INTERNATIONAL
JOURNAL OF LEPROSY
And Other Mycobacterial Diseases

VOLUME 36, NUMBER 3 JULY-SEPTEMBER, 1968

Pathologic Changes and Their Distribution in Peripheral Nerves in Lepromatous Leprosy[1]

C. K. Job and K. V. Desikan[2]

Leprosy, with all its variety of skin manifestations, is primarily a disease of the peripheral nerves ([17]). Several investigators have studied the cutaneous nerves as obtained from skin biopsies from leprosy patients ([4, 6, 13, 19, 24]), but reports of histopathologic changes in the larger nerves, such as the ulnar, median and radial nerves, are few ([8, 21]).

It is well known that certain specific sites in the peripheral nerve trunks are vulnerable to leprosy lesions. The general pattern of paralysis manifested in leprosy suggests that the lesions are largely confined to these sites of predilection, which are as follows: ulnar nerve at the region of the medial epicondyle, and at the wrist; median nerve just above the carpal tunnel; radial nerve at the wrist and slightly above the elbow; posterior tibial nerve at the flexor retinaculum; common peroneal nerve at the flexor retinaculum; common peroneal nerve as it turns around the neck of the fibula; facial nerve as it crosses the zygomatic process of the maxilla; and great auricular nerve as it crosses over the sternomastoid muscle (Fig. 1). During the acute stage of neuritis the nerves are swollen, painful, and tender, especially at the above named sites. As the lesions resolve there is gradual reduction of the swelling. Occasionally the nerves may regain their original size, but often they remain thickened, and are firm to hard in consistency.

This study was undertaken to investigate and describe in detail the lesions in the ulnar, median, and radial nerves in their entire course in the upper extremity in four autopsied patients with active lepromatous leprosy, and to find out if the histopathologic changes are confined to these sites of predilection, and to elucidate, if possible, reasons for this selective involvement.

MATERIALS AND METHODS

In four autopsied cases of lepromatous leprosy the entire ulnar, median, and radial

[1] Received for publication 11 December 1967.

[2] C. K. Job, B.Sc., M.D., M.C. Path., Professor of Pathology; K. V. Desikan, M.D., Lecturer in Pathology, Norman Institute of Pathology, Christian Medical College and Hospital, Vellore, South India. *Dr. Desikan's present address:* Central Leprosy Teaching and Research Institute, Chingleput, South India.

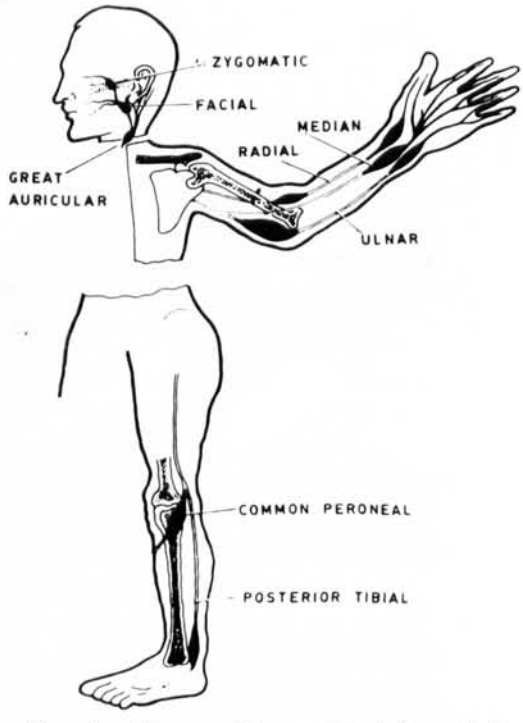

FIG. 1. Diagramatic representation of the common sites of trunk nerve lesions in leprosy.

nerves from one upper extremity, from the brachial plexus to the terminal ends in the skin, were dissected out. Some of the important branches also were removed along with the main trunk nerve. Segments approximately every 2.5 to 3 cm. along the length of the nerve were numbered and labelled serially, as shown in Figure 2, so that they could be identified in their proper anatomic position. The naked-eye appearance of the nerves was described in detail in relation to their anatomic position, and the thickness of each segment was measured and recorded. The known sites of predilection were carefully examined.

Two representative pieces were obtained from each labeled segment of the nerve and fixed in 10 per cent formalin. After the usual processing one piece was embedded transversely and the other vertically. Paraffin sections 7 μ thick were prepared and stained with the following stains:

Hematoxylin and eosin
Fite's modification of the acid-fast stain

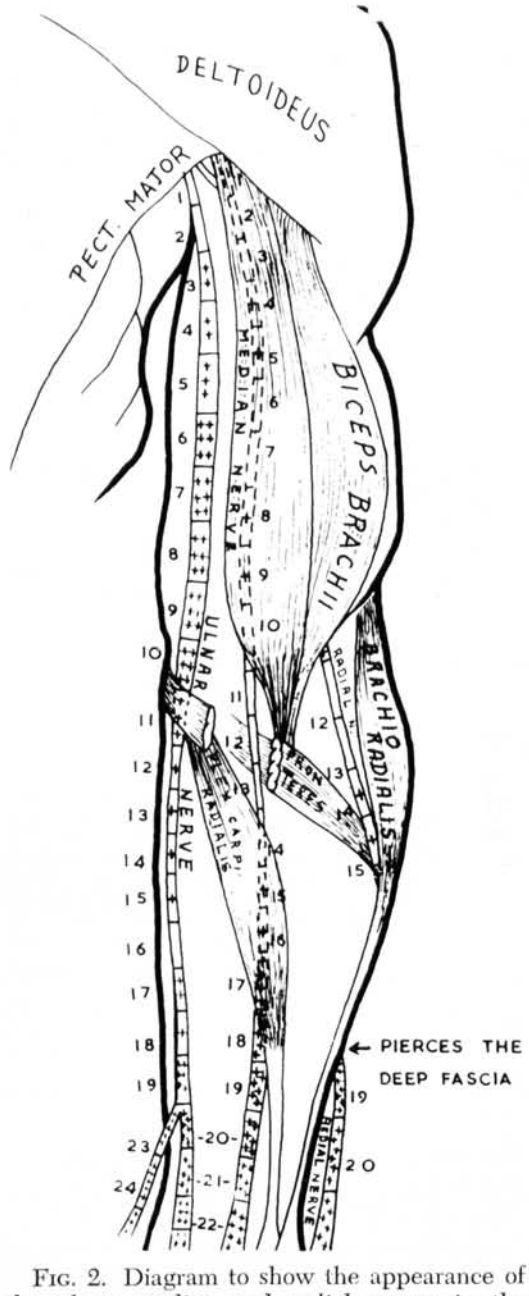

FIG. 2. Diagram to show the appearance of the ulnar, median and radial nerves in the cases studied. Note the enlargement of the nerves at the common sites of predilection.

Gomori methenamine silver (G.M.S.) stain for lepra bacilli
Loyez myelin stain
Bodian stain for axis cylinders

One case is described in detail in its gross and microscopic aspects.

CASE HISTORY

Gross Findings (Fig. 2)

Ulnar nerve. The ulnar nerve at its origin from the brachial plexus appeared to be normal in size and consistency, measuring about 0.2 to 0.3 cm. in diameter. A gradual thickening was noticed, which became obvious at a point 7.5 cm. from the brachial plexus. This swelling gradually increased in size and was present for a distance of about 18 cm., extending to the level of the medial epicondyle. The maximum thickening of the nerve was seen approximately 2 cm. above the medial epicondyle, where it measured about 1.2 cm. in diameter. Below the medial epicondyle the nerve dipped in between the two heads of the flexor carpi ulnaris, and there abruptly became normal or small in size, measuring only 0.3 cm. in diameter. It remained small during its course under the cover of this muscle for another 13 cm. As it emerged from underneath the muscle there was again an obvious increase in its thickness, and a maximum thickness of 0.6 cm. was reached when it was at the level of the proximal crease of the wrist.

Median nerve. The median nerve, from its origin from the brachial plexus along the upper arm and down through the forearm, up to 6 cm. proximal to the transverse carpal ligament, was of normal size, measuring 0.2 to 0.3 cm. in diameter. It was soft in consistency. The median nerve in the forearm was between the flexor digitorum profundus and flexor digitorum sublimis up to a point 6 cm. proximal to the transverse carpal ligament. As it emerged from the cover of the flexor digitorum sublimis, an abrupt thickening of the nerve was noted, which increased gradually to a diameter of 0.6 cm. at the level of the transverse carpal ligament.

Radial nerve. The radial nerve, from its origin at the brachial plexus throughout its course in the radial groove and along the forearm under the cover of the brachioradialis, was of normal size and consistency, measuring 0.2 to 0.3 cm. in diameter. In the lower fourth of the forearm the superficial branch pierced the deep fascia and divided into the medial and lateral branches. These two branches were thickened, especially the lateral branch, which measured 0.4 to 0.5 cm. in diameter at the region of the anatomic snuff box.

Histopathologic Findings

Ulnar nerve. In the first two segments there were a few scattered inflammatory cells consisting mainly of small round cells. In the next two segments there was some increase in the inflammatory cell infiltration. From the third to the seventh segment microgranulomata consisting of collections of macrophages, lymphocytes, and plasma cells were seen inside some of the funiculi (Fig. 3). Several foamy Schwann cells also were present. Most of the funiculi did not show any lesion. It appeared as though the granulomata had started around blood vessels and gradually increased in size, pushing the nerve fiber apart. Even inside the affected funiculi the granulomata were localized to one or two focal areas. From the eighth to the eleventh segment there was extensive infiltration of the entire nerve with a large number of foamy macrophages (Fig. 3). These granulomata were situated mainly either in the paravascular or perivascular region. There was tissue edema and pronounced increase in vascularity, as evidenced by numerous dilated blood vessels (Fig. 4). Diffuse and well marked increase in the intraneural fibrous tissue was apparent (Fig. 5). The perineurium showed slight thickening in the first few segments, which increased progressively, with marked thickening at the region of the eighth segment (Fig. 6). The nerve continued to be markedly thick until the eleventh segment, which was at the level of the medial epicondyle.

In the twelfth segment there was notable reduction in edema and inflammatory cell infiltration, and only a few focal granulomata, together with a few scattered round cells, were seen. The perineural thickening gradually decreased, and in the fourteenth segment there was no obvious thickening. Inflammatory cells were extremely rare, and the sixteenth segment did not show any signs of active inflammation. The nerve tissue was extensively replaced by fibrous tissue. From the seventeenth to the nineteenth segment scattered round cells and

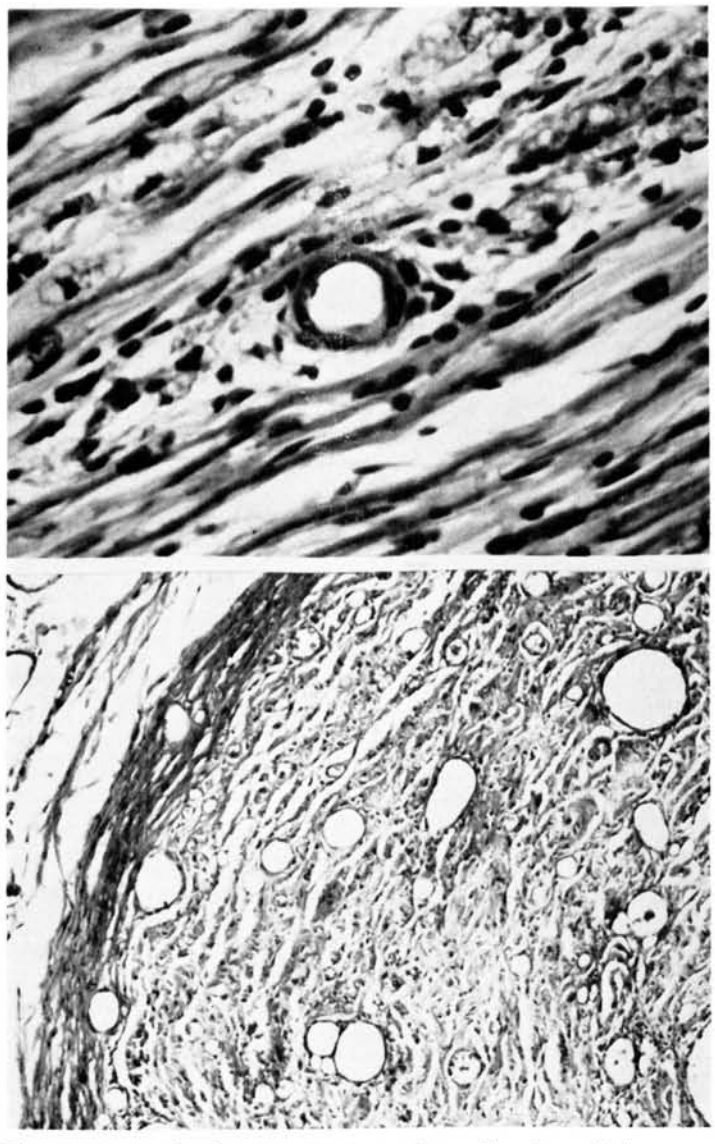

FIG. 3. Photomicrograph showing perivascular collection of foamy macrophages inside a nerve. Several of the Schwann cells also have a foamy cytoplasm. (H & E, 400X)

FIG. 4. Note the marked increase in vascularity of the nerve and also the adhesion between the thickened perineurium and the edematous fibrous tissue inside the nerve. (H & E, 100X)

macrophages reappeared. As the nerve emerged from the deeper areas into the subcutaneous tissue, the perineural thickening became pronounced and the intraneural cellular infiltrate and fibrosis increased significantly. Most of the inflammatory cells were foamy macrophages. There was tissue edema, increase in vascularity and proliferation of Schwann cells. The granulomatous inflammation persisted up to the terminations of the cutaneous branches.

Bodian stain to demonstrate axons showed well stained axis cylinders in the first segment. From the second segment to the eleventh there were pathologic changes indicating varying degrees of axonal damage and destruction (Figs. 7, 8). There was

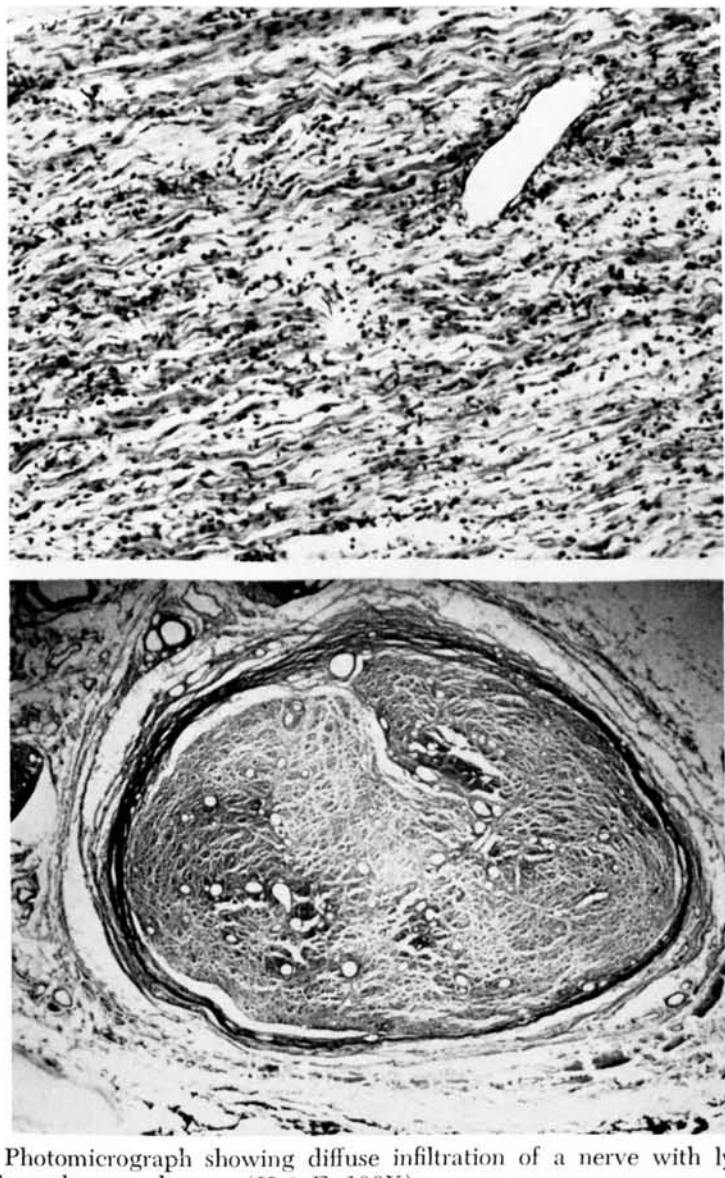

FIG. 5. Photomicrograph showing diffuse infiltration of a nerve with lymphocytes, plasma cells, and macrophages. (H & E, 100X)

FIG. 6. The axons in the funiculus are replaced by lepromatous granulomata and fibrous tissue. There is proliferation of the perineurium, producing the classic onion peel appearance. (H & E, 25X)

obvious reduction in the number of axons in each funiculus. The remaining axis cylinders were evidently separated from one another by edema and inflammatory cell infiltration. Most of them showed irregularity and fragmentation. A number of axis cylinders at intervals showed considerable thickening and some showed ballooning (Fig. 8). Some terminated in swollen end bulbs, emanating from which several small fine branches of axons were seen. In the region of the blood vessels there was a considerable amount of axonal debris. These degenerative changes were very marked at the level of the eighth and ninth segments.

From the twelfth to the eighteenth segment there was gross reduction in the number of nerve fibers. Several small funiculi were seen, containing numerous fine, pre-

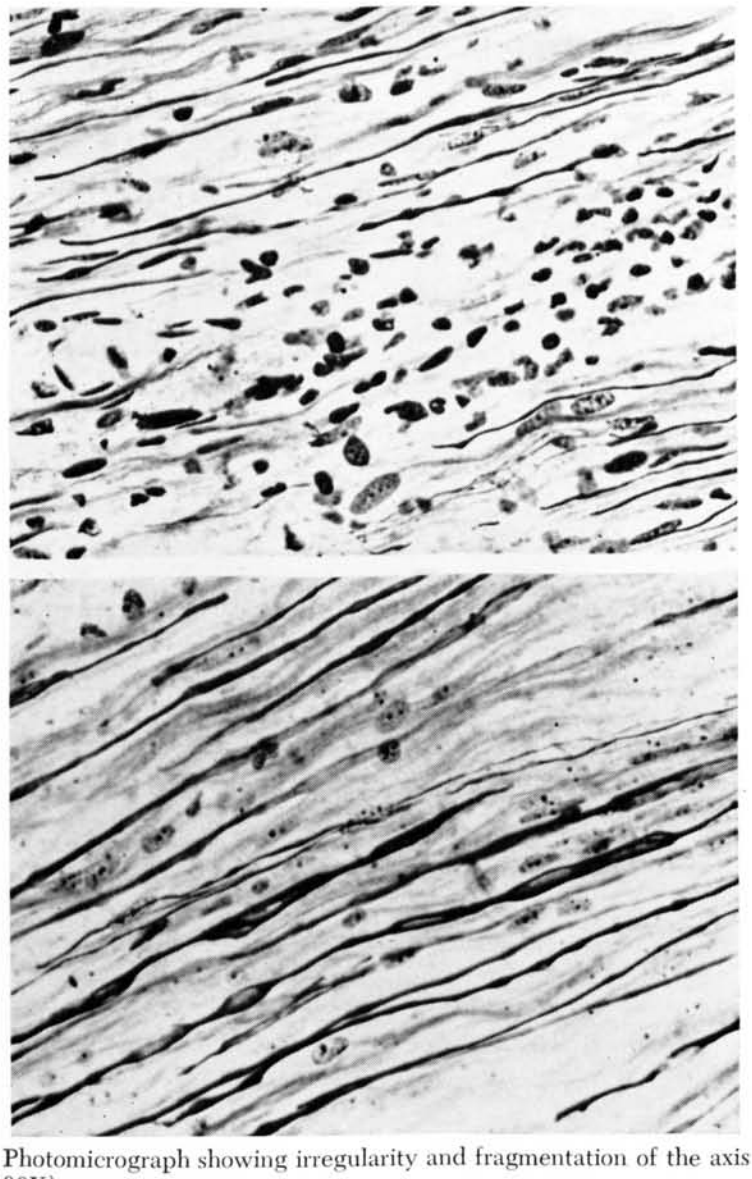

FIG. 7. Photomicrograph showing irregularity and fragmentation of the axis cylinders. (H & E, 400X)

FIG. 8. Some of the axis cylinders show irregular thickening and ballooning. (H & E, 400X)

sumably nonmyelinated axons, densely packed together. These were smooth in outline; a few were thicker than average and some showed elliptical swelling along the core, typical of regeneration. These were presumably branches of myelinated fibers.

The segments from the nineteenth to the terminal ends of the nerve contained numerous fine axons separated by edema fluid, inflammatory cells, and fibrous tissue. Some of them showed swelling and fragmentation, but these changes were minimal.

It seemed that the large majority of the axis cylinders, both myelinated and nonmyelinated, were destroyed in the region of the elbow and had undergone Wallerian degeneration. A few that survived and managed to go through the inflammatory granulomata put out numerous branches, which were crowded togeth-

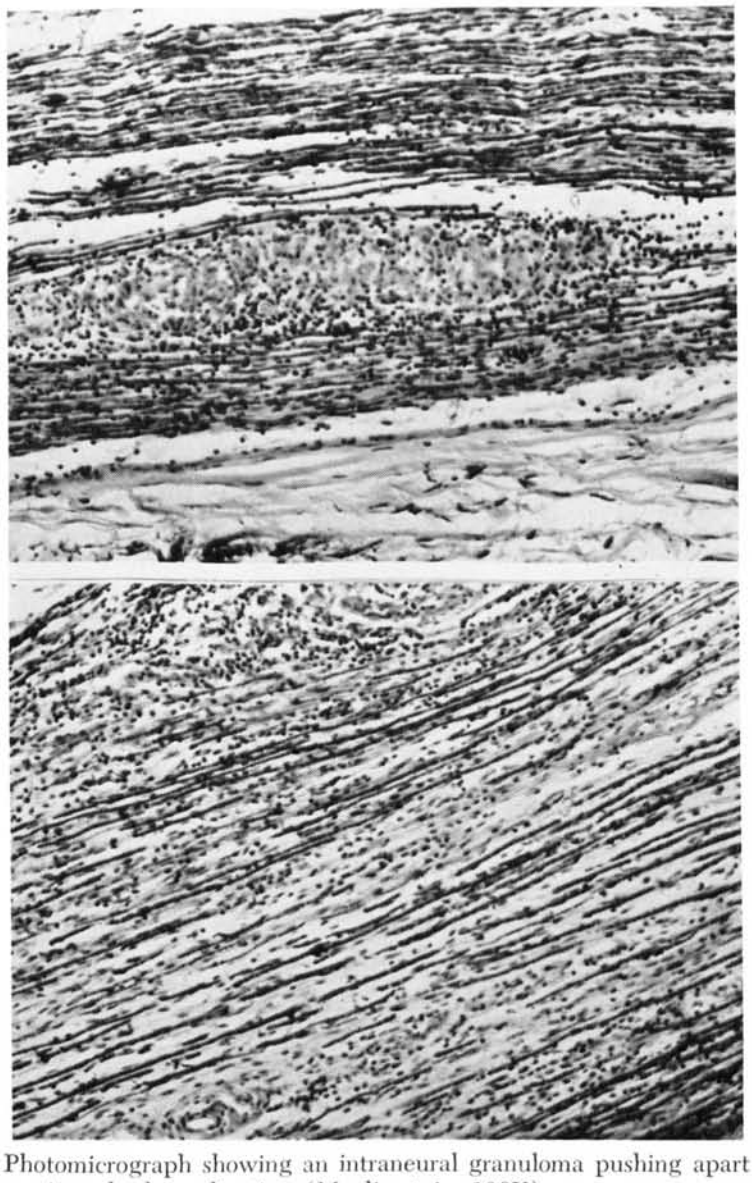

FIG. 9. Photomicrograph showing an intraneural granuloma pushing apart the nerve fibers. There is early demyelination (Myelin stain, 100X)

FIG. 10. Photomicrograph showing much demyelination. A few axis cylinders show fragmentated myelin around them. (Loyez myelin stain, 100X)

er in the nerve trunk in the forearm as numerous fine, smooth nonmyelinated fibers. Many of these fine fibers were traced through the inflammatory zone in and around the wrist, leading on to the subcutaneous tissue.

In the myelin stain the first segment showed mostly normal myelinated fibers. From the second segment to the terminal end of the nerve there was extensive demyelination (Fig. 9, 10). In the region from the second to the eleventh segments degenerating myelin was noted around the blood vessels as debris. In most sections at first sight it seemed as if the axons had taken up the stain, but on careful examination under oil immersion it was found that the appearance was due to staining of a thin rim of myelin around the axis cylinder. It was obvious that there was more demyelination than axonal destruction.

In the first two segments the acid-fast

FIG. 11. Photomicrograph showing a few Schwann cells distended with *M. leprae*. (G.M.S., 1,000X)

stain and G.M.S. stain showed only occasional organisms. They were mostly single and found along the nerve fibers. In the third segment two globi were seen, confined to two of the many funiculi. Several single bacilli were also present. The fourth and fifth segments showed a few scattered single organisms, most probably inside Schwann cells. However, from the sixth to the eleventh segments, reaching to the level of the elbow, the nerve was invaded by leprosy bacilli in groups and clusters (Fig. 11). The bacilli were inside macrophages, perineurial cells, and Schwann cells. The perineurium stood out prominently, with several layers of perineurial cells distended with bacilli. From the twelfth to the eighteenth segments only occasional organisms were detected, and then only after careful search under the oil immersion lens for several minutes. In some sections no organisms could be seen. From the nineteenth segment to the terminal end of the nerve there were abundant bacilli in groups and clusters inside macrophages, Schwann cells, and perineurial cells (Fig. 12).

Median nerve. In the H & E stain segments from one to fifteen showed an occasional round cell infiltrating the nerve bundles. There was some increase in the number of Schwann cells; the increase was marked in the fifteenth segment. The sixteenth segment showed a pronounced increase in inflammation in the cross section. One funiculus showed a small granuloma consisting mostly of macrophages with a few round cells. The perineurium was obviously thickened. Segments sixteen to twenty-two showed infiltration with numerous macrophages, increasing fibrosis, and perineural thickening, most pronounced in the twenty-second segment, which was located anatomically at the crease of the wrist.

In the Bodian stain the axis cylinders from the first to the sixteenth segments stained well. There were some swollen axons in the sixteenth segment, but no gross evidence of destruction or degeneration of axis cylinders. In the seventeenth segment numerous intrafascicular granulomata were seen. The axis cylinders showed fragmentation, vacuolation, and swelling. Some of them ended in bulbs with evidence of branching. These changes were seen in varying degree up to the end of the twenty-second segment.

The myelin stain showed nerves with well myelinated fibers from the first to the fifteenth segment. In the sixteenth segment there was swelling and vacuolation of myelin, together with patchy areas of total demyelination. From the next segment to the terminal ends of the nerve, sections showed mostly demyelinated nerve tissue. Myelin was present, however, in a few scattered fibers. The tissue around the intraneural blood vessels showed much mye-

lin debris. Demyelination was almost complete from the eighteenth to the twenty-second segment. It would seem that there was more demyelination than destruction of axis cylinders.

Acid-fast and G.M.S. stains showed only an occasional organism in sections from the third to the fifteenth segment. In the sixteenth segment clumps of bacilli were present. From the seventeenth segment onward there were numerous organisms, arranged in globi. From the nineteenth segment to the twenty-second almost every field in the sections showed numerous globi. There were also numerous single bacilli along nerve fibers. The perineurial cells, Schwann cells, and the macrophages were distended with bacilli (Fig. 12).

Radial nerve. No changes were obvious from the first to the sixteenth segments, where the nerve was more or less deeply placed. In the seventeenth segment, as the nerve emerged out of the deep fascia, there was much infiltration with round cells and an occasional collection of macrophages. In the eighteenth segment there were several small granulomata, consisting mostly of macrophages, around blood vessels inside the funiculi. There was much increase in intraneural fibrous tissue and also proliferation and thickening of the perineural tissue. Inflammatory change and perineural thickening were seen in increasing degree in the entire superficial branches of the nerve until the twenty-fifth segment.

The Bodian stain showed mostly normal axis cylinders up to the fifteenth segment. From the sixteenth segment to the terminal ends of the nerve fibers the axis cylinders showed irregular swelling, vacuolation, and fragmentation. There was also evidence of axonal regeneration, with numerous small, fine, smooth branches arising from the thick nerve fibers abruptly cut.

The myelin stain also showed lesions following the same pattern. The axis cylinders up to the fifteenth segment had well preserved myelin. In the sixteenth segment there were focal areas of demyelination, and the following segment, to the terminal ends of the nerve, showed almost totally demyelinated nerve tissue, except for a few scattered axis cylinders that showed some preserved myelin. Degenerating myelin material was present around blood vessels in the intraneural granulomata.

Acid-fast and G.M.S. stains to demonstrate organisms showed no bacilli in the first four segments. Only a very few scattered organisms were present from the

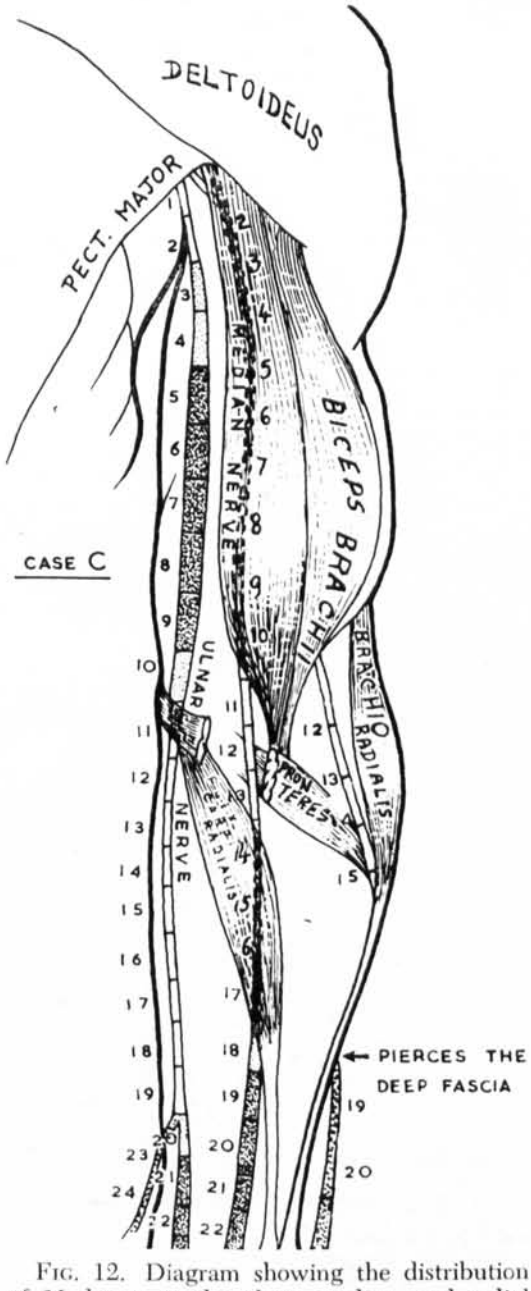

FIG. 12. Diagram showing the distribution of *M. leprae* in the ulnar, median, and radial nerves. Note the increase in the number of bacilli in the areas of thickening, which are usually in the subcutaneous regions.

fourth to the fifteenth segment. The sixteenth segment showed a few clumps of bacilli and several single bacilli along nerve fibers. From the seventeenth to the twenty-sixth segment there were numerous large collections of organisms throughout the neural and perineural tissue. Bacilli were present inside macrophages, Schwann cells and perineurial cells (Fig. 12).

Cases 2, 3 and 4

The appearance of the ulnar, median and radial nerves in Cases 2, 3 and 4 conformed largely, both grossly and microscopically, to the description given under Case 1, and therefore, a separate description is not given. However, in Case 3 the median nerve showed, in addition, a large segment of inflammatory lesion at the region of the cubital fossa.

DISCUSSION

In this study of four active cases of lepromatous leprosy the ulnar nerve was found to be thickened from an area about 3 to 5 cm. from the brachial plexus up to the level of the medial epicondyle. Below this region it became small abruptly and remained so until it emerged out of the cover of the muscle, where it became thick again. The regions where the nerve was thickened were situated in the subcutaneous tissue. The inflammatory response, which consisted of round cells and macrophages, was seen abundantly in the thickened areas, and obviously the thickening was due to edema and infiltration by the inflammatory cells, most of which were bacilli-filled macrophages, proliferating perineurial cells, Schwann cells, and fibrous tissue. The acid-fast stain to demonstrate bacilli showed a marked increase in the number of bacilli in the areas where the nerve was thickened and placed subcutaneously. The bacilli diminished in number when the nerve dipped deep under the muscle bundles, and were seen only occasionally or were absent in areas where the nerve was placed under the cover of the muscles.

The appearance of the median nerve was significant. All through its course until its emergence from under the cover of the flexor carpi radialis it showed no obvious thickening and only a few round cells and an occasional bacillus. Soon after it emerged from under the cover of the muscle, however, and became subcutaneous, there was marked increase in the inflammatory cell infiltrate, which consisted of lymphocytes, plasma cells, and macrophages. There was also marked proliferation of the Schwann cells and perineurial cells, together with fibrosis. Bacilli were abundant in Schwann cells, macrophages, and perineurial cells.

The radial nerve appeared normal from its origin at the brachial plexus until it pierced through the deep fascia in the forearm and became subcutaneous. At this point the nerve became markedly thickened through proliferation of the Schwann cells and perineurial cells and infiltration by macrophages, plasma cells, and lymphocytes. There was replacement of axons by fibrous tissue. Clusters of bacilli were seen inside perineurial cells, Schwann cells, and macrophages.

In four cases examined the picture was very nearly identical. The findings showed that leprous lesions in the peripheral nerves were produced in the areas where the nerve was subcutaneous.

In our studies active destruction of nerve fibers by intraneural bacillary proliferation within Schwann cells and macrophages was clearly demonstrated. There was also proliferation of the fibrous connective tissue in the perineurium and the endoneurium. Localized granulomatous inflammation and replacement of axons with fibrous tissue in trunk nerves in tuberculoid leprosy have been reported by Ermakova [9].

The number of bacilli present inside the nerves in the cases studied corresponded roughly to the number of bacilli in the skin lesions, and this finding was in agreement with the studies of Ermakova [8]. As mentioned in a previous report [20], the inflammatory response in the nerve to the large number of organisms present is very small. It was also found in our study that in segments of nerves proximal to the site of maximum destruction only small focal lesions were present in a few funiculi, and there too only some of the fibers were involved. Often these lesions were seen

around blood vessels. Fite noticed cells infiltrating the nerve along vascular pathways ([10]). It seems to us that these lesions in the nerves are produced by a blood-borne infection and not an ascending infection from the periphery via the axons, as described by Khanolkar ([18]), or through Schwann cells.

Sherron ([22]) reports that about a third of a nerve can be divided without producing demonstrable motor or sensory deficit. Sunderland ([23]) states that "owing to reassortment of fibers in progress in the proximal portion of the nerve and to the fiber composition of funiculi at high levels, the injury may involve those bundles which contain only a few fibers of some or all of the branches, so that the resultant loss of function could not be detected clinically." These reasons probably account for normal function of mildly or even moderately infected lepromatous trunk nerves. Nerves that are infected in focal areas may function normally without any signs of paralysis in the muscles supplied by the nerves or the skin innervated by them.

In all the nerves examined, demyelination, damage and destruction of the axis cylinders were prominent features. Demyelination is significantly more, and out of all proportion to the extent of destruction of the axis cylinders. Fite ([10]) had reported extensive demyelination in active leprous nerves, and he spoke of total demyelination as the number of bacilli increased. The Schwann cells are extensively parasitized by *M. leprae*, and it could easily be that Schwann cells are destroyed earlier than the axons to which they form a sheath, giving rise to demyelination followed by fibrosis.

Extensive destruction of most axons, with fibrous replacement, was observed at the site of the lesions in all the nerves. Regeneration of the fibers was also evident in the lesions. Numerous fine branches from the bulbous ends of a few nerve fibers were seen to escape through the granulomata, to reach down to the cutis. The sensations they mediate, or the stimulus they convey, may often be too inadequate to be of any functional use. They may still convey pain, however, or other sensation when the fibers are stimulated all at once, as in an acute episode like a large acute abscess in the hand.

Why must the lesion in the nerve tissue be selectively subcutaneous? Why should the bacterial population infecting the nerve be so abundant in the portions of the nerve that are subcutaneously placed?

Leprosy is a surface disease in that the granulomata containing the bacilli are present diffusely throughout the skin, the anterior aspect of the eye, the mucous membrane of the upper respiratory tract, and the testis. The nasal mucous membrane, which has a temperature of 31-33°C, has the most abundant growth of bacilli ([16]). The only internal organ functionally destroyed by active invasion of leprosy bacilli is the testis, which is the coolest internal organ in the human body ([14]). Even in the skin, the bacillary population is more in the ear lobes and extremities, where the temperature is somewhat less than in the trunk ([12]).

M. leprae may quite possibly be a temperature-dependent organism, and the optimum temperature for its active proliferation may be slightly lower than the normal body temperature. Binford, ([1]), as early as 1956, pointed out that in man the leprosy bacillus has a preference for sites of lowered temperature. Brand ([3]) observed that the nerves, tendons, cartilages, and bones close to the skin surface were more involved by leprous lesions than the deeper tissue. He suggested lowered temperature at the surface of the body as a possible cause. In animal experiments Binford ([2]) found that *M. leprae* does multiply in the cooler parts of several rodents, including mice, cotton rats, and Syrian hamsters, and that the nerve invasion in these animals resembled the nerve invasion that occurs regularly in human lepromatous leprosy.

Small collections of *M. leprae* are seen in granulomata in the liver ([15]), the inguinal, axillary and internal iliac lymph nodes ([7]), and the bone marrow (11). A number of the bacteria in these areas stain as rods with the acid-fast stain and are thus apparently viable. These granulomatous lesions, however, are extremely small, are seen usually only on microscopic examination, and

as a rule do not progress. Therefore, it is reasonable to state that in these regions the organisms do not multiply usually, and if they do grow the growth is limited.

Can trauma be the deciding factor in the localization and proliferation of the leprous granuloma? It is suggested that the subcutaneously placed large nerve trunks, which are found to be the sites of leprous lesions, are more prone to injury than those that are deep seated. Ear lobes and the testis are organs in the body that contain numerous bacilli and can often knowingly or unknowingly be traumatized. It is quite possible that trauma to nerve may be a factor in the localization of organisms at the sites where the trunk nerves are subcutaneous. With our present knowledge it is hard to know if trauma to the nerves influences the growth of the organisms in these areas.

Is the leprous lesion of trunk nerves an entrapment syndrome? Dastur ([5]) suggested compression of the inflamed nerve as a major factor in the localization of lesions. Clinically, median nerve lesions at the carpal tunnel in leprosy would compare well with the carpal tunnel syndrome seen in patients without leprosy. But histopathologic studies have shown that in leprosy the major lesion and the enlargement of the nerve are just above the carpal tunnel, rather than in it .There is no doubt that the narrow passage that the nerve has to negotiate will aggravate the lesion in an already inflamed nerve by constant pressure and trauma.

This study shows definitely that there are far more organisms in the subcutaneously placed region than in other parts of the nerve (Fig. 12), and it is quite possible that lowered temperature in these regions is an important factor in the growth of the organisms. Trauma sustained by the subcutaneously placed nerves, and the narrow channel the inflamed and enlarged nerve has to negotiate, may contribute to the destructive lesions in the nerve.

SUMMARY

A detailed histopathologic examination of the ulnar, median and radial nerves on one side of four cases of lepromatous leprosy was carried out. Stains to demonstrate leprosy bacilli, myelin, and axis cylinders were used. The findings in all the four cases were almost identical.

The inflammatory reaction in the nerves was minimal, as compared to the large number of organisms present. The population of *Mycobacterium leprae* in the nerves is roughly comparable to that in the skin. It was found that demyelination was out of all proportion to the axonal degeneration.

Lepromatous granulomata, with abundant bacilli, were present in the regions where the nerves were placed subcutaneously. It is suggested that lowered temperature might increase the rate of proliferation of the bacilli, and trauma and compression of the nerve might possibly be reasons for the localization of lesions at the sites of predilection in the body. It is also reasonable to conclude that repeated trauma and pressure to the nerves whose Schwann sheaths are already invaded by *M. leprae* in large numbers results in their destruction, followed by fibrosis.

RESUMEN

Se hizo un detallado examen histopatológico de los nervios ulnar, mediano y radial en un costado de cuatro casos de lepra lepromatosa. Las tinciones para demostrar bacilos de la lepra, myelina, y ejes de los cilindros, fueron usados. Los hallazgos en los cuatro casos fueron casi idénticos.

La reacción inflamatoria en los nervios fué mínima en comparación al largo número de organismos presentes en ellos. El número de *M. leprae* es dificilmente comparable con aquellos de la piel. Se encontró que la demyelinación estaba fuera de toda proporción comparada a la degeneración axonal.

Granulomas lepromatosos con abundantes bacilos estaban presentes en las regiones donde los nervios estaban colocados subcutaneamente. Se sugirió que bajas temperaturas podrían aumentar la tasa de proliferación de los bacilos, y el trauma y compresión de los nervios podría ser la razón posible de la localización de las lesiones en los sitios de predilección en el cuerpo. Es también razonable pensar que un trauma y presión repetido a los nervios cuyas vainas de Schwann están ya invadidas por *M. leprae* en gran número da por resultado su destrucción, seguida de fibrosis.

RÉSUMÉ

On a procédé à un examen histopathologique détaillé des nerfs cubital, médian et radial, d'un côté, chez quatre malades atteints de lèpre lépromateuse. On a recouru à des méthodes de coloration pour mettre en évidence les bacilles de la lèpre, la myéline et les cylindraxes. Dans les quatre cas les observations étaient presque identiques.

La réaction inflammatoire au niveau des nerfs était minime, quand on la comparait au grand nombre d'organismes qui y étaient présents. La population de *M. leprae* dans les nerfs est grosso modo comparable à celle trouvée dans la peau. On a observé que la démyélination était absolument hors de proportion, par rapport á la dégénérescence des axones.

Dans les régions où les nerfs suivaient un trajet sous-cutané, on a observé la présence de granulomes lépromateux avec bacilles abondants. On a suggéré que des températures basses peuvent augmenter le taux de prolifération des bacilles, et que la compression et le traumatisme du nerf peut fournir la raison éventuelle pour la localisation des lésions aux endroits de prédilection du corps. Il est également raisonnable de croire que les traumatismes répétés et al pression sur des nerfs dont les gaines de Schwann sont déià envahies par une grande quantité de *M. leprae*, entraînent la destruction de ces nerfs, suivie par de la fibrose.

Acknowledgments. This work was done in the Histopathology Laboratory of the Schieffelin Leprosy Research Sanatorium, Karigiri. We acknowledge with gratitude funds from The Leprosy Mission to support this project. We would like also to express our thanks to Mr. K. George William for secretarial help, Mr. S. Jesudass for technical help, and Mr. Sigamony and Mr. Guiry for illustrations.

REFERENCES

1. Binford, C. H. Comprehensive program for inoculation of human leprosy into laboratory animals. Publ. Hlth. Rep. **71** (1956) 995-996.
2. Binford, C. H. Present status of transmission of *M. leprae* to animals. Paper presented at the VIth International Congress of the International Academy of Pathology, Kyoto, Japan, 13 October 1966. (Unpublished)
3. Brand, P. W. Temperature variation and leprosy deformity. Internat. J. Leprosy **27** (1959) 1-7.
4. Dastur, D. K. Cutaneous nerves in leprosy. Relationship between histopathology and cutaneous sensibility. Brain **78** (1955) 615-633.
5. Dastur, D. K. The motor unit in leprous neuritis. A clinical-pathological study. Neurology (India) **4** (1956) 1-27.
6. Decoud, A. C. Comparative study of the nerve branches of the skin in tuberculoid and lepromatous leprosy. Internat. J. Leprosy **16** (1948) 451-458.
7. Desikan, K. V. and Job, C. K. Leprous lymphadenitis. Demonstration of tuberculoid lesions. Internat. J. Leprosy **34** (1966) 147-154.
8. Ermakova, N. E. Studies on leprosy. I. The central, sympathetic and peripheral nervous systems. Internat. J. Leprosy **4** (1936) 325-336.
9. Ermakova, N. E. The pathologic changes in the neural tissue in tuberculoid leprosy. Internat. J. Leprosy **6** (1938) 444. (Abstract of paper presented at Cairo Congress)
10. Fite, G. L. Leprosy from the histologic point of view. Arch. Path. **35** (1943) 611-644.
11. Gass, H. H. and Rishi, D. P. Examination of bone marrow for *M. leprae*. Leprosy in India **6** (1934) 8. (*Abstract in* Internat. J. Leprosy **3** (1934) 377)
12. Gideon, H. and Job, C. K. Skin smears in leprosy. Leprosy in India **37** (1965) 74-86.
13. Grieco, V. The histologic aspects of leprous neuritis. Internat. J. Leprosy **6** (1938) 361-370.
14. Job, C. K. Gynecomastia and leprous orchitis. A preliminary study. Internat. J. Leprosy **29** (1961) 423-441.
15. Job, C. K., Verghese, A. and Karat, A.B.A. Liver lesions in leprosy. Leprosy in India **37** (1965) 239-245. (Suppl. July)
16. Job, C. K., Karat, A.B.A. and Karat, S. The histological appearance of leprous rhinitis and pathogenesis of septal perforation in leprosy. J. Laryng. & Otol. **80** (1966) 718-732.
17. Khanolkar, V. R. Studies in the histology of early lesions in leprosy. Indian Council of Medical Research, Special Report Series No. 19, 1951, 18 pp.

18. KHANOLKAR, V. R. Perspectives in pathology of leprosy. Indian J. Med. Sci. **9** (1955) 1-44. (Suppl. 1)
19. MUKERJEE, N. and GHOSAL, P. Study of cutaneous nerve in leprosy by acid phosphatase method. Leprosy in India **29** (1957) 3-13.
20. PARDO-COSTELLO, V., TIANT, F. R. and PINEYRO, R. Nerve lesions in leprosy. Arch. Dermat. & Syph. **55** (1937) 783-792.
21. REDDY, D. G. and KRISHNAMURTHY, K. R. Changes in peripheral nerves and spinal cord in leprosy. Indian J. Med. Sci. **50** (1962) 692-697.
22. SHERRON, J. Injuries of Nerves and their Treatment. New York, William Wood & Co., 1907. Quoted by Sunderland, S., The intraneural tomography of the radial, median and ulnar nerves. Brain **68** (1945) 243-299.
23. SUNDERLAND, S. The intraneural tomography of the radial, median and ulnar nerves. Brain **68** (1945) 243-299.
24. WEDDELL, G., JAMISON, D. and PALMER, E. Recent investigations into the sensory and neurohistological changes in leprosy. *In* Leprosy in Theory and Practice. R. G. Cochrane, Ed. Bristol, John Wright & Sons Ltd.; Baltimore, Wililiams and Wilkins Co., 1st ed., 1959, pp. 96-113.