and were most severe at 2–4 weeks after injection and decreased thereafter. At 18 weeks after injection, the mean muscle fibre diameter was back in the normal range and most—but not all—of the structural changes in the muscle fibres had disappeared. The innervation of muscle fibres must have been resumed in approximately the sixth week post-injection or earlier as the muscle fibres could otherwise not have increased in size at the eighth week post-injection. This seems not too far off from what happens in human. One should realize, however, that recovery of innervation and of fibre sizes need not occur exactly in the same pace in human and rat.

Ultraterminal and nodal sprouting served primarily to enlarge the area of contact between the innervating axon and its own target fibre (Hassan et al., 1995). Some degree of collateral innervation by newly developed nodal sprouts was also observed but this need not imply that the collateral nerve terminals took over innervation from the original innervating nerve fibres. There was no appreciable degree of type grouping. Most fibres, or all fibres, were apparently reinnervated by new (or recovered?) synapses from the original innervating axons. We did not find, therefore, evidence for changes in the architecture of the motor units. This is compatible with the observation of Dr Odergren that the amplitude and duration of the motor units did not increase.

Structural changes in terminal and preterminal axons were also reversible, but took more time to disappear than those of muscle fibres. Six months post-injection, some muscle fibres still had multiple or enlarged synapses (end-plates) (Hassan et al., 1994).

Our observations showed that the toxic effects of botulinum toxin were probably not restricted to nerve terminals but also involved muscle fibres. Our finding that botulinum toxin causes transient vacuolization of muscle fibres needs confirmation in man. Most of the histological changes in muscle fibres were transient, at least in rat, but the innervation of muscle fibres was not completely normalized, not even 6 months post-injection.

### References


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**Guillain–Barré syndrome in northern China. The spectrum of neuropathological changes in clinically defined cases**

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We read ‘Guillain–Barré syndrome in northern China. The spectrum of neuropathological changes in clinically defined cases’ (Griffin et al., 1995) with interest. This paper is an excellent example of clinical pathological correlation. However, we disagree with the classification of these diseases because they are based on the assumption that the primary pathophysiology is often axonal loss as opposed to primary demyelination with secondary axonal dysfunction. We propose an alternative explanation for the clinical, neurophysiological and pathological findings in these cases of acute motor axonal neuropathy (AMAN): initial conduction block at the root level followed by potentially reversible dysfunction of axonal transport mechanisms.

Griffin et al. (1995) document the pathology in cases of AMAN, acute motor-sensory axonal neuropathy (AMSAN) and ‘minimal changes’. We propose that they are variations on the same theme. The initiating event is the macrophage entering the neurolemma (the Schwann cell sheath) through the nodes of Ranvier at the root level. This results in conduction block at the root level leading to acute onset of weakness eventually resulting in paralysis. Had cervical root stimulation (Berger et al., 1987; Cros et al., 1990) been performed within the first 24 h of the onset of weakness, a proximal conduction block might have been detected (Cornblath et al., 1991; Rhee et al., 1990). As the macrophage distorts the axolemma, it would interfere with axonal transport leading to dysfunction of the distal axon within the next few days. This could functionally impair conduction in these axons (‘stunned axons’), but would not preclude eventual recovery (Berger et al., 1988). If the macrophage ceased distorting the axolemma, the recovery would occur as is noted in classic cases of acute inflammatory demyelinating polyneuropathy (AIDP).

As noted by the authors, the cases they describe would be the most severe variant as these were the patients that came to be autopsied. However, Griffin et al. (1995) state that most of these patients are ambulatory within 1 year and recover in a
manner similar to those with AIDP. Also of note is the acute onset of paralysis with areflexia and elevated CSF protein in many instances (McKhan et al., 1992; Comblath, 1995). These facts are similar to what is noted in AIDP. Therefore, AMAN and AIDP seem to follow roughly the same time course of acute onset and relatively rapid recovery suggesting similar pathophysiological mechanisms.

The electrophysiological abnormalities noted can be explained within our hypothesis. Root stimulation performed within the first day of illness would have demonstrated proximal conduction block. Stimulation at or distal to Erb's point would likely be unrevealing as the lesion is proximal to this (at the root level). F waves were only reported in one patient. As only 1–5% of the largest motor axons contribute to this phenomenon, three or four unaffected large motor axons could give rise to an F wave of normal latency (Kimura, 1989). As axonal transport mechanisms become impaired resulting in 'neuropraxia’, only a small population of axons would be able to contribute to the compound muscle action potential resulting in the finding of low amplitudes and no evidence of 'slowing' or temporal dispersion. As some of the largest fibres survive this process, it is not surprising that the conduction velocities remain faster than those in the 'demyelinating range.'

The patients classified with 'mild paranodal and motor axon changes' represent the earliest stage of the disease. Proximal conduction block with paranodal demyelination or immune mediated physiological block by distortion of the normal architecture of the nodes of Ranvier could easily explain a conduction failure between the nerve roots and the target muscle. This would lead to paralysis and death. We would predict the occurrence of proximal conduction block in patients whose disease has not progressed to the point of axonal degeneration. All of these patients died within 9 days of presentation, most of them from respiratory complications.

The motor and sensory 'axonal' patients follow a similar pattern except that the sensory roots are variably affected. The most profound changes are noted in the patients who succumb later in the course of their illness. We agree that the pathological evidence of primary demyelination is mild but conduction block due to the disturbance of the nodes of Ranvier cannot be excluded. This hypothesis could only be tested in a living person.

We prefer the term pseudoaxonal Guillain–Barré syndrome to describe these cases because irreversible axonal loss does not occur until the later stages of the illness, which is similar to the course of AIDP. This heightens the need for acute intervention with immunomodulating agents. Classifying these diseases as 'axonal' rather than 'pseudoaxonal' implies that therapy may be futile if the opposite may be the case.

We would welcome the opportunity to collaborate with these groups in order to test our hypothesis. If root stimulation is performed within 24 h of symptom onset, proximal conduction block as is often seen in AIDP could be detected (D. Hood and D. Menkes, unpublished data). If these cases truly represent a primarily axonal variant of Guillain–Barré syndrome, it should not cause physiological conduction block. If our hypothesis is correct, aggressive treatment with intravenous Ig or plasma exchange would be likely to reduce the morbidity and mortality of this illness. Labelling this illness as axonal may lead to the misconception that it is untreatable.

References


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Reply

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