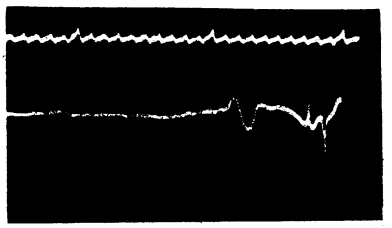

Fig 3 *Mixed nerve action potential (amplitude 10 μV) recorded from lateral popliteal nerve at head of fibula, stimulated at ankle. Average of 100 sweeps. Time-marks 1 msec*

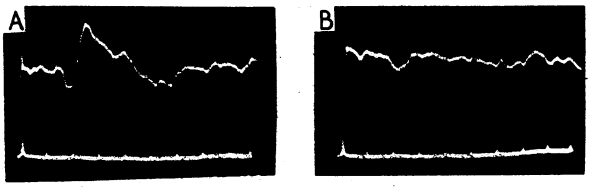

Fig 4 A, *evoked potential obtained from contralateral sensory cortex on ulnar nerve stimulation at the elbow, amplitude 25 μV.* B, *recording from ipsilateral sensory cortex. EEG electrodes and the same averaging technique as in Fig 3 were used. Time-marks 10 msec*

pheral neuropathy should have normal conduction speeds and Trojaborg (1962) has shown that in 16 cases of classical polyneuritis, of which 14 were considered to be severe, 9 (56%) had normal motor nerve conduction speeds. It is of interest and significance that 7 of these 9, however, had evidence of denervation on electromyography so that there can be little doubt that both methods should be used in suspected polyneuritis.

Children need special mention for a number of reasons. Firstly, in infancy, normal conduction speed is only around 30 metres per second; this figure rises to the lower limits of adult normal by the age of 3 and reaches the full adult range by 5. Then, because of the small limb length errors of measurement are proportionately increased so that the total error may be 20%. Thus, slowing in a child aged up to 2 has to be gross, with figures in the lower 20s, before it can be regarded as definite; in these circumstances, an electromyographic search for denervation potentials can be more useful. Nerve conduction speeds can be of help in the early diagnosis of Charcot-Marie-Tooth disease, in Guillain-Barré syndrome, in metachromatic leukodystrophy and in the assessment of treatment of abetalipoproteinæmia. Most children tolerate one or two conduction speed measurements well, but clearly the number of nerves that can be tested and the number of muscles that can be sampled by needle electromyography are limited, and only a restricted examination by adult standards is possible.

The conditions where nerve conduction measurements are most reliable are the entrapment neuropathies; here a short portion of the nerve trunk is compressed and the resultant ischæmia causes a slowing of conduction speed, probably by segmental demyelination. The ideal situation for testing is where the nerve can be stimulated a short distance above the suspected site of compression and the appropriate response collected a short distance below the site. The carpal tunnel is the prime example of this and sensory and motor latency measurements and the effects of treatment in carpal tunnel compression have previously been reported to this Section (Campbell 1962). More recently Payan (1969) has reported the result of similar measurements in ulnar nerve compression at the elbow. In both papers the accuracy of the investigation was around 90%.

In conclusion, the fallibility of nerve conduction measurements has been stressed because of their misleading impression of accuracy; best results can be obtained by correct selection of the electrodiagnostic techniques most appropriate to the clinical problem.

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The Morphological Basis for Alterations in Nerve Conduction in Peripheral Neuropathy

The first clinical application of the measurement of motor nerve conduction velocity in man was published in 1948 by Hodes *et al.* They described the results of their observations on regeneration after nerve section and suture. Conduction velocity was found to be greatly reduced during the early stages of regeneration, slowly increasing as the degree of recovery became more advanced. This finding was readily explicable in terms of the results of the experimental observations on nerve regeneration made by Berry *et al.* (1944), in which

a close relationship between fibre diameter and conduction velocity had been demonstrated. Sanders & Whitteridge (1946) also drew attention to the influence of myelin thickness. In addition, it had earlier been suggested by Hursh (1939) that conduction velocity might be related to internodal length, and the spacing of the nodes of Ranvier is reduced on regenerated fibres (Hiscoe 1947, Vizoso & Young 1948). However, although internodal length may have some influence on conduction velocity (Cragg & Thomas 1964*a*), observations by various workers have shown that it is not an important determinant of velocity (Wagman 1954, Cragg & Thomas 1957).

When nerve conduction studies came to be widely employed as a diagnostic procedure, it was found that in some neuropathies conduction velocity may be grossly reduced and that the degree of reduction was far too great to be explained in terms of the selective loss of faster conducting fibres (Thomas *et al.* 1959). The rapidity with which this reduction may develop meant that it could not be explained in terms of conduction in small regenerating fibres after degeneration of wallerian type. Moreover, it could not be due to fibres actually undergoing degeneration, as this is associated with very little change in conduction velocity (Gutmann & Holubář 1950, Kaeser & Lambert 1962). As is now well known, such gross reductions of velocity are found to be constantly related to the presence of segmental demyelination (Dyck & Lambert 1966, Gilliatt 1966), this relationship having initially been established by observations in experimental neuropathies (Kaeser & Lambert 1962, McDonald 1963, Cragg & Thomas 1964*b*, Fullerton 1966).

The precise way in which segmental demyelination gives rise to reduced conduction velocity is as yet uncertain. It is easy to see why velocity should be slow in fibres that are in the process of remyelination: in the remyelinated regions, axon diameter is diminished (Lubińska 1958), as is myelin thickness, and in the early stages of remyelination, the myelin lamellæ may not be fully compacted (Ballin & Thomas 1968). What is more problematical is the explanation of the reduced velocity in the earlier stages of a demyelinating process. The nodal widening that occurs probably does not reduce velocity substantially, the reduction being related to the demyelination of whole internodal segments (Morgan-Hughes 1968). Cragg & Thomas (1964*b*) found that in experimental allergic neuritis, velocity could be severely reduced at a stage when remyelination of the demyelinated segments was not evident, as judged by light microscopy. This finding was confirmed by Morgan-Hughes (1968) in experimental diphtheritic neuropathy. Cragg & Thomas suggested that propagation of the nerve impulse might take place by saltatory conduction in the region of the fibres with preserved myelin, but that it might be continuous, as in unmyelinated axons, in the demyelinated regions during recovery after an earlier conduction block. This suggestion requires verification by electron microscopy as very early remyelination could well be missed by light microscopy.

In certain chronic hereditary neuropathies in man, in addition to evidence of demyelination, axon diameter is often considerably diminished (Ulrich *et al.* 1965). This will also contribute to the reduction in conduction velocity. Some of the slowest velocities that are encountered are obtained in such disorders. The reason for this diminution in axon diameter is as yet uncertain, but will be discussed in more detail later.

As was emphasized by Gilliatt (1966), conduction velocity is not severely reduced in all peripheral neuropathies: in some it is never more than mildly diminished. In these disorders, segmental demyelination has been stated to be scanty or absent, the predominant histological change being one of axonal degeneration. It has therefore been suggested that the mild reduction of velocity that may be observed is the result of the selective loss of the faster conducting fibres. As will be shown later, this is probably not the only explanation.

These ideas led to the development of the concept that neuropathies can be divided into two categories on the basis of the pathological changes that occur. Thus a group can be recognized displaying extensive segmental demyelination and substantially reduced nerve conduction velocity. Examples in this category are the Guillain-Barré syndrome, diabetic neuropathy, hereditary hypertrophic neuropathy and metachromatic leukodystrophy. The presence of extensive segmental demyelination in such disorders has been considered to indicate that the disease process primarily affects the Schwann cells (Thomas & Lascelles 1965, 1966, Zacks *et al.* 1968). In the second group have been placed those neuropathies in which conduction velocity is only mildly reduced and which pathologically have shown axonal degeneration but little or no segmental demyelination. Examples in this category are alcoholic and porphyric neuropathy, and neuropathy due to triorthocresyl phosphate, thalidomide and isoniazid. It seems probable that in this group the disorder gives rise to a primary neuronal or axonal degeneration (Cavanagh 1964*a*, *b*, Gilliatt 1966).

Subsequent experience, however, suggests that this subdivision may not be as clear cut in pathological terms as was originally envisaged. As observations on the detailed histopathology of the neuropathies have accumulated, it has become

increasingly evident that a combination of axonal degeneration and segmental demyelination is found in most neuropathies. It has, of course, been recognized that, in those neuropathies in which demyelination is prominent, axonal degeneration almost invariably occurs to a greater or lesser extent (Gilliatt 1966, Dyck *et al.* 1968). It now seems that the converse is also likely to be true. Thus in porphyric neuropathy, although Cavanagh & Mellick (1965) found only axonal degeneration, personal observations on nerve biopsies from two cases have revealed a moderate degree of demyelination, confirming earlier reports by Denny-Brown & Sciarra (1945) and Gibson & Goldberg (1956). The demyelination is predominantly paranodal, but with some whole segment loss. Similarly, in alcoholic neuropathy, Lascelles (1970, unpublished observations) has found evidence of demyelination in addition to axonal degeneration, corresponding to the previous observations on beri-beri made by Pekelharing & Winkler (1893), Swank (1940) and Denny-Brown (1958). The abnormality in uræmic neuropathy is also mainly that of a distal axonal degeneration (Asbury *et al.* 1963). Yet the examination of nerve biopsies from this condition again reveals a moderate degree of demyelination (Hollinrake & Thomas 1968), also predominantly paranodal, but with some whole segment loss. Finally, as might be expected, diseases of the supporting tissues such as amyloidosis (King *et al.* 1971) tend to show a combination of axonal degeneration and segmental demyelination.

The conclusion that most neuropathies involve a combination of axonal degeneration and segmental demyelination in varying proportions is not surprising, since there is mounting evidence as to the close functional interrelationship between axons and Schwann cells. Cross-anastomosis experiments between myelinated and nonmyelinated nerves show that it is the axon that instructs the Schwann cells to produce myelin (Simpson & Young 1945, Hillarp & Olivecrona 1946). This probably also includes instructions as to the number of myelin spirals that are laid down, as there is a reasonably close relationship between axon diameter and myelin thickness (Sanders 1948, Thomas 1955). Reports that Schwann cells will produce myelin around glass threads in tissue culture require substantiation. If axonal degeneration takes place, myelin breakdown ensues, the possible stimulus for this being a reduction in the pressure exerted by the axon on the myelin (Young 1944). Conversely, there is some evidence to suggest that the Schwann cells provide metabolic support for the axons (Singer & Salpeter 1966), and the nature of the complex structural arrangements at the nodes would favour this view (Williams & Landon 1963).

These considerations make necessary a reappraisal of the pathological significance of segmental demyelination. There can be no doubt that some neuropathies involve a primary disturbance of Schwann cell function. Thus diphtheria toxin has a very selective action on Schwann cells, in some species giving rise to virtually no axonal breakdown (Cavanagh & Jacobs 1964). In experimental allergic neuritis (Lampert 1969) and the Guillain-Barré syndrome (Wisniewski *et al.* 1969), there is a selective attack by sensitized mononuclear cells on the myelin sheath, although axonal interruption may also occur. In certain inherited disorders of lipid metabolism such as Refsum's disease and metachromatic leukodystrophy (sulphatide lipidosis), it seems reasonable to believe that the demyelination is the result of a disturbance of the lipid metabolism of the Schwann cells. Repeated demyelination and remyelination will give rise to concentric Schwann cell proliferation producing the hypertrophic appearances that may be seen in Refsum's disease.

With regard to the explanation of the demyelination that may take place in neuropathies in which the primary fault is an axonal degeneration, there is the theoretical possibility of a failure in the axonal mechanisms responsible for instructing the Schwann cells to produce myelin. A more tangible mechanism could be a dwindling in axonal size, and there is some evidence that axon diameter may diminish without the occurrence of complete breakdown of the fibre. Anderson *et al.* (1970) observed that internodal length may be inappropriately long relative to fibre diameter in fibres central to a compressive lesion of the median nerve under the transverse carpal ligament in the guinea-pig. Predominantly paranodal demyelination was also noted to occur in this situation. It could therefore be postulated that if axon diameter becomes reduced in a neuropathy without axonal interruption taking place, the myelin may first retract from the nodes and, if the reduction in diameter is severe enough, the internodal segment may then break down completely. The segment would subsequently become remyelinated in the usual way with the formation of short intercalated segments and myelin formation would take place to a thickness appropriate for the altered axon diameter.

From these considerations it would be predicted that in acute neuropathies of this type, little segmental demyelination would be found and that the predominant histological change would be axonal degeneration. If the process pursued a more chronic course, evidence of demyelination and remyelination would be expected. This view could explain the observations made by Fullerton (1966) on experimental lead neuropathy in the guinea-pig. Axonal degeneration alone was

usually seen in animals that died after receiving large doses of lead over a short period of time, whereas segmental demyelination was conspicuous in animals that had received smaller doses over a long period.

A further extension of these considerations was raised as a theoretical possibility by Thomas & Lascelles (1967) when considering the pathogenesis of hypertrophic neuropathy. As an alternative to a primary disturbance affecting the Schwann cells, which is the more obvious explanation, it was speculatively suggested that in some instances a progressive diminution in axon diameter might lead to recurrent demyelination and remyelination as the Schwann cell repeatedly adjusted itself to a new axon diameter. However, there is as yet no evidence to indicate whether or not the reduction in axon diameter observed in chronic hereditary demyelinating neuropathies by Ulrich *et al.* (1965) is a primary disturbance. There are other explanations that could be adduced for the reduction: it might be secondary to the demyelination (Lubińska 1958) or perhaps the consequence of incomplete regeneration after axonal degeneration.

Although a number of the foregoing ideas are speculative, the occurrence of axonal degeneration in primary demyelinating processes and, conversely, the occurrence of demyelination in primary axonal degenerations, seems established. Finally, when those neuropathies are considered in which the initial lesions affect the connective tissues or vascular supply (Thomas 1969), the relative amounts of Schwann cell and axonal damage will be related to differences in the selective vulnerability of these two components of the nerve to the pathological process. Thus, Schwann cells have been shown to be more vulnerable to ischæmia than axons (Denny-Brown & Brenner 1944).

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