Brain 88: 335-356 (1965).

always distal first than proximal ? (350)

Segmental demyelination followed by degeneration of fibers (354)

NERVE CONDUCTION IN ALCOHOLIC POLYNEUROPATHY[1]

BY

C. MAWDSLEY[2] AND R. F. MAYER

(From The Department of Neurology, Harvard Medical School, and the Neurological Unit, Boston City Hospital)

They suggest thiamin deficiency biri biri really means to folic acid. Spinal cord (347)

SYMPTOMS of alcoholic peripheral neuropathy were first recognized by Lettsom (1787) who described hyperæsthesiæ and paralysis, affecting the legs more than the arms. He, and later Jackson (1822), delineated the late stage of peripheral nerve affection. Much clinical observation since then has shown that the neuropathy in alcoholics varies widely in severity. We have studied peripheral nerve conduction velocities in chronic alcoholics with the aim of assessing the pattern and development of alcoholic polyneuropathy.

SELECTION OF PATIENTS

** Very High Folic Acid dificiency 40% (351)

Seventy-six patients were studied. Most (64) were men. The criteria of selection were a clear and corroborated history of chronic alcoholism and a complication thereof which needed hospital treatment. We excluded patients who had coincidental diabetes or other diseases which might be accompanied by neuropathy. Patients with clinical signs of focal nerve palsies were not included.

These patients were admitted to the Medical Services of the Boston City Hospital. Victor and Adams (1953) reviewed the clinical syndromes evinced by alcoholics in the same hospital population and our patients presented frequencies and types of affection which conformed to their description.

** Vitamins (350) anti vitamins (351) (352)

All had been heavy drinkers for many years. Daily consumption by individuals varied from a pint of whisky to a gallon of wine daily and most of them increased their intake during periodic sprees.

The majority (44 patients) sought admission because of tremulousness, hallucinations or fits following recent withdrawal of alcohol. A large group (14 patients) suffered from Laennec's cirrhosis. Wernicke-Korsakoff's syndrome (8 patients) and trauma (3 patients) were less frequently seen.

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loss of large fibers preferentially (349)

small fibers conduct more slowly than large diameter fibers (349)

loss of myelin

what about squid

Few (9 patients) were admitted because of symptoms attributable to peripheral neuropathy. This listing of patients' complications is based on the primary cause of their most recent admission. Many had repeatedly been treated in hospital for a variety of alcoholic illnesses and usually proved, on investigation, to have several manifestations concurrently.

Denial of neurological symptoms is common, even in alcoholics with clear signs of neuropathy (Victor and Adams, 1953). Such patients seldom are discriminating sensory witnesses. However, it was possible to make adequate clinical assessments of our patients and to gauge the severity of their affection.

For comparative purposes, patients without clinical neuropathy were grouped together (Group 1). Those with sensory signs of peripheral neuropathy were subdivided into a smaller group whose tendon reflexes were preserved (Group 2) and a larger number in whom deep tendon reflexes were diminished or absent (Group 3). Clinical signs were more prominent in the legs. Motor and reflex changes in the arms were rare in this series which, because of the method of selection, probably includes fewer examples of the most severe degrees of alcoholic neuropathy than would a random sample or one selected wholly from a neurological unit.

The youngest patient was 25 years of age, the oldest, 69 years. Nerve conduction velocities are known to be slower in people past the age of 50 (Norris *et al.* 1953), so the groupings were further divided into two age ranges—20 to 50 years and 51 to 70 years.

Methods

Standard techniques were used to record nerve action potentials and to obtain conduction velocities in motor fibres. Details of the methods employed in this study were similar to those described by Mayer (1963).

Nerve action potentials were recorded from the median and ulnar nerves, at the wrist, after supramaximal electrical stimulation of the second and fifth digits respectively. The technique employed was that developed by Dawson and Scott (1949) and later modified by Dawson (1956) who showed that the potentials thus evoked were conducted in the fastest afferent fibres. Traces were also obtained from these nerves, at the elbow and in the axilla, after stimulation at the wrist. These potentials were elicited from centripetal impulses in mixed motor and sensory fibres. The times of onset of such responses are dependent on the rate of conduction in the fastest, sensory fibres.

Action potentials from the peroneal and tibial nerves could but rarely be recorded at the ankle after an appropriate digital stimulus. The most distal parts of these nerves could not, therefore, be effectively examined. Stimulation of the anterior tibial nerve, over the dorsum of the ankle, gave rise to a potential in the common peroneal nerve at the head of the fibula which was consistently obtained in young, normal subjects using the method described by Gilliatt *et al.* (1961). A nerve action potential could be elicited in the popliteal fossa from the tibial nerve following its stimulation at the ankle. These two nerves carry impulses proximally in motor and sensory fibres but, again, the earliest response recorded is determined by the conduction velocity in the fastest, afferent fibres.

Compound muscle action potentials were obtained from abductor pollicis brevis after stimulation of the median nerve at wrist, elbow and in the axilla and from the abductor digiti minimi by ulnar nerve stimulation at corresponding sites. In the leg, the tibial and peroneal nerves were stimulated at ankle and knee and muscle potentials recorded from abductor hallucis brevis or extensor digitorum brevis, respectively. The techniques used were those devised by Hodes *et al.* (1948). They afford an estimate of conduction velocity in the fastest motor fibres to the intrinsic muscles of hands and feet.

Amplified potentials from nerves and muscles were displayed on one beam of a dual beam oscilloscope whose sweep was triggered by the stimulus from a Grass S4 stimulator. Each tracing was photographed above a time scale carried on the second oscilloscope channel.

Latencies of nerve action potentials were measured from the beginning of the stimulus artefact, to the onset of the negative (upward) deflection of the triphasic response which reflects the arrival of the impulse under the active lead of the bipolar recording electrode (Lorente de Nó, 1947). Latencies of muscle potentials were measured from the onset of the stimulus, to the initial deflection from the baseline, of the compound tracing.

Distances between the various points of stimulation and the recording sites were measured, on the skin, along the course of the nerves and were then divided by the appropriate latencies to give velocities.

Conduction velocities were thus calculated for the fastest afferent fibres in the distal segments (digit to wrist) of the median and ulnar nerves. Velocities in each of these nerves, in the segments between wrist and elbow, and from elbow to axilla, were calculated for both motor and sensory fibres. No estimate of motor velocity in the distal segments could be obtained since the latency from stimulus at wrist to muscle response included the delay at the neuromuscular junction and conduction in the muscle itself. Similarly, in peroneal and tibial nerves, motor conduction in the segments distal to the ankle could only be expressed as latencies to the onset of muscle responses. These were very variable in normal subjects due to the variations in conduction distance.

In the leg, conduction velocities in the fastest motor and sensory fibres could be calculated, in both nerves, between ankle and knee.

In each patient, and for each segment of four nerves, maximal conduction velocities, in motor and sensory fibres, were obtained. Mean values were calculated for each clinical group of alcoholic patients and compared with corresponding results from 105 normal subjects.

The electrically induced late wave, described by Hoffmann (1918), was recorded from calf muscles after a submaximal stimulus delivered to the tibial nerve in the popliteal fossa (Magladery and McDougal, 1950). The mean latencies of this wave (H-wave) were estimated in the normal and alcoholic groups.

Throughout the recordings the temperature of the laboratory was maintained between 26° C. and 30° C. The range of temperature of the patients' limbs being 33° C. to 37° C.

Results

Table I shows the results of conduction studies in normal people, of whom 74 were between 20 and 50 years of age and 31 were 51 to 70 years old.

In the younger group the mean velocity, in the largest afferent fibres of the median nerve below the elbow, was 67 metres per second (M/sec.). Conduction velocity over corresponding segments of the ulnar nerve was slightly slower (65·3 M/sec.). In neither nerve was there any real difference

TABLE I.—NORMAL NERVE CONDUCTION VELOCITIES

	Age 20–50 yrs.				*Age 51–70 yrs.*			
Nerve	*N.A.P.*		*Motor*		*N.A.P.*		*Motor*	
Median Nerve	*Latency*	*Velocity*	*Latency*	*Velocity*	*Latency*	*Velocity*	*Latency*	*Velocity*
Digit-wrist	2·4±·3	67 ±4·3			2·6±·3	61·8±4·5		
Wrist-elbow	3·8±·4	66·7±3·8	4·3±·3	58·7±2·6	3·9±·4	63·2±4·6	4·7±·4	55·4±3·3
Elbow-axilla	1·9±·2	70 ±4	1·9±·2	65·6±4·1	1·9±·2	66·5±3·5	2·0±·2	62·9±3·4
Ulnar Nerve								
Digit-wrist	2·2±·2	65·3±3·4			2·4±·3	60·6±6·1		
Wrist-elbow	4·1±·4	65·2±3·5	4·6±·3	58·9±2·6	4·3±·4	60·1±5·7	5·1±·4	53·1±2·6
Elbow-axilla	1·9±·2	69·1±4·3	2·0±·2	63·7±3·3	1·9±·2	65·7±3·2	2·0±·1	61·6±2·3
Common Peroneal Nerve								
Ankle-knee	5·9±1·2	53 ±3·6	6·5±1·4	48·8±4·6	6·2±·8	48·1±5	6·6±1·2	45·4±4·2
Posterior Tibial Nerve								
Ankle-knee	7·1±1	54·5±4·8	8·5±1·5	45·8±3·4	7·7±1·1	50·3±3·3	9·3±1	42·9±4·6
H-wave latency		28·8±1·6				31·5±2·3		

All values recorded as mean ± one standard deviation. Latencies in milliseconds. Velocities in metres/sec.

between the rates of conduction estimated below the wrist, from the digit, and above the wrist, to the elbow. From elbow to axilla both nerves transmitted centripetal impulses at similar speeds (median 70 M/sec. and ulnar 69·1 M/sec.). The differences between sensory velocities estimated in the proximal segment and those found below the elbow, are statistically significant ($P < ·001$).

Conduction in the fastest motor fibres, throughout the length of the arm, was slower than in fastest afferent fibres. Motor conduction velocity, from elbow to wrist was similar in the two nerves (58·7 M/sec. and 58·9 M/sec.). In the axillary segment the median nerve gave a value of 65·6 M/sec., and the ulnar, one of 63·7 M/sec. The disparities between motor velocities, as measured in these two segments and between each of these and the pertinent sensory conduction speeds are significant ($P < ·01$).

In these younger people, rates of conduction in the nerves of the leg were slower than in the arms. From ankle to knee, peroneal and tibial nerves conveyed afferent impulses at 53 M/sec. and 54·5 M/sec. respectively. These mean velocities do not differ significantly ($P > ·05$) but there is a substantial ($P < ·001$) divergence between them and the slower motor velocities found in the same segments (48·8 M/sec. in peroneal nerve and 45·8 M/sec. in tibial nerve).

The mean latency of the H-wave in the younger age group was 28·8 milliseconds.

Results in the people over 50 years old showed a similar relationship between motor and sensory velocities in the arms and legs, but were consistently slower. Values were roughly 5 M/sec. less than the apposite figures found in younger subjects. The differences in corresponding segmental means of the age groups, listed in Table I, are all significant to at least the 1 per cent limit of confidence.

In the leg, slowing of conduction with ageing was accompanied by difficulty in recording nerve action potentials. These were invariably elicited at the knee in young people but could not be recorded in 20 per cent of those over 50 years old.

The mean latency of the H-wave was prolonged (significantly $P < ·01$), in the older group, to 31·5 milliseconds.

Table II presents the results from 20 alcoholic patients without signs of peripheral neuropathy (Group 1). Twelve of these were under 50 years old and 7 were aged between 51 and 70 years.

In the younger subdivision, velocities in sensory fibres, from digit to wrist, were slowed in the median (55·1 M/sec.) and ulnar (54·1 M/sec.) nerves. These values denote a highly significant ($P < ·001$) fall from the normal. A less marked, though equally valid ($P < ·001$) reduction occurred in afferent (61·6 M/sec.) and motor (53 M/sec.) fibres in the median nerve between wrist and elbow. In this segment, there was a more profound

TABLE II.—NERVE CONDUCTION IN VELOCITIES GROUP I ALCOHOLICS (PATIENTS WITHOUT NEUROPATHY)

	Age 20–50 yrs.				*Age 51–70 yrs.*			
	N.A.P.		*Motor*		*N.A.P.*		*Motor*	
Nerve	*Latency*	*Velocity*	*Latency*	*Velocity*	*Latency*	*Velocity*	*Latency*	*Velocity*
Median Nerve								
Digit-wrist	2·8±·3	55·1±5·3			2·9±·3	53·4±3·4		
Wrist-elbow	4·0±·4	61·6±3·6	4·6±·4	53 ±2·8	4·0±·3	58·1±4·5	4·6±·6	51·9±2·6
Elbow-axilla	1·9±·2	70·8±4·7	1·9±·2	65·6±4·1	2·0±·3	67·8±4·9	2·2±·2	61·5±2·6
Ulnar Nerve								
Digit-wrist	2·4±·4	54·1±4·8			2·4±·4	51 ±2·8		
Wrist-elbow	4·8±·4	55·9±3·3	5·0±4·3	53·1±4·3	5·2±·5	54·5±5·8	5·3±·5	52·6±3·8
Elbow-axilla	1·9±·2	67·8±4·3	2·1±·2	62·6±4·8	1·9±·2	66·2±3·2	2·0±·2	61·1±2·2
Common Peroneal Nerve								
Ankle-knee	7·0±1·2	45·5±4·4	7·4±1·2	42·8±4·2	7·7±1·4	40·8±5·3	8·1±1·3	40 ±4·5
Posterior Tibial Nerve								
Ankle-knee	8·7±1	44·8±2·8	9·5±3·4	41·1±3·4	9·5±1·1	43 ±3·3	10·8±1·4	38·2±5·4
H-wave latency		33·7±2·3				36 ±2·5		

All values recorded as mean ± one standard deviation. Latencies in milliseconds. Velocities in metres/sec.

slowing (55·7 M/sec.) of the sensory velocity of the ulnar nerve. This discrepancy between the two nerves is meaningful ($P < ·01$).

Mean conduction velocities in the proximal (elbow-axilla) segments in this subdivision show no real change from the normal figures.

In the peroneal and tibial nerves motor and sensory speeds were significantly ($P < ·001$) lower than normal. H-wave latency was increased ($P < ·01$) compared to the normal for the younger age range.

It is apparent from Table II that the patterns of change in nerve conduction in the older fraction of this alcoholic group resembled those found in the younger sample. Velocities generally were lower in older, than in younger, alcoholics, but this is in keeping with the normal findings mentioned above. The alterations from their respective normal values is of comparable degree in both old and young patients.

Displayed in Table III are results from patients with neuropathy who had retained normal tendon reflexes. This second alcoholic group comprised 12 patients below, and 7 above, the age of 50 years.

Of patients with fully developed neuropathy (Group 3) there were 18 in each of the two age groups. Their results are listed in Table IV.

Rates of conduction distal to the wrist were further reduced in these two neuropathic groups. They showed falls from normal values greater than those found in Group I alcoholics. Results for the intermediate (wrist to elbow) segments, of the arms, in Groups 2 and 3 show but little change from those recorded in patients without neuropathy.

Mean velocities between elbow and axilla fall off a little in Table III but their differences from normal reach the 5 per cent level of significance only with the further reduction listed in Table IV. Unequivocal slowing of conduction in the proximal part of the arms occurred only in those patients who were clinically most affected.

Median and ulnar nerve action potentials were obtained in all but one patient, who was elderly and whose neuropathy was severe. By contrast, in the legs, nerve potentials were unobtainable from 20 per cent of the patients whose neuropathy was incomplete and from 55 per cent of those whose tendon reflexes were diminished or absent.

Conduction velocities, calculated from the latencies of nerve potentials, very rarely fell below 40 M/sec. in peroneal and tibial nerves. Further slowing could not be estimated since the potentials were not recordable. Thus, the mean sensory velocities in the leg showed no real difference between alcoholic groups. In both nerves, in the three groups, the velocity was around 44 M/sec. Progressive affection of the peroneal and tibial nerves was evinced by the disappearance of recordable nerve potentials and by further slowing in motor fibres which was demonstrable at low velocities (22 M/sec. in one patient).

In only one patient, with the most severe neuropathy, could muscle potentials not be elicited after stimulation of peroneal and tibial nerves.

TABLE III.—NERVE CONDUCTION VELOCITIES IN GROUP 2 ALCOHOLICS (PATIENTS WITH NEUROPATHY)

	Age 20–50 yrs.				*Age 51–70 yrs.*			
Nerve	*N.A.P.*		*Motor*		*N.A.P.*		*Motor*	
Median Nerve	*Latency*	*Velocity*	*Latency*	*Velocity*	*Latency*	*Velocity*	*Latency*	*Velocity*
Digit-wrist	2·9±·4	53·7±5·8			3·1±·3	52·3±4·1		
Wrist-elbow	3·8±·4	60 ±3·5	4·1±·4	53 ±4	4·0±·4	59·4±3·7	4·3±·7	53·5±4·2
Elbow-axilla	2·1±·3	67·3±4·7	2·4±·3	62·1±5	2·0±·3	67·3±3·7	2·3±·4	60·7±2·2
Ulnar Nerve								
Digit-wrist	2·5±·3	51·4±4·6			2·7±·4	51·9±4·2		
Wrist-elbow	5·0±·4	55·9±3·7	5·3±·4	51·9±2·6	5·0±·6	55·3±3	5·3±·6	50·2±3·7
Elbow-axilla	1·9±·2	66·1±6	2·1±·3	60·2±5	1·7±·2	67·5±2·1	2·0±·2	61·2±3·1
Common Peroneal Nerve								
Ankle-knee	7·1±·8	44·3±4·6	7·6±1·2	42·5±4·5	7·1±·8	44·6±2·8	7·6±1·3	42 ±5
Posterior Tibial Nerve								
Ankle-knee	8·7±1·1	44·2±4·2	9·6±1	41·3±3·3	9·0±·7	44·7±2·4	10·1±·9	39·7±3·3
H-wave latency		35·7±2·3				36±3·8		

All values recorded as mean ± one standard deviation. Latencies in milliseconds. Velocities in metres/sec.

TABLE IV.—NERVE CONDUCTION VELOCITIES IN GROUP 3 ALCOHOLICS (PATIENTS WITH SEVERE NEUROPATHY)

	Age 20–50 yrs.				*Age 51–70 yrs.*			
Nerve	*N.A.P.*		*Motor*		*N.A.P.*		*Motor*	
Median Nerve	*Latency*	*Velocity*	*Latency*	*Velocity*	*Latency*	*Velocity*	*Latency*	*Velocity*
Digit-wrist	3·1 ± ·4	52·3 ± 5·7			3·2 ± ·4	49·2 ± 4·5		
Wrist-elbow	4·3 ± ·7	58·1 ± 3·7	4·5 ± ·4	53·4 ± 2·3	4·3 ± ·5	54·7 ± 3·6	4·9 ± ·7	48·9 ± 5·2
Elbow-axilla	2·2 ± ·3	66·2 ± 5·2	2·3 ± ·2	62·3 ± 4	2·2 ± ·3	63·6 ± 4·9	2·5 ± ·2	55·9 ± 5·4
Ulnar Nerve								
Digit-wrist	52·8 ± ·5	48·1 ± 6·4			3·1 ± ·7	47 ± 6·6		
Wrist-elbow	2·3 ± ·8	55·5 ± 4·2	5·2 ± ·5	52·6 ± 3·9	5·5 ± ·7	51·7 ± 4·3	6·2 ± ·8	46·8 ± 4·1
Elbow-axilla	2·0 ± ·3	65·3 ± 5·2	2·1 ± ·2	60·3 ± 4·3	2·1 ± ·3	60·6 ± 5·3	2·1 ± ·2	57·8 ± 4·2
Common Peroneal Nerve								
Ankle-knee	7·5 ± 1·3	44·1 ± 2·8	8·2 ± 1·2	39·9 ± 3·4	7·2 ± 1	43·1 ± 3·2	8·3 ± 1·4	38·5 ± 4·1
Posterior Tibial Nerve								
Ankle-knee	8·7 ± 1	45·6 ± 4·5	10·1 ± 1·6	40·5 ± 5·3	8·8 ± 1	44 ± 3·4	10·5 ± 1·4	37·7 ± 3·8
H-wave latency		36·6 ± 5·2				38·5 ± 3·2		

All values recorded as mean ± one standard deviation. Latencies in milliseconds. Velocities in metres/sec.

The average latency of the H-wave was further prolonged in the two neuropathic groups. H-waves became more difficult to record, and fell in amplitude as ankle-jerks became impaired. None could be evoked in the 50 per cent of alcoholics, with severe neuropathy (Group 3), who had lost their ankle reflexes.

Discussion

Our determination of normal conduction velocities in motor fibres are similar to those of Hodes *et al.* (1948), Thomas *et al.* (1959) and Thomas and Lambert (1960). Estimates of sensory conduction speeds are compatible with observations by Magladery and McDougal (1950) and Gilliatt and his colleagues (1958 and 1961). H-wave latencies of our normal subjects conform to the findings of Magladery and McDougal (1950).

Reduced conduction rates in older people, found in this study, were observed by Wagman and Lesse (1952) and Norris *et al.* (1953).

In the arm, velocities measured in distal segments were less than in proximal sections of nerve. Others have commented on this discrepancy (Magladery and McDougal, 1950; Mavor and Libman, 1962) which is not readily explicable. Neither peripheral cooling of the limb nor distal tapering of nerves are convincing explanations (Mayer, 1963). Speed of conduction has been related to distance between nodes of Ranvier (Hursh, 1939). Young (1950) doubted this association, but if true, distal shortening of internodal segments could explain higher velocities in proximal nerve sections. Such a change was found in nerves of rabbits (Lehmann, 1951) but has not been described in man. It is uncertain whether the distal slowing demonstrated, represents a real alteration of conduction or is merely a function of the methods of recording.

Inherent in techniques of stimulation and recording through the skin, are errors due to imprecise spatial relationships between electrode positions and nerve trunks tested. Despite these defects, valid results are obtained, which correlate well with anatomical studies of peripheral nerves. Hursh (1939) showed that the diameter of a fibre (micra) inclusive of its myelin sheath, was roughly a sixth of its conduction velocity (M/sec.). Division by this factor, of the velocity we found in the median nerve at the wrist (67 M/sec.), gives an estimate of fibre size (11 μ) which agrees with microscopic assessments made by Ranson *et al.* (1935). In those segments where it was measurable, speed of conduction in the leg was less than in the arm. This difference has its morphological counterpart in fibres which distally are smaller in the leg compared to the arm (Sunderland and Lavarack, 1949). Reduced rates of conduction in the elderly reflect the decrease in size of fibres in their peripheral nerves, seen histologically (Cottrell, 1940; Rexed, 1944).

In normal people conduction studies give fairly consistent and reproducible results. The means listed in Table I have standard errors narrow

enough to make them acceptable for comparison with means from alcoholic groups.

We found subnormal conduction speeds in alcoholic patients. Motor and sensory fibres alike were affected in arms and legs of both age groups.

Impaired rates of conduction in afferent fibres of median nerves are illustrated in fig. 1. In the normal, and each alcoholic, group mean velocities for three nerve segments are depicted graphically.

Slowing was manifest distally in patients without neuropathy (Group 1), became more pronounced in Groups 2 and 3 and extended proximally in Group 3. Individual records of nerve potentials from each of the

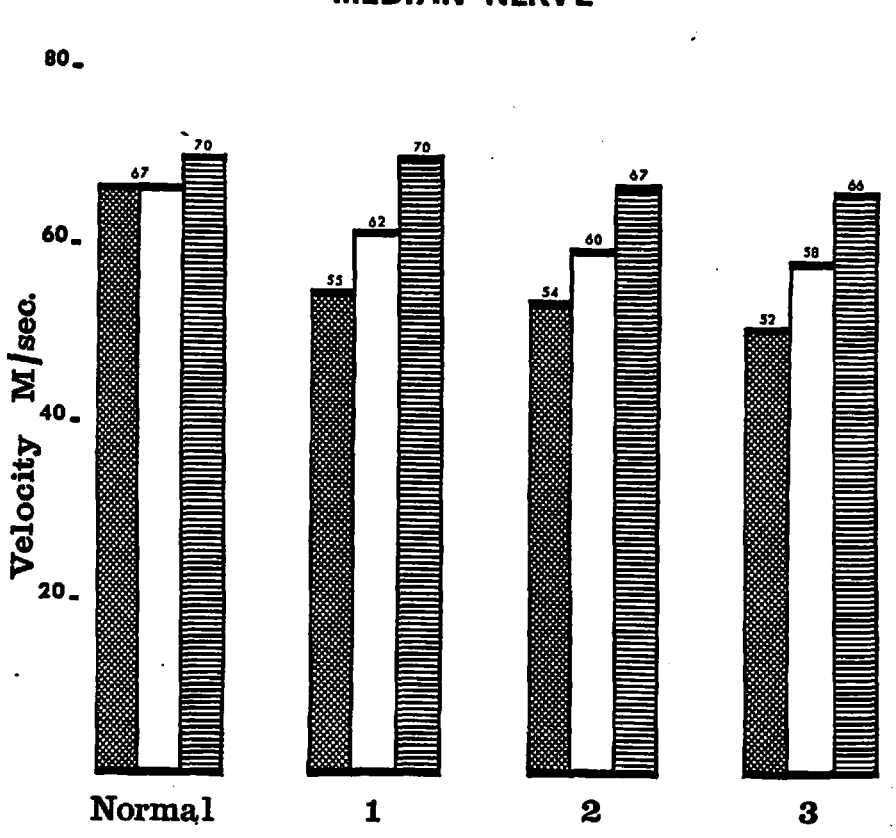

FIG. 1.—Histograms of mean velocities in largest afferent fibres of median nerves. Results from normal group and alcoholic groups 1, 2 and 3 (age range 20–50 years). Cross-hatched columns on left show mean speeds from digit to wrist, white columns represent wrist to elbow segments, horizontally striped bars on right show rates in proximal (elbow-axilla) segments.

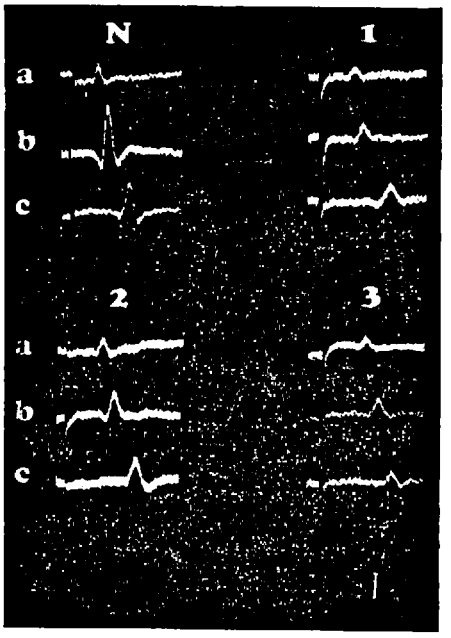

FIG. 2.

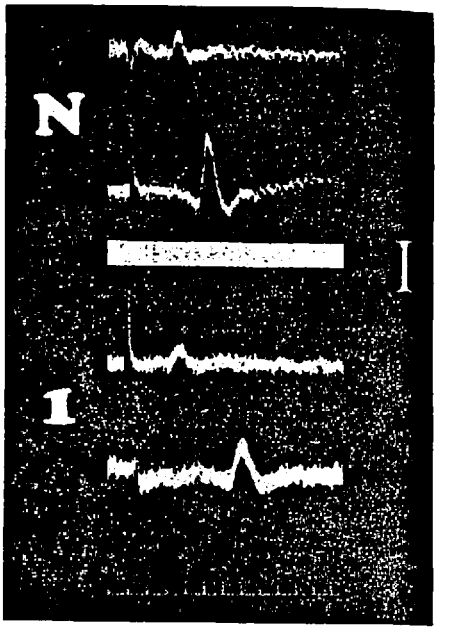

FIG. 3.

FIG. 2.—Recordings of median nerve action potentials from young patients in normal (N) group and each of alcoholic groups 1, 2 and 3. Tracings from 3 nerve segments in eahc patient: a—digit to wrist, b—wrist to elbow, c—elbow to axilla. Progressive increase in latencies, particularly in distal segments. Calibration 20 microvolts. Time intervals 1 millisecond.

FIG. 3.—Recordings of ulnar nerve action potentials from a young normal subject (N) and a young alcoholic without clinical neuropathy (I). Upper tracing in each case recorded at wrist after stimulation of fifth digit. Lower record from elbow after stimulation at wrist. Records labelled I show increased latencies, more marked in wrist-elbow segment. Calibration 20 microvolts. Time intervals 1 millisecond.

groups (fig. 2) typify these statistical alterations. The same type of change was repeated in ulnar nerves, which additionally were markedly affected in intermediate (wrist-elbow) segments. Exemplified in fig. 3, this added feature was probably due to a high incidence of mechanical compression of the nerve at the elbow. Many of our patients must have had subclinical degrees of ulnar pressure palsy, to which alcoholics are prone. It may be that nerves, already vulnerable in alcoholics, are more readily damaged by minor traumata and ischæmia than normal nerves would be.

Pattern and progression of affection in the leg were not so easily demonstrable as in the arm. Only between ankle and knee could conduction directly be measured. In this limited segment sensory speeds varied over a narrowly restricted range. Recordings of peroneal nerve

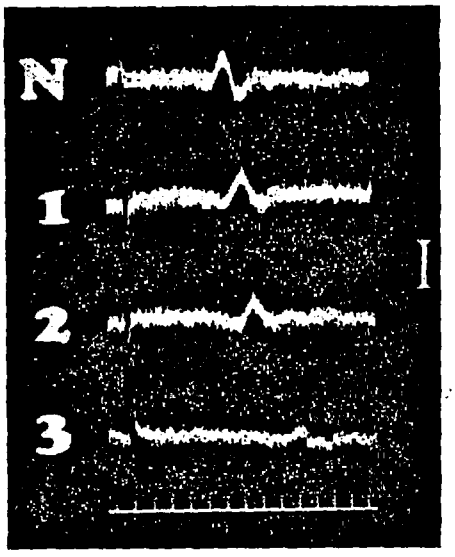

FIG. 4.—Peroneal nerve action potentials, recorded at knee after stimulation at ankle. Tracings from young normal subject (N) and from young patients in each alcoholic group (1, 2, 3). Progressive increase in latency. Calibration 20 microvolts. Time intervals 1 millisecond.

action potentials are seen in fig. 4. Latency is maximally increased in the tracing from a patient in Group 3. Velocity in this case was 36·5 M/sec. which was the lowest of the whole series.

Because of these limitations, we did not detect a graded slowing in sensory fibres, parallel to the clinical abnormalities found in tibial and peroneal nerves. A progressive fall of motor velocities in these nerves was seen in alcoholics. Changes in conduction observed in peroneal nerves are summarized in fig. 5.

Proximal affection of nerves in the leg may be inferred from the prolongation of H-wave latencies which occurred in alcoholics. It is generally accepted that this wave is of reflex origin and is subserved by the fastest afferent and efferent fibres in the sciatic nerve. This latency is determined by the conduction velocity in these fibres, the length of the sciatic nerve and by a short synaptic delay in the spinal cord. Latency is proportional to fibular length (Wagman, 1954) which serves as a convenient index of the length of leg, and hence of sciatic nerve. Means of fibular length in normal and alcoholic groups did not significantly differ. There was no reason to postulate an increased synaptic delay in our patients who had no evidence of cord lesions. It is likely therefore that delayed H-waves in alcoholics were due to slowed conduction in their sciatic nerves.

In patients without neuropathy the latency of the H response was

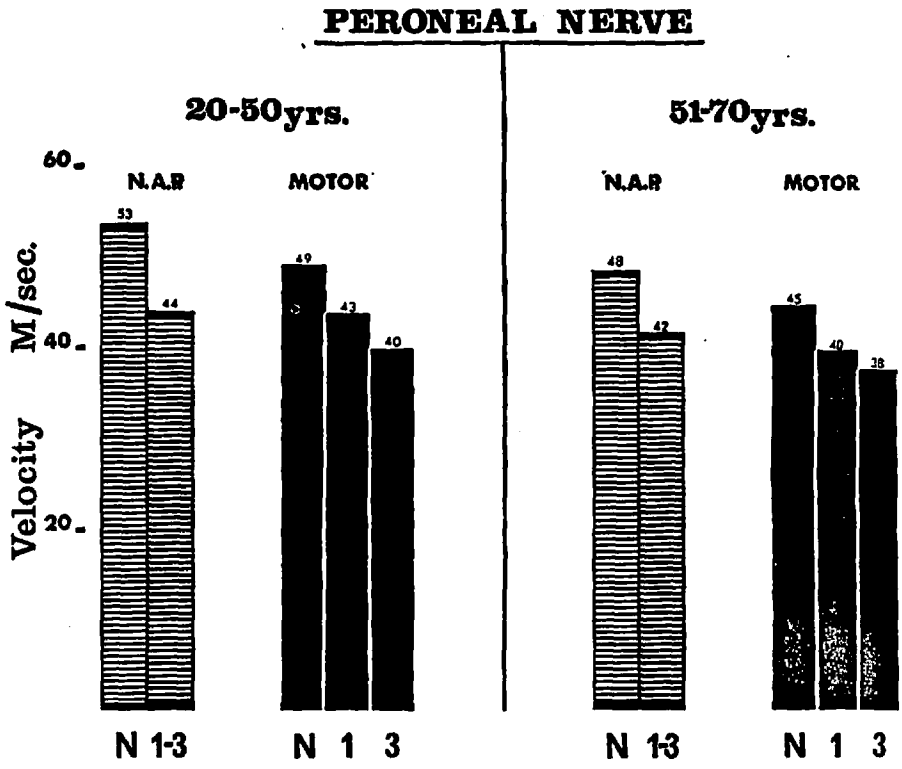

FIG. 5.—Histograms of mean velocities in peroneal nerves of patients above and below the age of 50 years. Horizontally-striped bars show speeds in largest afferent fibres, estimated from latencies of nerve action potentials (N.A.P.). Black columns represent rates in fastest motor fibres. Normal means labelled N. Afferent velocities shown in alcoholics (1–3) are mean results from all alcoholic patients (3 groups combined). Motor velocities give means for patients without neuropathy (1) and with severe neuropathy (3).

increased. They also had markedly reduced velocities between ankle and knee. The group showed proximal extension of neural dysfunction in the legs which contrasted with selectively distal impairment in the arms. These findings accord with clinical evidence that alcoholic neuropathy affects lower, more than upper, limbs.

Mean velocities significantly lower than normal were calculated for Group 1. Patients' individual results were sometimes within the normal range (normal mean ± 2 S.D.). Values for distal segments of median nerves serve as examples. Four younger patients had estimated velocities considered normal (58 M/sec. to 76 M/sec.), though less than the normal mean of 67 M/sec. The remaining 8 gave lower figures.

It seems from these results, that conduction velocity can be considerably reduced without causing disability. Further slowing of relatively minor

degree (in Groups 2 and 3) is accompanied by disturbed function which is clinically apparent. This illustrates, in operation, the safety factor of neural conduction, enunciated in principle by Meltzer (1907). These facts are in keeping with the normally insidious onset of neuropathy and with its occasionally acute development after a drinking bout, in alcoholics of long standing.

Deranged function has been demonstrated, by our results, only in the fastest-conducting, hence largest, of nerve fibres. They alone are assessed by the methods used. Velocities measured in nerve trunks could be reduced by two mechanisms. Firstly, there might be failure of conduction in the fastest fibres, either by their degeneration or by a complete block of impulse transmission in them. Lowered velocities would then be recorded from surviving smaller fibres, conducting at their normal rate. Secondly, there might be slowing of conduction in the largest fibres.

Help in differentiating these two processes is afforded by the size of nerve action potentials. The nerve potential recorded is the sum of potential changes propagated by a population of fibres. Interrupted transmission in some of these fibres leads to a dispersion of the excitation wave. Impulses arrive under the electrode asynchronously and hence the potential is reduced in size.

If this diminution is pronounced then no potential can be recorded through the skin. We have seen that this frequently occurred in our patients with neuropathy. Uniform slowing in large fibres leads to delayed but synchronous transmission of an applied stimulus and hence a nerve potential of normal size is obtained.

The size of a recorded potential is measured by the area it subtends above the isoelectric baseline. Height above the baseline, amplitude, is an adequate index of size. Amplitudes of nerve potentials vary widely. Deductions based on their alteration have but limited applicability (Gilliatt and Sears, 1958). In our young normal subjects the mean amplitude of median nerve potentials recorded at the wrist was 18 μv (range 13·2 to 33 μv). The corresponding figure for ulnar nerve was 14·7 μv (11 to 18·5 μv).

In our recordings, potential amplitude usually diminished as conduction velocity fell (e.g. figs. 2 and 4). This reduction in size was probably a concomitant to the loss of large myelinated fibres, described in alcoholic neuropathy by Greenfield and Carmichael (1935). Aring *et al.* (1941) in an alcoholic without neuropathy, found large fibres reduced by 25 per cent of the normal number, in the anterior tibial nerve. Degeneration and loss of fibres represent late results of pathological processes in peripheral nerves.

The earliest pathological changes in alcoholic neuropathy have been described by Denny-Brown (1958). He found segmental thinning or loss of myelin without destruction of axis cylinders in the most peripheral

parts of the longest peripheral nerves. Originally described by Gombault (1880), similar segmental demyelination was seen in cases of beriberi by Pekelharing and Winkler (1893).

Analogous changes in peripheral nerve were produced experimentally by Denny-Brown and Brenner (1944), who demonstrated that a partial and reversible conduction block accompanied segmental demyelination around the nodes of Ranvier. In recent work, Mayer and Denny-Brown (1964) have measured reduced velocities in cat-nerves which had paranodal myelin loss.

Five patients from Group 1 had nerve potentials of normal amplitude at the wrist, with reduced velocities distal to it. It is possible that these findings represent slowed conduction in demyelinated segments of nerves whose axis cylinders were preserved.

Our finding of early distal slowing in the nerves of the arm in alcoholics does not necessarily reflect distal origin of pathological change since primary affection of neurones may be manifest at the peripheral end of the nerve. However, initially distal impairment of conduction is consistent with histological changes which first occur at the peripheral parts of nerves.

The cause of alcoholic polyneuropathy, with its attendant defects in neural conduction, is uncertain. Alcohol itself probably does not directly damage nerves though indirectly it may influence and aggravate other harmful agents. Certainly, continued drinking, by increasing caloric intake, exaggerates demand for an inadequate vitamin supply (Jolliffe *et al.*, 1936). Alcoholic gastritis, vomiting and anorexia, further reduce the intake of essential foods. Complex metabolic effects of alcohol have been investigated. A breakdown product, acetaldehyde, is toxic to thiamine-deficient animals (Handler, 1958). Free fatty acids and triglycerides increase in the serum when blood alcohol levels are high (Schapiro, 1963). Low serum magnesium was found in up to 50 per cent of alcoholics (Martin *et al.*, 1959) and did not seem to be due to dietary factors. The possible implications, of this and similar work, in peripheral nerve affection have not yet been fully explored.

Empirical evidence against the neurotoxic effect of alcohol was adduced by Strauss (1935) whose patients treated with vitamins, recovered from their neuropathy despite drinking a pint of whisky daily. Low *et al.* (1962) found no change of motor conduction speeds in the ulnar nerves of their subjects who drank large amounts of alcohol for short periods.

Shattuck (1928) first proposed a nutritional cause for alcoholic neuropathy, citing its similarity to beriberi. Minot *et al.* (1933) studied the diets of alcoholic patients, and found them lacking but could not define a specific deficiency. This has been the experience of many others, including ourselves. Almost all of the patients in this series gave histories of malnourishment, often years in its duration, sometimes profound in its

degree. Collateral evidence of dietary deficiencies was found. In 4 patients, a loss of weight between 25 and 50 lb. over the past year, could be documented. Angular stomatitis was present in 14, and glossitis in 3 people. Forty per cent of our patients had macrocytic anæmia, with megaloblasts in the marrow, which responded to folic acid. A similar high incidence of folic acid deficiency in alcoholics was reported by Herbert *et al.* (1963).

Search for precise nutritional factors causing alcoholic neuropathy, has been intense. Thiamine lack has most often been impugned. Its deficiency has clearly been shown to cause the ophthalmoplegia, ataxia and nystagmus of Wernicke's disease (Phillips *et al.*, 1952; Victor and Adams, 1961), so often associated with neuropathy. Meiklejohn (1940) and Wintrobe and his colleagues (1942), however, doubted whether polyneuropathy was due to lack of thiamine. Experimental studies gave conflicting information. Swank (1940) produced peripheral nerve lesions in pigeons, partially deprived of thiamine for relatively long periods. In later experiments, Swank and Prados (1942), again in pigeons, described the developing pathology in nerves. They showed a distal degeneration, particularly affecting large fibres, which later extended proximally and was accompanied by slight shrinkage and sclerosis of cell bodies. In some birds the lesions were reversible when thiamine was given.

This clear-cut demonstration in pigeons could not easily be reproduced in mammals. Neither Engel and Phillips (1938) in rats nor Wintrobe and his colleges (1944) in pigs nor Berry *et al.* (1945) in cats could produce nerve pathology by thiamine deficiency. Follis (1948) said there was no good evidence that thiamine deficiency led to peripheral nerve lesions in mammalia.

North and Sinclair (1956) in a careful study of rats, defined strict criteria for histological examination, gave supplements of other vitamins and excluded inanition effects by using pair-fed control animals. They maintained their animals on an appreciable, but insufficient thiamine intake for a long period (156–165 days) and produced distal lesions in peripheral nerve, mainly affecting myelin sheaths but with slight irregular shrinkage of axis cylinders. They emphasized the need for long-continued deprivation of thiamine before peripheral neural damage occurred in experimental animals.

The significance of prolonged thiamine deficiency has been shown in human volunteers. Williams and his colleagues (1939) found that an almost complete absence of dietary thiamine led to prostration and anorexia in their subjects. The experiment had to be stopped before neural affection occurred. Therefore, in 1943, thiamine intake was less severely restricted and adjuvant doses of the vitamin were given at fortnightly intervals. The two volunteers complained of paræsthesiæ in the leg after two months. Clear signs of neuropathy were not found until

110 days after the experiment's start. This latter type of dietary restriction mimics the clinical stories of many alcoholics whose long-continued deficiency is occasionally relieved by intervals of adequate nutrition. It is such people who develop neuropathy. Patients with acute, complete thiamine deprivation suffer from cerebral neuronal lesions. Denny-Brown (1958) has emphasized the importance of the temporal evolution of thiamine lack, linking clinical syndromes to the experimental findings. It is likely that thiamine deficiency is at least an important factor in alcoholic neuropathy, if not its sole cause.

How thiamine lack impairs nerve function is not completely defined. Thiamine pyrophosphate participates in three reactions in the metabolism of glucose. Two of these are stages in the citric acid cycle; the decarboxylation of pyruvic acid and of d-ketoglutaric acid. The third, transketolase, reaction is a part of the direct oxidative pathway for glucose. Blood levels of pyruvate are raised in alcoholics (Bueding *et al.*, 1942; Joiner *et al.*, 1950), but inconstantly so in those with neuropathy. Excess blood pyruvate occurs in conditions other than thiamine deficiency (Simpson, 1962). Reduced transketolase activity in the blood, a more specific index of B_1 lack, was found in alcoholics with Wernicke's disease and polyneuropathy (Embree and Dreyfus 1963).

The effect on nerves of lack of thiamine pyrophosphate may be due to a failure of the nerve to obtain energy from adenosine triphosphate because of impaired glycolysis.

A second possibility is that products of reactions catalysed by thiamine are essential for nerve cell metabolism.

It may be that toxic intermediary products accumulate due to lack of thiamine. These may disrupt neural metabolism. Pyruvate and methyl glyoxal have been suggested for this role (Handler, 1958).

One other, direct effect of thiamine on neural conduction has recently been described by Von Muralt (1962). He found that thiamine was liberated in nerves with excitation and showed that an antimetabolite of thiamine decreased excitability, and caused a fall-off in action potential, at the node of Ranvier.

Thiamine deficiency alone may explain disturbed nerve conduction in alcoholics but other factors probably play a part.

Pyridoxine deficiency in swine (Follis and Wintrobe, 1945; Swank and Adams, 1948) causes changes in peripheral nerves and dorsal root ganglia. Victor and Adams (1956) showed patchy, segmental demyelination in the peripheral nerves of monkeys lacking in pyridoxine.

Pantothenic acid deficiency in human volunteers (Bean *et al.*, 1955) caused burning paræsthesiæ in the legs. It has been suggested that such a deficiency is the cause of the "burning feet syndrome" described by

Denny-Brown (1947) and Spillane (1947) in prisoners of war. Similar clinical features occur in alcoholics who present a picture distinct from the commoner type of polyneuropathy (Denny-Brown, 1958). There were 7 such patients among our alcoholics. They showed no significant difference, in their conduction speeds, from the remainder of the group.

Fennelly and his colleagues (1964) assayed vitamins in the blood and muscles of alcoholics. Thiamine levels were low in all patients with manifest neuropathy and in half of those without neuropathy. Niacin, folic acid and pantothenic acid were also reduced in many cases. These findings of vitamin deficiencies in alcoholics without clinically evident neuropathy provide causes for the slowed conduction we found in similar patients.

Evidence of liver damage, clinical signs or altered tests of function, was present in 45 per cent of our patients. The metabolic effects of liver disease may play a part in the development of neuropathy. Lipoic acid is formed in the liver and may be deficient in alcoholics (Hornabrook, 1961). This would derange the oxidation of pyruvate, adducing another possible method of interference with glycolysis.

Most of the agents which alcoholics may lack serve as co-factors in the oxidative metabolism of glucose. Common to their several deficiencies is an inhibition of enzymatic glycolysis. Neural tissue depends on this mechanism for energy. Various shortages would, therefore, interfere with nerve cell anabolism and hence with axis cylinder function (Weiss and Hiscoe, 1948). In addition there would be an effect on Schwann cell cytoplasm. Oxidative enzyme activity, in peripheral nerves, is concentrated around the nodes of Ranvier, as Romanul and Cohen (1959 and 1960) showed histochemically. These sites might be most susceptible to deprivation of cofactors, leading to early changes in the myelin sheaths. This could reduce myelin impedance, cause current leakage and delay excitation at the nodes, thus slowing transmission (Tasaki, 1955).

Experimental and pathological data, discussed above, suggest a sequence of changes in peripheral nerve affection which can be correlated with our results.

Paucity of thiamine in chronic alcoholics might first directly depress conduction in nerves. Von Muralt's (1962) work suggests this possibility which we have been unable to explore under clinical conditions. Continued shortage of vitamins, particularly of B_1, affects myelin sheaths at the nodes of Ranvier, causing defects which initially are biochemical. Later, structural alteration is seen, with retraction of myelin at the nodes. These changes occur first at the peripheral ends of the longest and largest fibres. We suggest that early, distal reductions of conduction speeds in alcoholics

are due to nodal disturbances with slow transmission in large fibres. A few of our patients in Group 1 probably had such lesions. At this stage the damage could presumably be quickly repaired by thiamine replacement. Prolongation of deficiencies disrupts neuronal metabolism in dorsal root ganglia and anterior horns. The consequences are initially manifest at the distal ends of axis cylinders where beading and fragmentation occur and conduction is blocked. Progressive fall in distal velocities (found in Groups 2 and 3) reflects the loss of transmission at the extremities of the largest fibres. As fibres degenerate distally, segmental demyelination extends proximally so that conduction velocities are reduced proximally (in Group 3). When dissolution of many of the largest fibres has occurred, slowed conduction speeds are recorded from smaller fibres; nerve potentials diminish in size and eventually are unrecordable.

Conduction studies in alcoholics give results which are consistent with the known pathological changes in peripheral nerves. They supplement clinical observations of alcoholic polyneuropathy. Changes in conduction velocities afford a more sensitive index of progression and regression of neuropathy than do clinical signs and would be useful in assessing the results of treatment.

Summary

Conduction studies in normal people and in chronic alcoholics are compared.

Limitations of the techniques used and the validity of results obtained are examined.

Conduction speeds are reduced in alcoholic patients. Motor and sensory fibres equally are affected in arms and legs. Subnormal velocities are found distally in patients without clinical signs of neuropathy. The changes become more marked and extend proximally as clinical signs increase in severity.

In the alcoholic group ulnar nerve conduction was also impaired by compression at the elbow.

The ætiology and pathogenesis of changes in conduction rates are discussed. It is suggested that nutritional deficiencies, particularly thiamine lack, first cause segmental demyelination in peripheral nerves and later degeneration of fibres.

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