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THE HISTOLOGICAL ASPECTS OF LEPROUS NEURITIS[1]

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From the abundant material in the Laboratory for Pathological Anatomy of the Departamento de Prophylaxia da Lepra of São Paulo there was selected for the purposes of this study a series of about 130 sections showing nerve lesions. This selected material may be divided as follows: (1) Nerves from cases of nodular leprosy. (2) Nerves from cases of pure nervous leprosy. (3) Nerves in tuberculoid lesions. (4) Terminal nerve branches in material from macules, lepromas, tuberculoid lesions, etc. Photographs of twenty of the specimens with the most typical lesions were selected to illustrate the conditions observed in the study. Those found in the other specimens were identical with them. The observations were made on sections stained by hematoxylin-eosin and by the Ziehl-Neelsen method for demonstration of the Hansen bacilli; they lack of course, the complete and detailed conclusions that would result from the use of the more refined techniques for staining and impregnation of the nervous tissue.

NEURITIS IN NODULAR LEPROSY

According to my observations on nerve lesions from cases of nodular leprosy, the process develops by localization of the leprotic infiltration in the interfascicular connective tissue. As it increases it dissociates the nerve fibers, which are displaced and compressed until they are completely destroyed. The con-

[1] This article, from the *Revista Brasileiro de Leprologia* **4** (1936) 271-305, has been prepared from a translation supplied by the author and illustrated from original photographs. Limitation of space has necessitated the elimination of the more detailed descriptions of the sections and a few of the photographs, but the notes on them are incorporated in the text. The original numbers of the pictures are given in parentheses.—Editor.

dition is, therefore, an interstitial neuritis, the nerve fibers being destroyed secondarily through compression, as has been observed by various authors who have dealt with the subject. The infiltrations are composed essentially of Virchow's vacuolized cells, full of bacilli. Besides these cells many lymphocytes are always found, frequently conglomerated, and occasionally some eosinophiles, plasmocytes and monocytes as well. Lesions of the blood vessels are always marked, they appearing much dilated and with thickened walls.

As the process develops there is seen the beginning of sclerosis which gradually replaces the lepromatous infiltration. As a rule bacilli are still to be found in large numbers even when there is marked sclerosis.

The following pictures illustrate the description of such lesions.

Plate 24, fig. 1 shows a section of a much thickened, very tender cubital nerve from a nodular case. It appears to be almost completely affected by a dense infiltration of Virchow's cells, with a bundle of nerve fibers remaining in the center. The epi- and perineureum are much thickened, with marked fibrosis, and in places the nerve itself is sclerotic. On the whole few traces of nerve fibers are left. Blood vessels are much dilated, with rather thickened walls. Innumerable bacilli are present, scattered and in globi.

In Figure 2 is shown another nerve from an advanced case of the mixed form of the disease. There is seen an elongated area of infiltration composed of Virchow's cells and lymphocytes, displacing and dissociating the nerve fibers, of which a large number are nevertheless visible. Fibrosis and vascular changes were present much as in the preceding specimen.

Figure 3 shows a section from the same case stained by the Ziehl-Neelsen method, with numerous bacilli both scattered and in globi.

NEURITIS IN PURE NERVE LEPROSY

Jeanselme (6), dealing with the histological characters of leprotic neuritis, says:

In the nodular form the trunks are full of leprotic infiltrations which may be as rich in bacilli as the nodules of the skin or of the mucous membranes; to the contrary, in the maculo-anesthetic form the changes of the nerve are chiefly degenerative, microbic foci are scanty, bacilli appear very scattered and it is as difficult to demonstrate them as it is in patches.

From my own observations of nerve lesions from this form of leprosy I cannot entirely agree with this opinion. Bacilli are as a rule very rare, it is true, or else it is not possible to demonstrate them, but I am led to believe that the neuritis in such cases, as in the nodular ones studied, is interstitial. The mechanism of its development is as follows: Between the nerve fibers, in the interfascicular connective tissue, there appear

small lymphocytic foci. Because of some irritative action these lymphocytes soon give way to fibrous tissue, which increases more and more and causes compression and destruction of the nerve fibers. Thus the neuritis in this form of the disease is also of interstitial nature.

All of these stages can be clearly distinguished in the microscopic sections studied. From them I have selected those which show most clearly the evolution of the process.

Plate 25, fig. 4 shows in low magnification a transverse section of the cubital nerve of a patient with advanced pure nerve leprosy, with severe trophic lesions of the extremities. At this magnification there can be made out only the several much enlarged nerve bundles, with thickened epi- and perineurium and marked fibrosis within the bundles. Here and there are small foci containing a few cells.

Figures 5 and 6 represent transverse and longitudinal sections of the same specimen, in greater enlargement. In them the small lymphocytic foci, the fibrosis and some still intact nerve fibers are distinctly visible. In this case bacilli could not be demonstrated.

[Another specimen (original fig. 7, not reproduced here), from the cubital nerve of a very advanced case, shows a much more advanced stage of fibrosis, the nerve having been totally replaced by fibrous tissue in which it was impossible to detect any nerve fibers. No bacilli could be found.]

The process may advance still further and the nerve may be reduced completely to dense fibrous tissue, in which there may even be deposition of calcium salts. This is shown in fig. 7 (ex-fig. 8), from a very advanced case with marked contractions and atrophy of the hands and feet. No nerve fibers can be found; no cellular infiltration except small lymphocytic foci here and there; no bacilli found. Conspicuous areas of calcification present.

TUBERCULOID LESIONS OF THE NERVES

In the nerves of leprosy patients we frequently find lesions with the tuberculoid structure; these usually come from cases of nerve leprosy. Yet sometimes the only clinical sign of the disease is the existence of thickened nerves and anesthetic areas of the skin. This type of lesion, called "tuberculoid hansenian neuritis," may undergo caseation, and in that event there may appear foci of fibrosis and calcification. In such cases bacilli are either not found or are very scanty.

To illustrate the conditions found in the numerous specimens examined, the following descriptions of the photomicrographs used here are given:

Plate 26, fig. 8 (ex-fig. 9) is of a longitudinal section of an enormously enlarged nerve of the superficial cervical plexus of the neck, removed by biopsy from a case of maculo-anesthetic leprosy. The structure of the infil-

tration which fills the nerve is typically tuberculoid, with large agglomerations of proliferated histiocytic cells which have all of the characteristics of epithelioid cells, and with lymphocytic accumulation located for the most part peripherally to these agglomerations and separating them (lymphocytic "halos"). Plasmocytes are present in numbers. There is no caseation.

Figures 9 and 10 (ex-figs. 10 and 11) are of a specimen from a case in which the only signs of leprosy were marked thickening of the superficial branch of the musculo-cutaneous nerve and anesthesia of the foot. Sections show tuberculoid neuritis with foci of caseation, the epi- and perineurium much thickened and capsule-like. A small number of nerve fibers are still present. In fig. 9, a transverse section, several caseous areas are seen. Fig. 10, a longitudinal section, shows extension of one of the foci of caseation.

Figure 11 (ex-fig. 12) was taken from another specimen of tuberculoid hansenian neuritis with caseation involving the cubital nerve ("abcess"). It was an old lesion, with several peculiarities not commonly found in such cases. The photograph shows the epithelioid-cell foci surrounded by extraordinarily large numbers of plasmocytes, which ordinarily are scarce. Most striking are the numerous giant cells of all shapes, some of which contain small fragments of calcified substance. These calcium salts have acted as foreign bodies, inducing the appearance of the large numbers of gigantacytes. Bacilli not found.

[Another illustration from the same specimen (original fig. 13, not reproduced), shows a large caseous area with masses of calcareous material scattered through it. This calcification is another unusual feature of this kind of lesion.]

LESIONS OF TERMINAL NERVE BRANCHES

At the level of the terminations of the skin nerves, penetration of germs and infiltrations may occur by continuity. This possibility, as pointed out by Guizzetti (5), finds its explanation in the anatomic structure of the small nerves. In their last branches the perineurium is reduced to a single, slender lamella, similar to the lamellar sheath which along the nerve trunk invests the nerve fibers; and even this covering, when approaching the terminations, loses itself in the diffuse connective tissue of the organ in which the termination is situated. In leprosy the invasion of the small nerves by adjacent infiltrations is frequently observed in the terminal branches localized in patches, lepromas and other skin lesions.

Dehio and Gerlach, who first investigated these types of lesions, demonstrated that the neuritis of leprosy starts in the peripheral extremities of the nerves, gradually ascending from there toward the centers. This, however, is not the only mechanism of the occurrence of leprotic neuritis, for, as Jeanselme has shown, bacilli can be brought to the nerve through the blood or lymph channels. In a previous paper (4) I reported

a case of neuritis which was primarily localized at one point of the nerve, after which a patch appeared. It must be admitted, therefore, that the neuritis in leprosy may be both ascendant and descendant.

The material at hand has permitted observation of a large number of histologic features of terminal nerve branches in numerous lesions of the skin. Very frequently, in skin lesions of any form of the disease, there is seen around these branches an infiltration consisting essentially of lymphocytes, though it may also contain histiocytic cells and rarely plasmocytes. This is the most simple lesion, and in such cases the nerve itself often seems to be absolutely normal, though at times it may contain some lymphocytes.

In a later stage the perineural infiltration becomes gradually more marked, as a rule taking the characters of the other infiltrations observed in the lesion in question. As the process goes on, the lamellar sheath is broken in its continuity and the infiltration penetrates the nerve, dissociating and compressing its fibers until they are completely destroyed. This means that frequently it is quite possible that in a section of a leprous lesion some of the lesion foci represent nerve branches replaced by the leprotic infiltration. Sometimes the nerve is still recognizable by its location, or by its form, or by remnants of the lamellar sheath.

The process described can be followed in every detail in the numerous sections examined. From among them the most typical pictures have been selected to illustrate the present report.

Plate 27, fig. 12 (ex-fig. 14) shows nerve branches in the subdermal layer. The specimen was obtained from a case in which there was only a small area of anesthetic skin on the leg, without any visible lesion. Microscopically, however, there were in the skin infiltrations with all of the characters of leprosy, composed of histiocytes and many lymphocytes, with a tendency to localization around the hair follicles, sweat glands and capillary blood vessels. The infiltration around the nerves shown is of similar character. The nerve filaments seem mostly to be of normal structure. No bacilli found.

[Another of the original illustrations (ex-fig. 16) shows a lesion in the subcutaneous layer beneath an old, retrogressive leprotic patch, with in the skin itself only minimal histologic abnormality consisting of noncharacteristic infiltration. The nerve branches shown are surrounded by an infiltration consisting of lymphocytes and some histiocytic cells and are considerably affected, in part invaded. No bacilli found.]

Figure 13 (ex-fig. 17), also of the subdermis, is of a specimen obtained from an erythematous, infiltrated leprotic patch on the buttock. The nerve

branches shown are surrounded, invaded and partly destroyed by an infiltration identical with that in the dermis itself—lymphocytes and histiocytic cells. At some points the nerve branches are invaded by infiltrations which destroy the lamellar sheath and, penetrating between the fibers, dissociate and destroy them through compression. Bacilli were found in this specimen, even inside the nerves.

[Original fig. 19 was of another specimen from an erythematous, infiltrated, anesthetic patch. The infiltration, of the usual composition, surrounds a dermal nerve, still easily recognizable by its lamellar sheath, the preservation of which suggests that the invasion occurred at some other point. The nerve fibers have in large part disappeared, having been replaced by an infiltration identical with that outside, but a few of them are still recognizable. Numerous bacilli inside the nerve.]

Figure 14 (ex-fig. 15) is of an illustrative section of a microscopically typical tuberculoid lesion within the dermis. In the infiltrative area shown, composed of epithelioid cells and lymphocytes, there is a recurved, longitudinally cut nerve, one end of which is invaded; the nerve fibers are displaced, compressed and partly destroyed. Within the nerve is a typical tuberculoid focus containing a giant cell. No bacilli found.

Plate 28, fig. 15 (ex-fig. 18) is also of a typical tuberculoid lesion, from a patch in the region of the knee. In an agglomeration of epithelioid cells some completely dissociated nerve fibers are seen, the lamellar sheath (perineurium) being no longer visible. If it were not for other structures found in serial sections it would be difficult, with ordinary staining methods, to identify these elements as nerve fibers. Bacilli not found.

Figure 16 (ex-fig. 20), a tuberculoid lesion (patch on the forearm), shows three closely related, deeply located nerve branches with changes of different grades of evolution. One of the nerves is still easily recognized by its sheath, though that is hyperplastic and dissociated, but in the others even this has disappeared almost completely. The nerve fibers have been totally destroyed and replaced by epithelioid and lymphocytic infiltration, in which a giant cell is seen.

Figure 17 (ex-fig. 21), also from a patch on the forearm, histologically tuberculoid, shows in the hypoderm two large masses (marked by a circle) which on careful examination can be identified as profoundly changed nerves; they are recognizable by their location, shape, the lamellar sheaths that surround them, and the presence of small groups of well preserved nerve fibers. Most of the fibers, however, have been replaced by the epithelioid and lymphocytic infiltration, which contains giant cells.

Plate 29, fig. 18 (ex-fig. 22) shows a tuberculoid lesion of the Boeck's sarcoid type. Deeply located is a plurifascicular mass recognizable as a nerve by the clearly identifiable remainders of the epineurium and perineurium. Nerve fibers are not recognizable. The infiltration has all of the characters of the other leprotic agglomerates of the derma. This lesion is one of the best in my collection to show the degree of similarity that may be seen in the dermis and in the nerves. Bacilli not found.

Figure 19 (ex-fig. 23) is from an old case of leprosy in which there was an anesthetic remnant of an old skin lesion and a small, palpable, thickened nerve. Microscopically there are small, noncharacteristic lymphocytic infil-

trations in the skin. In the hypoderm a greatly changed, hypertrophic nerve branch composed of two bundles is found. The epineurium and the perineurium, thickened and no longer discrete, form a sort of capsule around a small number of histiocytic cells, lymphocytes, plasmocytes and eosinophiles. In the centers two caseous masses are seen. No bacilli found.

Plate 6, fig. 20 (ex-fig. 24) represents a section of atrophic skin of the hand in an advanced case of nerve leprosy. Beneath the dermis is a mass which is recognizable as a nerve by the circular fibers of the lamellar sheath. Its whole structure has disappeared, a large part having been replaced by fibrous tissue and lymphocytes, with a few histiocytes. Bacilli, very few, were found, even inside the nerve.

Figure 21 (ex-fig. 25) is of a leproma. The nerve branches are integrated with the structure of the lesion. The large lepromatous infiltration, which invades the whole dermis, is composed of Virchow's vacuolized cells, lymphocytes and Darier's "cavities of colliquation." The nerves are still perfectly recognizable by their lamellar sheaths, which are preserved, and by some nerve fibers, though the latter have for the most part been replaced by the infiltration. Bacilli found in large numbers, both scattered and in globi, in the dermal infiltration and in that which is within the nerves.

DISCUSSION

In the literature on leprosy I have found only occasional references to the nerve lesions. Detailed descriptions are given by Jeanselme (6) and Guizzetti (5). Relatively much attention has been given to the nerve changes in tuberculoid lesions, concerning which there have appeared a considerable number of articles, as those by Lowe (7), Marestang (9), Muir and Chatterji (10), Chatterji (2, 3), Schujman (12), Campos (1), Ribeiro (11) and myself (4).

The purpose of the present paper is only to report my personal experience in the matter, after having observed a large number of sections with the most varied lesions of the nerves. The observations made on them enable me to draw an ensemble picture in which the findings are synthesized.

The first conclusion to be drawn is that all forms of neuritis in leprosy are of "interstitial" type, i.e., the leprotic infiltration originates in the interfascicular connective trabeculae, where they secondarily compress and destroy the nerve fibers. These infiltrations vary in nature according to the type of leprosy. In nodular leprosy Virchow's vacuolized cells, full of bacilli, and lymphocytes are predominant; sclerosis occurs secondarily. In pure nerve leprosy the infiltration in the early stage takes the form of small lymphocytic accumulations; intense fibrosis follows almost immediately, as the predominant element in

this type. In the fibrotic tissue deposition of calcareous salts may occur. Bacilli are very scanty, or are not found. Necessarily, a combination of these two forms of neuritis occurs in cases of mixed leprosy, which represent a combination of nodular and pure nerve leprosy.

An important feature of my investigation is the lesions observed in the nerve branches which terminate in patches, lepromas, anesthetic areas, etc. It is a fact of common observation that very frequently these nerves are injured in all of the skin lesions of leprosy, whether they be erythematous or dyschromic patches, lepromata, lesions of tuberculoid leprosy or simple anesthesia of the skin without visible lesions. Another noteworthy fact is that the nerve lesions may occur early in the beginning of the disease and persist even when the skin lesions are no longer macroscopically visible.

The process starts with a lymphocytic infiltration around the nerve branch. Later there may also appear histiocytes, and occasionally some plasmocytes. In this stage the nerve itself may present an absolutely normal aspect, or there may be some lymphocytes within it. Later the perineural infiltration increases, with a tendency to assume the characters of the other leprotic infiltrations of the skin. The lamellar sheath, which in the terminal branches is very thin, may be destroyed, the infiltration penetrating between the nerve fibers which are compressed until they become completely destroyed. This allows the conclusion that a nerve may be replaced by an infiltration that is identical with that which constitutes the skin lesion, though sometimes the nerve infiltration appears to be slightly different from that in the skin, tending to assume the tuberculoid characteristics. By examining a large number of sections it is possible to observe every stage of the process described.

Because the terminal nerve branches are easily affected by the dermal infiltration through continuity, these lesions naturally spread along the nerve up to the large trunks. The infection does not extend from these trunks to the neighboring tissues, nor are they themselves invaded by lesions that may by chance exist outside them, because of the barrier interposed by the perineurium or lamellar sheath and the epineurium. This form of neuritis would consequently be ascendant. But this is not the only mechanism of origin, for the nerve trunks may be affected through the blood or lymphatic circulation, by the vasa ner-

vorum. In this case the neuritis would be descendant.

With regard to the number of bacilli found in the infiltrations of the terminal nerve, they vary as a rule with the number found in the adjacent skin lesions. If the latter are rich in bacilli, these will be found in large numbers in the nerves as well. Conversely, if the skin lesions because of their nature are poor in bacilli (as in tuberculoid leprosy, for instance), these are usually not found in the nerve either.

SUMMARY

This study of leprotic neuritis deals with such lesions in (*a*) nodular leprosy, (*b*) pure nerve leprosy, (*c*) tuberculoid leprosy, and (*d*) terminal nerve branches in relation to leprotic skin lesions of various kinds.

In the neuritis of nodular leprosy the infiltration consists essentially of Virchow's vacuolized cells full of Hansen bacilli, insinuated between the nerve fibers, which are compressed and secondarily destroyed.

In the neuritis of pure nerve leprosy there appear between the nerve fibers small infiltrative foci consisting essentially of lymphocytes. Intense fibrosis follows, and in this tissue calcareous salts may be deposited. Bacilli are as a rule very scanty.

In tuberculoid neuritis the infiltration located between the nerve fibers is composed essentially of epithelioid cells, giant cells and lymphocytes; caseation and calcification may also occur. Bacilli are practically not demonstrable.

When the nerve branches ending in skin lesions of leprosy are affected, as they very frequently are, they show primarily slight leprotic infiltrations around the perineurium. In a more advanced stage the latter is destroyed, the nerve appearing to be invaded by the infiltration, which compresses the nerve fibers until they are completely destroyed.

I am indebted to my colleagues at the laboratory, Drs. A. Martins de Castro and H. Cerruti, for their courtesies in connection with the preparation of the present paper, and especially to Dr. Manuel de Abreu, director of the Instituto de Leprologia "Conde de Lara," for his continuous aid in the study. My best thanks are due Mrs. Anny Planet for her valuable assistance in preparing the English translation of this work.

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DESCRIPTION OF PLATES[2]

PLATE 24

FIG. 1. Cubital nerve in nodular leprosy. The normal structure of the nerve has been replaced by a dense infiltration of Virchow's vacuolate cells. In the center a small group of nerve fibers persists. Section 1, 90×.

FIG. 2. Cubital nerve in nodular leprosy. A large focus consisting of Virchow's vacuolized cells and lymphocytes, located between nerve fibers which for the most part are well preserved. Section 2, 160×.

FIG. 3. Section similar to that of Fig. 2, stained by the Ziehl-Neelsen method. Numerous bacilli, in globi and scattered. Section 2, 800×.

[2]The data on magnification apply to the original photomicrographs, which have been somewhat reduced in the reproductions.—EDITOR.

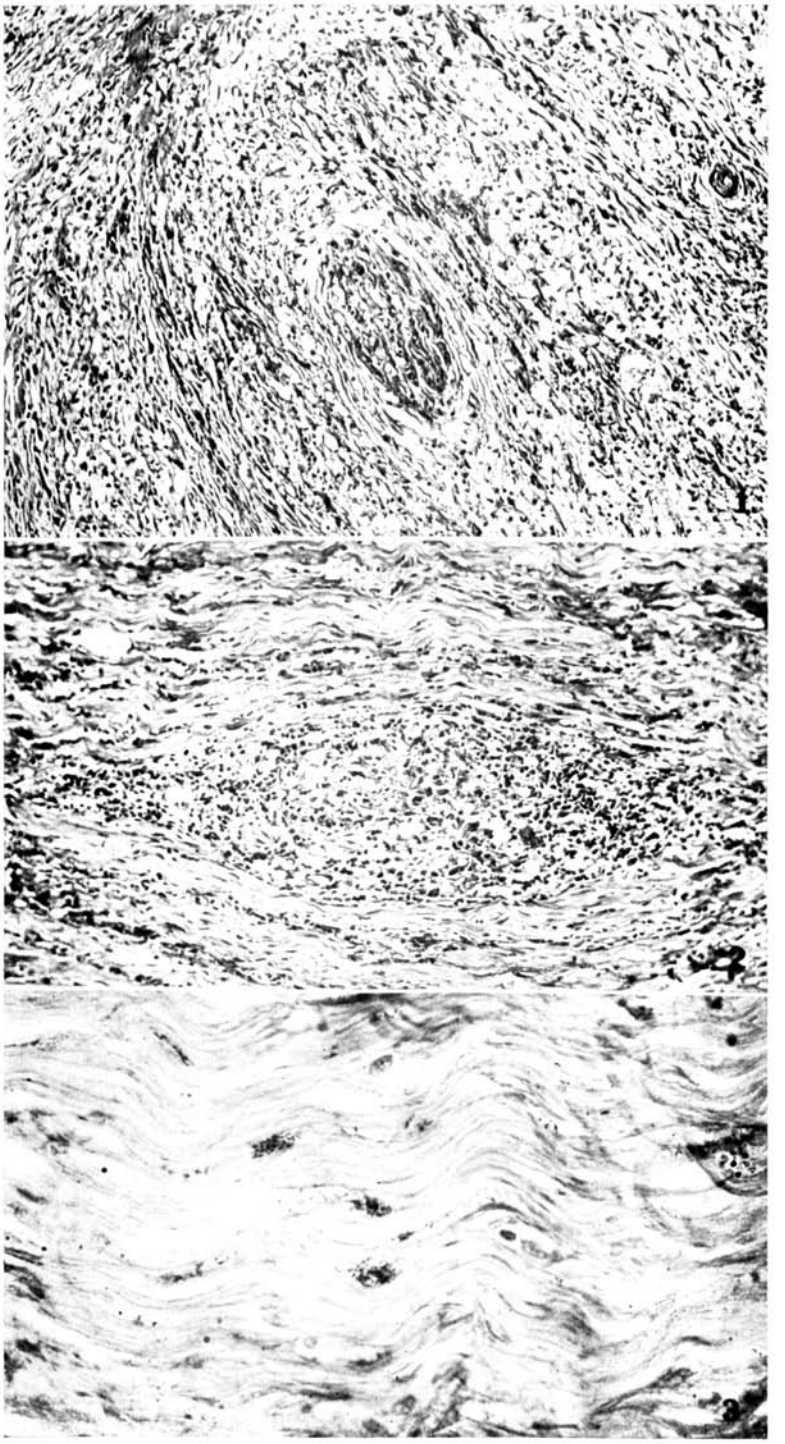

PLATE 24

PLATE 25

FIG. 4. Cubital nerve of pure nerve leprosy. The bundles of the nerve trunk appear much enlarged, and marked fibrosis is present. Section 3, 24 ×.

FIG. 5. Cubital nerve of pure nerve leprosy. Same case as in Fig. 4, higher magnification. The presence of thick connective tissue strands, large numbers of lymphocytes and well-preserved, nerve fibers is seen. Section 3, 240 ×.

FIG. 6. Cubital nerve of pure nerve leprosy. Longitudinal section of the same nerve as shown in the two preceding figures. As before, connective tissue, lymphocytes and nerve fibers are seen. Section 3, 240 ×.

FIG. 7. Cubital nerve of pure nerve leprosy. Complete fibrosis of the nerve, with large foci of calcification; an unusual condition. Section 5, 25 ×.

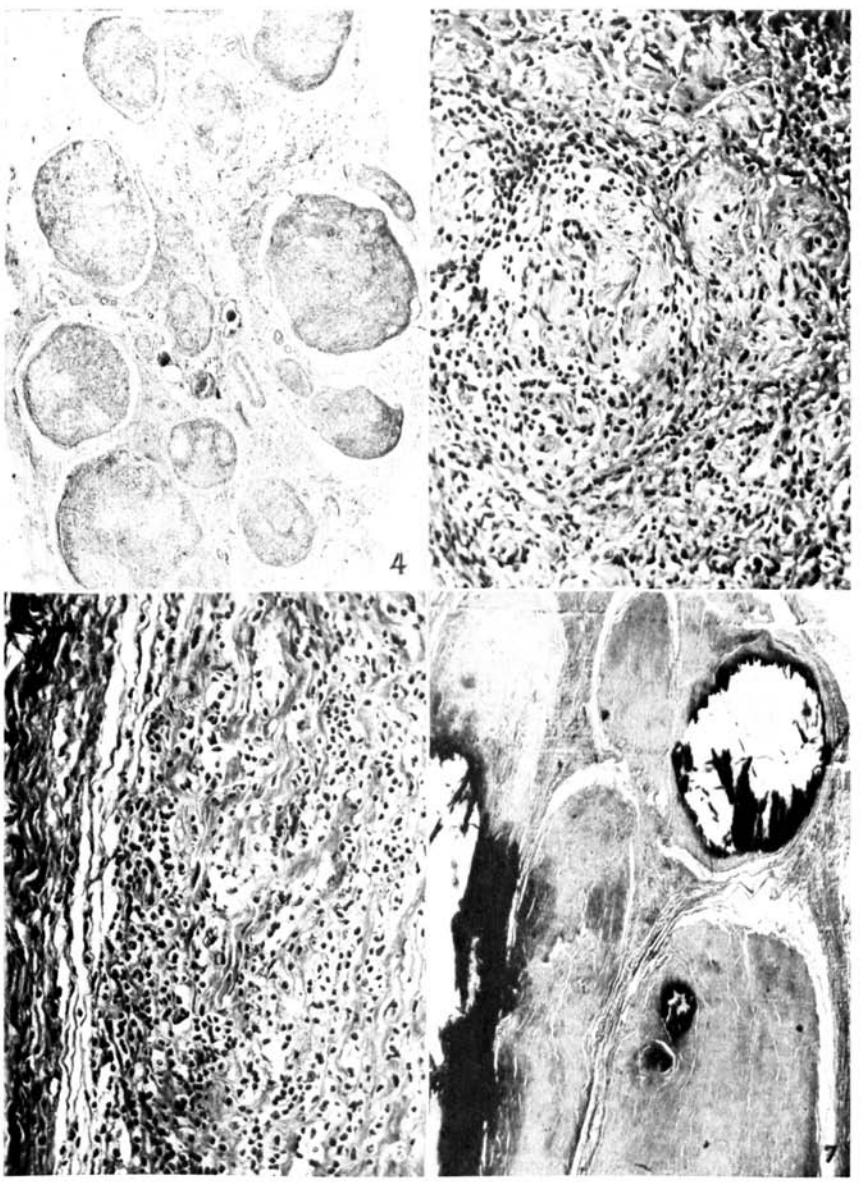

Plate 25

PLATE 26

FIG. 8. Superficial branch of the cervical plexus, from a case of maculo anesthetic leprosy. There is marked thickening, with abundant proliferation of epithelioid cells and lymphocytes. Section 6, 12 ×.

FIG. 9. Musculo-cutaneous nerve from nerve leprosy. Transverse section of the nerve, showing great enlargement of the fasciculi, with proliferation of epithelioid cells and lymphocytes. In some of the bundles are areas of caseation. Section 7, 25 ×.

FIG. 10. Musculo-cutaneous nerve in nerve leprosy; longitudinal section of same specimen as in Fig. 9. A nerve bundle with a large caseous area in the center is seen. There are numerous newly-formed blood vessels, the nerve fibers have disappeared almost completely, and the epineurium and the perineurium are much thickened. Bacilli not found. Section 7, 30×.

FIG. 11. Cubital nerve showing details of a zone bordering an area of caseation. There are epithelioid cells, a large number of giant cells, some with calcified fragments in their interior, and innumerable plasmocytes and lymphocytes. (Among these cellular agglomerations there are large zones of necrosis, like those seen in Figs. 10 and 11.) Newly-formed blood vessels are very numerous. Bacilli not found. Section 8, 85 ×.

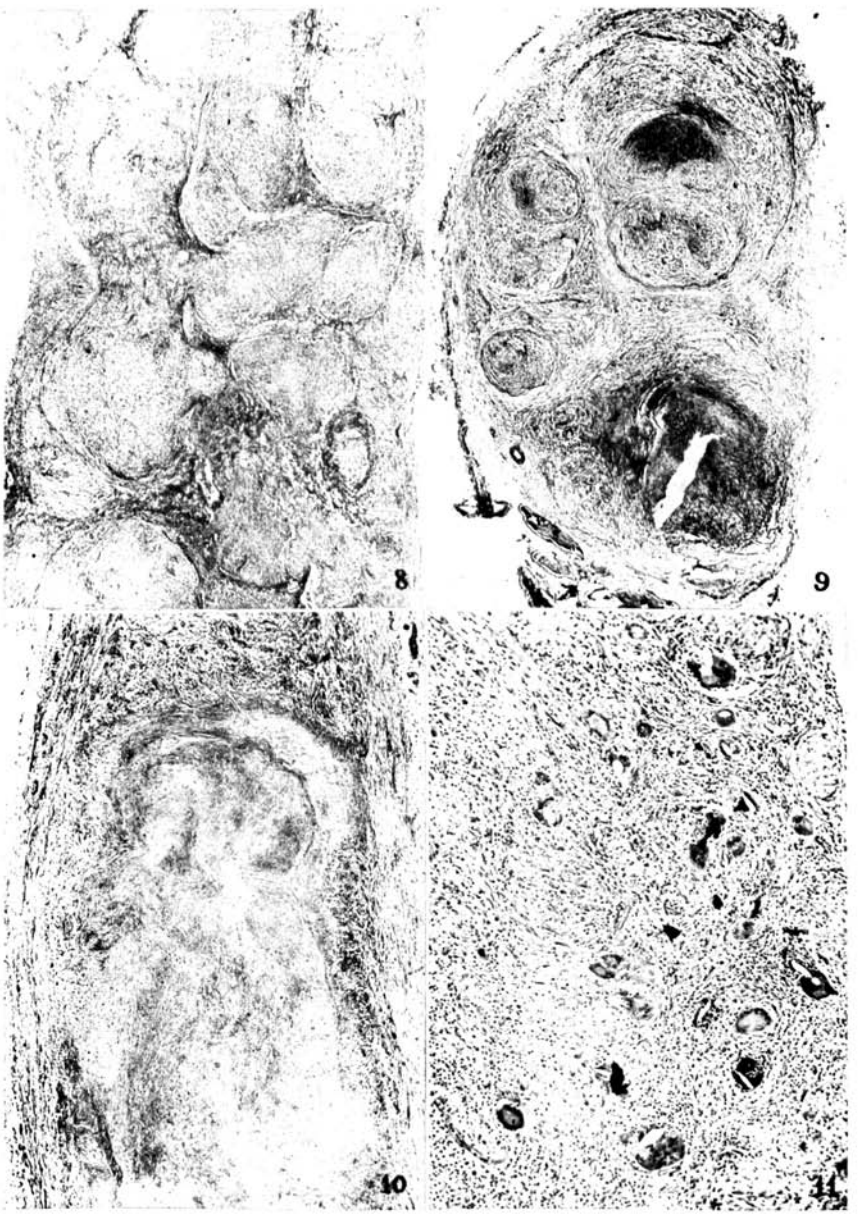

PLATE 26

PLATE 27

FIG. 12. Specimen from an anesthetic area of the leg with no visible lesion. Numerous nerve branches are located deep in the hypoderm, surrounded closely by a lymphocytic infiltration. Section 9, 32 ×.

FIG. 13. Section of an erythematous, anesthetic, infiltrated patch. Nerve branches are involved by an infiltration which has invaded and largely destroyed them. Section 12, 100 ×.

FIG. 14. Tuberculoid leprosy. A nerve filament is shown in the center of a tuberculoid infiltration. At one end of it the infiltration is seen to invade it, dissociating and displacing the nerve fibers, which are replaced by epithelioid cells, lymphocytes and one giant cell. Section 10, 300 ×.

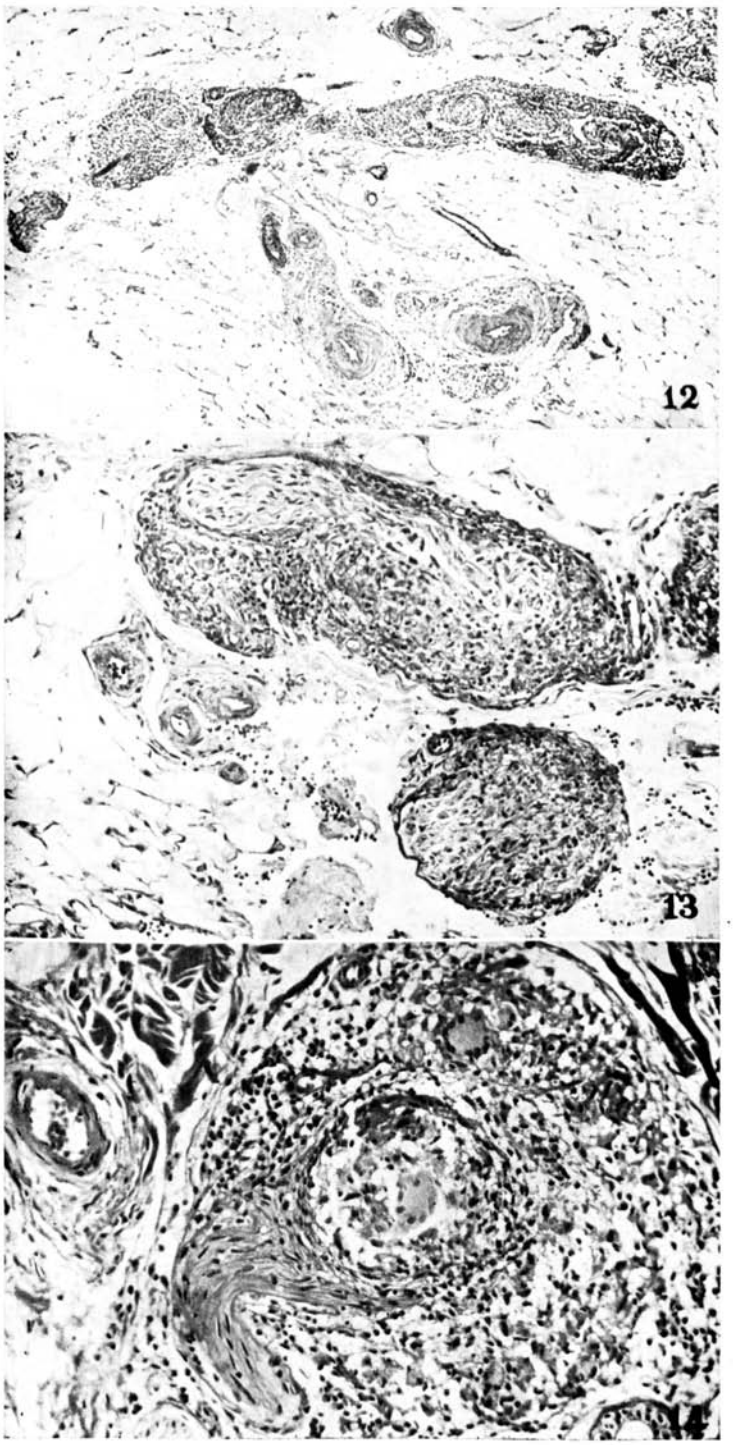

PLATE 27

PLATE 28

FIG. 15. Tuberculoid leprosy. In the infiltration is a group of dissociated nerve fibers (indicated by arrows). Section 13, 200 ×.

FIG. 16. Tuberculoid leprosy. Three much-changed nerve branches are shown. In one of them the lamellar sheath is still well shown. They are invaded by an infiltration consisting of epithelioid cells, lymphocytes and a giant cell. Section 15, 100 ×.

FIG. 17. Tuberculoid leprosy. The circle surrounds two structures which are nerve branches invaded by a marked infiltration that has enlarged them greatly. In one of them the fibers of the lamellar sheath are recognizable. Section 16, 22 ×.

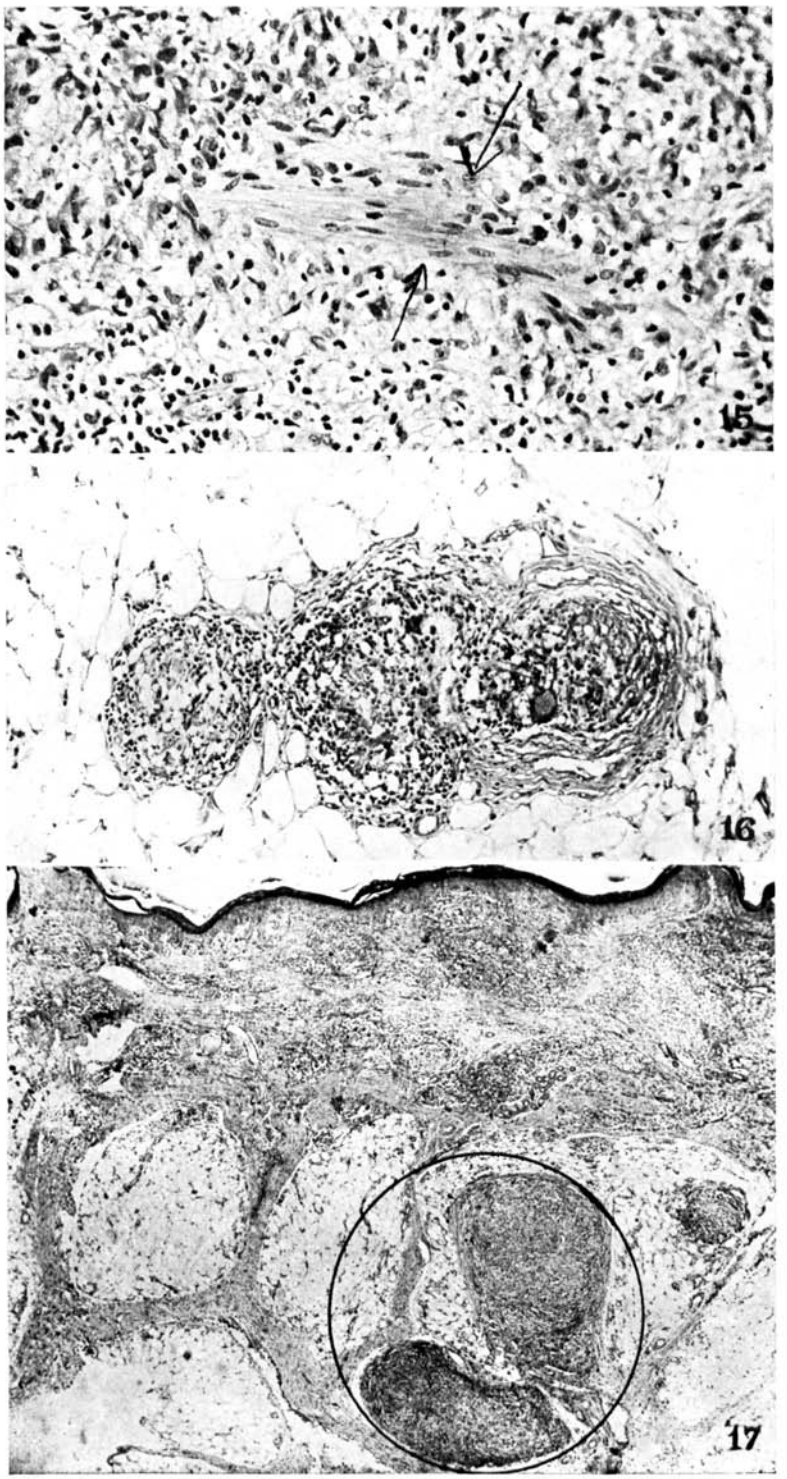

PLATE 28

PLATE 29

FIG. 18. Tuberculoid leprosy of the Boeck sarcoid type. Within the circle are nerve branches invaded by an infiltration similar to that of the dermis. Section 17, 12 ×.

FIG. 19. Section of an area of anesthetic skin in which a cord was palpable. Within the circle there are two nerve branches with fibrosis of the epineurium and perineurium and containing caseous masses. Section 18, 11 ×.

FIG. 20. Atrophic skin of the hand, with a deeply located, almost entirely fibrosed nerve. Section 19, 80 ×.

FIG. 21. Section of a leproma. The lepromatous infiltration consists of Virchow's vacuolized cells and "colliquative cavities" which involve nerve branches, which are invaded by vacuolized cells. Section 20, 32 ×.

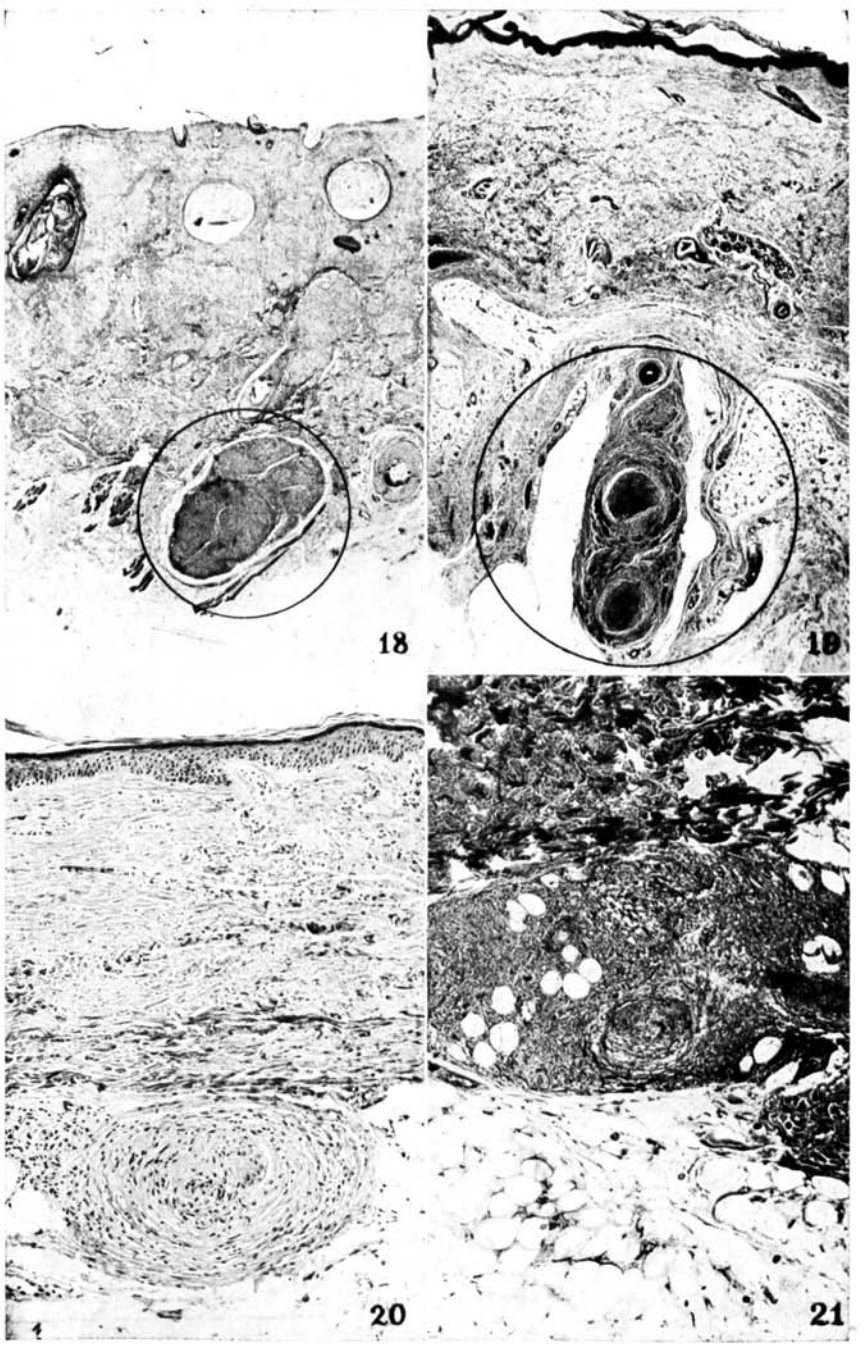

PLATE 29