Section of Neurology

President S P Meadows MD

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Applied Electrophysiology in Nerve and Muscle Disease [*Abridged*]

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Nerve Conduction in Human and Experimental Neuropathies

The two anatomical features of a myelinated nerve fibre which are of particular importance in relation to its conduction velocity are the diameter of the fibre and the distance between the nodes of Ranvier. Fig 1 is taken from a paper by Vizoso (1950); it shows that in normal nerves there is a linear relationship between fibre diameter and internodal length. However, there are obvious differences between the two peripheral nerves shown; in the ulnar nerve a large myelinated fibre with a diameter of 12 microns has an internodal length of about a millimetre, whereas in the facial nerve a fibre of similar diameter has internodes which are only half as long. This difference is due to the fact that internodal length is affected by growth of the body after the myelin has been laid down. As might be expected, the growth of the forelimb has produced a much greater effect on internodal length in the ulnar nerve than growth of the jaw in relation to the facial nerve.

We know that conduction in myelinated fibres is saltatory, involving excitation at the node of Ranvier by the action currents at an adjacent node, and we might expect an impulse to pass more rapidly down a fibre with widely separated nodes than down one in which the nodes are relatively close together. How important in fact is internodal distance in determining conduction velocity? There is now good evidence that it is relatively unimportant; as Rushton (1951) has suggested, the efficiency of impulse transmission in terms of the energy required may depend upon the spacing of the nodes of Ranvier, but as far as velocity is concerned it seems that fibre diameter is much more important, and that internodal length can vary within wide limits without velocity itself being affected. The evidence for this may be summarized as follows.

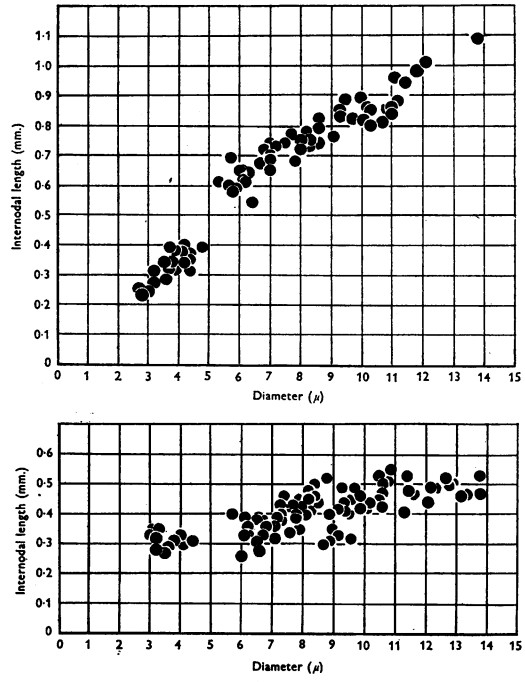

Fig 1 *Single internodes of the ulnar nerve (above) and of the facial nerve (below) in an 18-year-old girl. (From Vizoso 1950)*

In the first place we know that both fibre diameter and conduction velocity reach adult values fairly early in childhood, probably by the eighth year of life, and thereafter show little change (Rexed 1944, Thomas & Lambert 1960, Gamstorp 1963). In contrast to this, internodal length continues to increase for as long as body growth continues (Vizoso & Young 1948). Another situation in which conduction velocity and internodal length are dissociated arises when a nerve fibre is crushed or completely divided. When this is done, chromatolysis may occur in the nerve cell, accompanied by a reduction in both axon diameter and myelin thickness in the

nerve fibre proximal to the point of injury. Internodal length in the proximal part of the fibre is unchanged and yet conduction velocity may fall by as much as 30%, recovery of both velocity and diameter being dependent upon successful regeneration below the level of injury (Cragg & Thomas 1961). A further discrepancy between internodal length and velocity is seen in the distal part of the nerve during the process of regeneration. When the regenerating fibres have reached the periphery and made contact either with motor end-plates or with end-organs in the skin, there follows a period of maturation during which both fibre diameter and conduction velocity in the distal part of the nerve gradually increase over many months; by this time, however, the new internodal length of the regenerated fibres has already been established, so that the slow increase in velocity is independent of internodal length. As a result of regeneration the internodal length of the largest fibres may be reduced to about half of the normal figure, and it has been suggested by Cragg & Thomas (1964*a*) that in this situation conduction velocity may be somewhat less than one would expect from the diameter of the fibres concerned. It is therefore possible that if internodal length is grossly reduced by disease, then this may reduce conduction velocity, but we can be confident that lesser changes are unlikely to have any effect.

When we turn to the effects of disease on conduction velocity, two quite separate pathological processes must be considered. The first of these is wallerian degeneration; strictly speaking this term should only be applied to the changes which follow mechanical damage to the axon, but a histologically similar sequence of events may occur in certain types of toxic polyneuritis. For these the term 'axonal degeneration' is often used, but this should not obscure the fact that the degenerative changes in the axon may be secondary to the effect of a toxic substance on the anterior horn cell in the spinal cord or on the dorsal root ganglion cell. In such cases there is interruption of continuity of the axon with distal degeneration, recovery taking place by the relatively slow process of regeneration.

During the process of degeneration changes in conduction velocity are generally slight. The situation seems to be that if a fibre is capable of conducting impulses at all, it does so normally; and the most striking change from the electrophysiological point of view is a diminution in the number of functioning fibres rather than a change in conduction velocity. Fig 2 is taken from a paper by Kaeser & Lambert (1962) and shows the effect of nerve section and of acute thallium poisoning in guinea-pigs. The motor fibres were stimulated at the hip and at the ankle, and muscle action potentials recorded from the small muscles of the hind foot. The open circles indicate the amplitude of the muscle response, which fell almost to zero after forty hours in the case of wallerian degeneration and after seventy hours in the case of thallium poisoning. Conduction velocity (filled circles) showed little change during this time.

Kaeser & Lambert did not find that the injection of thallium was a very convenient way of producing an experimental neuropathy; large doses of the order shown in Fig 2 tended to kill the animals, whereas smaller doses failed to affect the peripheral nerves at all. However, Fullerton & Barnes (1966) have recently studied a toxic compound called acrylamide which produces a pure axonal degeneration in rats, and their findings in relation to conduction velocity have proved most interesting. Acrylamide (CH_2=CH-$CONH_2$) is used in industry for the synthesis of a polymer which has waterproofing properties. The first evidence that it might cause neuropathy was from industrial workers who had been in contact with the compound and who developed paræsthesiæ and numbness followed by weakness and ataxia. In rats it produces a mixed motor and sensory neuropathy which is most marked distally. Otherwise the animals remain well and recovery occurs after feeding with the toxic compound is stopped.

Fig 3 shows the maximal conduction velocities of motor fibres to the small muscles of the hind foot in the rat, before acrylamide, during the neuropathy, and after clinical recovery. The changes during the neuropathy are greater than

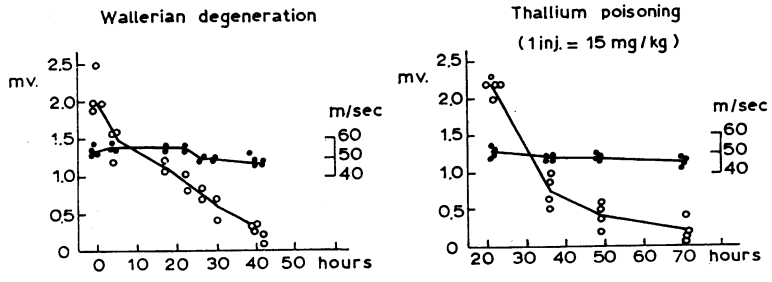

Fig 2 *Serial estimations of muscle action potential amplitude (open circles) and of motor nerve conduction velocity (filled circles) during axonal degeneration in guinea-pigs. (From Kaeser & Lambert 1962)*

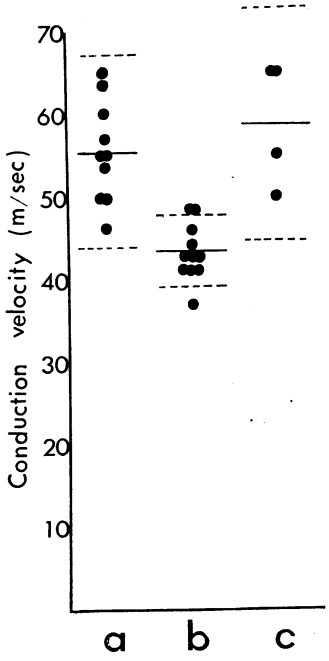

Fig 3 *Motor conduction velocity* (a) *before*, (b) *during and* (c) *after recovery from acrylamide neuropathy in rats.* (*From Fullerton & Barnes 1966*)

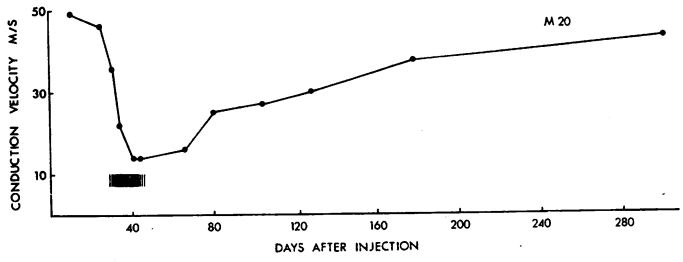

Fig 4 *Serial estimations of motor conduction velocity after the injection of diphtheria toxin into a guinea-pig. The presence of weakness and ataxia is indicated by the shaded area.* (*From Morgan-Hughes 1965*)

those which occurred in acute thallium poisoning, but they are still relatively mild and may mean nothing more than that the largest myelinated fibres underwent axonal degeneration, leaving smaller fibres with a somewhat lower velocity. What is perhaps surprising is that conduction velocity should return to the normal figure after the clinical illness, for it is known that, after mechanical division of a peripheral nerve, recovery of velocity in regenerated fibres is incomplete (Berry *et al.* 1944, Cragg & Thomas 1964*a*). This aspect of the neuropathy clearly requires further investigation.

A different pathological process which affects peripheral nerve is segmental demyelination, in which there is patchy degeneration of the myelin sheath. This may occur close to a node of Ranvier (paranodal demyelination) or it may involve a complete internodal segment. The important feature, however, is that there is no loss of continuity of the axon and no wallerian-type degeneration, recovery being by local remyelination of the affected segments.

This process was first described by Gombault (1880) in guinea-pigs poisoned by small repeated doses of white lead. However, lead neuropathy in the guinea-pig is a rather chronic affair and therefore not the best situation in which to correlate the histological appearances of demyelination and remyelination with conduction velocity (Fullerton 1966). The acute neuropathy produced in guinea-pigs by diphtheria toxin is a much better preparation for this purpose, and Fig 4, which is from a paper by my colleague Dr Morgan-Hughes, shows the velocity in motor fibres to the small muscles of the hind foot, recorded serially before, during and after an acute attack of diphtheritic neuritis in a guinea-pig. In the early stages of the acute illness, at a time when conduction velocity was falling abruptly, histological preparations showed paranodal demyelination and some completely demyelinated internodal segments. However, there was no evidence of remyelination at this stage, at least in so far as it could be detected by the light microscope, and so we have to accept that the axon, when it is apparently denuded of myelin, is still capable of conducting impulses, although at a much reduced velocity. This conclusion was also reached by Cragg & Thomas (1964*b*) on the basis of their studies of experimental allergic neuritis in guinea-pigs.

It can be seen from Fig 4 that the clinical illness was very short compared with the effect of the disease upon conduction velocity. We interpret this as meaning that the demyelination produced a complete conduction block in some fibres during the clinical illness, this being responsible for the weakness and ataxia. However, this block was rapidly reversible when remyelination began, the slow recovery of conduction velocity being related to the gradually increasing myelin thickness of the affected segments over the following months. Internodal distance was permanently altered in some segments with the production of new short internodes, and it is remarkable how little effect this had upon velocity, which finally returned almost to its previous level by the end of the follow-up period.

On the basis of these results we might expect those human neuropathies which result in marked slowing of conduction velocity to be those in which segmental demyelination is a particularly conspicuous histological feature. This expectation is borne out in the conditions shown in the left

Table 1
Segmental demyelination and polyneuropathy

Extensive segmental demyelination present in neuropathy due to	*Segmental demyelination scanty or absent in neuropathy due to*
Diabetes	Alcoholism
Guillain-Barré syndrome	Porphyria
Carcinoma	Tri-ortho-cresyl phosphate
Dejerine-Sottas disease	Isoniazid
Metachromatic leucodystrophy	Thalidomide

hand column of Table 1. It is not uncommon to find motor velocities of 10 or 20 metres per second instead of the normal 50–70 metres per second in any of these conditions (Lambert 1962, Gilliatt & Willison 1962, Fullerton 1964), and the sural nerve biopsies examined by my colleagues Dr Thomas and Dr Lascelles have shown profuse segmental demyelination in all of them (*see also* Webster 1962, Thomas & Lascelles 1965). This implies that the effect of the disease process is primarily upon Schwann cells and not upon neurones, but in saying this I do not wish to imply that no axonal degeneration occurs in such cases. It is very rare to find pure segmental demyelination without loss of continuity of the axon in at least a proportion of fibres. However, this does not necessarily mean that the disease process affects the neurones directly. It seems reasonable to postulate that when Schwann cell damage is very severe the axon itself may be interrupted, whereas with less severe degrees of damage only the myelin is affected, the Schwann cell being capable of remyelinating the segment or, if the cell divides, remyelinating part of the original segment.

A similar correlation between demyelination and reduced conduction velocity has recently been made by Ulrich *et al.* (1965); they make the interesting point that the most extreme changes in conduction velocity, that is to say reductions to figures of less than 10 metres per second, were seen most often in familial neuropathies in which the axons themselves appeared to be very thin as well as being demyelinated or poorly myelinated. This may be due to attempted regeneration without adequate remyelination, and it is obvious that in a chronic disease a combination of these factors becomes very difficult to analyse.

In the neuropathies on the right hand side of Table 1 the correlation between electrical and histological findings is less complete. In beriberi and alcoholic neuropathy, for example, both segmental demyelination and axonal degeneration have been described (Pekelharing & Winkler 1893, Swank 1940, Denny-Brown 1958). However, conduction velocity is rarely reduced by more than 30% in alcoholic neuropathy (Mawdsley & Mayer 1965), and in the few sural nerve biopsies which we have taken from alcoholic patients at Queen Square, little segmental demyelination has been present. It has also been claimed by Denny-Brown & Sciarra (1945) and by Gibson & Goldberg (1956) that segmental demyelination occurs in the neuropathy of porphyria, but the most recent evidence of Cavanagh & Mellick (1965) does not support this. In the case of neuropathy due to tri-ortho-cresyl phosphate, isoniazid or thalidomide, there is, I believe, no doubt on the pathological side that the typical lesion is a primary neuronal or axonal degeneration (Cavanagh 1964*a*, *b*, Klinghardt 1966), but nerve-conduction studies have been relatively few.

However, the published reports which I have been able to find (Fullerton & Kremer 1961, Sala 1962, Simpson 1962) and our own experience at Queen Square all seem to be compatible with the view that conduction velocity changes in such patients are usually slight. On this basis we may put forward the tentative hypothesis that the slightly reduced velocity merely reflects the loss of large diameter fibres, and that those fibres which retain their conductivity also retain their normal velocity.

It seems, therefore, that one can to some extent predict the nature of the underlying pathology from nerve conduction studies, and in our own clinic we accept motor velocities which are reduced by more than 40% as likely to indicate the presence of segmental demyelination. On this basis one might suggest that both leprosy and sarcoid neuropathy will turn out to be examples of segmental demyelination (Jopling & Morgan-Hughes 1965, Willison 1966, personal communication), although as yet we cannot provide histological proof of this.

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Disorders of Neuromuscular Transmission

Electrodiagnostic techniques should be used to explore the physiological properties of normal and pathological states of the lower motor neurone or muscle and not to make a nosological diagnosis. Measurement of the strength-duration relationships of electrical excitability and conventional electromyography provide information about (*a*) degeneration of peripheral nerve axons and muscle fibres, (*b*) the recruitment and frequency pattern of motoneurones, and (*c*) the muscle fibre constitution of motor units. From these data it is possible to decide whether muscular weakness is neural or myal (Simpson 1962). Measurement of nerve conduction velocity adds another parameter. Pathological slowing of conduction is probably due in the main to abnormality of the myelin-sheath of peripheral nerve fibres (Simpson 1964). If these studies, with the electromyographic evidence of axonal branching, point to a primary lesion of the lower motor neurones, the neurologist would like to have further information about the site of the lesion – is it polioclastic, axonal or at the neuromuscular junction? Some help may be obtained from a study of the muscular response to repeated stimulation of its motor nerve (Simpson & Lenman 1959, Simpson 1960*a*).

Stimulation and recording techniques are conventional. The stimulus must be brief and supramaximal and the muscle response is recorded with surface electrodes to integrate the electrical activity of a volume of muscle since the area of the response is assumed to be proportional to the number of responding muscle fibres for any particular rate of stimulation. If the muscle tension is recorded isometrically by a strain gauge it will be seen that the amplitude of the evoked potential does not bear the same relationship to the twitch tension at all rates of stimulation. The decreased amplitude at fast rates of stimulation is due to restimulation within the refractory period of the muscle (Farmer *et al.* 1960). Movement artifacts are minimized by splinting the limb during stimulation but some artifact of this type is almost inevitable in routine diagnostic studies.

Normal Neuromuscular System

Stimulation of a motor nerve at rates above 12/sec in the normal subject causes the evoked muscle action potential to increase progressively with the first 3–5 stimuli. This is accompanied by progressive shortening of the duration of the action potential, particularly the second phase of the diphasic deflection. It is probably due to improved synchronization of the muscle response (Harvey & Masland 1941, Simpson & Lenman 1959, Farmer *et al.* 1960). At 0·1–0·2 sec from the start (irrespective of the rate of stimulation) there is often a temporary decrease in amplitude of about 30% which is due to an artifact of movement. The action potential then remains at a constant level for a considerable period which depends on the frequency of stimulation. These normal increments and decrements must not be mistaken for the pathological types described below.

If fast stimulation is continued the muscle potential slowly decrements but does not disappear although the muscle contraction may cease from fatigue (Merton 1954). Decrement to 50% may occur in 30 seconds with supramaximal stimulation at 50 shocks per second but often takes much longer. If stimulation is interrupted and resumed there is no obvious post-tetanic potentiation. When tetanization is repeated with rests of 1–2 seconds there is no recovery of the earlier amplitude unless the stimulus frequency is reduced. This decrement is absent or long delayed at rates below 15/sec unless this is preceded by 'fatigue' induced by more rapid stimulation.

Pathological Decrement of Response

In partial denervation the amplitude of the evoked muscular response is always diminished in proportion to the fall out of motor units. Premature progressive decrement of the response is less common and occurs in several disorders.