Nerves in the Arm in Leprosy

2. Pathology, Pathogenesis and Clinical Correlations[1]

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Danielssen and Boeck (5) appear to have published the first systematic study of the morbid anatomy of leprosy, and described cellular infiltration of the sheaths and fibers of peripheral nerves. Virchow (26) believed that the primary seat of infection in leprosy was the peripheral nerve. Hoggan (15) first showed that mycobacteria could be seen in the numerous cells of the perineurium and endoneurium. Lie (19) observed mycobacteria within the myelin sheaths of the nerves. Dehio (10) reporting the work of his student Gerlach suggested that the primary seat of infection in "lepra nervosa" was in the skin, the peripheral nerves being affected secondarily by centripetal spread. They based this opinion on a very thorough histopathologic examination of different levels of an infected ulnar nerve, from its digital branches till its entry into the brachial plexus.

Torssujew (25) using silver impregnation methods, observed thickening and fragmentation of the nerve fibers in leprous granulomata and a decrease in the number of nerve twigs in atrophied leprous skin. Ermakova (12) reported similar changes in cutaneous nerve fibers and in the peripheral nerves obtained at autopsy, detecting acid-fast organisms in them.

That the brunt of the infection is borne by the peripheral or the cutaneous nerves in all types of leprosy has been observed and commented on by many, including Woit (29), Askanazy (1) and Muir and Chatterji (21) among the earlier workers, and Fite (13), Khanolkar (17, 18), Dastur (6, 8), Weddell *et al.* (28), and Lumsden (20) among the more recent. Fite (14) made the classical remark that "to the histopathologist all leprosy is neural leprosy."

The broad objectives of the present comprehensive investigation have already been presented in the introduction to Paper 1 (1). The emphasis in this paper will be on the pathologic changes in large and small nerves in the arm, including changes along different parts of the same nerve, and on the intramuscular nerves and the muscle tissue. The pathogenesis of neural change in leprosy will then be discussed on the basis of detailed histologic changes observed in various constituents of nerves. Finally, clinicopathologic correlations will be presented through selected case histories.

MATERIALS AND METHODS

The nature of the material employed in this study has already been presented in the corresponding section of Paper 1.

Nerves. The biopsy specimens obtained are indicated in Table 1. Fifty-two small biopsy specimens and five large portions of nerves were available for examination, derived from the ulnar and median nerves and their branches.

Muscles. The muscle biopsy specimens obtained are indicated in Table 2. Sixty-two muscle biopsy specimens are available for examination, derived from muscles innervated by the ulnar and/or the median nerves.

In all the cases the nerve tissue removed at operation, in the form of usual small biopsy specimens or in the form of large excised segments of nerves, was fixed in 10 per cent formalin and processed for embedding in paraffin; sections were cut at 6μ and 12μ. The former were stained by

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TABLE 1. *Nerve biopsy specimens obtained.*

Ulnar in lower ⅓ arm	Ulnar in elbow groove	Ulnar in forearm	Dorsal cutaneous branch-ulnar	Medial cutaneous nerve-forearm	Hypothenar digital branches	Branch to palmar accessory muscle
15	1	1	11	5	2	1

Median-lower ¼ forearm	Median under retinaculum	Palmar cutaneous branch of median	Thenar digital branches	Thenar muscular branch	Total excision -ulnar	Total excision -median
5	1	1	8	1	3	2

hematoxylin and eosin for cells, the Fite-Faraco method for acid-fast bacilli and by the Picro-Mallory method for connective tissue and myelin. The latter (thicker sections) were stained by Holmes' silver method for axons, and by the Heidenhain or Weil-Weight or Kluver-Barrera method for myelin. Muscle biopsy specimens were generally subjected to the same stains since most of them were from near the motor end-point of the muscle and hence included nerve twigs.

The processing of intravitally stained muscle biopsies ([1]) was carried out as described earlier by one of us ([7]).

OBSERVATIONS

Nerves. As was earlier noted ([1]), the adhesions around the ulnar nerve in the arm were so dense and misleading that, at times, biopsy of what appeared to be epineurial and extraneural deep fascial tissues, actually showed the presence of nerve bundles. Small groups of myelinated fibers evidently belonging to some of the peripheral funiculi of such a nerve were included in the biopsy specimen as a result of the intense perineural inflammatory reaction which was also present.

Examination of a medial wedge biopsy of an ulnar nerve from a case of tuberculoid leprosy showed unclear funicular outlines, diffuse and focal inflammatory exudates, some clearly tuberculoid, disrupting the nerve fibers (Fig. 1). Myelin and axon preparations showed some preservation of both these elements. The feature of interest was the presence in the latter of groups of fibers which were either thick, varicose or veil-like and obviously degenerating, or very fine, smooth, and regenerating (Figs. 2a, 2b). In another case of dimorphous (intermediate) leprosy a similar wedge biopsy of the ulnar nerve revealed the same axonal feature, but with many more degenerating fibers remaining and with the fine regenerating filaments in small groups (Fig. 4).

Fibrosis was an invariable feature of all types of leprous neuritis, differing only in

TABLE 2. *Muscle biopsy specimens obtained.*

Flexor carpi ulnaris	Flexor digitorum profundus	Hypothenar	Interossei	Flexor digitorum sublimis	Thenar	Lumbricals	Anomalous
25	12	2	4	6	5	5	3

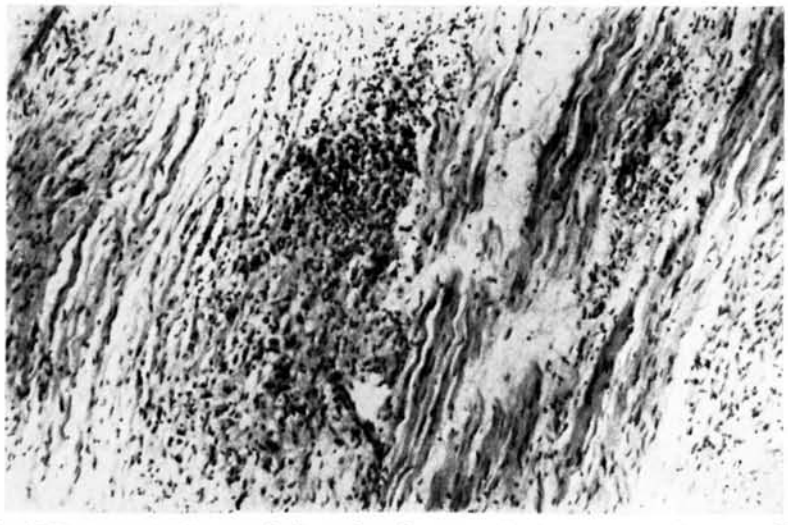

FIG. 1. (NP-C-370(3)): Medial wedge biopsy of ulnar nerve showing ill-defined bundles with parallel arrangement of sheath cells and mononuclear cell infiltration. (Hematoxylin and eosin stain, X105)

its pattern and severity. While in lepromatous or dimorphous cases, it tended to be more regularly dispersed among or along the fibers (Fig. 3), in tuberculoid cases (as in Fig. 4) it was more disruptive in character being profusely and irregularly proliferated. In Figure 3 (dimorphous case), though the fibrosis is breaking up the nerve into tiny bundles, it is not destroying it as much as the irregular collagen reaction seen in Figure 4 (tuberculoid leprosy).

Figure 5 demonstrates a feature of practical significance in the neural fibrosis of leprosy. In this case of tuberculoid leprosy, the transverse section of a wedge biopsy of the ulnar nerve shows the densely thickened epineurium, firmly adherent to the inner side of which is a solitary nerve bundle with a perineurial collar of granulomatous exudate. The difficulty in any form of "desheathing" or dissection of nerve bundles inherent in such a nerve will be discussed below.

Acid-fast bacilli when present either in large or small numbers, were usually confined to Schwann cells, being rarely seen in the histiocytes of interfunicular exudates. They were present in greatest numbers in lepromatous cases. While in the ulnar nerve there were a maximal number of bacilli at site of greatest damage at and above the elbow (*see* DISCUSSION), they were also seen in fair number just below (Fig. 6). Such bacillated Schwann cells do look like "fish swimming upstream" ([17]).

Figure 7 of ulnar nerve above the elbow, from the same patient as Figure 6, illustrates how even an advanced lepromatous case retains the normal parallel arrangement of fiber elements, as seen by means of a nerve fiber stain. At times the individual Schwann cells were enormously swollen and contained hundreds of acid-fast bacilli, mostly of the granular variety.

As a result of this preservation of the framework of the bundles and of nerves in lepromatous and dimorphous cases, it is possible to examine and evaluate the sheath cell reaction concerned chiefly with the sheath of Schwann. While this was seen in its simplest form in the median nerve of a case of early dimorphous leprosy (Fig. 13), the same lepromatous ulnar nerve illustrated in Figure 7 showed a most unusual proliferation of swollen Schwann cells interconnected probably by bands of Burgner and forming compact little syncytial groups. Although some separation of the sheath cells was seen in a number of nerves from all types of leprosy (as in Fig. 1), clear ballooning of Schwann cells consistent with an edematous change was observed only in one instance, that being in the medial cutaneous nerve in the forearm of a

dimorphous case. The vacuolated cells formed a honey-combed area which occupied the center of a large degenerating bundle at the periphery of which fibrosis, degenerated axons and some regenerating axons could be seen (Fig. 11). Stray acid-fast bacilli were seen in the Schwann cytoplasm bordering some of the swollen cells.

When the inflammatory reaction was overwhelming in any type of the disease, and nerve bundles almost disappeared from view (Fig. 12), very few and irregu-

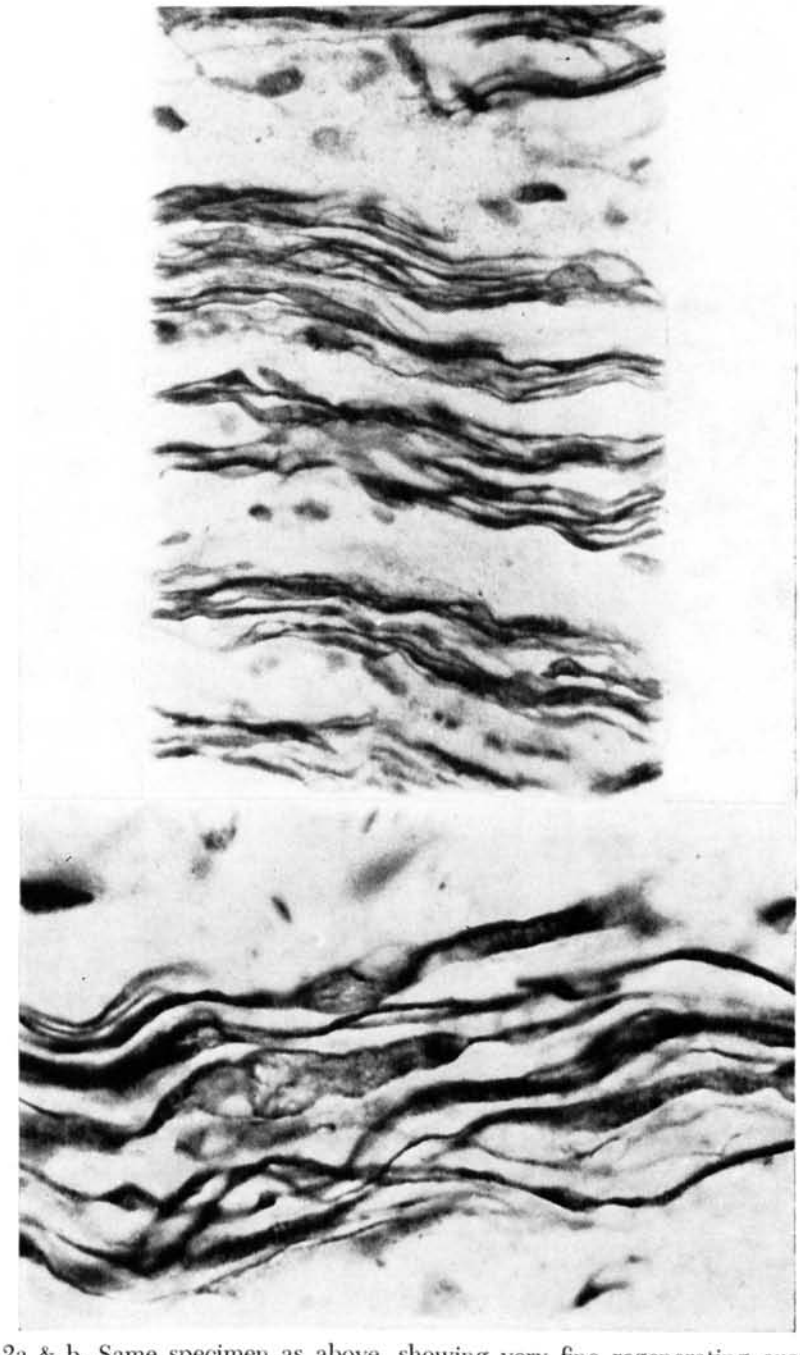

FIG. 2a & b. Same specimen as above, showing very fine regenerating axons along with irregularly thickened or veil-like degenerating fibers within the nerve bundles. (Holmes' silver impregnation, X660 and 1,500, respectively)

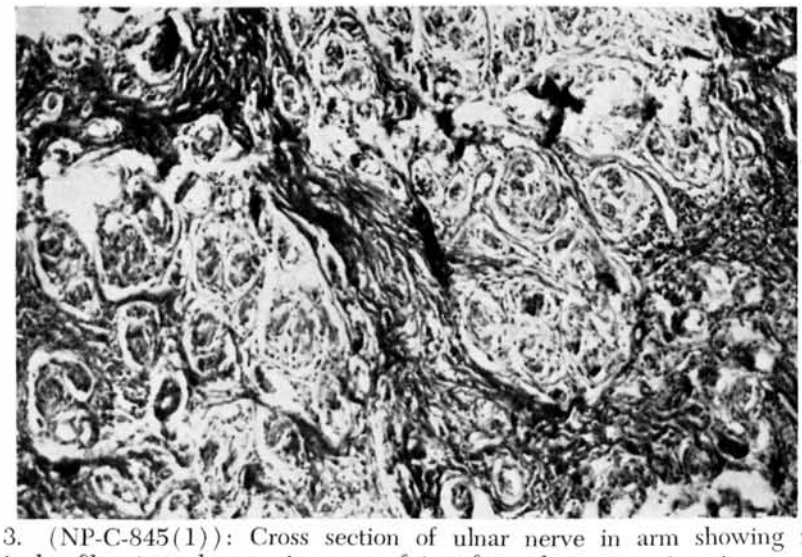

FIG. 3. (NP-C-845(1)): Cross section of ulnar nerve in arm showing irregular interfunicular fibrosis and some increase of intrafunicular connective tissue surrounding small groups of fibers. (Picro-Mallory stain, X105)

larly meandering nerve fibers were seen even in the less infiltrated portions (Fig. 8a), as demonstrated by this case of dimorphous-tuberculoid leprosy. A few stray degenerating and some possibly regenerating axons were encountered in the thickest portion of this median nerve. Around both these types of fibers, outlines of Schwann sheath were evident, with or without the presence of nuclei, in Holmes' silver preparations (Fig. 8b). At times, the regenerating axons appeared to form very small groups or "funiculets" making their way through a loose Schwannian meshwork (Fig. 9) as seen in an ulnar nerve with very slight inflammatory reaction from a near-lepromatous-dimorphous case. The appearance is very reminiscent of the free regeneration we have seen recently in the proximal part of irradiated homo-nerve grafts in experimental animals when fibrosis or inflammation did not hamper the process.

Examination of selected portions of the

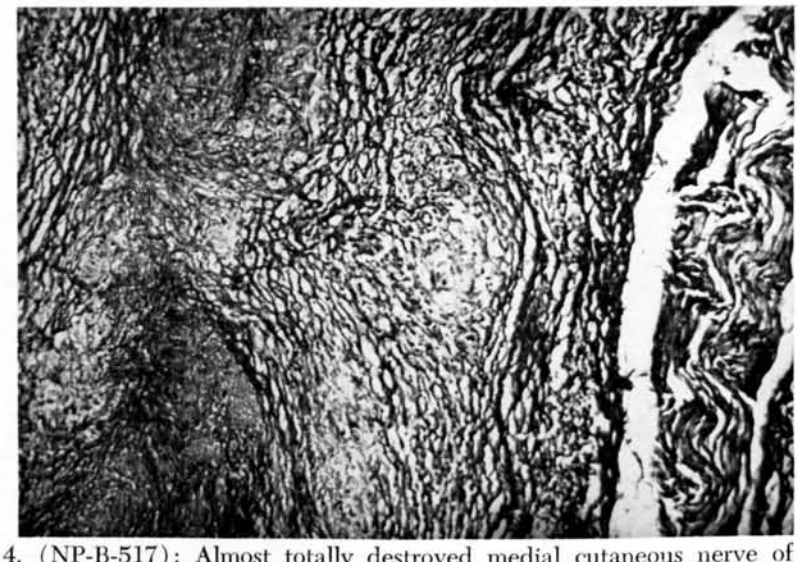

FIG. 4. (NP-B-517): Almost totally destroyed medial cutaneous nerve of forearm showing a collagenous network and areas of necrosis; one bundle on the right relatively spared. (Picro-Mallory, about X100)

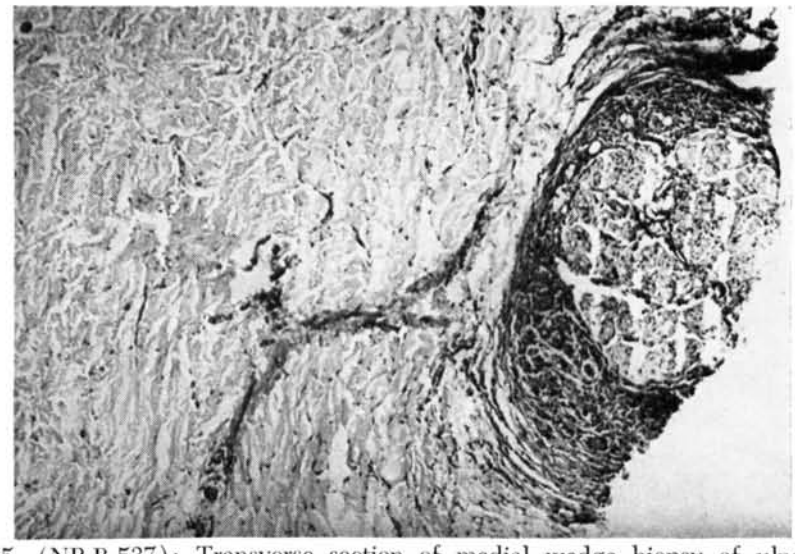

FIG. 5. (NP-B-537): Transverse section of medial wedge biopsy of ulnar nerve showing very thick epineurium and a single nerve bundle on inner side with tuberculoid reaction in the perineurium. (Hematoxylin and eosin stain, about X40)

nerves, excised *in extenso* at operation, merit special mention. The median nerve and its branches from an instance of tuberculoid leprosy are illustrated in Figures 10 through 12. The proximal portion of this nerve trunk in the middle of the forearm where it was not grossly thickened, showed undisturbed fiber arrangement and minimal inflammatory reaction but rich sheath cell proliferation (Fig. 10a). Corresponding to these, the axons were fairly well preserved at this site though showing early degenerative changes with the Schwann sheath also coming into view (Fig. 10b). By contrast, the same nerve in the lower third of the forearm just above its thickest part, showed more cell infiltration, more of degenerating nerve fibers and many clear, fine, smooth regenerating filaments in small groups (Fig. 11). In this case the regenerative activity persisted, though diminished, through the thickest and most affected part above the wrist, which also showed some acid-fast bacilli in Schwann cells, but then

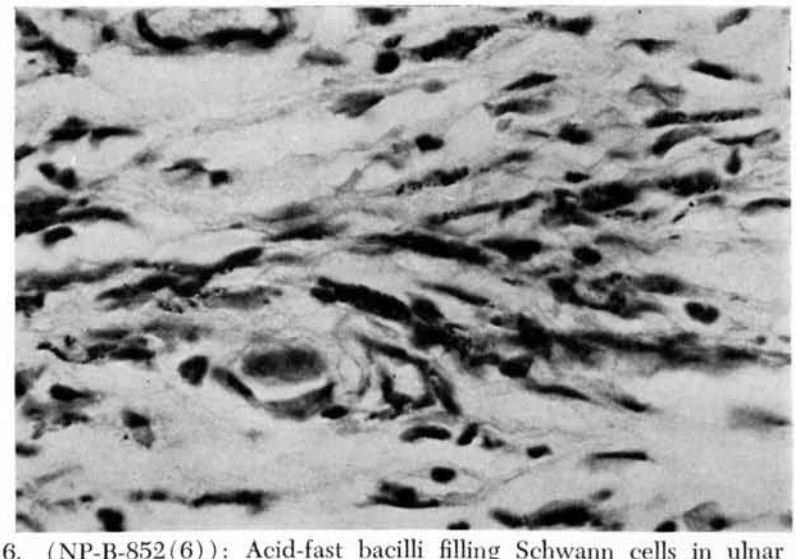

FIG. 6. (NP-B-852(6)): Acid-fast bacilli filling Schwann cells in ulnar nerve at wrist. (Fite-Faraco's stain, about X1,000)

FIG. 7. (NP-B-852(a)): Few remaining axons in fibrosed ulnar nerve. (Holmes' silver, X660)

it ceased completely. The digital branch of this median nerve (to the middle finger) showed extensive devastation, infiltration and fibrosis with only few axon remnants persisting along one side (Fig. 12). Similarly, the distal end of the digital branch to the index finger showed pleomorphism of funicular size and pattern, with the larger swollen bundles clearly containing a central caseous area characteristic of an active tuberculoid lesion.

The median nerve of another patient, with dimorphous leprosy, showed regenerative activity commencing at the highest point of nerve biopsy, namely in the middle of the forearm. There was no cellular reaction other than a very even Schwann cell proliferation (Fig. 13) which, perhaps, accounted for the unusually rich regenerative activity throughout the nerve with only a few thick degenerating fibers remaining (Fig. 14). However, this activity became almost insignificant by the time the nerve reached the lower forearm because of the combination of fibrosis (Fig. 15), and of inflammation, observed in this region. The few remaining myelinated fibers, seen about 4 cm. above the flexor carpal retinaculum (Fig. 15), disappeared along with the axons in the region of the wrist. Total hyalinizing fibrosis of an entire nerve, suggesting great chronicity, was evident in the palmar cutaneous branch of this median nerve (Fig. 16). It is noteworthy that acid-fast bacilli were present in greatest number in the maximally thickened portion of the nerve above the wrist, far fewer in the nerve above and below that region, and none in the distal digital branches.

Intramuscular nerves and muscle. The muscle biopsies were mainly of value in enabling examination of intramuscular nerves (see DISCUSSION). Since the interfascicular nerve twigs and bundles are known to survive to a greater extent and longer than the finer intrafascicular terminal fibers and myoneural endings ([7]), observations are possible mainly on the former nerves in the present series of advanced polyneuritic cases. In a case of dimorphous leprosy, where a good-sized intramuscular nerve was included in the vitally stained whole mounts of two parts of the flexor carpi ulnaris muscle biopsy, a clear distinction was observed. The grossly red part of the muscle (as seen at operation and which was responding to electrical stimulation), included fairly well-preserved axons in the nerve with only stray degenerating or regenerating fibers (Fig. 17a). In contrast, the grossly pale and thin part of the muscle (not responding to electrical stimulation), included a nerve showing only degenerated axon remnants and Schwann tubules (Fig. 17b).

The most frequent change in the interfascicular nerves was degeneration of a sort quite comparable to that seen in the nerve trunks, and accompanied by inflammatory

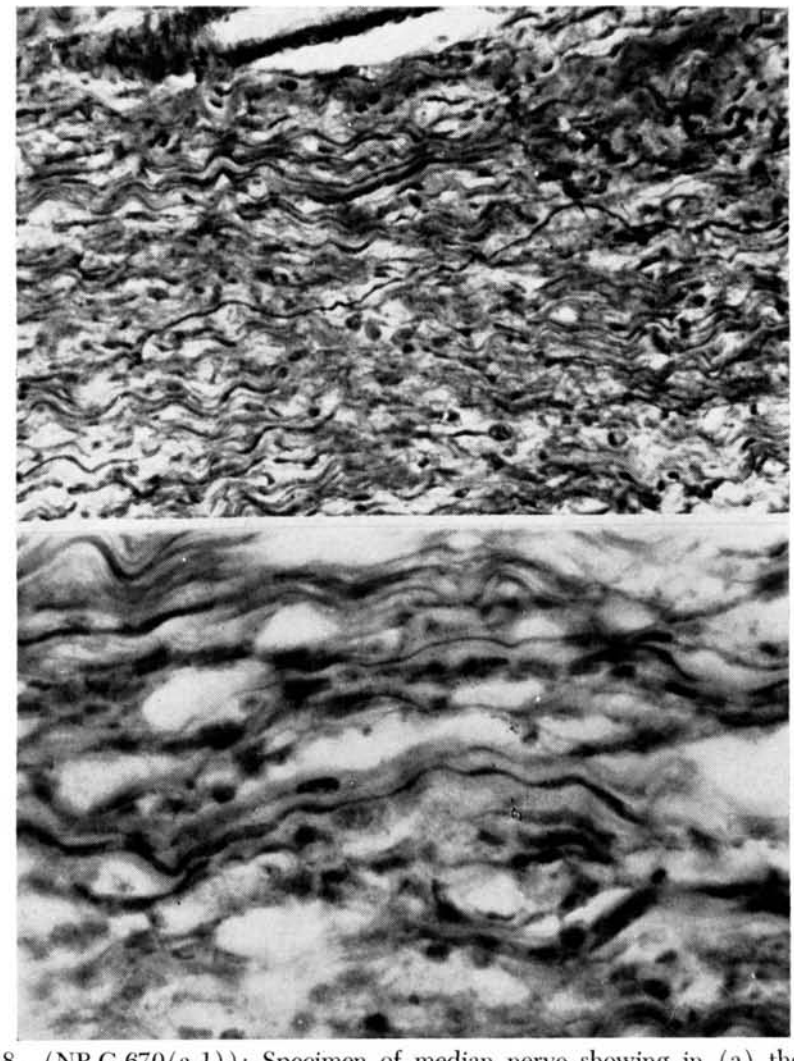

FIG. 8. (NP-C-670(a-1)): Specimen of median nerve showing in (a) the peripheral part of a nerve bundle with Schwann cell proliferation and predominant fiber degeneration; and in (b) outlines of Schwann sheath nuclei and possible attempt at regeneration. (Holme's silver, X265 and 660 respectively)

reaction outside the perineurium, or infiltrating the nerve. The former situation was encountered in dimorphous leprosy, where the reaction was of mononuclear cells only though the nerve was becoming fibrosed. In the latter, from a case of tuberculoid leprosy, lymphocytes and larger mononuclear cells (probably epithelioid cells) infiltrated and destroyed the intramuscular nerve. Figure 18 shows a totally degenerated nerve in the thenar muscle, with a reticular frame-work (in a silver impregnated section) with small epithelioid cell foci. In dimorphous, and especially in lepromatous cases, the intramuscular nerves contained acid-fast bacilli within Schwann cells. In about three-fourths of muscle biopsies in which nerves were included, some degree of nerve degeneration was seen. Acid-fast bacilli were observed in four of these nerves.

Clear denervation atrophy, in the form of group atrophy of varying degree and different muscle groups, was again found to be the basis of the wasting of muscle in leprosy ([7]), and is illustrated in Figure 19. It is of interest that one of these atrophied muscles was the anomalous muscle at the wrist mentioned in Paper 1 ([1]). However, there were instances of advanced atrophy where

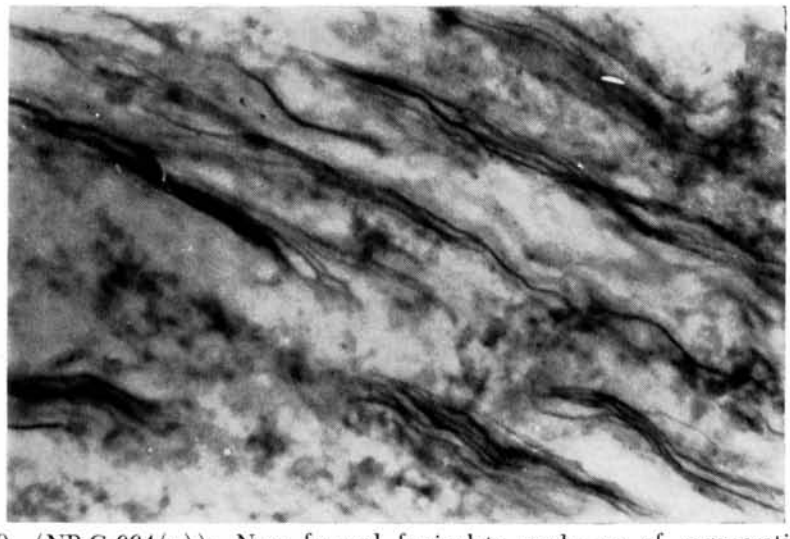

FIG. 9. (NP-C-664(a)): New formed funiculets made up of regenerating axon sprouts in ulnar nerve with very little inflammation and fibrosis (Holmes' silver, X600)

the group pattern was not so clearly evident, and a variation of fiber-size became noticeable as seen in Figure 20. There was no appreciable increase of connective tissue even among such fibers and fascicles. In the most severely affected muscles there was hardly any recognizable muscle tissue and only groups of residual muscle nuclei were evident (*see* Fig. 43 of Ref. 7). While the nonspecific chronic inflammatory reaction was generally confined to the nerves and vessels, it was occasionally seen infiltrating the muscle fascicles as well, constituting chronic nonspecific myositis. This was seen in 11 cases of the present series; frank granulomatous myositis was observed in two of these.

The muscle spindle and the intrafusal fibers are relatively spared in leprosy ([7]), in common with most other forms of denervation atrophy of muscles. Some thickening of the capsule or increase of intracapsular connective tissue might be seen at times, as in Figures 19 and 20. In Figure 20 the intrafusal "nuclear chain fibers" of the tandem spindle appear small, and perhaps represent the occasional truly atrophic change which these fibers manifest when denervated. A recent histologic study of muscle spindles observed in 1,000 biopsy specimens ([23]), showed the largest number of small intrafusal fibers in various conditions of neurogenic atrophy of extrafusal muscle. That paper also illustrates the only specimen of a leprous muscle where some intrafusal mononuclear cell reaction was encountered, with degeneration of the intrafusal fibers and the presence of clear clusters of acid-fast bacilli within or upon these fibers. With this exception, *Mycobacterium leprae* were not encountered in the striated muscle fibers of our biopsy specimens, but serial sections were not examined.

DISCUSSION

The details of histopathologic changes characterizing various components of peripheral nerve and, to a lesser degree of muscle, have been presented and illustrated. A few changes of possible practical and theoretical interest and their implication are worth discussion.

Acid-fast bacilli in nerves. The relation of *M. leprae* to Schwann cells was quite constant though the number of bacilli varied enormously (perhaps a million-fold) between the two polar types, with the dimorphous nerves being intermediate in this respect. Whether in rare singles or in profuse clusters, depending on the type of leprosy, they were invariably contained in sheath cells, longitudinally oriented within the nerve bundles. These cells could either be fibroblasts or Schwann cells. That they were the latter, generally if not always, is surmised from light microscopy but really demonstrated by electron microscopy by

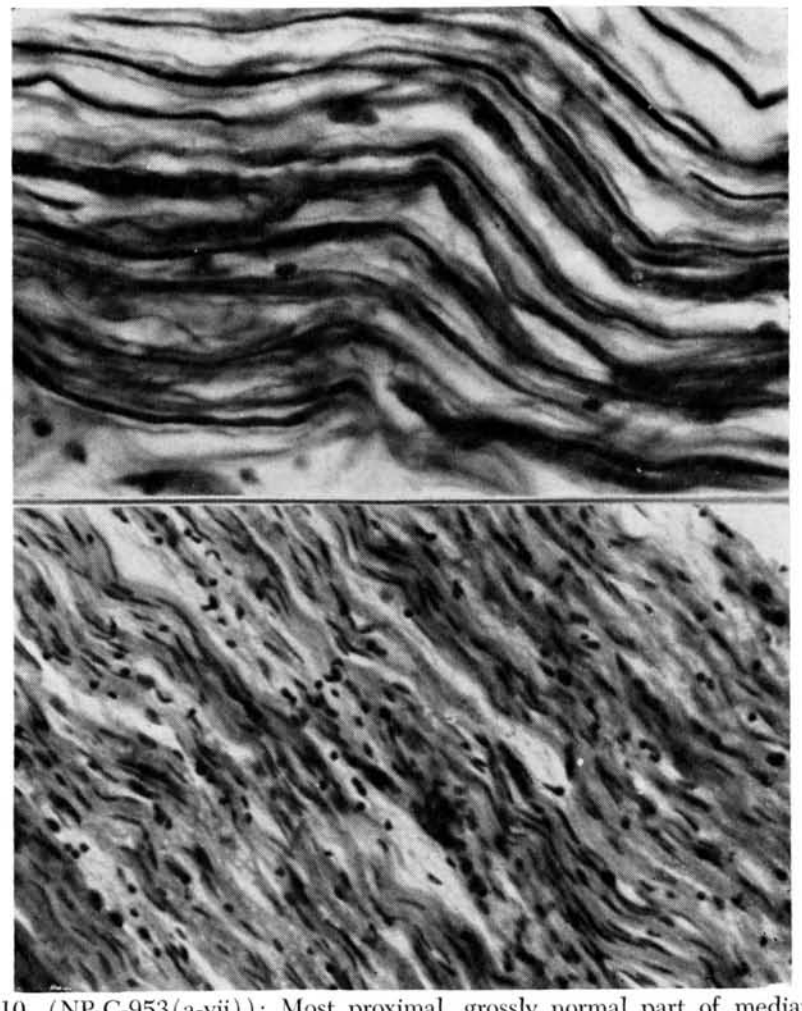

FIG. 10. (NP-C-953(a-vii)): Most proximal, grossly normal part of median nerve in forearm showing in (a) uniform sheath cell proliferation, and in (b) fair number of preserved axons, though with early signs of degeneration. (Hematoxylin and eosin stain, X265; and Holmes' silver X660, respectively)

which 80 to 95 per cent of the normal intrafunicular nuclear population appears to belong to Schwann cells ([4]). This has been discussed elsewhere ([8, 9]). The electron-microscopic observations of Nishiura ([21]) and of Weddell ([27]) also revealed intact leprosy bacilli within Schwann cell cytoplasm. Nishiura has occasionally seen them within degenerating axons, but this does not constitute the major route of passage of the bacilli as was suggested by Khanolkar ([17]). Lumsden ([20]) has found leprosy bacilli surviving and slowly multiplying within Schwann cells in tissue cultures prepared from human acoustic schwannomas. A macrophage-like function is suggested for the Schwann cells.

Degenerating sheath cells did not contain bacilli; even the granular forms of mycobacteria were observed generally in intact cells with clear nuclei. Interfunicular inflammatory reactions did reveal histiocytes containing acid-fast bacilli. Mast cells bearing fuschsinophil granules were observed both within and outside nerve bundles in all types of leprosy; these granules were clearly different, round and uniform, from acid-fast bacilli even when the latter were fragmented. The mast cells were seen in good numbers, irrespective of the presence, absence or density of mycobacteria. The almost symbiotic relationship between Schwann cells and *M. leprae* raises the possibility of a chemical affinity be-

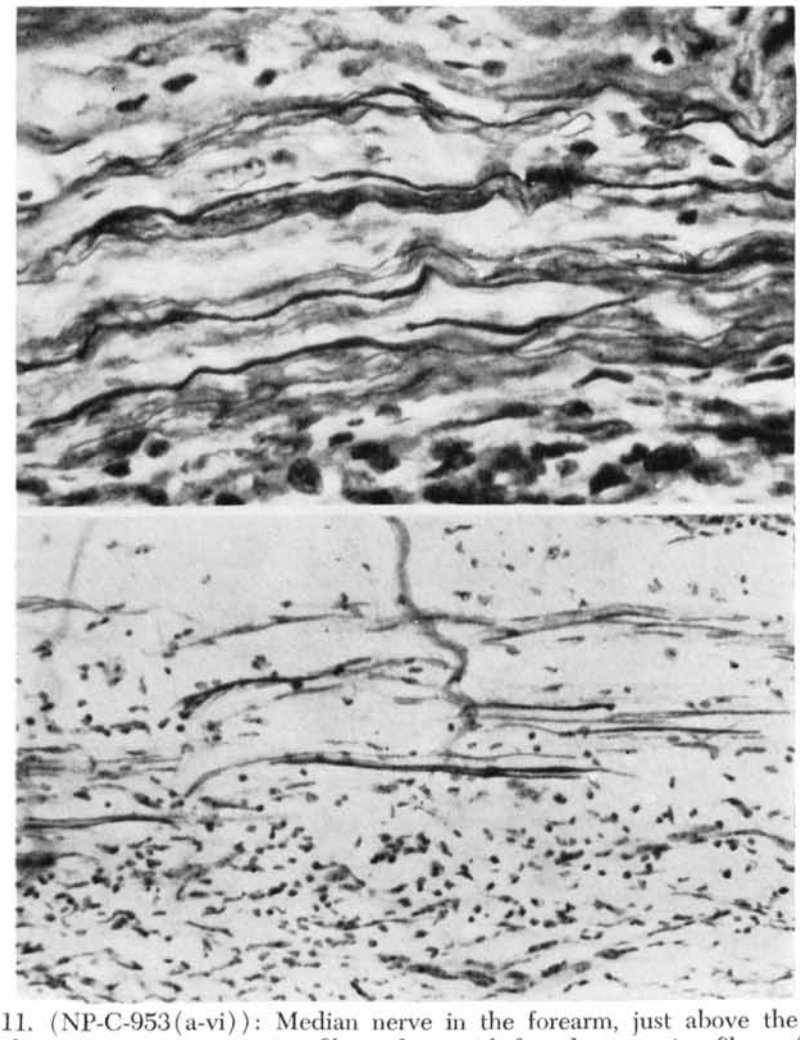

FIG. 11. (NP-C-953(a-vi)): Median nerve in the forearm, just above the swollen portion showing many regenerating fibers along with few degenerating fibers. (Holmes' silver, X660)

FIG. 12. Same case; digital branch to the middle finger showing fibroblast and mononuclear cell reaction with occasional fiber remnants. (Holmes' silver X265)

tween them. The two obviously thrive one upon the other, and it seems not implausible that the survival and multiplication of the organisms within the Schwann cells is an essential step in their subsequent dissemination in the case of lepromatous leprosy. On the other hand, their residence within the Schwann cells helps toward their containment within this secluded locality, in tuberculoid leprosy.

Neural pathogenesis. It was noteworthy that in all of our three cases of long excision nerve biopsy, the acid-fast bacilli were present in greatest number in regions of maximal nerve swelling, just proximal to sites of severest nerve damage, their density tapering off along with the inflammatory and fibrotic reaction, more proximally. This feature has been observed recently in the nerves of some of our autopsied cases also (Dastur, unpublished data). In both these sets of observations, nerve damage, i.e., loss and degeneration of axons and myelin and reactive fibrosis, was greatest (a) distally and (b) at predilective sites of nerve compression [1]. As has been previously noted [7, 8, 9], the area of compression also happens to be the area of exposure to outside temperatures, trauma and bending for the ulnar and the median nerves (as also for

the lateral popliteal and the posterior tibial nerves).

The greater distal damage is of significance in pointing to an ascending centripetally progressing pathogenesis of leprous neuritis, at least in the majority of cases. It has previously been shown ([6]) that this process begins in the intradermal nerves of cutaneous lesions of leprosy, wherein the finer superficial nerve fibers are damaged more and earlier than the thicker more clustered deeper perifollicular nerves. As stated above, the concept of centripetal spread of leprous infection and inflammation along neural pathways goes at least as far back as the 1890's (Gerlach and [10]).

Nerve degeneration and regeneration. One of the objectives of the current pathologic study was to assess the extent and nature of axonal degeneration and regeneration as studied in silver impregnated preparations. Similarly changes in the inflammatory and fibrotic reactions were studied by appropriate stains. Four important features were observed.

1. The histologic difference between tuberculoid and lepromatous nerves was evident not only in their bacillary content, but also with respect to the integrity of neural tissue. This was severely disturbed in tuberculoid nerves where the inflammatory cell reaction first infiltrated the interfunicu-

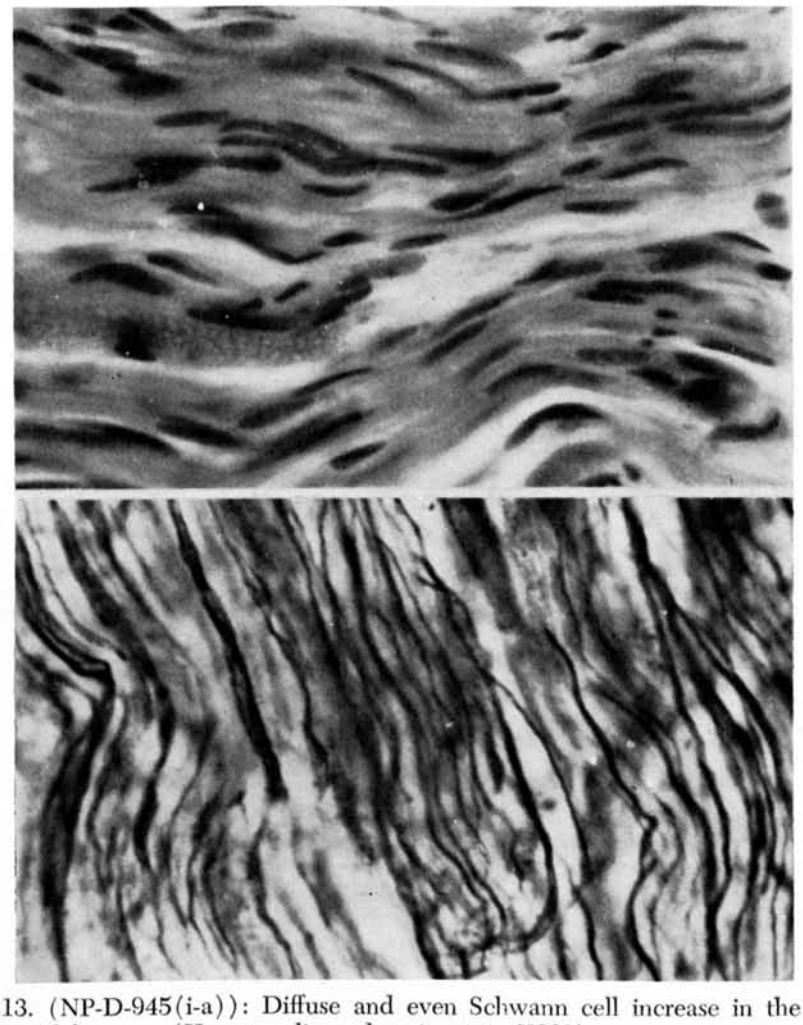

FIG. 13. (NP-D-945(i-a)): Diffuse and even Schwann cell increase in the median nerve at mid-forearm. (Hematoxylin and eosin stain, X660)

FIG. 14. Same specimen showing rich regenerative activity throughout. (Holmes' silver, X1,500)

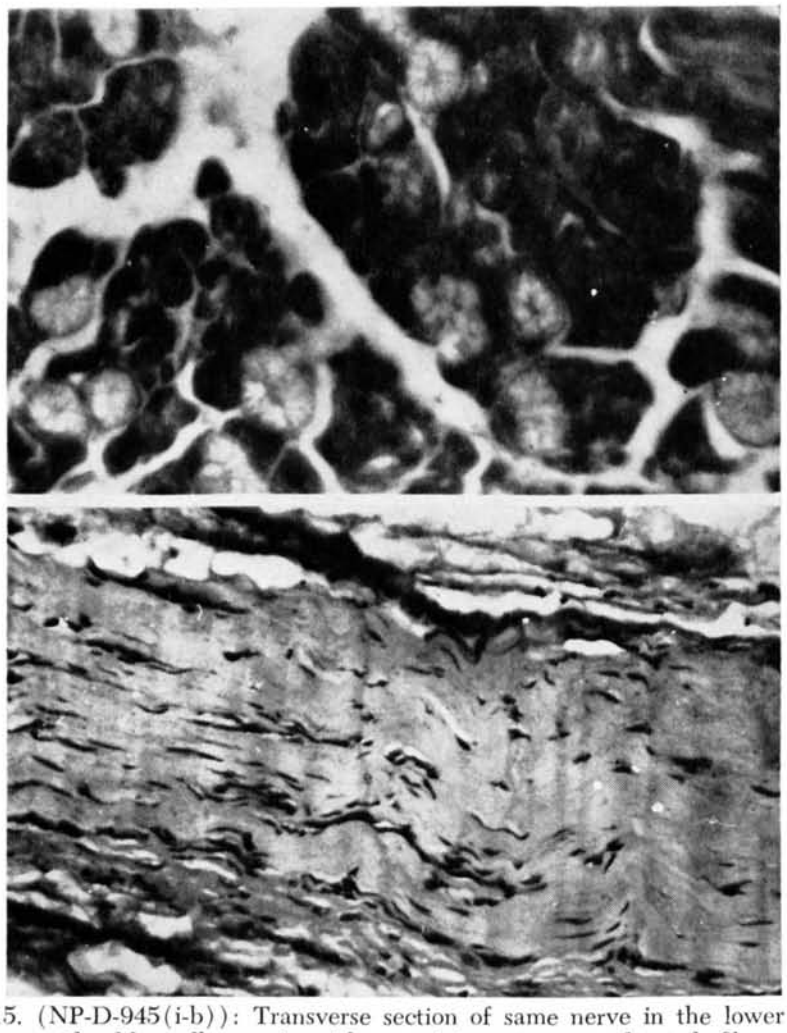

FIG. 15. (NP-D-945(i-b)): Transverse section of same nerve in the lower forearm showing considerable collagenosis with remaining stray myelinated fibers. (Picro-Mallory, X1,500)

FIG. 16. (NP-D-945(ii-a)): Total hyalinization of the palmar cutaneous branch of this nerve. (Hematoxylin and eosin stain, X265)

lar spaces and the perineuria, and then penetrated within the nerve bundles. This resulted in irregular, disorganized scarring, the fibrosis being quite severe. Perhaps, as suggested by Nishiura ([22]), the epithelioid cells play a significant role in disruption. The major factor conducive to nerve damage, however, appears to be the richness and irregularity of the cell exudate in tuberculoid nerves, the lepromatous being characterized by few and small perivascular mononuclear cell cuffs even in the presence of excessive Schwann cell proliferation and bacillary content.

2. Degeneration and regeneration of nerve fibers were found to be contemporary in time and space in all nerves and in different types of leprosy. Since axon preservation was greater in the lepromatous type, specimens from lepromatous leprosy provided generally greater opportunity for seeing these changes. In this respect, the situation was analogous to that observed in cutaneous lesions and intramuscular nerves in leprosy ([6, 7]). Such coexistence of degenerating and regenerating fibers suggests a stimulating influence, chemical or otherwise, of the former on the latter.

3. The regenerative effort was found on the whole to be greater than expected, and sometimes really profuse, confirming the

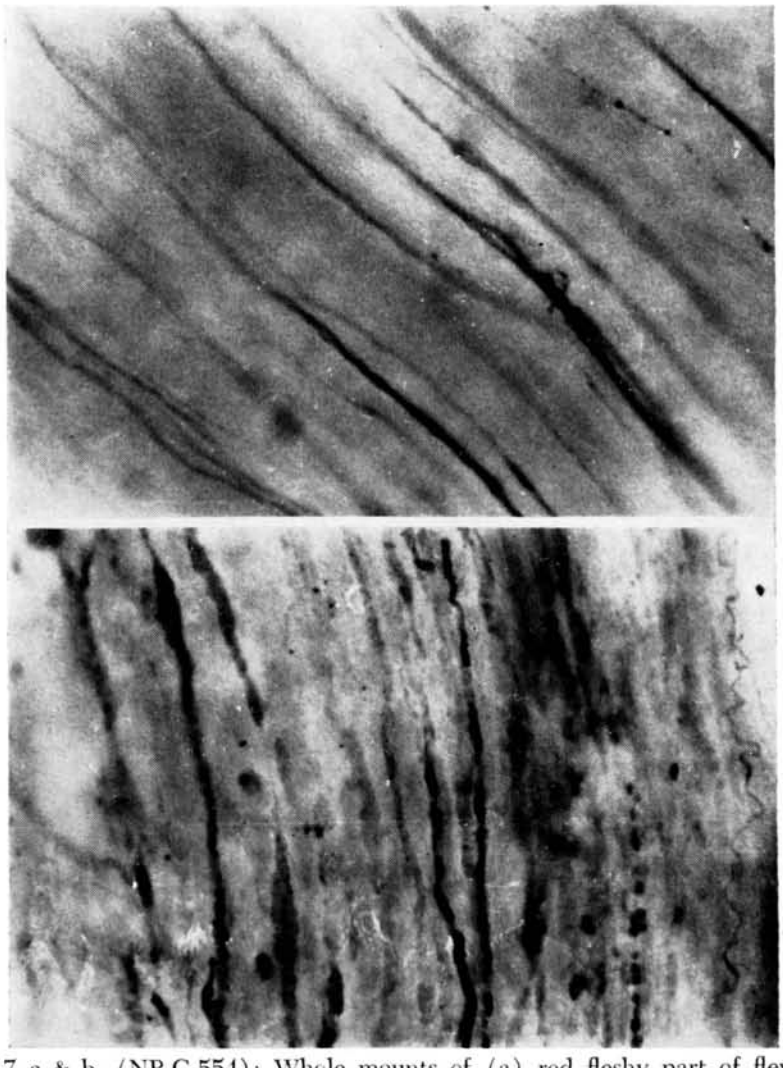

FIG. 17 a & b. (NP-C-554): Whole mounts of (a) red fleshy part of flexor carpi ulnaris (FCU) muscle showing an inter-fascicular nerve bearing smooth normal axons and one ?-regenerating fiber; and (b) a similar but degenerating intramuscular nerve in the pale atrophied part of the same muscle. (Intra-vital methylene blue staining, X660 and 265, respectively)

electromyographic findings of multiple large polyphasic potentials. However, this activity was in the proximal, relatively less affected parts of the median nerve in the middle of the forearm and of the ulnar in the middle of the arm. It did not reach up to the distal end of the nerves and was therefore rendered ineffective. This unfortunate result was due to the presence of road blocks of fibrosis in the distal areas of the same nerves, especially in the terminal digital branches. A total dependence of regenerating nerve fibers on the proper alignment of Schwann cells with a maintenance of the lumen of Schwann tubules, and an obstruction to regeneration by collagen even in experimental, cleanly sectioned nerves, have been reported by a number of workers, such as Holmes and Young ([16]). This pathologic finding, especially in the long excision nerve biopsies, makes the outlook for nerve grafting in leprosy somewhat dim. Thus, for instance, even a 10 cm. graft in the distal end of the median nerve would be unlikely to serve a useful purpose as the axon sprouts going through it would meet an insuperable barrier in the fibrosed palmar branches and

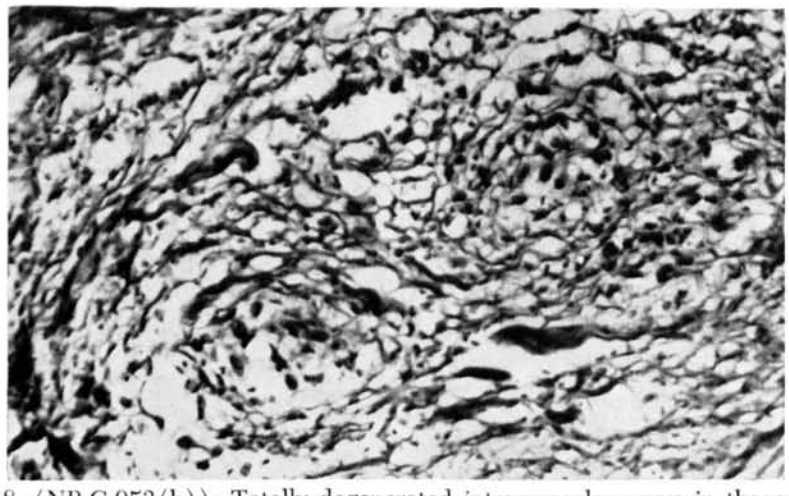

FIG. 18. (NP-C-953(h)): Totally degenerated intramuscular nerve in thenar muscle showing discrete tuberculoid lesions in a fibrous matrix. (Holmes' silver, X265)

would not make contact with the terminal denervated sensory area, namely the skin. Even using irradiated homo-nerve grarts, Campbell ([3]) found good results in traumatic cases, if the gap to be bridged was not more than 7 cm. Sir Herbert Seddon ([24]) has shown one of us (D.K.D.) two totally fibrosed and ineffective nerve grafts, each about 15 cm. in length, two years after their placement.

4. The irregular pattern of axonal degeneration and regeneration observed with silver stains suggested that a Wallerian type of degeneration occurs in leprous nerves. Recently, in teased nerve fiber preparations stained for myelin, a bizzarre irregular pattern of myelin loss has generally been observed, with only rare segmental demyelination (Dastur and Razzak, unpublished observations). Thin smooth regenerating fibers with just a film of myelin and with short internodal segments were observed. Such random degeneration makes possible the preservation of occasional thick myelinated axons, especially along the periphery of nerve bundles, even while there is overall severe neural destruction. This neurohistologic feature might be re-

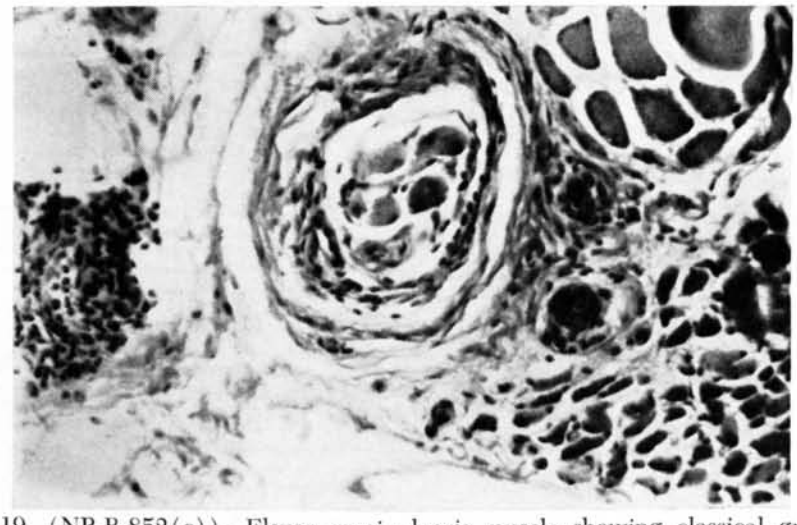

FIG. 19. (NP-B-852(c)): Flexor carpi ulnaris muscle showing classical groupwise neurogenic atrophy of extrafusal muscle and normal intrafusal fibers in the spindle. (Picro-Mallory, X265)

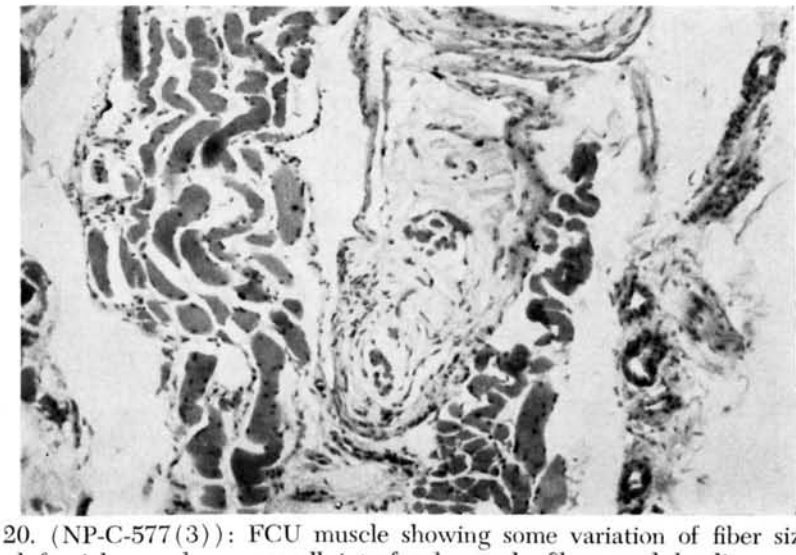

FIG. 20. (NP-C-577(3)): FCU muscle showing some variation of fiber size in the atrophied fascicles, and very small intrafusal muscle fibers and hyaline material in the spindle. (Hematoxylin and eosin stain, X105)

sponsible for the electromyographic observation (Paper 1) of a fairly well preserved conduction velocity on the part of the fast (thick) fibers. Similar axonal degeneration of myelinated fibers, unassociated with any appreciable reduction of conduction velocity, has been reported in neuropathies due to alcoholism, arsenic poisoning, periarteritis nodosa, the neuronal type of Charcot-Marie-Tooth disease, Friedreich's ataxia and in degeneration of dorsal root ganglion cells, by Dyck *et al.* ([11]). In contrast, the same authors have observed segmental demyelination associated with severe slowing of conduction velocity in the neuropathic form of Charcot-Marie-Tooth disease, in Dejerine-Sottas disease and in congenital myopathy associated with arthrogryposis multiplex. Thus there appear to be two different types of degeneration of myelinated fibers presently recognized.

Intramuscular nerves and muscles. The two main changes observed in these tissues have been described and discussed elsewhere. Dastur ([7]) presented the details of histologic changes in the various neural components of muscle and in the striated muscle in leprosy, using vitally stained whole-mounts of flexor carpi ulnaris muscle, as well as routine sections, and correlated the observed changes with clinical motor deficit. Not only were degenerative changes observed in muscle nerves and clear denervation atrophy detected in the muscle, but active inflammatory reactions and occasionally acid-fast bacilli were observed. As discussed then and later ([8, 9]), this points to the spread of the leprous infection to these nerves. Thus a dual mechanism of damage to striated muscle in leprous neuritis became evident through degeneration of motor nerve fibers in mixed nerve trunks and through actual invasion of intramuscular nerves. The local nonspecific or granulomatous myositis occasionally observed by us appears secondary to such local neuritis. The near absence of *M. leprae* in striated muscle fibers in contrast to their frequent occurrence in smooth muscle fibers, appears interesting.

The clear denervation pattern observed on electromyography ([1]) was obviously dependent on muscular atrophy. There is no conflict whatsoever between this and the near normal conduction velocity observed in many such cases as a result of the preservation of a few stray thick fibers in an otherwise severely degenerated nerve. It can now be appreciated why electromyography is a more sensitive indicator of muscle change in advanced polyneuritic leprosy than the measurement of conduction velocity. Besides, the atrophic change being histologically much more pronounced and constant than the focal myositis, the electromyograph in our cases almost always recorded the former only.

SUMMARY

Fifty-two nerve biopsy specimens, five long excised segments of nerves, and 62 muscle biopsy specimens were obtained from nerve explorations on 27 limbs of 22 patients with chronic polyneuritic leprosy (1).

The most conspicuous histologic feature was damage to the nerves, large or small, by a combination of inflammatory and degenerative changes. The former was frankly granulomatous in tuberculoid cases and with nonspecific mononuclear cell response in lepromatous leprosy, with the dimorphous form showing more of the latter type of reaction. Fibrotic degeneration accompanied the inflammation and was present in all leprous nerves, being more disruptive in the tuberculoid where even the funicular pattern was lost.

Acid-fast bacilli in nerves were almost confined to the Schwann cells which always proliferated in all types of the disease, but were more apparent in the dimorphous and lepromatous cases.

The long excised segments of median and ulnar nerves were valuable in showing greater nerve damage and bacillary content at certain selective sites, such as at the thickened part of the median nerve in the lower forearm and of the ulnar nerve in the lower arm.

Profuse degenerative and regenerative changes in axons were observed in many nerves, generally simultaneously. The regeneration was maximal just proximal to the site of damage, but was blocked more distally, especially at the wrist, by the severe fibrosis prevailing in these nerve trunks and in their distal digital branches. This suggested a centripetally progressing neuritis in leprosy.

Occasional thick axons were found spared along the periphery of funiculi, even in severely degenerating nerves, and explained the fair preservation of conduction velocity in such nerves.

Intramuscular nerves frequently showed the same degree and nature of inflammatory and degenerative changes as the nerve trunks, and these were also responsible for the typical denervation atrophy encountered in these muscles. Acid-fast bacilli were also observed in these nerves and, in one case, on the intrafusal muscle fibers as well.

RESUMEN

En 22 pacientes con lepra polineurítica crónica (1) se tomaron 52 muestras de nervios para biopsia, se incindieron cinco segmentos largos de nervios y se obtuvieron 62 muestras de músculos para biopsia, en exploraciones nerviosas hechas en 27 extremedidades.

La característica histológica más relevante fué el daño nervioso, grande o pequeño, producido por una combinación de lesiones inflamatorias y degenerativas. Las primeras fueron francamente granulomatosas en los casos tuberculoides y con una respuesta celular no específica de mononucleares en lepra lepromatosa; en la lepra dimorfa se encontró con mayor frecuencia este último tipo de reacción. La inflamación siempre estaba acompañada de degeneración fibrosa y esta última se encontró en todos los nervios afectados, siendo más severa en los tuberculoides, donde se perdía hasta el patrón fascicular.

Los bacilos alcohol-ácido resistentes que se observaban en los nervios estaban confinados casi exclusivamente a las células de Schwann, que proliferaban siempre en todos los tipos de la enfermedad, pero eran más aparentes en los casos dimorfos y lepromatosos.

Los segmentos largos de los nervios medianos y ulnares incindidos, fueron valiosos para demostrar la existencia de mayor daño así como contenido bacilar en ciertas áreas selectivas, (7), tales como la parte engrosada del nervio mediano en la parte inferior del antebrazo y del nervio ulnar en la parte inferior del brazo.

En muchos nervios se observaron alteraciones profusas degenerativas y regenerativas en los axones, por lo general simultáneas. La regeneración tenía su intensidda máxima exactamente proximal al sitio de la lesión, pero estaba bloqueada más distalmente, especialmente en la muñeca, por la fibrosis severa que prevalecía en estos troncos nerviosos y en sus ramas digitales distales. Esto ugería una neuritis centrípeta progresiva.

Ocasionalmente se encontraros gruesos axones intactos a lo largo de la periferia de los fascículos nerviosos, aún en nervios seriamente degenerados, lo que explicaba la discreta preservación de la velocidad de conducción en estos nervios.

Los nervios intramusculares mostraron frecuentemente el mismo grado y naturaleza en las alteraciones inflamatorias y degenerativas

que los troncos nerviosos. Estas alteraciones fueron también responsables de la atrofia de denervación típica que se encontró en estos músculos. En estos nervios también se observaron bacilos alcohol-ácido resistentes y, en un caso, también en las fibras musculares dentro de los husos.

RÉSUMÉ

A la suite d'explorations nerveuses pratiquées sur 27 membres, chez 22 malades souffrant de polynévrite lépreuse chronique, on a récolté 52 échantillons de biopsies nerveuses, 5 longs segments de nerfs excisés, et 62 échantillons de biopsies musculaires.

L'endommagement des nerfs, plus ou moins étendu, produit par la combinaison des modifications inflammatoires et dégénératives, a constitué la caractéristique histologique la plus remarquable. Dans les cas tuberculoides, la lésion inflammatoire était franchement granulomateuse, alors qu'on assistait à une réaction mononucléaire non spécifique dans la lèpre lépromateuse; la forme dimorphe présentait davantage ce dernier type de réaction. Cette dégénérescence, associée à l'inflammation et présente dans tous les nerfs lépreux, bouleversait davantage les structures dans la forme tuberculoide où l'on assistait même à la disparition de l'aspect funiculaire.

Dans les nerfs, les bacilles acido-résistants étaient presque entièrement confinés aux cellules de Schwann, qui montraient dans tous les cas, et dans chaque type de la maladie, une prolifération, celle-ci étant cependant plus apparente dans les cas de lèpre dimorphe et de lèpre lépromatuse.

Les longs segments qui ont été excisés au niveau du nerf median et du nerf cubital se sont révélés très utiles, car ils témoignaient d'une atteinte nerveuse plus étendue et livraient d'un nombre plus important de bacilles à certains endroits d'élection, telle que la partie épaissie du nerf median au niveau du segment inférieur de l'avant-bras, ainsi que le nerf cubital à la partie inférieure du bras.

Dans de nombreux nerfs, on a observé des modifications profuses, de dégénérescence et de régénération, survenant habituellement de manière simultanée. La régénération était la plus prononcée au niveau immédiatement voisin du site de la lésion; plus loin, et spécialement au poignet, cette régénération était bloquée par la fibrose grave présente au niveau de ces troncs nerveux et de leurs rameaux digitaux périphériques. Cette observation suggère l'existence d'une névrite à progression centripète dans la lèpre.

De temps à autre, on a relevé la présence d'axone épais qui étaient épargnés à la périphérie des funicules. Ceci pouvait même survenir au niveau de nerfs présentant une dégénérescence grave, et explique donc le fait que la vitesse de conduction soit relativement préservée dans ces nerfs.

Les nerfs intramusculaires ont fréquemment montré des modifications inflammatoires et dégénératives de même gravité et de même nature que celles observées au niveau des troncs nerveux; ces modifications étaient également responsables de l'atrophie typique de dénervation relevée dans ces muscles. Des bacilles acido-résistants ont également été observés dans ces nerfs; et, dans un cas, on en a également observés au niveau des fibres pénétrants dans le muscle.

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