The enigma of autonomic failure in diabetes

ABSTRACT — The extent of autonomic failure in diabetes and the damage that results both in terms of structure and function is seldom realised. This article focuses on the consequences of autonomic denervation of several different forms of smooth muscle, notably those of arterial wall, vas deferens, stomach, iris and bronchial wall. The clinical implications of these changes are described, in particular the problems arising from vascular (and vas deferens) calcification and abnormalities of vascular reactivity; insulin-induced postural hypotension and the splanchic circulation; the anaemia of autonomic neuropathy from failure of erythropoietin production; gastrointestinal as a cause of gastroparesis; iritis as a symptom related to diabetic autonomic neuropathy (DAN); the concept of an autoimmune basis for DAN; and failure of bronchial reactivity and respiratory arrests in DAN. The importance of clinical observation leading to clinical experiment and research, together with the stimulation of ideas by collaboration with clinical colleagues in other disciplines is emphasised throughout.

Clinical syndromes resulting from damage to the autonomic nervous system were described by Jordan in 1936 and a complete list of those now known is shown in Table 1. While the clinical syndromes of DAN are well known, the true extent of the structural and functional damage resulting from denervation of the many tissues receiving an autonomic innervation is less well recognised. Since a dense sympathetic meshwork covers arteries and to a lesser extent veins and other tissues containing smooth muscle, it is hardly surprising that extensive degenerative tissue changes should occur.

Arteries

Stiffening of large and small arteries is one of the characteristics of long-term diabetes. Sympathetic denervation of arteries leads to medial smooth muscle degeneration and calcification. Edmonds et al observed the extensive distal arterial calcification which can occur in young diabetics with neuropathy (Fig 1), and others have demonstrated that this can follow lumbar sympathectomy. Areas of calcification can assume the histological feature of bone which was found in 3 of 13 amputation specimens from our diabetic patients.

The mechanisms underlying the transformation of vascular smooth muscle cells (VSMC) are not understood. However, it is known that VSMCs can undergo transition from a contractile to a synthetic phenotype, and that this change may be prevented by an intact sympathetic nervous system. Recently, two extracellular matrix proteins involved in calcification and bone formation, osteopontin and matrix Gla protein, have been found to be expressed in synthetic VSMCs. The fact that proteins implicated in bone formation are also expressed in VSMCs suggests that they may represent a crucial early event in the development of inappropriate calcification in the diabetic artery.

Vas deferens

This structure comprises three smooth muscle coats and is lined by columnar epithelium. It has a rich sympathetic nerve supply and, as with other such tissues, has a high nerve growth factor content. Calcification of the vas has been described as a long-term feature of diabetes and the analogy with the development of calcification in denervated arteries is irresistible. Our attempt to demonstrate the presence of a calcified vas in severe autonomic neuropathy showed only 3 of 35 cases with this feature (Purewal, personal communication). However, radiological techniques for its detection are insensitive and this area of research merits further attention. Whether a calcified vas with smooth muscle damage may alter function and lead to absence of an ejaculate is another interesting speculation.

Vascular function

Sympathetic denervation causes loss of vasoconstrictor tone and peripheral vasodilatation, associated with opening of arteriovenous shunts. Skin blood flow increases to about five times normal, and this can occur before there is clinical evidence of neuropathy. These blood flow changes explain some of the clinical features of the neuropathic foot, notably the excessively warm skin, bounding pulses and marked venous distension. The venous PO₂ in the feet is increased because of arteriovenous shunting. Capillary pressure is raised and may lead to neuropathic oedema. However, nutritive capillary flow is not reduced by shunting, and has been shown directly by television microscopy to be normal or even increased. Bone blood flow is also high in these patients, and this is thought to contribute to the osteopenia which predisposes to the development of Charcot osteoarthropathy.

Blood flow responses to various stimuli are also abnormal. Sympathetic stimulation (eg by coughing or standing)
Table 1. Clinical features of autonomic neuropathy.

| Clinical syndromes          | Other abnormalities                                |
|-----------------------------|---------------------------------------------------|
| Cardiovascular              | • Orthostatic hypotension                         |
|                             | • Neuropathic oedema                              |
|                             | • High peripheral blood flow                      |
|                             | • Tachycardia                                    |
|                             | • Rigidity/calcification of arteries              |
| Sudomotor                   | • Nocturnal sweating                             |
|                             | • Gustatory sweating                             |
|                             | • Dry feet                                       |
|                             | • Impotence                                      |
|                             | • Neurogenic bladder                             |
| Gastrointestinal            | • Diarrhoea                                      |
|                             | • Gastroparesis                                  |
|                             | • Oesophageal motility                           |
| Respiratory                 | • Arrets                                         |
|                             | • ? Sudden deaths                                |
|                             | • ? Sleep apnoea                                 |
| Skeletal                    | • Charcot arthropathy                            |
|                             | • Foot bone density reduced                      |
| Eye                         | • Iritis                                         |
|                             | • Pupillary responses impaired                   |
|                             | • Pupil size reduced                             |
| Neuroendocrine              | • Catecholamines                                 |
|                             | • Glucagon                                       |
|                             | • Pancreatic polypeptide                         |
|                             | • Reduced responses                              |

normally induces peripheral vasoconstriction. Neuropathic patients show a variable blunting of these responses. Most strikingly, heating the skin of the neuropathic foot can induce paradoxical vasoconstriction (in contrast to the normal vasodilatation), probably because neuropathy has isolated the local axon reflex which governs this response. Maximal vasodilatation is also reduced in these patients. Although this defect is partly attributable to the effects of hyperglycaemia per se on the microvasculature, failure of nitric oxide dependent smooth muscle vasodilatation in diabetes and neuropathy has been described. Failure of arterial dilatation in response to direct application of the NO donor, sodium nitroprusside, provides further evidence of smooth muscle dysfunction in neuropathy. Denervation of vascular smooth muscle, therefore, seriously affects its function and this may account for at least some of the pathophysiology of diabetes itself. The discovery by Edmonds et al that ephedrine, a sympathomimetic agent, effectively alleviates neuropathic oedema, arose directly from the observations on blood flow changes, though so far no other new therapeutic measures have arisen from this work.

The cardiovascular effects of insulin are also paradoxical in autonomic neuropathy patients. In normal subjects, intravenous or subcutaneous insulin administration activate the sympathetic nervous system, causing an increase in circulating noradrenaline, supine blood pressure and peripheral vascular resistance, with a decrease in forearm blood flow. At supraphysiological levels (often used in treatment of diabetes), vasodilatation occurs with decrease in peripheral vascular resistance and increase in flow. In healthy subjects, blood pressure remains essentially unaltered despite the decrease in peripheral vascular resistance. These observations suggest that insulin has dual effects, namely a vasoconstrictor effect mediated by the sympathetic nervous system at low physiological insulin levels, and a vasodilator effect perhaps mediated by NO-release which

Fig 1. Arterial calcification of the feet in diabetic neuropathic patients. (Reproduced from Ref 2 by permission of the BMJ.)
dominates at supraphysiological insulin levels. In patients with autonomic neuropathy, insulin causes a decrease in supine BP and exacerbates postural hypotension which becomes much worse (Fig 2), or is provoked in neuropathic patients without postural hypotension\(^{13,17}\). These effects are due to hyperinsulinaemia. It is possible that the absence of the sympathetic activity in DAN results in dominance of NO-mediated vasodilatation with resulting insulin induced hypotension\(^{13,18}\). This hypotensive effect of insulin also occurs after sympathectomy. In patients with DAN the insulin induced exacerbation of hypotension may occasionally cause a blackout that might be confused with hypoglycaemia.

**The splanchnic circulation**

Failure of the splanchnic bed to vasoconstrict on standing could be an important mechanism in determining postural hypotension, as it is in primary autonomic failure. In DAN, using ultrasound techniques, we demonstrated diminished mesenteric vasoconstriction on standing. However, this was also observed in IDDM patients without postural hypotension\(^{19}\) (Fig 3), so the importance of this mechanism in DAN is uncertain. Eating causes a large increase in splanchnic blood flow, and postprandial exacerbation of postural hypotension is well known to occur in non-diabetic forms of autonomic neuropathy. It has been suggested that the meal causes release of vasodilator substances which increase mesenteric blood flow and splanchnic pooling. Possible agents include insulin, vasoactive intestinal peptide and neurotensin. Octreotide, which prevents the release of a wide range of peptides from the gut, can reduce postprandial hypotension.

In patients with DAN, food increases mesenteric blood flow to the same extent as in normal subjects whether or not insulin is administered at the same time. Yet, in our studies, there was no exacerbation of postural hypotension at the time of maximum splanchnic hyperaemia 30 minutes after patients finished eating. These are paradoxical findings; perhaps the observations should have been continued for longer than 30 minutes, since in other studies the hypotensive effects of insulin are not demonstrable before one hour\(^{13}\); the pathophysiology of postural hypotension in diabetes may have a different basis.

**Erythropoietin and diabetic autonomic neuropathy**

Erythropoietin (EPO) production by the kidney normally increases in anaemia and hypoxia. Its production is modulated by the sympathetic nervous system, and in animal models sympathectomy reduces levels of stimulated EPO. EPO depletion can occur in patients with autonomic neuropathy from multi-system atrophy and in diabetes\(^{20}\).

In 17 patients with severe symptomatic DAN, the mean haemoglobin was 11±1.6 g/dl (the lowest was 8.1 g/dl) (Winkler et al, unpublished observations). The EPO levels in these anaemic patients, none of whom had renal failure or other cause for anaemia, were substantially less than those of comparable anaemic patients with anaemia from iron deficiency. Thus, the normal mechanisms stimulating EPO production had failed, perhaps as a consequence of autonomic neuropathy.
In four patients administration of EPO by injection (25 iu/kg given subcutaneously thrice weekly for three months) increased haemoglobin by 2–3 g/dl which fell again within three months of stopping treatment (Fig 4). EPO treatment may also lessen the severity of postural hypotension. Treatment improved the patients’ overall health and sense of well being and they all asked to continue the injections.

Gastroparesis

The stomach wall comprises of another highly specialised form of smooth muscle. Denervation of gut normally causes smooth muscle hypertrophy\(^1\) which contrasts with the atrophy of the smooth muscle of the vasculature. We have been surprised therefore to find evidence of gastric smooth muscle degeneration in cases of autonomic gastroparesis, with some features similar to the smooth muscle degeneration in some rare primary degenerative disorders of the gut. Thus, there are patches of atrophic smooth muscle fibres with reduced cytoplasm and pyknotic nuclei, and an extensive increase of collagen between bundles of muscle fibres. Rounded refractile eosinophilic PAS-negative structures varying in size from 5–25 mm are scattered throughout the muscularis propria and referred to as ‘M’ bodies (Fig 5), not seen in the muscularis mucosa\(^2\,\text{to}\,\text{3}\). ‘M’ bodies, which represent a degenerative phenomenon, appear to be specific for diabetes. These histological changes, which occur with or without major vagal nerve degeneration, may represent a gastromyopathic process as a cause for gastroparesis in diabetes.

The rare cases of intractable vomiting from gastroparesis\(^4\) may require invasive treatments when conventional remedies have failed. Percutaneous endoscopic jejunostomy or gastrostomy may alleviate the problem until there is a natural remission of the vomiting, which can occur even after a long time. Patients with intractable autonomic gastroparesis are usually young and beset with multiple diabetic complications, often with a limited life prognosis; their management overall is never straightforward and sometimes requires a more definitive surgical

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**Fig 4.** Effect of erythropoietin administration (3 months) and withdrawal (3 months) on haemoglobin in four patients with severe symptomatic diabetic autonomic neuropathy. One patient failed to continue attendances after withdrawal of EPO.

**Fig 5.** Numerous ‘M’ bodies appear as round, dark stained masses amongst the smooth muscle cells of the muscularis propria of the stomach. The nuclei in the smooth muscle cells contain loose chromatin and prominent nucleoli. (Reproduced from Ref 22 by permission of Gustav Fischer Verlag.)
procedure. Some may benefit from 70% gastric resection with Roux-loop diversion of biliary and pancreatic secretions. This procedure prevents the potential complication of alkaline reflux gastritis that may complicate standard gastrectomy procedures and induce further vomiting later.

The iris: iritis, nerve growth factor and neurological mechanisms

The smooth muscle of the intrinsic muscles of the iris is innervated mainly by the parasympathetic nerves. Sympathetic nerves are distributed only to the blood vessels and the radial muscle of the iris. It is richly endowed with nerve growth factor which increases when denervated.

The altered pupillary reactions resulting from autonomic neuropathy are well described. We reported that iritis is a feature of severe symptomatic autonomic neuropathy in 1984. I have seen several cases since the first report, and have also observed that the iritis is usually (though not always) non-recurring, and non-deforming.

The underlying mechanism responsible for the iritis is not known; by analogy with other forms of iritis, it may have an immune basis. More than a decade ago, postmortem examination of severe DAN by Duchen showed infiltration of autonomic ganglia and nerve bundles with lymphocytes, macrophages and plasma cells which led him to suggest an immunological mechanism; activated T-cells are also present. Most recently, the presence of autoantibodies to autonomic neural tissues (vagus nerve, cervical ganglion and adrenal medulla) in DAN patients was described by Rabinowicz. Our own studies in 1993, and more recent work from Munich, have demonstrated their presence in 20–30% of insulin dependent diabetic patients (and only rarely in non-insulin dependent diabetics) compared with 3–4% in non-diabetic controls. Furthermore, serum from neuropathic patients can inhibit the growth of cultures of neuroblastoma cells in vitro. The relationship of the autoantibodies to autonomic neuropathy itself is disputed, though they are more often present in those with DAN than in those without. At present, their role is unknown; whether they merely reflect autonomic damage or have some part in causing it, or indeed, whether they have an entirely different significance in the context of IDDM, are questions that require further investigation.

Nerve growth factor (NGF)

NGF is produced by target organs receiving a sympathetic innervation, and their NGF content reflects its intensity. The presence of NGF is demonstrable in many tissues, including arterial smooth muscle. Especially high concentrations are found in two tissues with a particularly rich autonomic innervation – the vas deferens and the iris. The role of NGF as an intermediary in inflammatory processes by increasing cytokine release is increasingly recognised, and may underlie iritis in autonomic neuropathy.

Autonomic denervation and the respiratory system

Bronchial smooth muscle also receives an autonomic innervation and is affected by autonomic neuropathy. Airway tone is mainly under vagal control and is reduced in diabetics with autonomic neuropathy who have less bronchodilatation in response to anticholinergic agents. Diabetics with autonomic neuropathy also have less bronchoconstriction during inhalation of cold air (Fig 6), and even more strikingly, a diminished or even absent cough reflex in response to an inhaled irritant such as citric acid. These deficits are due to neuropathic denervation and not to any intrinsic abnormality in bronchial smooth muscle, which responds normally to direct stimulation by inhaled histamine. Whether the absence of these stimulated reflexes has any clinical implications is unknown.

The perception of respiratory sensations in diabetics has also been measured in patients breathing through a tube manifold apparatus with randomly varied air flow resistance. Diminished perception of respiratory resistance loads occurred in diabetics with neuropathy and this might render them prone to subclinical episodes of respiratory illness. The integrity of several ventilatory responses in autonomic neuropathy has also been investigated but with inconclusive results.

Sudden respiratory arrests have been described in DAN. In most of these episodes there was some interference with respiration either by anaesthesia, drugs, or bronchopneumonia. Such episodes are transient, and while temporary ventilation may be needed, full recovery is the rule. Anaesthetists need to be forewarned of this possibility when symptomatic autonomic neuropathy patients require even minor surgery. Sleep apnoea has also been reported in IDDM subjects, occasionally in association with autonomic neuropathy, and heart rate responses to apnoeic episodes may be abnormal. It is unclear whether or not respiratory

Fig 6. Bronchial reactivity (specific airways conductance, sGaw) to cold air inhalation in diabetic autonomic neuropathy. (Reproduced from Ref 29 by permission of the BMJ.)
arrests are responsible for the sudden unexplained deaths reported in diabetic autonomic neuropathy patients.

Conclusions
In this review, I have reported a number of novel clinical observations which result chiefly from autonomic denervation of several highly specialised forms of smooth muscle. They have all arisen from bedside observations made over several years, greatly enhanced by collaboration with colleagues in other disciplines. The need to continue this tradition of clinical research is paramount, and was well expressed by Sir Walter Bodmer in his Harveyian oration in 1996 – ‘We must at least ensure that the opportunity to do first class clinical research in the setting of our NHS is preserved.’

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