

EDITORIAL

Diabetic neuropathy: mechanisms and future treatment options

There is no single diabetic neuropathy. A wide variety of syndromes involving the peripheral nerves may be encountered in patients with diabetes mellitus, implying a correspondingly diverse range of underlying causative mechanisms. The classification of the diabetic neuropathies is not yet finalised and has required successive modifications in the light of accumulating knowledge. The scheme favoured by myself is given in the table. This broadly categorises the manifestations into (1) rapidly reversible phenomena, (2) generalised polyneuropathies, (3) focal and multifocal neuropathies, and (4) superimposed chronic inflammatory demyelinating polyneuropathy.

**Pathogenesis**

**HYPERGLYCAEMIC NEUROPATHY**

Patients with severe uncontrolled hyperglycaemia may complain of uncomfortable sensory symptoms, mainly in the lower limbs. They also show reduced nerve conduction velocity and increased resistance to ischaemic conduction failure. These phenomena have little clinical importance. They are rapidly corrected by the establishment of diabetic control and are thus presumably related directly to hyperglycaemia or to a metabolic abnormality correlated with it. Possible mechanisms have been discussed by Watkins and Thomas.<sup>1</sup> The increased resistance to ischaemic conduction failure may be related to a switch to anaerobic glycolysis in diabetic nerve. The positive sensory symptoms could be related to hypoxia, which is known to be present in human diabetic neuropathy. Experimentally, hyperglycaemic but not normoglycaemic hypoxia gives rise to alterations in fast K<sup>+</sup> conductance and afterpotentials in axons, related to axoplasmic acidification. This might lead to the generation of ectopic impulses and contribute to the occurrence of positive symptoms.

**DISTAL SENSORY/AUTONOMIC POLYNEUROPATHY**

The commonest type of diabetic neuropathy is a distal symmetric predominantly sensory polyneuropathy and there are indications that small fibre sensory modalities are

*Classification of the diabetic neuropathies*

- Hyperglycaemic neuropathy
- Generalised neuropathies
  - Sensorimotor polyneuropathy
  - Autonomic neuropathy
  - Acute painful sensory neuropathy
- Focal and multifocal neuropathies
  - Cranial neuropathies
  - Thoracoabdominal radiculoneuropathy
  - Focal limb neuropathies (including entrapment and compression neuropathies)
  - Proximal diabetic neuropathy
- Superimposed chronic inflammatory demyelinating polyneuropathy

From Watkins and Thomas.<sup>1</sup>

affected earlier. Minor distal motor involvement may coexist. Severe autonomic neuropathy is virtually only encountered in type I diabetic patients, but less prominent accompanying autonomic involvement is frequent both in type I and type II patients. The underlying pathology in the distal symmetric sensory polyneuropathy (DSSP) has been shown to consist of a distal axonal degeneration of dying back type<sup>2</sup> with relative preservation of dorsal root ganglion cells.<sup>3,4</sup> This may well be a central-peripheral distal axonopathy in which there is also a rostral degeneration of nerve fibres in the dorsal columns of the spinal cord.<sup>4</sup>

It is still not established whether the mechanism for DSSP is a direct metabolic effect or whether it is secondary to hypoxia from microvascular disease. The results of the Diabetes Control and Complications Trial (DCCT) have firmly demonstrated that strict control of blood glucose concentrations by an insulin pump or multiple daily insulin injections can prevent or greatly diminish the risk of developing neuropathy.<sup>5</sup> It seems unlikely that hypoxia is the major cause of DSSP as in other situations nerve ischaemia gives rise to predominant motor involvement and not to a sensory/autonomic neuropathy. Moreover, it would be difficult to explain the occurrence of a central-peripheral distal axonopathy on an ischaemic basis. Nevertheless, microvascular disease is often,<sup>6</sup> although not consistently,<sup>7</sup> present in diabetic polyneuropathy and a distally accentuated sensorimotor neuropathy can result from the summation of multiple proximal nerve trunk lesions.<sup>8</sup> Such cases could well have an ischaemic basis.

In considering possible metabolic causes for polyneuropathy, a major metabolic abnormality in nerve is the accumulation of sorbitol because of increased flux in the polyol pathway secondary to hyperglycaemia.<sup>9</sup> In this pathway, glucose is converted to sorbitol by the enzyme aldose reductase. The quantities of sorbitol present in diabetic nerve are insufficient to produce osmotic damage but it is possible that they may have deleterious effects on neural metabolism. On the other hand, as discussed later, trials with aldose reductase inhibitors to reduce the production of sorbitol have so far failed to show any substantial effects on diabetic polyneuropathy. Reduced nerve myoinositol concentrations have been implicated in a cascade of changes via reduced Na<sup>+</sup>K<sup>+</sup> - ATPase activity, leading to "axoglial dysfunction", paranodal swelling, axonal atrophy, and nerve fibre degeneration.<sup>10</sup> However, the reduction of nerve myoinositol concentrations that was found was in experimental diabetes in rats and this has not been confirmed in human diabetic nerve; neither has the presence of paranodal nerve fibre swelling and axoglial dysfunction.

Attention has also been directed towards alterations in the metabolism of essential fatty acids. These agents are necessary for the maintenance of normal cell membrane structure and eicosanoid production. In diabetes there is a defect in the conversion of linoleic to  $\gamma$ -linolenic acid by  $\delta$ -6 desaturase.<sup>11</sup> Administration of  $\gamma$ -linolenic acid to diabetic rats has been shown to improve nerve conduction velocity, probably by improving vascular perfusion in peripheral nerve.<sup>11</sup> Treatment of human diabetic neuropathy by the administration of  $\gamma$ -linolenic acid has not resulted in substantial beneficial effects on neuropathy.

Persistent hyperglycaemia results in the non-enzymatic glycation of proteins leading to the production of non-degradable advanced glycation end products (AGEs).<sup>12</sup> Axonal proteins have been shown to be abnormally glycosylated in human diabetic patients, and it is known that the formation of AGEs on the extracellular connective tissue matrix and blood vessels gives rise to functional alterations.<sup>12</sup> Whether these effects are important in the causation of diabetic neuropathy is not established. The formation of AGE can be inhibited by aminoguanidine, but the action of this agent in improving nerve blood flow and conduction velocity, shown experimentally in diabetic rats, is probably mediated by increased nitric oxide production and consequent vasodilatation.

As it seems likely that DSSP is a distal axonopathy of dying back type, the possibility arises that there may be an interference with the operation of growth factors by the diabetic state so that the nerve cells are unable to maintain their distal axons.<sup>13</sup> There is experimental evidence from observations on animal models of diabetes that insulin-like growth factor I (IGF-I) may improve regeneration and also that the availability of neurotrophins from peripheral targets may contribute to the pathogenesis of neuropathy.<sup>14</sup>

An important aspect of diabetic sensory polyneuropathy is a failure of axonal regeneration.<sup>15</sup> This is initially profuse but it later fails. This probably contributes to the lack of reversibility of the neuropathy once it is established, even with good glycaemic control. It is not yet clear whether the reduction in regeneration is related to alterations in the nerve microenvironment or whether it is due to a reduced capacity of the neurons to mount a regenerative response. Loss of dorsal root ganglion cells is relatively slight and cannot explain this finding.

Acute painful diabetic neuropathy<sup>16</sup> is an uncommon syndrome, distinct from DSSP. It is characterised by severe burning or aching pain felt mainly in the lower limbs but sometimes more widely. Sensory loss on examination is slight but there is intense cutaneous contact hyperaesthesia. Nerve biopsy shows acute axonal degeneration. The disorder resolves over the course of several months with adequate glycaemic control. Its mechanism is so far uncertain. It may be associated with precipitous weight loss and uncontrolled hyperglycaemia or at times is precipitated by treatment with insulin.

Rarely, subacutely evolving distal symmetric predominantly motor neuropathies of axonal type are encountered, usually in elderly patients, for which no explanation other than diabetes is evident. Such cases are so far poorly characterised.

#### FOCAL AND MULTIFOCAL NEUROPATHIES

Focal peripheral nerve lesions are more common in diabetic patients than in the general population. They include cranial neuropathies, particularly affecting the third and seventh nerves, thoracoabdominal neuropathies, focal limb neuropathies, and the proximal lower limb motor neuropathy (diabetic amyotrophy). The focal limb neuropathies are often at common sites of entrapment or external compression.

The abrupt onset of diabetic third cranial nerve palsies is consistent with an ischaemic basis and there are good pathological studies to support this.<sup>17</sup> It is of interest that these studies have shown focal demyelination, accounting for the usually satisfactory recovery that occurs, presumably by remyelination. It is noteworthy that nerve ischaemia usually gives rise to axonal loss rather than selective demyelination and it is possible that the demyelination in focal diabetic lesions is the result of reperfusion injury which is known to produce demyelination.<sup>18</sup>

Other focal peripheral nerve lesions are likely to result from an abnormal susceptibility of diabetic nerve to compression. The reason for this is uncertain. In non-diabetic subjects it has been shown that entrapment neuropathies are related to longitudinal axoplasmic displacement away from the site of compression and the consequent distortion and breakdown of the myelin sheath of larger myelinated nerve fibres. The basal lamina surrounding nerve fibres is known to be abnormally rigid in patients with diabetic neuropathy, possibly due to increased cross linking of collagen because of abnormal glycation related to AGE formation. The compliance of the basal laminal tubes around the fibres may therefore be reduced in diabetic nerve, rendering the fibres more vulnerable to mechanical damage.

Recent studies have shown that in a proportion of patients with proximal lower limb diabetic neuropathy, inflammatory lesions, including vasculitis, affecting small epineurial vessels, are present in the peripheral nerves,<sup>19, 20</sup> raising the possibility of a superimposed autoimmune process. Whether similar lesions account for some other focal and multifocal neuropathies is at present uncertain, but the coexistence of thoracoabdominal radiculoneuropathy that is sometimes encountered suggests that this may be so.

#### SUPERIMPOSED CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

Evidence is accumulating that chronic inflammatory demyelinating polyneuropathy (CIDP) is more frequent in diabetic patients.<sup>21</sup> This should be suspected in diabetic patients with a predominantly motor distal polyneuropathy in whom nerve conduction velocity is markedly slowed and, in particular, if there is evidence of conduction block. Again a secondary autoimmune process may be responsible. A similar association between CIDP and hereditary motor and sensory neuropathy is recognised.

#### Prospects for treatment

##### DISTAL SYMMETRIC SENSORY POLYNEUROPATHY

As already stated, it is now clear that strict control of glycaemia by an insulin pump or by multiple daily injections of insulin will prevent or even improve neuropathy.<sup>5</sup> This treatment, however, is only applicable to patients with type I insulin dependent diabetes and only to a small proportion of them. It is common experience that good glycaemic control can only be achieved in about 25% of patients. Once DSSP is established it fails to improve significantly even with satisfactory glycaemic control. Treatment is therefore required that will prevent the occurrence of neuropathy or halt its deterioration if present. After 25 years of diabetes, about 50% of patients will have developed neuropathy.<sup>22</sup> It would be helpful to be able to identify those patients who are more susceptible to this development—for example, by the detection of genetic markers associated with neuropathy,<sup>23</sup> so that they can receive particular attention. In addition, methods need to be devised so that treatment to prevent neuropathy can be given despite suboptimal glycaemic control. For this to be possible, increased understanding of the pathogenesis of neuropathy is essential.

The use of aldose reductase inhibitors held out considerable promise for the treatment of DSSP but so far the results

of trials have been disappointing.<sup>9</sup> Nevertheless, their potential utility cannot yet be dismissed. Some trials had to be abandoned because of side effects of the drugs and future trials would need to be continued over considerably longer periods than those performed hitherto in view of the fact that DSSP normally has a slow insidious onset over the course of several years. This also applies to other forms of metabolic intervention such as the use of agents to diminish the accumulation of advanced glycosylation end products.

#### NEUROPATHIES RELATED TO DYSIMMUNE MECHANISMS

The demonstration of inflammatory changes in the peripheral nerves of patients with proximal lower limb motor neuropathy or those with superimposed CIDP has raised the possibility of the use of immunomodulatory treatment. There have been reports of the successful treatment of patients with the former condition with intravenous human immunoglobulin, plasma exchange, corticosteroids, or cytotoxic drugs (cyclophosphamide, azathioprine) either alone or in combination.<sup>24</sup> However, the natural history of this disorder is often one of spontaneous improvement and a controlled clinical trial is now clearly needed.

Non-diabetic patients with CIDP may benefit from similar treatment and studies on limited numbers of cases have so far indicated that this also applies to CIDP in diabetic subjects.<sup>21–24</sup> Inflammatory lesions are known to be present in autonomic ganglia and nerve trunks in patients with severe autonomic neuropathy,<sup>25</sup> again suggesting a superimposed autoimmune process. Whether immunomodulatory measures would be beneficial in such cases is unknown.

#### POSSIBLE USE OF GROWTH FACTORS

Studies on animal models of diabetes indicate that IGF I enhances regeneration and nerve growth factor (NGF) has been shown to have a beneficial effect in other experimental neuropathies. Preliminary evidence from phase II clinical trials of human recombinant NGF has indicated that this agent may benefit symptoms related to dysfunction of small sensory fibres.<sup>26</sup> The results of phase III trials are therefore awaited with interest. Diabetes affects fibres of all sizes, both myelinated and unmyelinated, but the neurotrophic effect of NGF is mainly on small myelinated and unmyelinated axons. If the use of NGF is shown to be helpful, future treatment regimes may require combinations of growth factors—for example, with the addition of brain derived neurotrophic factor (BDNF)—so that the large fibre neuropathy is also targeted.

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## EDITORIAL COMMENTARY

# Treatment of X-linked adrenoleukodystrophy with Lorenzo's oil

Van Geel *et al* in this issue (pp 290–9)<sup>1</sup> provide a thorough multidisciplinary analysis of the clinical progression of 22 patients with X-linked adrenoleukodystrophy (X-ALD) who were treated with Lorenzo's oil (a 4:1 mixture of glyceryl trioleate and glyceryl trierucate). Four patients remained unchanged. One patient improved, 13 worsened, and in five some indices improved and others worsened.

Mild to moderate worsening was the most frequent finding and confirms previous reports.

The introduction of Lorenzo's oil therapy 10 years ago raised high expectations, heightened by the motion picture of the same name. The expectations were based mainly on the finding that the oil normalises the concentrations of very long chain fatty acids (VLCFA) in plasma. Accumulation of

VLCFA is the principal biochemical abnormality in X-ALD and there is evidence that excess of VLCFA contributes to pathogenesis.<sup>2</sup> Normalisation of the plasma concentration of the “offending” metabolite is of undisputed benefit in conditions such as phenylketonuria. These considerations, coupled with the tragic course of untreated childhood cerebral X-ALD, led myself and others to conduct non-randomised rather than placebo controlled therapeutic trials. Information obtained since that time highlights drawbacks of this decision and provides a lesson for the future. The drawback is that more than a decade after the first use of Lorenzo’s oil, we still do not know if it is of clinical value. Even though most symptomatic oil treated patients continue to progress, our incomplete knowledge of natural history and the lack of a control group may have masked a moderate benefit. The same concerns limit the power of a current non-randomised international study that involves 250 asymptomatic patients and aims to test whether oil administration diminishes later neurological disability. A lesson relevant to future studies is the realisation that normalisation of plasma VLCFA concentrations is not a valid marker of therapeutic success. Concentrations of VLCFA in plasma do not correlate with the degree of neurological disability,<sup>2</sup> and in the study of Van Geel *et al* patients worsened despite normalisation of plasma concentrations. Furthermore, erucic acid, the active principle of Lorenzo’s oil, does not seem to enter the brain.<sup>2</sup> These data diminish the rationale for the therapy.

The continued neurological progression in most patients treated with oil, combined with a 55% incidence of side

effects, supports the recommendation of van Geel *et al* that it should not be offered routinely as a therapy for patients who are already symptomatic. We do recommend continuation and completion of the important study designed to determine whether the oil can prevent later neurological disability. Patients enrolled in this study are monitored to guard against side effects and those who are candidates for bone marrow transplantation are identified. Bone marrow transplantation carries a high risk but has shown remarkable benefit in some patients with early brain involvement.<sup>2</sup> Two new promising therapeutic approaches have been proposed recently.<sup>4,5</sup> The Lorenzo’s oil experience highlights the importance of developing a study design that will permit timely evaluation of their clinical effectiveness.

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## EDITORIAL COMMENTARY

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### The Sydney multicentre study of Parkinson’s disease

Natural history studies of Parkinson’s disease with adequate duration of follow up are scarce and fraught with difficulty due to selection bias and retrospective assessment in hospital series, confounding effects of comorbidity and problems of diagnostic accuracy.<sup>1</sup> The pivotal study by Hoehn and Yahr<sup>2</sup> on a cohort of 672 patients with “primary parkinsonism” came up with a rather bleak prognosis, with 61% of patients severely disabled or dead after 5 to 9 years of follow up, increasing to more than 80% of those who were followed up for more than 10 years. Overall mortality was increased to about threefold the expected rate in the general population. Such poor longterm outcome is thought to reflect the history of idiopathic Parkinson’s disease in the prelevodopa era with some added negative bias due to less stringent diagnostic criteria used in those days. Early postlevodopa mortality studies in Parkinson’s disease indeed found mortality ratios of 1.5 or less, rising again, however, with extended follow up, suggesting that levodopa reduces excess mortality early in the course of Parkinson’s disease but fails to prevent increased mortality in the long term.<sup>3</sup>

This general trend is also confirmed in the 10 year prospective follow up results on progression and mortality of the Sydney multicentre study of Parkinson’s disease now published by Hely *et al* (this issue, pp 300–7). Regular fol-

low up of this cohort for a maximum of 13 years has provided valuable data on disease progression and mortality in those 126 patients in whom the original diagnosis could be upheld. By 10 years 38% had died, rising to 48% by last follow up, yielding a standard mortality ratio for the whole cohort of 1.58, which is similar to many of the previously published postlevodopa studies.<sup>3</sup> Significant risk factors for increased mortality included old age at onset, rapid initial progression on the Hoehn and Yahr scale, and—surprisingly—initial randomisation to bromocriptine. Although this finding certainly does not support claims of possible neuroprotective effects of bromocriptine or dopamine agonists in general<sup>4</sup> it is of limited relevance. Only very few patients originally randomised to bromocriptine continued such monotherapy for longer than 1 year and all patients taking bromocriptine had been switched to combined treatment with levodopa by year 5. So unfortunately the longterm outcome data of the Sydney study do not allow for conclusions about differential effects of levodopa monotherapy versus bromocriptine monotherapy versus combined treatment on longterm progression and prognosis.

The biggest surprise in the Sydney study, however, is that the percentages of patients severely disabled or dead after 10 years of follow up are very similar to the figures

originally reported in the Hoehn and Yahr study in the prelevodopa area. Does this mean that dopaminergic replacement with levodopa, dopamine agonists, or combinations of both has not significantly altered the longterm outlook for people with Parkinson's disease? Probably not. As the authors admit, their patients may have been undertreated due to the initial design of the study as a comparative trial of low dose levodopa versus low dose bromocriptine. Their outcome may not be representative for the treated parkinsonian population at large. By contrast the recent 9 year follow up results of the DATATOP cohort of patients showed supernormal life expectancy with a standard mortality ratio of 0.9.<sup>5</sup> Such discrepancies in outcome between prospective follow up studies over similar time periods are likely to reflect differences in baseline severity and comorbidity and possibly treatment strategies. Idiopathic Parkinson's disease is not a prognostically uniform entity; elderly patients with comorbid

dementia and cerebrovascular and heart disease face a high risk of significant disability or death after 10 years, contrasting with a near normal life expectancy in the younger onset patient without dementia or other significant comorbidity and optimal treatment under specialist supervision.

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## EDITORIAL COMMENTARY

# Deep brain stimulation in Parkinson's disease

This issue of *the Journal* sees the publication of two papers that increase our knowledge of the functions of the internal architecture of the thalamus and globus pallidus—an important achievement given the existing literature on stereotactic functional surgery for Parkinson's disease.

The paper by Caparros-Lefebvre *et al*<sup>1</sup> (pp 308-14) is fascinating, because one would have expected that after nearly 50 years of thalamic surgery every possible internal thalamic target would have been explored. However, the surgical outcomes have not always been studied carefully, or published for others to share. Caparros-Lefebvre *et al* compared the functional results and electrode positions obtained by two teams performing thalamic stimulation for parkinsonism. Anatomical comparisons were possible because ventriculography had been performed by both groups. The two teams used similar techniques for the implantation of electrodes into the ventralis intermedialis nucleus of the thalamus (VIM), although there were minor differences in the approach trajectory which led to team A's electrodes being placed an average of 2.9 mm posteromedial to those of team B. The result of this slight positional difference was that both tremor and drug induced choreic dyskinesias were abolished by the more posteromedial target, whereas only tremor was relieved by the more anterolateral electrode position. Evidence for this antichoreic dyskinesic effect being secondary to involvement of the centre median and parafascicularis complex (CM-Pf) nucleus is provided. It is noteworthy that no effect on dystonic dyskinesias was found, suggesting a segregation of the pathways involved in these two forms of dyskinesias. However, the clinical importance of this paper lies in the demonstration that surgery to a single posteromedial VIM target can achieve the same functional outcome as that involving both VIM and ventralis oralis posterior—a finding that may translate into a reduced risk of side effects.<sup>1</sup>

The paper by Durif *et al*<sup>2</sup> (pp 315-22) considers the possible causes for the variability in clinical outcome obtained

after pallidal surgery. The study focuses on the precise target site which in most series, including this one, lies within the posterior half of the pallidum. Durif *et al* report that within their pallidal target, ventral stimulation is more effective than dorsal stimulation for alleviating rigidity, bradykinesia, and drug induced dyskinesias, a finding that concurs with a recent study of pallidotomy and clinical outcome, but differs from the findings obtained by Krack *et al* who noted that ventral stimulation within GPi caused improvement in rigidity and alleviation of levodopa induced dyskinesias but caused severe akinesia and blocked the antiakinetic effect of levodopa.<sup>4,5</sup> There are two possible reasons for this discord: firstly, the target chosen by Krack *et al* is posterolateral to that selected by Durif *et al*, and secondly the approach angle may matter.

These studies show that from detailed assessments of the relation between surgical target and clinical outcome important clinical and physiological questions may be answered about the function of specific areas within the thalamus and globus pallidus.

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