

Microvasculitis in Non-Diabetic Lumbosacral Radiculoplexus Neuropathy (LSRPN): Similarity to the Diabetic Variety (DLSRPN)

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Abstract. Diabetic lumbosacral radiculoplexus neuropathy (DLSRPN) has been shown to be due to ischemic injury from microvasculitis. The present study tests whether ischemic injury and microvasculitis are the pathologic cause of non-diabetic lumbosacral radiculoplexus neuropathy (LSRPN), and whether the pathologic alterations are different between LSRPN and DLSRPN. We studied distal cutaneous nerve biopsies of 47 patients with LSRPN and compared findings with those of 14 age-matched healthy controls and 33 DLSRPN patients. In both disease conditions, we found evidence of ischemic injury (multifocal fiber degeneration and loss, perineurial degeneration and scarring, characteristic fiber alterations, neovascularization, and injury neuroma) that we attribute to microvasculitis (mural and perivascular mononuclear inflammation of microvessels, inflammatory separation, fragmentation and destruction of mural smooth muscle, and previous microscopic bleeding [hemosiderin]). Teased nerve fibers in LSRPN showed significantly increased frequencies of axonal degeneration, segmental demyelination, and empty nerve strands. The segmental demyelination appeared to be clustered on fibers with axonal dystrophy. The nerves with abnormal frequencies of demyelination were significantly associated with nerves showing multifocal fiber loss. We reached the following conclusions: 1) LSRPN is a serious condition with much morbidity that mirrors DLSRPN. 2) Ischemic injury from microvasculitis appears to be the cause of LSRPN. 3) Axonal degeneration and segmental demyelination appear to be linked and due to ischemia. 4) The pathologic alterations in LSRPN and DLSRPN are indistinguishable, raising the question whether these 2 conditions have a common underlying mechanism, and whether diabetes mellitus contributes to the pathology or is a risk factor in DLSRPN. 5) Both LSRPN and DLSRPN are potentially treatable conditions.

Key Words: Diabetic amyotrophy; Ischemic neuropathy; Lumbosacral plexopathy; Microvasculitis; Necrotizing vasculitis; Non-diabetic lumbosacral radiculoplexus neuropathy.

INTRODUCTION

Unilateral or asymmetric clinical involvement of the lumbar or lumbosacral plexus may be due to trauma, retroperitoneal abscess, hemorrhage or tumor (e.g. lymphoma), radiation injury, or an inflammatory-immune or other neuropathic process. Patients with diabetes mellitus (DM), especially of the type 2 variety, may develop a lumbosacral radiculoplexus neuropathy that causes considerable morbidity due to weakness, pain, paresthesia, and sensory loss. This lumbosacral neuropathy encompasses entities variously called the motor or paralytic variety of diabetic neuropathy (1, 2), diabetic myelopathy (3), diabetic amyotrophy (4, 5), femoral or femoral-sciatic neuropathy (6, 7), the Brun's Garland syndrome (8, 9), diabetic polyradiculopathy (10), diabetic mononeuritis multiplex (11, 12), proximal diabetic neuropathy (13, 14), diabetic lumbosacral plexopathy (15), and other names. We call it diabetic lumbosacral radiculoplexus neuropathy (DLSRPN) because we inferred from study of the distribution of clinical and electrophysiologic findings and pathologic study of distal cutaneous nerves that the pathologic alterations were multifocal, and to varying degrees affected lumbar and lumbosacral plexus, segmental

nerves, roots, and peripheral nerves (16). Previous investigators felt there were 2 subtypes of this disorder, and attributed the multifocal fiber degeneration and loss to ischemia and the segmental demyelination to metabolic derangement (14, 17, 18). Recently, some cases with ischemic injury have been attributed to vasculitis (19, 20). Unlike what others have concluded, we do not find different subtypes, and attribute both axonal degeneration and segmental demyelination to a single process—ischemic injury from microvasculitis (16).

Non-diabetic lumbosacral plexopathy or radiculoplexus neuropathy (LSRPN) was not designated a separate entity until 1981, when Sander and Sharp (21) and Evans et al (22) concurrently published the first clinical descriptions. Since then, rare case reports and small series have appeared (23–27), though much remains to be learned. Whether LSRPN and DLSRPN share similar clinical and pathologic characteristics is not known. There is also a dearth of information about the pathologic alteration of the lumbosacral plexus and contiguous nerves because the disorder is not fatal and biopsy of the plexus is generally not justified. Thus, inferences about the putative pathologic basis depend on clinical and electrophysiologic studies and study of biopsied regional or distal cutaneous nerves. Bradley et al (15) described the pathologic changes of peripheral nerves in 6 cases (3 with DM and 3 without DM) with elevated sedimentation rates. Evidence of ischemic injury and perivascular inflammatory cell cuffing was found.

Here we report the pathologic features of biopsied distal cutaneous nerves in LSRPN and compare them with

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both healthy and DLSRPN nerves. We characterize the nerve fiber and interstitial alterations to test whether there is similarity in the pathologic changes in the diabetic and non-diabetic varieties. Specifically, we test whether there is evidence of ischemic injury and whether microvasculitis is responsible, as it appears to be in DLSRPN. If microvasculitis is implicated, controlled trials of immune modulating therapy should be considered. We also question whether segmental demyelination occurs in LSRPN, whether it is linked to multifocal fiber degeneration, and whether both axonal degeneration and segmental demyelination result from ischemic injury.

MATERIALS AND METHODS

Patient Selection

We screened an inclusive list of medical conditions from Mayo Clinic patients (evaluated from January 1, 1983 to December 31, 1998), coded as proximal neuropathy, polyradiculopathy, polyradiculoneuropathy, lumbosacral plexopathy, lumbosacral radiculoplexus neuropathy (LSRPN), and femoral neuropathy. We reasoned that most cases of LSRPN should be included in such a broad survey. Next we identified those patients who had undergone a distal cutaneous nerve biopsy ($n = 265$) and reviewed their charts to identify cases with clinical evidence of LSRPN. The 47 cases selected had acute or subacute onset of pain, weakness or paresthesia of one or both lower extremities, and clinical or electrophysiologic characteristics not confined to the distribution of one segmental level or to one peripheral nerve. Excluded were cases with structural lesions that could explain the symptoms or the deficits, history or findings of DM, fasting blood sugars in the diabetic range by National Diabetes Data Group criteria, systemic vasculitis or connective tissue diseases, Lyme disease, sarcoidosis, history of radiation to the region, or other diagnoses that could explain the neurologic deficit. Patients were selected irrespective of whether the clinical involvement was localized to the buttock, thigh, or leg. Patients were not excluded if they were also found to have upper limb neurologic involvement, but the predominant impairment had to be of the lower extremities. All patients had to have electromyographic findings consistent with the diagnosis of LSRPN. The results of the nerve biopsies were not used in selecting patients.

Histologic Methods

The pathologic alterations of biopsied distal cutaneous nerves (45 sural, 1 superficial peroneal, and 1 saphenous) were compared with 14 age-matched control sural nerves from healthy paid volunteers, and with 33 nerves (31 sural and 2 superficial peroneal) from patients with DLSRPN, reported previously (16). Transverse and longitudinal paraffin sections were stained with hematoxylin and eosin (H&E), Masson's trichrome, Luxol fast blue-periodic acid Schiff, Congo red, methyl violet, van Gieson's (elastin stain), and Turnbull blue (for iron from previous bleeding). Immunohistochemistry preparations were obtained for leukocytes (leukocyte common antigen [LCA]); macrophages (KP-1), anti-human smooth muscle actin (Dako), and

endothelial cells (CD31). Approximately 60 to 100 paraffin sections were studied for each nerve (LSRPN, DLSRPN, and controls). Semithin epoxy sections were stained with methylene blue and p-phenylenediamine. Electron microscopy was performed on unrecognized profiles. Teased fibers from control and disease nerves were graded by previously defined pathological criteria (28). Sufficient strands of nerve tissue had been teased from every nerve so that at least 100 myelinated fibers or their breakdown products could be graded. In fixed sections, the pathologic alterations were graded semi-quantitatively for features of ischemic injury and vasculitis. To illustrate the approach, inflammatory cell collections were categorized as individual cells (<10 cells), small collections (≥ 10 –49 cells), moderate collections (≥ 50 –99 cells), and large collections (≥ 100 cells).

In 8 nerves with prominent inflammatory lesions (4 from LSRPN patients and 4 from DLSRPN patients), serial paraffin sections were cut at a distance of 3 to 4 mm to delineate the 3-dimensional features of the inflammatory vascular lesions, and to determine whether the inflammatory process was destructive of microvessel walls. At periodic intervals (every tenth section), we prepared consecutive slides for histologic details (H&E) and for reactivity to smooth muscle actin, leukocytes (LCA), and endothelial cells (CD31).

Analysis

The frequency of pathologic alterations was compared between disease groups (LSRPN, DLSRPN, and healthy subjects) using the Fisher exact test and the Wilcoxon rank sum test. Because multiple comparisons were made, for statistical significance we used a value of $p \leq 0.01$ and 2-tailed tests.

RESULTS

Clinical Features

The data on clinical, laboratory, and electrophysiologic features and natural history will be presented elsewhere. To summarize, our cohort had 24 men and 23 women, and their median age at biopsy was 67 years, range 28 to 87 years. The main symptoms were pain and weakness of the lower limbs, with lesser symptoms of atrophy, paresthesia, sensation loss, and autonomic symptoms. The disorder often had a definite date of onset, usually began unilaterally in the thigh or leg, and then spread to the other lower limb segment and later to the opposite side. The disease caused major morbidity and disability. In short, the clinical features of LSRPN are like those of our patients with DLSRPN except that the patients with DLSRPN had laboratory findings attributable to DM (hyperglycemia). In all cases of LSRPN, the fasting plasma glucose was in the euglycemic range (<126 mg/dl). Likewise, the glycated hemoglobin value for the 23 patients from whom it had been obtained was 5.6% median, 0.7% SD, and 4.6 to 7.4% range. The erythrocyte sedimentation rate of 44 LSRPN patients was 14.0 median, 14.6 SD, and 0 to 62 mm/h range.

TABLE 1
Pathologic Results of Distal Cutaneous Nerve Biopsies from LSRPN Compared with DLSRPN and Healthy Controls

Variable	LSRPN	DLSRPN		Healthy controls	
	<i>N</i>	<i>N</i>	<i>p</i>	<i>N</i>	<i>p</i>
Characteristics of Patients Biopsied					
<i>N</i>	47	33		14	
Sex, male	24	20	0.50	9	0.54
Median Age, y*	67.2	65.4	0.09	61.5	0.007
Paraffin and Epoxy Sections					
Endoneurial and Perineurial Abnormality					
Fiber degeneration or loss	37	25	0.79	0	<0.001
Multifocal fiber degeneration or loss	31	19	0.49	0	<0.001
Focal perineurial degeneration	7	6	0.76	0	0.19
Focal perineurial thickening	27	24	0.24	2	0.006
Injury neuroma†	16	12	1.00	0	0.01
Interstitial Abnormality					
Perivascular inflammation	47	33	0.23	2	<0.001
Individual cells (<10 cells)	5	0		2	
Small collections (11–50 cells)	29	21		0	
Moderate collections (51–100 cells)	6	7		0	
Large collections (>100 cells)	7	5		0	
Inflammation of vessel wall	24	15	0.66	0	<0.001
Diagnostic of microvasculitis	7	2	0.29	0	0.19
Hemosiderin in macrophages	25	19	0.65	0	<0.001
Neovascularization	21	21	0.11	1	0.01

LSRPN = lumbosacral radiculoplexus neuropathy; DLSRPN = diabetic lumbosacral radiculoplexus neuropathy.

* Wilcoxon rank sum test used for continuous data. All other significance calculated using Fisher's exact test for dichotomous data.

† Injury neuroma = abortive regenerative activity outside of the original perineurium.

Nerve Fiber Pathology

Most (37 of 47) nerves of patients with LSRPN showed an unequivocal decrease in density of myelinated nerve fibers when compared with controls. In 31 of 47 cases this decrease was focal or multifocal and unequivocal (Table 1; Fig. 1). As compared with DLSRPN, the number of LSRPN nerves with fiber decrease was not significantly different (Table 1). In regions of focal and multifocal fiber loss, fibers were often undergoing active axonal degeneration. It appeared that all diameter classes of fibers were decreased in these regions of fiber loss.

Abortive regeneration of nerve fibers within or beyond the original perineurium forming regenerating microfasciculi (injury neuroma, Fig. 1) were recognized in 16 of 47 LSRPN nerves, significantly more frequently than in healthy nerves ($p = 0.01$), but not significantly more frequently than in DLSRPN nerves. These injury neuromas were anatomically closely associated with damaged parent fascicles either showing focal fiber loss or fiber regeneration. Focal or multifocal regions with only small fibers and frequent regenerating clusters were encountered—presumably regions of fiber regeneration (Fig. 1).

Analysis of the graded conditions of teased fibers confirmed the impressions that fiber loss and axonal degeneration were the main fiber abnormalities. As compared with control nerves, there was an increased frequency of

nerve strands without myelinated fibers or their breakdown products (empty strands), fibers undergoing axonal degeneration, and fibers with segmental demyelination (Table 2).

These pathologic alterations of teased fibers were significantly more frequent in LSRPN than in controls, but not significantly different from DLSRPN nerves except that empty nerve strands were significantly more frequent in DLSRPN nerves than in LSRPN nerves (Table 2). Empty nerve strands and actively degenerating fibers were much more frequent than changes of segmental demyelination. The axonal degeneration and segmental demyelination appeared to be linked. Often, areas of demyelination and remyelination appeared to be clustered on individual teased nerve fibers, which suggests that the demyelination is secondary to underlying axonal pathology. Assessing changes along the lengths of individual teased fibers, we encountered fibers with proximal regions of paranodal demyelination and remyelination, and distal regions of axonal degeneration (Fig. 2). All 12 LSRPN nerves with an increased rate of segmental demyelination ($\geq 5\%$) were found to have multifocal fiber loss ($p = 0.01$). This association between focal fiber loss and segmental demyelination was also seen in the DLSRPN nerves (12 nerves with increased demyelination, 11 with multifocal fiber loss [$p = 0.01$]).

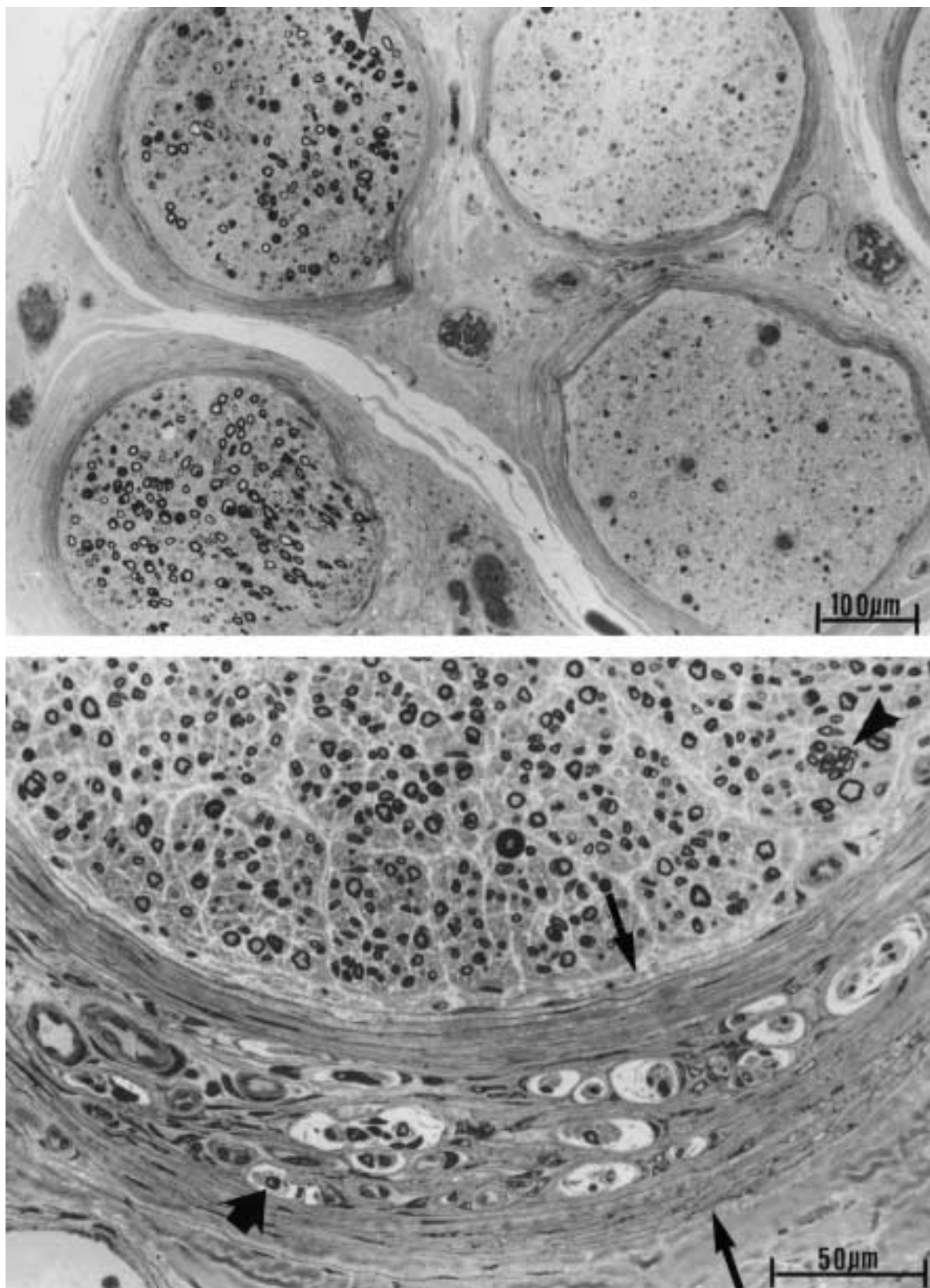


Fig. 1. Transverse semithin epoxy sections of sural nerve from patients with non-diabetic lumbosacral radiculoplexus neuropathy stained with methylene blue showing multifocal fiber degeneration and loss (upper frame) and reactive repair injury neuroma (lower frame), which we attribute to ischemic injury and repair. The left upper fascicle of the upper frame shows an admixture of normal and degenerating (arrowhead) fibers. The left lower fascicle shows an almost normal density of fibers and

TABLE 2
Teased Fiber Results from LSRPN Compared with DLSRPN and Healthy Controls

	LSRPN		DLSRPN			Healthy controls		
	Median	Range	Median	Range	<i>p</i> *	Median	Range	<i>p</i> *
Normal: A, B (%)†	60.7	0–88	45.7	0–92	0.25	85.7	72–95	<0.001
Demyelination: C, D (%)	2.6	0–13	2.6	0–25	0.82	0.0	0–2	<0.001
Remyelination: F, G (%)	14.6	0–38	11.9	0–33	0.32	13.7	5–28	0.67
Axonal: E, H (%)	17.2	0–100	30.9	0–100	0.17	0.0	0–3	<0.001
Classifiable (no.)	83.0	9–145	63.0	7–127	0.04	99.5	86–118	0.001
Empty (no.)	25.5	1–89	42.5	5–93	0.007	6.0	0–19	<0.001

LSRPN = lumbosacral radiculoplexus neuropathy; DLSRPN = diabetic lumbosacral radiculoplexus neuropathy.

* Wilcoxon rank sum test.

† Teased fiber types: A = normal, B = myelin wrinkling, C = demyelination, D = demyelination and remyelination, E = axonal degeneration, F = remyelination, G = myelin reduplication, H = regeneration after axonal degeneration, Empty = unclassifiable strands without myelinated fibers.

In a few nerves we studied the focal regions of fiber loss or degeneration with serial semithin sections by light microscopy and with skip-thin sections by electron microscopy proceeding from proximal to distal. Some fibers showed dark swollen axons (due to accumulation of organelles) that contained light cores (strands of preserved axoplasm). We traced the axons of several of these fibers from proximal to distal levels (Fig. 3). Proximally, the dark axons were markedly enlarged and packed with mitochondria (often degenerating), vesicles, dense bodies, and light cores. The large dark axons usually had become demyelinated, whereas the intermediate dark axons often had only a few lamellae of myelin. In more distal sections of these fibers, the axons either became transected and disappeared, or were attenuated and had no myelin or only thin myelin (probably remyelination) remaining (Fig. 3).

Vessel Pathology (Routine Sections)

Vascular and perivascular inflammation was encountered in all LSRPN nerves (Table 1). This occurred significantly more frequently than in control nerves, but not significantly more frequently than in DLSRPN nerves (Table 1). Vessels affected were in the epineurium, endoneurium, and perineurium, with the majority of affected vessels in the epineurium. Microvessels were typically affected much more frequently than larger vessels. The microvessels affected generally did not have internal elastic laminae but had a thin smooth muscle tunica media as demonstrated in histochemical reactions to smooth

muscle actin. Typically, the inflammatory infiltrates consisted of small collections of mononuclear lymphocytes in transverse sections, but not uncommonly the inflammatory infiltrates were larger (Table 1). Based on routine preparations, inflammatory cells were found within the vessel wall in 24 of 47 LSRPN nerves, in 15 of 33 DLSRPN nerves, and none in healthy control nerves. Features diagnostic of microvasculitis (destruction of vessel wall elements associated with vascular and perivascular inflammatory cells) were found in 7 LSRPN nerves, 2 DLSRPN nerves, and none in healthy control nerves. Fibrinoid degeneration of the vessel walls was only occasionally seen in vessel walls of both the LSRPN and DLSRPN groups. Based on immunohistochemistry, the perivascular and vascular mononuclear cells reacted to LCA in almost all (44 of 47) LSRPN nerves and to a lesser extent to the macrophage marker (KP-1). The involved vessels probably were venules, small arterioles, and capillaries; and the microvasculitis encountered was similar in LSRPN and DLSRPN.

Vessel Pathology (Serial Skip Sections)

From 8 nerves (4 from patients with LSRPN and 4 from patients with DLSRPN), serial sections were performed over a length of approximately 3 mm to follow the 12 LSRPN microvessels and the 7 DLSRPN microvessels that showed vascular inflammation. We saw unequivocal evidence that LCA positive mononuclear cells separated and surrounded smooth muscle cells of the microvessel

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an occasional degenerating fiber. In contrast, the right lower and upper fascicles are essentially devoid of intact fibers and only rare degenerating profiles remain. In the lower frame, we show a transverse section of part of a fascicle showing nerve regeneration. There is a crescent of microfasciculi (injury neuroma, short thick arrow) between the leaflets of thickened perineurium (edges demonstrated by long, thin arrows). The arrowhead identifies a cluster of regenerated fibers. Most of the fibers in the large fascicle are small myelinated fibers and are probably regenerating.

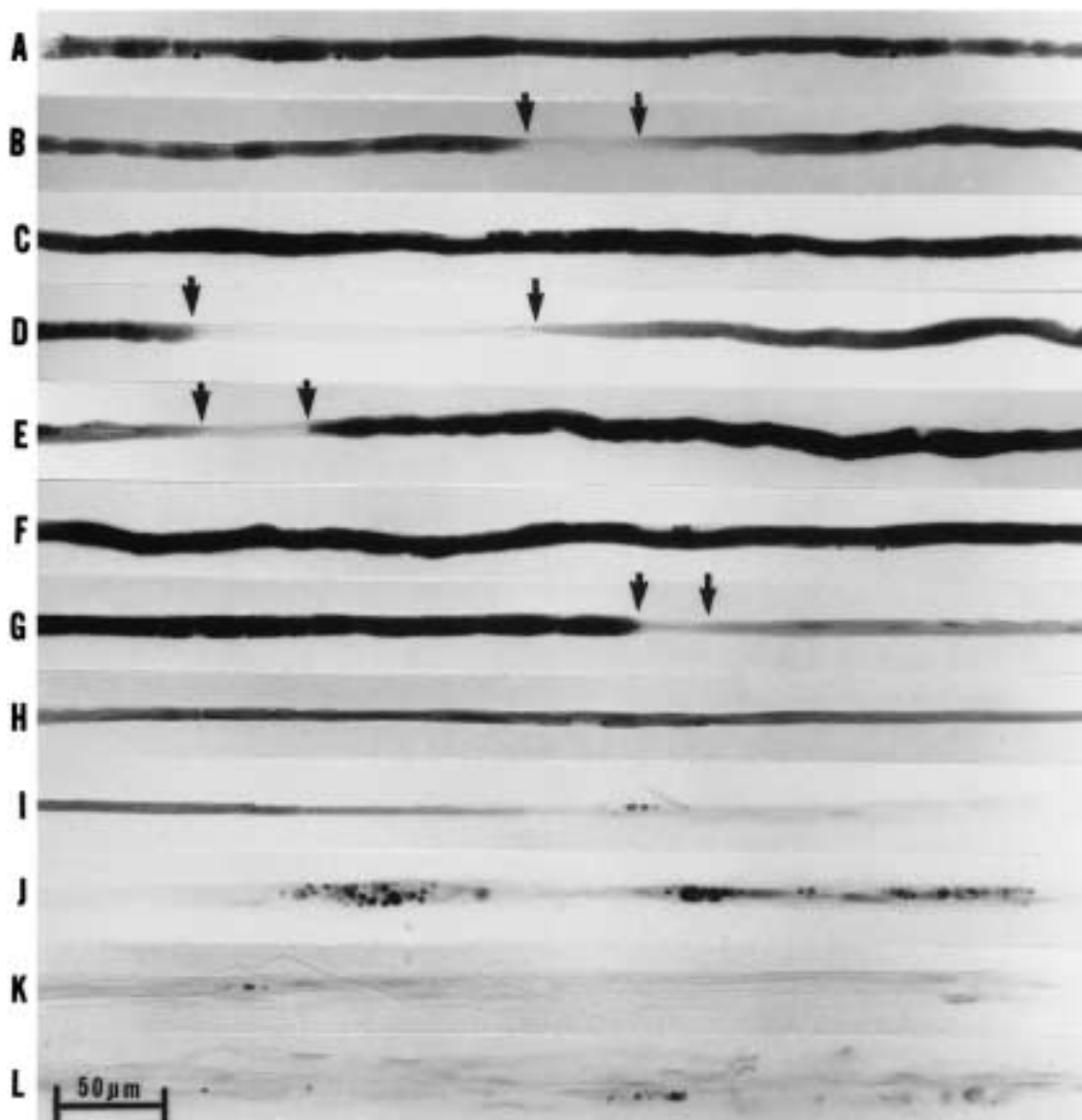
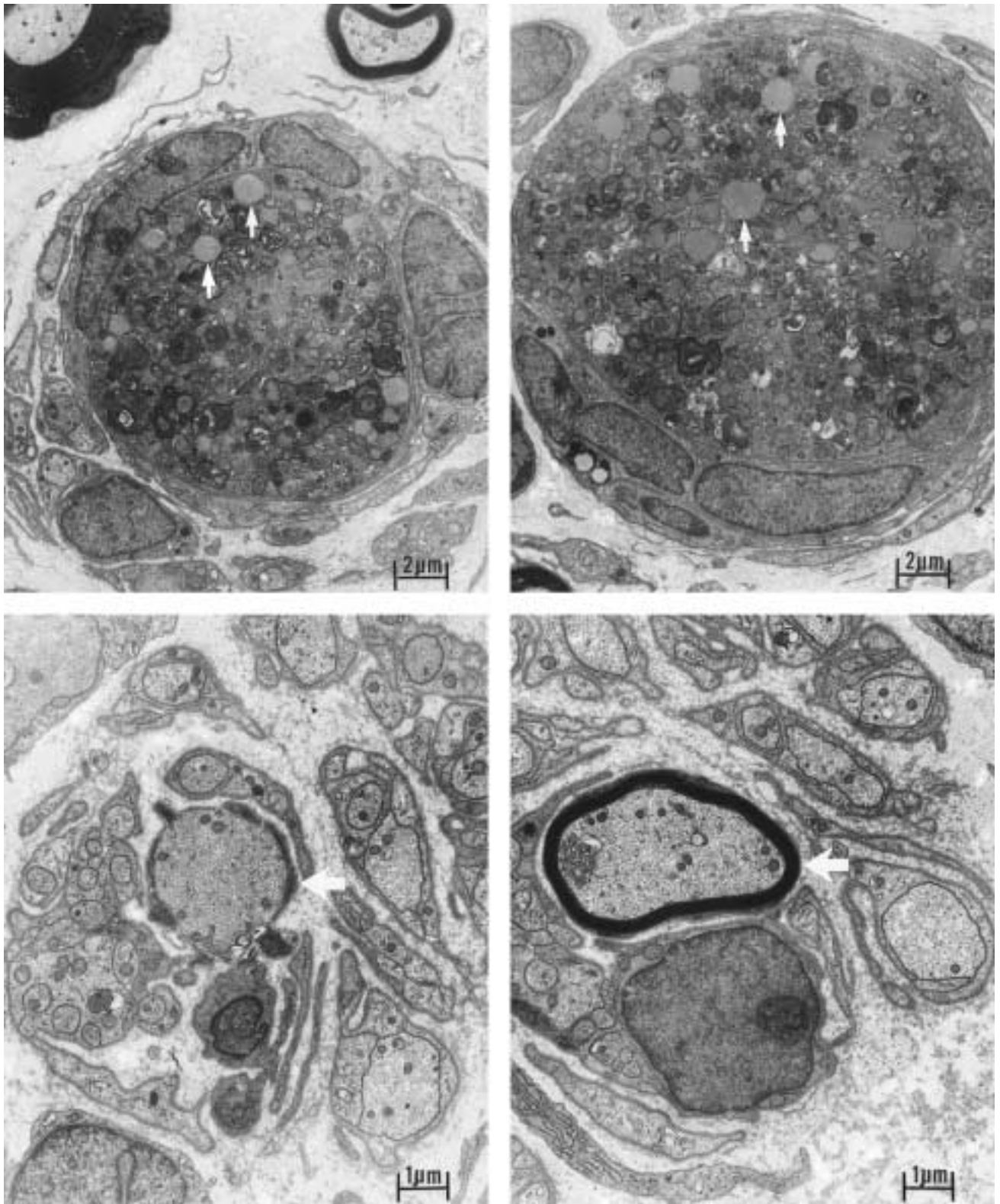


Fig. 2. Consecutive portions (A–L), teased from proximal to distal, along the length of a single teased fiber from a patient with non-diabetic lumbosacral radiculoplexus neuropathy showing multiple regions of proximal demyelination (between arrows in B, D, E, and G), a region of remyelination (the myelin thickness is 50% or less of the normal myelin thickness [G–I]), and distal axonal degeneration (I–L). Finding proximal demyelination and distal axonal degeneration is strong evidence that the processes of demyelination and axonal degeneration are linked and that the demyelination is probably secondary to an axonal dystrophy.

walls (Fig. 4). In some places the smooth muscle was separated, fragmented, and diminished in amount (in comparison to the amount of smooth muscle proximal or distal to the inflammatory lesion) (Fig. 5). These observations from serial sections indicate that microvasculitis is more common than we had recognized from routine sections.

These studies also showed that the inflammatory lesions were localized to only a short segment of the vessel. In those microvessels in which we could trace the entire inflammatory lesion, the focal inflammation in LSRPN nerves had a median length of 336 microns (range 256 to 496 microns, $n = 10$), whereas in DLSRPN nerves the

Fig. 3. Serial skip electron micrographs along the length of 1 nerve fiber from a non-diabetic lumbosacral radiculoplexus neuropathy nerve that are pictured from proximal (upper left) to distal (lower right) levels and show injury that we attribute to ischemia. The left and right upper panels show 2 levels of a markedly enlarged axon, with accumulated organelles and light



cores (relatively normal axoplasm, small white arrows). Notice that the axon has become demyelinated. The same axon (white arrow) taken from a more distal level (left lower) is much smaller in size (probably attenuated) and still is without myelin. At an even more distal level (right lower), the axon (white arrow) is somewhat larger and now is myelinated (probably remyelinated since the myelin is thin). In this case, the axon has not been transected. We suggest that axonal enlargement (presumably from interruption due to interference of rapid axonal transport due to ischemia) or attenuation may lead to demyelination. The fate of the axon distal to organelle accumulation may be attenuation and restoration or attenuation and degeneration.

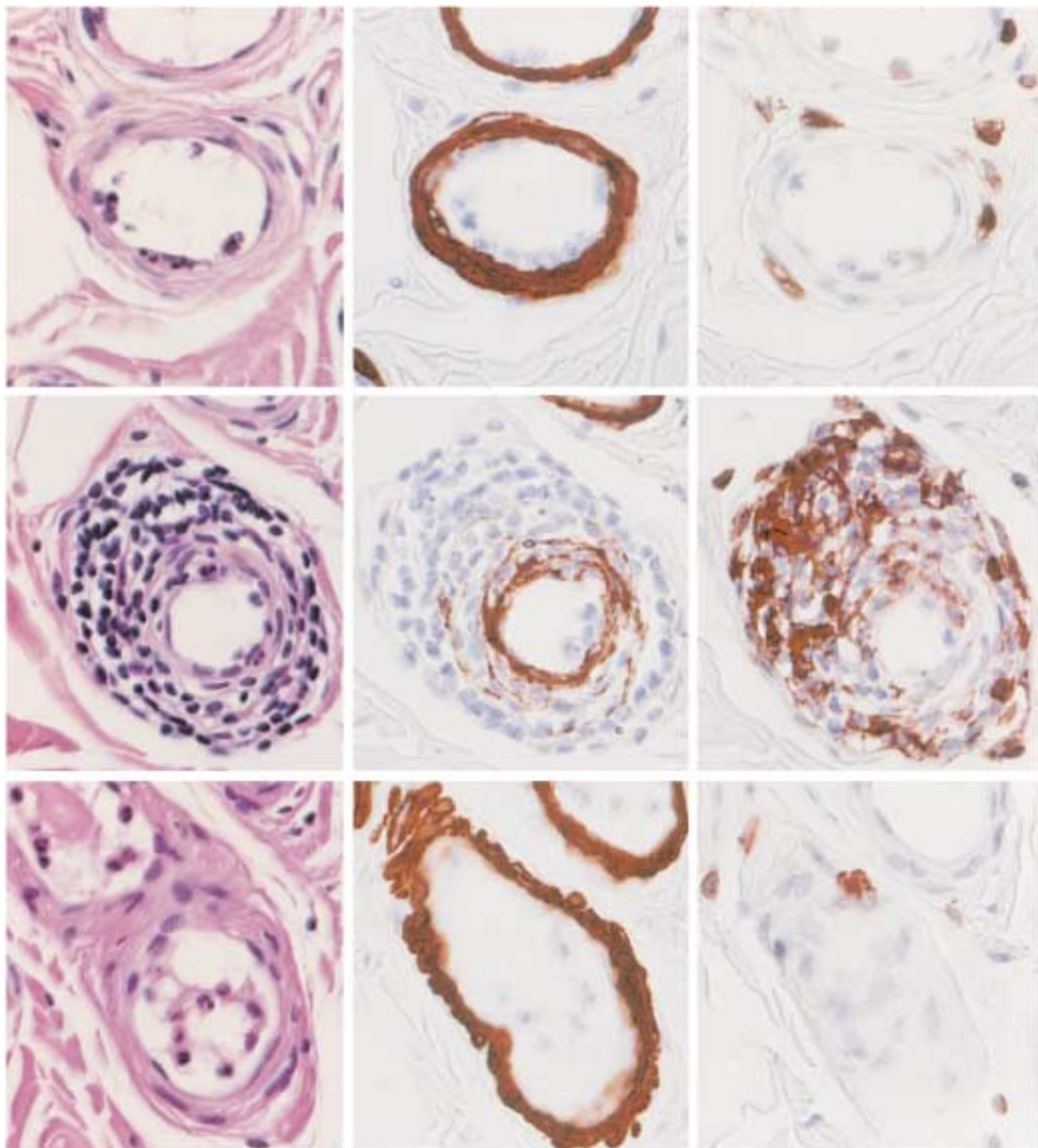


Fig. 4. Serial skip paraffin sections of a microvessel above (upper panel), at (middle panel), and below (lower panel) a region of microvasculitis in the sural nerve of a patient with non-diabetic lumbosacral radiculoplexus neuropathy. The sections on the left column are stained with H&E, the sections in the middle column are reacted to anti-human smooth muscle actin (Dako), and the sections on the right column are reacted to leukocytes (LCA). The smooth muscle of the tunica media in the region of microvasculitis (middle panel) is separated by mononuclear cells, fragmented, and decreased in amount. The changes are those of a focal microvasculitis.

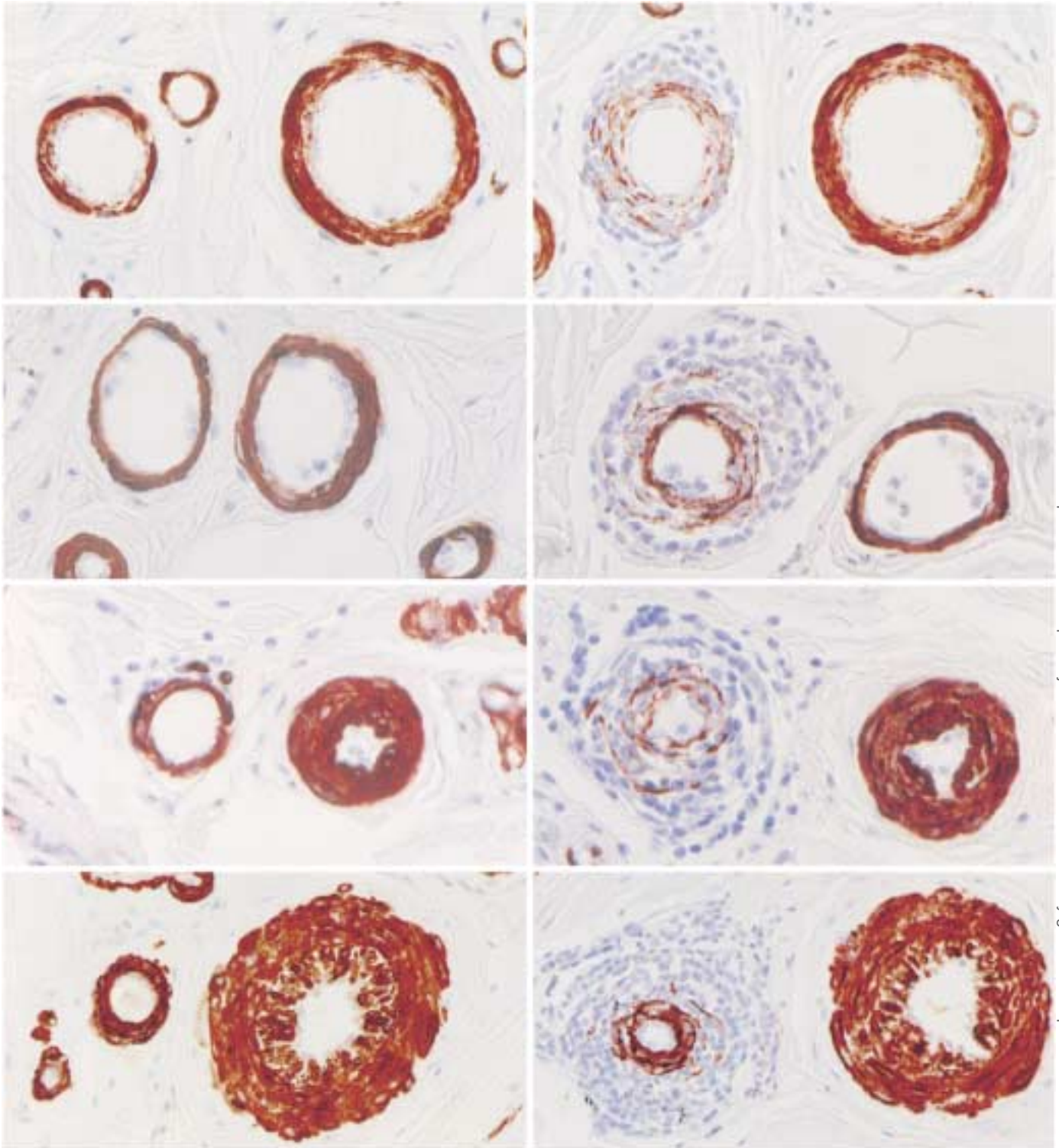


Fig. 5. Paraffin sections of sural nerve from patients with non-diabetic lumbosacral radiculoplexus (LSRPN) (upper 3 panels) and diabetic lumbosacral radiculoplexus neuropathy (DLSRPN) (lower panel) reacted for anti-human smooth muscle actin (Dako) and counter-stained with H&E showing microvasculitis of 4 nerve vessels (right column) and an unaffected level of the same vessel proximal or distal to the lesion (left column). Compared with the relatively unaffected regions of the same microvessels (left), in the regions of microvasculitis (right) the smooth muscle is separated by mononuclear cells, fragmented, displaced outward, and decreased in amount. We interpret these changes to be typical of microvasculitis. They were encountered most commonly in the epineurium but were also found in the endoneurium and perineurium. Note the similarity of the microvasculitis in the LSRPN nerves (top 3) and the DLSRPN nerve (bottom). Note also the adjacent unaffected vessels are often larger in size.

median length was 376 microns (range 280 to 1256 microns, $n = 6$). The endothelial cells did not appear to be affected (CD31). All 19 vessels with inflammatory lesions were microvessels and they were often located adjacent to unaffected, thicker walled vessels (Fig. 5).

Other Interstitial Changes

Three other interstitial pathologic changes occurred significantly more frequently in LSRPN nerves than in controls but not more frequently than in DLSRPN nerves. Focal degeneration of the perineurium was observed in 7 nerves, whereas perineurial thickening or scarring occurred in 27 nerves (Fig. 6; Table 1). Epineurial neovascularization was noted in 21 nerves (Fig. 6). Evidence of previous bleeding (as manifested by the Turnbull blue stain) was found in 25 nerves. The hemosiderin was frequently ($n = 18$) found in the sub-perineurium, often adjacent to microvessels and was distributed multifocally (Fig. 6). At some sites of hemosiderin deposition, we could not identify a microvessel that was the putative site of the previous bleeding. These 3 changes were often contiguous to regions of focal fiber loss, degeneration, and injury neuroma. We did not recognize pathologic derangement other than microvasculitis, which would explain new vessel formation or the pathologic alterations of fibers and the perineurium described here.

DISCUSSION

The different names (see Introduction) for the condition we call DLSRPN probably reflect different assumptions about clinical characteristics, nerves and levels of nerves affected, fiber classes involved, and pathological mechanisms. Historically, some of the cases were attributed to ischemia (rapid onset, asymmetric findings, and axonal degeneration), whereas other cases were attributed to metabolic derangement (slow onset, symmetric findings, and demyelination) (14, 17, 18). Thus, the only postmortem case (11, 12) had a rapid, asymmetric course with evidence of ischemic injury and an occluded vessel in the obturator nerve. In contrast, other cases (8, 17, 29, 30) had bilateral, symmetric, and insidious development with predominantly motor findings and weight loss and their conditions were attributed to metabolic derangement. Still others found evidence for a variable admixture of both ischemic (axonal) and metabolic (demyelinating) subtypes (19, 31). Therefore, it was unclear whether these subtypes represented 2 different disorders or were the extremes of a continuum (14). The viewpoint of the role of inflammation and necrotizing vasculitis in DLSRPN has evolved. Early authors (11, 12) interpreted the inflammation seen as reactive, but later authors tended to attribute some cases to vasculitis and other cases to metabolic derangement (19, 20). Still others have reported large inflammatory infiltrates in both DLSRPN nerves and diabetic polyneuropathy nerves (32).

We recently studied the pathologic alterations of cutaneous nerves in 33 prospectively seen patients with DLSRPN (16) and concluded that ischemic injury from microvasculitis probably was the main underlying pathologic mechanism for all cases. When compared with diabetic polyneuropathy, there was a much greater degree of inflammation in DLSRPN nerves. We also found that the demyelination seen was in areas of multifocal fiber degeneration, an indication that the demyelination was linked to axonal degeneration in regions of ischemic injury.

In contrast to the diabetic variety (DLSRPN), there is little information about the clinical features, natural history, outcome, and pathologic derangement in the non-diabetic variety (LSRPN). LSRPN has only recently been identified as a syndrome (21, 22) and all of the published series are small (23–27). As we will describe elsewhere, the clinical, laboratory, and electrophysiological features of DLSRPN and LSRPN appear to be similar. We find only 1 pathologic report (15) (describing 3 patients with LSRPN and 3 with DLSRPN) and this study included only patients whose sedimentation rates were elevated and whose biopsies did not show frank vasculitis. Nevertheless, ischemic injury was surmised from the multifocal fiber loss and an immune basis was inferred because of perivascular inflammatory cell cuffing (15). Also, therapeutic trials with immune modulating therapy (mainly IVIg) are not definitive since reported series are small and not controlled (15, 25, 27).

In the present study of 47 biopsied cutaneous nerves from patients with LSRPN, we find strong evidence that the primary pathologic process is ischemic injury from microvasculitis, and that this process explains both the axonal degeneration and the segmental demyelination observed. The evidence for ischemic injury includes the following: focal or multifocal fiber loss or degeneration, focal necrosis and scarring of the perineurium, neovascularization, abortive fiber regeneration (injury neuroma), myelinated nerve fiber alterations of a kind and in a distribution typically found in ischemia injury, and contiguous microvasculitis and previous bleeding (hemosiderin). These changes were not seen in healthy control nerves. The pathologic alterations found in LSRPN closely mirror alterations seen in human necrotizing vasculitis (33) and in DLSRPN (16).

In experimental models of ischemia, we and others have observed similar pathologic alterations, including focal or multifocal fiber degeneration or loss (34), injury neuroma with microfasciculation (35), perineurial degeneration and thickening (36), dark axons with light cores (34, 37), and neovascularization. In these ischemic models, the proximal to distal level of nerve affected and the 3-dimensional pathologic alterations depend on the number and the anatomical location of the vessels occluded.

The development of the pathologic lesions is also dependent on the degree and duration of ischemia and at what time the tissue was taken following the ischemic event. It takes many hours to a few days for the degenerative histologic events to develop and a much longer time for the reparative events to develop. In our 3-dimensional pathologic nerve studies of systemic necrotizing vasculitis in humans (33), the pattern was not as stereotypic as in experimental models because the vessel pathology was distributed in time and space with different ischemic lesions presumably overlapping.

Similarly, in LSRPN, we are probably dealing with vascular lesions at various stages of evolution, perhaps overlapping regions of ischemic injury, and the co-existence of degenerative and reparative events. Nevertheless, we think that ischemia is the cause of the pathologic alterations. First, ischemia explains the focal and multifocal loss of fibers adjacent to areas of perineurial degeneration and scarring. Second, regions of putative ischemic injury showed pathologic changes of myelinated fibers typically found in ischemic lesions; for example, focally enlarged, dark axons filled with accumulated organelles and light cores (remaining islands of normal axoplasm) and associated demyelination. Third, regenerative changes (injury neuroma, regenerating fibers and clusters, and neovascularization) typically found as reparative events following ischemic lesions, were seen. Fourth, we found focal inflammatory lesions causing separation and destruction of the smooth muscle of microvessel walls and contiguous evidence of bleeding in the region. Finally, we did not find evidence of a pathologic process other than microvasculitis to explain the observed pathologic lesions. Although local trauma could cause some of these pathologic alterations, one would not expect trauma to occur significantly more frequently in the LSRPN group than in the control group. Korthals et al (38) suggest that the enlarged dark axons with accumulated organelles are explained by interruption of fast axonal transport. It is known that anoxia can interrupt fast axonal transport and that such interruption can cause accumulation of organelles (37, 39–41).

Why was microvasculitis not demonstrated in all nerves and how does microvasculitis cause ischemia in LSRPN? In fact, mononuclear vascular or perivascular inflammation was demonstrated in almost all nerves. When we performed serial sections of such inflammatory lesions, we could demonstrate diagnostic changes of microvasculitis in most cases. The lesions typically included cellular disruption and degeneration of the smooth muscle layer of small blood vessels. The vessels involved were smaller than the arterioles typically involved in necrotizing vasculitis of polyarteritis nodosa, rheumatoid arteritis, Wegener's granulomatosis, Churg-Strauss syndrome, or hypersensitivity angiitis. These vessels generally were without internal elastic laminae and were

probably small venules or very small arterioles. Because of the small size of the affected vessels, fibrinoid degeneration of vessel elements was usually not observed. Like other vasculitides, the lesions were focal along the length of vessels. The findings of microvasculitis in LSRPN and DLSRPN were essentially alike. The mechanism by which these lesions cause ischemia has not yet been resolved. In systemic necrotizing vasculitis, closure of arterioles occurred at multiple sites and appeared to explain the ischemic results demonstrated (33). In the microvasculitis of DLSRPN or LSRPN, we encountered occasional occluded and re-canalized vessels; usually the walls of the affected microvessel were damaged but the lumen did not appear to be occluded. The distribution of hemosiderin (from previous bleeding) was typically found near sites of microvasculitis. It may be that vessel closure, hemorrhage, spasm, or frank dissolution of vessels are involved in ischemic injury. Further study of these issues is needed.

Because of the small size of the affected vessels, a common finding is microvasculitis without evident fibrinoid degeneration. The injured microvessel may have disappeared, leaving only hemosiderin deposition with or without inflammation. The lack of prominent vessel wall necrosis is characteristic of microvasculitis of other tissues; for example, kidney, lung, and skin (42). Finding hemosiderin in or near the perineurium may suggest that the bleeding occurred in the endoneurial space and that macrophages are clearing away the debris through the perineurium to the epineurium (28). Alternatively, the microvessels in the perineurium may be selectively vulnerable, though we did not find evidence for this possibility.

What is the explanation for the segmental demyelination seen in LSRPN? Several possible mechanisms might be considered—metabolic demyelination, macrophage-mediated demyelination, alteration of the blood nerve barrier exposing the nerve fibers to plasma constituents (as has been reported in animal models of perineurial injuries) (43), or ischemic injury. Our previous (16) and present studies suggest that ischemic injury cause both axonal degeneration and segmental demyelination in LSRPN and DLSRPN. First, there does not appear to be a clinical separation into 2 disorders (one metabolic-demyelinating and the other ischemic-axonal). Second, the focal fiber degeneration and segmental demyelination were typically found together in the same patients, often in the same regions of nerve injury and, in some cases, even on the same nerve fibers (Fig. 2). Third, finding demyelination at proximal regions of fibers with axonal enlargement from accumulated organelles and transection of the axon distally suggests that the process of demyelination and axonal degeneration are linked and are due to ischemia. Fourth, the pattern of demyelination observed is not that usually reported in primary demyelinating disorders. In both DLSRPN and LSRPN,

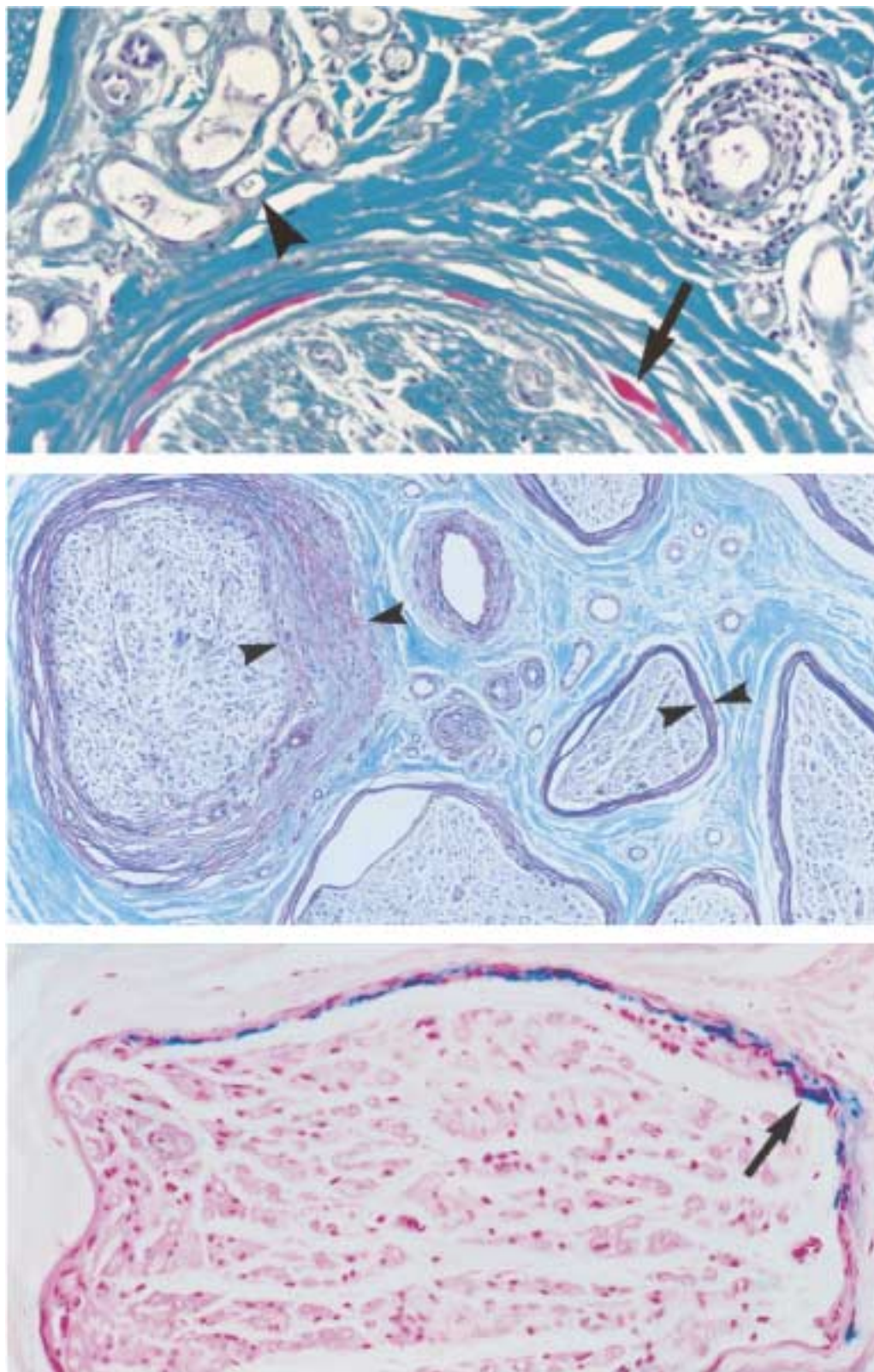


Fig. 6. Transverse paraffin sections of sural nerves showing typical changes seen in diabetic and non-diabetic lumbosacral radiculoplexus neuropathies as described in text. The upper frame (Masson's trichrome stain) shows inflammation in the wall of an epineurial microvessel (right upper), probable fibrinoid degeneration of the perineurium (long arrow), and a region of neo-vascularization (arrowhead). The middle frame (Luxol fast blue-periodic acid Schiff stain) shows several fascicles surrounded by normal thickness perineurium (right middle, between 2 arrowheads) and 1 fascicle with extremely thick perineurium (left middle, arrowhead).

demyelination and remyelination tended to be clustered on certain axons. This clustered pattern of demyelination is typical of secondary demyelination to axonal dystrophy, as reported in some human disease (44, 45), and in experimental models (46). Fifth, as outlined above, there is evidence of widespread ischemic damage and of microvasculitis in this condition. We have observed very similar fiber changes and linkage of axonal degeneration and segmental demyelination in experimental models of ischemia (37).

The association of focal fiber loss and demyelination is best explained by the observation that demyelination due to ischemic injury occurs at the margins of ischemic cores where the nerve fibers are damaged but may survive. Nerves that contain multifocal fiber loss have areas with fiber loss and other areas with preserved fibers and consequently contain the border zone between these 2 regions (the margins of the ischemic core). It is within this marginal region that the demyelination would be expected to occur (37).

We show here that the pathologic alterations of biopsied nerves of the 2 varieties of lumbosacral plexopathies (LSRPN or DLSRPN) are similar. The only statistically significant difference we found was a higher frequency of empty nerve strands in DLSRPN. This difference could be due to sampling a group of cases with more severe DLSRPN, or more likely, some of the cases with DLSRPN also have a co-existing diabetic polyneuropathy. We suspect that DLSRPN and LSRPN are essentially the same condition, with DLSRPN probably the more prevalent disorder. According to this viewpoint, diabetes mellitus may be a risk factor for DLSRPN but hyperglycemia may not be a primary cause. The prominence of inflammation and the findings of microvasculitis provide a rationale for conducting controlled trials of immune modulating therapy in both DLSRPN and LSRPN.

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between 2 arrowheads). We attribute the latter to scarring and repair after ischemic injury (note all fascicles are devoid of myelinated fibers). The lower frame (Turnbull blue stain) shows accumulation of hemosiderin (iron stains bright blue, arrow) deposited along the inner aspects of the perineurium. All of these pathologic features are frequently seen together and are best explained by ischemic injury.

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