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Quantitative Changes of Sural Nerves in Various Neurological Diseases

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Summary. Quantitative histological studies were made on sural nerve biopsies from 123 patients with various neurological disorders. The myelinated fibre density, nuclear density, and the thickness of the perineurium were measured and compared with the average and standard deviation of control material in different age groups.

Specimens from chronic polyneuritis and heredodegenerative neuropathy showed a reduction of myelinated fibres and an increase of nuclei, the decrease of large myelinated fibres being greater than that of small myelinated fibres.

In acute polyneuritis the large and small myelinated fibres decreased equally in number. In the sensory type of SMON, small myelinated fibres decreased more than large myelinated fibres, while in the sensorimotor type of SMON, the change was the reverse. Nuclear population remained unchanged in these diseases.

In spinocerebellar degeneration there was a close correlation between the decrease in myelinated fibres and the clinical findings such as sensory disturbance and diminished tendon reflexes, suggesting the presence of peripheral nerve involvement.

Myelinated fibres were reduced in cases of neurological diseases hitherto considered to be free of pathological changes in sensory nerves, including motor neurone disease, myopathy, tumours or vascular diseases of the brain and spinal cord. In motor neurone disease and myopathy the large fibres were decreased more than small fibres, and nuclear population was increased. In tumours or vascular disease of the central nervous system, the large and small fibres were decreased equally in number, and the nuclear population was within normal range.

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Key words: Sural nerves – Pathological changes – Quantitative study.

Introduction

This study is an attempt to elucidate quantitatively the characteristics of pathological changes of 123 sural nerve biopsies in various neurological diseases. It records the changes in the myelinated fibre density, the nuclear density, and also the thickness of the perineurium.

In the previous report the authors established in each age group the average and standard deviation of the myelinated fibre density, nuclear density, and the thickness of the perineurium in the sural nerve from 79 necropsies of ages from 1 week to 88 years (Tohgi et al., 1977). It is now possible to compare the quantitative results of pathological material with control material of the same age group. The extent of the abnormalities in one age group can also be compared with results from other age groups.

Materials and Methods

1. Materials

One-hundred and twenty-three sural nerve biopsies from patients with neurological diseases were selected for quantitative histopathologic study. The diseases included acute polyneuritis (8 cases), chronic polyneuritis (11 cases), subacute myelo-optico-neuropathy (SMON) (35 cases), heredodegenerative neuropathy (12 cases), spinocerebellar degeneration (15 cases), motor neurone disease (14 cases), myopathies (16 cases), and tumours or vascular disease of the central nervous system (12 cases); all are shown in Table 1. All cases of acute polyneuritis (so-called Guillain-Barré syndrome) with increased cerebrospinal fluid protein recovered completely, and were biopsied from 2 weeks to 2 months after the onset of the disease. Of 11 cases of chronic polyneuropathy, 2 were thought to be

Table 1. Biopsy materials

Acute polyneuritis	**8**
Chronic polyneuritis	**11**
SMON	**35**
Heredodegenerative neuropathy	**12**
Dejerine-Sottas disease	5
Charcot-Marie-Tooth disease	4
Roussy-Levy disease	1
Sensory radicular neuropathy	2
Spinocerebellar degeneration	**15**
Motor neurone disease	**14**
Myopathy	**16**
Duchenne muscular dystrophy	6
Myotonic dystrophy	2
Other muscular dystrophies	5
Polymyositis	3
Miscellany	**12**
Total	**123**

recurrent polyneuritis with raised cerebrospinal fluid protein which responded to corticosteroid treatment. Nine showed a chronically progressive course without any changes in the cerebrospinal fluid and did not respond to treatment with vitamins and corticosteroid. A biopay was performed on these patients 1 – 12 years after the onset of the disease.

Subacute myelo-optico-neuropathy (SMON) is a disease which has been prevalent in Japan for the last 15 years. The clinical manifestations consist of abdominal pain and/or diarrhoea followed by paraesthesia, dysaesthesia and with objective sensory disturbances in the lower extremities; spastic paraparesis or paraplegia with exaggerated patellar tendon reflexes; and, on occasions, impairment of visual acuity. Pathologically, degenerative changes are found in the peripheral nerves, posterior roots, gracile tracts, pyramidal tracts, and in some cases the optic nerves and the inferior olives. In recent years increasing evidence has accumulated suggesting that chinoform might be a cause of SMON (Tsubaki et al., 1971; Nakae et al., 1971; Shimada and Tsuji, 1971). Patients with SMON were biopsied from 10 days to 6 years after the onset of the disease. Cases with tumours or vascular disease of the brain and spinal cord were grouped into "central nervous system (CNS) diseases".

2. Histological Preparations and Quantitative Studies

The sural nerve was biopsied under local anesthesia at the level of the lateral malleolus. About 3 cm of the nerve were fixed in 10% formalin, embedded in paraffin, and sections 5 μm were stained by hematoxylin and eosin, Masson's trichrome method, and Bodian's silver stain. Quantitative studies were made of the myelinated fibre density, nuclear density, and the prineurial thickness as described in a previous report (Tohgi et al., 1977).

3. Standard Measurement

The quantitative measurement established for the control sural nerves of a certain age group should be used when measuring the quantitative histological changes of a sural nerve biopsy of the same age group. For this reason the value x of each measurement in the pathological samples was standardized according to the formula $t = (x-\bar{x})/s$. $\bar{X}$ and s are the average and standard deviation respectively of the control samples from the same age group as the patients from whom pathological samples were taken. In this formula t is called the standard measurement of x, and has the average of 0 and standard deviation of 1. When t is negative, x will be smaller than $\bar{x}$ by t times s. The average and standard deviation of myelinated fibre density, nuclear density, and perineurial thickness in each age group are shown in Table 2.

Results

1. Myelinated Fibre Density

Figure 1 shows the frequency distribution of the standard measurement of large (solid line) and small (dotted line) myelinated fibre densities in the control group and various neurological diseases. The abscissa shows the standard measurement of the myelinated fibre density, and the ordinate the number of cases. In the control group, the distribution of both large and small myelinated fibres was roughly Gaussian with a peak around 0.

In almost all the neurological diseases the peak of the distribution of the standard measurement of large and small fibre densities shifted from 0 to minus, indicating that the large and small fibre densities decreased when compared with control subjects of the same age group.

In acute polyneuritis and SMON, there was no differences in the degree of decrease of the large and small myelinated fibres. Cases of SMON were classified into sensory and sensorimotor types. The sensory type included cases which had paraesthesia, dysaesthesia, and objective sensory disturbances in the lower extremities, and the sensorimotor type cases which showed spastic paraparesis or paraplegia in addition to sensory disturbances. In the sensory type, the decrease of small myelinated fibres was greater than that of large myelinated fibres, while in sensorimotor type the reverse was the case as shown in Figure 2. In chronic polyneuropathy and heredodegenerative neuropathy, the decrease of large myelinated fibres was greater than that of small myelinated fibres. Spinocerebellar degeneration, motor neurone disease, and myopathy also showed a similar tendency.

The spinocerebellar degenerations were classified into 3 groups: 1. with exaggerated achilles tendon reflexes without sensory disturbances (3 cases), 2. with normal achilles tendon reflexes and sensory disturbance of the stocking type (9 cases), and 3. with both diminished achilles tendon reflexes and sensory disturbance in the lower extremities (3 cases). The standard measurement of the total myelinated fibre density decreased moderately in group 2, and most remarkably in group 3 (Fig. 3).

Table 2. Average and standard deviation of myelinated fibre density, nuclear population and perineurial index in each age group

Age groups	Myelinated fibre density[a]			Nuclear population[b]	Perineurial index
	large fibre	small fibre	total		
11–30	64.1 ± 15.4	90.8 ± 35.8	154.8 ± 31.7	40.7 ± 12.0	2.48 ± 0.92
31–50	52.9 ± 13.6	74.7 ± 28.2	127.7 ± 30.1	46.4 ± 11.3	2.64 ± 1.24
51–70	37.1 ± 12.6	75.1 ± 29.8	111.9 ± 36.9	51.6 ± 8.4	3.36 ± 0.97
71–88	31.9 ± 14.1	75.3 ± 28.9	107.2 ± 37.4	56.6 ± 30.7	3.52 ± 1.06

[a] Hundred fibres per sq. mm [b] Hundred nuclei per sq. mm

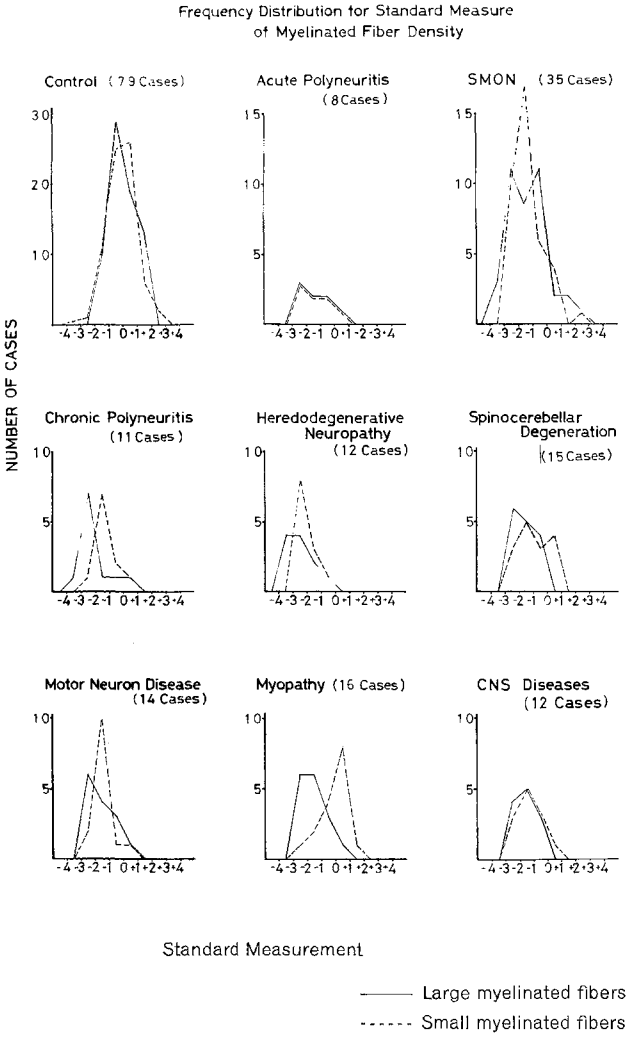

Fig. 1. Case frequency distribution of standard measurement of both large (solid line) and small (dotted line) myelinated fibre density. Abscissa: Standard measurement of myelinated fibre density. Ordinate: Number of cases

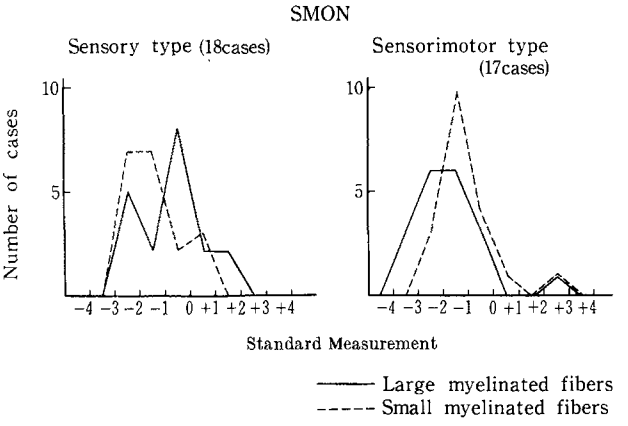

Fig. 2. SMON. Case frequency distribution of standard measurements of both large and small myelinated fibre densities is demonstrated in two types of SMON; cases predominantly with sensory disturbances (sensory type) and cases with sensorimotor disturbances (sensorimotor type)

2. *Nuclear Density*

Figure 4 shows the frequency distribution of the standard measurement of the nuclear density in the control group and in groups of various neurological diseases. In the control group, 58% of the cases had standard measurements between −1 and +1, and 22% less than −1. Cases in each disease were divided into the same 3 groups: cases with standard measurements of less than −1, those measuring between −1 and +1, and those measuring more than +1. The percentage of the number of cases in these 3 groups was shown.

The percentage of cases with a standard measurements more than +1 increased in chronic progressive diseases as follows: heredodegenerative neuropathy (92%), spinocerebellar degeneration (73%), chronic polyneuropathy (55%), and motor neurone disease (50%). In acute polyneuritis, SMON, and CNS diseases, the percentage did not differ from the control group.

3. *Perineurial Index*

Figure 5 shows the frequency distribution of the standard measurement of the perineurial index in the control group and in groups of various neurological diseases. In the control group, 80% of the cases had the standard measurement between −1 and +1, 15%

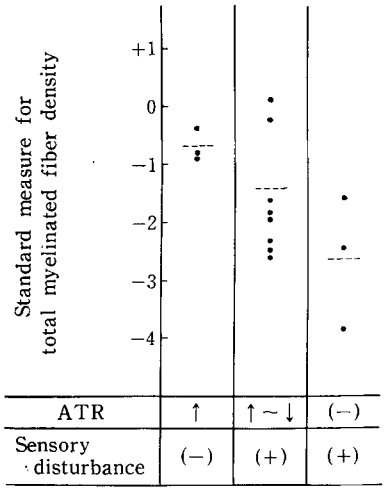

Fig. 3. Spinocerebellar degeneration. The correlation between standard measurement of total myelinated fibre densities in sural nerves and clinical findings of Achilles tendon reflexes (ATR) and sensory disturbances

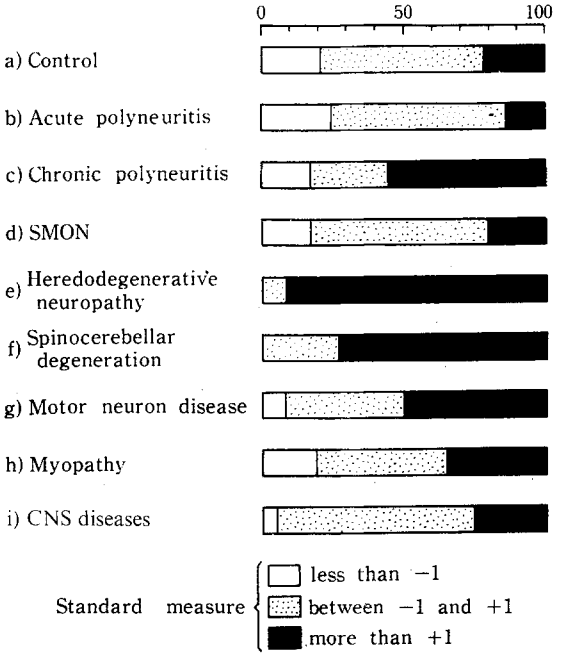

Fig. 4. Case frequency distribution of standard measurements of nuclear population in each neurological disease. The percentages of cases with standard measurement less than −1, between −1 and +1, and more than +1 are demonstrated

had that of more than +1, and 4% had less than −1. The percentage of cases with the standard measurement more than +1 increased in motor neurone disease (46%), and increased slightly in chronic polyneuropathy (27%).

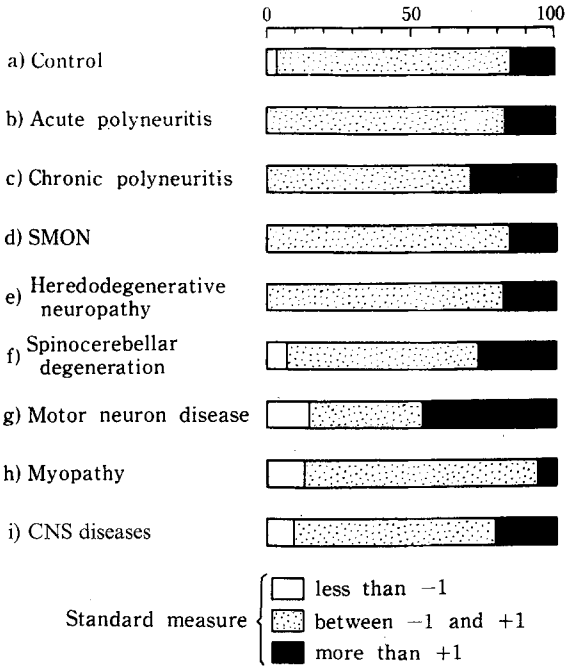

Fig. 5. Case frequency distribution of standard measurements of perineurial index. The percentages of cases with standard measurement less than −1, between −1 and +1, more than +1 are demonstrated

Discussion

The present results show differences in the changes of various types of fibres in chronic peripheral nerve diseases, acute polyneuritis, and SMON. In acute polyneuritis large and small myelinated fibres were equally reduced. Dyck and his co-workers (1968) showed that in acute polyneuritis characterized by axonal degeneration, the fibre spectrum is usually normal and the largest fibres may even be abnormally large. They also suggested that the quantitative histological measurements of a transverse section of a nerve containing myelinated fibres undergoing Wallerian degeneration may be misleading, because they include fibres which in a transverse section appear normal but which are not structurally intact or functional. In our material, however, it was shown by Bodian's silver staining combined with luxol fast blue that in all cases of acute polyneuritis the changes of myelinated fibres were almost exclusively of a demyelinating nature, with few fibres showing axonal swelling. In the sensory type of SMON, the decrease of small myelinated fibres was greater than that of large myelinated fibres. Bodian's silver staining combined with luxol fast blue revealed that in many cases of SMON the peripheral nerves were undergoing axonal degeneration. This would cause underestimation of the decrease of large myelinated fibres, because fibres that appeared normal actually had axonal swelling. But axonal swelling was

found not only in the sensory type of SMON, but also in the sensorimotor type, in which large myelinated fibres decreased more than small myelinated fibres. Therefore, the reason why large and small fibres were equally decreased in acute polyneuritis, and why small myelinated fibres were decreased more than large myelinated fibres in the sensory type of SMON can not be explained by the presence of axonal swelling alone.

Present results which showed that in chronic polyneuritis and heredodegenerative neuropathy, the decrease of large myelinated fibres is relatively greater than that of small myelinated fibres are consistent with the findings in chronic peripheral nerve diseases such as carpal tunnel syndrome (Thomas and Fullerton, 1963), ischemic neuritis (Gairn et al., 1960; Chopra and Hurwitz, 1967), and Charcot-Marie-Tooth disease (Dyck et al., 1968).

The proportion of the number of Schwann cell nuclei to the total number of cell nuclei inside the perineurium is known to be diverse among different nerves, and is about 90% in the sural nerve (Causey and Barton, 1969; Ochoa and Mair, 1969; Thomas, 1963). The magnitude of changes in the number of nuclei also varies among different nerves (Thomas, 1948). In this study there were many cases with increased nuclear density in chronic peripheral nerve diseases such as chronic polyneuropathy and heredodegenerative neuropathies. This may be partly explained by the fact that in regeneration and remyelination, several internodes are formed on a stretch occupied previously by only one internode, and that each internode corresponds to a Schwann cell. But Schwann cells associated with unmyelinated fibres and the fibroblast should also be taken into consideration. In the preliminary study, based upon quantitative electron microscopic observation, we have shown that changes in nuclear density depend largely upon alterations of unmyelinated fibres, since Schwann cells containing unmyelinated axons constitute a high percentage in the number of cells inside the perineurium (Ochoa and Mair, 1969). Details of this problem will be the subject of a following paper.

In biopsied cutaneous nerves from patients with Guillain-Barré syndrome, a few author have described degenerative changes (Finean and Wolf, 1961), increased cellularity and inflammatory cells (Chhutani et al., 1968). In the present study, cases of acute polyneuritis showed neither cell infiltration nor proliferation of Schwann cells, therefore also no change in nuclear density. In many cases with acute polyneuritis, including our cases, motor deficit is more pronounced than sensory disturbance. Pathological changes of this disease are known to be most severe in the spinal roots and the spinal nerves, just before they emerge from the dura (Haymaker and Kernohan, 1949; Krücke, 1955). It may be that since sural nerves are situated distally and contain few motor fibres, cell infiltration was not found in biopsied sural nerves in our cases with acute polyneuritis. An absence of proliferation of Schwann cells may in part be due to the short period of time between the onset of the disease and the date of the biopsy (from 2 weeks to 2 months).

Some previous reports described an increase of Schwann cells in the peripheral nerves of SMON upon observations of autopsy materials (Tsubaki et al., 1964; Shiraki and Oda, 1969), as well as biopsied sural nerves (Tsuksgoshi et al., 1971), and even onion bulb formation has been observed in the latter (Ohta, 1970). However, our present study on sural nerves revealed that the quantitative measurement of the nuclear density was unchanged in SMON when compared with the age-matched control groups.

It has been frequently speculated that spinocerebellar degeneration is closely related to Charcot-Marie-Tooth disease and hereditary sensory radicular neuropathy, and that these diseases sometimes appear in a patient in combination, or in different members of the same family. Brown (1959) classified 103 patients with degenerative ataxia into three forms: normoreflexic, hyperreflexic, and hyporeflexic. He showed that the clinical signs suggestive of peripheral nerve involvement such as sensory disturbance, distal muscle weakness and atrophy, pes cavus, and electromyographic evidence of degeneration were found in a high percentage of cases of the hyporeflexic form. Pathological studies of the peripheral nerves of spinocerebellar degeneration have dealt almost exclusively with Friedreich's ataxia in which a gross depletion of large myelinated fibres with a preservation of fine unmyelinated axons was the rule (Friedreich, 1863; Mott, 1907; Hughes, 1968). Our studies of the cases with spinocerebellar degeneration in general, revealed a decrease of both large and small myelinated fibres with a greater degree of reduction of large myelinated fibres. The nuclear density also increased. There was a close correlation between the extent of the decrease of the myelinated fibres and the clinical findings in achilles tendon reflexes and sensory impairment. These present results and those of Brown (1959) indicate that in cases with spinocerebellar degeneration there is a spectrum of involvement of peripheral nerves from completely unaffected to severely attacked peripheral nerves.

Histopathological studies to date have revealed no evidence of pathological changes in peripheral sensory nerves in motor neurone disease, tumours or vascular diseases of the central nervous system (Takahashi, 1964), and muscular dystrophies (Adams et al., 1962). Penfield (1920) demonstrated by experimenting on the

cat that lesions of the spinal cord involving the dorsal columns produce no changes in the cells of the dorsal root ganglia. Polymyositis associated with peripheral nerve involvement which was confirmed by autopsy is quite infrequent, but has been described in cases with sensory disturbance (McEntee and Mancall, 1965; Takahashi and Toyokura, 1968) and in cases without sensory disturbance (Kinney and Mahen, 1940). Physiologically, however, there are reports suggesting sensory nerve involvement in motor neurone disease (Shahani and Russell, 1969; Poole, 1957). These reports showed that in subjects with motor neurone diseases the ischemic or postischemic paraesthesiae responses were less than in normal subjects. The amplitude of action potentials and conduction velocities of sensory nerves were reported to be within normal range in amyotrophic lateral sclerosis (Fincham and Van Allen, 1964). There are also physiological studies on hemiplegics which have shown significantly lower conduction velocity on the paralyzed side than on the unaffected side (Panin et al., 1967; Namba et al., 1971).

The present study showed quantitatively a decrease of myelinated fibres in the sural nerves from patients with these diseases, though the cause remains unknown. Unspecific factors such as local compressions or ischemia may be responsible in cases where patients have been bedridden for a long time or with contractures of joints; there may be other causes for cases without such local problems. It remains to be determined whether the decrease of myelinated fibres in the sural nerves in patients with motor neurone diseases, muscular dystrophies, or polymyositis is the result of a primary change or a secondary change which has no direct bearing on the disease.

The percentage of cases with increased perineurial thickness was slightly higher in motor neurone diseases, in chronic polyneuropathies and in spinocerebellar degeneration than in other diseases. The significance of this fact remains unexplained, since our knowledge on perineurial responses to peripheral nerve diseases is insufficient.

References

Adams, R. D., Denny-Brown, D., Pearson, C. M.: Diseases of muscle. A study in pathology. 2nd. ed. New York: Harper and Row 1962

Blackwood, W., McMenemy, W. H., Meyer, A., Norman, R. M., Russel, D. S.: Greenfield's neuropathology. London: Edw. Arnold 1969

Brain, W. R., Walton, J. N.: Diseases of the nervous system. London: Oxford 1969

Brown, J. R.: Degenerative cerebellar ataxia. Neurology (Minneap.) **9**, 799–805 (1959)

Calmant, H.: In: Henke und Lubarsch's Handbuch der speziellen pathologischen Anatomie und Histologie, Vol. 13 (ii), p. 2639. Berlin-Göttingen-Heidelberg: Springer 1958

Causey, G., Barton, A. A.: The cellular content of the endoneurium of peripheral nerve. Brain **82**, 594–598 (1959)

Chhuttani, P. N., Chawla, L. S., Chugh, F. S., Singh, H.: Landry-Guillain-Garré syndrome in India. J. neurol. Sci. **7**, 581–592 (1968)

Chopra, J. S., Hurwitz, L. J.: Internodal length of sural nerve fibers in chronic occlusive vascular disease. J. Neurol. Neurosurg. Psychiat. **30**, 207–214 (1967)

Dyck, P. J., Gutrecht, J. A., Bastron, J. A., Karnes, W. E., Dale, A. J. D.: Histologic and teased-fiber measurements of sural nerve in disorders of lower motor and primary sensory neurons. Proc. Mayo Clin. **43**, 81–123 (1968)

Fincham, R. W., Van Allen, M. W.: Sensory nerve conduction in amyotrophic lateral sclerosis. Neurology (Minneap.) **14**, 31–33 (1968)

Finean, J. B., Woolf, A. L.: An electron microscope study of degenerative changes in human cutaneous nerve. J. Neuropath. exp. Neurol. **21**, 105–115 (1961)

Friedreich, N.: Über degenerative Atrophie der spinalen Hinterstrange. Virchows Arch. path. Anat. **26**, 391–419, 433–459; **27**, 1–26 (1863)

Gairns, F. F., Garven, H. S. D., Smith, G.: The digital nerves and the nerve endings in progressive vascular disease of leg. Scot. med. J. **5**, 382–391 (1960)

Haymaker, W., Kernohan, J. W.: The Landry-Guillain-Barré syndrome. A clinicopathologic report of fifty fatal cases and a critique of the literature. Medicine (Baltimore) **28**, 59–141 (1949)

Hughes, J. T.: The peripheral sensory pathway in Friedreich's ataxia. Brain **91**, 803–817 (1968)

Kinney, T. D., Maher, M. M.: Dermatomyositis. A study of five cases. Amer. J. Path. **16**, 561–594 (1940)

Krücke, W.: Erkrankungen der peripheren Nerven. In: Handbuch der speziellen pathologischen Anatomie und Histologie. Bd. 5. Berlin-Göttingen-Heidelberg: Springer 1955

McEntee, W. J., Mancall, E. L.: Neuromyositis. A reappraisal. Neurology (Minneap.) **15**, 69–75 (1965)

Mott, F. W.: Case of Friedreich's disease with autopsy and systematic microscopical examination if the nervous system. Arch. Neurol. Psychiat. (Chic.) **3**, 180–200 (1907)

Nakae, K., Yamamoto, S., Igata, A.: Subacute myelo-optico-neuropathy in Japan. Lancet **1971 II**, 510–512

Namba, T., Scjman, M. H., Grob, D.: Conduction velocity in the ulnar nerve in hemiplegic patients. J. neurol. Sci. **12**, 177–186 (1971)

Nichols, P. C., Dyck, P. J., Miller, D. R.: Experimental hypertrophic neuropathy: Change in fascicular area and fiber spectrum after acute crush injury. Proc. Mayo Clin. **43**, 297–305 (1968)

Ochoa, J., Mair, W. G. P.: The normal sural nerve in man. I. Ultrastructure and number of fibers and cells. Acta neuropath. (Berl.) **13**, 197–216 (1969)

Ohta, M.: Ultrastructure of sural nerves in myeloneuropathy associated with abdominal symptoms. Clin. Neurol. **10**, 487–500 (1970)

Panin, N., Paul, B. J., Policoff, L. D., Eson, M. E.: Nerve conduction velocities in hemiplegia. Arch. phys. Med. **48**, 606–610 (1967)

Penfield, W. G.: Alterations of the Golgi apparatus in nerve cells. Brain **43**, 290–305 (1920)

Poole, E. W.: Ischemic and post-ischemic parethesiae in motor neurone disease. J. Neurol. Neurosurg. Psychiat. **20**, 225–227 (1957)

Shahani, B., Russell, W. R.: Motor neuron disease. An abnormality of nerve metabolism. J. Neurol. Neurosurg. Psychiat. **32**, 1–5 (1969)

Shimada, Y., Tsuji, T.: Halogenated oxyquinoline derivatives and neurological syndromes. Lancet **1971 II**, 41–42

Thomas, G. A.: Quantitative histology of Wallerian degeneration. II. Nuclear population in two nerves of different fiber spectrum. J. Anat. (Lond.) **82**, 135–145 (1948)

Thomas, P. K.: The connective tissue of peripheral nerve: an electron microscope study. J. Anat. (Lond.) **97**, 35–44 (1963)

Thomas, P. K., Fullerton, P. M.: Nerve fiber size in the carpal tunnel syndrome. J. Neurol. Neurosurg. Psychiat. **26**, 520–527 (1963)

Takahashi, K.: A clinicopathologic study on the peripheral nervous system of the aged. III. With special reference to the spinal nerve roots. Clin. Neurol. **4**, 151–160 (1964)

Takahashi, K., Toyokura, Y.: An autopsied case of dermato-neuromyositis with severe lesion in the peripheral nervous system. Clin. Neurol. **8**, 693–698 (1968)

Tohgi, H.: Quantitative studies on the biopsied sural nerve – With reference to experimental neuropathy. Jap. J. Med. **12**, 108–111 (1973)

Tohgi, H., Tsukagoshi, H., Toyokura, Y.: Quantitative changes with age in normal sural nerves. Acta neuropath. (Berl.) to appear (1977)

Tsubaki, T., Honma, Y., Hoshi, M.: Neurological syndrome associated with clinoquinol. Lancet **1971 I**, 696–697

Tsubaki, T., Toyokura, Y., Tsukagoshi, H.: Subacute myelo-optico-neuropathy following abdominal symptoms. A clinical and pathological study. J. Jap. Soc. int. Med. **53**, 779–790 (1964)

Tsukagoshi, H., Tohgi, H., Toyokura, Y.: The peripheral nerve in cases of SMON. I. Histological study of sural nerve. Clin. Neurol. **11**, 392–399 (1971)

Tsukagoshi, H., Tohgi, H., Toyokura, Y.: The peripheral nerve in cases of SMON. II. Clinicopathological study of sural nerve. Clin. Neurol. **11**, 400–405 (1971)

Shiraki, H., Oda, M.: Neuropathology of subacute myelo-optico-neuropathy, SMON. Saishin Igaku **24**, 2479–2509 (1969)

Wechsler, I. S., Brock, S., Weil, A.: Amyotrophic lateral sclerosis with objective and subjective (neuritic) sensory disturbances. A clinical and pathologic report. Arch. Neurol. Psychiat. (Chic.) **21**, 299–310 (1929)

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