# INJURY OF NERVE ELEMENTS OF THE TONGUE ROOT IN LEPROMATOUS LEPROSY

by

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## Preliminary Report

In his work on the study of nerves in leprosy, Lie mentions that it is rarely possible to examine a nerve at an early stage of its infection with *M. leprae*. Usually the infection is of comparatively long standing, and it is impossible to trace its spread along the nerve fibers. In studying the problem of the selective affection of sensory conductors by leprosy bacilli, this author states that the process, most probably, begins in an area where the afferent and efferent nerve fibers are separated from each other.

Our own observations lead us to believe, that the leprosy bacillus possesses an affinity for the sensory nerve fibers.

Studies of the peripheral nervous system attracted our attention to the condition of nerve elements of the tongue root. The investigations were conducted on autopsies on cases of lepromatous leprosy in which the disease was of long standing.*

The postmortem examination revealed that the mucous lining of the tongue had not undergone macroscopic changes, while the skin, the mucosa of the upper respiratory organs, the peripheral nerves, and many other systems and organs were the seat of noteworthy pathologic changes. Only the circumvallate papillae, which are situated at the tongue root, differed from the surrounding mucosa in that they had a pale yellow tint.

In all, we examined 7 specimens from 7 autopsies, in which the macroscopic changes were analogous. In the histologic examination of the *Papillae vallatae* we found slight changes in the nerve elements, while the distribution of bacilli was characteristic. Perhaps these observations may serve as a model of the conditions which prevail in the primary penetration and spread of leprous infection in the human organism.

We used the method of impregnation of Gross-Bilshowvsky-Lavrentyev. In order to ascertain simultaneously the localization

* The neurologic work was done in the late Professor B. I. Lavrentyev's laboratory, under his direct guidance.

and the distribution of the bacilli in the nerve elements, we stained the sections by the method of Ziehl-Neelsen. The results of this complementary staining method exceeded our expectations. We were able to see simultaneously the bacilli and the nerve structure and to ascertain their relationship. We could, in the first place, ascertain the number of bacilli in the goblet gustatory cells of the papillae (Figure 1). The bacillary invasion, in isolated cases, was intense, the bacilli virtually flooding the goblet cells, while the adjacent epithelium was free of organisms. The bacilli were distributed longitudinally along the goblet axis. We are not assuming that the flow of liquid in the gustatory goblets takes place in a different direction, but the repeated distribution of the bacilli along the axis leads us to believe that it is not an accidental phenomenon.

Under the epithelium of the *Papillae vallatae* we observed receptors of the Meissner type or of simpler structure. The bacilli there were few in number; they could be seen singly in the perineural sheath of the fiber as it approaches the terminal corpuscle, or along the axon and closely attached to it. The slides impregnated with silver reveal a large number of nerve structures in the *Papillae vallatae* zone. There are numerous pulp- and pulpless nerve fibers spreading fanwise from the base of the papillae towards the periphery; somewhat deeper lie the small nerve branches and nerve bundles, also the ganglia of the autonomous nervous system.

Many bacilli were present in the above mentioned nerve routes. Bacillary bundles were encountered along the entire surface of the fanwise spreading nerve fibers, in the grooves of the perineural sheaths. Deeper, in the nerve bundles and small branches, the bacilli formed accumulations in the shape of strings along the peri- and endo-neural sheaths. The axons of isolated fibers, and also of those collected in bundles, showed varicose changes, the varicosity being of various types. Some of them formed beads along the fibers at regular intervals, others showed fibrillary structure, or having been markedly impregnated with silver, had become homogenous. Fibers also were encountered where a separation of the band between the varicosities took place, as a result of which they broke up in separate fragments. Another type of varicosity is one that is localized along the nerve fibers without formation of beads, is of various sizes, and contains bacilli. Also, very small varicosities are present, in which only one or two bacilli may be found (Figure 2).

Sometimes, a swelling of the axis cylinder, of exceptionally large size, full of bacilli, was encountered. The bacilli in them, under high magnification, appeared to fill virtually the entire space in solid rows. Particularly large areas were found in the bundles at the bases of the papillae, where the diameter of the varicosity

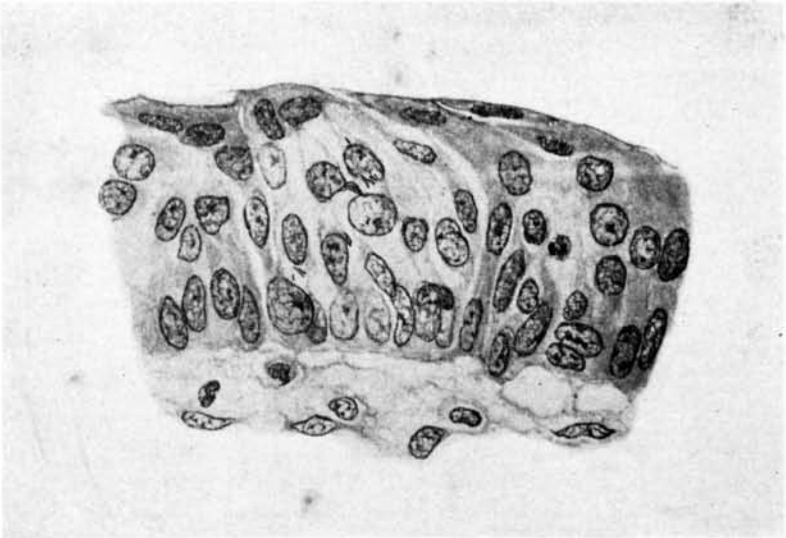

Figure 1: Gustatory goblet with bacilli.

Figure 2: Small varicosities filled with bacilli along the route of the nerve fiber in the *Papillaé vallatae* of the tongue.

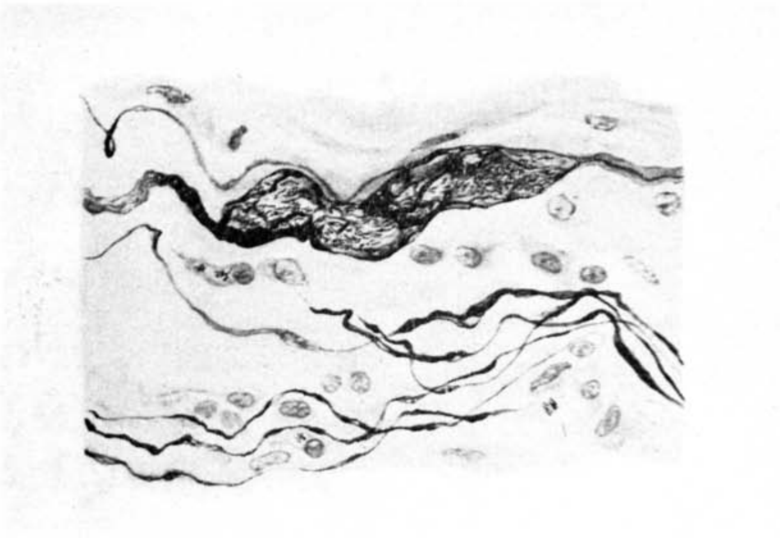

Figure 3: Immense varicosities on the axis cylinder filled with bacilli in the nerve bundle at the base of *Papillae vallatae*.

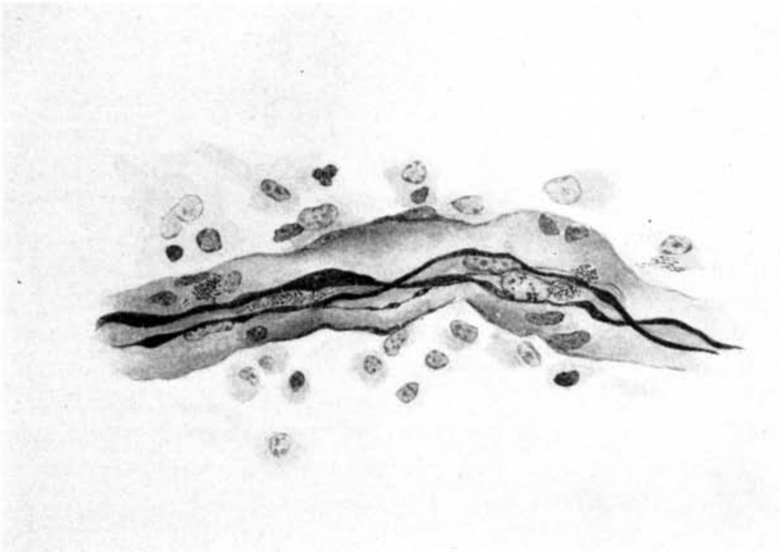

Figure 4: Bacillary bundles in the perineural lymph slits of the nerve bundle of a *Papilla vallata*.

exceeded by five to eight times the diameter of the nerve fiber, and the number of microbes was so great that one could speak of a bacillary depot along the route of the axon. The microbes fill out the spaces between separated neurofibrillae of the axis cylinder; the latter become thickened, interlaced, and form a net of large loops which stands out clearly against the background of brightly stained bacilli (Figure 3).

Clusters of microbes were encountered in the form of disconnected strings in the lymphatic grooves of perineural sheaths. Bacillary formations at times reached exceptional length and followed the convolutions of the axons. The presence of bacilli in perineural sheaths is clearly demonstrated in cases where the silver staining was successful; one can see the transparent sheath on the nerve fiber, while inside the bacilli stand out clearly (Figure 4). A large number of bacilli are concentrated in Schwann cells.

The bacillary invasion was not limited to nerve bundles in the region of *Papillae vallatae;* the microbes penetrated deeper in nerve trunks (branches) which pass through connective tissue on the border line of the muscular layer, but, the further towards the center, the fewer bacilli are encountered, and the less reaction on the part of nerve fibers and surrounding tissue. Nerve fibers which are laced around glands were also invaded by microbes. Here the bacilli lie in axis cylinders, in perineural sheaths, and in Schwann cells. In the latter, they are located on one of the poles of the cell, causing deformation and displacement of the nucleus.

The above observations strongly suggest the spread of the leprosy bacilli along nerve conductors of the *Papillae vallatae* in a centripetal direction.

As regards the reaction of the mesenchyma, it was most clearly noticeable in the region of the *Papillae vallatae* proper, where leprosy cells were encountered in isolated groups, in the connective tissue of the papillary base rich in lymphoid elements. We must emphasize that the changes in the connective tissue subside as the infection moves centripetally along the nerves; one can find areas where bacilli are present in the nerves, while the surrounding tissue is intact. A similar phenomenon was observed by E. Muir on examination of sections of skin in which he found bacilli in nerves located in regions otherwise free from the specific lesions. Takino, in touching on the importance of peri- and epineural lymphatic grooves in the spreading of the microbes, noted that the leprous process sometimes stems from changed nerve bundles.

The above leads us to believe that the spread of infection along nerve conductors precedes the development of the reaction on the part of the mesenchyma.

The selective involvement of the circumvallate papillae led us to conduct additional examinations of the tongue. We studied slides from various areas: the tip, dorsum, and lateral surfaces. The results were negative; we found no bacilli and no clusters of leprous cells.

On more detailed examination of the changes in the grooved papillae, we found that the nerve bundles and fibers which accompany the blood vessels were also invaded by the leprosy bacilli and were undergoing changes along the route of axis cylinders, in the form of varicosities.

The ganglia of the autonomous nervous system, which are located at the base of *Papillae vallatae*, deserve especial attention. Like all other nerve elements, these ganglia are subjected to a vigorous invasion by the microbes, which are located in the protoplasm of the nerve cells, (Figure 5), and also in the lymphatic grooves under the capsule of the nerve bundles, where they are found in large numbers. The bacillary clusters within the nerve cells vary in size from very small to very large ones which are observable under low magnification. Where the microbes are present, the protoplasm of the nerve cell is vacuolized; but, even without the presence of bacilli, this form of degeneration could be often observed in the protoplasm of the nerve cell. Many neurons are diminished in size, wrinkled, are of grotesque shape and are thickly surrounded with satellites. The excessive growth of the pericellular apparatus (of synapses), can be observed.

Particularly noticeable is the hypertrophy of the pericellular plexus around cells which contain a large number of microbes and have undergone considerable degeneration. When only fragments are left of the nerve cell, the entire area occupied by the neuron is surrounded by a large number of nerve threads, which form a thick ball (Figure 5). The hypertrophic pericellular threads undergo varicose thickening, are dense and argentophile. The excessive growth of synapses is clearly noticeable in separate neurons (Figure 6). In these cases, one can clearly see the bundles and spirals of the pericellular fibers against the background of the surrounding tissue (E. I. Belyaev in the laboratory of B. I. Lavrentyev).

The study of preparations of the muscular tongue layer showed that nerves which innervate the muscles of the tongue were not materially changed and were free of leprosy bacilli. In following the route of nerve bundles, in the muscles, up to their terminal branching off and to their final motor endings, (Figure 7), we found no bacilli or clusters of bacilli, which are so characteristic for the nervous elements of the grooved papillae *(Papillae vallatae)*. The absence of bacilli in the motor nerves of the tongue

Figure 5: Excessive growth of the pericellular apparatus (synapses) in an autonomic bundle of a *Papilla vallata*. Invasion by the bacilli into some neurons and capsular cells of the bundle.

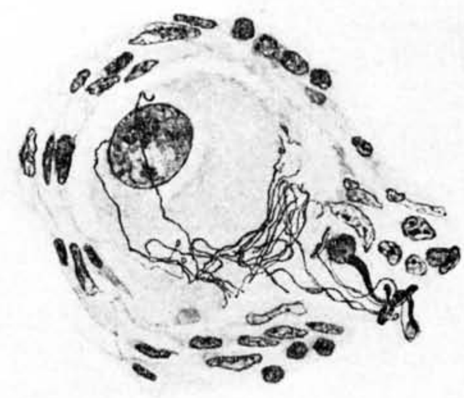

Figure 6: Enlacing by pericellular fibers of an isolated ganglion cell at the base of a *Papilla vallata*.

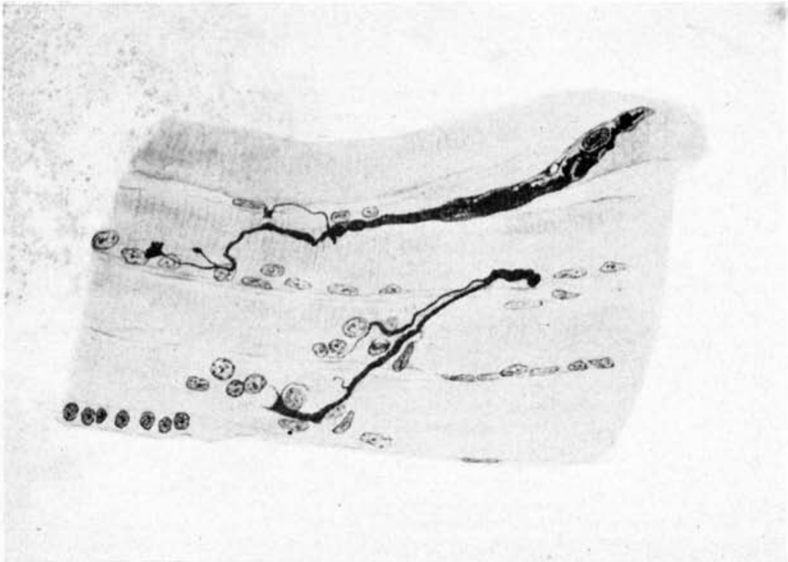

Figure 7: Ending of a motor nerve bundle in a lingual muscle.

again proves that there must be peculiar conditions suitable for the development of the pathologic process in the sensory and autonomic nerve conductors of the *Papillae vallatae*, which indicates the selective and early involvement of these systems.

In turning to the analysis of the data which we have obtained, we must again emphasize the delicacy of the changes in the mucosa of the base of the tongue, while there is a vast and spreading process in the skin, peripheral nerves, and also, in the tissues and nerve elements of other organs.

In far advanced stages of leprosy, the infection, no doubt, is transmitted along lymphatic and possibly vascular routes. However, there is a certain regularity in the involvement of the organs. Some are affected sooner (liver, spleen, testicle), others very rarely (ovary, uterus, heart) or are not affected at all, in spite of the fact that the infection can be carried to them via the blood stream. The explanation is difficult and may lie in properties of the microbe, or in particular conditions existing in the tissues themselves.

In our cases we cannot assert how the microbes penetrated into the *Papillae vallatae*, i. e., whether to consider the gustatory goblet as the portal of infection (any infection), or to attribute it to a particular affinity of Hansen's bacilli for nerve tissue, and particularly, for the afferent conductors. The presence of many bacilli in *Papillae vallatae* and their nervous structures certainly calls our serious attention to the above supposition.

On the basis of study of the peripheral nervous system by the impregnation method, we can state with certainty that the slits in the perineural sheaths play an important role in the spread of the bacilli. What forces attract the bacilli to these routes? How can their spread in the centripetal direction only be explained? According to recent investigations by V. F. Lashkov in the laboratory of B. I. Lavrentyev, each nerve fiber is clothed in an endothelial sheath in which there is a slit filled with lymph-like fluid. Lashkov demonstrated that these sheaths accompany the sensory nerve fibers up to the encapsulated ends, which they cover. If we scan the literature on the movement of fluid in perineural spaces, we find that this problem is still in the stage of investigation. Our scientists (Speranski, Ivanov, Spirov, Ramodanski), as well as foreign investigators (Horster, Whitman), have proven that the lymph spaces of the nerve fibers are connected with the cerebral arachnoid space.

Other authors (Funaoka, Yamada, Sakata, Morimura, Juien, Sato, Watanabe) introduced dyes into the nerve fiber and followed their spread in centrifugal as well as centripetal directions. Takino, in studying the vegetative nervous system in leprosy, states that peri- and endo-neural lymphatic routes play an important role in the spread of the infection. Likewise it has been thought that isolated sensory fibers play a part in spreading the bacilli. This, however, is contrary to Takino, who could find no connective tissue sheath around the fibers. He writes: "Isolated nerve fibers near their sensory ending histologically have no connective-tissue envelope. How, then, can the bacilli spread, if the lymphatic slits are absent?" We have stated that Lashkov has demonstrated the presence of perineural sheaths in isolated nerve fibers and that these sheaths merge with the capsule of the receptors thus enclosing the nerve elements in a sheath *sui generis*.

Our investigations have shown, that the spread of the bacilli follows nerve routes along the perineural sheaths and that the lymphoid fluid in the sheath seems to have a definite direction of flow, with the aid of which the infection is transmitted along a considerable distance.

The development of the process in the tongue does not give a clear indication as to whether the bacilli enter the nerve elements of the tongue root through the gustatory goblets, or via the surrounding tissue. However, our observations prove the existence of certain favorable conditions in the nerve conductors which attract lepra bacilli.

Our work will be justified if the above data will be of use in solving the difficult problems of leprology, mainly the study of routes of invasion and spread of leprosy infection in the human body.