9

Autonomic Neuropathy: its Diagnosis and Prognosis

DAVID J. EWING
BASIL F. CLARKE

In nineteenth century medical literature, occasional references were made to clinical abnormalities including sweating and bladder disturbances in patients with diabetes mellitus. As the enormous benefits of insulin became apparent after its introduction in 1922, it was disappointing that complications were increasingly observed in surviving patients. It took some time, however, for such diverse features as postural dizziness, impotence, decreased sweating, bladder problems, diarrhoea and gastric symptoms to be recognized as consequences of a damaged autonomic nervous system in diabetes mellitus. The clinical features delineating autonomic neuropathy were first described in detail by Jordan in 1936 and Rundles in 1945.

During the 1950s and 1960s other authors added further to the clinical descriptions of diabetic autonomic neuropathy, while physiologists devised a variety of techniques to ascertain the patterns of autonomic nerve damage. Although invasive and complex, these tests enabled the elucidation of some of the underlying pathophysiological mechanisms. At this time autonomic neuropathy was regarded as an obscure part of diabetic neuropathy affecting only a few patients. However, with the advent of simple non-invasive cardiovascular reflex tests in the 1970s, it soon became apparent that autonomic involvement was not only more common than previously thought but also much more widespread throughout the body.

Further changes of emphasis have taken place in the 1980s. It is now well recognized that peripheral neuropathy in diabetes encompasses many different patterns, of which autonomic (or small fibre) abnormalities are often prominent. These abnormalities can be demonstrated by a variety of tests even in the absence of symptoms or signs. Classical definitions of the autonomic nervous system are being enlarged to include the recently discovered neurotransmitters. No longer can autonomic nerves be regarded simply as belonging to 'parasympathetic' and 'sympathetic' divisions, but rather to a much more complex integrative system.

This review will therefore address several aspects of diabetic autonomic neuropathy: its clinical assessment using cardiovascular and other tests; its

various clinical presentations; its frequency, natural history and prognosis; and the treatment of specific symptoms. Chapter 8 gives an account of the possibility of prevention or reversal of metabolic nerve damage by improved glycaemic control and aldose reductase inhibitor drugs.

DIAGNOSIS

Although the diagnosis and classification of diabetic autonomic neuropathy were formerly based on symptoms, the development of simple tests using cardiovascular reflexes has allowed a more precise approach. These tests reflect both symptoms (Ewing et al, 1980; Mackay et al, 1980; Masoaka et al, 1985) and prognosis (Ewing et al, 1980) and it can be assumed that cardiovascular reflex abnormalities indicate diffuse damage throughout the autonomic nervous system. Support for this assumption comes from the close correlation between abnormalities of cardiovascular reflexes and autonomic abnormalities elsewhere such as those involving oesophageal (Channer et al, 1985), gastric (Campbell et al, 1977), pupillary (Pfeifer et al, 1985; Martyn and Ewing, 1986), and neuroendocrine (Ewing et al, 1986) function. However, early clinical manifestations such as sweating loss in the feet and impotence may precede abnormal cardiovascular tests. Tests in systems other than the cardiovascular are generally more complex, but for completeness some of them are described below.

Cardiovascular tests

Five simple non-invasive tests have been widely used in the assessment of autonomic neuropathy. They are the heart rate responses to the Valsalva manoeuvre, standing up and deep breathing, and the blood pressure responses to standing up and sustained handgrip. Descriptions of these tests are given below and the range of normal values shown in Table 1. Other cardiovascular tests used in diabetics include baroreflex responses, the heart response to intravenous atropine and the immediate heart rate response to lying down. Their respective merits have been reviewed (Ewing, 1983, 1984), but none of them appear to be as reliable in distinguishing normal from abnormal, or as easily performed. Recently we described a new approach looking at changes in heart rate variation by measuring the sudden beat by beat changes that occur frequently throughout the day and night, but are markedly reduced in diabetic subjects with autonomic neuropathy. This technique is more sensitive than the conventional cardiovascular reflex tests, but requires 24-h ECG monitoring (Ewing et al, 1984).

Heart rate response to Valsalva manoeuvre

During the strain period of the Valsalva manoeuvre, the blood pressure falls and the heart rate rises. After release the blood pressure promptly

Table 1. Normal, borderline and abnormal values for cardiovascular autonomic function tests.

	Normal	Borderline	Abnormal
Heart rate tests:			
Heart rate response to Valsalva manoeuvre (Valsalva ratio)	1.21 or more	—	1.20 or less
Heart rate (R-R interval) variation during deep breathing (maximum–minimum heart rate)	15 beats/min or more	11–14 beats/min	10 beats/min or less
Immediate heart rate response to standing (30:15 ratio)	1.04 or more	1.01–1.03	1.00 or less
Blood pressure (BP) tests:			
Blood pressure response to standing (fall in systolic BP)	10 mmHg or less	11–29 mmHg	30 mmHg or more
Blood pressure response to sustained handgrip (increase in diastolic BP)	16 mmHg or more	11–15 mmHg	10 mmHg or less

rises, overshooting its resting value, and the heart rate slows. With autonomic damage the blood pressure falls during strain and only slowly returns to normal after release with no overshoot rise in blood pressure and no change in heart rate. The test is performed by asking the subject to sit quietly and then blow into a mouthpiece attached to an aneroid pressure gauge at a pressure of 40 mmHg for 15 seconds. The ratio of the longest R-R interval shortly after the manoeuvre (within about 20 beats) to the shortest R-R interval during the manoeuvre is then measured. The result is expressed as the Valsalva ratio which is taken as the mean ratio from three successive Valsalva manoeuvres (Ewing, 1983).

Heart rate response to standing up

During the postural change from lying to standing a characteristic immediate rapid increase in heart rate occurs which is maximal at about the 15th beat after standing followed by a relative overshoot bradycardia maximal at about the 30th beat. Diabetics with autonomic neuropathy show only a gradual, or no increase in heart rate after standing (Ewing, 1983). To perform this test the subject is asked to lie quietly on a couch and then to stand up unaided. The characteristic heart rate response can be expressed by the 30 : 15 ratio, which is the ratio of the longest R-R interval around the 30th beat after starting to stand up to the shortest R-R interval around the 15th beat. Some authors refer to the 'R-R max/R-R min ratio' but for all practical purposes it is the same as the 30 : 15 ratio. An alternative way of expressing the response is to measure only the initial rise in heart rate on standing (Mackay et al, 1980).

Heart rate response to deep breathing

Normally the heart rate varies continually in sequence with respiration but in diabetics with autonomic neuropathy there is a noticeable reduction and sometimes complete absence of heart rate variation (Ewing, 1983). A number of techniques have been proposed but for clinical purposes deep breathing at six breaths a minute has proved most convenient. The patient sits quietly and then breathes deeply and evenly at six breaths per minute (five seconds in and five seconds out). The maximum and minimum heart rates during each 10-second breathing cycle are measured and the mean of the differences during three successive breathing cycles gives the 'maximum–minimum heart rate' (Hilsted and Jensen, 1979). An alternative way to express these changes is as a ratio of the heart rate at expiration to that at inspiration, the 'E:I ratio' (Sundkvist et al, 1979).

Blood pressure response to standing up

On standing, pooling of the blood in the legs causes a fall in blood pressure which is normally rapidly corrected by reflex peripheral vasoconstriction. In diabetics with postural hypotension the blood pressure falls on standing and remains low. This test is performed by measuring the blood pressure

while the subject is lying down, and again one minute after standing up. The difference in systolic blood pressure is taken as the measure of postural blood pressure change.

Blood pressure response to sustained handgrip

During sustained handgrip, a sharp rise in blood pressure normally occurs due to a heart rate dependent increase in cardiac output with unchanged peripheral vascular resistance. If the normal reflex pathways are damaged, as in diabetic autonomic neuropathy, the rise in blood pressure is abnormally small (Ewing, 1983). To perform this test handgrip is maintained at 30% of the maximum voluntary contraction up to a maximum of five minutes, using a handgrip dynamometer, and the blood pressure measured each minute. The difference between the diastolic blood pressure just before release of handgrip and before starting is taken as the measure of response.

We have based our assessment of autonomic nerve damage on the combined results from these five tests, which we have used over a number of years in a large number of diabetic subjects (Ewing et al, 1985). We now classify autonomic neuropathy according to the severity of damage into one of five groups:

1. Normal: all five tests normal or one borderline.
2. Early involvement: one of the three heart rate tests abnormal or two borderline.
3. Definite involvement: two or more of the heart rate tests abnormal.
4. Severe involvement: two or more of the heart rate tests abnormal, plus one or both of the blood pressure tests abnormal or both borderline.
5. Atypical pattern: any other combination of abnormal tests. (In our experience only about 6% of patients tested were 'atypical'.)

An alternative to this classification of severity is to give each individual test a score of 0, 1 or 2, depending on whether they are respectively normal, borderline or abnormal. An overall 'autonomic test score' of 0–10 can then be obtained. Although increasing scores from 0 to 10 correlate closely with the grades of severity given above, scoring of the tests in this way allows the 'atypical' pattern to be given an actual numerical value.

Previously the results of these tests have been categorized as 'parasympathetic' or 'sympathetic' depending on whether only heart rate control or both heart rate and blood pressure control was abnormal (Ewing, 1983; Watkins and Edmonds, 1983). This approach, although reflecting the apparent sequence of clinical abnormalities, is not physiologically precise as the cardiovascular reflex pathways are extremely complex and encompass both parasympathetic and sympathetic fibres to a greater or lesser extent. It is also apparent that tests involving heart rate are more sensitive than those concerned with blood pressure. Using the battery of five tests described above it seems more logical therefore to define autonomic involvement as early, definite, or severe, thus avoiding the need to label these reflex pathways as precisely parasympathetic or sympathetic (Ewing

et al, 1985). Use of a single cardiovascular reflex test, usually the heart rate response to deep breathing, can also be misleading. It presumes that autonomic neuropathy is 'all or nothing' and does not allow for a range of nerve damage from minimal to extremely extensive.

This battery of cardiovascular tests can be performed very easily in the clinic situation with only minimal equipment. All that is needed are a sphygmomanometer, ECG machine, aneroid pressure gauge attached to a mouthpiece by a rigid or flexible tube, and a handgrip dynamometer (Tephcotronics Ltd., 5 Hillview Drive, Edinburgh EH12 8QW). We have found in our own practice that with a simple planned sequence, all the tests can be performed within 15–20 minutes (Table 2).

Measurement and calculation of the various ratios can be done in two ways. Before the advent of microcomputer systems, and still useful when tests are only occasionally performed, all that is required is a ruler and the ECG strip. Nowadays, however, a number of computer programmes have been written which measure the R-R intervals automatically, calculate the required ratios, and group the results. Several such systems have been described (Smith and Smith, 1981; O'Brien and Corrall, 1985), but these only incorporate measurements of heart rate. In Edinburgh we have developed and now use routinely our own system based on the five tests described above (the 'Autocaft' system, UnivEd Technologies Ltd., 16 Buccleuch Place, Edinburgh EH8 9LN) which operates with BBC and other microcomputers. This particular system has the advantages of allowing blood pressure measurements to be entered, and automatically classifies the results.

Gastrointestinal tests

Oesophageal function can be assessed with cineradiography, manometry or scintiscanning. Abnormal manometric patterns have been described in association with diabetic autonomic neuropathy but their significance is uncertain. Recently scintiscanning techniques measuring both solid and liquid transit times have been applied to diabetics (Channer et al, 1985; Maddern et al, 1985).

Gastric emptying is a coordinated activity involving both parasympathetic and sympathetic nerves. Abnormalities in diabetics have been assessed by barium meal studies, by scintigraphic techniques using a radioactive meal (Campbell et al, 1977), by gastric impedance (Gilbey et al, 1985) and ultrasonography (Sakurada et al, 1985; Vogelberg and Kubler, 1985). The integrity of the vagal nerves supplying the stomach can be assessed by an insulin response test, which induces hypoglycaemia thereby causing gastric acid secretion if the vagal supply is intact, and is a standard procedure for determining the completeness of surgical vagotomy. Diminished gastric acid secretion is found in some diabetics, indicating damage to the vagal supply of the gastric parietal cells. If the parietal cells themselves are damaged or absent, there will be no acid output in response to pentagastrin or histamine stimulation. In diabetics with autonomic neuropathy, however, these tests of parietal cell function are usually normal.

Table 2. Flow plan for performing cardiovascular autonomic function tests.

Test (in following order)	Position	Approximate time of test (min)	Apparatus required
Heart rate response to Valsalva manoeuvre	Sitting	5	Aneroid manometer, electrocardiograph
Heart rate variation during deep breathing	Sitting	2	Electrocardiograph
Blood pressure response to sustained handgrip	Sitting	5	Handgrip dynamometer, sphygmomanometer
Immediate heart rate response to standing	Lying to standing	3	Electrocardiograph
Blood pressure response to standing	Lying to standing	3	Sphygmomanometer

Investigation of autonomic activity in the small and large bowel has produced conflicting results. There are still no simple or reliable methods available to assess transit time or motor function of the bowel, although certain marker techniques have been proposed. A number of detailed colonic motility studies have recently been described but the techniques are still in the 'research' phase. There are no simple, reliable or practical tests that have so far been developed that can be applied to diagnose diabetic autonomic neuropathy, and the gastrointestinal tract remains a fertile area for autonomic neuropathy research.

Bladder tests

Urologists use a number of specialized and invasive methods of assessing bladder function based usually on cystometry and urodynamic studies and requiring expert interpretation. They have been applied in the investigation of bladder function abnormalities in diabetics (Bradley, 1980). There are, however, three simpler tests that the physician can use although their exact place in diagnosis and management is still not clear. Ultrasound sonography of the bladder detects, non-invasively, the presence and approximate volume of residual urine. A second method is that of mictiography. Commercial mictiography machines are available which provide a flow profile of the urinary strain during voiding. The voiding pressures are recorded by a specially designed urine collecting container and can be related to the time of flow. From this, calculations can be made of the peak flow, length of flow and flow profile. Two characteristic patterns are found in diabetics. The first is a long peak flow with prolonged duration of flow, associated with an increased residual urine volume. The second consists of a straining pattern of voiding marked by short interrupted spurts of urine. The third test, intravenous pyelography, is a further way of estimating the post-micturition residual urine volume. These non-invasive tests, particularly mictiography, may be useful to detect the onset and follow the natural history of bladder involvement in diabetic autonomic neuropathy, but further evaluation is necessary before they can be recommended for routine use.

Sweat tests

Sweat tests such as the application of topical powders which change colour on contact with moisture can be used to define areas of loss of sweating. Postganglionic sudomotor function can also be tested by measuring the sweat responses to direct heat, faradic stimulation or intradermal acetylcholine (Ewing, 1983). Low and colleagues have recently described a more sophisticated quantitative sudomotor axon reflex test (Q-SART) (Low et al, 1983) where local sweating is stimulated by acetylcholine iontophoresis, using a specially designed 'sweat cell'. Another approach, counting the number of imprints made by sweat drops in a soft Silastic impression material after stimulating sweating with pilocarpine iontophoresis, has been described by Kennedy and colleagues (1984). The

earlier generalized sweating tests were cumbersome and imprecise but the more recently developed Q-SART and sweat imprint tests may give quantifiable ways to measure local sweat production and assess sympathetic involvement.

Pupil tests

Infrared television scanning pupillometry has enabled measurements to be made of resting pupil diameter and the responses to light and dark and to mydriatic agents (Hayashi and Ishikawa, 1979; Hreidarsson, 1981, 1982; Pfeifer et al, 1982a; Smith and Smith, 1983) but the techniques are complex and the equipment costly. Two simple methods have recently been described. The first measures the diameter of the dark-adapted pupil using a Polaroid photograph of the eye taken by electronic flash. When standardized against the outer diameter of the iris the dark-adapted pupil diameter provides a quantitative estimate of sympathetic innervation (Smith and Dewhirst, 1986). The second technique, measurement of pupil cycle time (PCT), depends on the observation that regular oscillations of the pupil can be induced with a slit lamp beam in normal subjects, and timed with a stopwatch. Pharmacological testing confirms that PCT is a sensitive measure of parasympathetic dysfunction, and in diabetic subjects with autonomic neuropathy it is considerably prolonged (Figure 1)

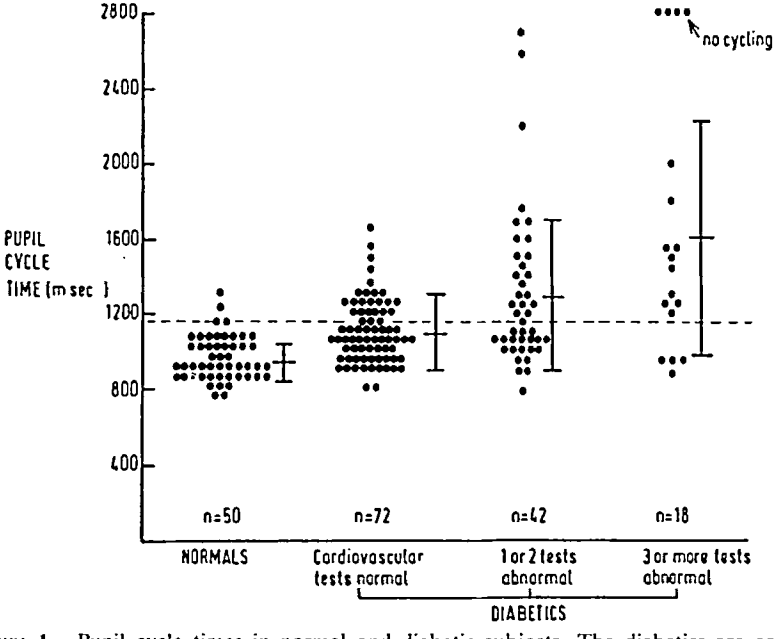

Figure 1. Pupil cycle times in normal and diabetic subjects. The diabetics are grouped according to the number of abnormal results found on cardiovascular reflex testing. The solid lines represent mean ± SD. The upper limit of normal is indicated by the dotted line. From Martyn and Ewing (1986), with permission.

(Martyn and Ewing, 1986). These techniques therefore provide two additional simple methods of testing autonomic reflexes, independent of cardiovascular pathways.

Neuroendocrine tests

Hormone tests, of course, require laboratory measurement facilities. The pancreatic polypeptide response to hypoglycaemia has been applied as a test of vagal integrity (Krarup et al, 1979) and measurements of plasma catecholamines used as an approximate indicator of sympathetic activity (Christensen, 1979).

CLINICAL PRESENTATIONS

Autonomic nerve damage can be found in many diabetics often without any accompanying symptoms. Cardiovascular reflex abnormalities can be detected at or shortly after diabetes has been diagnosed (Fraser et al, 1977; Canal et al, 1978; Xueli et al, 1981; Pfeifer et al, 1984), and in diabetics of longer duration without any symptoms of autonomic neuropathy (Murray et al, 1975; Mackay et al, 1980; Sundkvist, 1981; Pfeifer et al, 1982b; Bellavere et al, 1985; Masoaka et al, 1985).

Because autonomic symptoms are often vague and present insidiously the majority of diabetics with autonomic neuropathy may be unrecognized for a considerable time. Moreover physicians frequently fail to ask patients regarding specific symptoms which in any case they may have attributed merely to their diabetes and are then incorrectly interpreted. In these instances simple objective autonomic function tests can be invaluable in confirming or refuting the diagnosis. Over a period of years the symptoms may progress into the florid picture of diabetic autonomic neuropathy, which has been well recognized since the description by Rundles (1945), with a variable combination of postural hypotension, nocturnal diarrhoea, gastric problems, bladder symptoms, abnormal sweating, impotence and a failure to recognize hypoglycaemia. Diabetics with severe symptomatic features often have advanced retinopathy, nephropathy and somatic neuropathy. Autonomic neuropathy in diabetics has sometimes been described as 'patchy' because of the variability of the clinical features. Although this may be a useful clinical description, it is incorrect to think of autonomic neuropathy itself as 'patchy' as the underlying nerve pathology is almost certainly diffuse.

One unusual form of presentation is that following ingestion of the rat poison 'Vacor', which produces irreversible somatic and autonomic neuropathy together with diabetes. Case reports have included severe postural hypotension, usually needing treatment with fludrocortisone, dysphagia, constipation, diarrhoea, bladder dysfunction and impotence (Gallanosa et al, 1981; Peters et al, 1981).

Cardiovascular abnormalities

Heart rate

A resting tachycardia and a fixed heart rate have often been regarded as characteristic of cardiovascular denervation in the diabetic. Several reports refer to individual diabetics with resting heart rates in excess of 95 beats per minute (Ewing, 1984). In matched series of diabetics and controls an overall increase in group mean heart rate of about 10 beats per minute is usually found which is not necessarily confined to those with autonomic neuropathy (Ewing, 1984). We examined heart rate in 61 diabetics with various degrees of autonomic involvement and noted the slowest heart rates in those with no detectable damage, the fastest rates in those with cardiac parasympathetic damage, and slightly slower rates in those with additional sympathetic damage (Ewing et al, 1981). Since up to 40% of diabetics may have some asymptomatic autonomic involvement, this is probably enough to account for the 10 beats per minute increase observed in unselected diabetics.

The so-called fixed heart rate means that not only is the heart rate steady but also that it does not respond to reflex cardiovascular stimuli. Although many diabetics appear to have fixed heart rates with unaltered rates during cardiovascular reflex tests, more severe stresses will nevertheless provoke a change in rate. Lloyd-Mostyn and Watkins (1976) described one patient with a fixed rate and Bennett et al (1976) a further two. We examined the heart rate patterns over 24 hours in 61 diabetics using ambulatory ECG monitoring (Ewing et al, 1982). Only one patient conformed to this 'fixed' pattern and even this individual had a variation of 16 beats per minute between maximum and minimum, suggesting that other non-neuronal and extracardiac factors were influencing heart rate slightly. Transplanted hearts also show some heart rate variations in response to exercise.

The 24-h ECG tape analysis also showed that the diabetics generally had faster heart rates during waking hours than normal subjects, while during sleep there was less of the expected slowing with increasing autonomic damage. The abnormal heart rate pattern in these diabetics was not related to age, duration of diabetes or type of treatment. Only one diabetic had a heart rate exceeding 90 beats per minute throughout the 24 h.

Thus a number of minor and asymptomatic heart rate abnormalities result from involvement of the cardiac autonomic nerves, with slight rate increase, an occasional resting tachycardia, and loss of normal nocturnal slowing. With severe damage there is loss of normal minute-to-minute and second-to-second variation in heart rate, resulting in a relatively fixed rate. These changes can also be found in normal subjects during pharmacological autonomic blockade and in subjects with transplanted hearts.

Blood pressure

Postural hypotension, one of the clinical hallmarks of diabetic autonomic neuropathy, was well described many years ago. Arbitrarily it is usually defined as a systolic blood pressure fall of 30 mmHg or more on standing

up. Symptoms are not invariable in patients with postural hypotension. In a series of 73 diabetics with autonomic neuropathy, we found 33 with postural hypotension of whom 10 had no symptoms (Ewing et al, 1980). Postural weakness, faintness, visual impairment and syncope which may mimic hypoglycaemia have all been described as symptoms. They may be worsened by a variety of drugs including hypotensive agents, diuretics, tricyclic antidepressants, phenothiazines, vasodilators and glyceryl trinitrate. Insulin, too, may aggravate postural hypotension (Page and Watkins, 1976; Palmer et al, 1977) possibly by a direct vasodilator effect on peripheral blood vessels (Takata et al, 1985). Masking of postural hypotension can occur with fluid retention in association with congestive cardiac failure or the nephrotic syndrome (Campbell et al, 1976a).

Venous pooling in the legs leading to a fall of cardiac output and arterial blood pressure is the normal consequence of standing up. Reflex vasoconstriction and cardiac acceleration then occur to restore the blood pressure. In diabetics, failure to increase systemic vascular resistance by vasoconstriction, particularly in the splanchnic area but also in the subcutaneous tissues, is mainly responsible for postural hypotension (Hilsted, 1982). This is probably due to damaged sympathetic postganglionic innervation of resistance vessels with loss of reflex vasoconstriction (Bennett, 1983).

The small changes in blood pressure during graded bicycle exercise in diabetics with postural hypotension contrast with the rises seen in normal subjects and diabetics with normal cardiovascular reflexes and also suggest impairment of splanchnic vasoconstriction. As cardiac output during exercise in these subjects is also lower this suggests additional cardiac contractility abnormalities either due to a diabetic 'cardiopathy' or cardiac sympathetic nerve damage (Hilsted, 1982).

Normal postural blood pressure control is complex and other physiological mechanisms contribute in addition to vasoconstriction. Diminished catecholamine responsiveness in diabetics with autonomic neuropathy is well recognized. A subgroup of patients has also been described who have increased catecholamine responses, with a diminished intravascular volume rather than a neuronal defect (Tohmeh et al, 1979). Some (Christlieb and Bratten, 1974; Campbell et al, 1976b; Fernandez-Cruz et al, 1981), but not all (Hilsted, 1982), authors have also reported diminished renin responses on standing. Vasopressin responses (Zerbe et al, 1983; Grimaldi et al, 1985) and sodium homeostasis (Bell et al, 1985) are currently being studied.

Treatment of postural hypotension is only necessary if symptoms occur. Mild symptoms during the day can be treated by raising the bed head at night and thereby altering volume homeostasis. This is sometimes sufficient to relieve symptoms without resort to drugs. The drug usually employed in those with more marked symptoms is fludrocortisone, which probably acts directly on peripheral blood vessels and blood volume (Campbell et al, 1975, 1976a). Fludrocortisone is sometimes ineffective and other drugs tried include pindolol (Boesen et al, 1982), metoclopramide either alone or in combination with flurbiprofen (Beretta-Piccoli and

Weidmann, 1982), and a combination of H_1 and H_2 receptor antagonist therapy with diphenhydramine and cimetidine (Stacpoole and Robertson, 1982). The action of these drugs is not altogether clear but may be due to an increase in plasma volume or alternatively a direct vasoconstrictor effect. Anti-gravity suits and elastic tights have previously been used to prevent postural symptoms but these cumbersome methods are probably no longer necessary.

Gastrointestinal disorders

Diabetic autonomic neuropathy can involve the whole of the gut and several reviews have recently been published (Taub et al, 1979; Atkinson and Hosking, 1983; Feldman and Schiller, 1983). Damage to efferent autonomic nerves leads to hypotonia and poor contraction of the smooth muscle of the gut. Both sympathetic and parasympathetic nerve involvement occurs (Camilleri and Malagelada, 1984) but sensory denervation and its possible effects on reflex activity and awareness of symptoms have not been fully investigated. Studies of gastric motility suggest that both increased sympathetic and decreased parasympathetic input are involved (Feldman et al, 1979). However, oesophageal (Hollis et al, 1977), small intestinal (Drewes, 1971) and colonic (Battle et al, 1980) small muscle appear to be able to respond when adequately stimulated even when denervated. Gastrointestinal symptoms are often non-specific, fluctuating and intermittent. In asymptomatic patients radiological abnormalities and motility disturbances can often be found if looked for.

Oesophagus

Symptoms relating to the oesophagus are uncommon. Occasionally dysphagia, retrosternal discomfort and heartburn occur in diabetics with autonomic neuropathy. Despite the lack of symptoms, motility disturbances are well recognized (Figure 2) (Hollis et al, 1977; Channer et al, 1985; Maddern et al, 1985). Radiology may demonstrate mild dilatation, reduced primary peristaltic pressure waves, tertiary contractions and prolonged transit time (Forgacs et al, 1979). Diminished pharyngeal and oesophageal peristalsis after swallowing and reduced tone of the lower sphincter can be found using manometric techniques (Taub et al, 1979; Atkinson and Hosking, 1983). Multipeaked oesophageal peristaltic pressure waves have been described in diabetics with neuropathy (Loo et al, 1985). These alterations in motility are similar to those following surgical vagotomy. In diabetics with autonomic neuropathy, asymptomatic oesophageal dysfunction measured with a scintiscanning technique correlated with cardiovascular reflex abnormalities (Channer et al, 1985). If heartburn or dysphagia is troublesome, some relief may be obtained with domperidone although no objective improvement of solid emptying was found with this drug (Maddern et al, 1985).

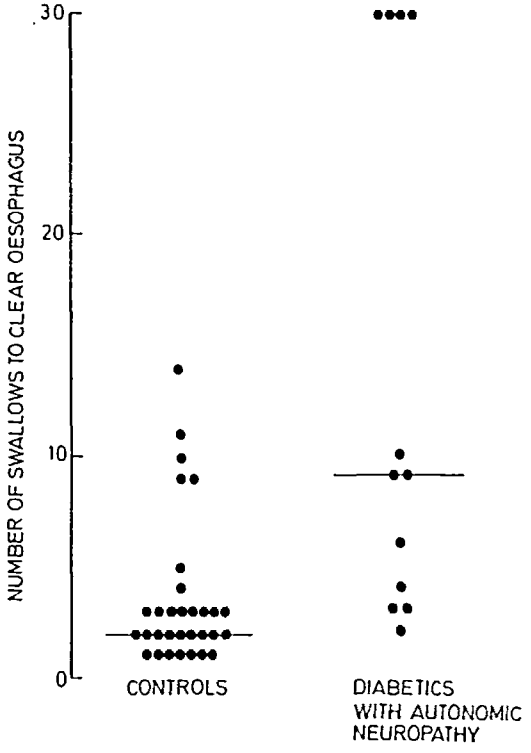

Figure 2. Oesophageal emptying of solids, measured by a scintiscanning technique, in 31 normal subjects and 12 diabetics with autonomic neuropathy. The solid lines indicate the median values for each group. From Maddern et al (1985), with permission.

Stomach

Delayed gastric emptying without symptoms is not uncommon in diabetic autonomic neuropathy. Kassander (1958) found one-fifth of asymptomatic patients had gastric retention demonstrated by radiology and he suggested the term 'gastroparesis diabeticorum' to describe the picture. The symptoms have been well reviewed (Taub et al, 1979; Atkinson and Hosking, 1983; Feldman and Schiller, 1983) and are often ill defined with anorexia and epigastric fullness during or after eating. A gastric splash may sometimes be elicited. Occasionally gastroparesis becomes intractable with persistent nausea and vomiting. Weight loss may be a feature, while control of diabetes may worsen with hypoglycaemic episodes owing to a mismatch between carbohydrate absorption and insulin action.

Increased fasting residue, dilatation, decreased or absent peristalsis, a patulous pylorus, delayed emptying of contrast and an atonic duodenal bulb can all be seen on barium meal (Taub et al, 1979) and are similar to the picture following truncal vagotomy. Normal liquid emptying but slow emptying of solids is usually demonstrated with isotopic gastric scanning (Feldman and Schiller, 1983; Loo et al, 1984; Wright et al, 1985). Impaired

gastric accommodation to distension has also been reported (Oliveira et al, 1984). Vagally mediated gastric acid secretion in response to insulin-induced hypoglycaemia (Hosking et al, 1975) and sham feeding (Feldman et al, 1979; Buysschaert et al, 1985) is reduced in diabetics both with and without gastric symptoms. An enhanced gastrin response in diabetics with abnormal cardiovascular reflexes has also been shown (Kanatsuka et al, 1984). Gut motility studies have suggested that the sympathetic nerve supply is also affected (Feldman et al, 1979; Camilleri and Malagelada, 1984).

Metoclopramide, a dopamine antagonist which increases gastric tone and amplitude of contraction (Figures 3 and 4) and also acts centrally with an anti-emetic effect, often gives symptomatic relief (Snape et al, 1982; McCallum et al, 1983; Achem-Karam et al, 1985). Its use may be limited by side effects, and loss of its gastrokinetic properties may result from chronic administration (Schade et al, 1985). Another effective drug is domperidone, which is also a potent peripheral dopamine antagonist but lacks cholinergic activity (Horowitz et al, 1985). For more intractable symptoms not responding to drug treatment surgical gastric drainage has occasionally been undertaken (Guy et al, 1984).

Gall bladder

While enlarged and poorly contracting gall bladders have been observed in diabetics with autonomic neuropathy no symptoms have been described (Clarke et al, 1979). In a study using ultrasonography impaired gall bladder contraction following stimulation was the more consistent finding with enlargement of the gall bladder being seen less frequently (Marumo et al, 1982).

Small intestine

The characteristic episodic nocturnal diarrhoea of autonomic neuropathy has been well described and although troublesome, there is usually no associated weight loss or malabsorption. Diagnosis has to be made by exclusion of other causes of diarrhoea. The pathophysiology of the condition is still not clearly understood (Taub et al, 1979; Atkinson and Hosking, 1983; Feldman and Schiller, 1983). Proximal small intestinal motility disturbances (Figures 3 and 4) involving both sympathetic and parasympathetic innervation have been described in diabetics with gastroparesis (Camilleri and Malagelada, 1984; Achem-Karam et al, 1985). Transit time through the small intestine is decreased in between bouts of diarrhoea, and fits the pattern of decreased peristalsis elsewhere in the gut (Scarpello et al, 1976). In some patients excessive bacterial growth occurs following small intestinal stasis (Taub et al, 1979; Feldman and Schiller, 1983). Bile salt malabsorption has been suggested as a further possible mechanism (Atkinson and Hosking, 1983). More recently α_2-adrenergic receptors on small intestinal enterocytes have been found to be denervated in experimental diabetes. As they are thought to be responsible for

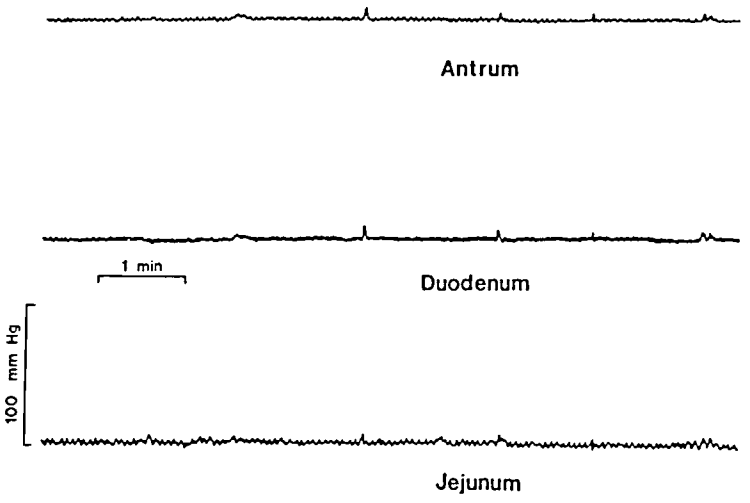

Figure 3. Gastrointestinal motor activity in a diabetic with gastroparesis. There is absence of phasic motor activity during the interdigestive period. From Achem-Karem et al (1985), with permission. Copyright 1985 by the American Gastroenterological Society.

electrolyte and fluid absorption their denervation might be a possible mechanism for diabetic diarrhoea (Chang et al, 1983; Fedorak et al, 1985).

Treatment of diabetic diarrhoea has traditionally been with tetracycline and other broad-spectrum antibiotics. About half of the subjects treated usually respond. In those who are unresponsive, specific α_2-adrenergic agonists have been proposed, for example, clonidine (Fedorak et al, 1985). Metoclopramide, too, is occasionally of benefit in diabetic diarrhoea.

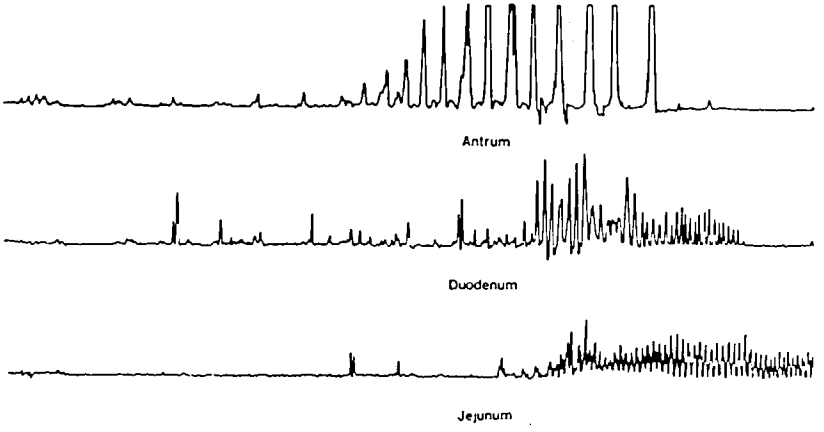

Figure 4. Metoclopramide-induced interdigestive migrating motor complexes in a diabetic with gastroparesis, 10 minutes after intravenous drug administration. From Achem-Karam et al (1985), with permission. Copyright 1985 by the American Gastroenterological Association.

Large intestine

Constipation is a relatively common symptom of autonomic neuropathy. Although its precise pathogenesis is not understood it is probably a result of colonic atony (Feldman and Schiller, 1983). Occasionally a megacolon can be demonstrated by radiology (Clarke et al, 1979). Diabetics with severe constipation have an absent gastrocolonic response to feeding which can be assessed by measuring distal colonic myoelectrical and motor activity (Battle et al, 1980). Loss of anal sphincter control occasionally occurs, particularly at night and during bouts of diarrhoea (Schiller et al, 1982). Intravenous metoclopramide improves the colonic responses suggesting that the hypotonic muscle, despite denervation, can still respond to exogenous stimulation. Domperidone (Gordon and Joseph, 1981) and metoclopramide (Snape et al, 1982) have both been used to treat constipation.

Bladder dysfunction

Bladder dysfunction is a well recognized feature of diabetic autonomic neuropathy although its prevalence is unknown as patients are often asymptomatic (Frimodt-Moller, 1978, 1980; Clarke et al, 1979; Bradley, 1980). Characteristically there is an enlarged bladder and residual urine volume after micturition. Cystometric and urodynamic studies have demonstrated that a hypotonic, insensitive, large capacity bladder is common with little or no pressure response to filling. These features are consistent with damaged afferent sensory pathways causing diminished appreciation of bladder filling and decreased reflex detrusor activity. With progression of the neuropathy, and possibly also because of persistent overdistension of the bladder wall, decreased motor activity of the detrusor muscle occurs with increasing volumes of residual urine.

The patient often remains asymptomatic in the early stages despite demonstrable bladder abnormalities. Symptoms are usually insidious and slowly progressive (Frimodt-Moller, 1978; Clarke et al, 1979). Lengthened intervals between micturition and an increased volume of the first morning urine specimen may result from loss of bladder sensation and increased bladder capacity. With more extensive involvement a weakened and prolonged urinary stream occurs with straining and post-micturition dribbling. Impotence is found in most male diabetics with bladder dysfunction. In those with florid autonomic neuropathy there may be a large residual urinary volume with a palpable bladder and overflow incontinence. Occasionally acute retention occurs, particularly if such patients are admitted to hospital or immobilized, and then catheterization is required. Urinary tract infection is also a consequence of bladder stasis and this in turn may accelerate deterioration of renal function (Clarke et al, 1979). Renal transplantation is contraindicated with severe neurogenic bladder dysfunction as there is a considerable risk of infecting the graft.

Diabetics with neurogenic bladder involvement should be encouraged to void three to four hourly during the day using manual suprapubic pressure. Parasympathomomimetic drug treatment, given to improve detrusor

contraction, is usually unhelpful. Chemotherapy, sometimes long-term, may be required for urinary tract infection. Where increasing residual urine is becoming a problem bladder neck resection can be considered (Frimodt-Moller, 1978).

Sweating problems

Diminished or absent sweating of the feet and in more severe cases the whole leg and lower trunk is well recognized clinically as a feature of diabetic autonomic neuropathy (Clarke et al, 1979). Increased sweating over the upper part of the body is also common. Drenching sweats over the head, upper chest and back occur particularly during warm weather, exercise and while in bed. These sweats are sometimes misdiagnosed as hypoglycaemic attacks. It is possible that the increased sweating is compensating for the diminished heat dissipation over the lower part of the body. Gustatory sweating, noted by Aagenaes (1962) and later detailed by Watkins (1973), is a further abnormal sweating pattern seen in diabetic autonomic neuropathy. Profuse sweating occurs within minutes of eating and is provoked by certain foods. It usually starts on the forehead and spreads to the face, scalp and neck. The mechanism is uncertain but it has been suggested that aberrant nerve regeneration occurs within territory supplied by the superior cervical ganglion (Watkins, 1973).

Anticholinergic drugs such as propantheline hydrobromide or poldine methylsulphate may be helpful if sweating is profuse. Side effects such as urinary retention may limit their use. A prophylactic dose of either drug taken before a meal is often effective in preventing socially embarrassing gustatory sweating.

Hypoglycaemic susceptibility

When blood glucose falls progressively there is normally an initial vagal response with an early bradycardia and mild hypotension which is asymptomatic followed later by easily recognizable symptoms due to adrenergic stimulation. Some diabetics with autonomic neuropathy lose their usual adrenergic early warning symptoms, so-called 'hypoglycaemic unawareness', and may suddenly become unconscious as they develop hypoglycaemia (Sussman et al, 1963). Also, because of inadequate counter-regulatory hormonal responses mediated by both vagal (Gerich et al, 1973; Campbell et al, 1977; Maher et al, 1977) and sympathetic (Cryer, 1981; Bolli et al, 1983; White et al, 1983) nerves there may be a steeper fall of blood glucose than usual contributing to a more rapid loss of consciousness.

Postural hypotension giving rise to sudden faintness or loss of consciousness without warning may sometimes cause diagnostic confusion by being mistaken for hypoglycaemic unawareness. Delayed gastric emptying can also contribute to more severe hypoglycaemia (Campbell and Conway, 1960). The patient with autonomic neuropathy is thus more prone to severe hypoglycaemia and should be encouraged to aim for less stringent blood glucose control.

Pupillary disorders

Abnormal pupillary responses caused by autonomic damage in diabetics have been well recognized for some years (Jordan, 1936; Rundles, 1945). Both sympathetic innervation with dysfunction of the dilatator pupillae, and parasympathetic pathways with dysfunction of the sphincter pupillae are involved. Clinically, the main abnormalities are a reduction in the pupil diameter at rest (Hreidarsson, 1982) and loss of spontaneous oscillations ('hippus') of the pupil (Smith et al, 1978). Sympathetic denervation probably causes small pupils. This can make dilatation of the pupil difficult in the clinic if atropine-like drugs are used. These act by blocking the parasympathetic supply to the sphincter pupillae, and the tone of the sympathetically innervated dilator fibres of the iris may then not be sufficient to dilate the pupil adequately. A common and early sign of diabetic autonomic neuropathy is failure of the pupil to dilate quickly in the dark (Smith et al, 1978; Pfeifer et al, 1982a, 1984).

Respiratory changes

Diabetic autonomic neuropathy has not been associated with any specific clinical respiratory abnormality. Impaired bronchomotor function has been detected by Douglas et al (1981) who found diminished bronchodilatation following inhalation of an atropine-like drug, ipratropium bromide, and by Heaton et al (1984) who showed no fall in specific airways conduction after a provocation test with cold air.

Studies of the control of breathing have produced conflicting results. Ventilatory responses to both transient hypoxia (Calverley et al, 1982) and to progressive hypoxia (Soler and Eagleton, 1982) were similar to controls; whereas one-quarter of diabetics studied by Williams et al, (1984) had abnormalities, and Montserrat et al (1985) found diminished responses to transient hypoxia in a group of 20 diabetics with autonomic neuropathy. The responses to hypercapnia have been found to be normal in two studies (Sakuta et al, 1982; Soler and Eagleton, 1982) and abnormal in three studies (Homma et al, 1981; Williams et al, 1984; Montserrat et al, 1985). Accordingly differing conclusions have been reached regarding the involvement of peripheral chemoreceptor and central ventilatory control mechanisms in diabetic autonomic neuropathy. A recent case report (Kageyama et al, 1985) described recurrent respiratory arrests in a diabetic in whom ventilatory responses to hypercapnia were decreased, indicating impaired central chemosensitivity. There was also evidence in this patient of lack of hypoxic drive mediated by peripheral chemoreceptors.

Apparent differences also appear in studies of sleep apnoea. Two studies (Guilleminault et al, 1981; Rees et al, 1981) have suggested that breathing abnormalities are common in diabetic autonomic neuropathy during sleep, but no account was taken of normal variability or the effects of age. In a third sleep study five diabetics, all insulin dependent and all but one with neuropathy, had abnormal sleep-related patterns, out of a mixed group of 19 patients studied (Mondini and Guilleminault, 1985). By contrast, a

carefully controlled study (Catterall et al, 1984) concluded that diabetic patients with severe autonomic neuropathy have normal breathing patterns and oxygenation during sleep and that it is unlikely that sleep apnoea causes the sudden and unexpected deaths in patients with autonomic neuropathy.

Neuroendocrine abnormalities

Deranged release and utilization of gastrointestinal hormones is being recognized with increasing frequency in diabetics with autonomic damage (Vinik and Glowniak, 1982). Modulation of these peptides requires an intact autonomic nervous system, and although still relatively unexplored, it now appears that abnormal secretion may be in part responsible for disordered gastrointestinal motility. Release of pancreatic polypeptide (PP) is partly under vagal control. In diabetics with autonomic damage, the PP responses to hypoglycaemia (Krarup et al, 1979; Levitt et al, 1980a; Hilsted, 1982), sham feeding (Figure 5) (Buysschaert et al, 1985) and to a meal (Ewing et al, 1986) are significantly diminished. The normal exercise response of PP is also abolished in patients with autonomic neuropathy (Hilsted, 1982).

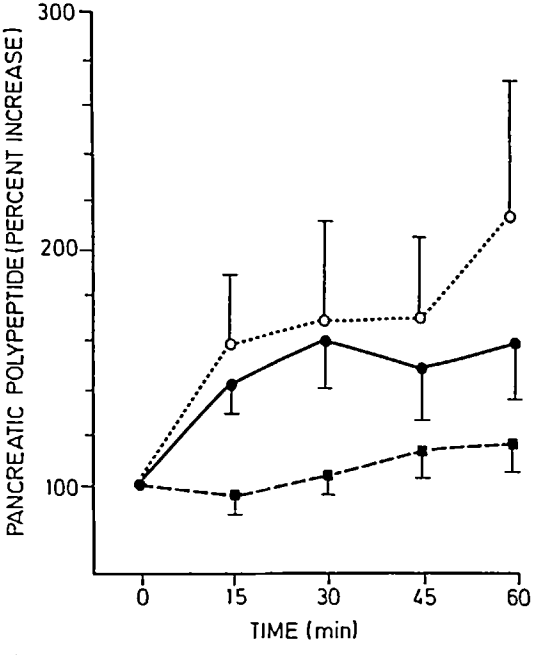

Figure 5. Mean (± SEM) pancreatic polypeptide responses to sham feeding in 8 normal subjects (●) 7 diabetics without (○) and 9 with (■) autonomic neuropathy. The results are expressed as percentages, with the value at time 0 considered as 100%. From Buysschaert et al (1985); reproduced with permission from the American Diabetes Association, Inc.

The exact neural mediation of somatostatin release is not known but vagal pathways may be involved (Glaser et al, 1981). The regulation of glucagon secretion is also partly under autonomic control (Bloom et al, 1974; Gerich et al, 1974). In diabetic neuropathy both somatostatin (Hilsted, 1982; Fernandez-Castaner et al, 1985a) and glucagon (Maher et al, 1977; Levitt et al, 1979; Hilsted, 1982) responses to hypoglycaemia have been reported as reduced although the role of autonomic nerves in glucagon release is currently disputed (Horie et al, 1984; Fernandez-Castaner et al, 1985a; White et al, 1985). The physiological role of gastric inhibitory peptide after a meal is uncertain, but its secretion has been shown to be reduced in non-insulin dependent diabetics with autonomic neuropathy (Levitt et al, 1980b). Whether this is secondary to delayed gastric emptying or a consequence of autonomic nerve damage is unclear.

Motilin release, too, is abnormal in diabetics with autonomic neuropathy (Funakoshi et al, 1982; Achem-Karem et al, 1985). This hormone may have a key regulatory role in gastric emptying and intestinal motility and is probably modulated primarily by vagal fibres (Funakoshi et al, 1982). High fasting and postprandial gastrin concentrations have been found in diabetics both with nausea and vomiting (Feldman et al, 1979). and with cardiac vagal denervation (Sasuki et al, 1983; Kanatsuka et al, 1984) although gastrin secretion is probably only partly under autonomic control (Vinik and Glowniak, 1982). The increased responses may be because normal vagal inhibition of gastrin secreting cells is lost (Sasuki et al, 1983).

While therefore the control of these gastrointestinal hormones is influenced by many factors, autonomic modulation partly governs the secretion of PP, glucagon, somatostatin, motilin, gastric inhibitory peptide and possibly gastrin. These peptides, in turn, play a regulatory function in gastrointestinal motility and digestion and absorption of nutrients. Their derangement may be in part responsible for delayed gastric emptying, diarrhoea and constipation. There is, however, much work still needed in this area in order to unravel the pathophysiology.

Abnormal catecholamine kinetics represent another neuroendocrine consequence of diabetic autonomic neuropathy. Reduced noradrenaline responses have been found during standing (Cryer et al, 1978; Caviezel et al, 1982), exercise (Hilsted, 1982), and after intravenous edrophonium (Figure 6) (Leveston et al, 1979; Ewing et al, 1986), but not following hypoglycaemia (Hilsted, 1982; White et al, 1985) although this has recently been challenged (Horie et al, 1984; Fernandez-Castaner, 1985a). Two response patterns, a 'hypoadrenergic' with diminished noradrenaline levels due to sympathetic damage, and a 'hyperadrenergic' resulting from a diminished intravascular volume have been described by one group of investigators (Cryer et al, 1978; Tohmeh et al, 1979). Production and turnover of noradrenaline also appear to be decreased in diabetics with autonomic neuropathy (Hoeldtke and Cilmi, 1984). Hypoglycaemia blunts adrenaline responses (Hilsted, 1982; Hoeldtke et al, 1982; Horie et al, 1984; Fernandez-Castaner, 1985a; White et al, 1985), but hydroxylation of dopamine seems to be normal (Hoeldtke and Stetson, 1981). Further

studies of catecholamine turnover and kinetics may answer some of the still unresolved questions about catecholamine metabolism in diabetic autonomic neuropathy.

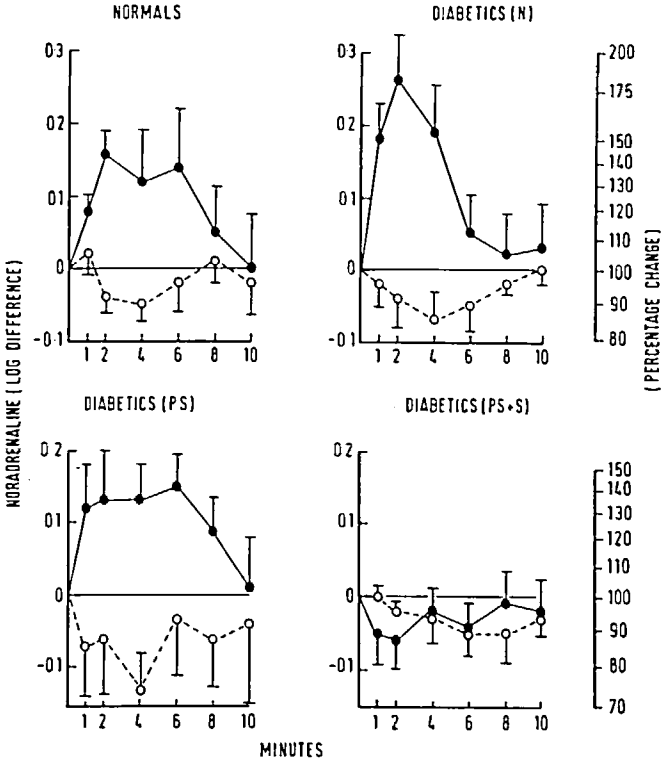

Figure 6. Group mean (± SEM) plasma noradrenaline responses following a mixed meal (○) or intravenous edrophonium (●) in 6 normal subjects, 7 diabetics with normal cardiovascular reflexes (N), 4 diabetics with cardiac parasympathetic damage (PS), and 5 with combined parasympathetic and sympathetic damage (PS + S). From Ewing et al (1986), with permission.

NATURAL HISTORY

Prevalence

The frequency of autonomic neuropathy in diabetes is difficult to ascertain reliably. Between 17 and 40% of consecutive or randomly selected adult diabetics have abnormal cardiovascular autonomic function tests according to most large series (Ewing, 1984). Thirty-one per cent of a group of teenage diabetics (Young et al, 1983) and 15% of a group of younger diabetic children (Mitchell et al, 1983) had abnormal cardiovascular reflexes.

The prevalence of symptoms of autonomic neuropathy in a diabetic clinic population has not been satisfactorily established, although several studies have considered selected groups of diabetics. In the earliest Rundles (1945) found constipation to be the most frequent symptom (42%) in 150 diabetics with neuropathy. Bladder problems (26%), diarrhoea (22%) and ankle oedema (21%) were slightly less frequent, while decreased sweating in the feet (10%), increased nocturnal sweating (5%) and postural hypotension (6%) were least common. Martin (1953) by contrast, found constipation to be rare and sweating problems to be common. He also noted 6% with Charcot arthropathy and 9% with pupillary abnormalities. Aagenaes (1962) found 7% of 120 diabetics with neuropathy to have hypoglycaemic unawareness and two subjects with gustatory sweating. Subsequently Fernandez-Castaner et al (1985b) found 63 (29%) of 214 unselected diabetics with symptoms suggestive of autonomic damage, and Canal et al (1978) found 4% of consecutive insulin dependent diabetics had symptoms in the first year of diabetes, rising to 28% in those of more than five years' duration. Krolewski et al (1985) in a large prospective study from the Joslin Clinic found the overall prevalence of postural hypotension to be around 12% and higher in older diabetics and younger diabetics of long duration. Impotence is relatively common according to most series of diabetic males studied, but this does not reveal what proportion is due to autonomic damage and what due to other causes. Other features of autonomic neuropathy in males are almost invariably accompanied by impotence (Ewing et al, 1980). Autonomic symptoms are uncommon in young diabetics although there have been occasional case reports of severe symptomatic autonomic neuropathy (Lloyd-Mostyn and Watkins, 1976; Blum et al, 1980). None of the teenage subjects studied by Young et al (1983) had any symptoms referable to the autonomic nervous system. As might be expected, the proportion of symptomatic subjects increases with longer durations of diabetes (Canal et al, 1978).

Physiology

All grades of severity of physiological autonomic abnormalities can be detected in diabetics from very minimal to extensive involvement. In a series of physiological studies on cardiovascular reflexes, Bennett and colleagues found that diabetics had several different response patterns. Some exhibited no damage or slight vasoconstrictor abnormalities and variable cardiac vagal damage, some had partial vasoconstrictor abnormalities and marked vagal impairment, a third group had both complete vasoconstrictor and vagal damage, while another group additionally had impaired sympathetic drive (Bennett et al, 1975; Bennett, 1983). Cardiac parasympathetic function can be impaired without detectable sympathetic damage, but not the reverse (Lloyd-Mostyn and Watkins, 1975; Wieling et al, 1983). There appears to be a greater prevalence of parasympathetic as compared with sympathetic impairment in diabetic autonomic neuropathy when assessed mainly by cardiovascular reflex tests (Gluck et al, 1979).

Prospective follow-up of diabetics has shown that heart rate first increases and later decreases as first parasympathetic and then sympathetic damage occurs (Ewing et al, 1981).

Different patterns of cardiovascular damage can thus be detected. Cardiac parasympathetic fibres are involved more extensively and earlier than cardiovascular sympathetic nerves. Further evidence to support this view comes from our own experience of cardiovascular reflex testing. In 543 diabetics heart rate tests were abnormal more commonly and earlier than blood pressure tests (Ewing et al, 1985). Of 237 diabetics whose tests were repeated three months or more apart, about three-quarters (71%) had unchanged tests on their subsequent visit and one-quarter (26%) had deteriorated. Only a very few (3%) improved. Other workers have also noticed deteriorating cardiovascular test results with time in some of their diabetic subjects (Bennett et al, 1980; Mackay et al, 1980; Sundkvist and Lilja, 1985).

As heart rate based tests are much more sensitive than blood pressure based tests and therefore more likely to show abnormalities, the early parasympathetic involvement might be more apparent than real. However, the detailed physiological studies referred to above show unequivocally that cardiac vagal fibres are damaged earlier than sympathetic fibres, possibly because they are longer and therefore more liable to damage (Ewing et al, 1981). Computer simulation models of random nerve damage where longer fibres were affected first also support this view (Waxman, 1980).

Outside the cardiovascular system studies of the patterns of autonomic damage are still in their infancy. A temporal sequence of damage has been noted by Guy et al (1985), who observed that thermal abnormalities in the feet occur before abnormal cardiovascular reflexes, which in turn precede abnormal thermal tests in the hand. Sweat tests in the feet, and bladder function (Beylot et al, 1982) may also be abnormal in the presence of normal heart rate tests.

Abnormal sympathetic function can be found in mild autonomic neuropathy if a sensitive enough method is used. Hilsted (1982) found that the catecholamine exercise response was reduced in diabetics with mild autonomic neuropathy (heart rate variation changes only), suggesting early sympathetic damage, while Pfeifer et al (1984) found that iris sympathetic function was altered shortly after diagnosis of diabetes, and concurrently with heart rate variation abnormalities. This implies, therefore, that the pattern and progression of cardiovascular autonomic damage in diabetes may not necessarily be reflected in other organs, and that factors such as fibre length, end organ responsiveness, and sensitivity of particular tests all need to be taken into account when interpreting abnormal autonomic function in diabetics.

Relationship of cardiovascular reflexes and symptoms

The relationship between abnormal cardiovascular reflexes and symptoms suggestive of autonomic damage has been addressed in two studies. We

found that in a prospective five-year study of 73 diabetics, 30 males presented with impotence alone, while the other 43 (32 males and 11 females) presented with one or more other symptoms, namely postural hypotension, intermittent diarrhoea, hypoglycaemic unawareness, sweating abnormalities and gastric fullness (Ewing et al, 1980). Most subjects with impotence alone had normal cardiovascular reflexes while the majority with other symptoms had abnormal tests. Mackay et al (1980) found that 54 of 64 diabetics with autonomic symptoms had abnormal heart rate variation in contrast to only 10 of 143 with no suggestive symptoms of neuropathy.

Progress

The progress of autonomic symptoms in diabetics followed for three to six years has been reported in four studies, three briefly (Bischoff, 1980; Mackay et al, 1980; Sundkvist and Lilja, 1985) and one in more detail (Ewing et al, 1980).

We found that in some men whose only symptom was impotence, cardiovascular reflex tests could remain normal over five years; in others who had impotence alone associated with normal tests, deterioration and development of other autonomic features was observed. Out of 73 diabetics, eight developed postural hypotension during follow-up, five decreased sweating, three diarrhoea, seven gastric symptoms and three hypoglycaemic unawareness. The appearance of these new symptoms coincided with deterioration in their cardiovascular reflex tests. The development of new gastric symptoms and hypoglycaemic unawareness carried a particularly ominous significance. Zitomer et al (1968) previously found that 12 of 35 patients with diabetic gastropathy died within three years during a restrospective three-year study, although no objective assessment of autonomic involvement had been made. Symptomatic postural hypotension, too, whether present initially or developing later, was also associated with a poor prognosis and more than half of these patients died during follow-up. Intermittent nocturnal diarrhoea, on its own, like impotence, was unreliable as a pointer to autonomic damage. Although impotence is difficult to evaluate, it is sometimes the earliest symptom of autonomic neuropathy (Ewing et al, 1980; McCulloch et al, 1984).

A possible sequence of autonomic abnormalities can therefore be proposed. Thermoregulatory function and sweating may be impaired first in the feet, followed by impotence and bladder problems; cardiovascular reflex abnormalities then appear, and finally the late severe symptomatic manifestations of upper body sweating disturbance, hypoglycaemic unawareness, postural hypotension and gastric problems. These latter symptoms carry with them a poor prognosis (see below). No evidence is available about the place of intermittent diarrhoea in this sequence of events. It remains uncertain whether autonomic neuropathy progresses inevitably through these various stages, or whether many diabetics have an 'arrested development' showing only a few of the early features with no suggestion of progressive deterioration.

Prognosis

Symptomatic autonomic neuropathy carries a poor prognosis. Half of the diabetics we followed with abnormal tests and autonomic symptoms were dead within two and a half years (Figure 7) (Ewing et al, 1980). Those with the most abnormal tests had the highest mortality (Clarke and Ewing, 1982). Watkins and Mackay (1980), who noted deaths in 17 of 64 symptomatic patients, and Sala et al (1983), who noted 10 deaths among 41 diabetics with cardiovascular autonomic neuropathy, have also reported a similar high mortality within five years. Hasslacher and Bassler (1983), following up 16 diabetics with cardiac autonomic damage for five years, found the mortality was between two and three times higher than that of a control group.

In our own series (Ewing et al, 1980) and in that of Watkins and Mackay (1980) approximately half the deaths were attributable to renal failure. Some sudden and unexpected deaths for which no cause could be found were described in both these studies and in the large prospective series of Sala et al (1983). Four possible explanations have been put forward. The first is that diabetics with damaged autonomic pathways do not respond normally to hypoxia: this is based on the observation of cardio-respiratory arrests in young diabetics with severe autonomic neuropathy occurring in certain circumstances, including chest infections or at the time

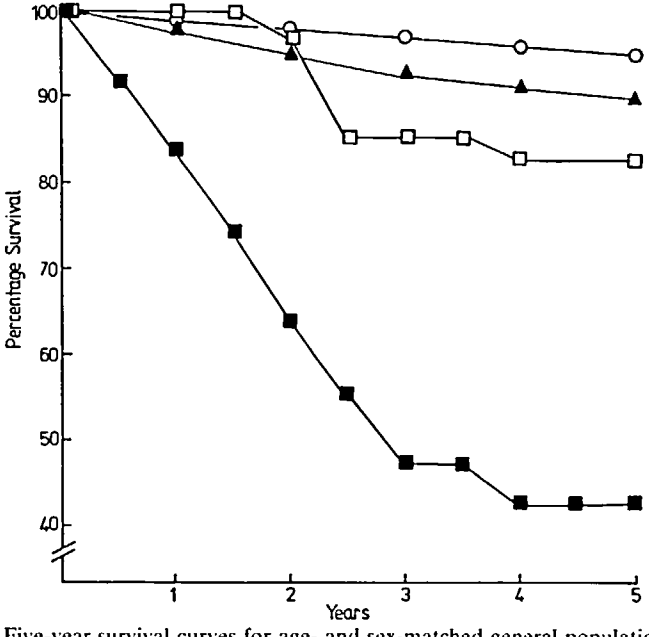

Figure 7. Five-year survival curves for age- and sex-matched general population (○), age- and sex-matched diabetic population (▲), 33 diabetics with normal (□) and 40 diabetics with abnormal (■) autonomic function tests. From Ewing et al (1980), with permission.

of surgery (Page and Watkins, 1978). Subsequently there have been a number of case reports (Garcia-Bunuel, 1978; Pont et al, 1978; Srinivasan and Sanders, 1978; Kageyama et al, 1985). There is, however, no clear evidence to support this suggestion as variable respiratory responses in diabetics with autonomic neuropathy have been described (see p 873). Cardiac arrhythmias might provide a second explanation for these unexpected deaths but diabetics are not more prone to arrhythmias during 24-h ECG monitoring than normal subjects (Ewing et al, 1982). The third possibility is sleep apnoea, but again diabetics do not appear to have abnormal breathing patterns during sleep (Catterall et al, 1984). The final possibility is that of some still unknown reflex, which fails to function under certain conditions and causes unexpected death. Any diabetic with autonomic neuropathy is a potential anaesthetic risk and particular care needs to be taken during and after surgery, and also during severe respiratory infections, to provide adequate oxygenation and appropriate monitoring.

SUMMARY

Autonomic neuropathy is now well established as a relatively common and significant complication of diabetes mellitus. Its importance has been clarified in recent years during which the extent of autonomic control over all areas of body function has been defined. Using simple cardiovascular reflex tests, autonomic abnormalities can be demonstrated without any corresponding symptoms. The often stated concept of 'patchy' involvement in diabetic autonomic neuropathy should now be rejected as too should the view that autonomic neuropathy is either 'present' or 'absent' based on a single test result. When generalized and predominantly metabolic disturbances, as in diabetes, give rise to impaired nerve function, autonomic as well as somatic components of the nerve are affected. Where damage is severe this leads to the characteristic florid picture of symptomatic autonomic neuropathy with its particularly poor prognosis.

For the physician in a busy clinic, much of the theoretical and experimental basis for autonomic neuropathy may not appear of direct relevance. However, he has now to be aware of the clinical implications of autonomic damage in the diabetic. This may have particular relevance in the care of the diabetic foot (see Chapter 10), the recognition of many of the vague symptoms associated with autonomic damage, the treatment of disabling features such as postural dizziness and nocturnal diarrhoea, and an awareness of the poor prognosis associated with symptomatic autonomic neuropathy. He will also need to be alert to the dangers of general anaesthesia in such patients, and the possibility of sudden unexpected deaths.

Diabetic autonomic neuropathy causes widespread abnormalities, some of which are clinically apparent, some of which can be detected by sensitive tests, and others which have yet to be discovered. Inclusion of the

neuropeptides and other hormones within the compass of autonomic control has opened up a whole new area of investigative interest, with many complex interrelationships which still need to be unravelled. This should lead to better understanding of the pathophysiological processes that cause damage to diabetic nerves. With so much research effort directed towards better glycaemic control and aldose reductase inhibitors (see Chapter 8), it may eventually be possible to reverse or prevent this potentially disabling and lethal complication of diabetes.

REFERENCES

Aagenaes O (1962) *Neurovascular Examinations on the Lower Extremities in Young Diabetics with Special Reference to Autonomic Neuropathy*. Copenhagen: C Hamburgers Bogtrykkeri A/S. 258 pp.

Achem-Karam SR, Funakoshi A, Vinik AI & Owyang C (1985) Plasma motilin concentration and interdigestive migrating motor complex in diabetic gastroparesis: effect of metoclopramide. *Gastroenterology* **88:** 492–499.

Atkinson MJ & Hosking DJ (1983) Gastrointestinal complications of diabetes mellitus. *Clinics in Gastroenterology* **12:** 633–650.

Battle WM, Snape WJ, Alavi A, Cohen S & Braunstein S (1980) Colonic dysfunction in diabetes mellitus. *Gastroenterology* **79:** 1219–1222.

Bell GM, Reid W, Ewing DJ & Clarke BF (1985) Abnormal urinary sodium excretion in diabetics with autonomic neuropathy. *Diabetic Medicine* **2:** 306A.

Bellavere F, Bosello G, Cardone C et al (1985) Evidence of early impairment of parasympathetic reflexes in insulin dependent diabetics without autonomic symptoms. *Diabète et Métabolisme* **11:** 152–156.

Bennett T (1983) Physiological investigation of diabetic autonomic failure. In Bannister R (ed.) *Autonomic Failure. A Textbook of Clinical Disorders of the Autonomic Nervous System*, pp 406–436. Oxford: Oxford University Press.

Bennett T, Hosking DJ & Hampton JR (1975) Cardiovascular control in diabetes mellitus. *British Medical Journal* **ii:** 585–587.

Bennett T, Riggott PA, Hosking DJ & Hampton JR (1976) Twenty-four hour monitoring of heart rate and activity in patients with diabetes mellitus: a comparison with clinic investigations. *British Medical Journal* **i:** 1250–1251.

Bennett T, Hosking DJ & Hampton JR (1980) Cardiovascular responses to graded reductions of central blood volume in normal subjects and in patients with diabetes mellitus. *Clinical Science* **58:** 193–200.

Beretta-Piccoli C & Weidmann P (1982) Metoclopramide alone or combined with flurbiprofen in the treatment of orthostatic hypotension associated with diabetes mellitus. *Klinische Wochenschrift* **60:** 863–865.

Beylot M, Marion D & Noel G (1982) Ultrasonic determination of residual urine in diabetic subjects: relationship to neuropathy and urinary tract infection. *Diabetes Care* **5:** 501–505.

Bischoff A (1980) The natural course of diabetic neuropathy: a follow-up. *Hormone and Metabolic Research Supplement* **9:** 98–100.

Bloom SR, Vaughan NJA & Russell RCG (1974) Vagal control of glucagon release in man. *Lancet* **ii:** 546–549.

Blum I, Barkan A, Kuritzky A, Doron M & Karp M (1980) Cardiac denervation and other multisystem manifestations caused by isolated autonomic neuropathy in a young diabetic patient. *American Journal of the Medical Sciences* **280:** 87–93.

Boesen F, Andersen EB, Kanstrup I-L, Hesse B & Christensen NJ (1982) Treatment of diabetic orthostatic hypotension with Pindolol. *Acta Neurologica Scandinavica* **66:** 386–391.

Bolli G, De Feo P, Compagnucci P et al (1983) Abnormal glucose counterregulation in insulin-dependent diabetes mellitus. Interaction of anti-insulin antibodies and impaired glucagon and epinephrine secretion. *Diabetes* **32:** 134–141.

Bradley WE (1980) Diagnosis of urinary bladder dysfunction in diabetes mellitus. *Annals of Internal Medicine* **92:** 323–326.

Buysschaert M, Donckier J, Dive A, Ketelslegers J-M & Lambert AE (1985) Gastric acid and pancreatic polypeptide responses to sham feeding are impaired in diabetic subjects with autonomic neuropathy. *Diabetes* **34:** 1181–1185.

Calverley PMA, Ewing DJ, Campbell IW et al (1982) Preservation of the hypoxic drive to breathing in diabetic autonomic neuropathy. *Clinical Science* **63:** 17–22.

Camilleri M & Malagelada J-R (1984) Abnormal intestinal motility in diabetics with the gastroparesis syndrome. *European Journal of Clinical Investigation* **14:** 420–427.

Campbell A & Conway H (1960) Gastric retention and hypoglycaemia in diabetes. *Scottish Medical Journal* **5:** 167–168.

Campbell IW, Ewing DJ & Clarke BF (1975) 9-Alpha-fluorohydrocortisone in the treatment of postural hypotension in diabetic autonomic neuropathy. *Diabetes* **24:** 381–384.

Campbell IW, Ewing DJ & Clarke BF (1976a) Therapeutic experience with fludrocortisone in diabetic postural hypotension. *British Medical Journal* **i:** 872–874.

Campbell IW, Ewing DJ, Anderton JL et al (1976b) Plasma renin activity in diabetic autonomic neuropathy. *European Journal of Clinical Investigation* **6:** 381–385.

Campbell IW, Heading RC, Tothill P et al (1977) Gastric emptying in diabetic autonomic neuropathy. *Gut* **18:** 462–467.

Campbell LV, Kraegen EW & Lazarus L (1977) Defective blood glucose counter-regulation in diabetics is a selective form of autonomic neuropathy. *British Medical Journal* **ii:** 1527–1530.

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*, pp 247–255. Amsterdam: Elsevier Biomedical Press.

Catterall JR, Calverley PMA, Ewing DJ et al (1984) Breathing, sleep, and diabetic autonomic neuropathy. *Diabetes* **33:** 1025–1027.

Caviezel F, Picotti GB, Margonato A et al (1982) Plasma adrenaline and noradrenaline concentrations in diabetic patients with and without autonomic neuropathy at rest and during sympathetic stimulation. *Diabetologia* **23:** 19–23.

Chang EB, Bergenstal RM & Field M (1983) Diabetic diarrhea: loss of adrenergic regulation of intestinal fluid and electrolyte transport. *Gastroenterology* **84:** 1121.

Channer KS, Jackson PC, O'Brien I et al (1985) Oesophageal function in diabetes mellitus and its association with autonomic neuropathy. *Diabetic Medicine* **2:** 378–382.

Christensen NJ (1979) Catecholamines in diabetes mellitus. *Diabetologia* **16:** 211–224.

Christlieb AR & Bratten JT (1974) Decreased response of plasma renin activity to orthostasis in diabetic patients with orthostatic hypotension. *Diabetes* **23:** 835–840.

Clarke BF & Ewing DJ (1982) Cardiovascular reflex tests in the natural history of diabetic autonomic neuropathy. *New York State Journal of Medicine* **82:** 903–908.

Clarke BF, Ewing DJ & Campbell IW (1979) Diabetic autonomic neuropathy. *Diabetologia* **17:** 195–212.

Cryer PE (1981) Glucose counter-regulation in man. *Diabetes* **30:** 261–264.

Cryer PE, Silverberg AB, Santiago JV & Shah SD (1978) Plasma catecholamines in diabetes. The syndromes of hypoadrenergic and hyperadrenergic postural hypotension. *American Journal of Medicine* **64:** 407–416.

Douglas NJ, Campbell IW, Ewing DJ, Clarke BF & Flenley DC (1981) Reduced airway vagal tone in diabetic patients with autonomic neuropathy. *Clinical Science* **61:** 581–584.

Drewes VN (1971) Mechanical and electrical activity in the duodenum with and without diarrhoea. *American Journal of Digestive Diseases* **16:** 628–634.

Ewing DJ (1983) Practical bedside investigation of diabetic autonomic failure. In Bannister R (ed.) *Autonomic Failure. A Textbook of Clinical Disorders of the Autonomic Nervous System*, pp 371–405. Oxford: Oxford University Press.

Ewing DJ (1984) Cardiac autonomic neuropathy. In Jarrett RJ (ed.) *Diabetes and Heart Disease*, pp 99–132. Amsterdam: Elsevier Biomedical Press.

Ewing DJ, Campbell IW & Clarke BF (1980) The natural history of diabetic autonomic neuropathy. *Quarterly Journal of Medicine* **49:** 95–108.

Ewing DJ, Campbell IW & Clarke BF (1981) Heart rate changes in diabetes mellitus. *Lancet* **i:** 183–186.

Ewing DJ, Borsey DQ, Travis P et al (1982) Abnormalities of ambulatory 24 hour heart rate in diabetes mellitus. *Diabetes* **32:** 101–105.

Ewing DJ, Neilson JMM & Travis P (1984) New method for assessing cardiac parasympathetic activity using 24 hour electrocardiograms. *British Heart Journal* **52:** 396–402.

Ewing DJ, Martyn CN, Young RJ & Clarke BF (1985) The value of cardiovascular autonomic function tests: 10 years experience in diabetes. *Diabetes Care* **8:** 491–498.

Ewing DJ, Bellavere F, Espi F et al (1986) Correlation of cardiovascular and neuroendocrine tests of autonomic function in diabetes. *Metabolism* **35:** 349–353.

Fedorak RN, Field M & Chang EB (1985) Treatment of diabetic diarrhoea with clonidine. *Annals of Internal Medicine* **102:** 197–199.

Feldman M & Schiller LR (1983) Disorders of gastrointestinal motility associated with diabetes mellitus. *Annals of Internal Medicine* **98:** 378–384.

Feldman M, Corbett DB, Ramsey EJ, Walsh JH & Richardson CT (1979) Abnormal gastric function in long standing insulin-dependent diabetic patients. *Gastroenterology* **77:** 12–17.

Fernandez-Castaner M, Webb S, Levy I et al (1985a) Somatostatin and counterregulatory hormone responses to hypoglycaemia in diabetics with and without autonomic neuropathy. *Diabète et Métabolisme* **11:** 81–86.

Fernandez-Castaner M, Mendola G, Levy I, Gomis R & Figuerola D (1985b) The prevalence and clinical aspects of the cardiovascular autonomous neuropathy in diabetic patients. *Medicina Clinica (Barcelona)* **84:** 215–218.

Fernandez-Cruz A, Noth RH, Lassman MN, Hollis JB & Mulrow PJ (1981) Low plasma renin activity in normotensive patients with diabetes mellitus: relationship to neuropathy. *Hypertension* **3:** 87–92.

Forgacs S, Keri Z, Osvath J & Fabian I (1979) Oesophageal dysfunction in diabetes mellitus. *Acta Diabetologica Latina* **16:** 227–234.

Fraser DM, Campbell IW, Ewing DJ et al (1977) Peripheral and autonomic nerve function in newly diagnosed diabetes mellitus. *Diabetes* **26:** 546–550.

Frimodt-Moller C (1978) Diabetic cystopathy. A review of the urodynamic and clinical features of neurogenic bladder dysfunction in diabetes mellitus. *Danish Medical Bulletin* **25:** 49–60.

Frimodt-Moller C (1980) Diabetic cystopathy: epidemiology and related disorders. *Annals of Internal Medicine* **92:** 318–321.

Funakoshi A, Glowniak J, Owyang C & Vinik AI (1982) Evidence of cholinergic and vagal noncholinergic mechanisms modulating plasma motilin-like immunoreactivity. *Journal of Clinical Endocrinology and Metabolism* **54:** 1129–1134.

Gallanosa AG, Spyker DA & Curnow RT (1981) Diabetes mellitus associated with autonomic and peripheral neuropathy after Vacor rodenticide poisoning: a review. *Clinical Toxicology* **18:** 441–449.

Garcia-Bunuel L (1978) Cardiorespiratory arrest in diabetic autonomic neuropathy. *Lancet* **i:** 935–936.

Gerich JE, Langlois M, Noacco C, Karem JH & Forsham P (1973) Lack of glucagon response to hypoglycaemia in diabetes: evidence of an intrinsic pancreatic alpha cell defect. *Science* **182:** 171–173.

Gerich JE, Langlois M, Naocco C, Schneider V & Forsham PH (1974) Adrenergic modulation of pancreatic glucagon secretion in man. *Journal of Clinical Investigation* **53:** 1441–1446.

Gilbey SG, Sutton RA, Thompson S & Watkins PJ (1985) A new, simple, non-invasive method for assessing gastric emptying and its application in diabetic autonomic neuropathy. *Diabetic Medicine* **2:** 510A.

Glaser B, Vinik AI, Valtysson G & Zoghlin G (1981) Truncal vagotomy abolishes the somatostatin response to insulin-induced hypoglycaemia in man. *Journal of Clinical Endocrinology and Metabolism* **52:** 823–825.

Gluck Z, Boll H, Weidmann P, Flammer J & Ziegler WH (1979) Evaluation of autonomic neuropathy in diabetes mellitus. Comparison of clinical, functional and biochemical parameters. *Klinische Wochenschrift* **57:** 457–466.

Gordon SJ & Joseph RE (1981) Diabetic gastroparesis and colonic dilatation treated with domperidone. *Lancet* **i:** 390.

Grimaldi A, Pruszczynski W, Thervet R & Ardaillou R (1985) Antidiuretic hormone response to volume depletion in diabetic patients with cardiac autonomic dysfunction. *Clinical Science* **68:** 545–552.

Guilleminault C, Briskin JG, Greenfield MS & Silvestri R (1981) The impact of autonomic nervous system dysfunction on breathing during sleep. *Sleep* **4:** 263–278.

Guy RJC, Dawson JL, Garrett JR et al (1984) Diabetic gastroparesis from autonomic neuropathy: surgical considerations and changes in vagus nerve morphology. *Journal of Neurology, Neurosurgery and Psychiatry* **47:** 686–691.

Guy RJC, Clark CA, Malcolm PN & Watkins PJ (1985) Evaluation of thermal and vibration sensation in diabetic neuropathy. *Diabetologia* **28:** 131–137.

Hasslacher C & Bassler G (1983) Prognose der kardialen autonomen Neuropathie bei Diabetikern. *Münchener Medizinische Wochenschrift* **125:** 375–377.

Hayashi M & Ishikawa S (1979) Pharmacology of pupillary responses in diabetics—correlative study of the responses and grade of retinopathy. *Japanese Journal of Ophthalmology* **23:** 65–72.

Heaton RW, Guy RJC, Gray BJ, Watkins PJ & Costello JF (1984) Diminished bronchial reactivity in cold air in diabetic patients with autonomic neuropathy. *British Medical Journal* **289:** 149–151.

Hilsted J (1982) Pathophysiology in diabetic autonomic neuropathy: cardiovascular, hormonal and metabolic studies. *Diabetes* **31:** 730–737.

Hilsted J & Jensen SB (1979) A simple test for autonomic neuropathy in juvenile diabetics. *Acta Medica Scandinavica* **205:** 385–387.

Hoeldtke RD & Stetson PL (1981) Dopamine beta-hydroxylation in diabetes and diabetic autonomic neuropathy. *Biochemical Medicine* **26:** 67–76.

Hoeldtke RD & Cilmi KM (1984) Norepinephrine secretion and production in diabetic autonomic neuropathy. *Journal of Clinical Endocrinology and Metabolism* **59:** 246–252.

Hoeldtke RD, Boden G, Shuman CR & Owen OE (1982) Reduced epinephrine secretion and hypoglycaemia unawareness in diabetic autonomic neuropathy. *Annals of Internal Medicine* **96:** 459–462.

Hollis JB, Castell DO & Braddom RL (1977) Oesophageal function in diabetes mellitus and its relation to peripheral neuropathy. *Gastroenterology* **73:** 1098–1102.

Homma I, Kageyama S, Nagai T et al (1981) Chemosensitivity in patients with diabetic neuropathy. *Clinical Science* **61:** 599–603.

Horie H, Hanafusa T, Matsuyama T et al (1984) Decreased response of epinephrine and norepinephrine to insulin-induced hypoglycaemia in diabetic autonomic neuropathy. *Hormone and Metabolic Research* **16:** 398–401.

Horowitz M, Harding PE, Chatterton BE, Collins PJ & Shearman DJC (1985) Acute and chronic effects of domperidone on gastric emptying in diabetic autonomic neuropathy. *Digestive Diseases and Sciences* **30:** 1–9.

Hosking DJ, Moony F, Stewart IM & Atkinson M (1975) Vagal impairment of gastric secretion in diabetic autonomic neuropathy. *British Medical Journal* **ii:** 588–590.

Hreidarsson AB (1981) Acute reversible autonomic nervous system abnormalities in juvenile insulin-dependent diabetes. A pupillographic study. *Diabetologia* **20:** 475–481.

Hreidarsson AB (1982) Pupil size in insulin-dependent diabetes. Relationship to duration, metabolic control and long-term manifestations. *Diabetes* **31:** 442–448.

Jordan WR (1936) Neuritic manifestations in diabetes mellitus. *Archives of Internal Medicine* **57:** 307–366.

Kageyama S, Sasoh F, Taniguchi I et al (1985) Cardiorespiratory arrest in a patient with advanced diabetic autonomic neuropathy. *Diabetes Research and Clinical Practice* **1:** 243–246.

Kanatsuka A, Osegawa M, An T et al (1984) Augmented gastrin responses in diabetic patients with vagal neuropathy. *Diabetologia* **26:** 449–452.

Kassander P (1958) Asymptomatic gastric retention in diabetics (gastroparesis diabeticorum). *Annals of Internal Medicine* **48:** 797–812.

Kennedy WR, Sakuda M, Sutherland D & Goetz FC (1984) The sweating deficiency in diabetes mellitus: methods of quantitation and clinical correlation. *Neurology (Cleveland)* **34:** 758–763.

Krarup T, Schwartz TW, Hilsted J et al (1979) Impaired response of pancreatic polypeptide to hypoglycaemia: an early sign of autonomic neuropathy in diabetics. *British Medical Journal* **ii**: 1544–1546.

Krolewski AS, Warram JH, Cupples A et al (1985) Hypertension, orthostatic hypotension and the microvascular complications of diabetes. *Journal of Chronic Diseases* **38**: 319–326.

Leveston SA, Shah SD & Cryer PE (1979) Cholinergic stimulation of norepinephrine release in man. Evidence of a sympathetic postganglionic axonal lesion in diabetic adrenergic neuropathy. *Journal of Clinical Investigation* **64**: 374–380.

Levitt NS, Vinik AI, Sive AA, Child P & Jackson WPU (1979) Studies on plasma glucagon concentration in maturity-onset diabetics with autonomic neuropathy. *Diabetes* **28**: 1015–1021.

Levitt NS, Vinik AI, Sive AA, Van Tonder S & Lund A (1980a) Impaired pancreatic polypeptide responses to insulin-induced hypoglycaemia in diabetic autonomic neuropathy. *Journal of Clinical Endocrinology and Metabolism* **50**: 445–449.

Levitt NS, Vinik AI & Child PT (1980b) Glucose-dependent insulin-releasing peptide in noninsulin-dependent maturity-onset diabetes: effects of autonomic neuropathy. *Journal of Clinical Endocrinology and Metabolism* **51**: 254–258.

Lloyd-Mostyn RH & Watkins PJ (1975) Defective innervation of heart in diabetic autonomic neuropathy. *British Medical Journal* **iii**: 15–17.

Lloyd-Mostyn RH & Watkins PJ (1976) Total cardiac denervation in diabetic autonomic neuropathy. *Diabetes* **25**: 748–751.

Loo FD, Palmer DW, Soergel KH, Kalbfleisch JH & Wood CM (1984) Gastric emptying in patients with diabetes mellitus. *Gastroenterology* **86**: 485–494.

Loo FD, Dodds WJ, Soergel KH et al (1985) Multipeaked esophageal peristaltic pressure waves in patients with diabetic neuropathy. *Gastroenterology* **88**: 485–491.

Low PA, Caskey PE, Tuck RR, Fealey RD & Dyck PJ (1983) Quantitative sudomotor axon reflex test in normal and neuropathic subjects. *Annals of Neurology* **14**: 573–580.

McCallum RW, Ricci DA, Rakatansky H et al (1983) A multicentre placebo-controlled clinical trial of oral metoclopramide in diabetic gastroparesis. *Diabetes Care* **6**: 463–467.

McCulloch DK, Young RJ, Prescott RJ, Campbell IW & Clarke BF (1984) The natural history of impotence in diabetic men. *Diabetologia* **26**: 437–440.

Mackay JD, Page MM, Cambridge J & Watkins PJ (1980) Diabetic autonomic neuropathy. The diagnostic value of heart rate monitoring. *Diabetologia* **18**: 471–478.

Maddern GJ, Horowitz M & Jamieson GG (1985) The effect of domperidone on oesophageal emptying in diabetic autonomic neuropathy. *British Journal of Clinical Pharmacology* **19**: 441–444.

Maher TD, Tanenberg RJ, Greenberg BZ et al (1977) Lack of glucagon response to hypoglycaemia in diabetic autonomic neuropathy. *Diabetes* **26**: 196–200.

Martin MM (1953) Diabetic neuropathy. A clinical study of 150 cases. *Brain* **76**: 594–624.

Martyn CN & Ewing DJ (1986) Pupil cycle time—a simple way of measuring an autonomic reflex. *Journal of Neurology, Neurosurgery and Psychiatry* **49**: 771–774.

Marumo K, Fujii S, Seki J & Wada M (1982) Studies on gallbladder dysfunction in patients with diabetes mellitus. In Goto Y, Horiuchi A & Kogure K (eds) *Diabetic Neuropathy*, pp 284–289. International Congress Series 581. Amsterdam: Excerpta Medica.

Masaoka S, Lev-Ran A, Hill LR, Vakil G & Hon EHG (1985) Heart rate variability in diabetes: relationship to age and duration of the disease. *Diabetes Care* **8**: 64–68.

Mitchell EA, Wealthall SR & Elliot RB (1983) Diabetic autonomic neuropathy in children: immediate heart rate response to standing. *Australian Paediatric Journal* **19**: 175–177.

Mondini S & Guilleminault C (1985) Abnormal breathing patterns during sleep in diabetes. *Annals of Neurology* **17**: 391–395.

Montserrat JM, Cochrane GM, Wolf C et al (1985) Ventilatory control in diabetes mellitus. *European Journal of Respiratory Diseases* **67**: 112–117.

Murray A, Ewing DJ, Campbell IW, Neilson JMM & Clarke BF (1975) R-R interval variations in young male diabetics. *British Heart Journal* **37**: 882–885.

O'Brien IAD & Corrall RJM (1985) Cardiovascular autonomic function testing: an automated method for measuring heart rate variation. *Diabetic Medicine* **2**: 143–144.

Oliveira RB, Troncon LEA, Meneghelli UG, Dantas RO & Godoy RA (1984) Gastric accommodation to distension and early gastric emptying in diabetics with neuropathy. *Brazilian Journal of Medical and Biological Research* **17:** 49–53.

Page MM & Watkins PJ (1976) Provocation of postural hypotension by insulin in diabetic autonomic neuropathy. *Diabetes* **25:** 90–95.

Page MM & Watkins PJ (1978) Cardiorespiratory arrest and diabetic autonomic neuropathy. *Lancet* **i:** 14–16.

Palmer KT, Perkins CJ & Smith RBW (1977) Insulin aggravated postural hypotension. *Australian and New Zealand Journal of Medicine* **7:** 161–162.

Peters KS, Tong TG, Kutz K & Benowitz NL (1981) Diabetes mellitus and orthostatic hypotension resulting from ingestion of Vacor rat poison: endocrine and autonomic function studies. *Western Journal of Medicine* **134:** 65–68.

Pfeifer MA, Cook D, Brodsky J et al (1982a) Quantitative evaluation of sympathetic and parasympathetic control of iris function. *Diabetes Care* **5:** 518–528.

Pfeifer MA, Cook D, Brodsky J et al (1982b) Quantitative evaluation of cardiac parasympathetic activity in normal and diabetic man. *Diabetes* **31:** 339–345.

Pfeifer MA, Weinberg CR, Cook DL et al (1984) Autonomic neural dysfunction in recently diagnosed diabetic subjects. *Diabetes Care* **7:** 447–453.

Pfeifer MA, Weinberg CR, Cook DL et al (1985) Correlations among autonomic, sensory, and motor neural function tests in untreated non-insulin-dependent diabetic individuals. *Diabetic Care* **8:** 576–584.

Pont A, Rushing JL, Kelsey T & Jacobs L (1978) Cardiorespiratory arrest in diabetic neuropathy. *Lancet* **i:** 386–387.

Rees PJ, Prior JG, Cochrane GM & Clark TJH (1981) Sleep apnoea in diabetic patients with autonomic neuropathy. *Journal of the Royal Society of Medicine* **74:** 192–195.

Rundles RW (1945) Diabetic neuropathy. General review with report of 125 cases. *Medicine (Baltimore)* **24:** 111–160.

Sakurada M, Oikawa N, Yoda B, Toyota T & Goto Y (1985) Gastric emptying time measured by simple two-step ultrasonographic method in diabetic patients. *Diabetes Research and Clinical Practice Supplement* **1:** S486.

Sakuta M, Kennedy W & Knox C (1982) Respiratory and cardiovascular reflex in diabetics. In Goto Y, Horiuchi A & Kogure K (eds) *Diabetic Neuropathy*, pp 243–246. International Congress Series 581. Amsterdam: Excerpta Medica.

Sala JMV, Saez JMG, Esteve RI et al (1983) Mortalidad en la neuropatia vegetativa cardiovascular de la diabetes mellitus. *Medicina Clinica (Barcelona)* **81:** 794–796.

Sasuki H, Nagulesparan M, Dubois A et al (1983) Hypergastrinaemia in obese noninsulin-dependent diabetes: a possible reflection of high prevalence of vagal dysfunction. *Journal of Clinical Endocrinology and Metabolism* **56:** 744–750.

Scarpello JHB, Greaves M & Sladen GE (1976) Small intestinal transit in diabetics. *British Medical Journal* **ii:** 1225–1226.

Schade RR, Dugas MC, Lhotsky DM, Gavaler JS & Van Thiel DH (1985) Effect of metoclopramide on gastric liquid emptying in patients with diabetic gastroparesis. *Digestive Diseases and Sciences* **30:** 10–15.

Schiller LR, Ana CAS, Schmulen AC et al (1982) Pathogenesis of fecal incontinence in diabetes mellitus. Evidence for internal-anal-sphincter dysfunction. *New England Journal of Medicine* **307:** 1666–1670.

Smith SA & Smith SE (1983) Reduced pupillary light reflexes in diabetic autonomic neuropathy. *Diabetologia* **24:** 330–332.

Smith SA & Dewhirst RR (1986) A simple diagnostic test for pupillary abnormality in diabetic autonomic neuropathy. *Diabetic Medicine* **3:** 38–41.

Smith SE & Smith SA (1981) Heart rate variability in healthy subjects measured with a bedside computer-based technique. *Clinical Science* **61:** 379–383.

Smith SE, Smith SA, Brown PM, Fox C & Sonksen PH (1978) Pupillary signs in diabetic autonomic neuropathy. *British Medical Journal* **ii:** 924–927.

Snape WJ, Battle WM, Schwartz SS et al (1982) Metoclopramide to treat gastroparesis due to diabetes mellitus. A double-blind controlled trial. *Annals of Internal Medicine* **96:** 444–446.

Soler NG & Eagleton LE (1982) Autonomic neuropathy and the ventilatory responses of diabetics to progressive hypoxaemia and hypercarbia. *Diabetes* **31:** 609–614.
Srinivasan G & Sanders G (1978) Cardiorespiratory arrest in diabetes. *Lancet* **i:** 504–505.
Stacpoole PW & Robertson D (1982) Combination H1 and H2 receptor antagonist therapy in diabetic autonomic neuropathy. *Southern Medical Journal* **75:** 634–635.
Sundkvist G (1981) Autonomic nervous dysfunction in asymptomatic diabetic patients with signs of peripheral neuropathy. *Diabetes Care* **4:** 529–534.
Sundkvist G & Lilja B (1985) Autonomic neuropathy in diabetes mellitus—a follow-up study. *Diabetes Care* **8:** 129–133.
Sundkvist G, Almer L-O & Lilja B (1979) Respiratory influence on heart rate in diabetes mellitus. *British Medical Journal* **i:** 924–925.
Sussman KE, Crout JR & Marble A (1963) Failure of warning in insulin-induced hypoglycaemic reaction. *Diabetes* **12:** 38–45.
Takata S, Yamamoto M, Yagi S et al (1985) Peripheral circulatory effects of insulin in diabetes. *Angiology* **36:** 110–115.
Taub S, Mariani A & Barkin JS (1979) Gastrointestinal manifestations of diabetes mellitus. *Diabetes Care* **2:** 437–447.
Tohmeh JF, Shah SD & Cryer PE (1979) The pathogenesis of hyperadrenergic postural hypotension in diabetic patients. *American Journal of Medicine* **67:** 772–778.
Vinik AI & Glowniak JV (1982) Hormonal secretion in diabetic autonomic neuropathy. *New York State Journal of Medicine* **82:** 871–886.
Vogelberg KH & Kubler HGW (1985) Gastric emptying and blood glucose in insulin-dependent diabetes mellitus with autonomic neuropathy. *Deutsche Medizinische Wochenschrift* **110:** 1249–1253.
Watkins PJ (1973) Facial sweating after food: a new sign of diabetic autonomic neuropathy. *British Medical Journal* **i:** 583–587.
Watkins PJ & Mackay JD (1980) Cardiac denervation in diabetic neuropathy. *Annals of Internal Medicine* **92:** 304–307.
Watkins PJ & Edmonds ME (1983) Clinical presentation of diabetic autonomic failure. In Bannister R (ed.) *Autonomic Failure. A Textbook of Clinical Disorders of the Autonomic Nervous System*, pp 337–370. Oxford: Oxford University Press.
Waxman SG (1980) Pathophysiology of nerve conduction: relation to diabetic neuropathy. *Annals of Internal Medicine* **92:** 297–301.
White NH, Skor DA, Cryer PE et al (1983) Identification of type I diabetic patients at increased risk from hypoglycaemia during intensive therapy. *New England Journal of Medicine* **308:** 485–491.
White NH, Gingerich RL, Levandoski LA, Cryer PE & Santiago JV (1985) Plasma pancreatic polypeptide response to insulin-induced hypoglycaemia as a marker for defective glucose counterregulation in insulin-dependent diabetes mellitus. *Diabetes* **34:** 870–875.
Wieling W, Borst C, Torman MA et al (1983) Relationship between impaired parasympathetic and sympathetic cardiovascular control in diabetes mellitus. *Diabetologia* **24:** 422–427.
Williams JG, Morris AI, Hayter RC & Ogilvie CM (1984) Respiratory responses of diabetics to hypoxia, hypercapnia and exercise. *Thorax* **39:** 529–534.
Wright RA, Clemente R & Wathen R (1985) Diabetic gastroparesis: an abnormality of gastric emptying of solids. *American Journal of the Medical Sciences* **289:** 240–242.
Xueli Z, Baidi Z, Guoxian H et al (1981) Peripheral and autonomic nerve function tests in early diagnosis of diabetic neuropathy. Correlation between motor nerve conduction velocity and fasting plasma glucose. *Chinese Medical Journal* **94:** 495–502.
Young RJ, Ewing DJ & Clarke BF (1983) Nerve function and metabolic control in teenage diabetics. *Diabetes* **32:** 142–147.
Zerbe RL, Henry DP & Robertson GL (1983) Vasopressin response to orthostatic hypotension. Etiologic and clinical implications. *American Journal of Medicine* **74:** 265–271.
Zitomer BR, Gramm HF & Kozak GP (1968) Gastric neuropathy in diabetes mellitus: clinical and radiologic observations. *Metabolism* **17:** 199–211.