site of injury to the muscle examined. The pattern of needle EMG signs of denervation assists in localization of the segmental level, whether unilateral or bilateral, although it may not be precise due to considerable overlap of paraspinal muscle innervation. Scalp somatosensory evoked potential recordings generally reveal delayed or absent responses. Normal peripheral nerve and T12 responses localize the lesion to above the T12 level. Absent or delayed T12 responses suggest that the lesion is in the region of the cauda equina or lumbosacral plexus if peripheral nerve somatosensory evoked potentials are normal. Unless the spinal cord lesion clearly involves the somesthetic pathways, somatosensory evoked potential results may be normal in the presence of a spinal cord lesion of considerable size.

Motor Neuron Disease

Motor neuron disease may present, for the first time and initially undiagnosed, as severe respiratory insufficiency (1). The combination of clinical upper and lower motor neuron signs, including hyperreflexia, weakness, wasting and fasciculation, makes the diagnosis inescapable; however, lingual signs may be overlooked in an intubated patient. Electrophysiologic studies confirm the diagnosis and exclude motor neuropathy with multifocal conduction block (2). Phrenic nerve conductions and needle EMG of the chest wall and diaphragm can be helpful in selected patients.

Acute Polynuropathy

Polyneuropathy is generally suspected (Fig. 2) in the presence of weakness, hyporeflexia, and distal sensory loss.

Acute Inflammatory Demyelinating Polynuropathy and Guillain-Barré Syndrome

The electrophysiologic features of GBS reflect peripheral nerve demyelination. In the initial stages, conduction velocities are mildly depressed or normal, F waves are prolonged or absent, and there may be evidence of conduction block and rapidly firing MUs without spontaneous needle activity (3). NCS and EMG of the diaphragm are particularly valuable in establishing the type and severity of phrenic nerve and diaphragm involvement (4,5). Serial electrophysiologic studies are valuable in following the course of the disease and response to treatment, after plasmapheresis, intravenous immunoglobulin, or corticosteroids. In our experience, symptomatic improvement precedes electrophysiologic improvement. Except for the Miller Fisher syndrome comprising ophthalmoplegia, ataxia and areflexia, primarily axonal variants of GBS (Table 1), require management in the ICU. Serology or stool culture evidence of Campylobacter jejuni may be a proximal precipitating factor in these axonal forms (6).

Acute Motor and Sensory Axonal Neuropathy

This form (7) of rapidly developing paralysis reaches completion over hours and requires prompt admission to the ICU for ventilatory assistance. With varying severity, virtually all muscles of the body, including cranial musculature, may be totally paralyzed. At the worst extreme, it clinically simulates brain death; however, the electroencephalogram is normal. The peripheral cranial nerves may be unresponsive to high-voltage and long-duration electrical stimulation. Sensory nerve action potential (SNAP) and CMAP are reduced or absent.

Acute Motor Axonal Neuropathy

This is an acute paralytic syndrome of children and young adults (8). It ascends symmetrically over days with normal sensation and often preserved deep tendon reflexes. The cerebrospinal fluid protein is increased without pleocytosis. Electrophysiologic studies reveal motor axonopathy. CMAP amplitudes are reduced with normal distal latencies and SNAP responses. There are varying degrees of denervation on needle EMG. There may be significant respiratory paralysis. Good recovery eventually occurs. This variant of GBS may be related to C. jejuni enteritis arising through cross-reacting anti-GM antibodies (9). Acute porphyria, Lyme disease, and human immunodeficiency virus infection may present with a similar syndrome.

Chronic Polynuropathies

Chronic polynuropathies occasionally evolve rapidly with respiratory insufficiency. Although rare, it may occur in chronic inflammatory demyelinating polynuropathy and diabetic polyneuropathy. In addition to the more typical clinical and electrophysiologic signs of these polynuropathies, phrenic NCS and needle EMG of the diaphragm confirm the neuropathic basis of the respiratory insufficiency.

Neuromuscular Transmission Defects

Defects in neuromuscular transmission (Fig. 2) are rare but present particular challenges in diagnosis. Respiratory insufficiency may be the presenting feature of myasthenia gravis or Lambert-Eaton myasthenic syndrome (10,11) accompanied by weakness in swallowing and breathing muscles. There is an experimental model of a rare variant of myasthenic crisis (12). The unequivocal diagnosis of myasthenia gravis rests on the presence of fluctuation of weakness in eye, facial, and limb muscles; a positive edrophonium test; and decremented response
of sequential CMAP with 3 per second supramaximal stimulation; and elevated titers of acetylcholine receptor antibodies. Phrenic NCS and needle EMG studies of the diaphragm may reveal partial denervation. Immunomodulating therapy improves all aspects of myasthenia gravis, including respiratory muscles, that precedes successful weaning from the ventilator.

The Lambert-Eaton myasthenic syndrome, hypocalcemia, hypermagnesemia, organophosphate poisoning, and wound botulism may affect presynaptic neuromuscular transmission and may be identifiable on electrophysiologic studies.

Myopathies

Patients with chronic myopathy (Fig. 2) may require intubation and admission to the ICU because of respiratory muscle weakness, although the diagnosis is usually evident as in the case of muscular dystrophy. In more acute myopathies, such as necrotizing myopathy with myoglobinuria, the diagnosis is later evident because of high serum levels of CK, myoglobinuria, and necrosis on a muscle biopsy.

ACUTE LIMB AND RESPIRATORY WEAKNESS DEVELOPING AFTER ADMISSION TO THE INTENSIVE CARE UNIT

At least 50% of patients in large medical and surgical ICUs have significant involvement of the nervous system. Neuromuscular problems are much more frequent than is generally recognized. Sepsis and multiple organ failure now occur in 20 to 50% of patients in a medical ICU (13), and 70% of such patients have CIP (14). Neuromuscular blocking agents and steroids may cause further distinctive neuromuscular syndromes (15,16). The difficulty in clinically evaluating patients with neuromuscular problems, often with difficulty in weaning from the ventilator, has led to increased reliance on electrophysiologic studies (17) and occasionally muscle and nerve biopsy. This subject has been recently reviewed (15,16,18,19).

Myelopathy

Myelopathies seen in the ICU are usually due to trauma, compression by neoplasm, hemorrhage, or infection in the epidural space or infarction of the spinal cord infarction secondary to surgical procedures on the aorta. In most instances the myelopathy occurs before admission to the ICU.

Acute Polynuropathy

Critical Illness Polynuropathy

Since its initial description 13 years ago (20), CIP has been recognized as a common polynuropathy, occurring in 50 to 70% of critically ill or injured patients (14,21, 22). Such patients are now included in the syndrome termed systemic inflammatory response syndrome (SIRS) (23). It occurs in response to both infection and several forms of trauma, including major surgery and burns. Because SIRS occurs in half of all patients in a general medical or surgical ICU, it should be regarded as a common polynuropathy (Table 2). Indeed, we encounter it almost as frequently as GBS. CIP has been reviewed by Leijten and de Weerd (18), Hund (19), Bolton (23), and Leijten (24). The latter investigator described 150 cases reported in the literature up to 1993 and added 50 cases of his own. Hund et al. (25) recently identified a low-molecular-weight humoral neurotoxic factor in the sera of patients with CIP.

The earliest nervous system manifestation of SIRS is septic encephalopathy, characterized by inattention and disorientation (26). The patient gradually slips into coma, usually without focal signs, seizures, myoclonus, or asterixis. The electroencephalogram is a sensitive indicator of the presence and severity of septic encephalopathy. Computed tomography (CT) and MRI of the brain and serial neurologic examinations are usually unremarkable (27).

If SIRS can be treated specifically with antibiotics, surgical drainage of an infected focus, inotropic drugs, or fluid replacement, the encephalopathy improves rapidly, but difficulty in weaning from the ventilator often persists. In our unit, CIP is the most common neuromuscular cause of ventilator dependency after cardiac and pulmonary etiologies have been excluded (10,28,29). Clinical signs of polynuropathy are present in about half of patients. Electrophysiologic studies are therefore necessary to firmly establish the diagnosis of CIP.

Central respiratory drive may be assessed by decreasing ventilatory support to 5 to 8 cm H₂O of pressure support or continuous positive airway pressure to overcome airway and ventilator resistance, for a maximum of 15 minutes. Mechanical ventilation is restored if there is evidence of respiratory distress, arterial oxygen saturation less than 90% based on a pulse oximeter reading, or a significant rise in heart rate or blood pressure. This is done at the time of needle EMG of the diaphragm.

The earliest electrophysiologic sign, usually within 1 week, is a reduction of CMAP amplitudes, with little or no change in distal latencies, typical of axonal damage. Fibrillation potentials and positive sharp waves do not generally appear for 3 weeks. MUPs, if they can be voluntarily activated by the patient, often appear normal or somewhat low in amplitude with increased polyphasias, suggestive of primary involvement of muscle by sepsis. These electrophysiologic changes are also consistent with primary myopathy; hence, it is important to demonstrate depression of SNAP amplitudes before a firm diagnosis of CIP is made. Repetitive nerve stimulation studies may be abnormal by coincidence if neuro-
TABLE 2. Neuromuscular conditions in the critical care unit associated with the systemic inflammatory response syndrome

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence</th>
<th>Clinical feature</th>
<th>Electromyography</th>
<th>Creatine phosphokinase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyneuropathy</td>
<td>Common</td>
<td>Flaccid limbs and respiratory weakness</td>
<td>Axonal degeneration of motor and sensory fibers</td>
<td>Near normal</td>
</tr>
<tr>
<td>Critical illness polyneuropathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor neuropathy</td>
<td>Common with neuromuscular blocking agents</td>
<td>Flaccid limbs and respiratory weakness</td>
<td>Axonal degeneration of motor fibers</td>
<td>Near normal</td>
</tr>
<tr>
<td>Neuromuscular transmission defect</td>
<td>Common with neuromuscular blocking agents</td>
<td>Flaccid limbs and respiratory weakness</td>
<td>Abnormal repetitive nerve stimulation studies</td>
<td>Normal</td>
</tr>
<tr>
<td>Transient neuromuscular blockade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myopathy</td>
<td>Common with steroids, neuromuscular blocking agents, and asthma</td>
<td>Flaccid limbs and respiratory weakness</td>
<td>Abnormal spontaneous activity</td>
<td>Elevated</td>
</tr>
<tr>
<td>Thick filament myopathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disuse (cachectic myopathy)</td>
<td>Common (?)</td>
<td>Muscle wasting</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Necrotizing myopathy of intensive care</td>
<td>Rare</td>
<td>Flaccid weakness, myoglobinuria</td>
<td>Abnormal spontaneous activity in muscle</td>
<td>Markedly elevated</td>
</tr>
</tbody>
</table>

CK, creatine kinase. Reproduced from Ref. 23, with permission.

Muscular blocking agents have been given, and their effects may persist beyond several hours to a number of days if the patient is in renal or liver failure (30). Phrenic NCS and needle EMG of the chest wall and diaphragm are useful in showing that CIP is the probable proximate cause of difficulty in weaning from the ventilator (31).

Knowledge of the presence of CIP aids management on the ventilator and, in particular, indicates that the patient has a neuromuscular problem, which may prolong care in the ICU. If it is mild, recovery occurs within a matter of weeks, but if severe, recovery may be prolonged by several months and incomplete (32). Physiotherapy and rehabilitation should be tailored to the severity of the polyneuropathy. In a prospective study by Leijten et al. (32), CIP was associated with increased mortality and rehabilitation problems. Other than management of the septic syndrome, there is no specific treatment of CIP. Wijdicks and Fulgham (33) failed to observe improvement after treatment with high-dose intravenous immunoglobulin. Even though sepsis and multiple organ failure are less common in pediatric patients, a few instances of pediatric CIP have been reported (34–36).

The morphologic aspects of CIP have been examined in peripheral nerve and muscle biopsies and in postmortem studies of the CNS and peripheral nervous system (28). They reveal evidence of a noninflammatory motor and sensory axonopathy. Muscle tissue shows acute and chronic denervation, with scattered grouped atrophic myofibers and occasional necrotic myofibers, suggesting associated primary myopathy as well. The only CNS manifestation is central chromatolysis of anterior horn cells and loss of dorsal root ganglion neurons, secondary to the axonopathy.

**Acute Motor Neuropathy Associated with Competitive Neuromuscular Blocking Agents**

Patients with forms of this polyneuropathy (37–43) have generally been in an ICU for days to weeks and have received competitive neuromuscular blocking agents, such as pancuronium bromide or the shorter acting agent vecuronium, for 48 hours or more and occasionally for days or weeks to ease mechanical ventilation. When the agents are discontinued, difficulty weaning from the ventilator and limb paralysis ensue. The serum CK level is mild or moderately elevated. There is electrophysiologic evidence of severe primary motor axonopathy with or without a defect in neuromuscular transmission on slow rates of stimulation. Muscle biopsy shows varying degrees of denervation atrophy and muscle necrosis.

The mechanism of the neuropathy is unknown, but sepsis appears to be an underlying factor in most if not all cases (16), because when the various contributing systemic complications are successfully treated, the neuromuscular condition itself improves and rapid recovery sometimes occurs. We (14) and others (21,22,44) have failed to implicate neuromuscular blocking agents as a cause of CIP.

**Neuromuscular Transmission Disorders and Myopathies**

Transient neuromuscular blockade, thick filament myopathy, cachetic myopathy, and acute necrotizing...
myopathy, in the order of their severity, may be the cause of difficulty in weaning from the ventilator in critical illness and injury.

Competitive neuromuscular blocking agents, often used to ease mechanical ventilation, are metabolized or cleared by the liver and kidney. In the presence of multi-organ failure, neuromuscular blockade may be prolonged for days after discontinuation (30). Repetitive stimulation studies will correctly identify the defect in neuromuscular transmission; however, by the time of testing, many patients will already have developed underlying CIP. Recovery may occur over a short period of time but may be prolonged for weeks or even months in severe cases.

Thick filament myopathy (41,45–49) occurs in children and adults during exacerbations of severe asthma or after organ transplantation (50). Endotracheal intubation and placement on a ventilator is usually necessary, accompanied by high-dose corticosteroids to treat the asthma and neuromuscular blocking agents to ease mechanical ventilation, often for days. On attempted weaning from the ventilator, the patient is found to have severe neuromuscular respiratory insufficiency and limb weakness. Ophthalmoplegia may be present (51). CK levels are often considerably increased. Repetitive nerve stimulation and sensory NCS are usually normal; however, motor NCS reveal low CMAP amplitudes. On needle EMG, MUPs tend to be low in amplitude, with short duration and excessive polyphasia, indicative of primary myopathy. Direct electrical stimulation of the muscle membrane may reveal inexcitability (52). Muscle biopsy shows central pallor of muscle fibers, which ultrastructurally is due to destruction of thick myosin filaments (46). It is possible that the administration of corticosteroids activates an ATP-ubiquitin-dependent proteolytic system that leads to myosin degradation, as postulated in two patients (49). Another possible mechanism of proteolysis postulated in five patients reported by Showalter and Engel (53) was increased expression of calpain, which itself alters calcium homeostasis. All patients were critically ill and suffered from SIRS, including one that had not received steroids or neuromuscular blocking agents. Thus, SIRS again appears to be the common etiologic factor. Recovery typically occurs rapidly. The clinical and electrophysiologic features are usually so distinctive in this syndrome that muscle biopsy is often not necessary. Although controversial, neuromuscular blocking agents at low doses and for short intervals can still be useful to ease mechanical ventilation in asthmatics.

Cachectic myopathy, disuse atrophy, and catabolic myopathy are terms used interchangeably (54) to describe this syndrome of muscle weakness and wasting (15,16). Motor and sensory NCS, needle EMG, and CK levels are all generally normal. Muscle biopsy may be normal or show nonspecific type 2 muscle fiber atrophy. An exception is the recent report by Gutmann et al. (55) of two critically ill patients, both of whom received prolonged neuromuscular blockade, but only in the one that received corticosteroids did severe muscle weakness and unusually severe atrophy of type 2 muscle fibers ensue, with regenerative changes on muscle biopsy.

Acute necrotizing myopathy of intensive care is a rare disorder (56,57). It is precipitated by a wide variety of infective, chemical, and other insults and enters in the differential diagnosis of acute myoglobinuria (15,16). Ramsay et al. (57) and Zochodne et al. (56) reported 11 such cases with severe weakness, high CK levels, and myoglobinuria. Electrophysiologic studies were consistent with severe myopathy, and muscle biopsy showed widespread fiber necrosis. Rapid and spontaneous recovery occurs in mild cases, but in more severe ones, notably the ones reported by Ramsay et al. (57), the prognosis was generally poor.

My colleagues and I have observed mild increases in CK levels, scattered necrosis of muscle fibers, and denervation atrophy on muscle biopsy in some critically ill patients, suggesting primary involvement of muscle and mild CIP. This may be due to a reduction in bioenergetic reserves, as measured by 31P nuclear MR spectroscopy. Two of our patients had very low ratios of phosphocreatine/inorganic phosphate, more than would be expected from denervation of muscle alone (15,16). These abnormalities returned toward normal as the patients recovered from the critical illness and from the polyneuropathy. Nonetheless, muscle biopsies performed in 11 patients were notable for denervation atrophy, presumably secondary to a CIP (58).

**Difficulty Weaning from the Ventilator and Electrophysiologic Studies of The Respiratory System**

Techniques of phrenic NCS and needle EMG of the diaphragm (31) have proved to be of great value in establishing a neuromuscular basis for respiratory insufficiency and failure to wean from the ventilator. In patients with GBS, NCS complemented vital capacity in determining the need for respiratory assistance (5). Documenting the degree of axonal degeneration or demyelination of phrenic nerves also aids in long-term prognostication. In a recent study of 40 patients with difficulty in weaning from the ventilator when a neuromuscular cause was suspected, 95% had diaphragmatic abnormalities (10). In an earlier study, Spitzer et al. (59) found a high incidence of both polyneuropathy and myopathy as causes of prolonged difficulty in weaning. Most had CIP, but there were varying combinations of unilateral phrenic nerve damage, neuromuscular transmission defects, and primary myopathies. Combined electrophysiologic studies of the limbs and respiratory system were of great assistance in identifying these conditions and rendering a prognosis.