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Diabetic Neuropathy

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INTRODUCTION

Polyneuropathy is one of the commonest complications of the diabetes and the commonest form of neuropathy in the developed world. Diabetic polyneuropathy encompasses several neuropathic syndromes, the most common of which is distal symmetrical neuropathy, the main initiating factor for foot ulceration. The epidemiology of diabetic neuropathy has recently been reviewed in reasonable detail *(1)*. Several clinic- *(2,3)* and population-based studies *(4,5)* show surprisingly similar prevalence rates for distal symmetrical neuropathy, affecting about 30% of all people with diabetes. The EURODIAB prospective complications study, which involved the examination of 3250 patient with type 1 from 16 European countries, found a prevalence rate of 28% for distal symmetrical neuropathy *(2)*. After excluding those with neuropathy at baseline, the study showed that over a 7-year period, about one-quarter of patients with type 1 diabetes developed distal symmetrical neuropathy; age, duration of diabetes, and poor glycemic control being major determinants *(6)*. The development of neuropathy was also associated with potentially modifiable cardiovascular risk factors such as serum lipids, hypertension, body mass index, and cigaret smoking *(6)*. Furthermore, cardiovascular disease at baseline carried a twofold risk of neuropathy, independent of cardiovascular risk factors *(6)*. Based on recent epidemiological studies, correlates of diabetic neuropathy include increasing age, increasing duration of diabetes, poor glycemic control, retinopathy, albuminuria, and vascular risk factors *(1,2,4,6)*. The differing clinical presentation of the several neuropathic syndromes in diabetes suggests varied etiological factors.

CLASSIFICATION

Clinical classification of the various syndromes of diabetic peripheral neuropathy has proved difficult. The variation and overlap in etiology, clinical features, natural history, and prognosis has meant that most classifications are necessarily oversimplified and none has proved capable of accounting for all these factors. Nevertheless, attempts at classification stimulate thought concerning the etiology of the various syndromes and also assist in the planning of management strategy for the patient.

Clinical manifestations *(7)* and measurement *(8,9)* of somatic neuropathy have recently been reviewed. There are a number of classifications for diabetic polyneuropathy. Based on the various distinct clinical presentations to the physician, Ward recommended a classification of diabetic polyneuropathy depicted in Table 1 *(10)*. This practical approach to

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Table 1
The Varied Presentations of the Neuropathic Syndromes Associated With Diabetes

Chronic insidious sensory neuropathy
Acute painful neuropathy
Proximal motor neuropathy
Diffuse symmetrical motor neuropathy
The neuropathic foot
Pressure neuropathy
Focal vascular neuropathy
Neuropathy present at diagnosis
Treatment induced neuropathy
Hypoglycemic neuropathy

Adapted from ref. *10* with permission.

Table 2
Classification of Diabetic Neuropathy

Symmetrical neuropathies	Asymmetrical neuropathies
Distal sensory and sensory-motor neuropathy	Mononeuropathy
Large-fiber type of diabetic neuropathy	Mononeuropathy multiplex
Small-fiber type of diabetic neuropathy	Radiculopathies
Distal small-fiber neuropathy	Lumbar plexopathy or radiculoplexopathy
"Insulin neuropathy"	Chronic inflammatory demyelinating polyradiculoneuropathy
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	

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the classification of diabetic neuropathies provides the clinician to have workable, crude definitions for the various neuropathic syndromes, and also assists in the management of the patient.

More recently, Watkins and Edmonds *(11)* have suggested a classification for diabetic polyneuropathy based on the natural history of the various syndromes, which clearly separates them into three distinct groups:

1. Progressive neuropathies are associated with increasing duration of diabetes and with other microvascular complications. Sensory disturbance predominates and autonomic involvement is common. The onset is gradual and there is no recovery.
2. Reversible neuropathies have an acute onset, often occurring at the presentation of diabetes itself, and are not related to the duration of diabetes or other microvascular complications. There is spontaneous recovery of these acute neuropathies.
3. Pressure palsies although are not specific to diabetes only, they tend to occur more frequently in patients with diabetes than in the general population. There is no association with duration of diabetes or other microvascular complications of diabetes.

Another method of classifying diabetic polyneuropathy is by considering whether the clinical involvement is symmetrical or asymmetrical. However, the separation to symmetrical and asymmetrical neuropathies, although useful in identifying distinct entities and perhaps providing clues to the varied etiologies, is an oversimplification of the truth as there is a great overlapping of the syndromes. This method was originally suggested

by Bruyn and Garland *(12)*, and later modified by Thomas *(13)*. More recently, Low and Suarez *(14)* have further modified this classification (Table 2).

SYMMETRICAL NEUROPATHIES

Distal Symmetrical Neuropathy

This is the commonest neuropathic syndrome and what is meant in clinical practice by the phrase "diabetic neuropathy." There is a "length-related" pattern of sensory loss, with sensory symptoms starting in the toes and then extending to involve the feet and legs in a stocking distribution. In more severe cases, there is often upper limb involvement, with a similar progression proximally starting in the fingers. Although the nerve damage can extend over the entire body including the head and face, this is exceptional. Subclinical neuropathy detectable by autonomic function tests is usually present. However, clinical autonomic neuropathy is less common. Autonomic neuropathy is considered in more detail on pages 118–121. As the disease advances, overt motor manifestations such as wasting of the small muscles of the hands and limb weakness become apparent. However, subclinical motor involvement detected by magnetic resonance imaging appears to be common, and thus motor disturbance is clearly part of the functional impairment caused by distal symmetrical neuropathy *(15)*.

The main clinical presentation of distal symmetrical neuropathy is sensory loss which the patient may not be aware of, or may be described as "numbness" or "dead feeling." However, some may experience a progressive buildup of unpleasant sensory symptoms *(16)* including tingling (paraesthesiae); burning pain; shooting pains down the legs; lancinating pains; contact pain often with daytime clothes and bedclothes (allodynia); pain on walking often described as "walking barefoot on marbles," or "walking barefoot on hot sand"; sensations of heat or cold in the feet; and persistent achy feeling in the feet and cramp-like sensations in the legs. Occasionally pain can extend above the feet and may involve the whole of the legs, and when this is the case there is usually upper limb involvement also. There is a large spectrum of severity of these symptoms. Some may have minor complaints such as tingling in one or two toes; others may be affected with the devastating complications such as "the numb diabetic foot," or severe painful neuropathy that does not respond to drug therapy.

Diabetic neuropathic pain is characteristically more severe at night, and often prevents sleep *(17,18)*. Some patients may be in a constant state of tiredness because of sleep deprivation *(17)*. Others are unable to maintain full employment *(17–19)*. Severe painful neuropathy can occasionally cause marked reduction in exercise threshold so as interfere with daily activities *(17,20)*. This is particularly the case when there is an associated disabling, severe postural hypotension resulting from autonomic involvement *(11)*. Not surprisingly therefore, depressive and symptoms are not uncommon *(17,20)*. Although, subclinical autonomic neuropathy is commonly found in patients with distal symmetrical neuropathy *(21)*, symptomatic autonomic neuropathy is uncommon.

It is important to appreciate that many subjects with distal symmetrical neuropathy may not have any of the above symptoms, and their first presentation may be with a foot ulcer. This underpins the need for carefully examining and screening the feet of all diabetic people, in order to identify those at risk of developing foot ulceration. The insensate foot is at risk of developing mechanical and thermal injuries, and patients must therefore be warned

about these and given appropriate advice regarding foot care. A curious feature of the neuropathic foot is that both numbness and pain may occur, the so-called painful, painless leg *(22)*. It is indeed a paradox that the patient with a large foot ulcer may also have severe neuropathic pain. In those with advanced neuropathy, there may be sensory ataxia. The unfortunate sufferer is affected by unsteadiness on walking, and even falls particularly if there is associated visual impairment because of retinopathy.

Neuropathy is usually easily detected by simple clinical examination *(23)*. Shoes and socks should be removed and the feet examined at least annually and more often if neuropathy is present. The most common presenting abnormality is a reduction or absence of vibration sense in the toes. As the disease progresses there is sensory loss in a "stocking" and sometimes in a "glove" distribution involving all modalities. When there is severe sensory loss, proprioception may also be impaired, leading to a positive Romberg's sign. Ankle tendon reflexes are lost and with more advanced neuropathy, knee reflexes are often reduced or absent.

Muscle strength is usually normal early during the course of the disease, although mild weakness may be found in toe extensors. However, with progressive disease there is significant generalized muscular wasting, particularly in the small muscles of the hand and feet. The fine movements of fingers would then be affected, and there is difficulty in handling small objects. Wasting of dorsal interossei is however usually because of the entrapment of the ulnar nerve at the elbow. The clawing of the toes is believed to be owing to unopposed (because of wasting of the small muscles of the foot) pulling of the long extensor and flexor tendons. This scenario results in elevated plantar pressure points at the metatarsal heads that are prone to callus formation and foot ulceration. Deformities such as a bunion can form the focus of ulceration and with more extreme deformities, such as those associated with Charcot arthropathy *(24)*, the risk is further increased. As one of the most common precipitants to foot ulceration is inappropriate footwear, a thorough assessment should also include examination of shoes for poor fit, abnormal wear, and internal pressure areas or foreign bodies.

Autonomic neuropathy affecting the feet can cause a reduction in sweating and consequently dry skin that is likely to crack easily, predisposing the patient to the risk of infection. The "purely" neuropathic foot is also warm because of the arterio/ venous shunting first described by Ward *(23)*. This results in the distension of foot veins that fail to collapse even when the foot is elevated. It is not unusual to observe a gangrenous toe in a foot that has bounding arterial pulses, as there is impairment of the nutritive capillary circulation because of arteriovenous shunting. The oxygen tension of the blood in these veins is typically raised *(25)*. The increasing blood flow brought about by autonomic neuropathy can sometimes result in neuropathic edema, which is resistant to treatment with diuretics but may respond to treatment with ephedrine *(26)*.

Small-Fiber Neuropathy

The existence "small-fiber neuropathy" as a distinct entity has been advocated by some authorities *(27,28)*, usually within the context of young patients with type 1. A prominent feature of this syndrome is neuropathic pain, which may be very severe, with relative sparing of large-fiber functions (vibration and proprioception). The pain is described as burning, deep and aching. The sensation of pins and needles (paraesthesiae) is also often

experienced. Contact hypersensitivity may be present. However, rarely, patients with small-fiber neuropathy may not have neuropathic pain, and some may occasionally have foot ulceration. Autonomic involvement is common, and severely affected patients may be disabled by postural hypotension and/or gastrointestinal symptoms. The syndrome tends to develop within a few years of diabetes as a relatively early complication.

On clinical examination there is little evidence of objective signs of nerve damage, apart from a reduction in pinprick and temperature sensation, which are reduced in a "stocking" and "glove" distribution. There is relative sparing of vibration and position sense (because of relative sparing of the large diameter Aβ-fibers). Muscle strength is usually normal and reflexes are also usually normal. However, autonomic function tests are frequently abnormal and affected male patients usually have erectile dysfunction. Electrophysiological tests support small-fiber dysfunction. Sural sensory conduction velocity may be normal, although the amplitude may be reduced. Motor nerves appear to be less affected. Controversy still exists as to whether small-fiber neuropathy is a distinct entity or an earlier manifestation of chronic sensory motor neuropathy *(27,28)*. Said et al. *(27)* studied a small series of subjects with this syndrome and showed that small-fiber degeneration predominated morphometrically. Veves et al. *(29)* found a varying degree of early small-fiber involvement in all diabetic polyneuropathies which was confirmed by detailed sensory and autonomic function tests. It is unclear, therefore, whether this syndrome is in fact distinct or merely represents the early stages of distal symmetrical neuropathy that has been detected by the prominence of early symptoms.

Differential Diagnosis of Distal Symmetrical Neuropathy

Diabetic peripheral neuropathy presents in a similar way to neuropathies of other causes, and thus the physician needs to carefully exclude other common causes before attributing the neuropathy to diabetes. Absence of other complications of diabetes, rapid weight loss, excessive alcohol intake, and other atypical features in either the history or clinical examination should alert the physician to search for other causes of neuropathy. Table 3 shows differential diagnoses for distal symmetrical neuropathy.

Natural History of Distal Symmetrical Neuropathy

Although distal symmetrical neuropathy is common in clinical practice, there are few prospective studies that have looked at its natural history, which remains poorly understood. This may partly be owing to our inadequate knowledge regarding the pathogenesis of distal symmetrical neuropathy, although several mechanisms have been suggested *(30–32)*, and the list of potential mechanisms is constantly growing. Unlike in diabetic retinopathy and nephropathy, the scarcity of simple, accurate, and readily reproducible methods of measuring neuropathy further complicates the problem *(8,9)*. One study *(33)* reported that neuropathic symptoms remain or get worse over a 5-year period in patients with chronic distal symmetrical neuropathy. A major drawback of this study was that it involved highly selected patients from a hospital base. A more recent study reported improvements in painful symptoms over 3.5 years *(34)*. Neuropathic pain was assessed using a visual analog scale, and small-fiber function by thermal limen, heat pain threshold, and weighted pinprick threshold. At follow-up 3.5 years later, one-third of the 50 patients at baseline had died or were lost to follow-up. Clearly this is a major drawback. There was symptomatic improvement in painful neuropathy in the majority of the remaining patients. Despite this

Table 3
Differential Diagnosis of Distal Symmetrical Neuropathy

Metabolic	Neoplastic disorders
Diabetes	Bronchial or gastric carcinoma
Amyloidosis	Lymphoma
Uremia	Infective or inflammatory
Myxedema	Leprosy
Porphyria	Guillain-Barre syndrome
Vitamin deficiency (thiamin, B_{12}, B_6, pyridoxine)	Lyme borreliosis
Drugs and chemicals	Chronic inflammatory demyelinating polyneuropathy
Alcohol	Polyarteritis nodosa
Cytotoxic drugs, for example, Vincristine	Genetic
Chlorambucil	Charcot-Marie-Tooth disease
Nitrofurantoin	Hereditary sensory neuropathies
Isoniazid	

symptomatic improvement, however, small-fiber function as measured by the above tests deteriorated significantly. Thus, there was a dichotomy in the evolution of neuropathic symptoms and neurophysiological measures.

Are Painful and Painless Neuropathies Distinct Entities?

One of the complexities of distal symmetrical neuropathy is the variety of presentation to the clinician *(16)*. A relative minority present with pain as the predominant symptom *(35)*. There is controversy concerning whether the clinical, neurophysiological, peripheral nerve hemodynamic/morphometric findings are distinctly different in subjects with painful and painless diabetic neuropathy *(16)*. Young et al. *(36)* reported that patients with painful neuropathy had a higher ratio of autonomic (small-fiber) abnormality to electrophysiological (large-fiber) abnormality. In contrast, they found that electrophysiological parameters were significantly worse in patients with foot ulceration compared with those with painful neuropathy. They concluded that in distal symmetrical neuropathy, the relationship between large- and small-fiber damage is not uniform, and that there may be different etiological influences on large- and small-fiber neuropathy in subjects with diabetes, with the predominant type of fiber damage determining the form of the presenting clinical syndrome *(36)*. This view is supported by the study of Tsigos et al. *(37)*, who also suggested that painful and painless neuropathies represent two distinct clinical entities with little overlap. However, a contrary view was expressed by Veves et al. *(38)* who found that painful symptoms were frequent in diabetic neuropathy, irrespective of the presence or absence of foot ulceration, and that these symptoms may occur at any stage of the disease. They concluded that there is a spectrum of presentations from varying degrees of painful neuropathy to predominantly painless neuropathy associated with foot ulceration, and that much overlap is present *(38)*. The author's clinical observations support this view, as painful symptoms are often similarly present in patients with and without foot ulceration, suggesting that painless and painful neuropathy represent extreme forms of the same syndrome. Thus, an

important clinical point is that the neuropathic foot with painful symptoms is just as vulnerable to foot ulceration as the foot with absence of painful neuropathic symptoms. The crucial determining factor is elevation of vibration perception threshold *(39)* and not the presence or absence of painful symptoms. Indeed, the "painful–painless" foot with ulceration, is frequently observed in the diabetic foot clinic, a phenomenon first described by Ward *(22)*.

Acute Painful Neuropathies

These are transient neuropathic syndromes characterized by an acute onset of pain in the lower limbs. Acute neuropathies present in a symmetrical fashion and are relatively uncommon. Pain is invariably present and is usually distressing to the patient, and can sometimes be incapacitating. There are two distinct syndromes, the first of which occurs within the context of poor glycemic control, and the second with rapid improvements in metabolic control.

Acute Painful Neuropathy of Poor Glycemic Control

This phenomenon occurs usually in patients with type 1 or -2 diabetes who have poor glycemic control. There is no relationship to the presence of other chronic diabetic complications. There is often an associated severe weight loss *(40)*. Ellenberg coined the description of this condition as "neuropathic cachexia" *(41)*. Patients typically develop persistent burning pain associated with allodynia (contact pain). The pain is most marked in the feet but often affects the whole of the lower extremities. As in chronic distal symmetrical neuropathy, the pain is typically worse at night although persistent pain during daytime is also common. The pain is likened to "walking on burning sand" and there may be a subjective feeling of the feet being "swollen." Patients also describe intermittent bouts of stabbing pain that shoot up the legs from the feet ("peak pain"), superimposed on the background of burning pain ("background pain"). Not surprisingly, these disabling symptoms often lead to depression.

On examination, sensory loss is usually surprisingly mild or even absent. There are usually no motor signs, although ankle jerks may be absent. Nerve conduction studies are also usually normal or mildly abnormal. Temperature discrimination threshold (small-fiber function) is however, affected more commonly than vibration perception threshold (large-fiber function) *(42)*. There is complete resolution of symptoms within 12 months, and weight gain is usual with continued improvement in glycemic control with the use of insulin. The lack of objective signs should not raise the doubt that these painful symptoms are not real. Many patients feel that people including health care professionals do not fully appreciate their predicament.

Acute Painful Neuropathy of Rapid Glycemic Control (Insulin Neuritis)

The term "insulin neuritis" was coined by Caravati *(43)* who first described the syndrome of acute painful neuropathy of rapid glycemic control. The term is a misnomer as the condition can follow rapid improvement in glycemic control with oral hypoglycemic agents, and "neuritis" implies a neural inflammatory process for which there is no evidence. The author has therefore recommended that the term "acute painful neuropathy of rapid glycemic control" be used to describe this condition *(44)*.

The natural history of acute painful neuropathies is an almost guaranteed improvement *(40)* in contrast to chronic distal symmetrical neuropathy *(33,34)*. The patient presents with burning pain, paraesthesiae, allodynia, often with a nocturnal exacerbation of symptoms, and depression may be a feature. There is no associated weight loss, unlike acute painful neuropathy of poor glycemic control. Sensory loss is often mild or absent, and there are no motor signs. There is little or no abnormality on nerve conduction studies, but there is impaired exercise-induced conduction velocity increment *(44,45)*. There is usually complete resolution of symptoms within 12 months.

On sural nerve biopsy, typical morphometric changes of chronic distal symmetrical neuropathy but with active regeneration, were observed *(46)*. In contrast, degeneration of both myelinated and unmyelinated fibers was found in acute painful neuropathy of poor glycemic control *(40)*. A recent study looking into the epineurial vessels of sural nerves in patients with acute painful neuropathy of rapid glycemic control demonstrated marked arteriovenous abnormality including the presence of proliferating new vessels, similar to those found in the retina *(44)*. The study suggested that the presence of this fine network of epineurial vessels may lead to a "steal" effect rendering the endoneurium ischemic, and the authors also suggested that this process may be important in the genesis of neuropathic pain *(44)*. These findings were also supported by studies in experimental diabetes which demonstrated that insulin administration led to acute endoneurial hypoxia, by increasing nerve arteriovenous flow, and reducing the nutritive flow of normal nerves *(47)*. Further work needs to address whether these observed sural nerve vessel changes resolve with the resolution of painful symptoms.

ASYMMETRICAL NEUROPATHIES

Asymmetrical or focal neuropathies are well-recognized complications of diabetes. They have a relatively rapid onset and complete recovery is usual. This contrasts with chronic distal symmetrical neuropathy, in which there is usually no improvement in symptoms 5 years after onset *(48)*. Unlike chronic distal symmetrical neuropathy they are often unrelated to the presence of other diabetic complications *(8–11)*. Asymmetrical neuropathies are more common in men and tend to predominantly affect older patients *(48,49)*. A careful history is therefore mandatory in order to identify any associated symptoms that might point to another cause for the neuropathy. A vascular etiology has been suggested by virtue of the rapid onset of symptoms and the focal nature of the neuropathic syndromes *(50)*.

Proximal Motor Neuropathy (Femoral Neuropathy, Amyotrophy, and Plexopathy)

The syndrome of progressive asymmetrical proximal leg weakness and atrophy was first described by Garland *(51)*, who coined the term "diabetic amyotrophy." This condition has also been named as "proximal motor neuropathy," "femoral neuropathy," or "plexopathy." The patient presents with severe pain which is felt deep in the thigh, but can sometimes be of burning quality and extend below the knee. The pain is usually continuous and often causes insomnia and depression *(52)*. Both patients with type 1 and type 2 over the age of 50 years are affected *(51–54)*. There is an associated weight loss, which can sometimes be very severe, and can raise the possibility of an occult malignancy.

On examination there is profound wasting of the quadriceps with marked weakness in these muscle groups, although hip flexors and hip abductors can also be affected *(55)*. Thigh adductors, glutei, and hamstring muscles may also be involved. The knee jerk is usually reduced or absent. The profound weakness can lead to difficulty from getting out of a low chair or climbing stairs. Sensory loss is unusual, and if present indicates a coexistent distal sensory neuropathy.

It is important to carefully exclude other causes of quadriceps wasting such as nerve root and cauda equina lesions, and the possibility of occult malignancy causing proximal myopathy syndromes such as polymyocytis. MR imaging of the lumbo-sacral spine is now mandatory in order to exclude focal nerve root entrapment and other pathologies. An erythrocyte sedimentation rate, an X-ray of the lumbar/sacral spine, a chest X-ray, and ultrasound of the abdomen may also be required. Cerebrospinal fluid protein is often elevated. Electrophysiological studies may demonstrate increased femoral nerve latency and active denervation of affected muscles.

The cause of diabetic proximal motor neuropathy is not known. It tends to occur within the background of diabetic distal symmetrical neuropathy *(56)*. Some have suggested that the combination of focal features superimposed on diffuse peripheral neuropathy may suggest vascular damage to the femoral nerve roots, as a cause of this condition *(57)*.

As in distal symmetrical neuropathy, there is scarcity of prospective studies that have looked at the natural history of proximal motor neuropathy. Coppack and Watkins *(52)* have reported that pain usually starts to settle after about 3 months, and usually settles by 1 year, whereas the knee jerk is restored in 50% of the patients after 2 years. Recurrence on the other side is a rare event. Management is largely symptomatic and supportive. Patients should be encouraged and reassured that this condition is likely to resolve. There is still controversy regarding whether the use of insulin therapy influences the natural history of this syndrome. Some patients benefit from physiotherapy that involves extension exercises aimed at strengthening the quadriceps. The management of pain in proximal motor neuropathy is similar to that of chronic or acute distal symmetrical neuropathies (*see* "Management of Diabetic Neuropathy").

Cranial Mononeuropathies

The commonest cranial mononeuropathy is the third cranial nerve palsy. The patient presents with pain in the orbit, or sometimes with a frontal headache *(50,58)*. There is typically ptosis and ophthalmoplegia, although the pupil is usually spared *(59,60)*. Recovery occurs usually over 3 months. The clinical onset and time-scale for recovery, and the focal nature of the lesions on the third cranial nerve, on postmortem studies suggested an ischemic etiology *(50,61)*. It is important to exclude any other cause of third cranial nerve palsy (aneurysm or tumor) by CT or MR scanning, in which the diagnosis is in doubt. Fourth, sixth, and seventh cranial nerve palsies have also been described in subjects with diabetes, but the association with diabetes is not as strong as that with third cranial nerve palsy.

Truncal Radiculopathy

Truncal radiculopathy is well recognized to occur in diabetes. It is characterized by an acute onset pain in a dermatomal distribution over the thorax or the abdomen *(62)*. The pain

is usually asymmetrical, and can cause local bulging of the muscle *(63)*. There may be patchy sensory loss and other causes of nerve root compression should be excluded. Some patients presenting with abdominal pain have undergone unnecessary investigations such as barium enema, colonoscopy, and even laparotomy, when the diagnosis could easily have been made by careful clinical history and examination. Recovery is usually the rule within several months, although symptoms can sometimes persist for a few years.

Pressure Palsies

Carpal Tunnel Syndrome

A number of nerves are vulnerable to pressure damage in diabetes. In the Rochester diabetic neuropathy study, which was a population-based epidemiological study, Dyck et al. *(64)* found electrophysiological evidence of median nerve lesions at the wrist in about 30% of subjects with diabetes, although the typical symptoms of carpel tunnel syndrome occurred in less than 10%. The patient typically has pain and paraesthesia in the hands, which sometimes radiate to the forearm and are particularly marked at night. In severe cases clinical examination may reveal a reduction in sensation in the median territory in the hands, and wasting of the muscle bulk in the thenar eminence. The clinical diagnosis is easily confirmed by median nerve conduction studies and treatment involves surgical decompression at the carpel tunnel in the wrist. There is generally good response to surgery, although painful symptoms appear to relapse more commonly than in the nondiabetic population *(65)*.

Ulnar Nerve and Other Isolated Nerve Entrapments

The ulnar nerve is also vulnerable to pressure damage at the elbow in the ulnar groove. This results in wasting of the dorsal interossei, particularly the first dorsal interossius. This is easily confirmed by ulnar electrophysiological studies, which localize the lesion to the elbow. Rarely, the patients may present with wrist drop resulting from radial nerve palsy after prolonged sitting (with pressure over the radial nerve in the back of the arms), whereas unconscious during hypoglycemia or asleep after an alcohol binge.

In the lower limbs the common peroneal (lateral popliteal) is the most commonly affected nerve. The compression is at the level of the head of the fibula and causes foot drop. Unfortunately complete recovery is not usual. The lateral cutaneous nerve of the thigh is occasionally also affected with entrapment neuropathy in diabetes. Phrenic nerve involvement in association with diabetes has also been described, although the possibility of a pressure lesion could not be excluded *(64)*.

PATHOGENESIS OF DISTAL SYMMETRICAL NEUROPATHY

Despite considerable research, the pathogenesis of diabetic neuropathy remains undetermined *(30–32)*. Morphometric studies have demonstrated that distal symmetrical neuropathy is characterized by pathological changes including:

1. axonal loss distally, with a “dying back” phenomenon *(27)*,
2. a reduction in myelinated fiber density *(67)*, and
3. focal areas of demyelination on teased fiber preparations *(27)*.

Nerve regenerative activity may also be seen with the emergence of “regenerative clusters” *(68)*, containing groups of myelinated axons and nonmyelinated axons sprouts.

Table 4
Proposed Hypotheses of Diabetic Peripheral Nerve Damage

Chronic hyperglycaemia
Nerve microvascular dysfunction
Increased free radical formation
Polyol pathway hyperactivity
PKC hyperactivity
Nonenzymatic glycation
Abnormalities of nerve growth

However, the small and unmyelinated fibers that make up around 80% of all nerve fibers have proved more difficult to assess.

Historically, there have been two distinct views regarding the pathogenesis of distal symmetrical neuropathy. The first view regards metabolic factors *(69)* to be primarily important in the pathogenesis of distal symmetrical neuropathy, the second contends that vascular factors *(32)* be the determining etiological factors for neuropathy (Table 4). However, most authorities now agree that the truth is probably in the middle and that both metabolic and vascular factors are important. Evidence for this comes from recent work that has demonstrated an interaction between some of the proposed metabolic hypotheses of peripheral nerve damage and the vascular endothelium *(32)*. Figure 2 shows current thinking with regard to the pathogenesis of diabetic neuropathy.

Chronic Hyperglycemia

Over the past decade, at least three large prospective studies have conclusively demonstrated that there is now little doubt that chronic hyperglycemia is implicated in the pathogenesis of diabetic neuropathy. The EURODIAB prospective study *(6)*, the Diabetes control and complications trial *(70)*, and more recently the United Kingdom prospective diabetes study *(71)* have demonstrated that poor glycemic control is related to the increased prevalence of neuropathy in patients with diabetes and that improved glycemic control may prevent/reverse distal symmetrical neuropathy. However, there are major gaps in our understanding of how exactly the effects of chronic hyperglycemia result in nerve damage.

Oxidative Stress

Hyperglycemia leads to an increase in free radical generation as a result of several metabolic derangements including nonenzymatic glycation and polyol pathway hyperactivity. Moreover the capacity to neutralize free radicals is also reduced because of several metabolic abnormalities including NADPH depletion as a result of polyol pathway hyperactivity *(72)*. Thus, oxidative stress may impair nerve function by direct toxic effect or by reducing nitric oxide and hence nerve blood flow. Recent studies in rats with experimental diabetes have shown that free radical scavengers may improve nerve conduction velocity abnormalities *(73)* although these findings need to be proven in human diabetic neuropathy. Future studies may also explore an alternative to free radical scavenging i.e., preventing free radical formation in the first place.

Increased Polyol Pathway Flux

In 1966, Gabbay et al. postulated that polyol pathway hyperactivity as a mechanism which could link hyperglycemia to neuropathy *(74)*. It was proposed that hyperglycemia led to sorbitol accumulation in the peripheral nerve because of increased conversion from glucose, via the enzyme aldose reductase. This is supported by the demonstration of elevated sorbitol levels in diabetic nerves *(75,76)*. Elevated sorbitol levels are associated with depletion of myoinositol, which is important in phosphoinositide metabolism, and reduction in Na^+ K^+-ATPase which has an important role of intracellular and extracellular sodium; hence, nerve membrane potential *(75,76)*. Indeed aldose reductase inhibitors administered to either animals *(77)* or man *(78)* result in an improvement in nerve conduction velocity. Some improvement in nerve fiber count has also been reported *(79)*, but there is no unequivocal demonstration of amelioration of symptoms and clinical signs in humans. Thus, there is as yet, no convincing evidence for the use of these agents in routine clinical practice particularly when one considers the possibility of side effects long term. A number of studies are currently taking place with newer and possibly more potent aldose reductase inhibitors, in "early" neuropathy, as in advanced neuropathy the nerve is highly disorganized and is unlikely to respond to treatment. The long-term safety of these drugs remains an important issue of concern for many clinicians.

Nonenzymatic Glycation

Glucose is highly reactive and free amino groups on proteins may be nonenzymatically glycated. From this reversible step there follows a series of reactions that are progressively irreversible; Amadori products and then advanced glycation end products (AGEs). Nonenzymatic glycosylation of proteins has been demonstrated in brain tubulin and peripheral nerve *(80,81)*. This process may be an important initiating factor for nerve demyelination *(68)* by interfering with axonal transport. AGE can also absorb ("quench") nitric oxide, a potent vasodilator, and hence lead to impaired nerve blood flow *(82)*. Aminoguanidine, which inhibits AGE formation, has been demonstrated to improve nerve conduction deficits and blood flow in experimental diabetes *(83)*, although its role in human diabetic neuropathy is still undetermined.

Neurotrophic Factors

Various neurotrophic factors support the growth and differentiation neurones. Among these neurotrophic agents are insulin-like growth factors-I and -II and the neurotrophin family. The neurotrophin family includes nerve growth factor (NGF), the levels of which are found to be reduced in experimental diabetes *(84)*. NGF treatment corrects some aspects of sensory neuropathy related to small-fiber dysfunction in diabetic rats. A recent clinical trial looking into the effect of parental NGF in human diabetic neuropathy was stopped because of lack of effect, and therefore the precise role of neurotrophic factors in human diabetic neuropathy and the potential use of trophic intervention in diabetic neuropathy remain undetermined.

Protein Kinase C Activation

Diabetes results in hyperactivity of vascular protein kinase C (PKC), in particular for the β-isoform *(85)*. Increased synthesis of diacylglycerol from glucose activates PKC. PKC activation is associated with abnormalities in vascular function seen in preclinical models

of diabetes. In rats with streptozotocin diabetes, retinal blood flow is decreased in parallel with an increase in retinal PKC activity. PKC inhibitor treatment corrected deficits in retinal perfusion and prevented the early glomerular hyperfiltration and increased urinary albumin excretion in diabetic rats *(85)*. Moreover, a PKC inhibitor has recently been shown to correct nerve conduction velocity and perfusion deficits and to protect endothelial dependent relaxation, in diabetic rats *(86)*. There is currently a clinical trial of a PKC inhibitor in subjects with early distal symmetrical neuropathy taking place and the results are awaited.

Vascular Factors

The view that microvessel disease may be central to the pathogenesis of diabetic neuropathy is not new *(87)*. Severe neural microvascular disease has been demonstrated in subjects with clinical diabetic neuropathy *(88)*. Several workers have reported basal membrane thickening of endoneurial capillaries, degeneration of pericytes and hypoplasia, and swelling of endothelial cells and sometimes vessel closure (Fig. 3). The degree of microvascular disease has been correlated with the severity of neuropathy by Malik and colleagues *(89)*.

In vivo studies looking at the exposed sural nerve in human subjects have demonstrated epineurial arteriovenous shunting, which appears to result in a "steal" phenomenon diverting blood from the nutritive endoneurial circulation *(44,90)*. The consequent impairment of nerve blood flow causes a fall in endoneural oxygen tension *(91)*. In addition, several other studies provide indirect evidence supporting a vascular etiology for diabetic neuropathy. Strenuous exercise increases nerve blood flow, and thereby increases nerve conduction velocity by an average of 4 m/second in nonneuropathic subjects with diabetes *(45)*. However, this significant increase in nerve conduction velocity, with exercise, is absent *(45)* in neuropathic subjects as the nerve microvasculature is severely diseased *(90)*. Moreover, there is a strong correlation between nerve conduction velocity and lower limb transcutaneous oxygenation measurements in diabetes; macrovascular disease appears to exacerbate neuropathy and surgical restoration of perfusion improves nerve conduction velocity *(92)*. A recent epidemiological study has also found a strong correlation between diabetic neuropathy and cardiovascular risk factors including; body weight, hypertension, smoking, and reduced HDL cholesterol *(6)*.

In addition to human studies impairment of blood flow has been found to be an early feature in rats with streptozotocin diabetes. Several vasodilators have also been found to enhance nerve blood flow and nerve function in diabetic animals *(72)*. In human diabetic neuropathy ACE inhibitors have been found to improve nerve function *(93,94)*. The presence of severe microvascular changes in subjects with acute painful neuropathy of rapid glycemic control (insulin neuritis), hitherto thought to be purely metabolic in origin, provides an even more compelling evidence for the importance of microvascular factors in the pathogenesis of distal symmetric neuropathy *(44)*.

A number of metabolic derangements brought about by the diabetic state mentioned earlier (Table 4) have an impact on nerve perfusion, the vascular endothelium being a major target *(32)*. Oxidative stress, activation of the PKC system, and nonenzymatic glycation lead to reduced nerve nitric oxide. Occlusion of endoneural capillaries and the presence of hemorrheological abnormalities associated with diabetes further exacerbate the impairment of nerve blood flow leading to nerve hypoxia and hence nerve structural and functional abnormalities (Fig. 1).

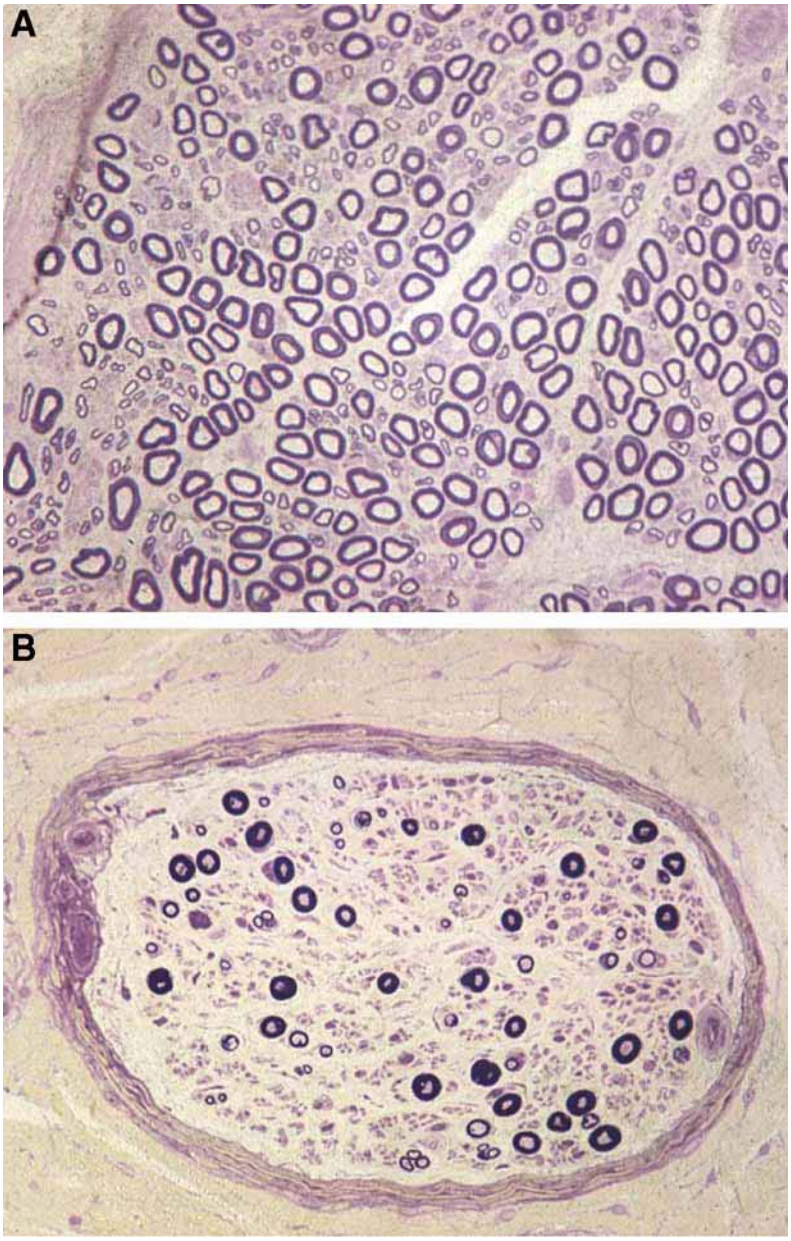

Fig. 1. Sural nerve biopsies from a healthy control **(A)** and a neuropathic patient **(B)**. A considerable loss of myelinated nerve fibers can be seen in the neuropathic patient.

AUTONOMIC NEUROPATHY

Abnormalities of autonomic function are very common in subjects with longstanding diabetes, however, clinically significant autonomic dysfunction is uncommon. Several systems are affected (Table 5). Autonomic neuropathy has a gradual onset and is slowly progressive. The prevalence of diabetic autonomic neuropathy depends on the type of

Table 5
Autonomic Neuropathy

Autonomic neuropathy	Gastrointestinal
Cardiovascular	Gastroparesis
Resting tachycardia	Diarrhea
Heart rate abnormalities	Constipation
Edema	Dermatological
Postural hypotension	Gustatory sweating
Arrhythmias	Dry skin
Sudden death	Sudomotor dysfunction
Genitourinary	Arteriovenous shunting
Erectile dysfunction	Neurological
Retrograde ejaculation	Pupillary dysfunction
Atonic bladder	Respiratory
Bladder infection	Bronchoconstrictor dysfunction
Abnormal renal sodium handling	
Nephropathy	

population studied, and a number of tests of autonomic function employed. In the EURODIAB study the prevalence of autonomic neuropathy defined as the presence of two abnormal cardiovascular autonomic function tests, was 23%, and the prevalence increased with age, duration of diabetes, glycemic control, and presence of cardiovascular risk factors, in particular hypertension *(95)*.

Cardiovascular Autonomic Neuropathy

Cardiovascular autonomic neuropathy causes postural hypotension, change in peripheral blood flow, and may be a cause of sudden death.

Postural Hypotension

It is now generally accepted that a fall in systolic blood pressure of >20 mmHg is considered abnormal *(95)*. Coincidental treatment with tricyclic antidepressants for neuropathic pain, and diuretics may exacerbate postural hypotension, the chief symptom of which is dizziness on standing. The symptoms of postural hypotension can be disabling for some patients who may not be able to walk for more than a few minutes. In clinical practice the severity of dizziness does not correlate with the postural drop in blood pressure. There is increased mortality in subjects with postural hypotension, although the reasons for this are not fully clear. The management of subjects with postural hypotension poses major problems, and for some patients there may not be any satisfactory treatment. Current treatment includes improving glycemic control, advising patients to get up from the sitting or lying position slowly, treatment with fludrocortisone whereas carefully monitoring urea and electrolytes, and the use of support stockings. In severe cases "antigravity or space suits" which may compress the lower limbs, the α-1 adrenal receptor agonist, midodrine or occasionally octreotide may be effective.

Table 6
Reference Values for Cardiovascular Function Tests

	Normal	Borderline	Abnormal
Heart rate tests			
Heart rate response to standing up (30:15 ratio)	≥1.04	1.01–1.03	≤1
Heart rate response to deep breathing (maximum minus minimum heart rate)	≥15 beats/ minute	11–14 beats/ minute	≤10 beats/ minute
Heart rate response to Valsalva maneuver (Valsalva ratio)	≥1.21	–	≤1.20
Blood pressure (BP) tests			
BP response to standing up (fall in systolic BP)	≤10 mmHg	11–29 mmHg	≥30 mmHg
BP response to sustained hand-grip (increase in diastolic BP)	≥16 mmHg	11–15 mmHg	≤10 mmHg

Changes in Peripheral Blood Flow

Autonomic neuropathy can cause arteriovenus shunting, with prominent veins in the neuropathic leg *(23)*. Leg-vein oxygen tension *(25)* and capillary pressure *(96)* are increased in the neuropathic leg resulting from sympathetic denervation. Thus, in the absence of peripheral vascular disease the neuropathic foot is warm, and this may be one of the factors that cause osteopenia associated with the development of Charcot neuroarthropathy *(24)*.

Cardiovascular Autonomic Function Tests

Five cardiovascular autonomic function tests are now widely used for the assessment of autonomic function. These tests are noninvasive, and do not require sophisticated equipment (all that is required is an electrocardiogram machine, an aneroid pressure gauge attached to a mouthpiece, a hand-grip dynamometer, and sphygmomanometer). Table 6 shows reference list for cardiovascular autonomic function test *(97)*.

Gastrointestinal Autonomic Neuropathy

Gastroparesis

Autonomic neuropathy can affect the upper gastrointestinal system by reducing esophageal motility (dysphagia and heartburn), and gastroparesis (reduced gastric emptying, vomiting, swings in blood sugar) *(98)*.

Management of diabetic gastroparesis includes optimization of glycemic control, the use of antiemetics (metoclopramide and domperidone), the use of the cholinergic agent which stimulates oesophageal motility (erythromycin which may enhance the activity of the gut peptide, motilin). Gastric electrical stimulation has recently been introduced as a treatment option in patients with drug refractory gastroparesis to increase the quality

of life by alleviating nausea and vomiting frequencies *(99)*. Improvement in diabetic control has also been reported by one study *(100)*.

The diagnosis of gastroparesis is often made on clinical grounds by the evaluation of symptoms and sometimes the presence of succussion splash, whereas barium swallow and follow-through, and gastroscopy may reveal a large food residue in the stomach. Gastric motility and emptying studies can sometimes be performed in specialized units, and may help with diagnosis.

Severe gastroparesis causing recurrent vomiting, is associated with dehydration, swings in blood sugar and weight loss, and is therefore an indication for hospital admission. The patient should be adequately hydrated with intravenous fluids and blood sugar should be stabilized by intravenous insulin, antiemetics could be given intravenously and if the course of the gastroparesis is prolonged, total parenteral nutrition or feeding through a gastrostomy tube may be required.

Autonomic Diarrhea

The patient may present with diarrhea which tends to be worse at night, or alternatively some may present with constipation. Both the diarrhea and constipation respond to conventional treatment. Diarrhea associated with bacterial overgrowth may respond to treatment with a broad spectrum antibiotic such as erythromycin, tetracycline, or ampicillin.

Abnormal Sweating

Increased sweating usually affecting the face, and often brought about by eating (gustatory sweating) can be very embarrassing to patients. There may also be reduced sweating in the feet of affected patients, which can cause dry feet that are at risk of fissuring and hence infection. Unfortunately, there is no totally satisfactory treatment for gustatory sweating, although the anticholinergic drug poldine may be useful in a minority of patients.

Abnormalities of Bladder Function

Bladder dysfunction is a rare complication of autonomic neuropathy involving the sacral nerves. The patient presents with hesitancy of micturition, increased frequency of micturition, and in serious cases with urinary retention associated with overflow incontinence. Such a patient is prone to urinary tract infections. Ultrasound scan of the urinary tract, intravenous urography, and urodynamic studies may be required. Treatment maneuvers include mechanical methods of bladder emptying by applying suprapubic pressure, or the use of intermittent self-catheterization. Anticholinesterase drugs such as neostigmine or peridostigmine may be useful. Long-term indwelling catheterization may be required in some, but this unfortunately predisposes the patient to urinary tract infections and long-term antibiotic prophylaxis may be required.

MANAGEMENT OF DIABETIC NEUROPATHY

The two chief presentations of diabetic neuropathy are pain *(16)* and the numb foot which predisposes the patient to foot ulceration. The problems associated with the numb foot are discussed in detail elsewhere in this book. The treatment scenario for painful neuropathy is less than satisfactory as currently available treatment approaches are highly symptomatic and often ineffective *(16)*. As the pathological processes leading to diabetic nerve damage become to clear, potential therapeutic agents that have the capacity to prevent or reverse the neuropathic process, will emerge.

A careful history and examination of the patient is essential in order to exclude other possible causes of leg pain such as peripheral vascular disease, prolapsed intervertebral disks, spinal canal stenosis, and corda aquina lesions *(16)*. Unilateral leg pain should arouse a suspicion that the pain may be because of lumbar-sacral nerve root compression. These patients may well need to be investigated with a lumbar-sacral magnetic resonance imaging. Other causes of peripheral neuropathy such as excessive alcohol intake and B_{12} deficiency *(16)*. Where pain is the predominant symptom the quality and severity should be assessed. Neuropathic pain can be disabling in some patients and an empathic approach is essential. In general patients should be allowed to express their symptoms freely without too many interruptions. The psychological support of the patient's painful neuropathy is an important aspect of the overall management of the pain.

Glycemic Control

There is now little doubt that good blood sugar control prevents/delays the onset of diabetic neuropathy *(6,70,71)*. In addition, painful neuropathic symptoms are also improved by improving metabolic control, if necessary with the use of insulin in type 2 diabetes *(101)*. The first step in the management of painful neuropathy is a concerted effort aimed at improving glycemic control *(102)*.

Tricyclic Compounds

Tricyclic compounds are now regarded as the first line treatment for painful diabetic neuropathy *(18,102)*. A number of double blind clinical trials have confirmed their effectiveness beyond any doubt. As these drugs do have unwanted side effects such as drowsiness, anticholinergic side effects such as dry mouth and dizziness resulting from postural hypotension in those that have autonomic neuropathy, patients should be started on imipramine or amitriptyline at a low dose (25–50 mg taken before bed), the dose gradually titrated if necessary up to 150 mg/day. The mechanism of action of tricyclic compounds in improving neuropathic pain is not known, but their effect does not appear through their antidepressant property, as they appear to be effective even in those with a depressed mood *(103)*.

Anticonvulsants

Anticonvulsants, including carbamazepine, phenytoin, gabapentin *(104)*, more recently pregabalin *(105)* have also been found effective in the relief of more severe neuropathic pain. Unfortunately treatment with anticonvulsants is often complicated with troublesome side effects such as sedation, dizziness and ataxia, and therefore treatment should be started at a relatively low dose and gradually increased to maintenance dose of these drugs, when carefully looking for side effects. However, pregabalin and gabapentin appear to have less unwanted side effects and are hence better tolerated *(104,105)*.

Topical Capsaicin

Topical capsaicin (0.075%) applied sparingly three to four times per day to the affected area has also been found to relieve neuropathic pain. Topical capsaicin works by depleting substance "P" from nerve terminals, and there may be worsening of neuropathic symptoms for the first 2–4 weeks of application *(106)*.

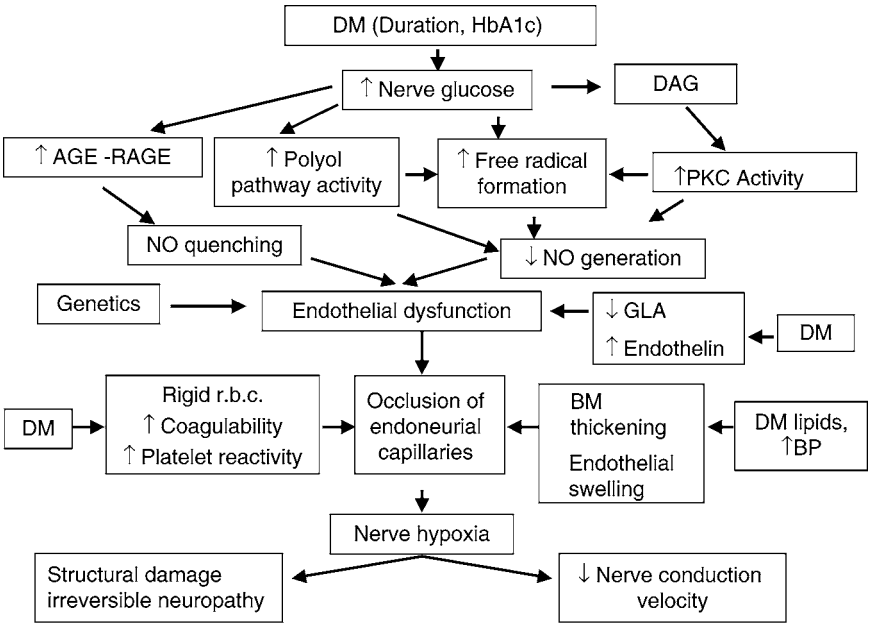

Fig. 2. Metabolic and vascular factors in the pathogenesis of diabetic distal symmetrical neuropathy.

Intravenous Lignocaine and Oral Mexiletine

Intravenous lignocaine at a dose of 5 mg/kg body wt with another 30 minutes with a cardiac monitor *in situ*, has also been found to be effective in relieving neuropathic pain for up to 2 weeks *(107)*. This form of treatment is useful in subjects that are having severe pain which is not responding to the above agents, although it does necessitate bringing the patient into hospital for a few hours. Oral mexiletine, which has similar structure to lignocaine, may have a beneficial effect at reducing neuropathic pain, although in the author's experience treatment is disappointing.

α-Lipoic Acid

Infusion of the antioxidant α-lipoic acid at a dose of 600 mg intravenously per day over a 3-week period (5–5–4 days), has also been found to be useful in reducing neuropathic pain *(108)*.

Opiates

The opiate derivative tramadol has been found effective in relieving neuropathic pain *(109)*. Recently, the combination of morphine and gabapentin was found to be more effective than either in the management of neuropathic pain *(110)*.

Management of Disabling Painful Neuropathy Not Responding to Pharmacological Treatment

Neuropathic pain can sometimes be extremely severe, interfering significantly with patients' sleep and daily activities. Unfortunately some patients are not helped by conventional pharmacological treatment. Such patients pose a major challenge for they are

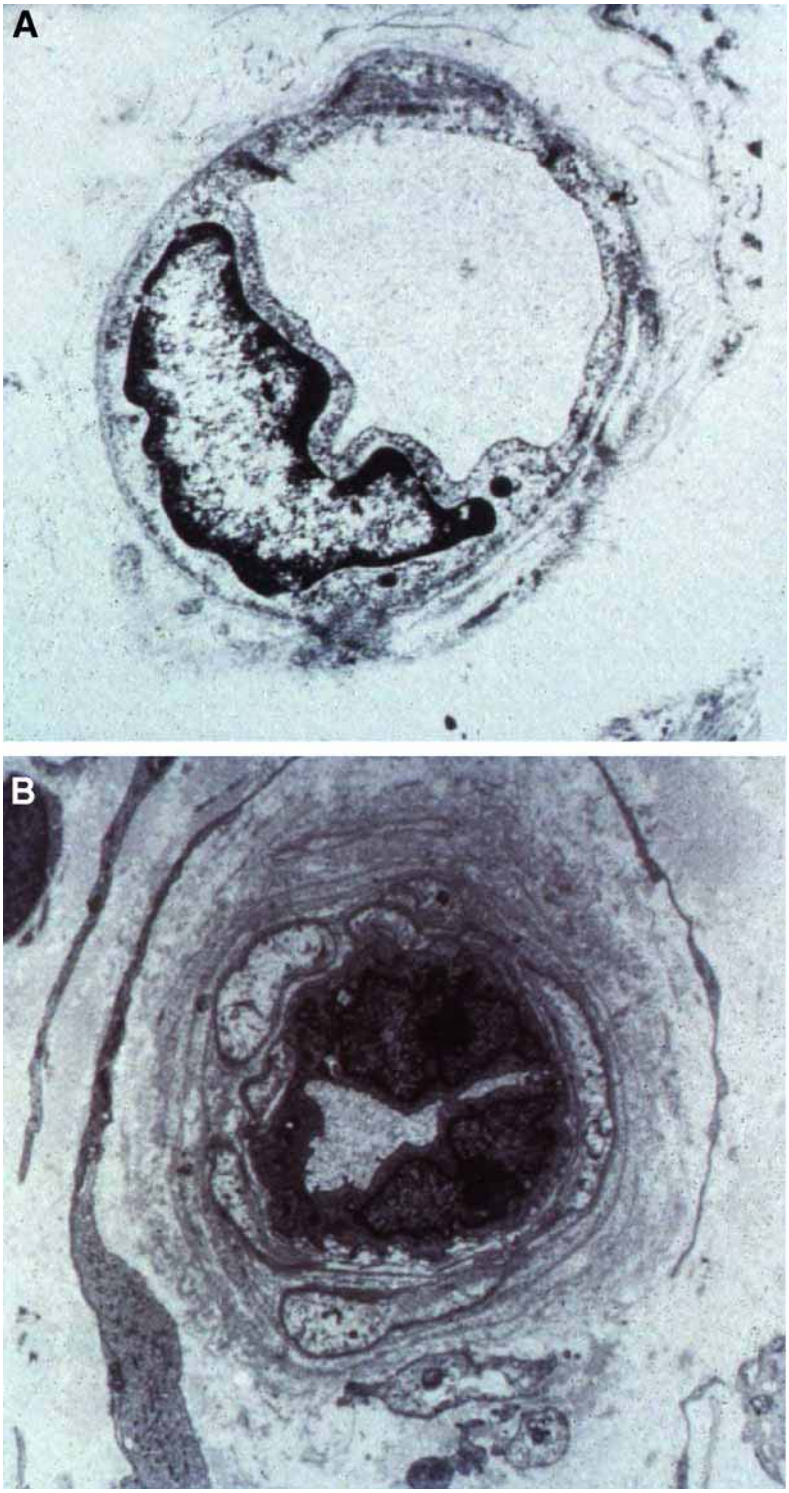

Fig. 3. Photomicrographs of endoneurial capillaries from sural nerve biopsies showing a normal **(A)** capillary from a subject with diabetes without neuropathy and a closed capillary from a subject with chronic diabetic neuropathy **(B)** showing endothelial cell proliferation and basement membrane thickening (Pictures from Dr. RA Malik).

severely distressed and sometimes wheelchair bound. A recent study has demonstrated that such patients may respond to electrical spinal cord stimulation which relieves both background and peak neuropathic pain *(19)*. This form of treatment is particularly advantageous, as the patient does not have to take any other pain relieving medications, with all their side effects. A recent follow-up of patients fitted with electrical spinal cord stimulators found that stimulators continued to be effective 5 years after implantation. Transcutaneous electrical nerve stimulation may also be beneficial for the relief of localized neuropathic pain in one limb.

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