Peripheral Neuropathies

N. Canal and G. Pozza Editors

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PERIPHERAL NEUROPATHIES

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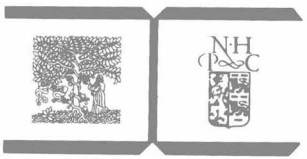
and
G. POZZA



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PREFACE

This volume is the Proceedings of the Symposium on Peripheral Neuropathies held on June 26-28, 1978 at the University of Milan.

The initial idea was to devote the entire meeting to the metabolic and genetic neuropathies, but then we thought it more interesting and complete to divide the Symposium into different "Main Themes" in order to enlarge the interest in peripheral neuropathies and also in other scientific branches. In this way, pharmacologists and anatomists, orthopaedists, diabetologists and nephrologists have discussed, together with neurologists, subjects such as axonal transport, neuropathies in chronic renal failure, compression neuropathies and diabetic neuropathies.

Naturally we did not completely forget our initial purpose and an entire session was devoted to the metabolic and genetic neuropathies.

We also had a good number of contributions on basic problems in peripheral nerve pathology which were of such an outstanding quality to be grouped in another special Session.

The volume includes almost all the invited lectures presented at the Symposium and some of the free communications which were more strictly related to the chapters of the book.

The Editors would have liked to have been able to include all the 100 and more communications, of excellent quality, but this would have brought us to considerably exceed the number of pages agreed upon with the Publishers.

The Organizers gratefully acknowledge the support given by FIDIA Research Laboratories.

N. Canal and G. Pozza

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Peripheral Neuropathies
N. Canal and G. Pozza, eds.

SENSORY ACTION POTENTIALS AND BIOPSY OF THE SURAL NERVE IN NEUROPATHY

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ABSTRACT

In 167 consecutive patients with various types of neuropathy the amplitude of the sensory potential and the maximum conduction velocity along the sural nerve were compared with conduction in other sensory nerves and related to nerve biopsy. Electrophysiological findings in the sural nerve were similar to those in the superficial peroneal and the median nerve, though the distal segment of the median nerve was normal in 20% of the patients when it was abnormal in the sural nerve. Quantification of histological findings was a more sensitive method than the electrophysiological study in that two-thirds of 33 patients with normal electrophysiology in the sural nerve showed slight loss of fibres or signs of remyelination in teased fibres. Of the 95 nerves from which teased fibres were obtained, maximum conduction velocity was abnormal in 43. In 18 nerves slowing in conduction was due to axonal degeneration: the velocity was as to be expected from the diameter of the largest fibres in the biopsy ("proportionate slowing"). In nine nerves slowing was severe and more marked than to be expected from loss of the largest fibres ("disproportionate slowing"); these nerves showed paranodal or segmental demyelination in more than 30% of the fibres. In 16 nerves from patients with neuropathy of different ætiology, among these three from patients with diabetic neuropathy, neither loss of fibres nor demyelination could explain the moderate slowing. When an incidence of teased fibres with demyelination over a length of 10 mm of the nerve is extrapolated to 140 mm of the nerve, 50% of the fibres would have no myelin defects (either de- or remyelination).

The cause of the slowing is possibly a functional defect in the excitable membrane of the nerve.

Finally the limitations are discussed and minimal requirements are suggested for the electrophysiological diagnosis of a peripheral neuropathy with discrete clinical symptoms and signs.

INTRODUCTION

Experimental and clinical science advances as much by the development and application of new techniques as by new theories. In the field of peripheral neuropathy the progress in techniques lies essentially in the quantification of morphological and electrophysiological findings. The progress in theory was inspired by the concept that neuropathies can be divided into two types: One with extensive demyelination and marked reduction in conduction velocity primarily affecting the Schwann cell. Another larger group is characterized by axonal degeneration and little or no demyelination. Slowing in conduction is less than in nerves with extensive demyelination. This concept, originally based on findings in experimental neuropathy, has greatly stimulated work in the field. It was, however, soon recognized that a neuropathy with extensive demyelination is nearly always associated with marked loss of fibres[1,2,3,4]. In our material of 85 nerves from which teased fibres were obtained, segmental demyelination without fibre loss was present in two nerves. Moreover, signs of paranodal demyelination were found in axonal neuropathy, possibly indicating involvement of the Schwann cell secondary to the involvement of the axon[5,6]. To suggest demyelination as the underlying pathology for slowing in conduction encounters difficulties when slowing is of the order of 30 to 40%. This degree of slowing occurs in axonal neuropathy in the absence of segmental or paranodal demyelination.

Based on electrophysiological and biopsy findings in 167 patients with neuropathy (Table 1) we shall adress two problems, the one concerns the relation between morphometric findings in the sural nerve, conduction velocity and amplitude of the evoked potentials. The other problem concerns the early recognition of neuropathy. This problem has attracted interest because of growing awareness of possible toxic agents in the environment.

Table 1[7]

167 PATIENTS WITH POLYNEUROPATHY

Acquired neuropathy of different ætiology	No. of patients	Hereditary neuropathy	No. of patients
Diabetic	12	Peroneal muscular atrophy	
Postinfectious	14	neuronal type	19
Alcoholic	38	hypertrophic type	10
Postgastrectomy	6	*neuronal "plus"	9
Paraneoplastic	4	Spino-cerebellar ataxia	3
Collagen disease	3	Hered. liability to	
Uræmic	2	pressure palsies	10
Lead intoxication	9		
Hepatic	1		
B_{12} Malabsorption	1		
Acute interm. porphyria	1		
Unknown	25		

*Peroneal muscular atrophy of the neuronal type plus involvement of the central nervous system.

METHODS

The method of stimulation and recording has been described[8,9,10]. Fig. 1 shows the sites of recording in the median and sural nerves and the site of the biopsy of the sural nerve and Fig. 2 shows the position and dimensions of the near-nerve electrode at an optimal distance from the sural nerve. Electronic averaging of 500 to 2000 responses was used to estimate amplitudes of less than 3 μV (lower limit 0.02 μV) and to record the conduction velocity of the fastest and of the slow components.

Biopsy: 3 to 5 cm of the sural nerve were removed in toto and prepared for light and electron microscopy and for preparation of 50 to 70 teased fibres as described[12,13,14,15]. In each biopsy the transverse endoneurial area was measured. Moreover, the total number and size distribution of myelinated fibres and of groups of three or more regenerating fibres ("clusters") were determined within an area of 0.4 to 0.6 mm^2, sampled from all fascicles.

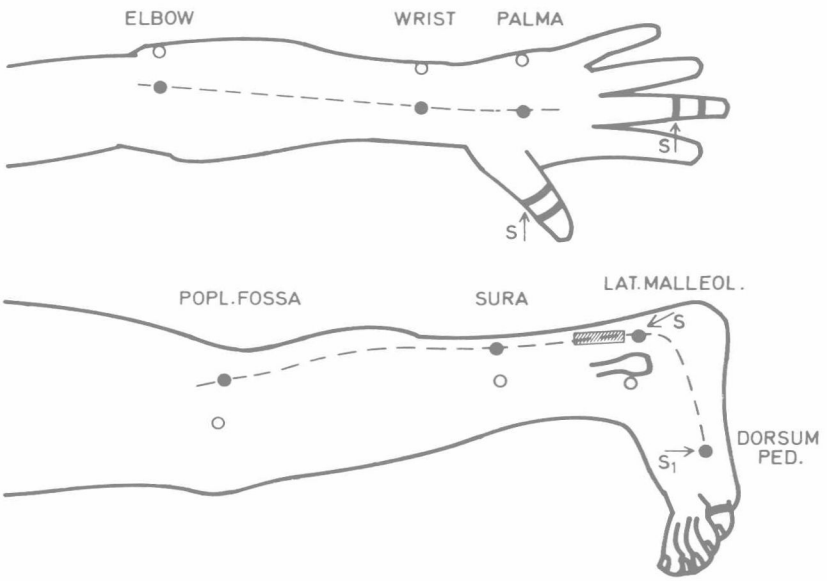

Fig. 1. Placement of the near-nerve (●) and remote (o) needle electrodes to record from different segments of the median and sural nerves. S, stimulating cathode (surface or needle). S_1, cathode to stimulate the sural nerve. "Sura" denotes the site of recording 12 to 14 cm proximal to the lateral malleolus. The shaded area shows the 3-5 cm long segment of the sural nerve taken in toto as biopsy[11].

In addition, we counted sites with clumps of myelin and determined the incidence of degenerated fibres and of bands of Büngner in electron micrographs. In teased fibres the incidence of fibres, of segments with segmental and paranodal demyelination, of remyelination and of regenerated fibres was determined.

RESULTS

The most frequent histological abnormality that changes nerve conduction and amplitude of the sensory potentials is loss of myelinated fibres. The amplitude of the potential recorded via needle

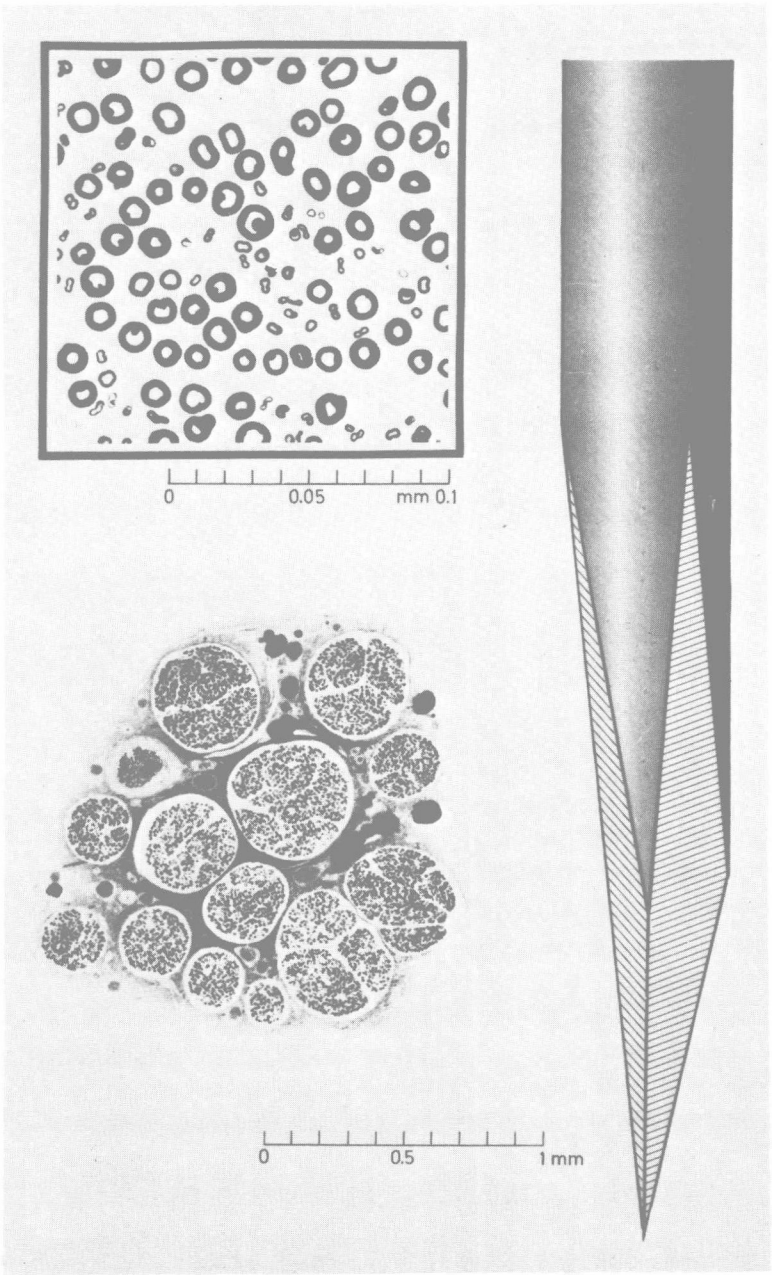

Fig. 2. Recording electrode (right) at an optimal distance from the sural nerve (left) to ascertain that the action currents from the fibres of all fascicles are about equally represented when they reach the leading-off surface of the electrode. Above, left, cross-section through the sural nerve at a 10 times higher magnification (courtesy of Professor Annelise Rosenfalck).

electrodes from the sural nerve increases with the number of large myelinated fibres [11,14,18,7]. Since loss of large fibres was equally prominent in nerves with axonal degeneration as in those with demyelination[15], the question arises whether the type of pathology can be predicted from the degree of slowing in conduction. We have tried to answer this question by determining whether and when the slowing in conduction in a given sural nerve from a patient with polyneuropathy could be predicted from the largest fibres found in the biopsy of the same nerve. The prerequisite for the prediction of the maximum conduction velocity is the fact that conduction velocity varies proportionally with the diameter of the nerve fibre[16]. The fastest component of the sensory potentials was related to the myelinated fibres of largest diameter in the histogram of diameter of the same nerve as shown in Fig. 3. In the human sural nerve the maximum conduction velocity was 4.3 (S.D. 0.3) times the fibre diameter. Findings in nerves with purely axonal degeneration showed that the conversion factor was the same for fibres of more than 7 μm in diameter[11,17].

To calculate conduction velocity from the diameter of the largest fibres, we have assumed that at least 10 fibres must be present to give a response distinguishable from noise when 500-2000 responses are averaged. This assumption is based on the relation between amplitude of the sensory potential and number of large myelinated fibres in the sural nerve[11,14,17,18].

When slowing in maximum conduction velocity deviates by less than 20% from that to be expected from the fibres of largest diameter, it can be explained by axonal loss and demyelination does not slow the maximum conduction velocity. The scatter of 20% is derived from findings in controls[14,18].

From counts of myelinated fibres and from quantitation of abnormalities in teased fibres axonal degeneration was shown to be the dominating pathology in 20 sural nerves from patients with alcoholic neuropathy[19,14]. The incidence and extent of paranodal and segmental demyelination (0.3%) and remyelination (20%, compared with 5-20% in controls) was unimpressive[14]. This was the case even when fibre loss was insignificant and when the neuropathy had lasted for only a few weeks. When present at all, myelin damage was distributed over multiple sites of a given fibre

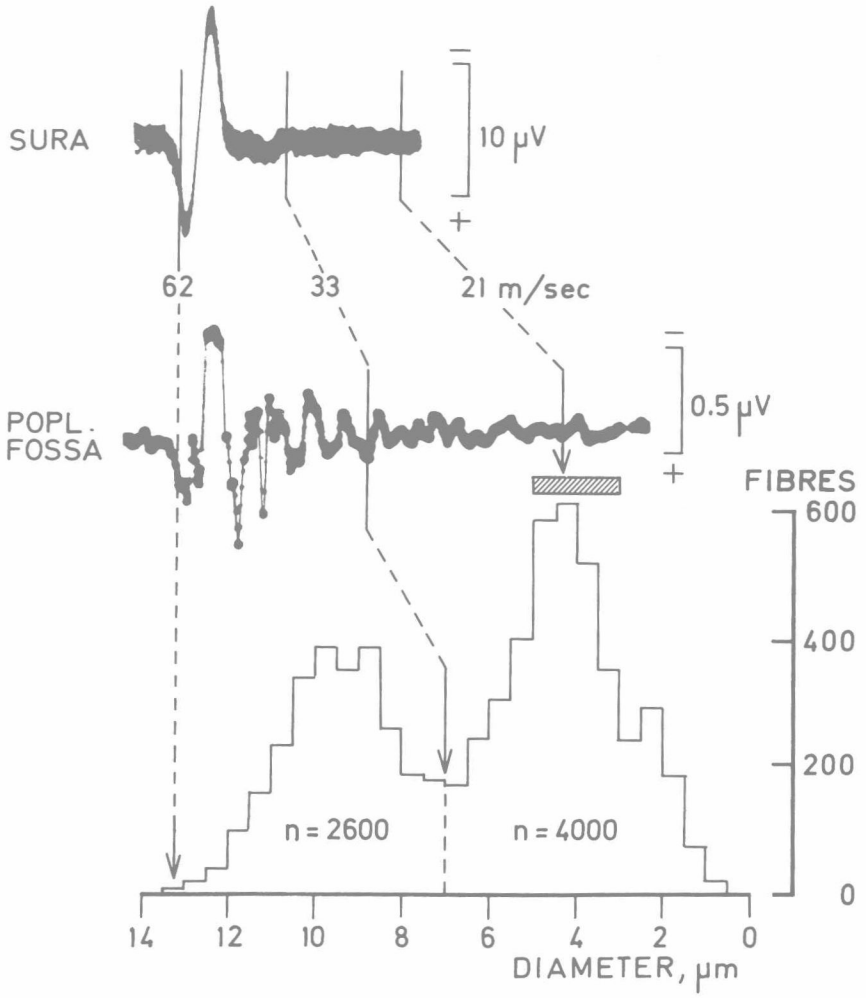

Fig. 3. Components of the sensory potential and distribution of diameters of myelinated fibres in a normal sural nerve. Above and middle: The nerve was stimulated maximally at the lateral malleolus and the potential was recorded 15 cm (sura) and 50 cm (fossa poplitea) proximally to it. The dashed lines connect components conducted at the same velocity and point to the corresponding fibre diameter in the histogram below (6600 fibres). Note that the diameter of the fibres is plotted from right to left[11,17].

in one third of the fibres, interpreted to be secondary to beginning axonal degeneration[56]. Axonal degeneration was also the main pathology in 19 biopsies from patients with the neuronal type of peroneal muscular atrophy[15], in Friedreich's ataxia[20], in three of four patients with paraneoplastic neuropathy, in patients with rheumatoid neuropathy, polyarteritis nodosa, hepatic neuropathy, acute intermittent porphyria[7] and in lead neuropathy[21].

In alcoholic neuropathy, in the neuronal type of peroneal muscular atrophy, in paraneoplastic neuropathy, in lead neuropathy and in lead-exposed men the recorded conduction velocity was equal to the velocity expected from the fibres of largest diameter, i.e. the slowing in conduction could be explained by axonal degeneration (Fig. 4). A decrease in conduction velocity from the normal 53 m/s to 30 m/s (to 55% of normal) could be due solely to loss of the largest fibres. Not unless the recorded sensory conduction velocity was disproportionally slower than expected or - when no biopsy was available - not unless the velocity was slowed to less than 60% of normal is it justified to assume causes other than axonal degeneration for the diminution in conduction velocity.

A reduction in amplitude and conduction velocity is also seen in regenerating fibres. This is illustrated by the recovery of the sensory potential after section and suture of the nerve[23]. The sensory potential of regenerating nerve is characterized by 30 to 50 components of low amplitude. Five months after suture of the median nerve at wrist, when the first response could be distinguished, the cumulative amplitude, obtained by adding the amplitude of component potentials, was 1 to 3 μV, the fastest component was conducted at 10 to 25 m/s, the slowest at 2 to 3 m/s. 40 months after suture, when tactile sensibility had become normal, the potential was still split-up in 20 to 30 components, the cumulative amplitude was normal as was the maximum conduction velocity. The velocity of the slowest components was still markedly diminished (Fig. 5). Fig. 6 shows the time course of recovery of the cumulative amplitude of the sensory potential recorded just proximal to the site of the end-to-end suture at wrist. The left plot shows the much faster recovery after a transient compression of the ulnar nerve at the elbow, that presumably has caused segmental demyelination[23].