evidence of demyelination and remyelination, 21% had axonopathy, 13% had features of both myelinopathy and axonopathy, and 18% were normal; only 11% had inflammation; however, lymphocyte marker immunohistochemistry was not performed.

Motor Neuropathy and Motor Neuron Disease

Our present concepts of motor neuropathy have evolved over the past two decades, influenced by the delineation of several lower motor neuron (LMN) syndromes separable from classic CIDP and motor neuron disease (MND). In 1982, Lewis and Sumner (34) described 5 patients from among 40 cases of CIDP with a primarily motor form of mononeuritis multiplex especially involving the arms, with multifocal conduction block of mixed nerves severe enough to account for the observed weakness. This syndrome, termed multifocal demyelinating motor neuropathy, was considered a variant of CIDP. Sural nerve biopsies in three patients so studied showed primarily demyelination and remyelination with varying axon loss. Treatment with immunosuppressant medication led to neurologic improvement. In the same volume of the journal Neurology, Lewis and Sumner (35) demonstrated that conduction block was specific for acquired immune demyelination and rarely if ever occurred in inherited neuropathy.

Several years later, Parry and Clarke (36), Pestrunk et al. (37), Bradley et al. (38), and Krarup et al. (39) described other patients with focal weakness, wasting, and fasciculation without sensory involvement that resembled progressive spinal muscular atrophy. The defining feature of so-called multifocal motor neuropathy (MMN) was conduction block restricted to motor axons with normal conduction in uninvolved nerves. Other laboratory findings have included high serum titers of GM1 antibodies in many, but not all, patients and demyelination and remyelination leading to large caliber axons with thinly myelinated fibers, minor onion bulbs, and variable axon loss in sural and mixed nerve biopsy specimens (Fig. 11A and B). The distinction between MMN and MND has been important because motor neuropathy is treatable with immunomodulating and immunosuppressant medications, whereas MND is irreversibly fatal.

In the same period, morphometric and later immunohistochemical studies were undertaken in the nerves of patients with ALS, and these in turn led to improved understanding of motor neuropathy. The concept that weakness and wasting resulted from neuronal degeneration or neuropathy initially stemmed from neuropathologic studies of patients with ALS. However, there was lingering uncertainty as to contribution of focal proximal axonopathy and distal “dying back” degeneration of peripheral motor axons, an issue that was addressed during a symposium sponsored by the Muscular Dystrophy Association in 1981 in Scottsdale, Arizona. Dyck (40) presented morphometric data showing selective loss of motor neurons in ALS spinal cords, with evidence of acute axonal degeneration in peripheral motor axons. In a discussion of that article, Bradley et al. (41) commented that an equal proportion of acute axonal degeneration was observed along proximal and distal segments of the phrenic nerve of patients with

![FIG. 11. Multifocal motor neuropathy. A: A sural nerve biopsy in semithin section stained with toluidine blue shows increased numbers of thinly myelinated large caliber fibers (arrows) and a single degenerating axon (arrowhead). B: Electron microscopy of the sural nerve shows thinly myelinated large fibers and minor onion bulbs.](image-url)
ALS at autopsy, with only a 16% loss of distal large myelinated fibers. Corbo et al. (13) later showed statistically more frequent regenerative clusters of small myelinated fibers in motor nerve biopsy specimens of patients with motor neuropathy than in those with MND in which few or no regenerative clusters were found (Fig. 12A–C).

Direct immunofluorescence staining of sural nerve cryosections in over 50 cases of ALS generally showed no morphologic differences compared with normal control subjects (42); however, two reported patients had exceptional findings. The first was a 73-year-old woman with typical ALS, before breast cancer, and a monoclonal IgA serum paraprotein. Sural nerve biopsy showed deposits of IgA and light chains along axons. At postmortem examination, indirect immunofluorescence revealed binding of IgA to axons and the perikarya of nerve cells and specificity for the high-molecular-weight subunit of neurofilament protein and a neuronal surface antigen (43,44). The second patient was a 38-year-old woman with atypical ALS because of progressive paraplegia in association with multifocal motor conduction block and a high serum IgM GM1 antibody titer (45). Sural nerve biopsy showed granular IgM deposits at nodal and paranodal regions of myelinated nerve fibers. When the patient's serum was injected into rat sciatic nerve, the serum IgM bound to the nodes of Ranvier, and this binding activity was removed by preincubation with GM1 (46).

LNM syndromes associated with lymphoma presented additional challenges to nomenclature and etiopathogenesis of motor disorders. First described in 1963 by Rowland and Schneck (47), and then named by Schold et al. (48), so-called subacute motor neuronopathy presents with progressive painless asymmetric limb weakness, with few or no signs of sensory involvement, reminiscent of motor neuropathy. Altogether, LNM disease accounts for some patients with MND and lymphoma (49) and includes patients that differ clinically and pathologically from sporadic forms of MND. Among 26 reported patients with MND and lymphoma seen over the past two decades at Columbia Presbyterian Medical Center in New York (50), all 3 with pure LNM disease improved with treatment of the underlying malignancy. One patient had multifocal motor conduction block and chronic lymphocytic leukemia (49). A second patient had IgM paraproteinemia with reactivity to GM1 and GD1b gangliosides (51); sural nerve biopsy in that patient showed axon loss, focal demyelination, and increased numbers of regenerative clusters. A third patient had progressive paraplegia with

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FIG. 12. Motor nerve biopsy studies in motor neuropathy and motor neuron disease. Semithin sections of a motor nerve in a patient with motor neuron disease (A), showing a reduction of myelinated fibers and a few foci of myelin debris (arrows). (B and C) Motor nerve fascicle from a patient with motor neuropathy demonstrates in addition many thinly myelinated fibers (arrows) and small onion bulbs (arrowheads). At higher power, a motor fascicle shows four regenerative clusters of myelinated fibers, a band of Bungner (arrow), a demyelinated axon (arrowhead), and myelin ovoid (curved arrow). Reproduced by permission of John Wiley and Sons Publishers.
IgA monoclonal paraproteinemia (61). Whereas the postmortem examination of patients with ALS and lymphoma differs little from sporadic ALS, those with subacute motor neuronopathy demonstrate, in addition, mild inflammatory cell infiltration and degeneration of the posterior columns sparing the corticospinal tracts, with patchy demyelination in peripheral nerves (47,48,52,53).

Diabetic Neuropathy

There are several recognizable clinicopathologic neuropathic syndromes associated with diabetes mellitus and different methods of classification; significant motor involvement is not uncommon (54). Progressive painful pelvicemoral weakness is the predominant manifestation of proximal diabetic neuropathy, lumbosacral plexitis, and diabetic amyotrophy, further separable by electrodiagnostic studies. Distal weakness parallels the severity of sensory involvement in distal polyneuropathy. Weakness occurs in the arms in the distribution of mixed or motor nerve trunks in mononeuritis multiplex and simplex.

Although early investigations of diabetic neuropathy used nerve trunks from amputated limbs or postmortem specimens (55–57), the modern analysis of peripheral nerve biopsies has played an important role in elucidating the pathology of peripheral nerve injury in this disorder. Although it can still be debated how much ischemia, metabolic alterations, and immunologic mechanisms of nerve injury each contribute to diabetic microangiopathy or to a particular form of neuropathy, one fact is clear: Nerve biopsy is an important tool in appreciating the type and extent of pathologic alterations in a given patient (54).

Diabetic microangiopathy refers to the collective morphologic and biochemical alterations of nerve microvessels and is the major determinant of neuropathy. Under the influence of microangiopathy and accelerated atherosclerosis, a range of ischemic events occur in a given patient, ranging from a mild reduction in the delivery of oxygen and essential nutrients to frank infarction of one or more fascicles, depending on the severity of the vascular alterations, acuteness of the injury, and the efficiency of the collateral circulation. Microscopically, there is thickening of microvessels due to reduplication of basal lamina, pericyte degeneration, and deposition of polysaccharide in vessel walls, recognized by positive periodic acid-Schiff staining (58). Although early ultrastructural studies found abnormal closure of endoneurial capillaries and intraluminal platelet thrombi in sural nerve microvessels (59), these findings were not confirmed in later analyses (60). Using immunohistochemical studies, we noted an increased density of microvessels in diabetes compared with normal control subjects.

Chronic sustained hyperglycemia leads to diverse metabolic sequelae in peripheral nerve fibers including increased flux in the polyol pathway, nonenzymatic glycation of protein elements, an accumulation of vasoactive substances, alterations in lipid metabolism, and abnormal neurotropism (10). It is proposed that these, in turn, lead to alterations in basement membrane structure, impaired axon transport mechanisms, and further perturbation of neuropathy.

Humoral and cellular autoimmunity also contribute to the development of diabetic microangiopathy and neuropathy. Direct counting of immunoperoxidase stained T cells in peripheral nerve sections of patients with severe proximal diabetic neuropathy, distal polyneuropathy, and mononeuritis multiplex revealed significant vascular and endoneurial infiltrates compared with normal control subjects and other patients with IgM antibodies to antinemylin associated glycoprotein (54). Up to 60% of severely affected cases overall had evidence of epineural T-cell microvasculitis in a sural nerve biopsy and the remainder had variable perivascular lymphocytic infiltrates (Fig. 13A and B). Most T cells expressed the acti-
vation marker interleukin-2 receptor (CD25) and MHC Class II antigen. The significance of the T-cell infiltrates in diabetic nerves is not well understood; however, they might be directed against antigens specific for the peripheral nerve or shared by pancreas and nerve. T-cell clones might become sensitized early in the course of the illness by superantigens expressed in pancreatic islets or they might be induced by the metabolic stress of diabetes.

Complement mediated injury of microvessels also contributes to microangiopathy by the deposition of MAC along peripheral nerve microvessels detectable by immunofluorescence staining methods (Fig. 14) (11). The initiating factor in the abnormal activation of complement in diabetic nerves is still speculative, but one possibility is a defect in the expression of certain regulatory membrane proteins that normally protect cells by limiting activation of MAC.

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