

The acquired demyelinating polyneuropathies include acute (AIDP, Guillain-Barré syndrome, GBS) and chronic (CIDP, dysproteinemic) forms which differ primarily in their temporal profile. They are inflammatory-demyelinating diseases of the peripheral nervous system and likely have an immunologic pathogenesis. Although these neuropathies usually have a characteristic presentation, the electromyographer plays a central role in their recognition, since the demyelinating component of the neuropathy, which greatly reduces the differential diagnosis, is often first identified in the electromyography laboratory. In AIDP, the electromyographer, in addition to establishing the diagnosis, can sometimes predict the prognosis. Recognition of the chronic and dysproteinemic forms of acquired demyelinating polyneuropathy is important since they are treatable. The dysproteinemic forms also may be associated with occult systemic disorders that also may require treatment, independent of the neuropathy.

## ACQUIRED INFLAMMATORY DEMYELINATING POLYNEUROPATHIES: CLINICAL AND ELECTRODIAGNOSTIC FEATURES

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**P**olyneuropathies are frequently difficult diagnostic problems,<sup>76</sup> especially for clinicians who do not regularly deal with neuromuscular disorders or who lack adequate neuromuscular laboratory support. Increased diagnostic yield in polyneuropathies results from identification of the clinical and electrodiagnostic characteristics of demyelination.<sup>64</sup> Some investigators<sup>28,46</sup> have estimated that up to 25% of idiopathic neuropathies are autoimmune in nature, the majority being of the demyelinating type, including acute and chronic forms differing primarily in their temporal profile. Both are inflammatory-demyelinating diseases of peripheral nerves and nerve roots, although there may be extensive secondary axonal degener-

ation. Specific etiologies have not been identified, but immunologic mechanisms almost certainly are involved. A major advance has been the recognition and understanding of demyelinating neuropathies associated with plasma cell dyscrasias. Although fewer in number, they are important because the circulating monoclonal protein itself likely damages nerve fibers. Understanding the mechanisms involved may help clarify the mechanisms of other obscure neuropathies, as well. The evaluation of patients with suspected acute inflammatory demyelinating polyneuropathy (AIDP, Guillain-Barré syndrome, GBS), or chronic inflammatory demyelinating polyneuropathy (CIDP) includes electrodiagnostic examination, such as that shown in Table 1. This examination is directed toward detecting evidence of segmental or multifocal demyelination.

### ACUTE INFLAMMATORY DEMYELINATING POLYNEUROPATHY

**Clinical Features.** The incidence of AIDP is 0.5–1.6/million/month, increasing slightly with advancing age until about 75 years, and diminishing thereafter.<sup>83</sup> There are no known genetic or geographic predilections, although incidence is slightly higher for men than for women.<sup>68</sup> Diagnostic criteria are descriptive and based upon recognition of a relatively characteristic clinical picture.<sup>6</sup> Typical findings include rapidly progres-

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**Table 1.** Suspected inflammatory-demyelinating polyneuropathy: suggested electrodiagnostic protocol.

Conduction Studies<sup>a</sup>

1. Test most involved site when mild or moderate, least involved if severe.
2. Evaluate the peroneal motor (extensor digitorum brevis); stimulate ankle, fibular head, and knee. Measure the F response latency.<sup>b</sup>
3. If abnormal, evaluate the tibial motor (abductor hallucis); stimulate ankle and knee. Measure the F response latency.
4. If no responses, evaluate the
  - a. Peroneal motor (anterior tibial); stimulate fibula head and knee.
  - b. Ulnar motor (hypothenar); stimulate clavicle, elbow, below elbow, and wrist. Measure the F response latency.
  - c. Median motor (thenar); stimulate elbow and wrist. Measure the F response latency.
5. Evaluate the sural sensory (ankle); stimulate 14 cm from recording electrode; perform conduction velocity unless the amplitude is supernormal.
6. Evaluate the median sensory (index); stimulate the wrist and elbow. If antidromic response is absent or focal entrapment is suspected, record from the wrist while stimulating the palm.
7. Additional peripheral nerves can be evaluated if findings are equivocal. Definite abnormalities should result in
  - a. Evaluation of contralateral extremity
  - b. Proceeding to evaluation of specific suspected abnormality
8. If prominent cranial involvement:
  - a. Evaluate the facial motor (orbicularis oculi): stimulate at the angle of jaw.
  - b. Conduct blink reflex studies (orbicularis oculi): stimulate the supraorbital nerve.

Needle Examination

1. Examine the anterior tibial, medial gastrocnemius, vastus lateralis, biceps brachii, interosseous (hand), and lumbar paraspinal muscles.
2. Any abnormality should be confirmed by examination of at least one contralateral muscle.

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<sup>a</sup>Words in parentheses indicate recording site for conduction studies.

<sup>b</sup>All F response latency measurements are for distal stimulation sites only.

sive weakness, often with bulbar and respiratory involvement; hyporeflexia or areflexia; slightly diminished sensation; autonomic dysfunction; and cerebrospinal fluid (CSF) protein elevation without pleocytosis.<sup>5,7,48,68,88,96</sup>

An antecedent event, most commonly a respiratory tract infection or gastroenteritis, is evident within 1 month (an average of 15 days) in over 60% of patients.<sup>4</sup> Other antecedent events include other infections (e.g., hepatitis B, Epstein-Barr virus, cytomegalovirus, toxoplasmosis), immunization,<sup>83</sup> malignant disease, and surgery.<sup>5</sup> AIDP also has been associated with acquired HIV1 infections, Lyme disease, Hodgkin's disease, and non-Hodgkin's lymphoma.<sup>59</sup>

Initial manifestations include symmetrical motor and/or sensory symptoms.<sup>4</sup> The most common complaint is leg weakness,<sup>5</sup> and many patients demonstrate spread in a distal-to-proximal fashion. Prominent facial weakness occurs in about 50% of patients,<sup>5</sup> and unilateral facial involvement has been described in up to 10% of patients,<sup>4</sup> consistent with an isolated mononeuropathy superimposed on a generalized polyneuropathy. Other cranial nerve involvement leads to weakness of mastication, swallowing, and, rarely, eye movements.<sup>13</sup> Despite common sensory symptoms, objective sensory loss is infrequent.<sup>13</sup> When present,

large myelinated fiber modalities (vibratory and joint position sensations) are involved. Back and extremity pain are frequent complaints during the early stages of the illness and may be severe.

Autonomic nervous system involvement includes bowel and bladder impairment, cardiac dysrhythmia, labile heart rate and blood pressure resulting in hypertension or hypotension, and impaired thermoregulation.<sup>5,93</sup> The syndrome of inappropriate antidiuretic hormone secretion (SIADH) has been associated with AIDP, perhaps related to abnormalities of autonomic afferents arising from vascular stretch receptors.<sup>38,75</sup>

The Fisher syndrome is considered a variant of AIDP, consisting of ophthalmoplegia, ataxia, and areflexia.<sup>31</sup> The temporal profile and CSF findings are indistinguishable from AIDP, and electrodiagnostic studies in some patients show a demyelinating polyneuropathy.<sup>35</sup> Although some consider the syndrome a brainstem encephalitis,<sup>10</sup> others<sup>80</sup> propose peripheral explanations for all of the clinical signs.

The interval from the first neurologic symptom to peak impairment is less than 20 days in over 75% of patients,<sup>4</sup> and 50% of patients reach their nadir by 2 weeks.<sup>13</sup> Progression exceeding 4 weeks should be viewed cautiously and alternative diagnoses considered. Diaphragm and intercostal

muscle involvement leads to respiratory paralysis in about 30% of patients. Mechanical ventilation usually is initiated between 6 and 18 days after onset (mean of 10 days).<sup>4</sup> Initial improvement is observed within 40 days in over 80% of the patients,<sup>4</sup> and the overall prognosis is quite good, with most patients demonstrating substantial clinical recovery within 6 months.<sup>4,59</sup>

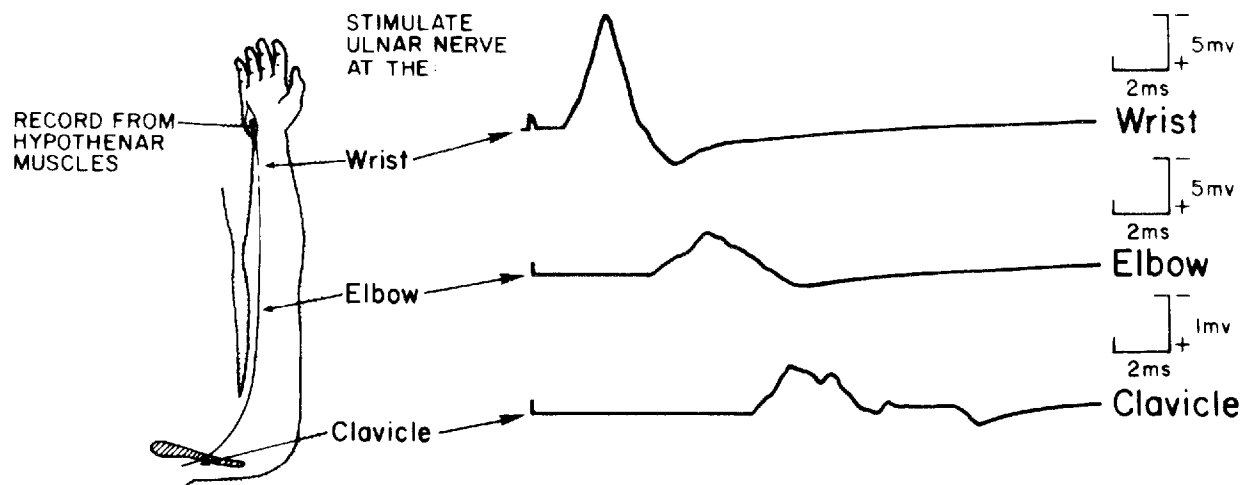
The question of relapse in AIDP is difficult because of potential confusion with other disorders associated with relapsing polyneuropathy, including acute intermittent porphyria,<sup>3</sup> systemic lupus erythematosus, and the chronic relapsing forms of inflammatory polyneuropathy. Distinct relapses in patients with otherwise typical AIDP do occur, although the rate is probably less than 5%. In the multicentered, randomized trial of plasma exchange in the treatment of AIDP,<sup>90</sup> four relapses were reported out of 254 patients during the study period.

**Electrophysiologic Findings.** A variety of electrodiagnostic findings has been reported,<sup>2,29,51,62,63,74,78,79</sup> perhaps due to the temporal changes that occur in response to cumulative demyelination and axonal degeneration. The syndrome also may encompass patients with primary axonal degeneration as well as patients with severe distal conduction block resembling axonal degeneration.<sup>30,81</sup> Nevertheless, the majority of patients demonstrate an evolving picture of a demyelinating polyneuropathy with superimposed axonal degeneration.<sup>2</sup> A model of peripheral motor nerve, useful in predicting the electrophysiologic findings in multifocal demyelination, is de-

scribed in the Appendix. Included is a discussion of the importance of abnormal temporal dispersion in distinguishing acquired from hereditary demyelinating polyneuropathies.<sup>54</sup>

Studies performed early in the course of AIDP, when the diagnosis may be unclear, often demonstrate only delayed or absent F responses or H reflexes. Occasionally F responses appear normal but are difficult to elicit. During subsequent examinations, evidence of segmental conduction block and conduction slowing become apparent, with abnormal temporal dispersion of evoked responses, reduced conduction velocity, and prolonged distal latency. Identification of abnormal temporal dispersion and partial conduction block is the most reliable electrodiagnostic indicator of an acquired demyelinating polyneuropathy<sup>12</sup> but not diagnostic of AIDP.<sup>11,23</sup> A characteristic motor conduction recording from a patient with AIDP is shown in Fig. 1. The electrodiagnostic recognition of primary demyelination is imprecise and depends upon identifying abnormalities that cannot be explained by axonal involvement alone. This differentiation is most straightforward in acute disorders in previously well individuals without other sources of conduction slowing. Criteria suggestive of acute demyelination (Table 2) have been modified from those initially proposed by Kelly,<sup>43</sup> recognizing that the distinction between "demyelination" and "axonal degeneration" is not always clear.

Evidence of segmental demyelination is present in about 50% of patients during the first 2 weeks of illness.<sup>1,2</sup> This increases to 85% during the third week of illness. Throughout the course



**FIGURE 1.** Abnormal temporal dispersion with partial conduction block of ulnar compound muscle action potential, recording from hypothenar muscles of patient with acute inflammatory demyelinating polyneuropathy.

**Table 2.** Criteria suggestive of demyelination in the electrodiagnostic evaluation of acute inflammatory polyneuropathy.

Demonstrate at least three of the following in motor nerves (exceptions noted below):

1. Conduction velocity less than 90% of lower limit of normal if amplitude exceeds 50% of lower limit of normal; less than 80% if amplitude less than 50% of lower limit of normal (two or more nerves).<sup>a</sup>
2. Distal latency exceeding 115% of upper limit of normal if amplitude normal; exceeding 125% of upper limit of normal if amplitude less than lower limit of normal (two or more nerves).<sup>b</sup>
3. Evidence of unequivocal temporal dispersion or a proximal-to-distal amplitude ratio less than 0.7 (one or more nerves).<sup>b,c</sup>
4. F-response latency exceeding 125% of upper limit of normal (one or more nerves).<sup>a,b</sup>

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<sup>a</sup>Excluding isolated ulnar or peroneal nerve abnormalities at the elbow or knee, respectively.

<sup>b</sup>Excluding isolated median nerve abnormality at the wrist.

<sup>c</sup>Excluding the presence of anomalous innervation (e.g., median to ulnar nerve crossover).

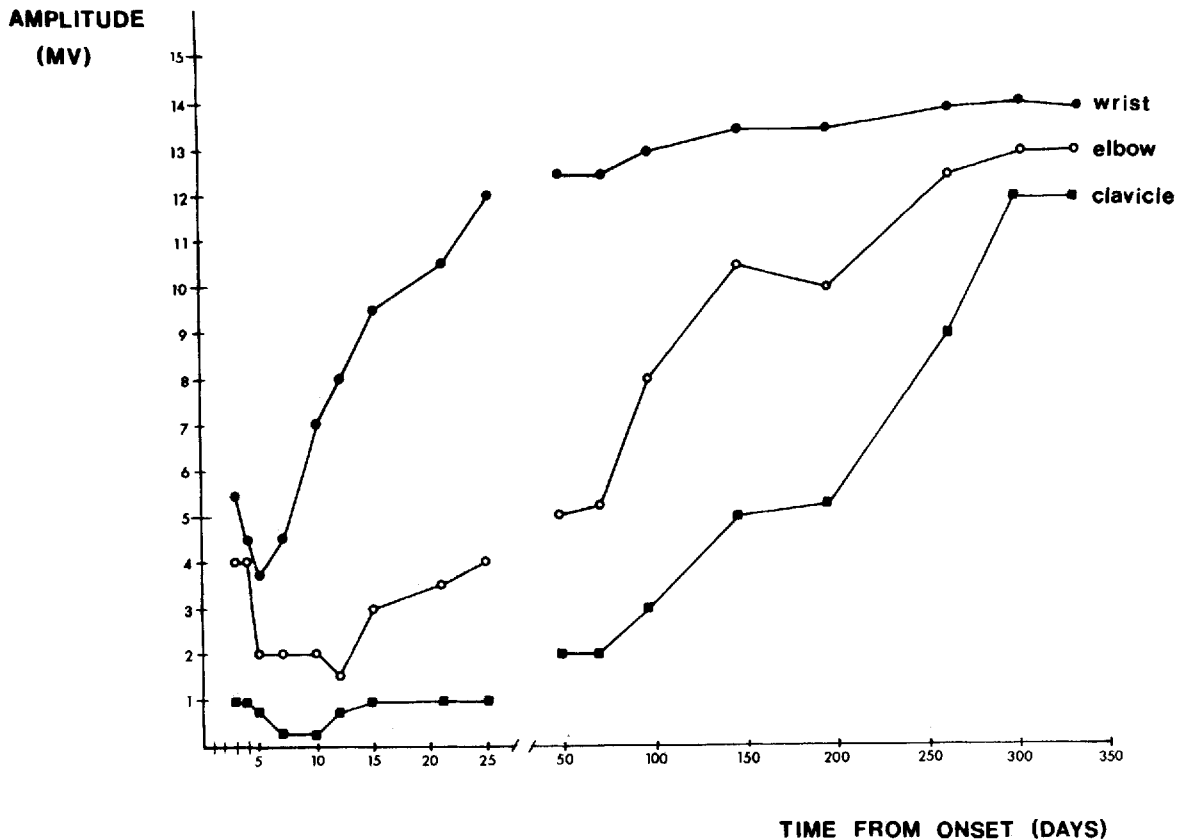
of AIDP, 10% of patients never fulfill electrodiagnostic criteria for demyelination because responses are unobtainable. About 3% of patients studied sequentially demonstrate evidence of axonal degeneration only. Motor nerve abnormalities peak between the third and fourth weeks, although individual patients may demonstrate absent evoked responses within days of onset, presumably reflecting distal conduction block, and/or axonal degeneration. Conversely, some patients demonstrate progressive amplitude loss through the fifth or sixth weeks. Patients having only prolonged distal latencies during the first 3 weeks of illness<sup>51</sup> may demonstrate partial conduction block and conduction velocity slowing in the following weeks.

The degree of conduction block, not the amount of motor conduction slowing, best correlates with clinical impairment. Sequential CMAP amplitude recordings for proximal and distal stimulation for one patient are shown in Fig. 2. The reduced CMAP amplitude with proximal stimulation (clavicle) cannot be explained by temporal dispersion alone and likely represents partial conduction block. Early recordings demonstrated progressively decreasing amplitudes, reflecting axonal degeneration or progressive conduction block. During subsequent recordings when the neurologic impairment was unchanged, the evoked amplitude with distal stimulation improved dramatically. This rapid improvement cannot be explained by axonal regeneration or collateral reinnervation but is explainable by reversal of distal conduction block.

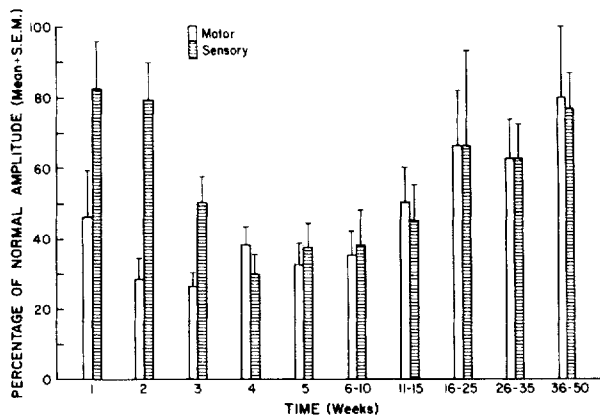
During the first few weeks of illness, motor abnormalities are much more common than sensory abnormalities. Motor and sensory evoked amplitudes expressed as a percentage of the normal mean were averaged for 70 patients with AIDP (34 patients had sequential evaluations) versus time after disease onset and are shown in Fig. 3.<sup>2</sup> Although almost 90% of patients have some mo-

tor conduction abnormalities during the first few weeks of illness, only 25% of patients have sensory abnormalities during the same interval. By the third week, however, almost 80% of patients had abnormal sensory studies. Motor abnormalities for a given patient tended to be homogeneous, with the lower limbs showing greater involvement than the upper limbs. Conversely, sensory studies frequently demonstrated abnormalities of individual nerves. Sural and median sensory conduction studies are shown in Table 3. During initial evaluation, a common finding was an abnormal median sensory response with normal sural nerve conduction studies.<sup>69</sup> The median sensory nerve action potential (SNAP) usually was absent or markedly reduced in amplitude with prolonged distal latency. Patients with an abnormal sural and normal median sensory conduction study, a finding characteristic of most mild, chronic polyneuropathies, were uncommon. This finding of a normal, relatively spared sural response in the presence of an abnormal median sensory response, in association with the appropriate clinical syndrome, is characteristic of AIDP.

Several explanations exist for the discrepancy between motor and sensory studies as well as the discrepancy between the sural and median sensory conduction studies. Neuromuscular transmission failure following a distal axonal lesion would result in reduced CMAP amplitudes prior to reduction in SNAP amplitudes. If the amount of myelin protected the axon or preserved conduction, the larger myelinated sensory fibers would be preferentially preserved relative to the smaller motor fibers. This also could explain prolonged sural nerve function compared to median sensory function, because the sural recording is obtained from the more proximal nerve as compared with the terminal median sensory fibers. This distal predilection is consistent with reported centripetal demyelination in some patients<sup>95</sup> and also consistent



**FIGURE 2.** Serial ulnar compound muscle action potential amplitudes with proximal and distal stimulation, recording from the hypothenar muscles of a patient with acute inflammatory demyelinating polyneuropathy. Amplitudes (mV) are expressed as a function of time from disease onset. (Reprinted with permission from Albers JW: Electromyography in the prognosis of nerve injury. American Academy of Neurology Special Course #22: Clinical Electromyography, 1980.)



**FIGURE 3.** Motor- (open bar) and sensory- (shaded bar) evoked response amplitudes expressed as a percentage of the normal mean as a function of time after disease onset in 70 patients with acute inflammatory demyelinating polyneuropathy. The responses are significantly ( $P < 0.05$ ) different for weeks 1, 2, and 3. No significant differences exist thereafter. (Reprinted from Ref. 2 by permission of John Wiley & Sons, Inc, Copyright © 1985.)

with the observations of Sumner,<sup>89</sup> who found, using a humorally induced demyelination in rat sciatic nerve, that smaller diameter myelinated fibers were affected earlier and more completely than larger diameter fibers. Nerve roots were highly permeable to antiserum, and distal motor nerve twigs and common compression sites were identified as potential areas of vulnerability because of an impaired blood-nerve barrier.

Electromyography (EMG) has a secondary role in evaluating patients with AIDP. Decreased motor unit action potential (MUAP) recruitment, without evidence of configuration abnormalities or abnormal spontaneous activity, is the initial finding, reflecting the clinical distribution of weakness. Occasionally, myokymic discharges are observed during the first few weeks of illness.<sup>18</sup> They may be found in facial or extremity muscles and may be present in the absence of clinical myokymia. Fibrillation potentials and positive waves appear between 2 and 5 weeks, simultaneously in proximal and distal muscles (Fig. 4), consistent with either

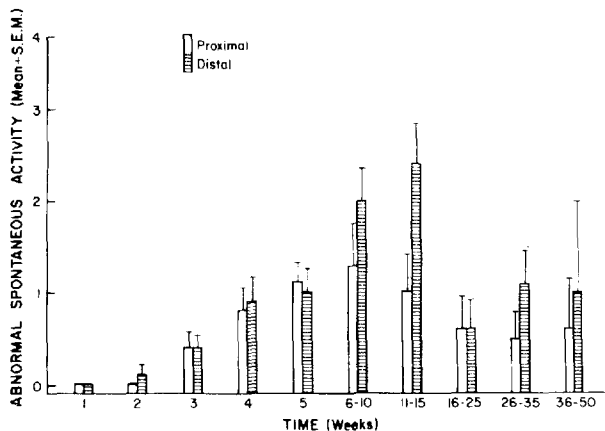
**Table 3.** Comparison of median and sural sensory conduction studies in patients with acute inflammatory demyelinating polyneuropathy: results at the time of initial and follow-up evaluation.

	All studies (n = 86)	Initial eval. first 3 weeks (n = 39)	Follow-up (n = 39)
Both normal	30 (35%)	11 (28%)	13 (33%)
Both abnormal	20 (23%)	9 (23%)	13 (33%)
Median abnormal and sural normal	36 (42%)	19 (49%)	13 (33%)
Median normal and sural abnormal	0 (0%)	0 (0%)	0 (0%)

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random axonal degeneration at any point along the axon or predominant distal involvement. Proximal fibrillation potentials are maximal between 6 and 10 weeks, with distal fibrillation potentials persisting for many months. The amount of abnormal spontaneous activity ranges from none to extensive denervation with profuse (4+) positive waves and fibrillation potentials. The early reduction in fibrillation potentials in proximal compared with distal muscles likely reflects reinnervation from axonal sprouting or regeneration in proximal compared with distal muscles. This can be explained both by the greater probability of regeneration in a short axon and by the increased likelihood of collateral reinnervation from a greater number of surviving axons.

**Prognostic Indicators.** Clinical and CSF findings are poor predictors of outcome in patients with AIDP.<sup>74</sup> A prolonged interval to onset of recovery indicates a poor prognosis,<sup>60</sup> as does rapid evolution of weakness and ventilator dependency.<sup>66</sup>



**FIGURE 4.** Abnormal spontaneous activity in proximal (open bar) and distal (striped bar) muscles as a function of time after disease onset in 70 patients with acute inflammatory demyelinating polyneuropathy. Fibrillation potential scores range from 0 to 4+, with 0 = none and 4+ = profuse fibrillation potentials in all areas of muscle. (Reprinted from Ref. 2 by permission of John Wiley & Sons, Inc., Copyright © 1985.)

Nevertheless, some ventilator-dependent patients recover promptly and completely, whereas seemingly identical patients have a prolonged recovery. The most powerful predictor of poor outcome is reduced CMAP amplitude to less than 10% of the lower limit of normal.<sup>66</sup> Neurologic recovery is positively and significantly correlated with preserved mean CMAP amplitude, when the studies are performed between weeks 3 and 5. These findings support the hypothesis that evidence suggestive of predominant demyelination is correlated with relatively rapid recovery, whereas findings suggestive of severe axonal destruction are correlated with slow recovery.<sup>66,73</sup> The amount of fibrillation is a relatively poor predictor of prognosis when used alone.

**Treatment.** The supportive treatment of patients with AIDP involves maintenance of respiratory function and prevention of circulatory failure and thromboembolism.<sup>4</sup> The advent of respiratory intensive care units has been important in preserving life, although a mortality rate of approximately 5% persists even with aggressive pulmonary treatment. Most deaths follow medical complications of respiratory paralysis, including pneumonia.<sup>42</sup> Approximately half of patient deaths are sudden, presumably related to cardiac dysrhythmias or hypotension. All patients require observation for respiratory deterioration. The decision of whether or not to intubate a patient depends upon both the extent and rate of respiratory deterioration. General thresholds are difficult to define, but intubation and respirator support generally are needed if the forced vital capacity falls below 15 ml/kg. Elective intubation should be performed if there is a rapid decline of vital capacity, early signs of hypoxia, aspiration with poor tracheopulmonary toilet, pulmonary infection with shunting, or signs of respiratory distress or fatigue. Arterial blood gases represent a poor measure of respiratory function, deteriorating late in the clinical course. A low PO<sub>2</sub> and low or normal

PCO<sub>2</sub> indicates shunting from early atelectasis and often precedes respiratory failure. Hypercapnia is a late finding of respiratory failure and dangerous criterion for elective intubation. Prolonged intubation without tracheostomy is now possible with soft endotracheal tubes, although meticulous tracheopulmonary toilet is facilitated by tracheostomy, and the use of a talking tracheostomy may facilitate psychological care.

Autonomic instability requires monitoring in an intensive care setting. Hypotension is best managed by increasing fluids, and sympathomimetics usually are avoided. Hypertension is best not treated unless severe. When necessary, medications with a short half-life such as nitroprusside or propranolol are preferred. The most common cardiac dysrhythmias are a second- or third-degree AV block. Temporary pacemaker insertion is an effective treatment.

Additional medical management includes proper bladder care, prompt identification and treatment of superimposed infection, restriction of fluids in patients who are hyponatremic, and antiembolism protection, including low-dose heparin (5000 units subcutaneous twice daily) and antiembolus stockings in quadriparetic patients. Appropriate laboratory studies should be performed, monitoring for occult blood loss, anemia and thrombocytopenia, infection, and electrolyte imbalance.

Corticosteroids are of unproven efficacy in AIDP, and their use is controversial. The most recent controlled study<sup>39</sup> reported that prednisone may have slowed the recovery rate and increased the chance of relapse. Anecdotal reports<sup>24</sup> exist of single patients who responded dramatically to steroids.

The potential importance of humoral factors in the pathogenesis of AIDP suggested that therapeutic plasma exchange (TPE) might modify the disease course.<sup>68</sup> The multicenter randomized trial of TPE in the treatment of AIDP<sup>90</sup> demonstrated significant benefit of TPE when compared with conventional medical treatment, excluding steroids. By all criteria, TPE had a beneficial effect. The median time on a respirator was reduced by 11 days and the time to unassisted ambulation shortened by an average of 73 days for respirator-dependent patients who received TPE. Similar results have been reported in two additional controlled, randomized trials.<sup>15,71</sup> Two smaller controlled trials were inconclusive, although the trends favored the TPE group.<sup>32,65</sup> TPE is not effective for all patients. Patient age

and the CMAP amplitudes are important predictors of early responsiveness.<sup>34</sup> TPE appears particularly effective for patients who begin treatment within 7 days of disease onset, although early, aggressive TPE may be associated with initial improvement followed by relapse, perhaps related to termination of treatment too early in the course of the disease.<sup>82</sup>

### **CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY**

**Clinical Features.** CIDP is a chronic progressive or relapsing disorder of peripheral nerves that clinically resembles AIDP. Reliable incidence estimates are unavailable, although it is probably less than that of AIDP. Because of the prolonged course, however, the prevalence probably exceeds that of AIDP. CIDP occurs in both sexes and all ages with little evidence of peaks other than a predominance in the fifth and sixth decades.<sup>77</sup>

Diagnostic criteria differ only slightly for those used for AIDP. At present, the only reliable method for differentiating the two disorders is by an arbitrary clinical judgment regarding the temporal evolution of neurologic symptoms. Patients with CIDP usually have an interval between onset and peak impairment exceeding 4 weeks, and the average duration from onset to peak deficit averages approximately 3 months, with a range of 3 weeks to 16 months.<sup>77</sup>

CIDP is characterized by sensory loss and weakness, areflexia, elevated CSF protein, and electrodiagnostic evidence of multifocal demyelination with or without superimposed axonal degeneration.<sup>5,26,91</sup> The etiology is unknown, but the results of nerve biopsy and reports of response to steroids,<sup>17,91</sup> azathioprine,<sup>77,94</sup> or TPE<sup>53,84,85,92</sup> suggest an immunologic etiology.<sup>56</sup> An identifiable antecedent event is rare compared with AIDP, although CIDP has been associated with immune complexes of hepatitis B virus.<sup>41</sup>

Symmetric sensory and/or motor symptoms are the initial manifestation, and weakness usually begins in the legs. Rarely, asymmetric findings are present, consistent with multifocal demyelinating mononeuropathies.<sup>55</sup> Cranial nerve involvement is common, especially orbicularis oculi weakness, but less prominent than in AIDP. Maximal weakness usually is distal, and 15 of the 23 patients described by Prineas and McLeod<sup>77</sup> were nonambulatory during their most severe episode. Occasional patients require respiratory support, either during an exacerbation or during the terminal phase. Muscle wasting may be severe but often is

mild compared with the degree and severity of muscle weakness. Sensory symptoms and signs usually are mild but may be associated with a sensory ataxia. All modalities of sensation may be affected,<sup>77</sup> although large fiber loss predominates. Muscle stretch reflexes are usually absent at some time during the illness; rare patients fulfill all other diagnostic criteria but have hypoactive, preserved reflexes. Autonomic involvement is uncommon.

The clinical course in CIDP is variable. The term chronic relapsing polyneuropathy (CRP) has been used to describe patients with clear relapses and remissions. Dyck and associates<sup>26</sup> estimated that approximately 50% of patients had a progressive course (slow or stepwise), one-third had a relapsing course, and the remaining patients experienced a monophasic illness with the peak deficit remaining or developing after 6 months. With current treatments, many patients who may have had progressive disease seemingly respond to treatment but relapse when therapies are tapered or discontinued. The distinction between therapy-associated relapse in CIDP and idiopathic relapse in CRP is unclear.

In CRP, the average interval between relapses is about 10 months, although relapses have been reported 31 years after initial attacks.<sup>77</sup> Patients with CRP may remit after many years, without further exacerbations. In early reports of outcome for 53 patients with CIDP who were followed for an average of 7 years, 9 died (6 from the disease), 6 were confined to wheelchair or bed, 36 had a mild to moderately severe impairment, and only 2 had complete resolution.<sup>26</sup> Recent experience suggests that more patients experience remission, with fewer patients demonstrating progressive deterioration. This may reflect earlier detection and treatment or recognition of milder cases.

**Electrophysiologic Features.** The electrodiagnostic findings in CIDP resemble those described late in the course of AIDP and are consistent with multifocal demyelination with variable amounts of

superimposed axonal degeneration. The chronic progressive, stepwise progressive, and relapsing forms cannot be differentiated electrophysiologically. Electrodiagnostic criteria suggestive of demyelination in CIDP (Table 4) differ slightly from those described for AIDP. These differences reflect the possible development of axonal stenosis or regeneration, changes that may result in substantial conduction slowing without segmental demyelination. Nevertheless, electrodiagnostic evidence of demyelination is present in virtually all patients with CIDP, and many consider this part of the diagnostic criteria.<sup>1</sup> Motor conduction velocities may be markedly reduced, F response latencies very prolonged (or absent), and temporal dispersion more prominent than observed in AIDP, although individual variations are large. The combination of absent or abnormal SNAPs with normal sural responses occurs but is uncommon in CIDP compared with AIDP. EMG abnormalities are present in most patients with CIDP. Like AIDP, needle examination is useful for defining the chronicity and extent of axonal degeneration.

**Treatment.** The supportive care of patients with CIDP is identical to that described for AIDP. Unlike AIDP, corticosteroids are of demonstrated benefit in controlled trials of both the CRP and CIDP.<sup>8,26,27,77,91</sup> Many prednisone treatment protocols exist, including high-dose daily or alternate-day schedules, with slow taper depending upon clinical response. Azathioprine also has been reported to be effective in several case reports and small clinical trials of CIDP patients,<sup>94</sup> including patients previously steroid unresponsive or intolerant.<sup>72</sup>

Isolated case reports described TPE as beneficial in CIDP.<sup>33,53,61,84</sup> A consecutive patient trial of TPE demonstrated substantial clinical improvement within 3 weeks in about 50% of progressive CIDP patients.<sup>22</sup> The temporal association between improvement and TPE in patients with

**Table 4.** Criteria suggestive of demyelination in the electrodiagnostic evaluation of chronic inflammatory polyneuropathy.

Evaluation should satisfy at least three of the following in motor nerves (exceptions noted below):

1. Conduction velocity less than 75% of the lower limit of normal (two or more nerves).<sup>a</sup>
2. Distal latency exceeding 130% of upper limit of normal (two or more nerves).<sup>b</sup>
3. Evidence of unequivocal temporal dispersion or conduction block on proximal stimulation consisting of a proximal-to-distal amplitude ratio less than 0.7 (one or more nerves).<sup>b,c</sup>
4. F-response latency exceeding 130% of upper limit of normal (one or more nerves).<sup>a,b</sup>

<sup>a</sup>Excluding isolated ulnar or peroneal nerve abnormalities at the elbow or knee, respectively.

<sup>b</sup>Excluding isolated median nerve abnormality at the wrist.

<sup>c</sup>Excluding the presence of anomalous innervation (e.g., median to ulnar nerve crossover).



longstanding, progressive deterioration seemed more than coincidental. A subsequent prospective double-blind trial in which patients with static or progressive CIDP were randomized to TPE or sham exchange groups demonstrated significant improvement in electrodiagnostic and clinical measurements after 3 weeks, favoring patients receiving TPE.<sup>25</sup>

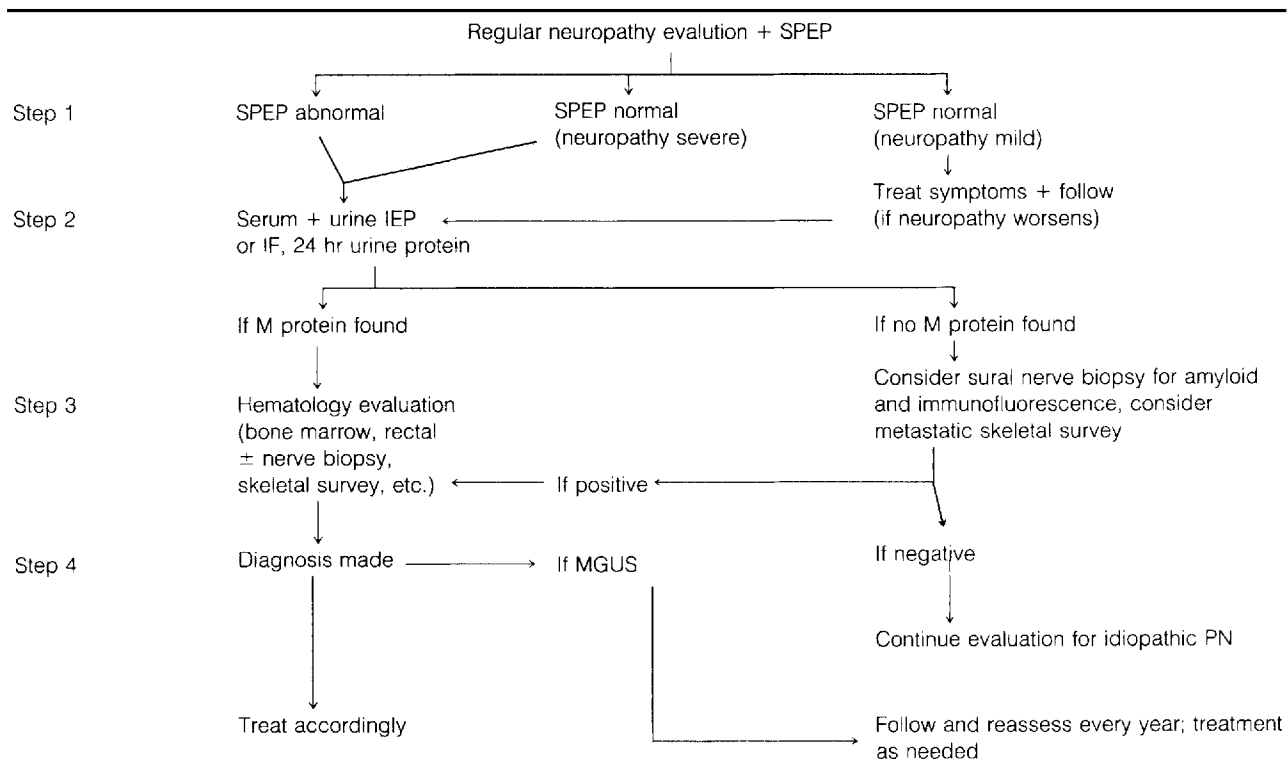
### DYSPROTEINEMIC OR PARANEOPLASTIC NEUROPATHIES

A subset of patients with acquired demyelinating polyneuropathy exists which differs from CIDP only by the presence of an underlying systemic illness. Because the systemic illness may not be apparent when the polyneuropathy is diagnosed, these patients often are classified as having CIDP or even AIDP, although most clinicians restrict these terms to exclude patients with systemic illness. Included are patients with Waldenstrom's macroglobulinemia,<sup>19</sup> gamma heavy chain disease,<sup>50</sup> cryoglobulinemia,<sup>58</sup> lymphoma,<sup>20</sup> systemic lupus erythematosus,<sup>26</sup> Castleman's disease,<sup>14</sup> and HIV1 infections.<sup>57,67</sup>

Acquired demyelinating polyneuropathy rarely can be due to an occult malignancy.<sup>16</sup> The polyneuropathy with malignancy can be motor dominant, distal and/or proximal in distribution, evolve rapidly or slowly, and develop a relapsing or remitting course. EMG and pathologic studies are the same as in idiopathic cases. The etiology is assumed to be an immunologic process triggered by the underlying malignancy. The association is rare, however, and there is no reason to routinely evaluate all patients for a malignancy. Far more common is the association of an acquired demyelinating polyneuropathy and a plasma cell dyscrasia syndrome. Because of the high prevalence compared with other systemic disorders, these syndromes will be described further below.

**Demyelinating Polyneuropathy Encountered in the Plasma Cell Dyscrasia Syndromes.** All idiopathic polyneuropathy patients, and particularly those with presumed CIDP, should be evaluated for possible occult plasma cell dyscrasias.<sup>44</sup> A suggested approach is detailed in Table 5. Up to 10% of patients with idiopathic polyneuropathy harbor

**Table 5.** Flow chart for evaluation of polyneuropathy patient



SPEP = serum protein electrophoresis, IEP = immunoelectrophoresis, IF = immunofixation, MGUS = monoclonal gammopathy. Source: Reprinted with permission from Kelly JJ: Polyneuropathies associated with plasma cell dyscrasias, in Brown MJ (ed): Seminars in neurology. Neuropathy 7:30-39, 1987.

**Table 6.** Features of polyneuropathy M protein syndromes.

Type of polyneuropathy	Topography	Weakness	Sensory loss	Autonomic loss	Course	CSF protein elevation	Pathology	EMG
MGUS (IgM)	Distal, symmetric	++	+++	0	Chronic	++	SD	Slow CV
MGUS (IgG, IgA)	Distal, rarely proximal	++	++	+	Chronic	++	SD	Slow or mildly slow CV
AL	Distal, symmetric	+ / ++	+++	++	Chronic	±	AD	Mildly slow CV
OSM	Distal, symmetric	+++	++	0	Chronic	++ / +++	SD (AD)	Slow CV
WM	Distal, symmetric	++	++	0	Chronic	++	SD	Slow CV

Note: 0 = none, ± = equivocal or occasional, + = minimal, ++ = moderate, +++ = marked, MGUS = monoclonal gammopathy, AL = amyloidosis, OSM = osteosclerotic myeloma, WM = Waldenstrom's macroglobulinemia, SD = segmental demyelination, AD = axonal degeneration, CV = conduction velocity.

Source: Reprinted with permission from Kelly JJ: Polyneuropathies associated with plasma cell dyscrasias, in Brown MJ (ed): Seminars in neurology. Neurology 7:30-39, 1987.

an occult plasma cell dyscrasia which may directly relate to the etiopathogenesis of the neuropathy and respond to treatment. These patients are of investigational importance because the monoclonal protein may cause the polyneuropathy. The features of the polyneuropathy in the different plasma cell dyscrasia syndromes are summarized in Table 6.

Primary systemic amyloidosis of the amyloid light-chain type forms an important subset of the plasma cell dyscrasia syndromes. The polyneuropathy, however, is axonal and usually involves small fibers without evidence of conduction slowing, and therefore should not be confused with the demyelinating dysimmune polyneuropathies. Similarly, typical multiple myeloma is associated with a very high monoclonal protein level, widespread lytic skeletal lesions, anemia, and hypercalcemia. It is rarely associated with polyneuropathy.<sup>47</sup> When it is, polyneuropathy is heterogeneous in type with little relationship to the status of the myeloma.

**Monoclonal Gammopathy of Undetermined Significance.** In evaluating patients with presumed CIDP, a monoclonal gammopathy occasionally is identified. This hematologic disorder, referred to as monoclonal gammopathy of undetermined significance (MGUS), was formerly called "benign monoclonal gammopathy" but was renamed because up to 20% of these patients develop more serious hematologic disease or secondary changes elsewhere, including neuropathy.<sup>49</sup> By definition, these patients have a low monoclonal protein concentration (<3 g/dl), no malignant plasma cell infiltration of the bone marrow, and no bony lesions (Table 7). This group accounts for about one-half of plasma cell dyscrasia, polyneuropathy patients (Table 8).

Patients with MGUS-associated neuropathy include IgM and non-IgM types. The IgM group is of interest because one-half of these patients have a characteristic polyneuropathy, and the monoclonal immunoglobulin possesses antinerve activity, most commonly directed at an antigen on the

**Table 7.** Hematologic diagnostic criteria of M protein syndromes.

Syndrome	Anemia	M protein serum	M protein urine	Bone marrow	Skeletal survey	Tissue biopsy
MGUS	No	+*	±	±	Normal	—
AL	+ / ++	++	+	+	Normal	++ (amyloid)
MM	+++	+++**	++	+++	Abnormal (lytic)	+++ (myeloma)
OSM	No	+*λ	No	++ / +++	Abnormal (sclerotic)	+++ (sclerotic myeloma)
WM	+++	+++**	±	++ / +++	±	—
GAMMA-HCD	+++	+	+	++	N	—

Note: ± = equivocal or occasional, + = rare, ++ = common, +++ = almost always or severely abnormal, MM = multiple myeloma, Gamma-HCD = gamma heavy-chain disease, other abbreviations same as Table 6.

\* Less than 3 g per deciliter.

\*\* More than 3 g per deciliter.

λ = Almost always lambda light chain.

Source: Reprinted with permission from Kelly JJ: Polyneuropathies associated with plasma cell dyscrasias, in Brown MJ (ed): Seminars in neurology. Neurology 7:30-39, 1987.

**Table 8.** Final hematologic diagnosis in 28 patients with polyneuropathy and M proteins.

Monoclonal gammopathy of undetermined significance	16
Amyloidosis, light-chain type	7
Myeloma (including osteosclerotic cases)	3
Waldenstrom's macroglobulinemia	1
Gamma heavy-chain disease	1
Total	28

Source: Reprinted with permission from Ref. 46.

myelin sheath.<sup>36,52</sup> The vast majority of patients with antinerve-reactive IgM polyneuropathy have a slowly progressive, sensory polyneuropathy which superficially resembles the sensory neuronopathy syndrome seen with cancer. These neuropathies, however, tend to be much more chronic and indolent, and weakness and atrophy may develop when the neuropathy is advanced. Pansensory impairment with sensory ataxia occurs. Other cases are very mild and nonprogressive over several years. Electrodiagnostic findings differentiate these patients from those with pure sensory neuronopathy. Motor conduction is markedly slowed in the range associated with segmental demyelination,<sup>36</sup> and CMAP amplitudes are reduced. Needle EMG confirms loss of motor axons. The CSF protein is usually markedly elevated unless the polyneuropathy is very mild.

Nerve biopsy demonstrates combined axonal degeneration and demyelination. Direct immunofluorescent staining for immunoglobulins<sup>37</sup> shows deposition of monoclonal IgM (Fig. 5) on the myelin sheath. The monoclonal protein is almost always of the kappa light-chain type. Studies have demonstrated in vitro reactivity of this immunoglobulin with myelin-associated glycoprotein (MAG) and other carbohydrate epitopes of glycoproteins or glycolipids on the myelin sheath.<sup>40</sup>

Treatment with immunosuppressives and TPE decreases the immunoglobulin level and patients may improve (Ref. 87 and Kelly et al., unpublished). Injection of serum from these patients into animal nerves causes focal demyelination.<sup>37</sup> Rarely, other IgM polyneuropathies are associated with axonal degeneration, and IgM is deposited on axons and perineurial tissue. Studies have shown in vitro reactivity with axonal pellets and axonal antigens such as chondroitin sulfate.<sup>86</sup>

Patients with nonreactive IgM neuropathies form a more heterogeneous group. Some closely resemble MAG-reactive polyneuropathies, and some resemble axonal neuropathy. They may re-

spond to immunosuppression. The mechanism of nerve fiber damage is unknown.

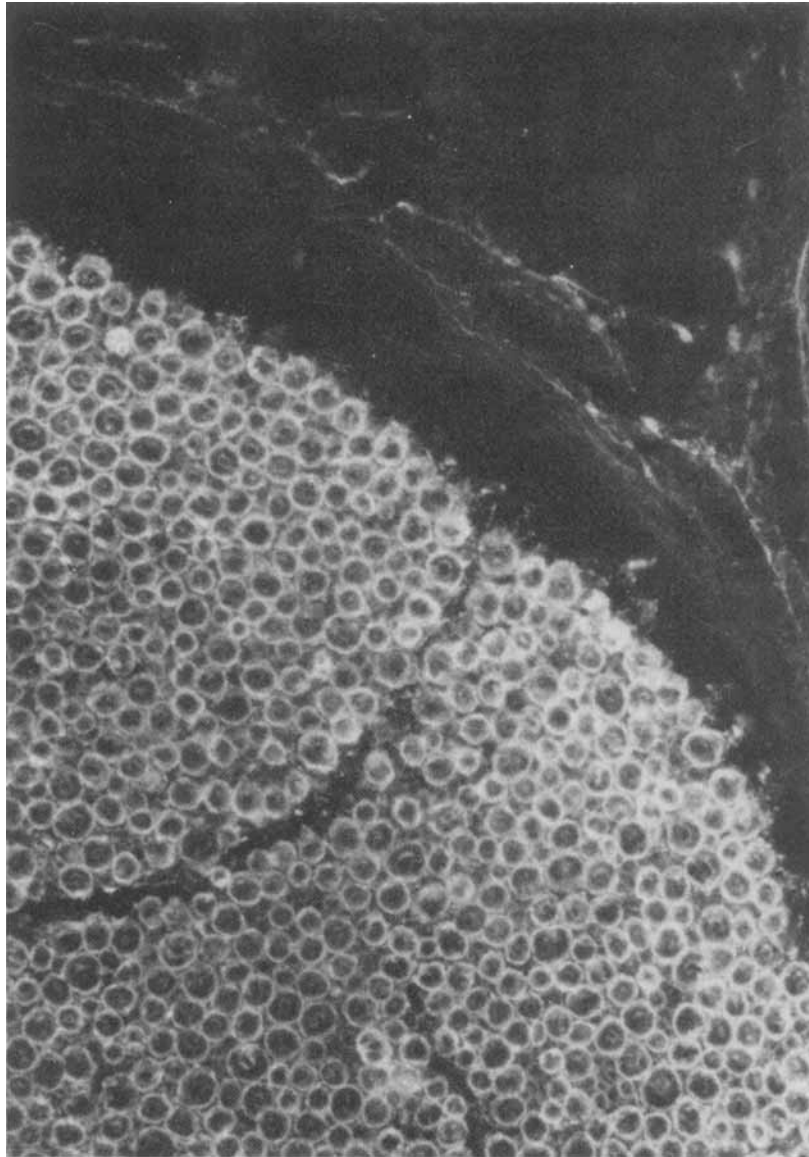
Patients with the IgG or IgA polyneuropathies are a heterogeneous group, and a relationship, if any, between the gammopathy and polyneuropathy is not clear. Nevertheless, such patients may have an unequivocal demyelinating polyneuropathy indistinguishable from patients with CIDP- or IgM-associated dysimmune neuropathy. Response to immunosuppression is variable.<sup>87</sup>

**Osteosclerotic Myeloma.** Osteosclerotic myeloma differs from typical multiple myeloma.<sup>45</sup> Less than 3% of patients with osteosclerotic myeloma account for about two-thirds of cases of polyneuropathy in large myeloma series; about one-half of all osteosclerotic myeloma patients have a polyneuropathy. Osteosclerotic myeloma is more indolent than multiple myeloma, occurs at a younger age, and is associated with longer survival. The polyneuropathy tends to be slowly progressive, distal, symmetric, and mainly motor, without autonomic dysfunction. CSF protein is very high, and there is frequently papilledema.

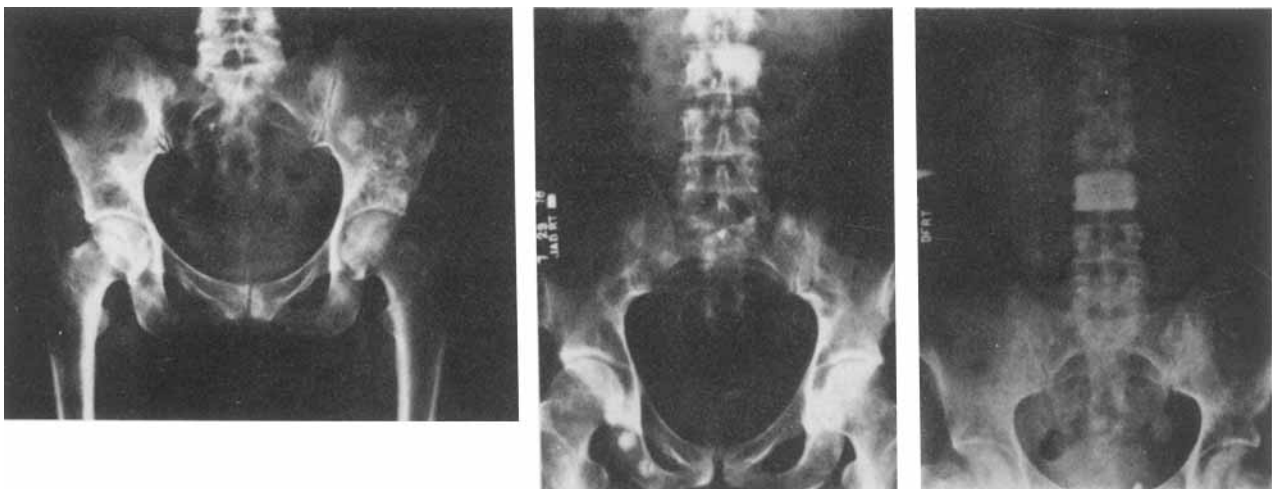
Electrodiagnostic findings<sup>21,43,45</sup> include marked slowing of motor nerve conduction velocities, partial conduction block, and prolonged or absent F-response latencies. SNAPs are decreased or absent. EMG needle examination shows acute and chronic neurogenic changes. Most patients have monoclonal protein of the IgG or IgA and lambda light-chain type, but occasionally, kappa light-chains are present. There are no reports of direct immunofluorescent staining of nerves from these patients, and the monoclonal protein is not MAG-reactive.<sup>36</sup> Microinjection of the serum into animal nerves does not cause focal demyelination or conduction block.<sup>46</sup> The key to diagnosis is recognition of the monoclonal protein and bony lesions.

The polyneuropathy resembles monophasic CIDP, and consideration of this diagnosis mandates protein studies and a metastatic skeletal survey. Bony lesions occur in the proximal skeleton and may be sclerotic or mixed sclerotic and lytic (Fig. 6). Biopsy of any suspicious lesion is mandatory. Treatment depends on the nature of the plasmacytoma. If solitary, surgical extirpation or radiation therapy is indicated, and patients improve following effective treatment. Many, or possibly all, eventually relapse. If lesions are multiple, chemotherapy occasionally provides benefit.<sup>21</sup>

Some patients<sup>9</sup> develop widespread findings with polyneuropathy, organomegaly, endocrinop-



**FIGURE 5.** Immunofluorescent staining shows intensely stained deposits of IgM especially along the outer lamellae of the myelin sheaths of myelinated axons. Less intense staining is seen around the axon. (Reprinted from Ref. 37 with permission.)



**FIGURE 6.** Osteosclerotic lesions in patients with polyneuropathy. (A) Mixed lytic and sclerotic lesion of the left ilium in a 56-year-old woman. (B) Multiple sclerotic lesions involving vertebral bodies, sacrum, ischium, and pelvis in a 42-year-old man. (C). "Ivory" L-3 vertebra in a 47-year-old woman. (Reprinted from Ref. 45 with permission.)

athy, M protein, and skin changes (POEMS syndrome). This multisystem disorder also has been called "Crow-Fukase syndrome" and "Takatsuki's syndrome".<sup>70</sup> None of these terms is satisfactory because they are too restrictive. Most of these patients have monoclonal proteins of the IgG or IgA type with lambda light-chains. One-half to two-thirds have osteosclerotic lesions. The common denominator may be the lambda light-chain or some other secretory product of the plasma cell lesion. Thus, osteosclerotic myeloma may be one end of a spectrum, with POEMS at the other.

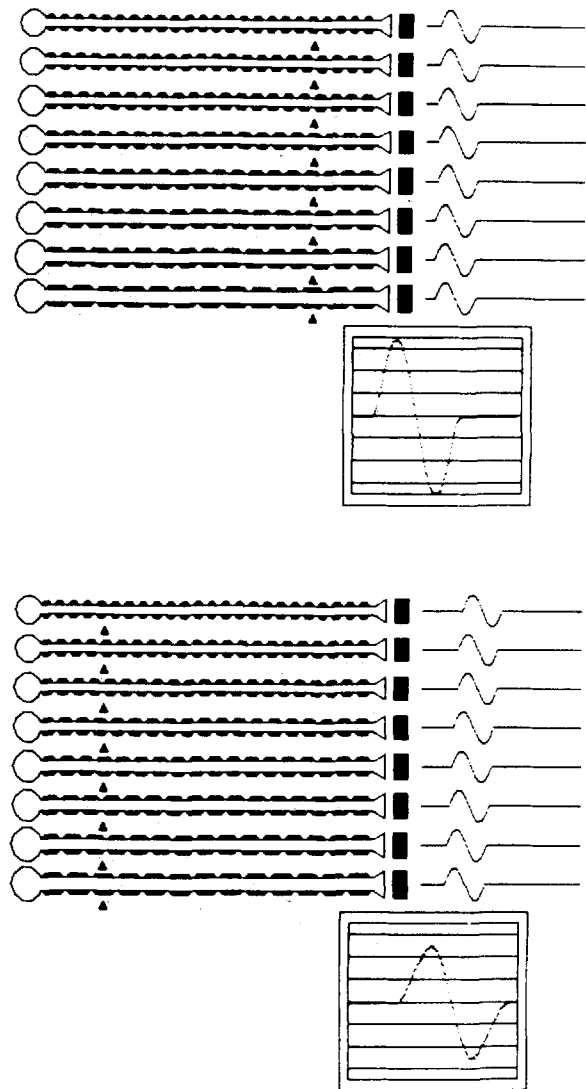
### CONCLUSION

Patients with acquired demyelinating polyneuropathies comprise a substantial portion of those patients with undiagnosed polyneuropathies presenting for evaluation. Their importance is disproportionate to their numbers, since many are treatable, some are associated with unrecognized systemic disorders, and most provide clues to the etiopathogenesis of other obscure neuropathies. Although their relationship is unclear, the acute, chronic, and dysimmune inflammatory demyelinating polyneuropathies have characteristic presentations, some of which are easily recognized. Not surprisingly, the electromyographer plays a central role in the evaluation of these patients and is in a position to recognize the patterns of involvement and suggest possible diagnostic alternatives. Thus, the ability to identify an acquired demyelinating polyneuropathy, coupled with a thorough knowledge of these syndromes, is important for any electromyographer who studies neuromuscular patients.

### APPENDIX

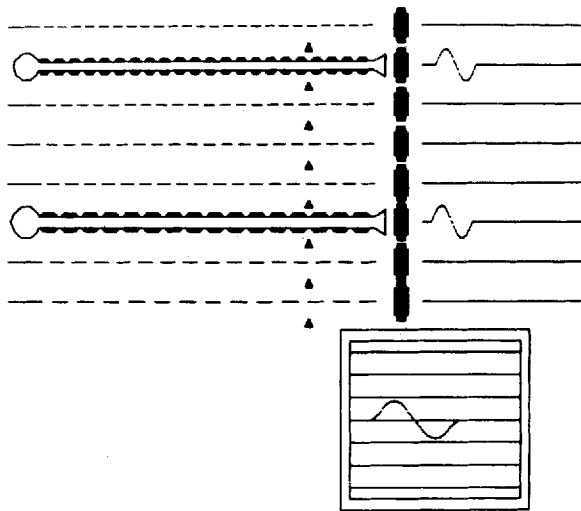
#### Motor Nerve Model: Prediction of Electrodiagnostic Findings in Multifocal Demyelination.

A simple model of the peripheral motor nerve can predict electrodiagnostic findings in acute inflammatory demyelinating polyneuropathy (AIDP). This model, together with empiric electrodiagnostic observations, can be used to anticipate the electrodiagnostic findings for acute, multifocal demyelination. The model is represented in Figs. 7-9, consisting of eight axons of variable diameter, ranging from the largest (top) to smallest (bottom). Individual muscle fiber action potentials (MFAPs) are shown to the right of each axon following stimulation of all axons (arrow). Conduction is fastest in the largest and slowest in the smallest axon; the difference in conduction between the largest and smallest fibers constitutes



**FIGURE 7.** Computerized model of peripheral motor nerve, demonstrating summation of eight individual muscle fiber action potentials to produce the compound muscle action potential (CMAP) shown below each nerve in the schematic screen. Individual axons are of slightly different sizes and therefore conduct at different rates. Muscle fibers are denoted by solid bars to the right of each axon. Arrows represent stimulation sites. Upper recording: resultant CMAP following distal nerve stimulation. Lower recording: resultant CMAP following proximal nerve stimulation. (Reprinted from Ref. 1 with the permission of Butterworths, Copyright © 1987).

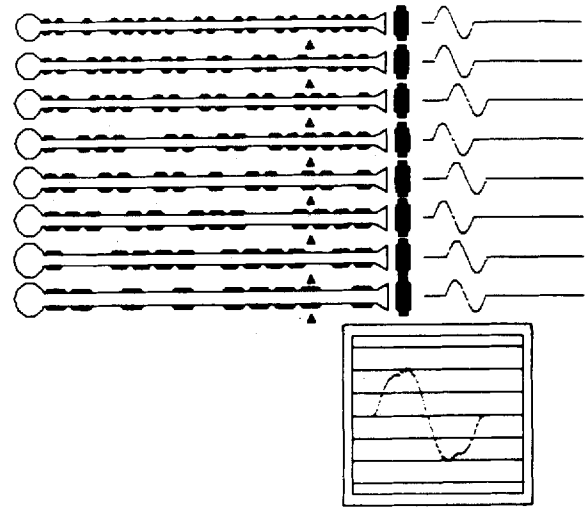
the range of conduction velocities. Individual MFAPs are summed to obtain a compound muscle action potential (CMAP), shown below the modeled nerve. In the figures, the simulated CMAP is demonstrated for distal nerve stimulation (upper half of each figure) and proximal nerve stimulation (lower half of each figure). Latencies could be calculated and a conduction velocity for the fastest axon determined using the distance between stim-



**FIGURE 8.** Computerized model of axonal degeneration in peripheral motor nerve described in Fig. 7, following random loss of 75% of axons. Resultant CMAP after distal (upper screen) and proximal (lower screen) stimulation. Arrows represent stimulation sites. (Reprinted from Ref. 1 with the permission of Butterworths, Copyright © 1987).

ulation sites. In this model of normal nerve (Fig. 7), the CMAP amplitude can be measured following proximal and distal stimulation. The reduced CMAP amplitude following proximal stimulation reflects the expected temporal dispersion of individual MFAPs and would be increased if either the distance between stimulation sites or the range of conduction velocities were increased.

Following extensive axonal degeneration (Fig. 8), CMAP amplitude diminishes for both proximal and distal stimulation with little change in distal latency or conduction velocity. If the largest axon had remained intact, conduction velocity and dis-



**FIGURE 9.** Computerized model of multifocal demyelination in peripheral motor nerve described in Fig. 7. Resultant CMAP after distal (upper screen) and proximal (lower screen) stimulation. Arrows represent stimulation sites. The diminished CMAP amplitude with proximal stimulation results from temporal dispersion of individual muscle fiber action potentials and conduction block in some axons. (Reprinted from Ref. 1 with the permission of Butterworths, Copyright © 1987.)

tal latency would have been unchanged. The greatest abnormality relative to axonal degeneration would result if only the smallest fiber remained. Both conduction velocity and distal latency would be abnormal, but the magnitude of abnormality would be small compared with the reduced CMAP amplitude.

For comparison, random, multifocal demyelination is demonstrated in Fig. 9. In the model, propagation is slowed across a single demyelinated node, and conduction is blocked if two ad-

adjacent nodes are demyelinated. With distal stimulation, CMAP amplitude is slightly reduced and duration slightly increased because of increased dispersion. Distal latency is slightly prolonged because the largest two fibers are demyelinated distally but the third largest fiber is intact. Proximal stimulation results in pronounced temporal dispersion of the CMAP, explained by the variable amounts of demyelination in some axons compared with the others, producing an increase in the range of conduction velocity. This results in the initial component of the CMAP (representing the fastest conduction time) being greatly separated from the trailing portion of the CMAP (representing the slowest conducting axon). The CMAP amplitude with proximal stimulation is reduced to a greater extent than can be explained by temporal dispersion alone, because of conduction block in two of the axons. The likelihood of continuous propagation along the nerve decreases with increasing fiber length because of

the increased probability of having demyelination in two adjacent nodes. F response latencies would be increased or unobtainable, depending upon the extent of conduction block. The findings of abnormal temporal dispersion and partial conduction block are very useful in establishing a diagnosis of acute inflammatory polyneuropathy. A representative recording from a patient early in the course of inflammatory polyneuropathy is shown in Fig. 1 for comparison to the model.

The presence of abnormal temporal dispersion is useful in distinguishing acquired demyelinating neuropathies from hereditary demyelinating neuropathies.<sup>54</sup> In the latter, demyelination is uniform and involves all fibers. The range of conduction velocity is not dramatically increased, because all fibers demonstrate conduction slowing to a similar extent. Therefore, conduction velocity may be markedly slowed, but abnormal temporal dispersion does not result.

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