Electrophysiological properties were monitored in detail in chronically constricted peripheral nerves by implanted, multicontact nerve cuff electrodes and correlated with morphometric histology in selected cases. The physiological and histological responses in nerve to a range of constricting cuffs of standard sizes were readily graded. The initial response to any significant constriction was a transient, focal conduction slowing or block at the constriction, followed by more protracted distal effects; the latter ranged from loss of excitability consistent with "dying-back" degeneration to reductions in conduction velocity consistent with histologically observed atrophy. Smaller myelinated fibers tended to have similar but less pronounced changes than larger diameter fibers. Recordings from ventral and dorsal roots showed that distal degeneration was more pronounced in motor than in sensory fibers of similar caliber. Electronmicroscopical measurements showed that basal laminas were relatively preserved around even the most atrophic and demyelinated axons. Perimeter measurements of the basal lamina could be used to estimate the diameter of the original nerve fiber.
Key words: implanted electrodes • nerve constriction • peripheral nerve atrophy • "dying-back" degeneration • secondary demyelination

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CONDUCTION STUDIES IN PERIPHERAL CAT NERVE USING IMPLANTED ELECTRODES: III. THE EFFECTS OF PROLONGED CONSTRICTION ON THE DISTAL NERVE SEGMENT

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Changes in peripheral nerve fiber caliber occur as a consequence of traumatic lesions. Retrograde atrophy of mature peripheral nerve occurs proximal to a lesion causing Wallerian degeneration[2,12] and may be related to disruption of neurofilament transport from the cell-body in regenerating axons.[22] Distal, anterograde atrophy and even degeneration have been demonstrated in nerve fibers with a proximal constriction.[4] Distal atrophy was also seen in animals intoxicated with β,β′-iminodipropionitrile (IDPN),[11] which causes cytoskeletal disorganization of neurofilaments[19] and impairment of slow axoplasmic transport.[20]

The aim of this study was to examine the process of atrophy and degeneration in nerve fibers with a proximal constriction and to determine (1) whether such degeneration was selective for particular groups of nerve fibers and (2) whether the spatial extent of nerve fiber atrophy and degeneration was related to the degree of focal constriction. We used chronically implanted stimulating and recording electrode arrays which allow serial measurements at several sites along the damaged part of the nerve.[23] A preliminary report has been published.[24]

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MATERIALS AND METHODS

The methods of stimulation and recording via implanted electrodes and findings in control nerve have been described in detail.[23]

Experimental Animals. Surgery was performed in 16 limbs from 11 adult cats (2.4–5.3 kg) under aseptic conditions during deep anesthesia induced by intraperitoneal pentobarbital (40 mg/kg body weight) and maintained intravenously. The tibial nerve was constricted just distal to the branch to the deep toe flexors (at the asterisk in Fig. 1 from Krarup and Loeb[23]) using a silicone rubber tube[1] 1–3 mm in length and with an internal diameter of 0.75–1.45 mm which reduced the transverse area of the nerve by 40–70%. At this time, cuff electrodes were implanted distally around the tibial nerve and proximally around the sciatic nerve; two patch electrodes were placed in the sole of the foot as described previously.[23]

Electrophysiological Studies. Serial observations began the day after implantation of the electrodes and were repeated every 5–8 days for 6–8 weeks and then every 2–3 weeks for 2–3 months. On each occasion, the cats were anesthetized with subcutaneous ketamine (70 mg/kg) and xylazine (3 mg/kg), repeated as necessary. Temperature was controlled by placing the animal on a heating pad. Findings in constricted nerves were compared with seven control nerves.[23]

In six legs with nerve constriction, a laminectomy was performed under pentobarbital anesthesia just before sacrifice. Ventral and dorsal roots from L7 to S2 were each tied separately with a ligature and cut proximally. The cut roots were placed on platinum hooks in mineral oil (37°C) for stimulation or for recording.

Nerve Stimulation and Recording of Responses. In order to ascertain axonal continuity on the distal side of the constriction, the tibial and plantar nerves were stimulated at the different electrode sites available in each multicontact cuff. The ascending compound nerve action potentials (CNAP) were recorded similarly at multiple sites both distal and proximal to the constriction. By using the difference in latency between CNAPs, we could determine the conduction velocity along small segments of nerve either proximal or distal to the constriction. For example by stimulating distally and recording at two proximal sites, we could determine the proximal conduction velocity of the fastest (i.e., largest) conducting fibers in continuity through the lesion. In addition to the CNAP, the compound muscle action potential (CMAP) evoked by stimulating the tibial and plantar nerve was recorded from plantar muscle.

Distances between the various electrodes were measured along the exposed nerve following the chronic experiments.

Histological Studies. The plantar, tibial, and in some instances the sciatic nerves were fixed, and morphometric analysis was performed at multiple levels in three nerves.[23] In the constricted nerves, the cuff was fixed in situ with the nerve. After 24 hours of fixation, the cuff was removed with a minimum of disturbance of scar tissue. Subsequent examination of transverse sections of the

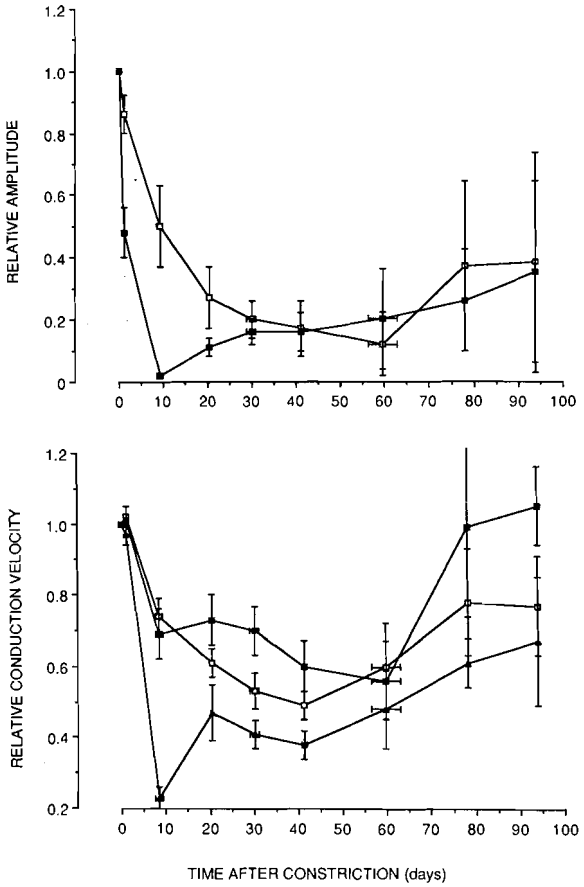


FIGURE 1. Reduction in mean relative amplitude and conduction velocity of ascending action potentials over time (days 1–94) after constriction in 12 nerves. The responses, evoked by stimulation of the plantar nerve, were measured in the tibial and the sciatic nerves. The values were normalized (1.0) to the corresponding values in normal nerve at day zero. **Above:** Amplitude of the tibial (□) and the sciatic (■) nerve action potential. **Below:** Conduction velocities within the tibial (□) nerve segment distal to the constriction, the tibial-sciatic (▲) segment through the constriction, and the sciatic nerve (■) proximal to the constriction. Vertical and horizontal bars denote standard errors of mean.

nerve and the surrounding collagen tissue excluded the presence of aberrant nerve fibers outside the constricting tube.

Electronmicroscopy was performed as described preivously.[25] For detailed analysis of the circumference of the basal lamina, the outside of myelin, and the axon, 50–100 fibers were digitized after magnification at 5,400–20,000×.

RESULTS

Changes Localized to the Site of Nerve Constriction. Two distinct patterns of responses to constriction were discernible in the electrophysiological and histological data. Four of the 16 constricted nerves responded with almost complete loss of conduction through the constriction within the first day after application of the constriction, followed within a few days by complete loss of electrical excitability of the tibial nerve distal to the constriction. Excitability first returned at 43–59 days postconstriction, at which time the conduction velocity of excitable fibers within the distal segment was about 4 m/sec. This sequence of events resembles that recorded during regeneration after complete nerve crush[25] and suggested that these four nerves had undergone degeneration of most or all myelinated fibers. These nerves were excluded from the analysis presented below.

In the remaining 12 constricted nerves, conduction block (complete or partial) through the constricted region developed later and was more transient (Fig. 1). At 7–10 days, the conduction velocity through the constriction was markedly reduced, as was the amplitude of the CNAP recorded proximally from the sciatic nerve. Over the ensuing 2–3 weeks conduction through the constriction gradually recovered. The conduction velocity through the constriction remained more reduced than the velocity distal and proximal to the constriction.

The nerve response was poorly related to the inside diameter or the length of the constricting cuff. The tightness of the constriction was therefore gauged from the degree of slowing of impulse conduction through the constriction.

Changes Distal to Nerve Constriction. In parallel with and following recovery of conduction through the constriction, the amplitude of the CNAP recorded from the tibial nerve distal to the constriction gradually diminished. By day 30–50 postconstriction, both regions proximal and distal to the constriction had similar reductions in amplitude of the CNAP, and they appeared to undergo parallel, gradual, and partial recovery over the next 50–60 days.

Mechanisms of Conduction Changes. Reduced conduction velocity and amplitude of whole nerve CNAPs can arise by two different mechanisms: (1) generalized atrophy or demyelination or both of all nerve fibers distal to the constriction or (2) selective loss of the largest diameter fibers at or distal to the constriction. The relative contribution of these two processes was assessed by determining the conduction velocity for those axons that could be excited by stimulation at different distal sites. Previous studies suggested only minor retrograde effects on conduction in the stem fibers proximal

Table 1. Conduction velocities (m/sec) in control and constricted nerves.

	Nerve segment			
	Sciatic nerve	Sciatic-tibial nerve	Tibial nerve	Plantar nerve
Normal nerve*	102 ± 1 (121)	105 ± 1 (146)	92 ± 1 (109)	64 ± 1 (55)
Paired *t*-test†	NS	$P < 0.001$	$P < 0.001$	
95% confidence limits	75–129	81–129	72–112	49–80

	Nerve segment		
	Proximal to constriction	Constricted segment	Distal to constriction
Constricted nerve‡			
20–94 days after constriction	76 ± 3 (65)§	49 ± 2 (65)§	54 ± 2 (65)§	41 ± 3 (38)§
Paired t-test†	$P < 0.001$	$P < 0.001$	$P < 0.001$	

**Mean ± SEM in control nerves (number of observations in seven nerves).*
†Comparison of conduction velocities in different nerve segments.
‡ Mean ± SEM in constricted nerves (number of observations in 12 nerves followed serially).
§Significantly slower conduction velocity at $P < 0.001$ in nerves with chronic constriction (20–94 days after implantation) than in nerves with acute constriction (one day after implantation) and in control nerves.

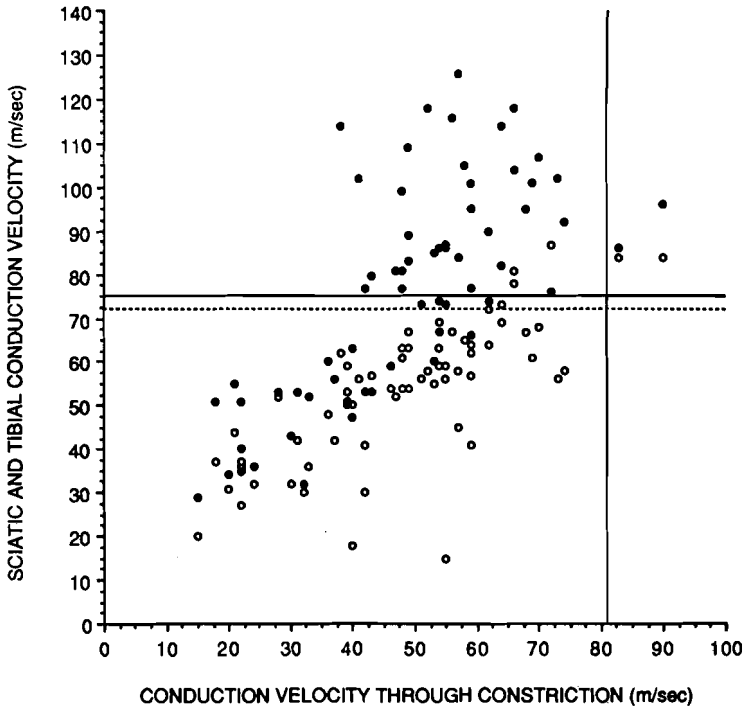
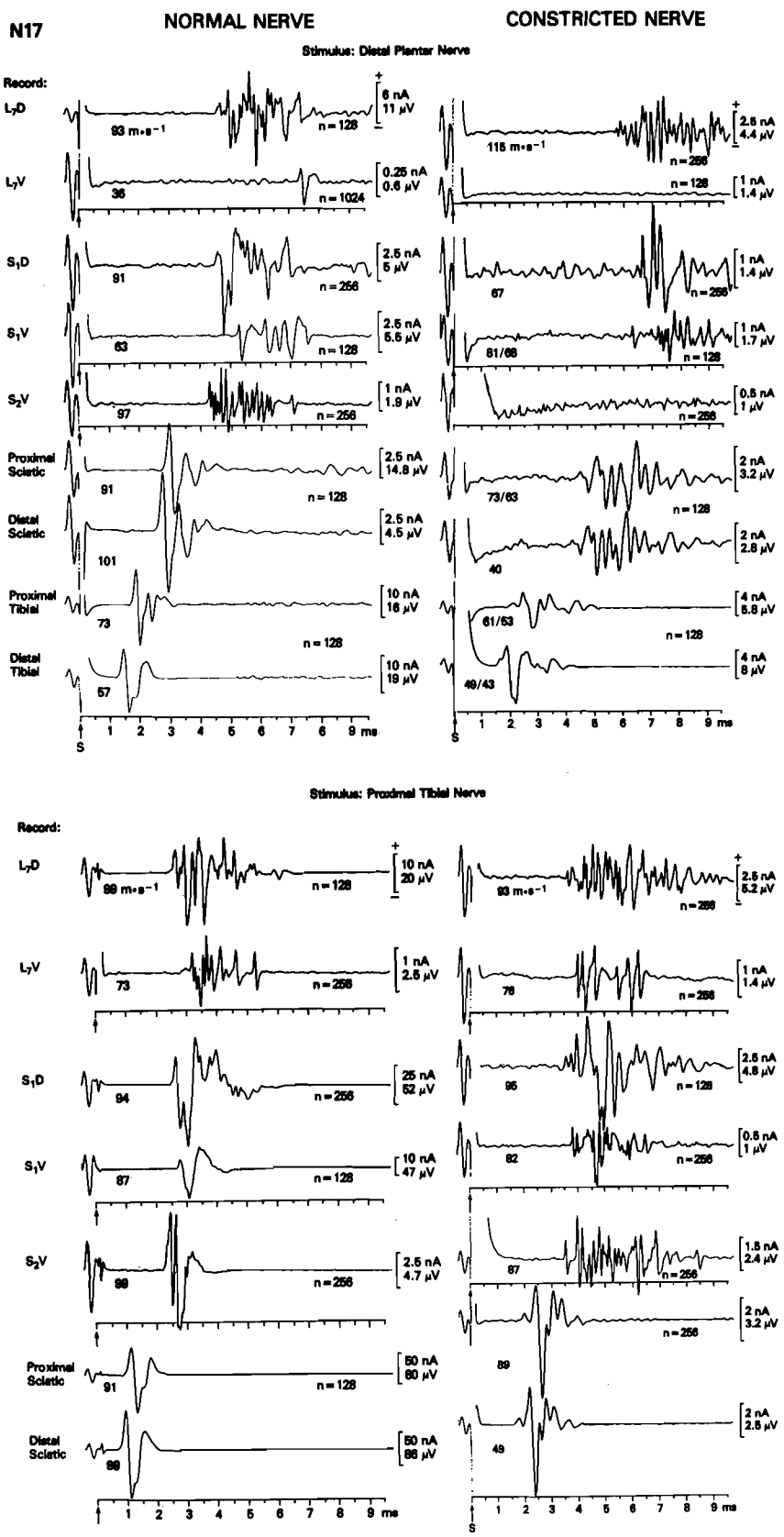


FIGURE 2. Conduction velocities distal and proximal to the constriction (ordinate) as function of the conduction velocity through the constricted region (abscissa) in 65 serial observations from 12 constricted nerves. The horizontal and vertical lines indicate the lower 95% confidence limits obtained from seven sciatic (full line) and tibial (dashed line) control nerves.[23] The tibial nerve conduction velocities (○) varied directly with the conduction velocity through the constriction ($r = 0.753$, least-square method, $P < 0.001$). The sciatic nerve conduction velocities (●) consisted of two groups which distributed mainly within or below the normal range when the velocity through the constriction was less than 40–50 m/sec.

to a peripheral nerve lesion.[25] As seen in Fig. 1, the impulse conduction velocity decreased by 30–40% along the sciatic nerve but tended to be less affected than the conduction velocity distally within the tibial nerve segment. Similarly, the average segmental conduction velocities of all serial studies during the chronic phase of constriction (Table 1) showed a reduction in the sciatic nerve of 25 ± 3%, which was significantly less ($P < 0.0005$, paired t-test) than the reduction of 42 ± 2% in the tibial nerve. The slowing of conduction in the sciatic compared with the tibial nerve suggested that both the above-mentioned mechanisms should be considered. The sciatic nerve conduction velocities ranged widely from 29 to 126 m/sec, suggesting a wide variation of the extent of fiber loss. The degree of slowing of conduction along the sciatic nerve was dependent on both the tightness of the constriction and on the length of nerve distal to the constriction.

In order to assess the influence of the tightness of the constriction, the distal tibial and the proximal sciatic nerve velocities were plotted against the conduction velocity through the constriction in 65 serial observations from 12 nerves (Fig. 2). The velocities recorded within the tibial nerve changed linearly with the tightness of the constriction while sciatic nerve values distributed in two main groups, one group (35 of 45 values) being mainly within normal limits when the velocity through the constriction was >40 m/sec. In the other group, the proximal velocities were reduced in 19

FIGURE 3. Traces of root and nerve action potentials in normal and constricted nerves. Each nerve was stimulated at two sites to show loss of action potentials as a function of distance distal to the constriction. **Above:** The distal plantar nerve was stimulated 125 mm from the constriction, and the ascending action potentials were recorded from the tibial nerve distal to the constriction and from the sciatic nerve and ventral (L7V, S1V, S2V) and dorsal roots (L7D, S1D) proximal to the constriction. The conduction velocities calculated from changes in conduction time between recording sites are indicated below the traces. On the constricted side potentials were absent from the S2 ventral root which on the control side showed a large response. **Below:** The tibial nerve was stimualted 19 mm distal to the constriction. The responses were recorded at two sites along the sciatic nerve and at ventral and dorsal roots similar to **Above.** The action potentials were calibrated in current units and voltage units by injecting a 3 kHz signal through the electrodes *in situ* (seen to the left at each trace during the predelay).[23]


N17
NORMAL NERVE
CONSTRICTED NERVE
Stimulus: Distal Plantar Nerve
Record:
L7D
L7V
S1D
S1V
S2V
Proximal Sciatic
Distal Sciatic
Proximal Tibial
Distal Tibial
Stimulus: Proximal Tibial Nerve
Record:
L7D
L7V
S1D
S1V
S2V
Proximal Sciatic
Distal Sciatic
1 2 3 4 5 6 7 8 9 ms
S

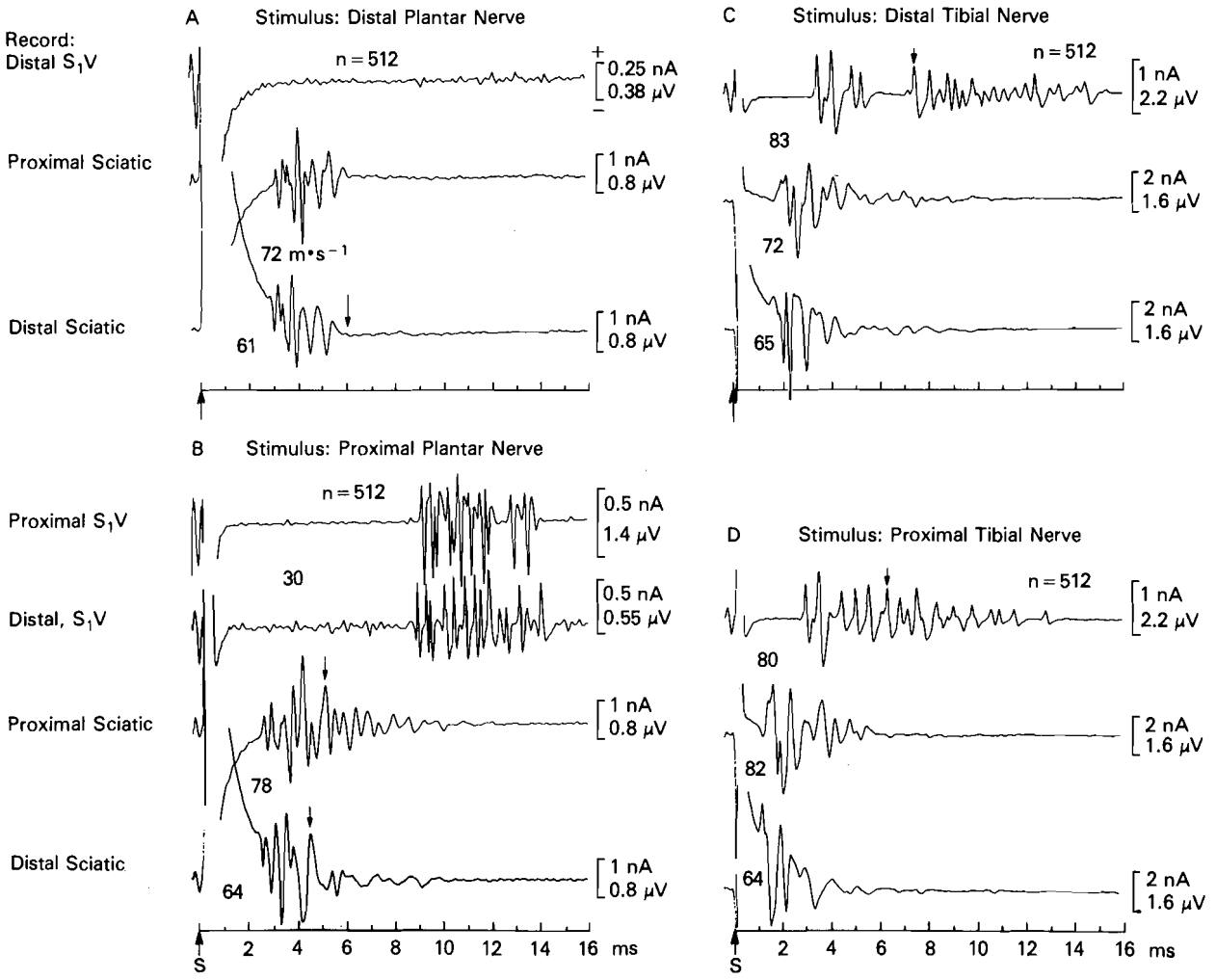
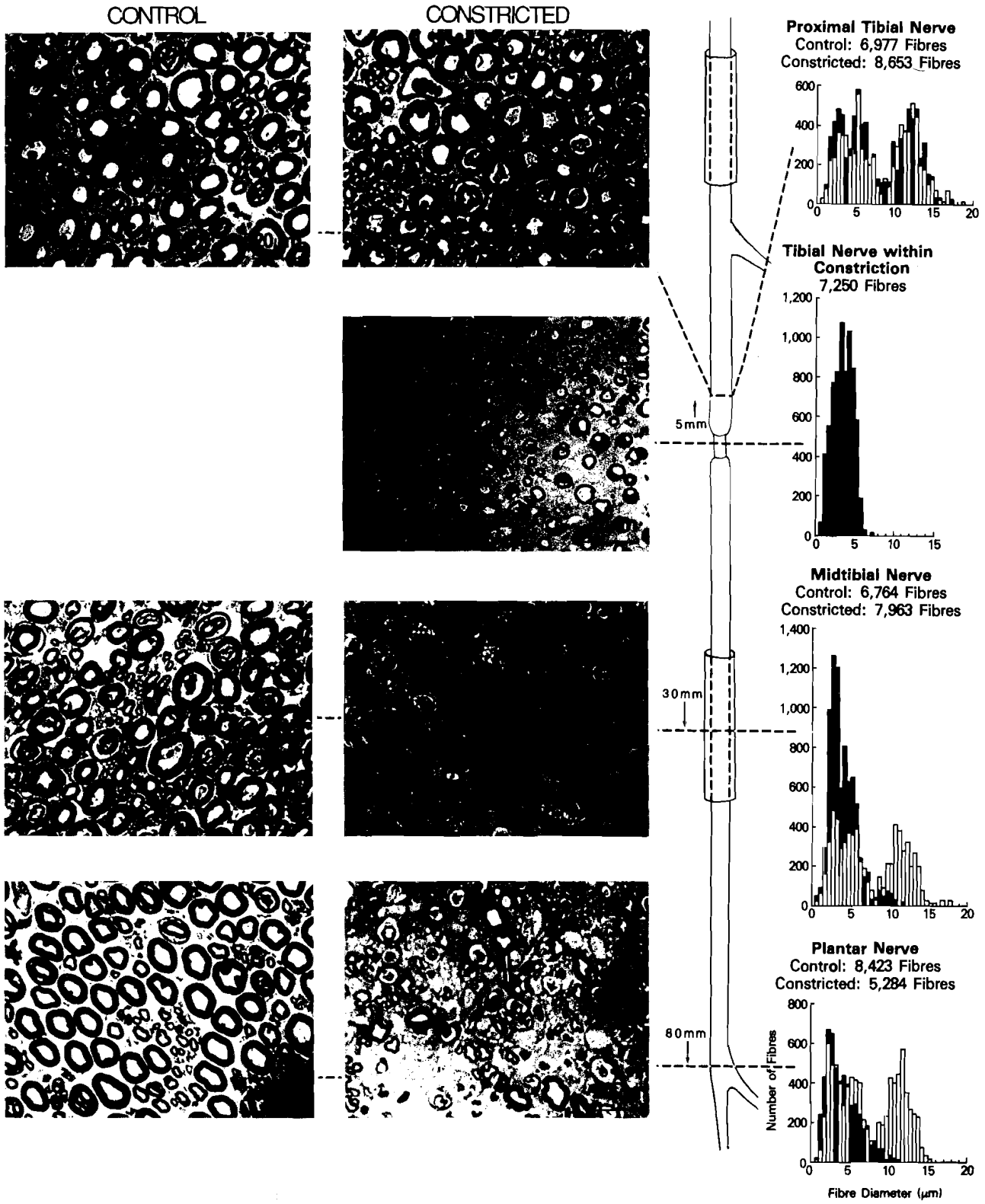


FIGURE 4. Recruitment of slow and fast conducting motor fibers at different distances from the constriction. **(A)** Plantar nerve stimulation 115 mm distal to the constriction. No potential could be recorded from the S1 ventral root but a potential was present in the sciatic nerve. Conduction velocities are indicated below the traces. **(B)** Stimulus 85 mm from constriction. Potentials with interelectrode conduction velocities of 30 m/sec were recorded at the root, and additional slow components appeared in the sciatic nerve tracing (absent in **A**, arrows). **(C)** Stimulus 44 mm distal to constriction. In addition to the slowly conducted potential (arrow at 30 m/sec), a separate faster root component with a conduction velocity of 83 m/sec was recorded. **(D)** Stimulus 14 mm from the constriction. At the shorter conduction distance, the two bursts with conduction velocities of 80 m/sec and 30 m/sec (arrow) merged.

of 20 observations when the velocity through the constriction was ≤40 m/sec (χ^2-test, $P < 0.001$), indicating loss of fast conducting fibers in tightly constricted nerve. In the 36 observations with sciatic nerve conduction velocities within normal limits, the average sciatic nerve conduction velocity was 95 ± 2 m/sec. However, the tibial nerve conduction velocity was 61 ± 2 m/sec, 34% lower than

FIGURE 5. Composite of transverse sections in normal and contricted nerve **(left)** and of fiber diameter histograms **(right)** measured at a magnification of 1000×. The distance from the constricting cuff to the proximal section was 5 mm **(middle).** Distal to the constriction, sections were taken from the tibial nerve (30 mm from the constriction) and the plantar nerve (80 mm from the constriction). Open and solid columns show results from control and constricted nerves, respectively. The absolute fiber counts were calculated from the relative distribution of about 500 fibers in each section, from the fiber density, and from the total fascicular area. Bars = 20 μm. Cat N15, 34 days after implantation.


34 days post-implant
CONTROL
CONSTRICTED
Proximal Tibial Nerve
Control: 6,977 Fibres
Constricted: 8,653 Fibres
Tibial Nerve within Constriction
7,250 Fibres
5mm
Midtibial Nerve
Control: 6,764 Fibres
Constricted: 7,963 Fibres
30mm
Plantar Nerve
Control: 8,423 Fibres
Constricted: 5,284 Fibres
80mm
Number of Fibres
Fibre Diameter (μm)

normal, a significant reduction ($P < 0.0005$) that could not be explained by fiber loss.

In the remaining 29 observations, the sciatic nerve velocity was 53 ± 2 m/sec and the tibial nerve velocity was 45 ± 2.5 m/sec, both much lower than normal ($P < 0.0005$). When paired in individual recordings, the sciatic nerve conduction velocity was 24 ± 6% faster than the tibial nerve velocity. In controls the conduction velocity along the sciatic nerve was only 11 ± 2% faster than in the tibial nerve, in agreement with other studies showing a similar change distributed equally among large and small myelinated fibers.[32] This larger difference ($P < 0.02$) between the distal and proximal conduction velocities in constricted nerves than in control nerves suggested that smaller diameter fibers that remained functional through the constriction were, nevertheless, somewhat atrophic distally.

In order to investigate the influence of the length of nerve distal to the constriction, the impulse conduction in the sciatic nerve was measured when the nerve was electrically stimulated at different electrode sites. In controls the conduction velocity in the sciatic nerve was similar regardless of whether the plantar nerve (105 ± 2 m/sec, $n = 31$) or the tibial nerve (108 ± 3 m/sec, paired t-test) was stimulated. By contrast, in constricted nerve the plantar nerve stimulation evoked ascending CNAPs with lower sciatic nerve velocity (72 ± 5 m/sec, $n = 25$) compared with those evoked at the tibial nerve (87 ± 4 m/sec, $P < 0.0005$). Figure 3 illustrates that the distal site of excitation evoked action potentials in slower conducting fibers than those activated by more proximal stimulation. The sciatic nerve conduction velocity was 18% lower when the plantar nerve was stimulated than when the tibial nerve was stimulated. On the control side, no such difference was apparent.

Over a period of 1–3 weeks after implantation, no ascending response could be elicited from the distal plantar nerve in 6 hindlimbs. Excitability was preserved closer to the constriction in all 12 nerves.

Effects of Constriction on Motor as Compared with Sensory Nerve Fibers. In 8 of the 11 nerves with serial recordings of the CMAP, the response in plantar muscle disappeared completely. The loss of the response was permanent in four nerves and transient in another four. In 13 of the 18 observations with loss of a CMAP, an ascending CNAP could, nevertheless, be elicited by stimulation of the distal plantar nerve. Two mechanisms may explain this finding: (1) preserved conduction in both sensory and motor fibers with focal degeneration at terminal motor branches[18] and (2) preserved conduction in sensory fibers with general loss of motor fibers. To distinguish between these possibilities, responses evoked by distal stimulation were recorded from ventral and dorsal roots. In the case shown in Fig. 3, the amplitude of the plantar CMAP on the constricted side was 0.7 mV compared with 9 mV on the control side. On the control side (Fig. 3, above, left), plantar nerve stimulation evoked large responses at S1 and S2 ventral roots and a small response at L7. In contrast, a response was present only at the S1 ventral root on the constricted side, whereas dorsal root responses were preserved (Fig. 3, above, right). With more proximal stimulation (Fig. 3, below), potentials were present at all three ventral roots both on the constricted and the control side.

Figure 4 shows further details regarding the pattern of degeneration in motor fibers. In this case of constriction, there was no evoked potential in the plantar muscles and no ventral root activity following stimulation of the distal plantar nerve, although an ascending, presumably sensory, action potential could be recorded from the sciatic nerve (Fig. 4A). Slightly more proximal stimulation at the heel patch-electrode produced potentials with a conduction velocity of 30 m/sec along the ventral root (Fig. 4B). Even more proximal stimulation at the distal tibial nerve elicited two groups of action potentials with overall conduction velocities of about 30 and 80 m/sec (i.e., within the ranges of gamma and alpha motoneurons, respectively; Fig. 4C). The two responses merged for the most proximal stimulation site just distal to the constriction (Fig. 4D).

Histological Correlates of Conduction Changes. In nerves which remained electrically excitable distal to the constriction, the most conspicuous change was a marked diminution of the diameters of myelinated fibers as illustrated in the sections in Fig. 5. At the midtibial level, 30 mm distal to the constriction, the largest fibers were 11–12 μm in diameter compared with 17–18 μm on the contralateral control side. Only 5% of the fibers had diameters >7 μm compared with 50% in the control nerve. Nevertheless, the total number of fibers was similar to control, reflecting a doubling of small fibers of <7 μm diameters. In the plantar nerve, 80 mm distal to the constriction, the total number of fibers was diminished in addition to

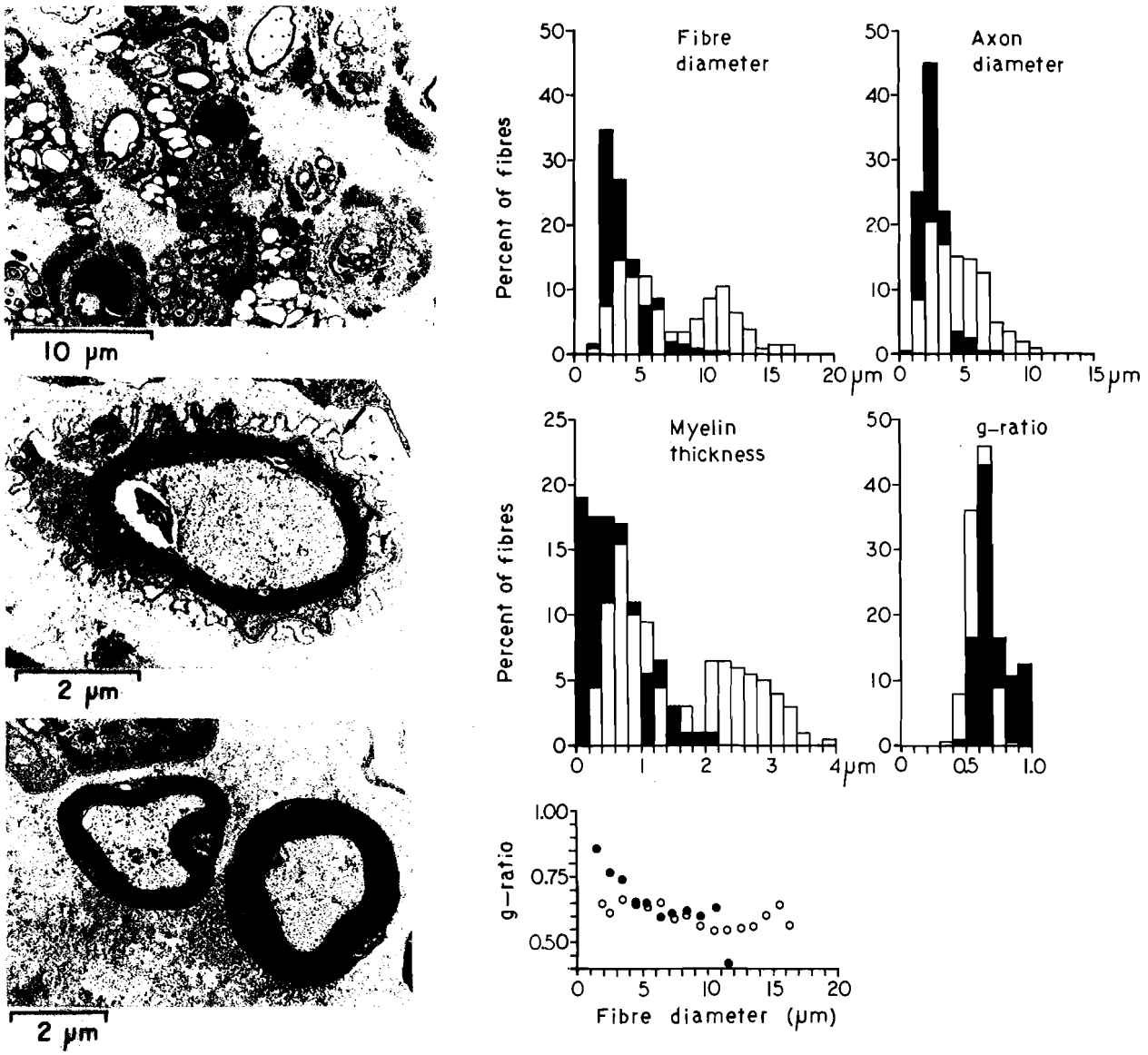


FIGURE 6. Electronmicrographs taken from the same tibial nerves as Fig. 5. **Left:** The section at top was magnified to 5400× and shows thinly myelinated fibers and myelin and fiber debris from degenerating fibers. **Middle:** Folded redundant basal lamina (large arrow) and internalized myelin (small arrow) debris within the axon (23,800×). **Bottom:** the two fibers at 18,500× had normal myelin and axon structure and the basal lamina had a normal relationship to the myelin. **Right:** Various parameters in 200 fibers from the nerve with a proximal constriction (filled columns) and from the contralateral control nerve (open columns) were measured at 5400×.

the reduction of the diameters of large fibers. At the level of the constriction, the fibers were thinly myelinated and the range of calibers was narrow, no fibers being more than 6 μm in diameter. Measurements 5 mm proximal to the constriction showed a similar distribution of fiber diameters compared with control, although the number of small fibers was somewhat larger probably due to the presence of some regenerating fibers.

Electronmicroscopic Findings. The tibial nerve 30 mm distal to the constriction showed fibers with myelin debris (Fig. 6, left, top). Apart from the diminution in fiber and axon diameters dital to the constriction, the myelin thickness was diminished to <0.6 μm in half of the fibers, and the ratios of the axon to the external fiber diameters (g ratios[33]) were >0.8 in 20% of the fibers (Fig. 6, right).

The thinly myelinated fibers in this and one of two other constricted nerves were surrounded by redundant folds of basal lamina (Fig. 6, left, middle) which did not occur in normal-appearing fi-

bers (Fig. 6, left, below). None of the folded basal lamina profiles contained more than one fiber. For more detailed analysis of these fibers, the diameters of the axon, fiber, and basal lamina (Fig. 7) were determined in 50 fibers with folded basal lamina and in 40 fibers with smooth basal lamina and compared with 50 fibers from the control side. In control nerve there was a close correspondence between the diameter of the basal lamina and the external fiber diameter (Fig. 7, above and below, A). In constricted nerves, the perimeters of folded basal lamina equaled circles 8–16 μm in diameter, but they contained fibers which were only 2–6 μm in diameter (Fig. 7, above and below, A). These fibers were thinly myelinated and had g ratios of 0.87 ± 0.02 which was larger ($P < 0.01$) than in control fibers with a diameter of 2–6 μm (0.74 ± 0.015). In the plantar nerve, 80 mm distal to the constriction, the folded basal lamina also corresponded to larger fibers, but they were in most instances devoid of axonal structures and contained only Schwann cell profiles. The few axons present in folded basal lamina were completely demyelinated and <1–2 μm in diameter.

The equivalent diameters of the smooth basal lamina were less than 10–11 μm and contained fibers of similar diameters (Fig. 7, above and below, A), suggesting that large fibers were predominantly affected by the proximal constriction. However, the smaller nerve fibers in the tibial nerve with smooth basal lamina showed signs of axonal atrophy. Since none of these fibers was larger than 11 μm in diameter, they were compared with a subgroup of the control fibers with similar diameters. The mean index of circularity,[3] Φ, of these axons distal to the constriction was reduced to 0.74 ± 0.02, compared with 0.84 ± 0.01 in controls ($P < 0.0005$). The g ratio in these fibers was reduced to 0.54 ± 0.01, compared with 0.65 ± 0.01 in controls ($P < 0.0005$). The relative thickening of myelin was apparent when the myelin thickness was plotted against the axon diameter (calculated from area measurements). In Fig. 7 (below, B) an exponential relationship was present in normal nerve as described by Berthold[8] and Boyd and Kalu.[9] The myelin of fibers with smooth basal lamina was on average 50% thicker for a given axon diameter ($P < 0.0005$) than in control nerve. The myelin values from fibers with folded basal lamina were distributed at the foot of the curve.

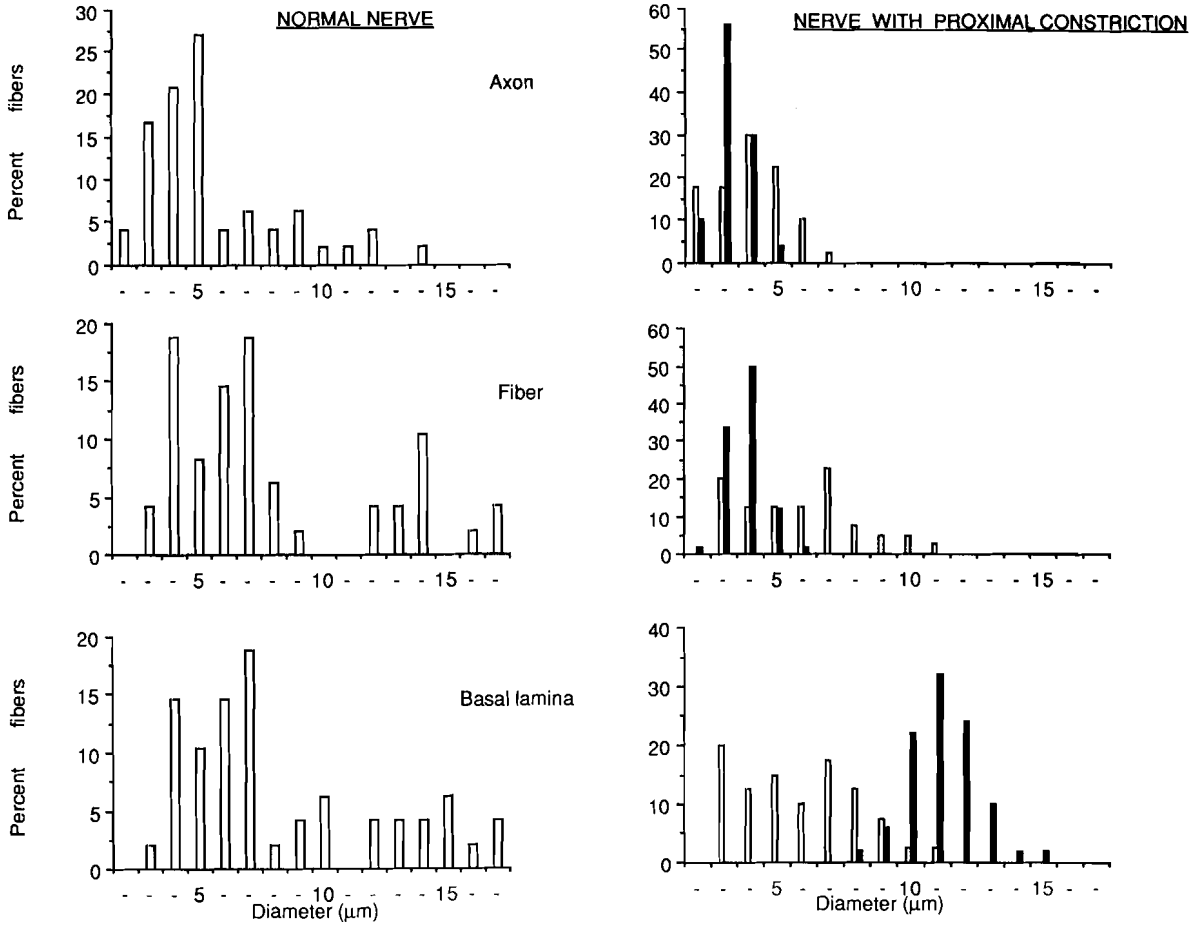
DISCUSSION

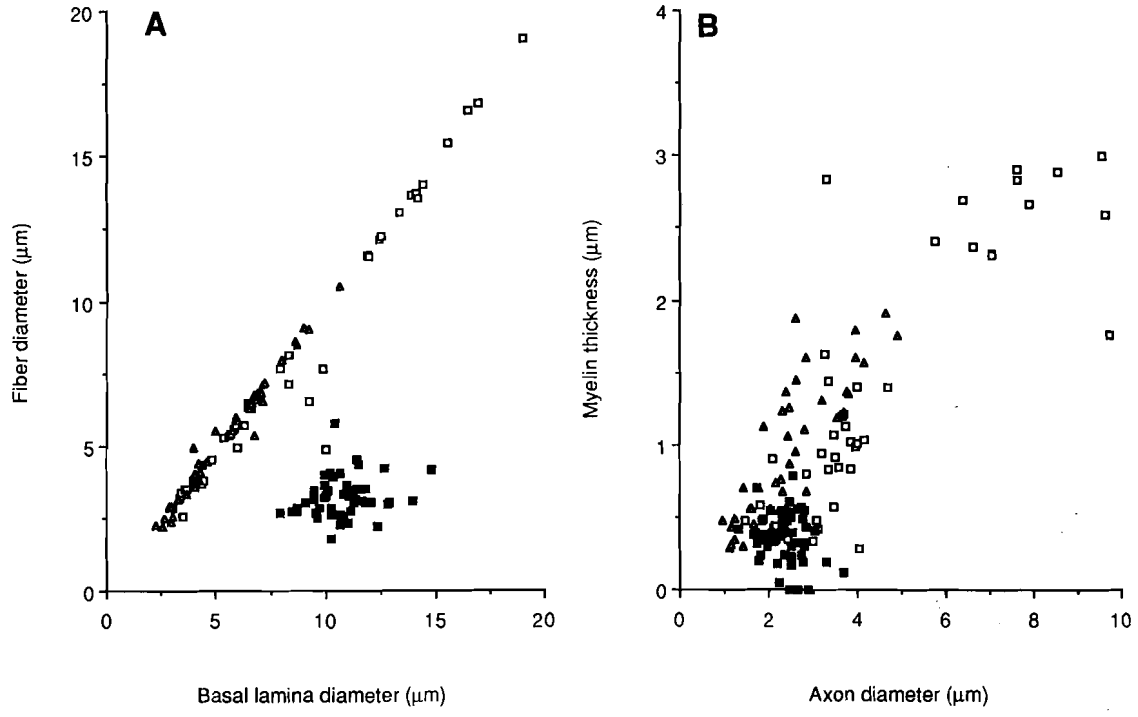
To delineate changes in conduction properties and excitability of nerve fibers distal to a nerve constriction, we have used implanted electrodes[23] with fixed, well-defined sites for stimulating and recording nerve and muscle action potentials. This method was well-suited for localizing pathophysiological changes to particular regions of the nerve and particular times following the onset of a chronic constriction. In comparison, a diminution of the muscle action potential distal to a nerve constriction[4,6] may be due to fiber loss at or anywhere distal to the constriction. The recording conditions with tripolar nerve cuff electrodes allow resolution of averaged action potentials from single myelinated fibers,[23] which is particularly advantageous when recording from severely affected nerves.

A complex series of events followed implantation of the nerve constriction. Changes with acute and chronic time courses occurred at the constriction and distal to it, with different effects in sensory and motor axons of different initial size. Our main objective in these experiments was to study nerves with maintained electrical excitability on the distal side of the constriction. In the interpretation of our findings, sources of error associated with (1) the method of recording and (2) the complexity of the preparation should be considered:

1. Cuff electrodes with an internal diameter 30–40% larger than the nerve were used to prevent compression damage. However, a nerve en-

FIGURE 7. Above: Histograms of axon, fiber, and basal lamina diameters calculated from equivalent circles measured from perimeters (see Materials and Methods). Measurements were performed in 50 fibers from control nerve (left panel), 50 fibers from constricted nerve with folded basal lamina (right panel, solid columns), and 40 fibers from constricted nerve with smooth basal laminas (right panel, open columns) using electronmicrographs at a magnification of 5,400–20,000×. The diameters of the folded basal laminas suggested that they had belonged to fibers with diameters of 8–16 μm. The fibers within these basal laminas had markedly thin fiber and axon diameters. **Below: (A)** Relationship between the fiber and the basal lamina diameters (corresponding to circles calculated from the perimeter measurements). In control nerve (□) there was a close relationship between the parameters except in 2–3 fibers probably measured too close to the Schwann cell nucleus. Nerve fibers with a proximal constriction followed this relationship when the basal lamina was smooth (▲) but not when the basal lamina was folded (■). **(B)** Relationship between myelin thickness and the axon diameter (corresponding to circles calculated from area measurements). Control fibers (□) had a logarithmic relationship.[8,9] Fibers with smooth basal lamina (▲) had 50% thicker myelin for a given axonal diameter than did control fibers. The thin fibers with folded basal lamina (■) had much thinner myelin than expected from the diameter.


NORMAL NERVE
NERVE WITH PROXIMAL CONSTRICTION
Axon
Fiber
Basal lamina
Percent fibers
Diameter (μm)

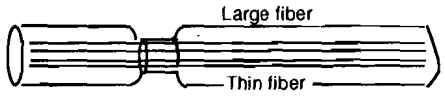
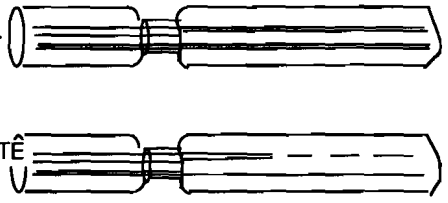

A
B
Fiber diameter (μm)
Basal lamina diameter (μm)
Myelin thickness (μm)
Axon diameter (μm)

closed by a cuff-electrode might be more susceptible to compression due to additional swelling caused by Wallerian degeneration at the constriction.[27] However, it is unlikely that such a "double crush" effect[35] was significant since the nerve distal to constriction remained smaller than the inside of the cuff electrode. In addition, pathophysiological changes were the same when the constriction was implanted well before the electrodes and when they were implanted simultaneously.

2. Compression of nerve fibers results in focal demyelination,[13,16,17,28,29] and if severe enough the continuity of axons is disrupted and is followed by Wallerian degeneration. In our experiments, the most severely constricted nerves showed early conduction block probably due to focal loss of axonal continuity. Complete loss of excitability distal to the constriction indicated that Wallerian degeneration had occurred in most or all myelinated nerve fibers and was followed by regeneration after long delays. In less severely constricted nerve, conduction block was delayed by 5–10 days. This conduction block was short lasting, and within 2 weeks conduction through the constriction was secure, although the conduction velocity was markedly reduced. Distal effects of the constriction on fibers in continuity through the lesion could only be ascertained after recovery of the block.

Distal Effects of the Nerve Constriction. Distal deterioration of impulse conduction continued after partial recovery at the site of the constriction. This observation has the important implication that focal demyelination at the site of the lesion in compression neuropathies may recover while the distal changes persist or even progress. A general interpretation of the distal nerve fiber changes in nerves with different degrees of constriction is suggested schematically in Table 2. The possibility that atrophy of large nerve fibers had caused reduced conduction velocity distally but not proximally was supported by the greater proportion of small diameter fibers in some tibial nerves with normal numbers of fibers. Electronmicrographs further suggested that large fibers showed more pronounced changes distal to the constriction than small fibers, in accordance with earlier findings at the site of entrapment.[28] Large fibers, identified by the diameters of their basal laminas, showed severe axonal atrophy, secondary demyelination, and distal degeneration. Smaller fibers showed more subtle evidence of atrophy,[22,31] with increased axonal iregularity and a greater myelin

Table 2. Effect of constrictions of different tightness on the function and structure of nerve fibers within and distal to the lesion.

	PROXIMAL TO CONSTRICTION	WITHIN CONST.	DISTAL TO CONSTRICTION
MILD			Slowing of conduction through the constricted segment. Normal conduction distal to the constriction.
MODERATE			In addition to slowing of conduction through the constriction, the conduction velocity distal to the constriction was slow and large fibers showed atrophy and secondary demyelination. Loss of distal excitability in large fibers in a 'dying-back' distribution. The excitability closer to the constriction was retained but the conduction velocity was low. Fibers were atrophic with secondary demyelination and distal degeneration. Smaller fibers showed less pronounced slowing of conduction. Large fibers were inexcitable distal to the constriction. Small fibers showed distal loss of excitability but could conduct action potentials closer to the constriction.
SEVERE			Degeneration of all myelinated fibres at, and distal to, the constriction. Just proximal to the constriction fibers showed large dilatations.

thickness than expected from the axonal diameter. Distal degeneration occurred in small fibers in severely constricted nerve, and in the most pronounced constrictions, all myelinated fibers degenerated from the site of the lesion. When degeneration from the site of constriction occurred, the fibers proximal to the constriction showed large dilatations as described by Spencer.[34]

Abnormalities in myelin owing to axonal atrophy were previously described in uremic neuropathy[14] and in cats with pronounced retrograde atrophy following chronic nerve section.[15] Baba et al.,[4,6] using a ligature around the nerve in rabbit, found that the axon collapsed without initial changes in myelin, although a greater than normal demyelinating effect of diphtheria toxin could be demonstrated in the constricted nerves.[5]

The phenomenon of atrophy of nerve fibers distal to a constriction of the nerve was originally suggested by Weiss and Hiscoe[36] and has been proposed to occur in human nerve. Bauwens[7] used the term "axonocachexia" distal to "axonostenosis" and suggested that this phenomenon could be recognized in clinical electrodiagnosis; this was later confirmed in patients with carpal tunnel syndrome.[10] Moreover, the possibility of a "dying-back" type of degeneration of nerve fibers distal to a constriction might be partly responsible for the recovery of distal conduction velocity in patients with release of carpal tunnel syndrome.[10,26] The recovery was too rapid to be due to regeneration of large fibers from the wrist but could represent the shorter regeneration distance for fibers with only distal "dying-back" degeneration. The possibility of a shorter regeneration distance in patients with entrapment neuropathies than that envisaged from the site of the constriction may have consequences for the prognosis in patients with apparent loss of nerve fibers.

The atrophy of nerve fibers distal to a constriction and the development of distal loss of excitability predominantly in large fibers might be related to changes in axoplasmic flow.[30] The distal changes occurred too rapidly to be due to impairment of slow axoplasmic transport of cytoskeleton elements thought to play a major role in the control of axon caliber of large fibers.[22] However, in normal nerve fibers incorporation of rapidly transported glycoproteins into the axolemma is seen,[21] suggesting a turnover of constituents which may be of relevance in degeneration and atrophy distal to a constriction. Another possibility is increased distal degradation of axonal constituents subsequent to restriction of retrograde axoplasmic transport at the proximal constriction (Griffin, personal communication).

The combination of the chronic electrophysiological methods introduced here with more conventional acute, terminal experiments suggest that motor axons are, in general, more susceptible to constriction than sensory fibers (e.g., Figs. 3 and 4). Although the results here need to be confirmed in a more extensive study, the findings suggest that degeneration of the distal processes caused neuromuscular failure while sensory fibers of comparable size remained electrically excitable. The "dying-back" process appeared more extensive in the alpha motor fibers than in the gamma fibers. This may be related to the large metabolic requirements for supporting the widespread terminal arborization and synaptic transmission of typical alpha motoneurons.

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