endothelium (Plate 10, Figs. 17 and 18).

Progress: After calcium injections for one month, ulceration on the forehead commenced to cicatrize and plaque on superciliary region to flatten out. At present (August, 1935) ulcer completely healed. Plaque on face and many on the extremities have flattened greatly, although the congestion and infiltration persist.

Comment.—Tuberculoid lepra reaction which, after eight months, has commenced to regress.

SUMMARY

Among twenty-five cases of tuberculoid leprosy the author has observed seven with "tuberculoid lepra reaction." Five of them have been studied clinically, bacteriologically and histologically.

The differential diagnosis between tuberculoid lepra reaction, nonreaction cutaneous leprosy, and lepra reaction in cutaneous leprosy is established.

The sedimentation rate and leprolin reaction have been studied in these cases and have been found of value in establishing the differential diagnosis and prognosis of this condition.

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DESCRIPTION OF PLATES

PLATE 7

FIG. 1. Plaque with wide, infiltrated, congested, smooth border. The center is violet-maroon in color and finely scaly. Lesion of Case 1 during the reaction. (See also Plate 9, Figs. 11 and 12.)

FIG. 2. Same lesion as in Fig. 1, taken six months later. Regression of the reaction.

FIG. 3. Wholly infiltrated plaques on the lips and chin and a wide-bordered annular lesion on the neck. Disseminated small tubercles and nodules here and there. Lesions of Case 2 during the reaction.

FIG. 4. Regression of the reaction in Case 2. Almost total disappearance of the plaques on the lips and chin, and of some of the nodules. The lesion on the neck is now flat and the border narrow.

FIG. 5. Annular lesions with infiltrated, smooth, congested borders and non-elevated centers. There are also small, uniformly infiltrated plaques and nodules of various sizes. Lesions of Case 2 during the reaction. (See also Plate 9, Figs. 13 and 14.)

FIG. 6. Regression of the reaction in Case 2. Infiltration completely disappeared and lesions flat, represented only by residual marks.

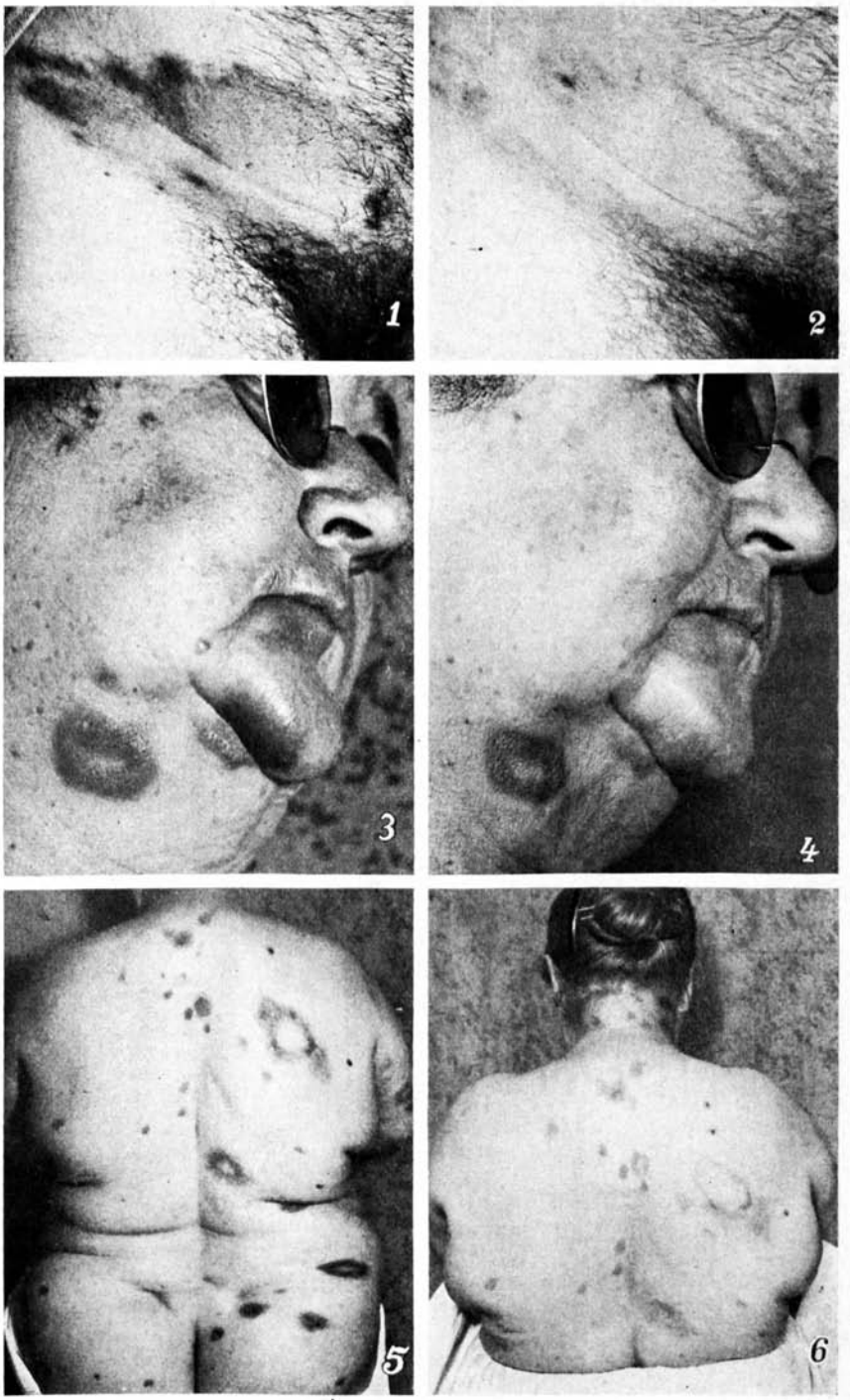

PLATE 7

Plate 8

Fig. 7. Local reaction. The lesions on the arms are in frank reaction, their borders much infiltrated and congested, while those on the scapular region and back show no evidence of reaction. Case 4.

Fig. 8. Erythematous, scaly, ulcerated plaques on the leg, Case 4, after the condition had become aggravated. Smears negative.

Fig. 9. Infiltrated plaques, with elevated borders, maroon and rose colored, scaly throughout, simulating psoriasis, in Case 4 after the condition had become exaggerated. (See Plate 10, Figs. 15 and 16.)

Fig. 10. Giant plaque involving the forehead, eyebrow and eyelid, greatly infiltrated and ulcerated centrally. Nodular and tubercular lesions on the face and arms. The spot marked with a circle is the result of the leprolin test, which was strongly positive. (See Plate 10, Figs. 17 and 18.)

PLATE 8

PLATE 9

FIG. 11. Section from lesion of Case 1 (see Fig. 1). Distribution of the infiltration in the superficial, medial and deep portions of the dermis. Typical follicular formations with Langhan's giant cells.

FIG. 12. Same lesion as Fig. 11, higher magnification. Invasion of the papillary portion of the dermis and of the epidermis by the infiltration, destroying the basal membrane and penetrating the Malphigian layer. Note the intensity of the infiltration and the Langhan's cells.

FIG. 13. Section from lesion of Case 2 (see Figs. 3 and 5). The infiltration occupies the whole extent of the dermis, but especially the papillary and subpapillary layers. In the deeper levels are seen separate follicles with giant cells, and confluence of follicles forming nodules.

FIG. 14. Same lesion as Fig. 13, higher magnification. Note the abundant infiltration with predominating epithelioid cells and lymphocytes. There is one giant cell of the Langhan's type, and a dilated capillary with swollen endothelium.

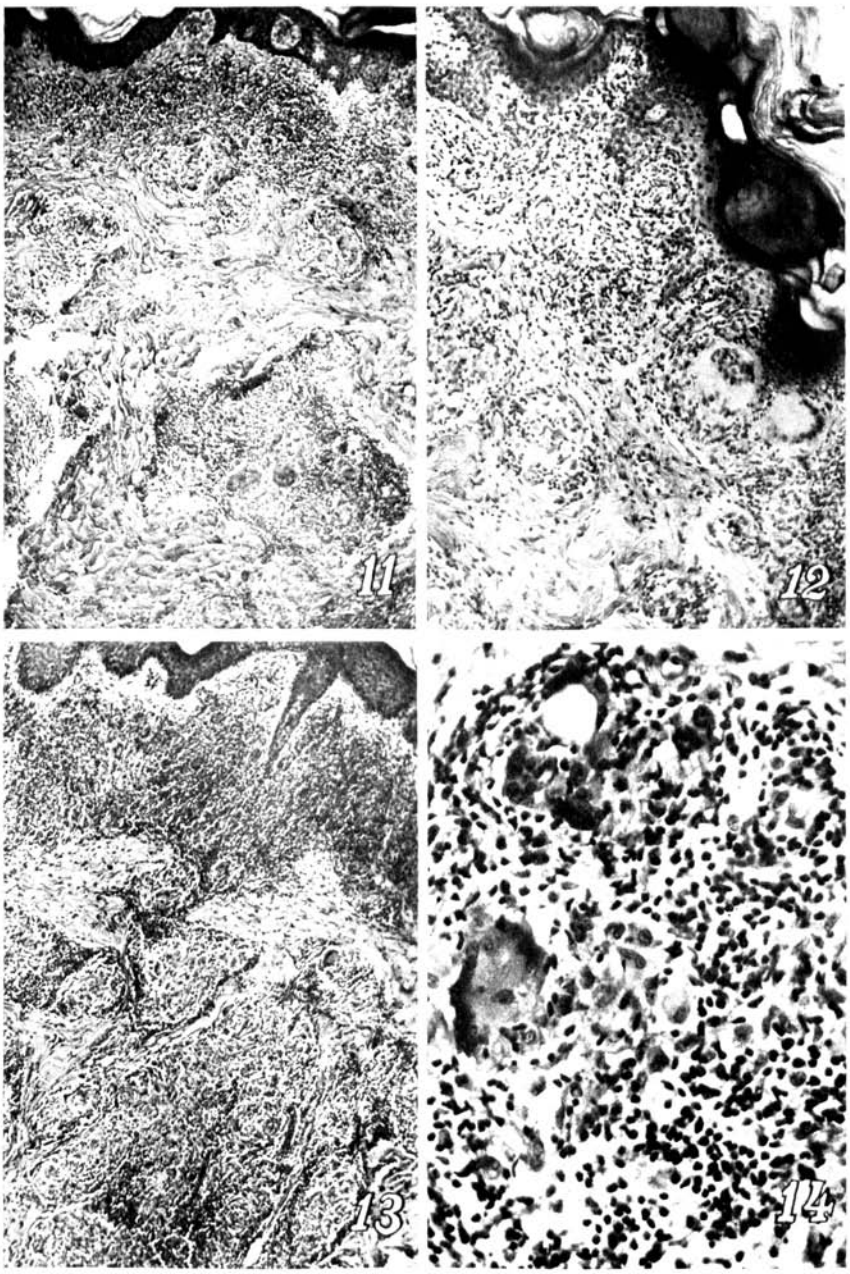

Plate 9

Plate 10

Fig. 15. Section from Case 4, after progression of the condition (see Figs. 8 and 9). Nodular condensation in the intermediate and deeper portion of the dermis, formed by the confluence of numerous follicles. The clear centers and the surrounding lymphocytic halos are prominent.

Fig. 16. Same lesion as Fig. 15, higher magnification. Follicular infiltration around the capillaries and sweat glands. There is one typical giant cell, markedly reticular tissue, and capillary dilatation.

Fig. 17. Section from lesion of Case 5 (see Fig. 10). The dermis is completely occupied by the follicular infiltration. Giant cells and capillary dilation are observed.

Fig. 18. Same lesion as Fig. 17, higher magnification. An individual follicle with several giant cells are seen, and the swelling of the surrounding dermal tissue.

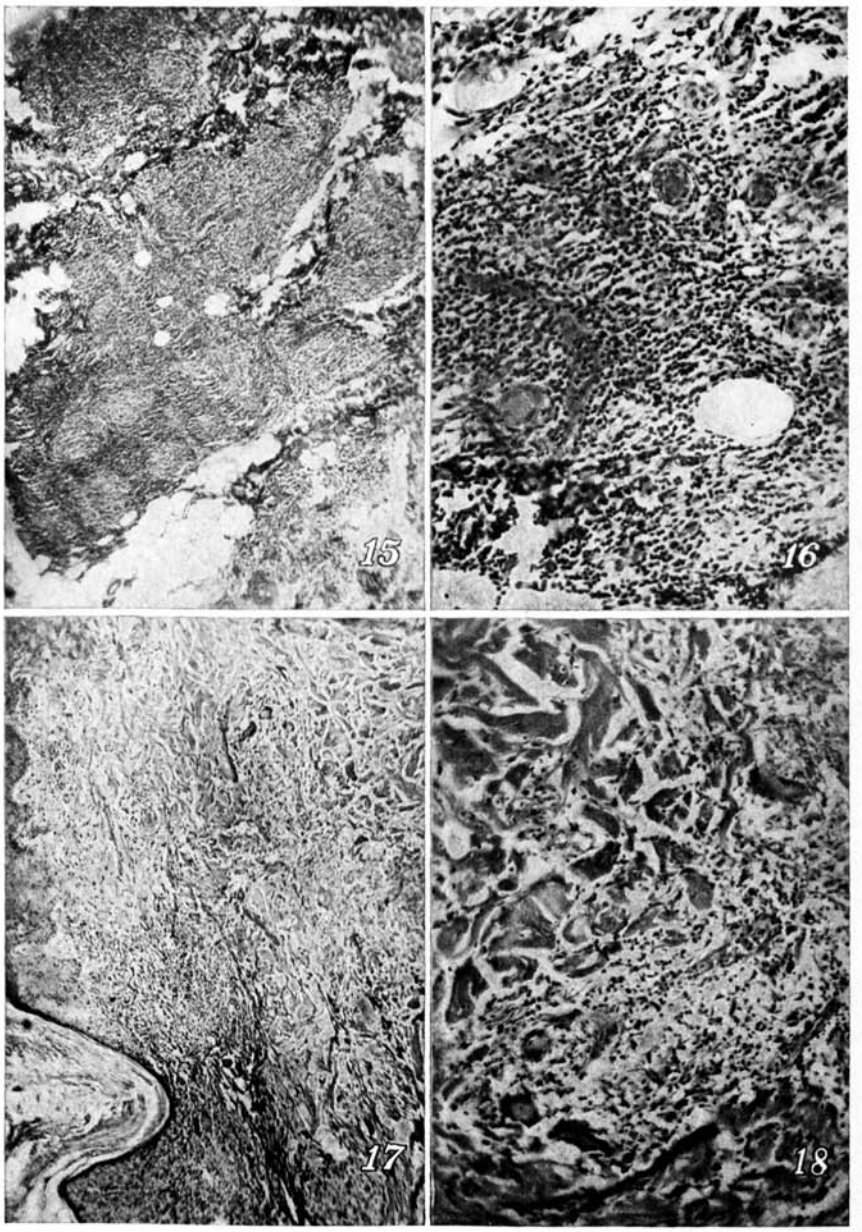

PLATE 10