within the fascicle of severe demyelination. Electron microscopy showed large diameter axons with very thin myelin (Fig. 3A) and some axons that were completely devoid of myelin, being surrounded only by Schwann cell processes and redundant basal lamina (Fig. 3B). Some thinly myelinated axons were surrounded by supernumerary Schwann cells, forming rudimentary onion bulbs. There was an increase in the endoneurial interstitial space, concentrated in the subperineurial area, suggesting endoneurial edema, and the perineurium was thickened. Inflammatory cells were also absent. A third patient had a biopsy of a supraclavicular mass that was found to consist of nerve, and MMN was diagnosed several years later (41). The paraffin-embedded nerve showed exuberant onion bulb formation (Fig. 4A). The endoneurial interstitial space was markedly increased, and there was prominent mononuclear cell infiltration concentrated around endoneurial venules but also extending into the general endoneurial compartment (Fig. 4B). The infiltrate consisted mainly of lymphocytes with many macrophages.

The pathology in this case differed from those described by Kaji et al. (10) and Auer et al. (40) in the more severe onion bulb formation, the presence of prominent mononuclear cell inflammation, and the degree of interstitial edema but more closely resembled those described by Adams et al. (42) and Bradley et al. (43) in the lack of classic clinical and electrophysiologic features of MMN. The first report described two patients with steroid-responsive sensory and motor multifocal neuropathy with nerve hypertrophy, a clinical picture resembling the neuropathy described by Lewis et al. (3) ("Lewis-Sumner syndrome") that closely resembles MMN. Pathologically, the nerves showed marked interstitial hypertrophy and onion bulb formation with both focal and diffuse mononuclear inflammatory cell infiltration. The second report described a patient with a motor neuropathy that was asymmetric but not strikingly multifocal as is typical of MMN. Electrophysiologic studies showed multifocal MCB, but sensory nerve action potential amplitudes were reduced. Once again, the brachial plexus biopsy showed marked interstitial hypertrophy, onion bulb formation, and mononuclear cell inflammation.

The pathologic changes in mixed nerves support the concept that MMN is an autoimmune disorder. Mononuclear cell and macrophage infiltration with demyelination and onion bulb formation are features common to other autoimmune neuropathies, and identical abnormalities are seen in the sensory nerves of patients with CIDP. Impressed by the failure to reestablish normal conduction despite remyelination, Kaji et al. (10) postulated the pres-
ence of a factor that blocks sodium channels or prevents their redistribution. Further argument in favor of blocking antibodies comes from the often rapid response to treatment. Conduction block may result from minimal morphologic changes at the node of Ranvier, and conformational changes may remodel the paranodal apparatus sufficiently to reestablish conduction within days of starting treatment. Nonetheless, it is curious that fixed conduction block at one site may remain for years, suggesting the presence of a soluble factor that inhibits recovery, whether by blocking sodium channels or preventing remyelination. The remarkable similarity of the pathologic changes in patients with classic MMN or Lewis-Sumner syndrome and typical CIDP suggests that slight differences in similar primary antigens triggering the immune response may account for the clinical differences.

**Sensory Nerve Pathology**

Mild pathologic changes in sensory nerves also occur in MMN. Parry and Clarke (2) noted mild loss of myelinated axons in the sural nerve of the one patient, although quantitative morphometry was not done. Mild perivascular inflammatory cell infiltration (7,14), mild fiber loss (2,14), subtle demyelination (14,44), and regeneration (44) were described. There was only one systematic quantitative study of sensory nerves in MMN (45). The mean total fiber density in 10 patients so studied did not differ from normal control subjects, although one patient had a total fiber density of less than 50% of the normal mean. In six patients, there was a significant reduction in the number of large fibers measuring more than 7 μm. The most common abnormality, seen in all 11 nerves, was mild demyelination consisting of an increased number of thinly myelinated fibers, miniature onion bulbs, rare demyelinated fibers, and active macrophage-mediated demyelination, without endoneurial edema or endoneurial or epineurial inflammation. The abnormalities in sensory nerves underscore the extent of fiber type involvement and support the kinship of MMN to CIDP.

**Treatment of Multifocal Motor Neuropathy**

All effective treatments for MMN involve immune modulation or suppression. The rationale for immunotherapy in MMN derives from its similarity to CIDP. The discovery of high titers of GM1 antibodies often seen in MMN supported the concept of an immune basis, and the pathologic features, previously described, provided further support for this concept. Attempts to define the best treatment of MMN are still based on anecdotal reports and small controlled series. However, a consensus has emerged in favor of high-dose intravenous immunoglobulin (IV Ig) therapy for most affected patients.

**Intravenous Immunoglobulin**

High-dose IV Ig is the most widely used and effective treatment for MMN. The literature contains reports on such treatment in nearly 50 patients. Kaji et al. (46) reported improvement with IV Ig in two patients that failed prednisone, plasmapheresis, and oral cyclophosphamide. In general, clinical improvement occurred in 2 to 4 weeks. One patient required monthly treatment, whereas the other was treated for 5 months with sustained benefit. Chaudhry et al. (47) treated nine patients and all improved, usually within hours to days, peaking at 2 weeks and lasting about 2 months, although one obtained sustained remission. The response to treatment was independent of the initial GM1 antibody titer, the change in GM1 antibody titer, or obvious change in conduction block. Nobile-Orazio et al. (48) noted dramatic and sus-
tained improvement; one patient returned to normal within a few months of receiving a single course of IVlg and was in sustained remission at 12 month follow-up. Other patients treated, in addition, with oral cyclophosphamide increased the intertreatment interval of IVlg, but they generally had elevated GM1 antibody titers that were unaffected by immune suppression.

Several placebo-controlled observations soon followed. Yuki et al. (49) noted improvement with IVlg but not with placebo in a single-blinded protocol. Azulay et al. (50) treated five patients with MMN in a double-blind placebo-controlled trial and showed increased muscle strength. Van den Bergh et al. (51) treated six respondents in an open-label trial, who then received IVlg or placebo in a double-blind protocol. Five patients responded to IVlg but not placebo, whereas the sixth responded equally to both.

Our experience with IVlg has generally been similar. All seven of our patients responded to treatment (Table 1), but improvement was not sustained for more than 2 months after a single course, and long-term treatment was always needed. In three patients, there was improvement in MCB that paralleled treatment (Fig. 1) (11), whereas the others improved without demonstrable changes in MCB. The rapidity of the clinical improvement can only be explained by reversal of conduction block. The inability to document reversal of conduction block in some cases probably reflects conduction block at sites technically difficult to evaluate such as nerve roots and proximal nerve trunks. Segmental amplitude ratios may not improve with treatment because of the slowly conducting components, giving rise to dispersed responses that occur too late to contribute to the CMAP amplitude. There has not been a consistent relationship between treatment response and either the initial or later GM1 antibody titer. We found that response to treatment tended to be less over time but that no patient became unresponsive. Others also found that the effectiveness of IVlg diminished with longer treatment (44) and that some patients became refractory (52). In some of our patients, addition of azathioprine or prednisone enabled the intertreatment interval to be increased.

### Table 1. Quantitative Muscle Strength Testing

<table>
<thead>
<tr>
<th></th>
<th>June 1993</th>
<th>August 1993</th>
<th>November 1993</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoulder flexion</td>
<td>10.4</td>
<td>18.6</td>
<td>22.0</td>
</tr>
<tr>
<td>Shoulder extension</td>
<td>25.0</td>
<td>40.0</td>
<td>44.0</td>
</tr>
<tr>
<td>Elbow flexion</td>
<td>7.3</td>
<td>12.9</td>
<td>14.6</td>
</tr>
<tr>
<td>Wrist extension</td>
<td>6.0</td>
<td>7.4</td>
<td>10.8</td>
</tr>
</tbody>
</table>

**Improvement in strength in affected muscles after monthly treatment with high-dose intravenous immunoglobulin in a patient with multifocal motor neuropathy. Numbers refer to the weight in kilograms that the patient could lift. All values shown are from the right arm.**

### Cyclophosphamide

Pestronk et al. (13) reported responsiveness of MMN to cyclophosphamide. One patient was treated with a single course of 3 g/m² intravenous cyclophosphamide over 8 days, followed by oral therapy for 10 months. Strength improved to near normal even after discontinuation of treatment. A second patient received the same dose without additional oral therapy and relapsed after 8 months. He was later retreated with intravenous followed by oral therapy, and improvement was later maintained. The response to treatment was paralleled by a fall in GM1 antibody titers. These observations were extended to nine patients with similar results (53). However, cyclophosphamide dosages were high, incurring a significant risk of serious adverse effects. In recognition of this, Pestronk et al. (54) lowered the dose of intravenous cyclophosphamide preceded by 2 days of plasmapheresis and achieved similar benefits with a 50 to 70% reduction in drug dose. With either of these regimens there was 1 to 2 years of sustained improvement after cessation of treatment, although relapses were common and required retreatment. Tan et al. (55) administered intravenous cyclophosphamide, but the response in their patients was independent of a change in GM1 antibody titers.

Other treatments for MMN have generally been ineffective. A few patients respond to prednisone (55,56), but in most it was ineffective and occasionally caused rapid deterioration (57). In one atypical patient with rapidly evolving weakness there was improvement with prednisone and plasmapheresis (7). No other patient has responded to plasmapheresis.

### Relationship of Multifocal Motor Neuropathy to Chronic Inflammatory Demyelinating Polyneuropathy

There are clinical, electrophysiologic, morphologic, and immunologic similarities between MMN and CIDP. Classically, CIDP is a largely symmetric, sensory, and motor neuropathy (51); however, motor features predominate and can be strikingly asymmetric. The patients described by Lewis et al. (3) were similar to those with MMN in view of the motor predominance and predilection for the arms. Conversely, most patients with MMN have subtle sensory symptoms or signs and abnormalities of quantitative sensory testing, sensory nerve conduction, and frequent morphologic abnormalities in sensory nerves. Elevated GM1 antibody titers can be seen in both disorders, although they are always higher in MMN. Thus, in the autoimmune demyelinating neuropathies, there may be a continuum of features, including predominantly sensory, sensory-motor, and predominantly motor, which may be symmetric, asymmetric, or even strikingly multifocal.
SUMMARY

MMN is a strikingly asymmetric predominantly motor variant of CIDP. The resemblance of MMN to MND has been exaggerated, and the two can generally be readily distinguished on clinical and electrophysiologic grounds. Further studies are clearly needed to fully clarify the relationship between MMN and other motor syndromes associated with glycolipid antibodies.

REFERENCES

42. Adams RD, Asbury AK, Michelsen JJ. Multifocal pseudohypertrophic neuropathy. Trans Am Neurol Assoc 1965;90:30–34.