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Microneurographic Findings in Diabetic Polyneuropathy with Special Reference to Sympathetic Nerve Activity

J. Fagius

Departments of Neurology and Clinical Neurophysiology, University Hospital, Uppsala, Sweden

Summary. Microneurographic recordings of naturally occurring nerve activity in the median or peroneal nerve were made in 25 patients with diabetes mellitus, 17 of whom had signs of polyneuropathy. In patients without polyneuropathy, the electrical findings did not differ from those in healthy subjects. In patients with polyneuropathy, sensory afferent impulses were always normal qualitatively, whereas muscular afferent activity was weak or entirely absent in some patients. Sympathetic activity, if found, showed normal characteristics in muscle and skin fascicles, except that it was difficult to obtain a good signal-to-noise ratio. In 16 of 25 recordings with the electrode positioned intraneurally, sympathetic activity could not be detected in patients with polyneuropathy. The failures correlated with impaired skin sympathetic effector organ responses and reduction of motor nerve conduction velocity. The results suggest that impairment of sympathetic outflow occurs frequently in diabetic polyneuropathy and that sympathetic involvement occurs earlier than in many other types of polyneuropathy.

Key words: Diabetic polyneuropathy, microneurography, sympathetic recordings, sympathetic dysfunction, impaired muscular afferents.

Autonomic dysfunction is a recognized and, at times prominent, feature of diabetic polyneuropathy [31, 32]. Although attention was paid to this problem relatively late [25], it has become evident that signs of impaired autonomic function are common even in patients without clinically overt dysfunction [4, 5]. A variety of effector organ tests are available for indirect assessment of sympathetic and parasympathetic function [2, 19, 37].

In 1968 Hagbarth and Vallbo introduced a new nerve recording technique, microneurography [16]. With micro-electrodes inserted intraneurally through the intact skin in alert, unanaesthetized man, naturally occurring nerve discharges can be recorded in peripheral nerves. The technique allows recording of muscular and sensory afferent activity and efferent sympathetic impulses [33]. Thus, sympathetic impulses can be studied directly in normal and diseased nerves. This technique has contributed considerably to our present knowledge of sympathetic outflow in healthy man [33, 34].

Sympathetic activity has different characteristics in skin and muscle nerve fascicles. Muscle nerve sympathetic activity is characterized by pulse-synchronous bursts of vasoconstrictor impulses [6, 16], the outflow of which is modulated by arterial baroreflex mechanisms. Manoeuvres producing blood pressure changes (e.g. the Valsalva manoeuvre) affect its outflow [7]. Skin nerve sympathetic activity is made up of a mixture of sudomotor and vasoconstrictor impulses, the function of which is primarily thermoregulatory. At normal temperatures, bursts of activity occur spontaneously and irregularly without a clear relationship to cardiac or basal respiratory rhythms. In addition, inspiratory and arousal stimuli are usually followed by a strong burst of skin nerve sympathetic activity. Emotional stress may evoke repeated bursts [1, 8, 17]. The evidence for the sympathetic nature of these activities has been summarized by Vallbo et al. [33].

Well defined reflexes can be recorded in both muscle and skin sympathetic activity. Their latencies depend on conduction time in post-ganglionic C-fibres to a considerable extent and therefore provide indirect measures of conduction velocities in these fibres [12].

In a recent study of polyneuropathies of different aetiology [13], muscle and skin sympathetic activity could be recorded in most cases, even in the presence of a pronounced somatic polyneuropathy. However, complete failure to detect sympathetic activity occurred more frequently than in healthy subjects.

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Table 1. Clinical features of the patients studied

		Type of diabetes	Age (years)	Duration of diabetes (years)	Therapy
Patients without polyneuropathy	($n=8$)	I	32.9 ± 6.9	19.3 ± 10.3	Insulin
Patients with polyneuropathy	($n=17$)	I ($n=13$)	48.1 ± 14.7	23.7 ± 7.2	Insulin ($n=13$)
		II ($n=4$)			Oral antidiabetic therapy ($n=3$)
					Combination of insulin and oral antidiabetic therapy ($n=1$)

Results expressed as mean ± SD

The aims of the present study were: (1) to compare the occurrence of detectable sympathetic activity in diabetic patients with and without polyneuropathy and (2) to investigate whether there are consistent differences between diabetic and healthy subjects, and patients with other types of polyneuropathy.

Methods

Patients

Recording attempts were made from the median or peroneal nerve in 25 patients with diabetes mellitus. Clinical features of the patients are given in Table 1. Eight were free of clinical and electrophysiological signs of polyneuropathy (i.e. reduced conduction velocities or prolonged F-responses – the F wave is the late muscular response following supramaximal motor nerve stimulation [20]). In three subjects, both muscle and skin fascicles were impaled, giving a total of 11 recording sites. The other 17 patients had symptoms and signs of diabetic polyneuropathy. In this group, two had recordings of both nerves, giving a total of 19 nerves studied. Both muscle and skin fascicles were impaled in some patients during the recording attempt, giving a total of 25 electrode sites examined.

All patients gave informed consent. None had any complaints after the procedure. The study was approved by the Ethical Committee of the Medical Faculty of Uppsala University.

Recording Equipment

Tungsten micro-electrodes, with an uninsulated tip diameter of 1–5 μ, were used for the nerve recordings. A similar reference electrode was inserted subcutaneously about 2 cm from the recording electrode. The nerve signal was amplified in two steps (total gain × 20,000) and then fed first through a band-pass filter with a band width of 700–2,000 Hz, and subsequently through an amplitude discriminator to improve the signal-to-noise ratio. A mean voltage display of the signal (integrated neurogram) was obtained from an RC-integrating network (time constant 0.1 s). The ECG was recorded with surface electrodes. During the recordings the signals were monitored with a storage oscilloscope (Tektronix 549, Tektronix, Beaverton, Oregon, USA), loudspeaker, and an ink-jet recorder (Mingograph 800, Siemens-Elema, Stockholm, Sweden). The ECG, original and mean voltage neurograms were stored on tape (Sangamo Sabre VI tape recorder, Sangamo Weston-Schlumberger, Sarasota, Florida, USA) for subsequent analysis.

Motor conduction velocity of the nerve under study was determined with a standard technique [20]. Sudomotor function and skin vasoconstriction were tested by evoking a startle reaction and recording the change in skin resistance (galvanic skin response) with AgAgCl electrodes and reduction in digital pulse amplitude (digital pulse plethysmography) with a photoelectric plethysmograph (van Gogh ILP-ZA, van Gogh, Amsterdam, Netherlands) [13]. These tests were performed in the same hand or foot in which the nerve recording was made.

Recording Procedure

Subjects were seated comfortably in a quiet room with an ambient temperature of 22–24 °C. The recording electrode was inserted manually through the skin into the median nerve at the elbow, or the peroneal nerve at the fibular head. The nerve was localized with electrical stimuli delivered through the electrode. When a nerve fascicle was impaled, it was identified as subserving muscle or skin by the response to electrical stimulation (muscle twitches or paraesthesiae reported by the subject) and the necessary stimulus to evoke afferent impulses (muscle stretch or tap or light skin touch). When the nerve fascicle was identified, small adjustments of electrode position were made in a search for a multiunit sympathetic recording site.

When sympathetic activity was encountered, it was recognized by its highly characteristic temporal pattern (see above), and the responses to arousal stimuli (skin) and the Valsalva manoeuvre (muscle). Spontaneous muscle sympathetic activity was recorded for 5–10 min with the subject at rest, and thereafter, manoeuvres to change heart rate and blood pressure were performed (slow deep breathing and the Valsalva manoeuvre). Bursts of skin sympathetic activity were evoked by electrical stimuli to the skin (not on the extremity recorded from).

Sympathetic Reflex Latency Determination

The inhibitory baroreflex was used for muscle nerve sympathetic activity. During blood pressure reductions, baroreceptor activity is strong enough to inhibit its outflow only during systole. This is the underlying mechanism of the pulse-synchrony of muscle nerve sympathetic activity. Thus, the latency can be measured from the R-wave of the ECG to the start of inhibition, i.e. the peak of the appropriate burst in the neurogram (Fig. 1). The appropriate burst was identified by comparing the R-wave/burst relationship at different heart rates [12]. Muscle sympathetic latencies were determined by feeding the mean voltage neurogram into an averager (Medelec DAV6, Vickers Medical Company, Woking, Surrey, UK), triggered by the R-wave of the ECG.

The excitatory arousal reflex was used for skin sympathetic nerves and the latency was measured from the stimulus artefact to the onset of the evoked burst (Fig. 1). Skin sympathetic latencies were measured manually from an ink-jet recorder paper display.

The results were compared with those in a previous study of patients with polyneuropathy of different aetiology (uraemia, sarcoidosis, chronic alcoholism, chloroquine intoxication, Guillain-Barré syndrome, hereditary polyneuropathy, and polyneuropathy of unknown origin – a total of 40 recordings after the exclusion of nine patients with diabetic polyneuropathy) [13].

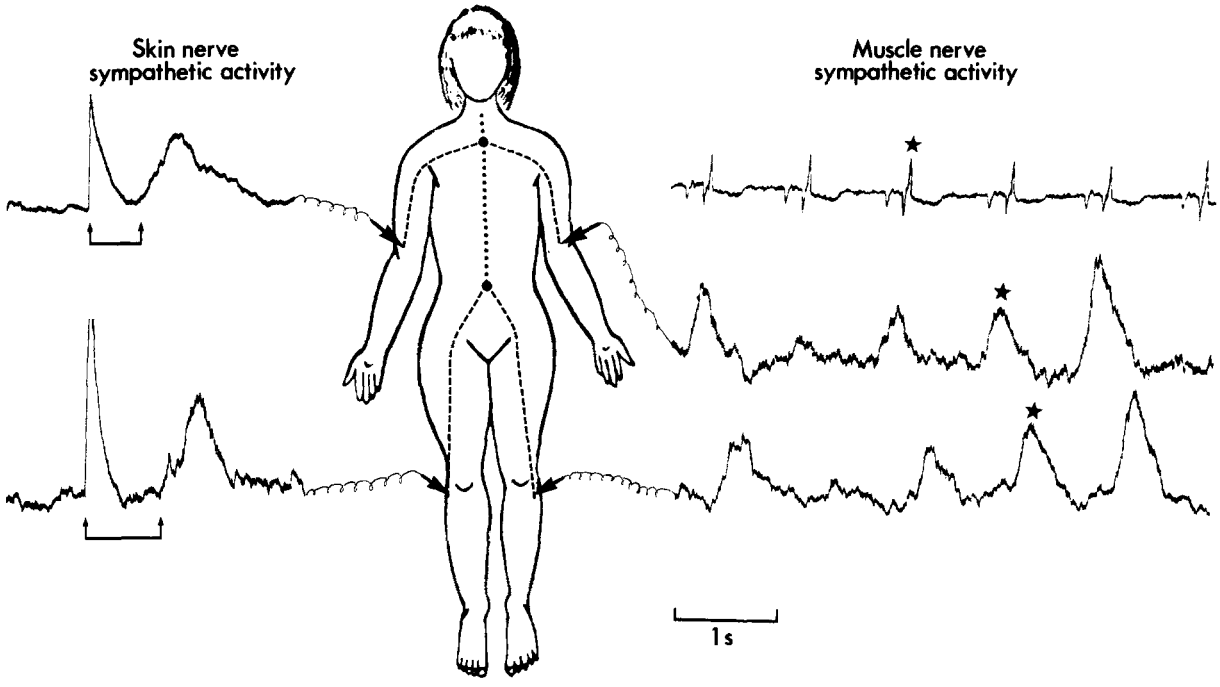

Fig. 1. Principle of sympathetic reflex latency determination. Recordings of skin nerve sympathetic activity and muscle nerve sympathetic activity from the median and peroneal nerves. Mean voltage neurograms and ECG. The reflex latency of skin sympathetic activity is indicated by pairs of arrows from stimulus artefact to onset of evoked burst. The latency of muscle sympathetic activity is indicated by asterisks at inhibiting heart beat and peaks of appropriate sympathetic bursts. Note longer reflex latency in the leg than in the arm, due to a longer post-ganglionic conduction time

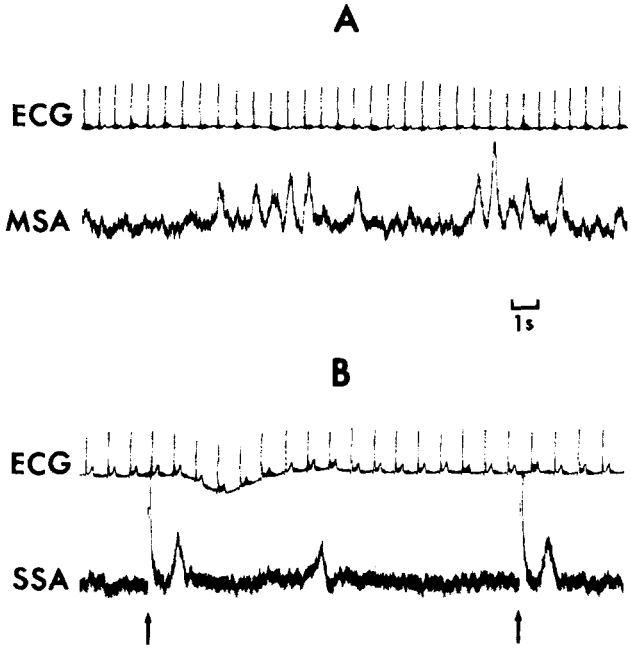

Fig. 2. Normal patterns of peroneal nerve sympathetic activity from two patients with diabetic polyneuropathy. Mean voltage neurograms. *(A)* Muscle nerve sympathetic activity *(MSA)*: note sequences of pulse synchronous bursts alternating with periods of neural silence. *(B)* Skin nerve sympathetic activity *(SSA)*: two evoked bursts (stimulus artefact indicated by arrows) and one spontaneous burst. Same time scale in both tracings

Results

Diabetic Patients Without Polyneuropathy

No patient had symptoms of autonomic dysfunction. Galvanic skin response and digital pulse plethysmography were normal in all patients. During the nerve recordings, sympathetic activity with a good signal-to-noise ratio was easily found in all patients (skin nerve activity in six and muscle nerve activity in five patients; both skin and muscle fascicles were impaled in three subjects). Sympathetic reflex latencies fell within the normal range. Sensory and muscular afferent activity was qualitatively normal.

Diabetic Patients with Polyneuropathy

Twelve patients reported one or more symptoms of impaired autonomic function (postural hypotension, dry hands and feet, bladder dysfunction, impotence). Two patients had normal cutaneous effector organ responses, while in the remaining 15, one or both responses were weak or absent. In a given extremity, sudomotor and skin vasoconstrictor functions could be impaired independently.

Sympathetic Activity: When muscle or skin sympathetic activity was found, this had a normal appearance

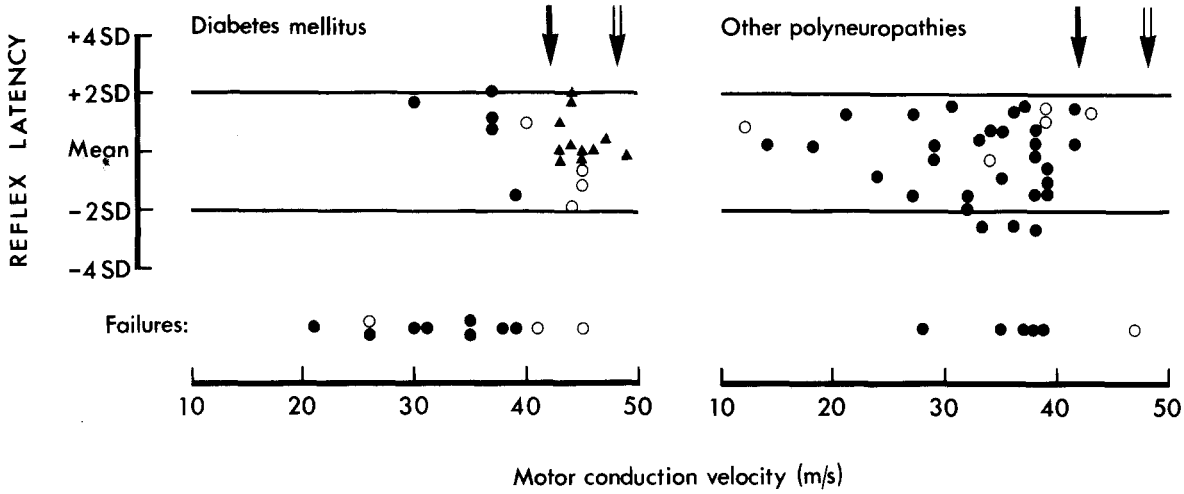

Fig. 3. Sympathetic reflex latencies, expressed as standard deviations from the normal mean value, related to motor conduction velocity of the peroneal and median nerves. ● and ○ = patients with polyneuropathy, peroneal and median nerves respectively and ▲ = diabetic patients without polyneuropathy, peroneal nerve. Failures = motor conduction velocity of the nerves in which no sympathetic activity could be found in the two patient groups. Lower normal limit for motor conduction velocity in the peroneal and median nerves indicated by filled and open arrows, respectively

Table 2. Microneurographic findings in diabetic polyneuropathy

	Electrode site	No of recording sites	Motor nerve conduction velocity reduction (m/s) Mean (range)[a]	Autonomic symptoms[b]	Results of galvanic skin response recording and digital pulse plethysmography[b]	Afferent activity
Recordings with sympathetic activity detected	skin nerve fascicles	5	6.5 (3–12)	yes 3 no 2	both normal 2 one abnormal 3 both abnormal 0	normal 5
	muscle nerve fascicles	4	3.8 (3–5)	yes 2 no 2	both normal 0 one abnormal 4 both abnormal 0	normal 4
Recordings without sympathetic activity detected	skin nerve fascicles	5	8.0 (3–22)	yes 3 no 2	both normal 0 one abnormal 2 both abnormal 3	normal 5
	muscle nerve fascicles	11	10.2 (3–26)	yes 9 no 2	both normal 0 one abnormal 4 both abnormal 7	normal 6 weak 3 absent 2

[a] Reduction from lower normal limit value for the nerve under study

[b] Numbers in all columns (except conduction velocity) refer to number of recording sites, which means that patients with two recordings are counted twice in this column.

(Fig. 2). The Valsalva manoeuvre caused a considerable increase of muscle sympathetic outflow as in normal subjects [7]. Activity was found on only nine out of 25 occasions with intraneural electrode sites. A good signal-to-noise ratio was only obtained in five; in the other four, only weak bursts of activity were detected, despite repeated adjustments of the electrode position. Sympathetic reflex latencies were within normal limits irrespective of the presence of autonomic symptoms and no correlation was found with the motor conduction velocity reduction (as compared with the lower normal limit of motor conduction velocity of the nerve under study). Figure 3 shows the reflex latencies, plotted against motor conduction velocity of the nerve recorded from. In the remaining 16 recording attempts (64%), sympathetic activity could not be detected despite repeated adjustments of electrode position. Such failure was not accepted unless at least two different intraneural sites in the same type of fascicle (muscle or skin) were obtained. In the patients with non-diabetic polyneuropathy, failure frequency was only 19% [13]; the proportion of failures was significantly higher in diabetic polyneuropathy ($p < 0.001$; chi square test with Yates's correction).

Table 2 summarizes the nerve recording results. Symptoms of autonomic impairment were more common in those patients in whom no sympathetic activity could be recorded. Two-thirds of patients without detectable sympathetic activity had both galvanic skin re-

sponse and digital pulse reduction abnormal. The corresponding figure for patients in whom muscle or skin sympathetic activity was recorded was 0%. Figure 3 shows that the motor conduction velocity of nerves without detectable sympathetic activity was lower than that in nerves with sympathetic impulses (mean motor conduction velocity: 33.3 versus 38.6 m/s; $0.05 < p < 0.10$; t-test for non-dependent variables).

Afferent Mechanoreceptor Activity: During the search for sympathetic activity, afferent impulses are evoked in sensory or muscle nerve fascicles and used for identification of the fascicle impaled. When skin nerve fascicles were impaled, afferent activity was always easily evoked by a light touch in the area innervated by that nerve. With muscle nerve fascicle electrode positions, afferent impulses evoked by muscle stretching or tapping were sometimes weak or totally absent on two occasions (in these two nerves, motor conduction velocity was markedly reduced to 21 and 26 m/s). Identification of the muscle nerve fascicle was therefore made from the muscle twitches evoked by low-voltage electrical stimulation through the electrode; normally, afferent impulses are always present in this situation. Muscle sympathetic activity was never found in nerves with impaired muscular afferent activity (Table 2).

Discussion

In the present study, sympathetic activity was recorded without difficulty in diabetic patients without symptoms or signs of polyneuropathy, but in only a few patients with polyneuropathy.

When sympathetic recording sites were found, the activity had a normal appearance. Theoretically, slowed post-ganglionic C-fibre conduction would cause an increased temporal dispersion of sympathetic bursts and a disturbed pulse synchronous grouping of muscle sympathetic activity, but neither occurred in any recording. Similarly, normal sympathetic reflex latencies suggest that C-fibre conduction velocity was not reduced. Conduction velocity depends on fibre size, the presence of a myelin sheath, myelin thickness, and the ratio between axon diameter and the total myelinated nerve fibre diameter [24, 26, 27, 36]. Since a decrease in conduction velocity results mainly from demyelination [30], the present lack of reduced conduction velocity in sympathetic C-fibres is not surprising. However, a smaller C-fibre diameter, reported in some types of polyneuropathy [21, 23], should theoretically cause slowing of conduction. A possible explanation for the failure to detect slowed C-fibre conduction may be that the diseased C-fibres become rapidly functionally deranged to an extent incompatible with impulse conduction. The findings from a larger group of patients with non-diabetic polyneuropathies of different aetiology were identical [13] (Fig. 3).

Recording of sympathetic activity depends on successful electrode insertion into the nerve. For technical reasons, a recording attempt occasionally fails in a healthy subject (maximally 5% of attempts). Thus, no conclusion can be drawn from a single failure. However, in the present group of polyneuropathy patients, the frequent failure to detect sympathetic activity was remarkable when compared with the normal results found in diabetic patients without polyneuropathy. Furthermore, reduced effector organ responses accompanied this failure. These findings suggest that the recording failures are due to a real impairment of sympathetic outflow. With progression of the disease, more and more individual sympathetic fibres will cease to conduct, and consequently multiunit activity will be reduced successively until it can no longer be recorded. This conclusion is in accordance with previous studies of C-fibre conduction in vitro in polyneuropathy [9, 10].

The patients with polyneuropathy were older than those without signs of nerve damage. This age difference cannot explain these results as recording sympathetic activity is not difficult in older healthy subjects. It may be easier to detect in older subjects due to an age dependent increase of muscle sympathetic burst frequency [28].

The difference in failure frequency between diabetic and non-diabetic polyneuropathy is in accordance with the general opinion that autonomic impairment is more common in diabetic than in other neuropathies. Another difference between diabetic and non-diabetic polyneuropathy was the tendency to correlation between degree of motor conduction velocity reduction and lack of detectable sympathetic impulses. In other polyneuropathies, sympathetic activity of normal appearance could be seen with motor conduction velocity as low as 12 m/s [13] (Fig. 3). A correlation between somatic nerve damage and autonomic dysfunction in diabetic polyneuropathy has been reported by other investigators [3, 11, 15, 18, 29].

Afferent mechanoreceptor impulses were qualitatively normal in skin nerve fascicles in all patients, and weak or absent in muscle nerve fascicles in some. In non-diabetic polyneuropathies the findings were similar [13], but the relation between muscular afferents and detection of muscle sympathetic activity differed. In non-diabetic patients, sympathetic discharges could often be recorded in fascicles with impaired or absent muscular afferent activity; thus this contrasts with the present findings where sympathetic bursts were never seen when the afferents were abnormal. Instead, sympathetic activity was often not detectable even with normal muscular afferent activity. This relation suggests that sympathetic involvement in diabetic polyneuropathy occurs relatively early in the disease process. This finding has been reported previously for both sympathetic and parasympathetic dysfunction [22, 35]. On the other hand, the normal findings in diabetics without signs of neuropathy suggest that the autonomic dys-

function is part of the polyneuropathy and not a separate entity.

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References

1. Bini G, Hagbarth K-E, Hynninen P, Wallin BG (1980) Thermoregulatory and rhythm-generating mechanisms governing the sudomotor and vasoconstrictor outflow in human cutaneous nerves. J Physiol (Lond) 306: 537–552
2. Campbell IW, Ewing DJ, Clarke BF (1980) Tests of cardiovascular reflex function in diabetic autonomic neuropathy. In: Gries FA, Freund HJ, Rabe F, Berger H (eds) Aspects of autonomic neuropathy in diabetes. Thieme, Stuttgart New York, pp 61–68
3. Canal N, Comi G, Saibene V, Musch B, Pozza G (1978) The relationship between peripheral and autonomic neuropathy in insulin dependent diabetes: a clinical and instrumental evaluation. In: Canal N, Pozza G (eds) Peripheral neuropathies. Elsevier/North Holland, Amsterdam, pp 247–255
4. Clarke BF, Ewing DJ, Campbell IW (1979) Diabetic autonomic neuropathy. Diabetologia 17: 195–212
5. Clarke BF, Ewing DJ, Campbell IW (1980) Clinical features of diabetic autonomic neuropathy. In: Gries FA, Freund HJ, Rabe F, Berger H (eds) Aspects of autonomic neuropathy in diabetes. Thieme, Stuttgart New York, pp 50–60
6. Delius W, Hagbarth K-E, Hongell A, Wallin BG (1972) General characteristics of sympathetic activity in human muscle nerves. Acta Physiol Scand 84: 65–81
7. Delius W, Hagbarth K-E, Hongell A, Wallin BG (1972) Manoeuvres affecting sympathetic outflow in human muscle nerves. Acta Physiol Scand 84: 82–94
8. Delius W, Hagbarth K-E, Hongell A, Wallin BG (1972) Manoeuvres affecting sympathetic outflow in human skin nerves. Acta Physiol Scand 84: 177–186
9. Dyck PJ, Lambert H (1966) Numbers and diameters of nerve fibers and compound action potential of sural nerve: controls and hereditary neuromuscular disorders. Trans Am Neurol Assoc 91: 214–217
10. Dyck PJ, Lambert EH (1969) Dissociated sensation in amyloidosis. Arch Neurol 20: 490–507
11. Ewing DJ, Burt AA, Williams IR, Campbell IW, Clarke BF (1976) Peripheral motor nerve function in diabetic autonomic neuropathy. J Neurol Neurosurg Psychiatry 39: 453–460
12. Fagius J, Wallin BG (1980a) Sympathetic reflex latencies and conduction velocities in normal man. J Neurol Sci 47: 433–448
13. Fagius J, Wallin BG (1980b) Sympathetic reflex latencies and conduction velocities in patients with polyneuropathy. J Neurol Sci 47: 449–461
14. Fagius J, Wallin BG (1982) Direct recordings of sympathetic activity in diabetic neuropathy. In: Boström H, Dunér H, Ljungstedt N (eds) Recent trends in diabetes research. Almqvist & Wiksell International, Stockholm, pp 225–234
15. Glück Z, Boll H, Weidmann P, Flammer J, Ziegler WH (1979) Evaluation of autonomic neuropathy in diabetes mellitus. Klin Wochenschr 57: 457–466
16. Hagbarth K-E, Vallbo ÅB (1968) Pulse and respiratory grouping of sympathetic impulses in human muscle nerves. Acta Physiol Scand 74: 96–108
17. Hagbarth K-E, Hallin RG, Hongell A, Torebjörk HE, Wallin BG (1972) General characteristics of sympathetic activity in human skin nerves. Acta Physiol Scand 84: 164–176
18. Hilsted J, Jensen SB (1979) A simple test for autonomic neuropathy in juvenile diabetics. Acta Med Scand 205: 385–387
19. Johnson RH, Spalding JMK (1974) Disorders of the autonomic nervous system. Blackwell Scientific Publications. Oxford
20. Kaeser HE (1970) Nerve conduction velocity measurements. In: Vinken PJ, Bruyn GW (eds) Handbook of clinical neurology, Vol 7, Diseases of nerves. North-Holland, Amsterdam, pp 116–196
21. Low PA, McLeod JG, Prineas JW (1978) Hypertrophic Charcot-Marie-Tooth disease. J Neurol Sci 35: 93–115
22. Martin MM (1953) Involvement of autonomic nerve-fibres in diabetic neuropathy. Lancet I: 560–565
23. Ochoa J (1970) Isoniazid neuropathy in man: quantitative electron microscope study. Brain 93: 831–850
24. Paintal AS (1978) Conduction properties of normal peripheral mammalian axons. In: Waxman SG (ed) Physiology and pathobiology of axons. Raven Press, New York, pp 131–144
25. Rundles RW (1945) Diabetic neuropathy. General review with report of 125 cases. Medicine 24: 111–160
26. Rushton WAH (1951) A theory of the effects of fibre size in medullated nerve. J Physiol (Lond) 115: 101–122
27. Smith RS, Koles ZJ (1970) Myelinated nerve fibers: computed effect of myelin thickness on conduction velocity. Am J Physiol 219: 1256–1258
28. Sundlöf G, Wallin BG (1977) The variability of muscle nerve sympathetic activity in resting recumbent man. J Physiol (Lond) 272: 383–397
29. Tackmann W, Kaeser HE, Berger W, Rüeger AN, Violier E (1981) Autonomic disturbances in relation to sensorimotor peripheral neuropathy in diabetes mellitus. J Neurol 224: 273–281
30. Thomas PK (1971) The morphological basis for alterations in nerve conduction in peripheral neuropathy. Proc R Soc Med 64: 13–16
31. Thomas PK, Eliasson SG (1975) Diabetic neuropathy. In: Dyck PJ, Thomas PK, Lambert EH (eds) Peripheral neuropathy. Saunders, Philadelphia London Toronto, pp 956–981
32. Thomas PK, Ward JD (1975) Diabetic neuropathy. In: Keen H, Jarrett J (eds) Complications of diabetes. Arnold, London, pp 151–177
33. Vallbo ÅB, Hagbarth K-E, Torebjörk HE, Wallin BG (1979) Somatosensory, proprioceptive and sympathetic activity in human peripheral nerves. Physiol Rev 59: 919–957
34. Wallin BG (1981) New aspects of sympathetic function in man. In: Stålberg E, Young R (eds) Neurology 1, clinical neurophysiology. Butterworths, London Boston, pp 145–167
35. Watkins PJ, Mackay JD (1980) Assessment of diabetic autonomic neuropathy using heart rate monitoring. In: Gries FA, Freund HJ, Rabe F, Berger H (eds) Aspects of autonomic neuropathy in diabetes. Thieme, Stuttgart New York, pp 69–72
36. Waxman SG (1978) Variations in axonal morphology and their functional significance. In: Waxman SG (ed) Physiology and pathobiology of axons. Raven Press, New York, pp 169–190
37. Wheeler T, Watkins PJ (1973) Cardiac denervation in diabetes. Br Med J 4: 584–586

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Jan Fagius, MD
Department of Neurology
University Hospital
S-750 14 Uppsala
Sweden