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Article abstract—We describe five patients with a chronic asymmetric sensorimotor neuropathy most pronounced in the upper extremities with focal involvement of individual nerves. Diagnosis was established by electrophysiologic evidence of persistent multifocal conduction block. Sural nerve biopsy in three patients showed primarily demyelinating-remyelinating changes with varying degrees of fiber loss. Two patients had acute optic neuritis, indicating that the disorder was not always restricted to the peripheral nervous system. Two patients treated with corticosteroids improved, whereas three untreated patients had static deficits or steady progression of symptoms. Chronic multifocal demyelinating neuropathy with persistent conduction block seems to be a variant of chronic acquired demyelinating polyneuropathy and may be immunologically mediated.

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Chronic acquired demyelinating neuropathy, also called chronic inflammatory polyradiculoneuropathy and chronic relapsing polyneuritis, is characterized by delineable clinical, electrophysiologic, and pathologic features: symmetric sensorimotor disorder of arms and legs, loss of tendon reflexes, variable course, elevated CSF protein content, widespread slowing of nerve conduction velocities, and morphologic evidence of primary demyelination.^{1,2} We encountered five patients with a pattern of chronic demyelinating neuropathy that differed because of a clinical picture of mononeuritis multiplex and electrophysiologic evidence of multifocal persistent conduction block.

Methods. Of 40 patients with chronic acquired demyelinating neuropathy identified since 1975, five had multifocal conduction block on electrodiagnostic testing (figures 1 through 3). None of the five had family history of neuropathy, toxic exposure, or known systemic disease. Laboratory evaluation included hematocrit, white blood cell count and differential, sedimentation rate, serum protein electrophoresis, antinuclear antibody titer, rheumatoid factor, lupus erythematosus preparation, serum electrolytes, plasma glucose and urea

nitrogen, serum and spinal fluid Venereal Disease Research Laboratory (VDRL), urinalysis, and urine samples for porphyrin precursors and heavy metals. These tests were normal unless otherwise stated.

Electrodiagnostic studies were performed, at least once for each patient at the Hospital of the University of Pennsylvania (HUP). In patients 1 and 2, our studies could be compared with prior examinations done elsewhere. Studies at HUP were done with standard electromyographic equipment (TECA-4). Subcutaneous uninsulated needle electrodes (Grass E2) were used to record both motor and sensory responses. Median and ulnar sensory potentials were recorded orthodromically at the wrist, whereas radial and sural sensory potentials were recorded antidromically at wrist and ankle, respectively. Computer averaging (TECA DAV 6) was used to differentiate low-amplitude sensory responses. Motor nerve conduction studies were performed by conventional methods, using percutaneous nerve trunk stimulation at several levels. Conduction block was suspected when there was a 50% reduction in the amplitude of the evoked response elicited from proximal as compared with distal sites of stimulation. By measuring and comparing both the amplitudes and the areas of the

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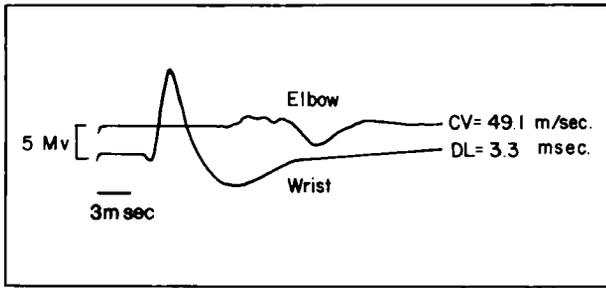


Figure 1. Left median motor conduction study of patient 3, demonstrating partial conduction block. Area beneath the negative (above the baseline) potential representing the response on proximal stimulation is 40% of the area of the response on distal stimulation.

compound action potentials, we ensured that these differences in amplitude represented an absolute conduction block and were not simply due to increased dispersion of action potentials. In all instances of conduction block, we required that the total area beneath the negative spike of the evoked response on proximal stimulation be less than 60% of the area obtained on distal stimulation (figure 1). In instances of block in the ulnar nerve, care was taken to exclude a Martin-Gruber anastomosis.

Case reports. Pertinent clinical features are provided in table 1. The brief case histories following point to the multifocal nature of the clinical picture.

Patient 1. A 23-year-old woman presented with pain and numbness in bilateral ulnar distributions. Over the next 3 years, sensorimotor symptoms evolved in the right peroneal nerve territory and bilaterally in median and radial nerve distributions. Examinations 16 and 24 months after onset revealed atrophy and severe weakness of intrinsic hand muscles and moderate weakness in flexors and extensors of the wrists and fingers and in dorsiflexors of the right foot and toes. Vibration and position sense were impaired in the arms below the shoulders but were normal in the legs.

Patient 2. A 67-year-old woman developed pain and numbness in the right median distribution 20 years ago. A progressive asymmetric neuropathy gradually appeared, involving bilateral ulnar, median, and peroneal nerves with relative sparing of radial and posterior tibial nerves. Examination disclosed bilateral paresthesia deficit distal to midcalves and midforearms, sensory ataxia, and weakness, most evident in forearms and hands.

Patient 3. A 28-year-old man with a history of alcohol, heroin, and amphetamine abuse developed pain and numbness in the right ulnar distribution. The next month, he presented with bilateral ulnar neuropathies without other involvement. Over the next 8 months, asymmetric weakness and numbness affected all four extremities.

He was treated with Prednisone, 60 mg every other day. Within 3 weeks his neuropathy had begun to improve. He stopped taking Prednisone after 6 weeks, despite persistent numbness and weakness in his hands.

Six months later, he developed subacute bilateral visual loss, large central scotomas, optic atrophy, and prolonged visual evoked responses. At that time, he had a normal motor and sensory exam of his legs, but intrinsic hand muscles and finger and wrist flexors were weak. Prednisone therapy was renewed, and visual acuity partially improved.

Patient 4. A 50-year-old woman experienced pain, weakness, and numbness in the right ulnar distribution. Over the next 6 months, symptoms involved the left ulnar and left peroneal and bilateral radial distributions. Alternate-day Prednisone (60 mg) therapy was associated with dramatic improvement in pain, numbness, and weakness, but two attempts to reduce the dose below 30 mg were associated with exacerbation of symptoms.

Patient 5. First symptoms in a 55-year-old woman were patchy numbness and pain of the right hand. Over the next 4 months, painful dysesthesias appeared consecutively in her right foot, left foot, and left hand. Left visual acuity deficit, afferent pupillary defect, left central scotoma, and optic atrophy evolved subacutely. At that time there was weakness and reduced sensitivity to pin and temperature in the right ulnar distribution as well as reduced position and vibratory sensation in all fingers and toes. She refused corticosteroid therapy and remained stable over the next 18 months.

Electrodiagnostic studies. Table 2 outlines the sensory studies, and figure 2 demonstrates the motor conduction studies. Serial examinations of each patient showed persistent localized conduction block of 8 months, 3 years, 9 months, 9 months, and 12 months, respectively. After corticosteroid therapy, patient 3 showed improvement in conduction block at three sites, but the left median nerve conduction block was still apparent.

Nerve morphology. Sural nerve biopsy was carried out in patients 2, 3, and 4; specific findings on light- and phase-contrast microscopy of semithin plastic sections are illustrated in figure 4 and described in the legends. Despite careful search in multiple blocks and sections of each biopsy, no evidence of active or healed vasculitis was found. Teased myelinated fiber studies of the biopsies from patients 2 and 3 showed remyelinated internodes in 17 of 26 consecutive fibers (65%) and 14 of 47 consecutive fibers (30%), respectively. These observations indicate chronic demyelinating-remyelinating neuropathy. There were too few remaining myelinated fibers in the biopsy from patient 4 to allow an adequate sample for teasing.

Taken together, the findings in these three sural nerve biopsies were indistinguishable from those found in common forms of chronic acquired demyelinating neuropathy, either in our own experience or that of others.¹⁻⁴ Although we searched for electrophysiologic conduction block in cutaneous

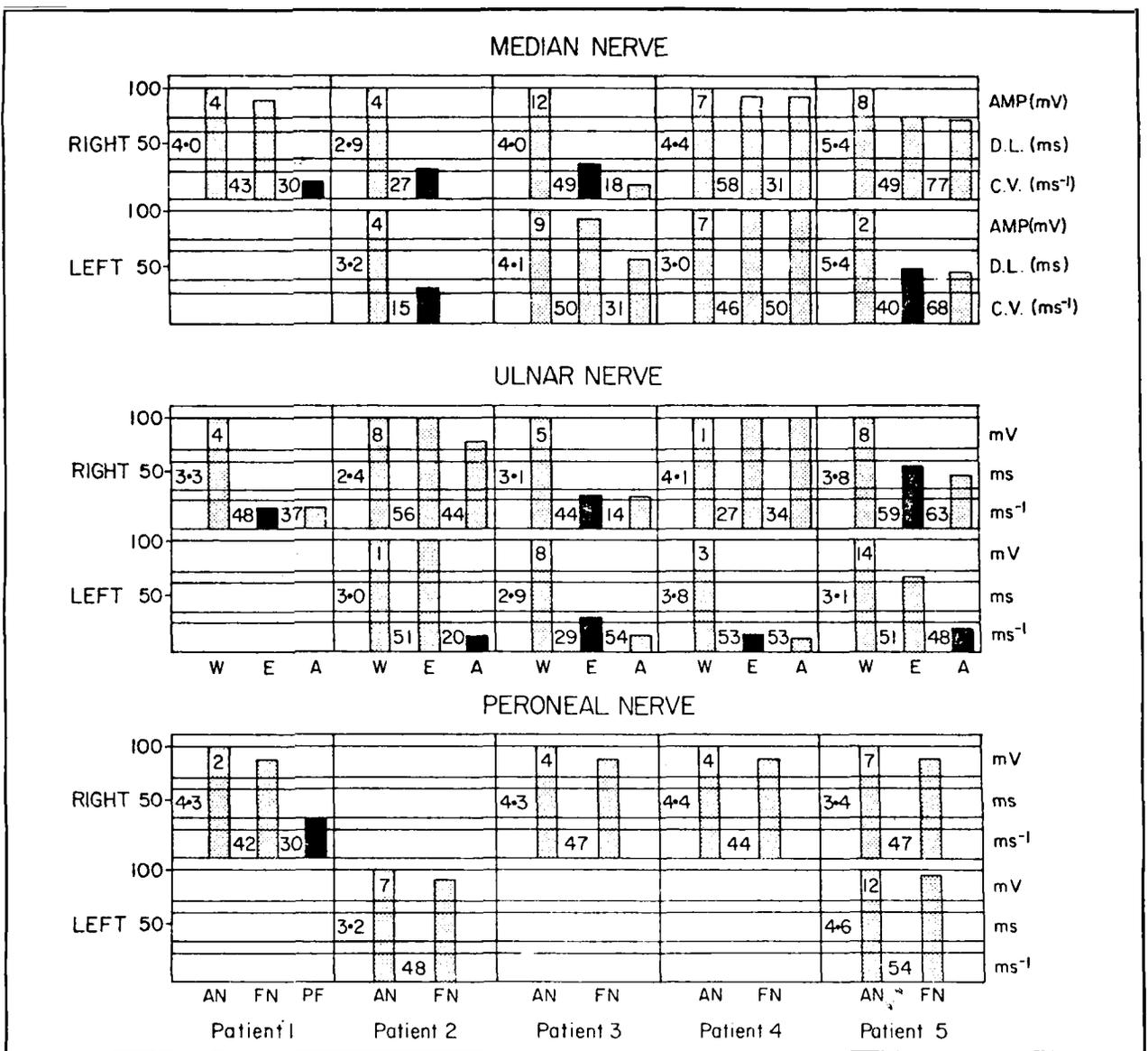


Figure 2. Bar graphs of the median, ulnar, and peroneal motor conduction studies for each patient. The bars represent the relative amplitudes of the compound motor action potentials as a percentage of the distal response elicited by stimulation at the wrist (W), elbow (E), axilla (A), ankle (AN), fibula neck (FN), and popliteal fossa (PF). Dark bars represent sites of conduction block. The number within the bars represent the amplitude (AMP; mV) in millivolts of the response upon distal (wrist or ankle) stimulation. The numbers between the bars from left to right are the distal motor latencies in milliseconds (D.L.; ms), forearm and leg conduction velocity, and proximal limb conduction velocity in meters per second (C.V.; ms⁻¹).

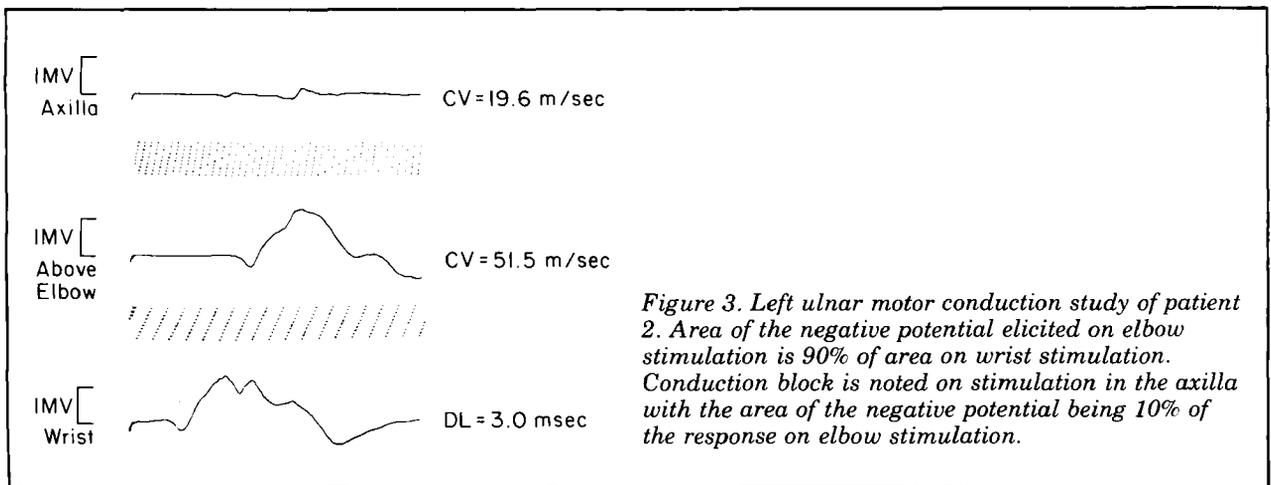


Figure 3. Left ulnar motor conduction study of patient 2. Area of the negative potential elicited on elbow stimulation is 90% of area on wrist stimulation. Conduction block is noted on stimulation in the axilla with the area of the negative potential being 10% of the response on elbow stimulation.

Table 1. Multifocal demyelinating neuropathy with persistent conduction block

Patient	Duration (years)	Clinical findings	Tinel sign	Reflexes		CSF protein (mg%)	Course and therapy
1	4	Multifocal sensorimotor neuropathy	Left ulnar n. at elbow Left axilla	Arms Legs	0 2+	Normal (21)	Slow progression No therapy
2	22	Generalized distal neuropathy with superimposed nerve trunk abnormalities	0	Arms Legs	0 0	Normal (19, 35, 45, 22)	Slow progression No therapy
3	1½	Mild generalized sensorimotor neuropathy with superimposed multifocal nerve trunk lesions Optic neuritis (VER = 120 msec)	0	Arms Legs	1+ 0	Mild increase (68, 50)	Neuropathy improved with prednisone Optic neuritis developed when steroids stopped
4	2½	Multifocal sensorimotor neuropathy	Left ulnar n. in forearm	Arms Knees Ankles	0 2+ 0	—	Clinical improvement on prednisone Relapse when dose was reduced
5	2	Mild multifocal sensorimotor neuropathy with optic neuritis (VER = 142 msec)	Left median n. in forearm and at wrist	Arms Legs	0 2+	Mild increase (90)	Condition stable without medication

Table 2. Sensory conduction studies

	Normal			Patient 1		Patient 2		Patient 3		Patient 4		Patient 5	
	AMP (µv)	CV (m/sec)		AMP	CV								
Ulnar	12 ± 4	54 ± 3	Right	5	39	0.3	18	2.5	50	NR		7	40
			Left	ND		ND		1.5	44	ND		6	37
Median	16 ± 5	54 ± 4	Right	20	45	0.3	15	11	52	2	50	10	40
			Left	ND		ND		8	52	ND		9	37
Radial	28 ± 8	56 ± 4	Right	7	41	0.5	8	17	55	5	69	ND	
			Left	20	47	ND		8	62	ND		ND	
Sural	21 ± 17	48 ± 6	Right	22	47	ND		8	43	8	33	10	41
			Left	ND		0.8	18	ND		NR		ND	

NR = no response.
ND = not done.

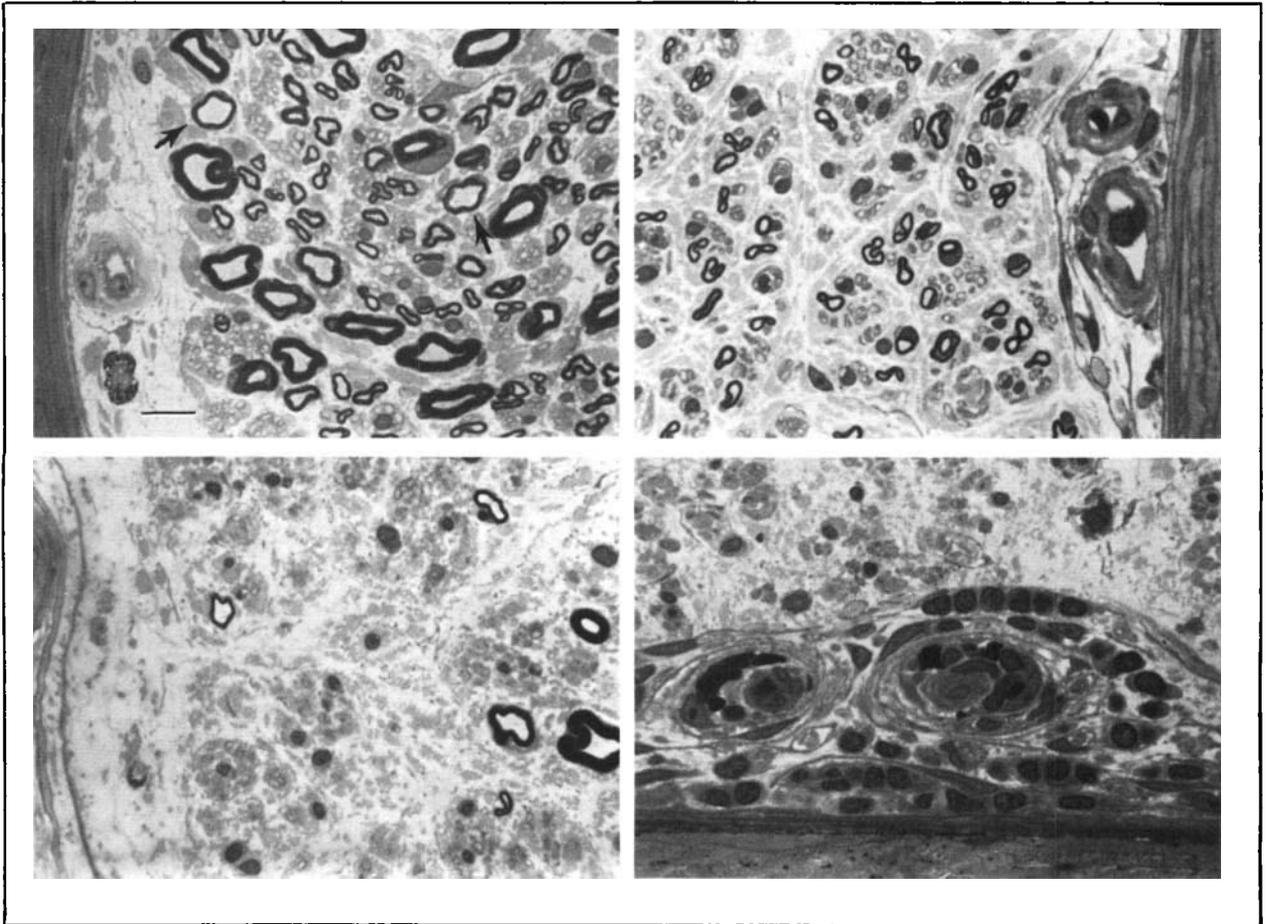


Figure 4. Cross-section photomicrographs of biopsied sural nerves from three patients with multifocal demyelinating neuropathy. All are at the same final magnification. One- μ m epoxy sections. MAB stain. (Top left). Patient 3, mild demyelinating neuropathy. There is subperineurial edema and slight decrease in myelinated fiber density. Occasional myelinated fibers have thin sheaths for axonal size, indicating remyelination (arrows). Schwann cell nuclei are increased in number. Bar = 10 μ m. (Top right). Patient 2, moderately severe neuropathy. There is a mild degree of endoneurial edema. Myelinated fiber density is reduced, especially of the larger-diameter population. Unmyelinated fiber numbers are also reduced. Schwann cell numbers are increased. (Bottom left). Patient 4, severe neuropathy with demyelinating and inflammatory features. There is subperineurial and endoneurial edema and a marked paucity of myelinated and unmyelinated fibers. Remaining myelinated fibers often have disproportionately thin sheaths, indicating remyelination. (Bottom right). Patient 4. Endoneurial capillaries in one fascicle are surrounded by mononuclear cell infiltrate. Vasonecrosis was not found.

nerve at a site that could be biopsied, we found none. Therefore, the precise morphometric correlation with physiologic conduction block cannot be stated.

Discussion. *Clinical aspects.* All five patients presented with subacute onset of sensorimotor symptoms involving one or two nerves in the arms, usually the median or ulnar (table 1). Progression was slow and relentless as distinct new nerve lesions became apparent. In all cases, examination confirmed the asymmetry of the sensorimotor neuropathy. In three patients (patients 1, 4, and 5), individual nerve lesions were clearly identified.

In the others (patients 2 and 3), the deficits eventually blended. Arms were always more affected than legs. Tendon reflexes generally were absent in the arms but preserved in the legs (patients 1, 4, and 5). The sensory disturbance seemed to involve primarily large-fiber modalities (vibration, position, and light touch) with relative sparing of pain and temperature, although all modalities were affected in severely involved nerves. Pain was prominent in four patients (patients 1, 2, 4, and 5), with dysesthetic sensations and shocklike radiating pain in the distribution of involved nerves. Focal nerve tenderness was seen in three patients; percussing these sites sometimes caused local and radiating

paresthesias. These tender areas, noted in the axilla (patient 1), forearm (patients 4 and 5), and at the elbow (patient 1), were sites of partial conduction block on electrophysiologic testing.

Two patients (patients 3 and 5) developed subacute visual loss, with marked visual acuity deficits, central scotomas, optic atrophy, and prolonged visual evoked responses. Visual symptoms partially improved over 4 weeks. The two patients with optic neuritis had mildly elevated CSF protein levels; two other patients had normal protein levels. CSF agarose gel electrophoresis was normal in the three patients studied, including the two with optic neuritis.

The course of the disease varied. Patients 1 and 2 progressed for 3 years and 20 years, respectively, without improvement and had severe functional disability. Patient 5 progressed for 6 months with mild disability and was then stable for 1½ years. Two patients who progressed for 8 months and 7 months, respectively, had moderate deficits and were treated with corticosteroids. In both, symptomatic improvement was noted within 3 weeks and functional improvement was obvious by 6 weeks. Both relapsed when the steroid dosage was reduced and improved when steroids were reinstated.

A multifocal mononeuropathy pattern suggests underlying vasculitis, but the long history of progression without systemic disorder and the consistently negative laboratory evaluation made this unlikely. In addition, the demyelinating features noted on electrodiagnostic testing and on sural nerve biopsy contrast with the prominent axonal degeneration of vasculitic mononeuritis multiplex.³ Finally, evidence of vasculitis was not found in the vasa nervorum of three sural nerve biopsies subjected to multiple section analysis.

We are aware of only one previous report of this disorder. Adams et al⁵ described two cases of asymmetric chronic inflammatory neuropathy with prominent onion-bulb formations. Clinical features were similar to those of our patients, and they also responded to steroid therapy. We believe that our patients had a demyelinating disorder that differs from the larger group of chronic acquired demyelinating neuropathies. Our patients had more focal asymmetric nerve involvement, and the normal or mildly increased CSF protein suggested only minimal root involvement; two patients had optic neuritis. In contrast, patients with the more common forms of chronic acquired demyelinating neuropathy have had symmetric sensorimotor symptoms involving the legs and the arms, without focal involvement of individual nerves.^{1,2} Generalized areflexia was the rule, and CSF protein was almost always increased, usually above 100 mg per deciliter. Dyck et al¹ noted clinical and pathologic evidence of nonspecific central nervous system lesions in a few patients, but not optic

neuritis. Other descriptions of specific combinations of central and peripheral lesions have been reported but with no electrodiagnostic or morphologic evidence of demyelinating neuropathy.⁶⁻⁸

Electrophysiologic aspects. The key to the diagnosis was the electrodiagnostic study. Unlike chronic acquired demyelinating neuropathy, in which there are widespread nerve conduction abnormalities with prolonged distal motor latencies, slow nerve conduction velocities, and prolonged F-wave latencies,¹ our patients had more focal abnormalities. Distal motor latencies were normal, and many segments of nerve had normal or nearly normal conduction velocity, but focal conduction block of sufficient degree to account for the clinical findings was noted. These electrophysiologic lesions were not located at the usual sites of compression, and we do not believe that compression could account for the abnormalities. For example, in patient 2, maximal volitional contraction of the left abductor digiti minimus activated only two small units (200 μ V), but direct stimulation of the ulnar nerve at the wrist and above the elbow evoked responses exceeding 1 mV at normal latencies. Stimulation in the axilla evoked a tiny response consisting of the same two units seen volitionally (200 μ V) (figure 3). Thus, this functional ulnar nerve deficit could be explained by focal conduction block in the upper arm. Distal sensory amplitudes were often preserved despite severe large-fiber sensory deficit on clinical examination; this sensory deficit was also probably due to proximal conduction block.

The conduction block persisted at the same sites for months or years. Conduction block is a potentially reversible abnormality, because the axon remains intact. It is characteristic of acute demyelination and is the primary pathophysiologic abnormality in acute compressive neuropathy^{9,10} or Guillain-Barré syndrome.¹¹ Experimentally, conduction block can be induced by tourniquet,¹² diphtheria toxin,^{13,14} or experimental antisera.¹⁵⁻¹⁷ Restoration of conduction usually begins within 2 weeks after the lesion is most severe, and recovery is complete within 2 months. Persistence of conduction block suggests failure of the blocked, demyelinated segments of nerve to remyelinate.

Why conduction block persisted in our patients is not known, but we suspect an immunologic mechanism was responsible for failure of remyelination. In tissue culture, demyelinated dorsal root ganglia fail to remyelinate when exposed to a level of rabbit antiserum to bovine white matter that is by itself too low to initiate demyelination.¹⁸ Low levels of circulating factors against myelin might prevent remyelination of demyelinated nerve fibers in our patients. Persistence of focal conduction block might also be related to continuing breach of the blood-nerve barrier at that site.

There is no direct evidence to support our as-

sumption that multifocal demyelinating neuropathy is an immunologically mediated disease, but humoral mechanisms have been implicated in other demyelinating neuropathies. Serum from animals with experimental allergic encephalitis¹⁹ or experimental allergic neuritis²⁰ or immunized with galactocerebroside²¹ or from patients with Guillain-Barré syndrome²²⁻²⁴ cause demyelination after injection into peripheral nerve. Improvement of acute or chronic demyelinating neuropathy after plasma exchange also implicates circulating factors.^{25,26}

It is not yet clear whether multifocal demyelinating neuropathy represents a distinct nosologic entity or is simply a subset of chronic acquired demyelinating neuropathy. In either case, this treatable disorder should be considered when evaluating patients with clinical evidence of mononeuritis multiplex.

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