Peripheral motor nerve function in diabetic autonomic neuropathy

D. J. EWING¹, A. A. BURT, I. R. WILLIAMS, I. W. CAMPBELL,
AND B. F. CLARKE

*From the University Departments of Medicine and Medical Neurology and the
Diabetic and Dietetic Department, Royal Infirmary, Edinburgh*

SYNOPSIS Motor conduction velocity was measured in the median, ulnar, and common peroneal nerves of 32 diabetics with clinical features of autonomic neuropathy. The responses to the Valsalva manoeuvre and sustained handgrip, and the postural fall in blood pressure were used to assess the integrity of the autonomic nervous system. Abnormalities in the three autonomic function tests were significantly correlated with the forearm conduction velocity of the ulnar nerve, the conduction velocity and motor latency of the common peroneal nerve, and the H reflex. These results show that, in diabetics with autonomic neuropathy, abnormalities in the autonomic nervous system parallel changes in the peripheral nerves. Any diabetic with peripheral neuropathy should be examined for evidence of autonomic nervous system involvement.

Peripheral neuropathy is a well-recognized complication of diabetes mellitus which can be detected even at diagnosis (Ward *et al.*, 1971). With increasing duration of diabetes there is increasing impairment of nerve conduction (Gregerson, 1967). Autonomic neuropathy is likewise common, and, although it does not become clinically manifest until the later stages, tests of autonomic function show abnormalities before the onset of symptoms (Sharpey-Schafer and Taylor, 1960; Ewing *et al.*, 1974; Murray *et al.*, 1975).

This study compares autonomic and peripheral nerve function in diabetics with clinical features suggestive of autonomic neuropathy to see whether the nerve damage known to occur in the peripheral motor nerves was paralleled by similar changes in the autonomic nerves. A preliminary report of nerve conduction in diabetic autonomic neuropathy has been published elsewhere (Ewing *et al.*, 1973); this paper gives the findings in more detail and analyses them in relation to the autonomic function tests.

METHODS

PATIENTS Thirty-seven diabetics with features suggestive of autonomic neuropathy were selected for study. All patients had normal levels of serum vitamin B₁₂, except one who was excluded; four others were excluded as complete nerve conduction data could not be obtained. The ages of the remaining 32 patients ranged from 26 to 63 years (mean 48 ± 10 years), and the duration of diabetes from two to 33 years (mean 19 ± 9 years). All but four were insulin dependent, and none had cardiac failure or was receiving hypotensive therapy. None of the patients was known to be an alcoholic, all had normal protein bound iodine values, and 18 had blood urea levels within normal limits (less than 6.6 mmol/l). Of the remainder 11 had blood urea levels between 6.6 and 10.0 mmol/l, while only three had higher levels of 10.5, 10.6, and 12.1 mmol/l. All patients had one or more of the following features: impotence (25 patients); symptoms of postural hypotension (seven patients); intermittent diarrhoea (nine patients); gastric fullness or delay in emptying (four patients); a history of hypoglycaemic unawareness (11 patients); gustatory sweating (two patients); and reduced sweating in the legs (one patient). Ten patients had symptoms of a peripheral neuropathy including numbness and painful cramps in the legs but without signs. Nineteen had signs of peripheral neuropathy on clinical examination including absent

¹ Address for correspondence: Dr D. J. Ewing, Department of Medicine, Royal Infirmary, Edinburgh EH3 9YW.

(Accepted 13 January 1976.)

knee and ankle jerks and diminished sensation in the lower limbs.

Autonomic function was assessed by the Valsalva manoeuvre, the response to sustained handgrip, and the postural fall in blood pressure. The Valsalva manoeuvre was carried out using a standardized technique as previously described (Ewing *et al.*, 1973). The heart rate response was measured by a simultaneous electrocardiograph (ECG). The results were expressed as the Valsalva ratio (the ratio of the longest RR interval in the ECG after the manoeuvre to the shortest RR interval during the manoeuvre), a ratio of 1.10 or less being defined as an abnormal response, 1.11 to 1.20 as borderline, and 1.21 or more as a normal response. A standardized sustained handgrip test was also performed as described previously (Ewing *et al.*, 1974). A rise in diastolic blood pressure of less than 10 mmHg was defined as abnormal, 11–15 mmHg as borderline, and 16 mmHg or more as normal. Postural hypotension was defined as a fall in systolic blood pressure of 30 mmHg or more immediately on standing up from the supine position.

Motor conduction velocity (MCV) was measured in the median, ulnar, and common peroneal nerves. The latency of the H reflex in the triceps surae was measured after stimulation of the medial popliteal nerve at the popliteal fossa. Surface electrodes were used for stimulating with 1 cm silver discs placed 5 cm apart. Standard DISA surface recording electrodes and a DISA two channel electromyograph were used in all studies, which were performed in the same environment with skin temperatures maintained above 30°C.

The physical examination of the patients, the autonomic function tests, and the nerve conduction studies were carried out by three independent observers. Standard statistical methods were used to calculate the significance of the results.

RESULTS

CLINICAL FEATURES OF AUTONOMIC NEUROPATHY AND AUTONOMIC FUNCTION TESTS (Table 1) When the patients were grouped into those with impotence alone and those with other features of autonomic neuropathy, there were significant differences between the results of the autonomic function tests in the two groups.

CLINICAL FEATURES OF PERIPHERAL NEUROPATHY AND NERVE CONDUCTION (Table 2) Patients with symptoms and signs of a peripheral neuropathy did not, as a group, differ significantly in mean age from those having no such features.

However, they had a significantly longer duration of diabetes, their conduction velocity was slower and terminal latency longer.

RELATION BETWEEN THE CLINICAL FEATURES OF AUTONOMIC AND PERIPHERAL NEUROPATHY (Table 3) Five patients with impotence alone had signs of a peripheral neuropathy in contrast with 14 of those with other features of autonomic neuropathy ($\chi^2=5.15$, $P<0.05$).

CLINICAL FEATURES OF AUTONOMIC NEUROPATHY AND NERVE CONDUCTION (Table 4) When the MCV results were analysed in terms of the clinical features of autonomic neuropathy, there were significant differences between the groups only in the terminal motor latency of the common peroneal nerve ($P<0.02$).

CLINICAL FEATURES OF PERIPHERAL NEUROPATHY AND AUTONOMIC FUNCTION TESTS (Table 5) Table 5 shows the results of the autonomic function tests when the subjects were grouped according to the clinical features of peripheral neuropathy.

NERVE CONDUCTION AND AUTONOMIC FUNCTION TESTS *MCV and Valsalva manoeuvre* (Table 6) The Valsalva ratio was significantly correlated in the group as a whole only with the forearm conduction velocity in the ulnar nerve ($r=0.375$, $P<0.05$); but, when the group was divided into those with normal and abnormal Valsalva ratios, those with abnormal ratios had significantly more abnormal MCV measurements in the forearm conduction velocity in the ulnar nerve ($P<0.01$), the motor latency ($P<0.005$), and conduction velocity ($P<0.02$) of the common peroneal nerve and the H reflex latency ($P<0.05$).

MCV and response to sustained handgrip (Table 6) Within the whole group the rise in diastolic blood pressure correlated significantly with the forearm conduction velocity in the ulnar nerve ($r=0.356$, $P<0.05$), the motor latency of the common peroneal nerve ($r=0.552$, $P<0.01$) and the conduction velocity of the common peroneal nerve ($r=0.390$, $P<0.05$). When normal and abnormal handgrip responses were separated, there was a significant difference only in the motor latency of the common peroneal nerve ($P<0.005$).

TABLE 1
AUTONOMIC FUNCTION TESTS IN PATIENTS WITH DIFFERENT CLINICAL FEATURES OF
AUTONOMIC NEUROPATHY (MEAN $\pm$ SD)

Group	No.	Age (yr)	Duration of diabetes (yr)	Increase in diastolic BP during handgrip (mmHg)	Valsalva ratio	Fall in systolic BP on standing (mmHg)
Impotence alone	14	44 $\pm$ 11	18 $\pm$ 8	27 $\pm$ 6	1.47 $\pm$ 0.47	13 $\pm$ 12
Other features with or without impotence	18	51 $\pm$ 8	19 $\pm$ 9	14 $\pm$ 8	1.11 $\pm$ 0.15	35 $\pm$ 24
Significance		P > 0.05	NS	P < 0.001	P < 0.005	P < 0.005

TABLE 2
CLINICAL AND ELECTROPHYSIOLOGICAL FEATURES OF PERIPHERAL NERVE FUNCTION (MEAN $\pm$ SD)

Group	No.	Age (yr)	Duration of diabetes (yr)	Median nerve			Ulnar nerve			Common peroneal nerve		H reflex Latency (ms)
				Motor latency (wrist to muscle) (ms)	Forearm conduction velocity (m/s)	Upper arm conduction velocity (m/s)	Motor latency (wrist to muscle) (ms)	Forearm conduction velocity (m/s)	Upper arm conduction velocity (m/s)	Motor latency (ankle to muscle) (ms)	Leg conduction velocity (m/s)	
No symptoms or signs of peripheral neuropathy	10	48 $\pm$ 10	15 $\pm$ 9	3.8 $\pm$ 0.6	53.0 $\pm$ 5.2	67.6 $\pm$ 11.5	3.1 $\pm$ 0.4	55.8 $\pm$ 8.6	59.3 $\pm$ 3.2	4.4 $\pm$ 0.6	42.6 $\pm$ 8.5	34.6 $\pm$ 2.1
Symptoms and signs of peripheral neuropathy	19	48 $\pm$ 10	21 $\pm$ 7	4.3 $\pm$ 0.7	43.0 $\pm$ 6.1	61.3 $\pm$ 10.7	3.5 $\pm$ 0.8	43.9 $\pm$ 5.5	51.6 $\pm$ 12.9	6.3 $\pm$ 2.2	34.6 $\pm$ 6.6	38.2 $\pm$ 3.3
Significance		NS	P < 0.05	NS	P < 0.001	NS	NS	P < 0.001	NS	P < 0.02	P < 0.02	P < 0.005
Symptoms but no signs of peripheral neuropathy	3	49 $\pm$ 13	20 $\pm$ 16	3.5 $\pm$ 0.3	49.8 $\pm$ 8.1	65.2 $\pm$ 10.7	2.9 $\pm$ 0.2	51.5 $\pm$ 3.5	54.9 $\pm$ 5.4	4.7 $\pm$ 1.0	41.4 $\pm$ 7.6	33.4 $\pm$ 2.3
Normal values for this laboratory				3.5 $\pm$ 0.4	54.1 $\pm$ 3.0	67.6 $\pm$ 12.8	2.9 $\pm$ 0.5	58.4 $\pm$ 8.4	66.5 $\pm$ 9.6	4.4 $\pm$ 1.3	47.2 $\pm$ 5.1	30.0 $\pm$ 1.8

TABLE 3
PATIENTS WITH CLINICAL FEATURES OF AUTONOMIC
AND PERIPHERAL NEUROPATHY

	Peripheral neuropathy	
	No symptoms or signs	Symptoms and signs
Impotence alone	7	5
Other features with or without impotence	3	14

$\chi^2=5.15$, $P<0.05$.

TABLE 4
MOTOR NERVE CONDUCTION VELOCITIES IN PATIENTS WITH DIFFERENT CLINICAL FEATURES OF
AUTONOMIC NEUROPATHY (MEAN $\pm$ SD)

Group	No.	Median nerve			Ulnar nerve			Common peroneal nerve			H reflex
		Motor latency (wrist to muscle) (ms)	Forearm conduction velocity (m/s)	Upper arm conduction velocity (m/s)	Motor latency (wrist to muscle) (ms)	Forearm conduction velocity (m/s)	Upper arm conduction velocity (m/s)	Motor latency (ankle to muscle) (ms)	Leg conduction velocity (m/s)	Latency (ms)	
Impotence alone	14	3.9 $\pm$ 0.6	47.3 $\pm$ 7.1	63.0 $\pm$ 10.2	3.2 $\pm$ 0.8	50.4 $\pm$ 8.0	55.6 $\pm$ 12.8	4.4 $\pm$ 0.6	39.6 $\pm$ 6.6	35.4 $\pm$ 2.8	
Other features with or without impotence	18	4.2 $\pm$ 0.8	46.4 $\pm$ 8.0	64.2 $\pm$ 11.9	3.3 $\pm$ 0.5	46.8 $\pm$ 8.6	53.3 $\pm$ 12.7	6.2 $\pm$ 2.2	37.1 $\pm$ 9.2	37.6 $\pm$ 3.8	NS
Significance		NS	NS	NS	NS	NS	NS	$P<0.02$	NS	NS	

TABLE 5
AUTONOMIC FUNCTION TESTS IN PATIENTS WITH AND WITHOUT CLINICAL FEATURES OF PERIPHERAL NEUROPATHY (MEAN ± SD)

Group	No.	Increase in diastolic BP during handgrip (mmHg)	Valsalva ratio	Fall in systolic BP on standing (mmHg)
No symptoms or signs of peripheral neuropathy	10	24 ± 10	1.57 ± 0.53	12 ± 10
Symptoms and signs of peripheral neuropathy	19	17 ± 10	1.13 ± 0.16	33 ± 24
Significance		NS	P < 0.005	P < 0.02
Symptoms but no signs of peripheral neuropathy	3	22 ± 4	1.16 ± 0.09	18 ± 22

TABLE 6
MOTOR NERVE CONDUCTION VELOCITIES IN PATIENTS WITH DIFFERENT RESPONSES TO AUTONOMIC FUNCTION TESTS (MEAN ± SD)*

Group	No.	Median nerve			Ulnar nerve			Common peroneal nerve			H reflex	
		Motor latency (wrist to muscle) (ms)	Forearm conduction velocity (m/s)	Upper arm conduction velocity (m/s)	Motor latency (wrist to muscle) (ms)	Forearm conduction velocity (m/s)	Upper arm conduction velocity (m/s)	Motor latency (ankle to muscle) (ms)	Leg conduction velocity (m/s)	Latency (ms)		
Handgrip												
Abnormal	10	4.1 ± 0.7	46.0 ± 7.8	62.4 ± 11.8	3.4 ± 0.6	45.1 ± 7.7	53.9 ± 15.5	6.8 ± 2.5	34.8 ± 8.5	38.3 ± 3.9		
Normal	20	3.9 ± 0.6	47.2 ± 7.0	64.8 ± 10.9	3.3 ± 0.7	50.7 ± 8.4	55.3 ± 11.7	4.5 ± 0.7	40.8 ± 7.6	35.7 ± 3.2		
Significance		NS	NS	NS	NS	NS	NS	P < 0.05	NS	NS		
Valsalva												
Abnormal	15	4.3 ± 0.8	44.3 ± 7.6	64.2 ± 11.4	3.3 ± 0.6	44.4 ± 6.6	53.4 ± 13.6	6.5 ± 2.2	34.0 ± 7.4	37.7 ± 3.8		
Normal	12	3.9 ± 0.6	49.9 ± 6.4	64.8 ± 11.9	3.3 ± 0.8	53.2 ± 8.5	56.9 ± 13.5	4.3 ± 0.5	41.9 ± 8.0	34.7 ± 2.7		
Significance		NS	NS	NS	NS	P < 0.01	NS	P < 0.005	P < 0.02	P < 0.05		
Postural drop												
Abnormal	14	4.1 ± 0.6	44.7 ± 8.2	64.2 ± 11.5	3.4 ± 0.6	45.6 ± 8.2	54.1 ± 13.9	6.5 ± 2.4	34.7 ± 8.5	37.5 ± 3.9		
Normal	17	4.0 ± 0.8	48.6 ± 6.8	63.0 ± 11.2	3.2 ± 0.7	51.1 ± 8.0	54.9 ± 12.1	4.9 ± 1.4	40.1 ± 7.7	35.9 ± 3.1		
Significance		NS	NS	NS	NS	NS	NS	P < 0.05	NS	NS		

*Patients with borderline responses to the Valsalva manoeuvre and sustained handgrip have been omitted from this table. Postural blood pressure was not measured in one subject.

MCV and postural fall in blood pressure (Table 6) The fall in systolic blood pressure also correlated significantly with the forearm conduction velocity in the ulnar nerve ($r=0.466$, $P<0.01$), the motor latency of the common peroneal nerve ($r=0.681$, $P<0.001$), the conduction velocity of the common peroneal nerve ($r=0.573$, $P<0.001$), and also the H reflex latency ($r=0.374$, $P<0.05$). Again, however, when those with a normal and an abnormal fall in systolic blood pressure were separated, there was a significant difference only in the motor latency of the common peroneal nerve ($P<0.05$).

Renal function, MCV, and autonomic function tests The level of the blood urea correlated significantly, in the group as a whole, with the forearm conduction velocity in the ulnar nerve ($r=0.447$, $P<0.05$), and the motor latency of the common peroneal nerve ($r=0.452$, $P<0.01$). It was also significantly correlated with the sustained handgrip response ($r=0.356$, $P<0.05$) but not with the Valsalva ratio ($r=0.286$ NS) nor with fall in systolic blood pressure ($r=0.214$ NS).

DISCUSSION

This study shows that, in diabetics with autonomic neuropathy, abnormalities in the autonomic nervous system parallel changes in peripheral nerves. Previous workers have demonstrated that peripheral nerve function, as determined by motor nerve conduction velocity, is impaired in diabetics and that, although this is reflected by the presence of peripheral neuropathy, some diabetics have early changes of MCV without clinical evidence of a neuropathy (Mulder *et al.*, 1961; Lawrence and Locke, 1961; Skillman *et al.*, 1961). Others have documented abnormal autonomic function tests in diabetics both with and without clinical features of autonomic neuropathy (Sharpey-Schafer *et al.*, 1960; Ewing *et al.*, 1974; Murray *et al.*, 1975). It is surprising perhaps that there has been little attempt to relate the two, either in terms of clinical features, or in terms of objective testing. Early authors considered autonomic neuropathy as one part of the spectrum of diabetic neuropathy (Rundles, 1945; Martin, 1953a); but, with the development of objective means of testing both nerve conduction and autonomic function, later workers have looked

more specifically at the peripheral and the autonomic nervous systems independently. Martin (1953b) showed abnormalities of sudomotor and vasomotor function in 20 patients with diabetic peripheral neuropathy, and another study attempted to assess the amount of autonomic nerve damage in patients with peripheral neuropathy by using the Valsalva manoeuvre (Bishnu and Berenyi, 1971). The present study, however, has examined the relationship in more detail from the opposite viewpoint by measuring peripheral nerve function in patients with autonomic neuropathy.

As has been demonstrated previously (Ewing *et al.*, 1973), the study shows that diabetics with impotence alone, which is often stated to be the only manifestation of diabetic autonomic neuropathy in some patients (*British Medical Journal*, 1974), had more normal autonomic vascular reflexes than those with other features of autonomic neuropathy. Similarly, the clinical symptoms and signs of peripheral neuropathy were closely reflected by the changes in MCV. As might be expected, therefore, few patients with impotence alone also had signs of a peripheral neuropathy.

In addition, this study now provides more detailed information of the relation between MCV and autonomic vascular reflex responses. Whether one examines the regression relationship between the individual values, or the differences between groups with and without abnormal autonomic function tests, it is clear that changes in the common peroneal nerve and in the forearm conduction velocity of the ulnar nerve are closely related. The three autonomic responses measured—the Valsalva manoeuvre, sustained handgrip, and postural fall in blood pressure—are all cardiovascular reflexes. Although autonomic neuropathy affects all systems of the body, it is the vascular responses that are both simplest to measure non-invasively and easiest to quantify, and they bear a close relation to symptoms (Ewing *et al.*, 1973). Their reflex pathways are not clear in their entirety, but probably involve efferent fibres to the blood vessels in the lower limbs in all three responses and this would therefore suggest that damage to the nerves conveying the reflexes occurs in parallel with the motor nerve damage measured by the nerve conduction studies.

Peripheral neuropathy in diabetics is common in the lower limbs, but rare in the upper limbs (Noel *et al.*, 1971; Noel, 1973), and, although the neuropathy is predominantly sensory, changes in the motor fibres correlate well with the clinical picture (Lamontagne and Buchthal, 1970) and with changes in the sensory nerves (Gilliatt and Willison, 1962). On the basis of these observations, it would be expected that the leg MCV gives a better correlation than the arm MCV with the autonomic function tests.

Although the level of blood urea correlated both with the MCV findings and the autonomic function tests, and could be presumed to be the cause of both abnormalities, this does not stand up to critical analysis. In chronic renal failure the blood urea, although a crude index of renal function, is usually much higher than the levels in this study before changes in MCV are detected. Of those patients with normal blood urea values, seven had clinical signs of peripheral neuropathy; and although changes of autonomic function have been described in chronic renal failure (Ewing and Winney, 1975), eight patients with normal blood urea levels had abnormal autonomic function tests. Impaired renal function, although it cannot be incriminated causally, may nevertheless contribute to the neuropathy.

Fibres mediating the autonomic responses are both myelinated and unmyelinated, while the MCV is measured in large myelinated fibres ending at neuromuscular junctions. The most constant underlying lesion in the peripheral neuropathy of diabetes has been shown to be segmental demyelination (Thomas and Lascelles, 1965, 1966; Locke, 1967). This is usually thought to be due to disturbance of the Schwann cells, but it has been suggested that segmental demyelination may result from axonal disturbance (Dyck, 1971; Thomas, 1971). Axonal loss has been demonstrated in more severe cases (Chopra *et al.*, 1969). Histological studies of autonomic nerves in diabetics are limited, but widespread changes have been noted in the sympathetic chain and ganglia in patients dying from various complications (Appenzeller and Richardson, 1966; Olsson and Sourander, 1968). Damage has also been noted to the autonomic fibres supplying the bladder wall (Faerman *et al.*, 1973); the corpora cavernosa (Faerman *et al.*, 1974), the innervation of the oesophagus (Smith,

1974), the greater splanchnic nerves (Low *et al.*, 1975), and the lumbar sympathetic ganglia (Kott *et al.*, 1974).

Diabetic peripheral neuropathy and diabetic autonomic neuropathy are often considered as distinct clinical entities, with their different symptomatology and features. They share, however, a common pathogenesis, and the present study shows that abnormalities occurring in the autonomic nervous system are paralleled by changes in the peripheral nervous system. In practice, therefore, as diabetic peripheral neuropathy has been more closely studied and understood, it means that any patient with peripheral neuropathy due to his diabetes should be examined carefully for evidence of autonomic nerve involvement.

REFERENCES

- Appenzeller, O., and Richardson, E. P. (1966). The sympathetic chain in patients with diabetic and alcoholic polyneuropathy. *Neurology (Minneapolis)*, **16**, 1205-1209.
- Bishnu, S. K., and Berenyi, M. R. (1971). Circulatory reflex response in diabetic patients with or without peripheral neuropathy. *Journal of the American Geriatrics Society*, **19**, 159-166.
- British Medical Journal* (1974). Editorial: diabetic autonomic neuropathy, **3**, 2-3.
- Chopra, J. S., Hurwitz, L. J., and Montgomery, D. A. D. (1969). The pathogenesis of sural nerve changes in diabetes mellitus. *Brain*, **92**, 391-418.
- Dyck, P. J. (1971). The concept of secondary segmental demyelination. *Proceedings of the 2nd International Congress of Muscle Diseases. Excerpta Medica International Congress Series*, no. 237, 74.
- Ewing, D. J., Campbell, I. W., Burt, A. A., and Clarke, B. F. (1973). Vascular reflexes in diabetic autonomic neuropathy. *Lancet*, **2**, 1354-1356.
- Ewing, D. J., Irving, J. B., Kerr, F., Wildsmith, J. A. W., and Clarke, B. F. (1974). Cardiovascular responses to sustained handgrip in normal subjects and in patients with diabetes mellitus: a test of autonomic function. *Clinical Science and Molecular Medicine*, **46**, 295-306.
- Ewing, D. J., and Winney, R. (1975). Autonomic function in patients with chronic renal failure on intermittent haemodialysis. *Nephron*, **15**, 424-429.
- Faerman, I., Glocer, L., and Celener, D. (1973). Autonomic nervous system and diabetes. Histological and histochemical study of the autonomic nerve fibres of the urinary bladder in diabetic patients. *Diabetes*, **22**, 225-237.
- Faerman, I., Glocer, L., Fox, D., Jadzinsky, M. D., and Rapaport, M. (1974). Impotence and diabetes. Histological studies of the autonomic nervous fibres of the

- corpora cavernosa in impotent diabetic males. *Diabetes*, **23**, 971-976.
- Gilliatt, R. W., and Willison, R. G. (1962). Peripheral nerve conduction in diabetic neuropathy. *Journal of Neurology, Neurosurgery and Psychiatry*, **25**, 11-18.
- Gregerson, G. (1967). Diabetic neuropathy: influence of age, sex, metabolic control and duration of diabetes on motor conduction velocity. *Neurology (Minneapolis)*, **17**, 972-980.
- Kott, I., Urca, I., and Sandbank, U. (1974). Lumbar sympathetic ganglia in atherosclerotic patients, diabetic and non-diabetic. *Archives of Surgery*, **109**, 787-792.
- Lamontagne, A., and Buchthal, F. (1970). Electrophysiological studies in diabetes mellitus. *Journal of Neurology, Neurosurgery and Psychiatry*, **33**, 442-452.
- Lawrence, D. G., and Locke, S. (1961). Motor nerve conduction velocity in diabetes. *Archives of Neurology (Chicago)*, **5**, 483-489.
- Locke, S. (1967). Axons, Schwann cells and diabetic neuropathy. *Bulletin of the New York Academy of Medicine*, **43**, 784-791.
- Low, P. A., Walsh, J. C., Huang, C. Y., and McCleod, J. C. (1975). The sympathetic nervous system in diabetic neuropathy—a clinical and pathological study. *Brain*, **98**, 341-356.
- Martin, M. M. (1953a). Diabetic neuropathy. A clinical study of 150 cases. *Brain*, **76**, 594-624.
- Martin, M. M. (1953b). Involvement of autonomic nerve fibres in diabetic neuropathy. *Lancet*, **1**, 560-565.
- Mulder, D. W., Lambert, E. H., Bastron, J. A., and Sprague, R. G. (1961). The neuropathies associated with diabetes mellitus. A clinical and electromyographic study of 103 unselected diabetic patients. *Neurology (Minneapolis)*, **11**, 275-284.
- Murray, A., Ewing, D. J., Campbell, I. W., Neilson, J. M. M., and Clarke, B. F. (1975). RR interval variations in young male diabetics. *British Heart Journal*, **37**, 882-885.
- Noel, P. (1973). Sensory nerve conduction in the upper limb at various stages of diabetic neuropathy. *Journal of Neurology, Neurosurgery, and Psychiatry*, **36**, 786-796.
- Noel, P., Lauvaux, J. P., and Pirart, J. (1971). Upper limb diabetic neuropathy: a clinical and electrophysiological study. *Hormone and Metabolic Research*, **3**, 386-392.
- Olsson, Y., and Sourander, P. (1968). Changes in the sympathetic nervous system of diabetes mellitus. A preliminary report. *Journal of Neurovisceral Relations*, **31**, 86-95.
- Rundles, R. W. (1945). Diabetic neuropathy. General review with report of 125 cases. *Medicine (Baltimore)*, **24**, 111-160.
- Sharpey-Schafer, E. P., and Taylor, P. J. (1960). Absent circulatory reflexes in diabetic neuritis. *Lancet*, **1**, 559-562.
- Skillman, T. G., Johnson, E. W., Hamwi, G. J., and Driskill, H. J. (1961). Motor nerve conduction velocity in diabetes mellitus. *Diabetes*, **10**, 46-51.
- Smith, B. (1974). Neuropathology of the oesophagus in diabetes mellitus. *Journal of Neurology, Neurosurgery, and Psychiatry*, **37**, 1151-1154.
- Thomas, P. K. (1971). The morphological basis for alterations in nerve conduction in peripheral neuropathy. *Proceedings of the Royal Society of Medicine*, **64**, 295-298.
- Thomas, P. K., and Lascelles, R. G. (1965). Schwann cell abnormalities in diabetic neuropathy. *Lancet*, **1**, 1355-1357.
- Thomas, P. K., and Lascelles, R. G. (1966). The pathology of diabetic neuropathy. *Quarterly Journal of Medicine*, **35**, 489-509.
- Ward, J. D., Barnes, G. C., Fisher, D. J., Jessop, J. D., and Baker, R. W. R. (1971). Improvement in nerve conduction following treatment in newly diagnosed diabetes. *Lancet*, **1**, 428-431.