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Review Articles

Diabetic Autonomic Neuropathy

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Summary. This review attempts to outline the present understanding of diabetic autonomic neuropathy. The clinical features have been increasingly recognised but knowledge of the localization and morphology of the lesions and their pathogenesis remains fragmentary. A metabolic causation as postulated in somatic nerves accords best with clinical observations. Most bodily systems, particularly the cardiovascular, gastrointestinal and urogenital, are involved with added disturbances of thermoregulatory function and pupillary reflexes. Possible effects on neuroendocrine and peptidergic secretion and respiratory control await definition. Current interest centres around the development of a new generation of tests of autonomic nerve function that are simple, non-invasive, reproducible and allow precision in diagnosis and accurate quantitation. Most are based on cardiovascular reflexes and abnormality in them is assumed to reflect autonomic damage elsewhere. Probably no single test suffices and a battery of tests reflecting both parasympathetic and sympathetic function is preferable. Little is known of the natural history. The prevalence may be greater than previously suspected and although symptoms are mild in the majority, a few develop florid features. The relation of control and duration of diabetes to the onset and progression of autonomic neuropathy is not clearly established. Once tests of autonomic function become abnormal they usually remain abnormal. Symptomatic autonomic neuropathy carries a greatly increased mortality rate possibly due to indirect mechanisms such as renal failure and direct mechanisms such as cardio-respiratory arrest. Improved treatment of some of the more disabling symptoms has been possible in recent years.

Key words: Diabetic autonomic neuropathy, morphology, pathogenesis, clinical features, assessment, cardiovascular reflexes, natural history, prognosis, treatment, diabetes mellitus.

Shortly after Langley [1] established the concept of an autonomic nervous system in the late nineteenth century it became increasingly apparent that damage to it might occur in a variety of systemic disorders, most commonly diabetes mellitus, but also tabes dorsalis, polyneuropathies, amyloidosis, porphyria, chronic renal failure and chronic alcoholism [2]. Primary disorders are also recognised and include familial dysautonomia or the Riley-Day syndrome [3, 4] and idiopathic orthostatic hypotension or the Shy-Drager syndrome [5–7]. The historical aspects of the autonomic nervous system have been reviewed recently [8].

Before 1900 and in the early part of this century there were occasional references to clinical features now attributed to diabetic autonomic neuropathy including those of De Calvi [9] on neurogenic bladder disturbance, Pavy [10] on abnormal sweating, Buzzard [11], Auché [12] and Pryce [13] on vasomotor disturbance, Pitres [14] on loss of testicular sensation and absence of pupillary reflexes, and Naunyn [15] and Von Noorden [16] on impotence. Diabetic autonomic neuropathy as an entity, however, only became generally recognised following the reviews by Jordan in 1936 [17] and Rundles in 1945 [18].

Although the autonomic nervous system is usually regarded as an efferent system innervating smooth muscle of hollow viscera and arterioles as well as certain exocrine and endocrine tissue, it is helpful to include the accompanying visceral afferent sensory fibres. Diabetic autonomic neuropathy thus

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encompasses disturbance of motor, sensory and reflex function particularly in the cardiovascular, gastrointestinal and urogenital systems, as well as impairment of sudomotor and vasomotor thermoregulatory mechanisms, disturbance of autonomic control of endocrine secretion, changes in pupillary reflex function, and possibly interference in control of respiration.

Morphological Changes

Morphological changes in peripheral nerves of diabetics include patchy segmental demyelination [19–21], proliferation of Schwann cells [22] and thickening of the Schwann cell basement membrane [23]. Degeneration in nerve roots [24, 25] and axons [20, 21] were considered late changes but the latter occurs earlier and more commonly than previously thought [26, 27]. By contrast morphological studies of autonomic nerves in diabetics have been few, because of inaccessibility and difficulty in isolating the nerve elements, and have usually relied on autopsy or surgical material from small numbers of patients.

The paravertebral and prevertebral sympathetic ganglia have most frequently been studied [28–35] showing segmental loss of myelin and variable axonal degeneration of neurones in the rami communicantes, similar to peripheral nerve changes. The main lesions of the sympathetic ganglia were large vacuoles in the cytoplasm of the cell bodies, abnormally large ('giant') neurones with all stages of degeneration, and swelling of dendrites. Whether the abnormalities of the cell bodies represent primary damage, are due to retrograde change following distal involvement, or are secondary to damage of preganglionic neurones with trans-synaptic degeneration, has not been resolved.

Examination of intrinsic innervation of the oesophagus has shown few abnormalities [36]. Similarly fibres of the vagus nerve [31, 37], splanchnic nerve [31] and intrinsic gut plexus [38, 39] obtained at autopsy from patients with diabetic diarrhoea showed no consistent change. A recent study of the greater splanchnic nerve, however, showed reduction in myelinated fibre density, segmental demyelination and axonal degeneration, similar to changes in the sural nerve [40].

Faerman and co-workers have isolated parasympathetic and sympathetic neurones supplying the bladder wall [34], parasympathetic fibres supplying the corpus cavernosum of the penis [41] and autonomic fibres supplying heart muscle [42] from diabetics by biopsy or autopsy. The lesions in the different tissues were similar with thickening, hyperargentophilia and fragmentation of the autonomic nerve fibres with a decrease in number. Bladder wall neurones showed marked reduction in cholinesterase activity [34].

Sural nerve biopsies from diabetics with peripheral or autonomic neuropathy showed a relatively greater loss of small myelinated and unmyelinated axons [40, 43, 44]. These fibres convey, in addition to pain and temperature sensation, sympathetic vasomotor and sudomotor efferents and their loss in less severely affected nerves suggested early involvement of peripheral autonomic fibres [43]. Ultrastructural examination of small blood vessels obtained by skin biopsy from longstanding diabetics has also revealed terminal denervation [45].

Pathogenesis

Autonomic and somatic neuropathy are usually assumed to share a common pathogenesis although it is still not clear whether any of the postulated mechanisms in somatic nerves also apply to autonomic nerves. Any hypothesis of causation of autonomic neuropathy needs to take account of acute changes that occasionally occur at diagnosis and during the early course of diabetes [46, 47] as well as later cumulative and usually irreversible features. The pathogenesis of diabetic neuropathy is controversial and has been previously reviewed [48–50]. The main hypotheses are grouped as vascular and metabolic.

Vascular Hypothesis

The early view that arteriosclerosis involving intraneural blood vessels might be a significant factor in peripheral neuropathy [51] was based on material from diabetics with severe arterial damage in the legs. Dry and Hines [52] found an association between atherosclerosis, retinopathy and neuropathy and considered changes in nutrient blood vessels the common mechanism. In a later study no correlation was however found between neuropathy and occlusive vascular disease [53].

Lundbaek [54, 55] proposed a further unifying hypothesis of widespread small vessel angiopathy underlying most diabetic complications based on clinical observations of the eye, kidney and nerves. A concept thereafter arose of a common microvascular aetiology for diabetic neuropathy, retinopathy and neuropathy exemplified by the term "triopathy" [56]. Support for this hypothesis was provided by histological studies of vasa nervorum of peripheral nerves from patients with neuropathy showing thick-

ening, hyalinization and accumulation of PAS-positive material in the vessel walls and narrowing or occlusion of the lumen [57, 58]. Later studies have not confirmed these findings [19, 20, 21, 24] but Timperley et al. [59] have recently described intraluminal changes of the vasa nervorum with intravascular coagulation, in sural nerve biopsies.

In the limited studies of autonomic nerves it is not clear to what extent vascular lesions are involved. Microvascular changes were noted in autonomic ganglia and peripheral autonomic nerves [30, 33] but not confirmed by others [34, 35].

Metabolic Hypothesis

Somatic and autonomic neuropathy might alternatively result from metabolic disturbances directly affecting some component of the nerve particularly the cell body and axon, or the Schwann cell and myelin sheath. Possible defects are increased accumulation of sorbitol, abnormalities of lipid metabolism, myoinositol deficiency and abnormal glycosylation of protein.

Sorbitol Pathway: Excess sorbitol and fructose are formed in tissues which are freely permeable to glucose, such as nerve, when the ambient blood glucose concentration is elevated [60–63]. The enzymes concerned in the sorbitol pathway, aldose reductase and sorbitol dehydrogenase, have been localised in Schwann cells of peripheral nerves, spinal cord and brain [64]. In alloxan diabetic rats increased concentration of sorbitol in peripheral nerves was associated with slowing of motor conduction velocity but improvement occurred when the blood glucose was lowered [63]. These observations in animals may explain the role of hyperglycaemia in some of the acute and reversible neurological syndromes in human diabetes. Whether accumulation of sorbitol in nerves results in long-term changes in structure and function is however unclear.

Lipid Abnormalities: Biochemical studies of peripheral nerve myelin in diabetic man [65] and alloxan diabetic rats [66] demonstrated a reduced lipid concentration and an alteration of the normal lipid pattern. Acetyl thiokinase activity, necessary for fatty acid synthesis from acetate, was depressed in myelin from experimental diabetic animals [67]. The lipid changes can be attributed to insulin lack and probably reflect the metabolic disturbance of the diabetes rather than making a direct contribution to nerve damage.

Myoinositol Disturbance: Peripheral nerve myoinositol concentration is decreased in experimental diabetic animals with diminished intracellular entry, elevated blood levels and increased urinary excretion [68]. Improvement of motor nerve conduction was demonstrated in streptozotocin rats by dietary administration of myoinositol [69]. This has not been confirmed in humans [70] although another study demonstrated increased evoked action potentials following dietary myoinositol administration [71].

Glycosylation of Protein: A further possible mechanism is abnormal glycosylation of structural protein in nerve. Haemoglobin A_{1c}, a minor haemoglobin formed by irreversible glycosylation of haemoglobin A, may be increased from the normal 5% upto 20% of the total haemoglobin in diabetics depending on the ambient glycaemia during the erythrocyte life span [72]. Increased glycosylation may not be an isolated process referable to haemoglobin alone, but by involving other proteins occurring on basement and cell membranes could contribute to specific diabetic complications including nerve damage [73].

Clinical Features

The delineation of clinical features resulting from autonomic nerve damage in diabetics only became well recognised following the classical review by Rundles [18]. The symptoms are often non-specific and vary from minor disturbance to extreme disability. Their interpreation is aided by simple tests of autonomic function.

Cardiovascular System

Resting Tachycardia: A resting tachycardia of 90–100 beats per minute has occasionally been observed [18, 74, 75]. The heart rate may be fixed and unresponsive to manoeuvres that influence it reflexly and similar to that following blockade with atropine and propranolol [76] or cardiac transplantation [77]. More rapid rates up to 130 beats per minute sometimes occur [78] and may represent an earlier stage of parasympathetic damage alone. Diabetics as a group have faster heart rates than controls [79] and a resting tachycardia is probably unreliable as a marker of autonomic neuropathy.

Loss of Beat-to-Beat Variation in Heart Rate: Cyclical heart rate variation, which depends on vagal innervation, is reduced and is the basis of one of the tests of cardiovascular reflex function described below [75, 80–83].

Postural Hypotension: Postural hypotension is the most striking feature of cardiovascular involvement

[18, 40, 84–89] and may be arbitrarily defined as a fall in systolic blood pressure of 30 mmHg or more on changing from the lying to standing position. The main lesion is probably in the efferent limb of the baroreflex arc [74, 84, 85] with damaged sympathetic vasoconstrictor fibres to the splanchnic bed, muscle and skin. The importance of splanchnic vasoconstriction in orthostatic blood pressure control has been demonstrated both in sympathectomized patients [90] and experimentally [91], while splanchnic nerve damage occurs in diabetics with neuropathy [40]. The hypotension may be augmented by a diminished plasma renin response to standing [88, 92], itself due to impaired sympathetic innervation of the juxtaglomerular apparatus. Decreased basal and 'standing' plasma noradrenaline levels may also contribute [93–95]. Occasionally elevated 'standing' plasma noradrenaline concentrations are found in diabetics with postural hypotension (hyperadrenergic postural hypotension) but the mechanism for this is not clear [96].

The patient may be asymptomatic despite a large drop in systolic blood pressure or may have postural weakness, dizziness, faintness, visual impairment or syncope. These symptoms may be mistaken for hypoglycaemia and worsened by a variety of drugs including hypotensive agents, diuretics, tricyclic antidepressants, phenothiazines, vasodilators and glyceryl trinitrate. Insulin may aggravate the postural hypotension [97–100], possibly due to decreased venous return [98] or altered capillary endothelial permeability with reduction in plasma volume [101]. Development of congestive cardiac failure or the nephrotic syndrome ameliorates the postural hypotension [102].

Painless Myocardial Infarction: The increased prevalence of painless myocardial infarction in diabetes [103] has been attributed to autonomic neuropathy. Damage to autonomic nerve fibres from the myocardium of patients dying from painless myocardial infarction has recently been reported [42]. Patients with florid autonomic neuropathy may nevertheless develop typical cardiac pain during myocardial infarction [104]. Painless myocardial infarction has been considered the cause of sudden death in diabetics but recent evidence suggests that abnormal autonomic reflexes may account for some of these deaths [105–107].

Gastrointestinal System

Although the entire gastrointestinal tract may be involved with generally hypotonic and poorly contractile smooth muscle, the patient is often asymptomatic. The relative role of damage parasympathetic, sympathetic and afferent sensory fibres is not clear. Possible additional effects of autonomic neuropathy on neuroendocrine [108] and peptidergic [109] innervation related to the gut and pancreas await study. The gastrointestinal manifestations of diabetes have been reviewed [110–112].

Oesophageal Atony: Oesophageal motility disturbances are often demonstrable [113, 114] but symptoms, which include dysphagia, retrosternal discomfort and heartburn are uncommon. Radiology shows mild dilatation, reduced or absent primary peristalsis, tertiary contractions and delayed oesophageal emptying [113–115]. Manometry, which is more sensitive than radiology [116] demonstrates diminished pharyngeal and oesophageal contractions and reduced lower sphincter tone [113, 116–120]. The motility changes are similar to those following vagal section in animals and consistent with vagal neuropathy [121]. Damage to preganglionic fibres rather than the myenteric plexus has been implicated because of lack of denervation hypersensitivity [119].

Gastric Atony: Delayed gastric emptying, first noted by Rundles [18] became generally recognised when Kassander [122] introduced the term gastroparesis diabeticorum. The gastric muscularis receives parasympathetic innervation from the vagus, sympathetic fibres from the coeliac plexus and is also influenced by enteric hormones, but their relative contribution in delayed emptying is not clear. The patient is usually asymptomatic, possible due to afferent sensory denervation. Symptoms include anorexia and vague upper abdominal fullness, and a gastric splash may be present. Diabetic control may become difficult with frequent hypoglycaemic episodes [123] and unexplained weight loss [124]. Severe gastric atony may cause acute bouts of nausea, vomiting and hiccup [125] simulating uraemia.

Radiology shows increased fasting residual contents, atonic dilatation, diminished or absent peristalsis, and delayed emptying of the contrast medium [122, 126–128]. Duodenal atony may be a further finding. Measurement of gastric emptying using scintiscanning permits recognition of gastric stasis not apparent radiologically [129]. Rapid early emptying does not occur in diabetics with autonomic neuropathy, and in those without stasis the normal differentiation between gastric emptying of liquids and solids is impaired. These findings contrast with those seen in surgical patients where loss of vagal innervation causes accelerated early gastric emptying [130] and preservation of liquid and solid differentiation [131]. Neither gastric nor duodenal atony appear

to predispose to peptic ulcer and in general its prevalence is decreased in diabetics [132]. This may be due partly to sensory impairment but also to loss of vagally mediated gastric acid secretion [133].

Gallbladder Atony: Asymptomatic gallbladder enlargement and poor contraction in diabetics is attributed to autonomic dysfunction [134, 135]. The gallbladder can be enlarged to more than three times the normal size [136, 137]. Similar changes follow bilateral vagotomy [138] and partial gastrectomy interfering with vagal innervation [139]. There is no evidence that gallbladder atony predisposes to infection or gallstones.

Diabetic Diarrhoea: Diabetic diarrhoea, first described by Bargen et al. [140] is the best recognised manifestation of autonomic neuropathy involving the gut. The symptoms are characteristic with intermittent episodes lasting from hours to several days, with frequent fluid stools up to twenty or sometimes more daily, often worse following meals and during the night, and with faecal incontinence [110, 141–143]. During remission, which can last several weeks, there may be normal bowel function or constipation. Body weight is maintained and improvement may occur with time [143].

The mechanism and reason for the episodic nature of diabetic diarrhoea remain unexplained. Small intestinal radiology may show non-specific changes with dilated loops, coarsening and irregularity of the mucosal folds and disordered movement [110]. Measurement of small intestinal transit time has given conflicting results [39, 126, 142–144] but it is probably prolonged [145]. Jejunal biopsy shows no specific changes [38, 39, 110, 146]. Tests of small bowel absorption are normal [110]. Small intestinal bacteriology shows no consistent abnormality although some patients have excessive bacterial growth [39, 147] also indicated by the ^{14}C-glycocholate test [148]. Bile salt malabsorption resulting from gallbladder dysfunction may also be a factor in the diarrhoea [149, 150]. Although there are similarities with post-vagotomy diarrhoea, oesophageal [119] and gastric [133] function are often normal. Histological studies of gut innervation in patients with diabetic diarrhoea have yielded fragmentary data with no consistent abnormality, [31, 37–39] as already discussed.

Colonic Atony: Constipation has been described as a common symptom in patients with autonomic neuropathy [18, 151] but documented evidence to support this is hard to find. It may be associated with atony of the large bowel and rectum, sometimes with megacolon [152]. Measurement of rectal sphincter pressure showed no difference between normal subjects and diabetics, and loss of sphincter control was attributed to impaired sensory innervation [110].

Urogenital System

Bladder Atony: Neurogenic bladder disturbance in diabetics was originally noted by De Calvi [9] and described in more detail by Jordan and Crabtree [153], Gill [154], Rudy and Muellner [155] and Rundles [18]. Afferent fibre damage results in diminished bladder sensation, damage to parasympathetic innervation results in decreased tone and weakness of the detrusor, and loss of sympathetic innervation of the trigone and internal sphincter (proximal urethra) causes sphincter dysfunction.

The patient is often asymptomatic despite abnormalities on intravenous pyelography and cystometry [156–158]. Early involvement, preceding cystometric abnormality can be revealed by electrophysiological measurement [159]. Symptoms develop insidiously and progress slowly [160]. Loss of bladder sensation occurs early with lengthened intervals between micturition, absence of nocturia and increased volume of the first morning specimen [156, 157, 160]. Later, parasympathetic involvement causes a weak, slow urinary stream and increased straining. In advanced cases incomplete bladder emptying, increasing residual volume, a palpable bladder and overflow incontinence occur [160]. Acute retention is uncommon and occurs only in patients with florid autonomic neuropathy. Urinary stasis is invariably associated with infection [156, 161, 162] with added symptoms of urgency and dysuria. Further loss of renal function due to infection may contribute to increased mortality [105]. Urinalysis as a guide to blood glucose control is unreliable because of incomplete bladder emptying.

Intravenous pyelography shows bladder distension and a residual volume after micturition. Cystoscopy [154, 160, 161, 163] reveals an enlarged atonic bladder with decreased trabeculation and no obstruction. Cystometry [18, 157, 163–165] and urodynamic examination [162, 166] show diminished awareness of filling, only a small rise in pressure with few or no contractions, increased bladder capacity, a lack of thermal sensibility and on voiding a low flow rate with diminshed detrusor activity.

Impotence: Loss of penile erection with normal libido follows damage to parasympathetic innervation of the erectile tissue. The prevalence of impotence in diabetic males is up to 50 per cent [15, 16, 18 167–170] considerably greater than in non-diabetic

males [171]. Impotence in diabetes may have causes other than autonomic neuropathy. It can occur as an isolated feature [167] and with normal autonomic function tests [87]. Some patients do in fact later develop other features of autonomic neuropathy and abnormal tests [105, 172]. Despite earlier reports [167, 168] there is no evidence that endocrine dysfunction contributes and recent studies showed normal plasma gonadotrophins [173, 174] and testosterone [175] in diabetics with impotence.

Impotence due to autonomic neuropathy has a gradual onset with progression to complete impotence over 6 months to 2 years. It differs from psychogenic impotence which has an abrupt onset, periodicity, preservation of morning erections and nocturnal penile tumescence confirmed by strain gauge monitoring [176]. An association between impotence and bladder dysfunction was observed by Rundles [18] and emphasised by Ellenberg [169]. In males presenting with other features of autonomic neuropathy impotence is almost invariable. The development of impotence may explain why autonomic neuropathy is more frequently diagnosed in males.

Failure of Ejaculation: Retrograde ejaculation from the prostatic urethra into the bladder occasionally occurs [177, 178] and follows loss of sympathetic innervation of the internal sphincter which normally contracts during ejaculation. Complete loss of ejaculation probably indicates widespread pelvic sympathetic involvement with denervation of the vas deferens and failure of emission of semen into the posterior urethra which, like retrograde ejaculation, causes infertility.

Loss of Testicular Sensation: Loss of testicular pain to pressure in diabetics was described by Pitres [14] but the sign was neglected until recently [179]. It probably results from damaged afferent fibres accompanying the sympathetic supply of the testis. Diminished or absent testicular pain may occur early and correlates with other clinical features of autonomic neuropathy and abnormal cardiovascular reflexes [179].

Thermoregulation

Sudomotor and vasomotor activity are influenced reflexly by changes in skin temperature, and directly by central hypothalamic receptors which monitor body core temperature. Damage to sympathetic pathways to the skin causes loss of sweating, inability of denervated arterioles to respond to changes in endogenous or environmental temperature and with more extensive involvement, disturbance in body thermoregulation.

Sudomotor Abnormalities: Diminished or absent sweating (anhydrosis) follows damage to sympathetic innervation of eccrine sweat glands [180] which occurs in diabetics [18, 43, 85] and is probably localised to post-ganglionic fibres [181]. The anhydrosis usually has a patchy distribution over the feet and legs but in severe cases may involve the lower trunk and arms [85, 181]. Because post-ganglionic sudomotor fibres accompany peripheral nerves, sensory and vasomotor disturbances are usually also present in the affected areas. Loss of vasomotor tone was however found more commonly than loss of sudomotor activity in diabetics with peripheral neuropathy [182]. The areas of sweating loss can be defined with quinizarin powder [183], cobalt chloride solution [185], iodine solution and starch [181], alazarine red powder [40] or by skin conductivity [184].

Hyperhydrosis involving the upper trunk and head is compensatory and follows decreased ability of the lower body to dissipate heat [185]. There may be heat intolerance with profuse sweats in the upper body, particularly during exercise, warm weather and while in bed, which may be mistaken for hypoglycaemia. Indirect heating in patients with autonomic neuropathy resulted in a greater rise of rectal temperature than in control subjects [186].

Profuse sweating over the face, head and neck within seconds of eating and provoked by foods which normally excite salivation (gustatory sweating) was noted in diabetics with autonomic neuropathy by Aagenaes [186] and described in detail by Watkins [187] and may be due to aberrant nerve regeneration. It needs to be distinguished from compensatory hyperhydrosis involving the head and the response of some normal individuals to spicy foods [188].

Vasomotor Abnormalities: Autonomic neuropathy causes failure of reflex vasodilation and vasoconstriction of denervated skin vessels in response to body temperature change [18, 43, 74, 186, 189, 190]. The pattern of vasomotor change is not constant with either abnormal vasoconstriction or vasodilation [43, 191] possibly depending on sensitivity to the prevailing environmental temperature [191].

Abnormal vasoconstriction may result from hypersensitivity of denervated arterioles to catecholamines and cold [191–193] and represents an early state of denervation [194]. The patient may complain of cold and sometimes painful feet with failure of reflex vasodilation in response to body heating [43, 74, 191]. Abnormal vasodilation follows loss of sympathetic vasoconstriction. The normal thermal gradient is reversed so that the toes are warmer than the fingers, resembling bilateral lumbar sympathectomy [85]. There may be failure of reflex vasocon-

striction of skin vessels of the feet following body cooling [18, 43, 191]. Vascular response to local heating or cooling are however retained [181, 191].

Changes in vasomotor tone were thought to cause oedema of the legs [18] but in diabetics other factors such as cardiac disease or nephropathy need to be excluded. There is still a lack of studies in diabetics showing the relation of vasomotor changes to neuropathy, microangiopathy, peripheral vascular disease and circulating catecholamines.

Hypoglycaemic Unawareness

A progressive fall of blood glucose normally produces an asymptomatic 'parasympathetic' response with bradycardia and mild hypotension, followed by a 'sympathetic' response with easily recognisable symptoms due to catecholamine release alerting the patient to take adequate measures to prevent coma [195]. Patients with autonomic neuropathy may lose their usual warning symptoms. The failure of the 'sympathetic' response to insulin-induced hypoglycaemia, has been confirmed by decreased catecholamine secretion [195].

Pancreatic glucagon release with glucose mobilisation, which provides an early counter-regulatory mechanism for glucose homeostasis and depends on vagal innervation [196], is decreased in long-standing diabetics [197] and absent in diabetics with autonomic neuropathy [198]. This results in a steeper fall of blood glucose and may contribute to more rapid loss of consciousness. The failure of glucagon response may be an early selective form of autonomic neuropathy [199]. Some patient with autonomic neuropathy may mistakenly be thought to have hypoglycaemic unawareness, with sudden faintness or loss of consciousness without warning, due to symptoms of postural hypotension.

Pupillary Abnormalities

Pupillary disturbances have long been recognised [14, 17, 18] and attributed to diabetic autonomic neuropathy, but cause no symptoms. The main abnormalities are reduced resting pupillary diameter, especially in the dark, delayed or absent reflex response to light and diminished hippus [200, 201]. A true Argyll-Robertson pupil is rare.

Respiratory Control

Cardio-respiratory arrests have been observed in relatively young patients with severe autonomic neuropathy, with subsequent sudden death in some of them [106, 202]. The patients became apnoeic and pulseless but responded rapidly to resuscitation. In most episodes there was interference with respiration by drugs, anaesthesia or bronchopneumonia, suggesting that the arrests were caused by defective respiratory rather than cardiovascular reflexes. This may account for some sudden and unexplained deaths in diabetic autonomic neuropathy [105, 107]. The mechanism of these attacks is unclear, but carotid chemoreceptor denervation with abolition of the normal ventilatory response to hypoxia has been postulated [106]. In patients with severe autonomic neuropathy the ventilatory response to hypoxia was however normal, indicating intact peripheral chemoreceptor pathways [203]. Other possible mechanisms have been suggested whereby alteration in autonomic reflexes might cause cardio-respiratory arrest [204, 205].

Table 1. Newer tests of autonomic nerve function in diabetes mellitus

Tests based on heart rate
Heart rate response to the Valsalva manoeuvre [87, 212].
Beat-to-beat (R-R interval) variation in heart rate:
(a) during deep breathing [75, 83, 217]
(b) with measurement of 'standard deviation' [80]
(c) with measurement of 'mean square successive difference' [81]
(d) following a single deep breath [82]
Heart rate response to standing [78, 219]
Heart rate response during apnoeic facial immersion [82]
Tests based on blood pressure
Blood pressure response to standing [87]
Blood pressure response to sustained muscle exercise [79]
Blood pressure response to lower body negative pressure [224]
Tests of pupillary responses [200, 201]
Drug tests [40, 202, 226]

Assessment

Until the 1970s tests of autonomic nerve function were usually complex, difficult to interpret and lacking in control measurements. Current interest centres around the development of a new generation of tests that are simple, non-invasive and reproducible (Table 1). They have the aims of confirming the presence, assessing the severity and allowing the quantitation of autonomic neuropathy. Most of the newer tests attempting to satisfy these criteria are based on cardiovascular reflexes and have been reviewed recently [206]. By inference they are assumed to reflect autonomic nerve changes in the other systems.

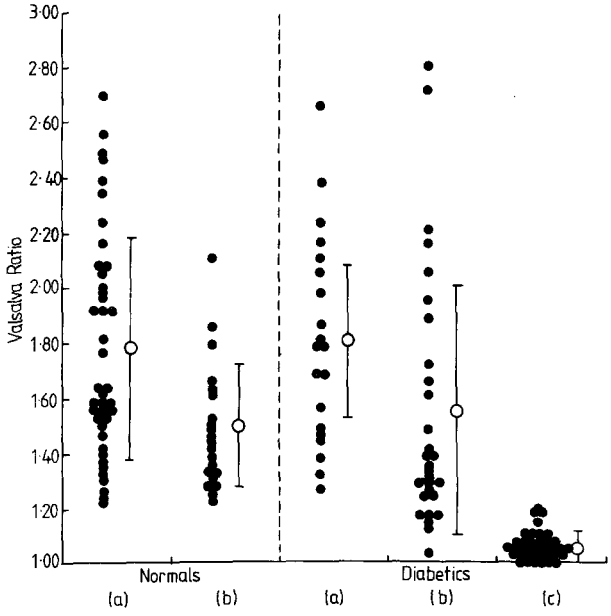


Fig. 1. Valsalva ratios in normal subjects (a) 41 young aged 16–42 years (b) 21 older aged 48–61 years and in diabetics (a) 20 with no autonomic neuropathy, aged 20–63 years (b) 29 with impotence alone, aged 24–62 years (c) 36 with autonomic neuropathy, aged 24–60 years

Tests Based on Heart Rate

Heart Rate Response to the Valsalva Manoeuvre: The baroreflex response to the Valsalva manoeuvre (forced expiration against resistance) includes tachycardia and peripheral vasoconstriction during strain followed, after release, by an overshoot rise in blood pressure and bradycardia [207]. Intra-arterial blood pressure changes were regarded as the standard method for interpreting the response and can still be used to assess autonomic function [208, 209] but have the disadvantage of being invasive. Heart rate changes during and after the maneovure are however a reliable guide to the associated haemodynamic events [210]. The subject blows into a mouthpiece connected to a manometer held at 40 mmHg pressure for fifteen seconds and using a continuous ECG the response can be expressed by the Valsalva ratio, which is the longest R-R interval after the manoeuvre (reflecting the overshoot bradycardia) to the shortest R-R interval during the manoeuvre (reflecting the tachycardia during strain). Although a ratio of 1.50 or greater has been defined as normal [211] there is a wide scatter in normal subjects. A lower limit of 1.20 usually clearly distinguishes between normal subjects and diabetics with autonomic neuropathy [87, 212] (Fig. 1). In our practice we define a Valsalva ratio of 1.21 or greater as normal, 1.11 to 1.20 as borderline and 1.10 or less as abnormal [213].

The Valsalva manoeuvre has the advantages of being simple, easy to perform, non-invasive and reproducible [212]. It is effort dependent and subjects can cheat but providing these minor limitations are appreciated it is a useful test. It has been suggested that the post-manoeuvre bradycardia is a better index of response than the Valsalva ratio [82] but this assertion was based on small numbers of diabetics with abnormal responses and no definition given of the normal post-manoeuvre bradycardia.

Beat-to-Beat Variation in Heart Rate: Normal cyclical beat-to-beat (or R-R interval) variation in heart rate is dependent on parasympathetic innervation [75, 214]. It is most marked at slow heart rates or on deep breathing [75]. It is diminished by faster heart rates [75] in older subjects, in the presence of cardiac failure [215] and following intracranial lesions [216], and is absent in transplanted hearts [77]. Wheeler and Watkins [75] showed that diabetics with autonomic neuropathy had marked reduction or absence of beat-to-beat variation. Vagal damage, as evidenced by beat-to-beat variation, occurs more widely than the symptoms of autonomic neuropathy would suggest and is found in diabetics without clinical evidence of autonomic neuropathy [80, 81]. Various tests to measure beat-to-beat variation in heart rate have been described:

a) Heart Rate Variation during Deep Breathing: This test analyses beat-to-beat variation with subjects lying quietly and breathing deeply at approximately six breaths per minute, which produces maximum variation in heart rate [75, 78, 217]. Using an instantaneous monitor the difference between the maximum and minimum heart rate is measured, the normal response being a difference of 15 beats per minute or more (Fig. 2a) and abnormal being less than 10 beats per minute (Fig. 2b). A recent modification, using an ECG, measures the 'E:I' ratio which is the mean of the longest R-R intervals during expiration to the mean of the shortest R-R intervals during inspiration [83].

b) R-R Interval Variation during Standing with Measurement of 'Standard Deviation': This method records the ECG for 5 minutes on magnetic tape with later computer analysis, while the subject stands and breathes quietly, the standard deviation of the mean R-R interval over that period being used as a measure of beat-to-beat variation [80] (Fig. 3). Although the method has been criticized as being insensitive [81, 82] atropine abolishes the R-R interval variation measured by this technique [213, 218].

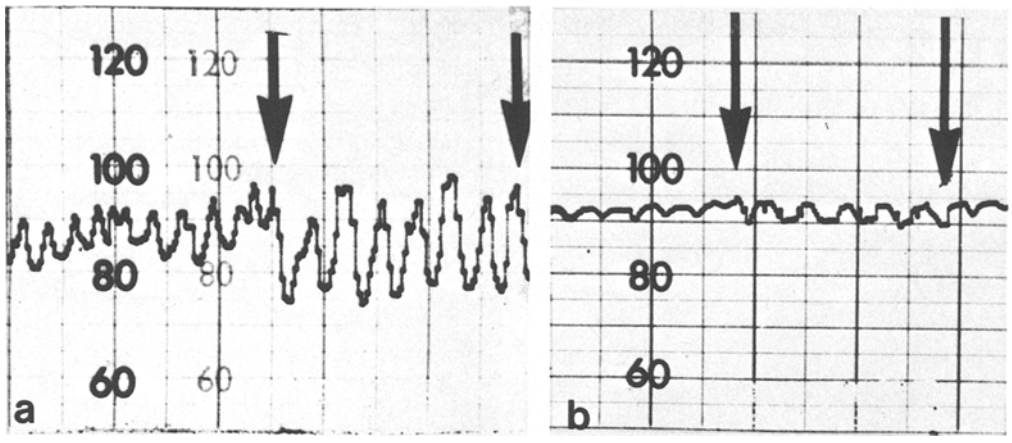
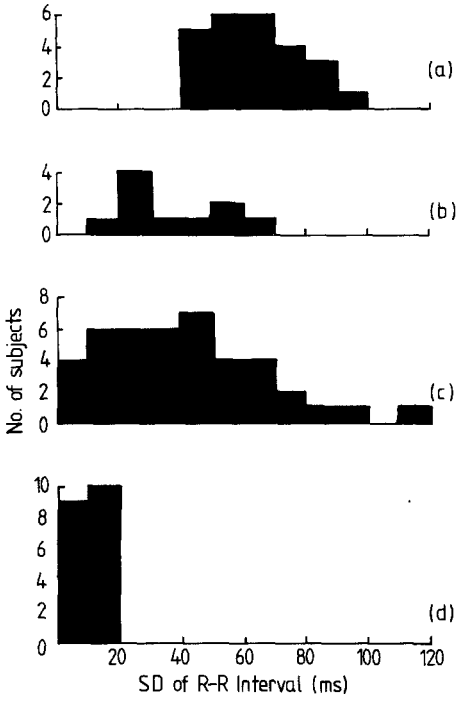


Fig. 2. a Beat-to-beat heart rate recording from a normal subject at rest and during deep breathing at 6 breaths/min. (between the two arrows). Vertical axis shows heart rate (beats/min) and horizontal axis shows time in 15 second intervals. Each 'wave' is composed of several heart beats and each heart beat indicated by an individual 'notch'. **b** Beat-to-beat heart rate recording from a diabetic with autonomic neuropathy showing marked reduction in variation. Arrows mark the period of deep breathing (from: [78] with permission from the authors and publishers)



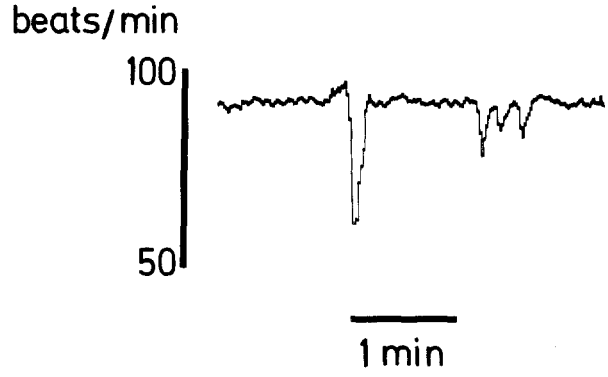


Fig. 3a–d. R-R interval variation determined by the method of Murray et al. 1975 (80) in **a** 25 young normal subjects aged 20–35 years **b** 10 older normal subjects aged 48–67 years **c** young diabetics aged 20–35 years and **d** 19 diabetics with autonomic neuropathy, aged 27–71 years (from: [206] with permission from the publishers)

◀ **Fig. 4.** Changes in instantaneous heart rate in response to a single deep breath and to three deep breaths (at 6 breaths/min.) in a diabetic subject. There was greater heart rate variation in response to the single breath than to repeated breaths (from: [82] with permission from the authors and publishers)

c) R-R Interval during Lying with Measurement of 'Mean Square Successive Difference': Using an ECG 150 consecutive beats are recorded with the subject lying and breathing quietly. Each R-R interval is measured and the mean of the squares of the differences between successive intervals, the 'mean square successive difference' is used as a measure of beat-to-beat variation [81].

d) R-R Interval Variation Following a Single Deep Breath: The instantaneous heart rate response to a single maximum inspiration and expiration is measured by recording the difference between the maximum and minimum heart rate using a monitor [82]. This manoeuvre is more sensitive than repeated deep breaths as described above (Fig. 4).

These various techniques of measuring beat-to-

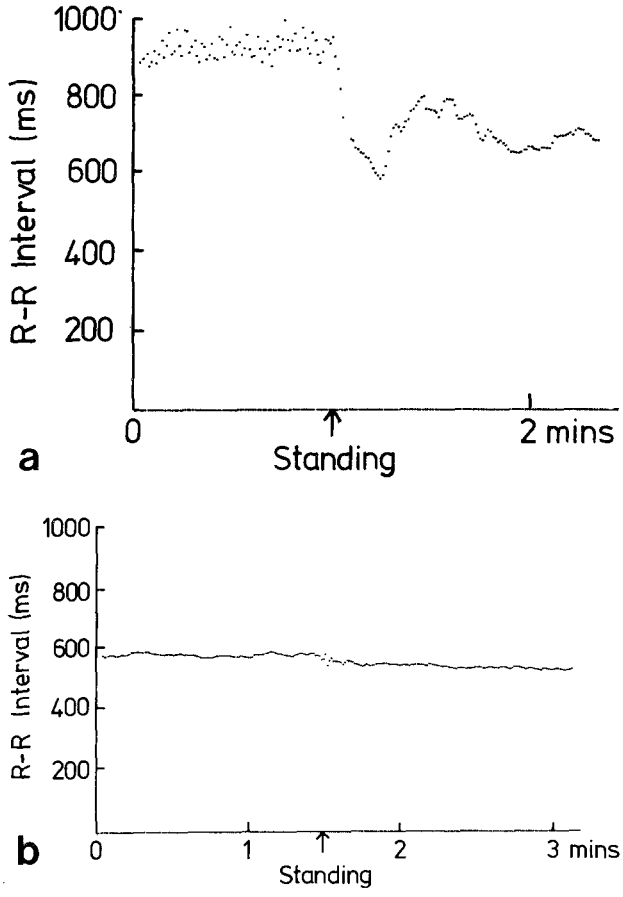


Fig. 5. a Instantaneous R-R interval recording of the response to standing in a normal 31-year old man showing a tachycardia (shortened R-R interval) maximal between beats 10 and 20, and a relative bradycardia (lengthened R-R interval) maximal between beats 25 and 35 after standing (from: [219]). **b** Instantaneous R-R interval recording of the response to standing in a 30-year old man with diabetic autonomic neuropathy showing a 'flat' response with only a small increase in heart rate and no relative bradycardia (from: [219] with permission from the publishers)

beat variation in heart rate are objective and require little co-operation, but some require complex equipment and there is a wide range of response in normal subjects. Poor reproducibility was found with the technique of Murray et al. [206] but adequate reproducibility studies with the other methods are lacking. In comparing some of these techniques, a single deep breath was the most sensitive method of enhancing heart rate variation [82] but its usefulness as a diagnostic test in patients with autonomic neuropathy was not demonstrated.

Heart Rate Response to Standing: Changing from horizontal to vertical produces an integrated cardiovascular reflex response which includes alteration

Table 2. Comparison of heart rate response to standing ('30:15' ratio), Valsalva ratio and R-R interval variation in young and older normal subjects and diabetics with autonomic neuropathy (mean ± SD)

Group (age range – yrs)	(n)	30:15 ratio	Valsalva ratio	R-R interval variation (ms)
Young normals (21–45)	(5)	1.24±0.05	1.56±0.35	36.9±13.1
Older normals (48–67)	(10)	1.17±0.22	1.46±0.20	36.9±16.9
Diabetics with autonomic neuropathy (28–65)	(15)	0.98±0.03	1.07±0.06	10.6± 3.3

in heart rate. This response has usually been studied with a tilt table and little attention given to the immediate heart changes during standing. Detailed computer analysis of the response in normal subjects shows a characteristic and consistent rapid increase in heart rate maximal at about the fifteenth beat after standing and a subsequent relative bradycardia maximal at about the thirtieth beat [219] (Fig. 5). Diabetics with autonomic neuropathy show only a gradual increase in heart rate if at all [78, 217, 219]. Pharmacological studies indicate that the response is mediated by the vagus nerve [218, 219]. The test can be simplified by using a continuous ECG recording and the lengths of the R-R intervals at beats 15 and 30 after standing give the '30:15' ratio. In normal subjects values are greater than 1.03 whereas in diabetics with autonomic neuropathy values are 1.00 or less. The test is objective, reproducible in normal subjects and not dependent on age or resting heart rate [219]. It correlates well with the Valsalva ratio and beat-to-beat variation in heart rate [213] (Table 2).

Heart Rate Response during Apnoeic Facial Immersion: Breath holding combined with immersion of the face in water is a powerful stimulus for bradycardia which is mediated by the vagus [220]. In diabetics this test provided no information that was not forthcoming with simpler tests [82].

Tests Based on Blood Pressure

Blood Pressure Response to Standing: On standing there is immediate pooling of blood in the legs with a fall in blood pressure, but provided there is normal

baroreflex function, this is rapidly corrected by peripheral vasoconstriction and tachycardia. Postural hypotension is easily detected using a cuff sphygmomanometer, and a fall is systolic blood pressure of 30 mmHg or more upon standing is regarded as significant [87]. This is one of the simplest tests to assess possible autonomic neuropathy.

Blood Pressure Response to Sustained Muscle Exercise: Sustained (isometric) muscle exercise causes a heart rate dependent increase in cardiac output and increased systemic blood pressure with no change in peripheral vascular resistance [221]. A simple test based on this reflex uses a handgrip dynanometer standardised at 30 per cent of the maximum voluntary contraction with measurement of the blood pressure [87]. Patients with autonomic neuropathy have an abnormally small diastolic blood pressure rise [87, 222]. A rise of diastolic pressure of 16 mmHg or more is defined as normal, between 11 and 15 mmHg as borderline and less than 10 mmHg as abnormal [79]. The test is simple and reproducible but has the disadvantage of being effort dependent.

Blood Pressure Response to Lower Body Negative Pressure: This manoeuvre, applying negative pressure to the body below the level of the iliac crests, results in pooling of blood which elicits cardiovascular reflexes to maintain systemic arterial pressure [223]. During lower body negative pressure diabetics with other evidence of autonomic neuropathy showed hypotension despite forearm vasoconstriction indicating possible impairment of splanchnic vasoconstriction [224]. The test is, however, difficult, time consuming and requires complex equipment.

Other Tests

Pupillary Response: Light induced changes in pupillary area and hippus (pupillary fluctuation) using infra-red videopupillography [200, 201] can be used as tests of autonomic neuropathy and correlate with tests based on cardiovascular reflexes [201]. In practice however these tests, including the simpler measurement of resting pupil size [201], are difficult without special facilities and expensive equipment.

Drug Tests: The heart rate responses to changes in blood pressure induced by drugs such as phenylephrine or nitroglycerine have been used to measure baroreceptor function [225] and have also been applied to detect disordered autonomic function in diabetics [40, 202, 226]. Atropine and propranolol, producing cardiac blockade, can be used as tests to localize parasympathetic or sympathetic damage [202].

Comparison and Correlation of Tests

Although the clinical features of autonomic neuropathy, at least in the early stages, appear patchy, involvement is probably diffuse as abnormal tests can be present without clinical features [80, 81, 217]. Parasympathetic damage can be demonstrated by abnormal tests of vagal function such as loss of beat-to-beat variation in heart rate [75, 82], an abnormal Valsalva manoeuvre [87] and an abnormal heart rate response to standing [219]; whereas sympathetic damage is indicated by a postural fall of blood pressure [87] and an abnormal response to handgrip [87]. Sympathetic innervation may remain intact even in the presence of severe parasympathetic damage [89, 202]. Any evaluation of autonomic function therefore requires a battery of simple tests assessing both parasympathetic and sympathetic involvement.

In practise we use the Valsalva manoeuvre (Valsalva ratio), beat-to-beat variation in heart rate and the heart rate response to standing (30:15 ratio), together with the postural fall in blood pressure and the blood pressure response to handgrip [213]. The evaluation of these tests, particularly their correlation, reproducibility and applicabilitiy is receiving active attention at present [82, 206, 213, 217].

Natural History

The prevalence and natural history of diabetic autonomic neuropathy are not yet clearly elucidated. It is still considered relatively uncommon [227] but this may be untrue. The prevalence may be underestimated as patients developing florid autonomic neuropathy have a poor prognosis [105, 107], while others have non-specific symptoms that remain undiagnosed, or are asymptomatic.

Marked structural and physiological changes unaccompanied by symptoms may occur; and previously unsuspected autonomic neuropathy may be discovered following barium meal, cholecystography or intravenous pyelography. Cardiac vagal damage has been observed in asymptomatic patients [80, 81] and at diagnosis [46]. Asymptomatic patients may have abnormalities of oesophageal motility [116, 119] and cystometry [156–158]. The development of symptoms, which are variable, appears to be relatively late and their onset is often insidious. The clinical features are slowly progressive and usually irreversible [105, 172]. Whether the onset and progression is

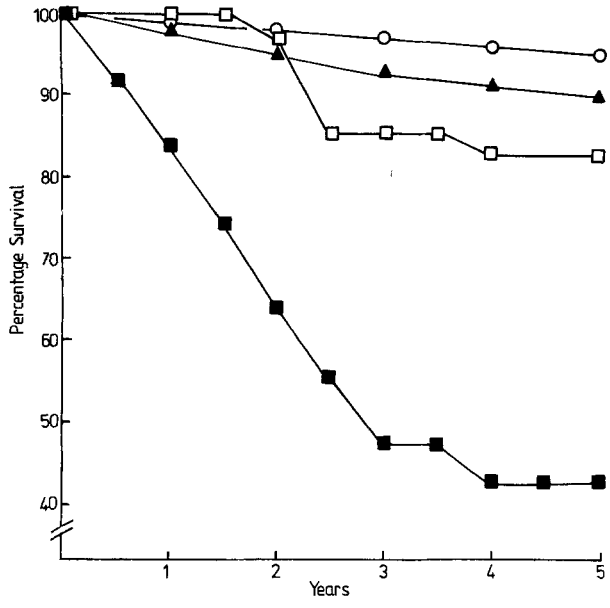


Fig. 6. 5-year survival curves for age and sex matched general population (from Registrar-General of Scotland, 1972–1976) (○), age and sex matched diabetic population (from survey of all diabetics in Edinburgh 1968–1973) (▲), 33 diabetics with normal (□) and 40 diabetics with abnormal (■) autonomic function tests (from: [107])

modified by diabetic control, genetic or environmental factors awaits further study. Tests of cardiovascular reflex function once abnormal, remain abnormal, and tend to deteriorate further with time [105, 172, 217]. A few patients progress to a uniform picture of florid autonomic neuropathy and are severely disabled by postural hypotension, gastric symptoms and bladder disturbance. Such patients usually have other complications including proliferative retinopathy, nephropathy and peripheral neuropathy [107, 172].

Cardiac parasympathetic damage occurs early [75] while sympathetic innervation is preserved [89] possibly because of greater susceptibility to axonal degeneration by the longer vagal fibres. Afferent sensory denervation may also be an early feature as shown by bladder function studies [160, 162, 166] and loss of testicular pain sensation [179]. Sympathetic damage, characterised by postural hypotension, sweating disturbances and hypoglycaemic unawareness occurs later, with parasympathetic damage usually already present [228]. The patchy nature of autonomic neuropathy is illustrated by some patients who, despite severe diarrhoea, have normal oesophageal [119] and gastric [133] motility. Similarly patients with postural hypotension may retain normal reflex vasoconstriction in the feet [229] and arms [224]. Individual symptoms suggestive of autonomic neuropathy vary in diagnostic significance. Patients with impotence alone often have normal tests of cardiovascular reflex function [87] but within five years approximately one quarter developed other symptoms and abnormal tests [172]. At the other extreme patients presenting with postural hypotension invariably have other symptoms of autonomic neuropathy and abnormal cardiovascular reflexes [105, 172].

Patients with symptomatic autonomic neuropathy usually have peripheral neuropathy [39, 75, 187, 232] but it occasionally occurs in isolation [40, 78]. In one of the few studies of this relationship abnormal cardiovascular reflexes correlated with slowing of motor conduction velocity in the legs [230].

Prognosis

In the only prospective study in diabetics with clinical features of autonomic neuropathy and abnormal tests of cardiovascular reflex function there was an excess mortality risk after 2½ years [105]. When followed further for periods up to 5 years there was a calculated mortality rate of 56% compared with 11% for the general diabetic population [107] (Fig. 6). Those with one or more symptoms suggestive of autonomic neuropathy, but with normal tests, had a calculated mortality similar to the general diabetic population. Certain symptoms, particularly postural hypotension, sudden hypoglycaemic attacks and gastric disturbance were associated with a very poor prognosis [172]. Attention has been drawn to 'sudden' and unexplained deaths possibly caused by diabetic autonomic neuropathy [105, 107] and previously some of these deaths may have been wrongly attributed to painless myocardial infarction [103].

The increased mortality may be partly accounted for by an indirect association with accelerating microvascular complications, particularly nephropathy. There may also be a more direct association with autonomic neuropathy by interference in the control of respiration [106] or other autonomic reflexes [204, 205] resulting in 'sudden' death, postural hypotension causing diminished cerebral blood flow and an increased risk of cerebral vascular accidents [231], and urinary stasis and infection leading to worsening renal function.

Treatment

The symptomatic relief of diabetic autonomic neuropathy has often proved difficult. However, certain measures are currently available which make it possible to ease some of the troublesome problems.

Symptomatic postural hypotension may be helped with 9-alpha-fluorohydrocortisone. A small dose of 0.1 to 0.3 mg daily is usually effective, being less than that required in idiopathic postural hypotension [102, 232]. Treatment should be withdrawn if congestive cardiac failure or the nephrotic syndrome develop. If symptoms are exaggerated by insulin a change of timing of the injections may help [233]. Mechanical methods such as elastic stockings or anti-gravity trousers are probably no longer needed.

Symptomatic gastric atony was previously treated by regular small meals, antiemetics, cholinergic drugs, cholinesterase inhibitors [122, 128] and gastric drainage surgery [124]. More recently metoclopramide ('Maxalon') 10 mg three or four times daily before meals, has been shown to produce symptomatic relief in some patients [129, 234–239]. Improved gastric emptying following metoclopramide has been demonstrated by solid-phase meal [237] and scintiscanning [129] techniques. Whether metoclopramide has beneficial effects on oesophageal dysfunction or atony elsewhere in the alimentary tract awaits study.

Diabetic diarrhoea can be treated with broad spectrum chemotherapy [143, 147, 240] although improvement may coincide with natural remission. Patients appeared to respond best to antibiotics when the ^{14}C-glycocholate test was abnormal [148]. Oral cholestyramine, 4 g three times daily, has been recommended [149]. The diarrhoea is probably best initially treated symptomatically, with broad spectrum chemotherapy, and possibly cholestyramine given in more intractable cases.

Patients with bladder dysfunction should be encouraged to void, using manual suprapubic pressure, three to four hourly during the day. Treatment with parasympathomimetic drugs, such as carbachol or distigmine, to improve detrusor contractility has usually proved unhelpful. Chemotherapy, sometimes long-term, is required for urinary infection. Increasing residual urine is best treated by bladder neck resection, provided the patient is fit, allowing the weak bladder to overcome the outflow resistance of the bladder neck muscle, [241].

The treatment of impotence due to autonomic neuropathy is difficult. Testosterone and chorionic gonadotrophin [168] have not been helpful and the former worsens the situation by increasing sexual drive. More helpful has been the development of penile prostheses such as the Small-Carrion type, a semi-rigid silicone rod [242] or the more complex inflatable type [243] which are implanted into each corpus cavernosum. Experience in Europe is limited but the use of these prostheses in small numbers of diabetic patients, in the short-term, has been encouraging [242, 243]. In diabetic males with infertility due to retrograde ejaculation it may be possible to induce pregnancy by artificial insemination using spermatoza obtained from a post-ejaculatory urine sample as described in non-diabetics [244].

Gustatory sweating may be relieved by the anticholinergic drugs propantheline hydrobromide or poldine methylsulphate [187] but troublesome side effects including acute retention of urine may occur. Patients prone to hypoglycaemia without warning should be encouraged to adjust their insulin doses to show more glycosuria. Cardio-respiratory arrest may occur during lower respiratory tract infections or anaesthesia, and any diabetic with autonomic neuropathy need to be closely monitored during these situations; also the use of respiratory depressants should be avoided [106].

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