# STUDIES ON LEPROSY. I. THE CENTRAL, SYMPATHETIC AND PERIPHERAL NERVOUS SYSTEMS[1]

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## INTRODUCTION

Danielssen and Boeck (2), whose classical work gave powerful impetus to the study of the pathology of leprosy in general, were the first to study the changes of the nervous system in this disease. They described changes in the brain and spinal cord that are not specific of leprosy, but in the peripheral nerves they observed a pathologic process of peculiar character. This process was the development, among the nerve fibers inside the nerve sheaths, of a granulation tissue in which large "brownish" cells prevailed. Virchow (13), on the basis of observations made in Norway in 1859, characterized this leprotic process as a neoplasm without exudative manifestations, and ascribed special significance to the brownish cells. He was very reserved with regard to the changes in the central nervous system; those in the peripheral nerves he characterized as an interstitial neuritis.

Déjerine and Leloir (4), studying one case of nodular leprosy, found no changes in the central organs, but in the peripheral nerves they observed changes similar to those described by Virchow. They emphasized the significance of parenchymatous changes in the nerve fibers, which they regarded as primary, because in their opinion the insignificant interstitial process which they noted could not explain the destruction of the nerve fibers. However, they could not determine the causative factor of this primary parenchymatous change.

[1] From the Astrakhan Clinical Leprosarium (Prof. I. N. Perevodchikov, Director), and the Leprosy Department, Tropical Institute, State Health Department, Moscow, R. S. F. S. R. (Prof. W. I. Kedrowsky, Chief). The material presented here was collected in the former institution and studied in the latter, with the closest cooperation of Professor Kedrowsky, to whom warmest thanks are due for his assistance and advice.

Hoggan and Hoggan (6) reported their findings in the nervous system in three cases of anesthetic leprosy.[2] They concluded that the primary affections are not localized in either the central nervous system or the terminal branches of the peripheral nerves, but in their main course. As an example they pointed to the ulnar nerve, which is usually affected near the bend of the elbow. There they found a massive infiltration of lepra cells leading to the destruction of the nerve fibers, and in some fibers they observed degenerative changes in the myelin sheath and axis cylinder. They also saw what they considered indications of regeneration of nerve fibers, and assumed that processes of degeneration and regeneration go on simultaneously and recur many times until complete destruction of the nerve takes place.

Neisser (9) insisted that primary affection in anesthetic leprosy occurs in the skin nerves, interstitial changes preceding the parenchymatous. He was of the opinion that all of the macules in maculoneural leprosy are of secondary character, and that their appearance is closely related to the affection of the corresponding nerve branches.

Sudakévitch (10), a pupil of Münch, studied the gasserian, intervertebral, and upper cervical ganglia, and the pacchionian bodies in two cases of nodular leprosy. In the ganglion cells he found disappearance of pigment, vacuolization of the cytoplasm, and the presence of large numbers of bacilli. Bacilli were also observed in the interstitial tissue of the ganglia, in foci of granulation tissue. The changes in the pacchionian bodies he distinguished according to whether they were or were not caused by the presence of the bacilli. In the bodies where no bacilli were seen the central nerve fibers were thinned and atrophied. The bodies that contained bacilli had increased in size, and in and around them there was granulation tissue rich in lepra cells.

Especially interesting is the work of Gerlach (5), who reported a consecutive study of the changes in the peripheral nerves of a case of maculo-anesthetic leprosy, from the superficial branches in the region of the macules to the large trunks. The greatest changes were in the small skin branches, while the subcutaneous nerves were either quite unchanged or had only slight inflammatory infiltration around them. The nearer to the center the less was the affection,

[2] Lie does not consider these cases as pure anesthetic, since in their histories is mentioned the presence of nodular skin changes.

and this author concluded that the nerves are primarily affected in the skin. In the ulnar nerves there were ascending changes that also began in the skin and reached the bend of the elbow. No bacilli were found.

The work of Gerlach led Dehio (3) to make the following statements at the first international leprosy conference (Berlin).

> At first a small area of the skin becomes diseased, and a leprous macule is formed. This area loses its sensitivity, not on account of affection of the corresponding nerve trunk but because the terminal sensory branches in the skin are destroyed. Next there is an ascending degeneration above the macules. Ascending still further, this degenerative process involves the mixed nerve trunks. The process develops slowly, and in its course there appears a round- and epithelioid-cell infiltration. The muscular branches soon become involved, and finally the process reaches the terminal areas, as for example the bend of the elbow in the ulnar nerve. This leads to degeneration and atrophy of all the nerve branches situated below, though they themselves may be free from the leprous process, and as a result there develop atrophies and mutilations, and anesthesia of cutaneous areas which formerly had not been affected.

Babes (1), in his monographic Histologie der Lepra, gave a detailed description of the changes in the peripheral nerves, intervertebral ganglia and spinal cord. In the peripheral nerve branches there is a lepra-cell infiltration containing a considerable number of bacilli, in connection with which there is deterioration of the myelin sheaths, swelling and distortion of the axis cylinders, and thinning of the nerve fibers. In the larger branches the changes are less important. In the intervertebral ganglia Babes observed changes similar to those described by Sudakévitch. In the ganglion cells of the anterior horn of the spinal cord single leprosy bacilli were found, and around the bacilli there were cytoplasmic vacuoles which sometimes occupied the greater part of the cell, the nucleus of which had become homogenous and stained very lightly.

At about the same time Samgin described an ascending degeneration of the tract of Goll in the spinal cord of a maculo-anesthetic case. He regarded the process as secondary to degeneration of the posterior roots. In the intervertebral ganglia there was an overgrowth of interstitial tissue and pronounced pigmentation of ganglion cells. No bacilli were found in the cells. In the peripheral nerves there was infiltration of the nerve sheaths.

Woit (14) studied the cord and nerves of five maculo-anesthetic cases. In three he found considerable degeneration in the tracts of Goll and Burdach, and in two there were degenerative changes in

the posterior roots. The ganglion cells of the cord showed very slight changes (a haziness of the cytoplasmic picture and light staining of the nucleus), but no bacilli were found. In the peripheral nerves there was round-cell infiltration, considerable proliferation of the connective tissue, and destruction of the neurofibrils. Bacilli were found in the lymphatic spaces between the fibers in only one case.

Finally, one of the most important works in this field was published in 1904 by Lie (8). This deals with twenty cases of leprosy, ten of the nodular form and ten of the nervous. The cord, intervertebral ganglia and peripheral nerves were studied in fifteen cases, the peripheral nerves only in the other five.

In the cord Lie observed an ascending degeneration of the bundles of Goll and Burdach, and in the posterior roots there were degenerative changes and atrophy of individual fibers. In the intervertebral ganglia there was vacuolization of the ganglion cells, which contained large numbers of bacilli. The changes in the peripheral nerves Lie connects inseparably with the skin lesions. The dissemination of the bacilli, in his opinion, proceeds from the periphery toward the center, and in none of the cases could the opposite be demonstrated. However, though he regards the ascending character of the neuritis as the rule, he is very reserved as to final conclusions, emphasizing the importance of carrying out investigations in the early stages of the disease, when the picture of the early development of the pathological process must appear more clearly.

This process, according to Lie, is concentrated in the nerve sheaths. Here he observed round-cell infiltration, with thinning and destruction of the neurofibrils and subsequent substitution by connective tissue. In the individual fibers there could be noted destruction of the myelin sheaths and swelling of the axis cylinders. Leprous neuritis is characterized, not by the destruction of the myelin sheath and the axis cylinder, but by marked thinning of the fibers. In spite of the fact that he had studied a large number of cases, Lie does not give a precise differentiation of the nerve changes in the nodular and maculo-anesthetic types of leprosy.

For a long time after the work of Lie this question was utterly ignored, and it was only recently, in 1929, that Dvijkov in Russia and Kobayashi in Japan have confirmed Lie's observations, though they added nothing new to them.

Takino (11, 12) studied the sympathetic nervous system. In the nodular form of the disease he observed very small numbers of bacilli, and vacuolization of the protoplasm in the cells of the sympathetic ganglia. In the anesthetic form the changes were limited to perivascular round-cell infiltration. No bacilli were found. Round-cell infiltration was also seen in the vagus nerve.

PRESENT REPORT

During four years of work in the Astrakhan Clinical Leprosarium I gathered a large collection of autopsy material. The present report is based on the study of twenty cases, of which eighteen were of the nodular form and two of the nervous.

In the brain and spinal cord I found no macroscopic changes that could be ascribed to leprosy, either in the nodular or the maculoneural form. In certain cases there was acute exudative inflammation of the meninges, with hemorrhages, but those lesions were a secondary condition. Furthermore, these organs showed no histological changes characteristic of this disease; the changes that were observed occur in a variety of other exhausting diseases of long duration. In most cases there were amyloid-like bodies in the white and gray matter of the brain and cord, accumulation of brownish pigment in ganglion cells of the anterior and posterior horns, and their nuclei stained lightly and sometimes showed tigrolysis. These changes occurred in the same degree in young persons and in older ones. In all cases the search for bacilli gave negative results, though very many slides were examined.

Sections of the intervertebral ganglia from cases of the maculoneural leprosy gave similarly negative findings, but the case was quite otherwise in the nodular form of the disease. In this type the ganglia showed changes entirely analogous to those described by Sudakévitch, Babes and Lie. These changes consisted of marked vacuolization of the ganglion cells, the vacuoles being sometimes so large that the cytoplasm showed only thin trabeculae surrounding them; in such cells the nuclei were compressed and deformed, and there were large numbers of bacilli distributed mainly between the vacuoles in the remnants of the cytoplasm (Plate 41, fig. 1). Bacilli were also found in the cells of the capsule, lying singly or in groups. It must be emphasized that this condition was not found in any particular ganglion or ganglion group (thoracic, cervical, etc.), but in all the nodes of the first and second order along the whole length of the spinal column. The same changes were found in the sympathetic ganglia in these cases, the only difference being that the extent of vacuolization was not as great as in the intervertebral ganglia, and the bacilli were much fewer.

In the peripheral nerves in nodular leprosy the nerve branches passing through the subcutaneous tissue to the skin were found to

be most markedly involved. Macroscopically they were thickened and of a yellowish or brownish color. The larger nerve trunks were less affected; they were not diffusely thickened along their whole length, but only in certain places. For example, the radial becomes nodular and of a yellowish or brownish hue in the region of the radio-carpal joint, where it comes into close contact with the skin, but higher in the arm it is unthickened and of its usual milky-white color and soft, elastic consistence. The median nerve is also thickened at the wrist, and normal in appearance above that. The ulnar nerve, like the others, is thickened or nodular at the wrist and normal in appearance higher in the forearm, where it lies between muscles, but it is again thickened (spindle-shaped, firm, and colored) at the bend of the elbow, where it again passes under the skin; above that it again gradually regains its normal appearance.

The nerves of the lower limbs are affected in the same way. The more marked changes are found in the cutaneous branches. The tibial nerve shows characteristic changes at the level of the tendon of Achilles, where it is thickened and more compact and of a brownish hue; less noticeable changes may be seen in the region of the knee. No macroscopic changes were found in the ischiadic nerve.

For microscopic examination of the nerves of the arm, material was usually taken from the skin branches, the large nerves at the thickened places, and also parts that were not outwardly changed (i.e., from the forearm, the upper arm, the brachial plexus, and above that plexus at the point where the nerves enter the intervertebral ganglia), and finally from the ganglia themselves. The same order was followed when material was taken from the lower extremity.

Histologically, the cutaneous nerves are affected along their entire course, being transformed into continuous bands of leprous granulation tissue that consists almost entirely of foamy cells filled with leprosy bacilli and lipoid material. The nerve fibers are almost completely destroyed by this newly formed tissue, and frayed fibers can be discovered only with difficulty when the section is stained for myelin by the Spielmeyer method (Plate 41, fig. 2). The perineurium becomes considerably thickened on account of marked proliferation of the connective tissue. Around the nerves in the cellular tissue there are also found larger and smaller accumulations of foamy cells, mostly around the blood vessels.

In the large trunks, at the places where they are thickened, the process has the same aspect, but the structure of the nerve is less

affected. As a rule the perineural sheath is much thickened, and under it and within the endoneurium there are infiltrations of foamy cells. This infiltration presses on the neurofibrils, which become thinned and finally are destroyed, being replaced by the slowly and progressively proliferating connective tissue. The thin fibers of the latter at first penetrate into the granuloma and then, as the fibrosis gradually increases in the later stages of the disease, it completely displaces the specific leprous tissue.

The number of bacilli found in these nodular cases is very great. They fill the cytoplasm of the foamy cells and literally clog the lymphatic spaces, forming dense clumps that appear as globi. In preparations along the length of the nerve it is clearly seen how the bacilli disseminate towards the center from the place of the lesion, especially in the case of lesions in which the presence of the bacilli has not yet caused any tissue reaction.

In the nerve plexuses (brachial, sacral), and the adjacent portions of the nerves, I have never found any bacilli or any changes characteristic of leprosy. Therefore, my findings confirm those of the older authors, that in nodular leprosy there is an ascending neuritis.

Quite another picture was found in the two cases of maculo-anesthetic leprosy studied. Previous authors (Hansen and Looft, Neisser, Deycke), demonstrated long ago that the changes found in this type of the disease differ from those characteristic of the nodular form. Here the entire process is expressed by the formation of ordinary productive-inflammatory infiltrations, consisting of round cells with a small admixture of epithelioid cells. The infiltrations usually develop around the blood vessels, and especially in connection with the small cutaneous nerve trunks. There are only a few bacilli in these lesions, and they are demonstrated with great difficulty. It was just such a picture that I found in my cases.

The changes in the nerves begin in the small branches in the dermis and subcutaneous tissue. They then gradually extend upwards and involve the large trunks, which become affected in the same areas as in the nodular form (wrist, elbow, ankle), but they differ from the latter in that there is a more uniform thickening of the nerves, without nodular swellings, and their white color is preserved.

Microscopically the perineurium and endoneurium show ordinary round-cell infiltration, with a small admixture of epithelioid cells.

The specific lepra cells, characteristic of nodular leprosy, are absent. The infiltrations, penetrating into the substance of the nerves, break up and destroy the neurofibrils (Plate 41, fig. 3). In some sections this picture is seen very clearly. From the various sections studied it can be seen how the round-cell infiltration is first modified by the production of loose connective tissue, which later becomes fibrotic (scarred) and completely destroys the nerve fibers. In the scar tissue remnants of the myelin fibers can be demonstrated with difficulty by the Spielmeyer method (Plate 41, fig. 4).

In conclusion, I would like to emphasize the difference in the pathologic-anatomical changes in the nodular and maculo-neural forms of the disease. In the former, marked changes are found in the ganglion cells of the intervertebral and sympathetic ganglia and (according to the observations of Babes) in the anterior horns of the spinal cord. In the macular form such changes have not been observed, either by myself or any of the older authors. The involvement of the peripheral nerves in the nodular form is expressed by the formation of a typical leprotic granuloma which is rich in "lipoid-degenerated" cells that contain large numbers of the bacilli. In the maculo-neural type, on the contrary, the process leads to the formation of nonspecific infiltration of ordinary appearance which causes swift destruction of the nerve fibers.

Modern clinicians are not satisfied with the old morphological classification of leprosy, and are seeking new methods of classifying cases on the basis of clinical manifestations. These so-called dynamic classifications must play an extremely important part in the further study of the disease and especially in its treatment. However, they would be more valuable were all the features of the clinical course of the disease completely correlated with the pathological substratum. As yet we have seen no adequate attempts made in that direction. We do not yet know how the changes in the ganglion cells of the sympathetic and intervertebral ganglia (not to consider those in the anterior horns of the cord), are reflected clinically. Nor has any attempt in that respect been made with regard to the peripheral system. However, the experience of some of the older authors (Woit, Gerlach) permits such a correlation.

My own observations allow me to approach the solution of this question more nearly than any of the previous authors. It is well known that in nodular leprosy symptoms referable to the peripheral

nervous system are most evident in the later stages of the disease, at a time when it is quite possible that the processes in the skin may come to an end and the nodules become stationary or undergo retrogression. In other words, there comes a period of remission or even definite improvement which some authors have regarded as the beginning of recovery. That view is certainly not correct, for it is just during that period that there appear more or less marked symptoms which indicate severe affection of the nervous system: atrophies, contractions, trophic ulcers, mutilations. Münch, in his day, properly called this stage of the disease "secondary nervous leprosy."

These consecutive changes of clinical manifestations, somewhat enigmatic to the clinician, are clearly explained on the basis of the pathological changes. The leprotic granulation tissue that develops in the nerve sheath has little capability of any further metamorphosis, and slowly undergoing organization it is converted into scar tissue that compresses and completely destroys the nerve fibers. This explains the late development of nervous symptoms in nodular leprosy.

Quite another condition is seen in maculo-neural leprosy. Here the destruction of the nerve fibers and nerve trunks takes place comparatively quickly, sometimes with lightning-like swiftness, in accord with the rapid growth of the inflammatory infiltration and its penetration into the substance of the nerve trunk. Consequently the nervous manifestations set in very early, and rapidly reach high grades of development.

## CONCLUSIONS

1. In the nodular form of leprosy the peripheral nerves as well as other organs and tissues involved by the leprotic process show lesions characterized by the presence of numerous bacilli, and lepra cells containing bacilli, lipoids and hemosiderin.[3]

2. The maculo-anesthetic form of the disease is characterized by the appearance in the nerves, as well as in other organs affected, of ordinary round-cell infiltrations containing small numbers of bacilli and hemosiderin. These bacilli are found in the nerves, evidently in larger quantities than in the skin lesions.

[3] The question of the presence of pigment of hematogenic origin in the lesions of leprosy is discussed in a separate article to appear shortly in this JOURNAL.

3. In the ganglion cells of the intervertebral and sympathetic ganglia in nodular leprosy there occurs vacuolization of the cytoplasm, and quite large numbers of the leprosy bacilli are present in these cells. In the maculo-anesthetic form no vacuolization or bacilli have been noted in the cases studied.

4. In the nodular form the granuloma, which is rich in foamy cells that are but slightly or not at all capable of further differentiation, undergoes organization very slowly, which explains the slow deterioration of the nerve trunks and the very slow increase of clinical manifestations on the part of the nervous system in this form of the disease.

5. In the maculo-anesthetic form the rapid invasion of the depths of the nerve trunks by the inflammatory infiltration, with subsequent rapid destruction of their fibers, is accompanied by the early appearance of clinical manifestations referable to the peripheral system.

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## DESCRIPTION OF PLATE

### PLATE 41

FIG. 1. Numerous leprosy bacilli in a ganglion cell of an intervertebral ganglion, from a case of nodular leprosy.

FIG. 2. Destruction of nerve by the granulomatous process, in a case of nodular leprosy.

FIG. 3. Destruction of nerve by round-cell infiltration, in a case of maculo-neural leprosy.

FIG. 4. Connective tissue in a nerve, replacing a former infiltration, in a case of maculo-neural leprosy. Destruction of neurofibrils.

FIG. 5. Round-cell infiltration of testis in a case of maculo-neural leprosy.

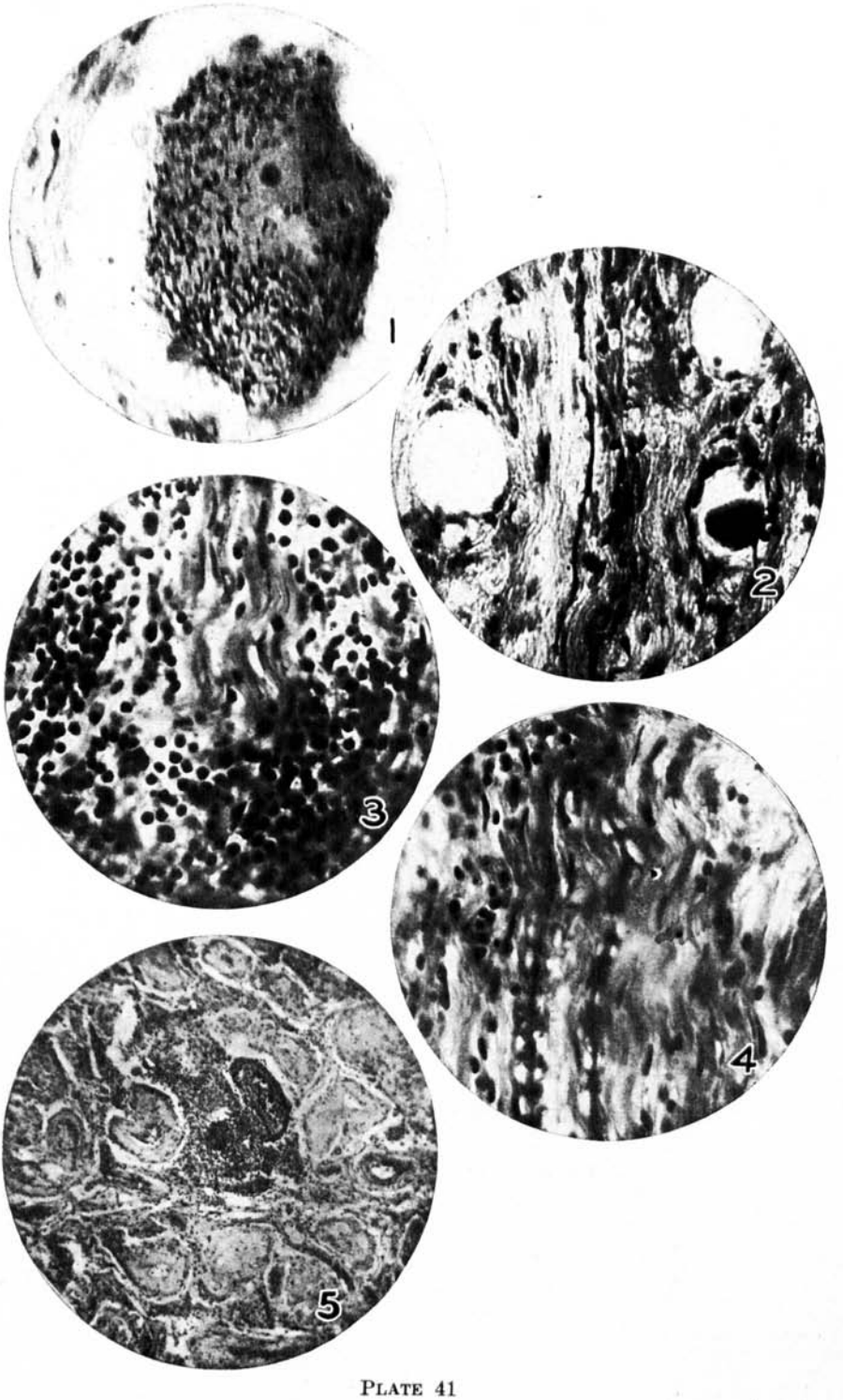


PLATE 41