Diabetic Somatic Neuropathies

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SECTION 1: INTRODUCTION

— The neuropathies are among the most common of the long-term complications of diabetes, affecting up to 50% of patients (1–4). Their clinical features vary immensely, and patients may present to a wide spectrum of specialties, from dermatology to podiatry, for example, or from urology to cardiology. Neuropathies are characterized by a progressive loss of nerve fibers, which may affect both principle divisions of the peripheral nervous system. This review will focus on the somatic neuropathies; those affecting the autonomic division were recently reviewed by Vinik et al. (5). There is increasing evidence that measures of neuropathy, such as electrophysiology and quantitative tests, are predictors of not only end points, including foot ulceration, but also of mortality (6).

The epidemiology and natural history of diabetic neuropathy (DN) remain poorly defined, partly because of poor patient selection and the variable criteria for what constitutes a diagnosis of DN. These aspects, as well as the pathogenesis of DN, will be covered in detail in this review. Studies have confirmed the major contribution of prolonged hyperglycemia in the etiopathogenesis of neuropathy and neuropathic pain (7–10), and this and other putative mechanisms will be discussed.

The clinical features, diagnosis, and management of the focal and multifocal neuropathies will be described. A major portion of this review will discuss the clinical features, assessment, and management of the patient with the most common form of DN, diabetic distal sensory polyneuropathy (DPN). The late sequelae of DPN and their prevention will also be described.

Finally, practical guidelines for the screening of DPN in clinical practice will be provided. For further details on this topic, please refer to recent reviews (11–18).

SECTION 2: DEFINITIONS AND CLASSIFICATION OF THE DNs

A. Definitions

Members of an international consensus meeting on the outpatient diagnosis and management of DN agreed on a simple definition of DN as "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes " (19). It was also agreed that neuropathy cannot be diagnosed without a careful clinical examination—absence of symptoms cannot be equated with absence of neuropathy, as asymptomatic neuropathy is common. The importance of excluding nondiabetic causes was emphasized in the Rochester Diabetic Neuropathy Study, in which up to 10% of peripheral neuropathy in diabetic patients was deemed to be of nondiabetic causation (1).

A more detailed definition of neuropathy was previously agreed upon at the San Antonio Consensus Conference: "diabetic neuropathy is a descriptive term meaning a demonstrable disorder, either clinically evident or subclinical, that occurs in the setting of diabetes mellitus without other causes for peripheral neuropathy. The neuropathic disorder includes manifestations in the somatic and/or autonomic parts of the peripheral nervous system" (20). It is generally agreed that DN should not be diagnosed on the basis of one symptom, sign, or test alone: a minimum of two abnormalities (from symptoms, signs, nerve conduction abnormalities, quantitative sensory tests, or quantitative autonomic tests) is recommended by Dyck (21). Certainly, for clinical trials or epidemiological studies, one of these two abnormalities should include quantitative tests or electrophysiology.

B. Classification of DNs

Numerous classifications of the variety of syndromes affecting the peripheral nervous system in diabetes have been proposed in recent years. Some have been based on presumed etiology, topographical features, or pathological features. However, until we have a clear understanding of the etiopathogenesis of neuropathy, classifications based on the clinical manifestations are most commonly used (22–25). Three slightly different clinical classifications are presented in Table 1. Table 1*A* describes a purely clinical classification (11,22), whereas Table 1*B* bases its classification on a mixture of clinical and anatomical findings (25). The classification proposed by Thomas (23,24) will be used throughout this review (Table 1*C*). This classification is based on the premise that DN is not a unitary condition but is the result of a number of disturbances in the peripheral

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Abbreviations: AGE, advanced glycation end product; AR, aldose reductase; ARI, AR inhibitor; CIDP, chronic inflammatory demyelinating polyneuropathy; CMAP, compound muscle action potential; CTS, carpal tunnel syndrome; DAG, 1,2-diacylglycerol; DCCT, Diabetes Control and Complications Trial; DN, diabetic neuropathy; DPN, diabetic distal sensory polyneuropathy; GLA, γ-lipoic acid; ICNT, intermediate cutaneous nerve of the thigh; IGT, impaired glucose tolerance; IL, interleukin; LA, lipoic acid; MMP, matrix metalloproteinase; MNSI, Michigan Neuropathy Screening Instrument; MRI, magnetic resonance imaging; NAD, neuroaxonal dystrophy; NCV, nerve conduction velocity; NDS, Neuropathic Disability Score; NGF, nerve growth factor; NIS, Neuropathy Impairment Score; PKC, protein kinase C; PNS, Peripheral Nerve Society; QOL, quality of life; QST, quantitative sensory testing; RAGE, AGE receptor; SNAP, sensory nerve action potential; SSRI, selective serotonin-reuptake inhibitor; STZ, streptozotocin; VEGF, vascular endothelial growth factor; VPT, vibration perception threshold.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Three classification systems for DNs*

A: **Clinical Classification of DNs**

Polyneuropathy	Mononeuropathy
Sensory	Isolated peripheral
• Acute sensory	
• Chronic sensorimotor	Mononeuritis multiplex
Autonomic	
• Cardiovascular	Isolated peripheral
• Gastrointestinal	
• Genitourinary	Truncal
• Other	
Proximal motor (amyotrophy)	
Truncal	

Adapted from Boulton and Ward (22) and Boulton and Malik (11).

B: **Patterns of Neuropathy in Diabetes**

Length-dependent diabetic polyneuropathy
- Distal symmetrical sensory polyneuropathy
- Large fiber neuropathy
- Painful symmetrical polyneuropathy
- Autonomic neuropathies

Focal and multifocal neuropathies
- Cranial neuropathies
- Limb neuropathies
- Proximal DN of the lower limbs
- Truncal neuropathies

Nondiabetic neuropathies more common in diabetes
- Pressure palsies
- Acquired inflammatory demyelinating polyneuropathy

Adapted from Said (25).

C: **Classification of DN**

Rapidly reversible
- Hyperglycemic neuropathy

Generalized symmetrical polyneuropathies
- Sensorimotor (chronic)
- Acute sensory
- Autonomic

Focal and multifocal neuropathies
- Cranial
- Thoracolumbar radiculoneuropathy
- Focal limb
- Proximal motor (amyotrophy)

Superimposed chronic inflammatory demyelinating neuropathy

Adapted from Thomas (23,24).

nervous system as a consequence of hyperglycemia.

Rapidly reversible hyperglycemic neuropathy. It has been recognized for many years that rapidly reversible abnormalities of nerve conduction may occur in patients with recently diagnosed or transiently poorly controlled diabetes; these abnormalities may be accompanied by distal uncomfortable sensory symptoms (11,23,24). Such changes are unlikely to be caused by structural abnormalities, as recovery soon follows restoration of euglycemia. It remains unknown whether these temporary abnormalities result in a greater risk of developing other chronic neuropathies in later life.

Generalized symmetrical polyneuropathies.

Chronic sensorimotor neuropathy is the most common form of DN that is discussed in detail below. It is usually of insidious onset and may be present at the diagnosis of type 2 diabetes in >10% of subjects (8,26). Whereas up to 50% of patients may be asymptomatic, 10–20% may experience troublesome sensory symptoms that require specific treatment. Sensorimotor neuropathy is often accompanied by autonomic dysfunction. Late sequelae of neuropathy, which include insensate foot ulceration, Charcot (neuropathic) arthropathy, and occasionally even amputation (27), are also discussed below.

Acute sensory neuropathy is a distinct variety of the symmetrical polyneuropathies with an acute or subacute onset characterized by severe sensory symptoms, usually with few if any clinical signs. The natural history is one of gradual improvement of these symptoms with establishment of stable glycemic control.

Autonomic neuropathy is also common, though rarely severely symptomatic. Autonomic neuropathy was a topic of focus in a recent technical review by Vinik et al. (5) and will not be further described here.

Focal and multifocal neuropathies. All the neuropathies under this heading are recognized as being more common in older type 2 diabetic patients. Focal limb neuropathies are often, but not always, due to entrapment (e.g., carpal tunnel syndrome), indicating the greater susceptibility of diabetic nerve to compression. Recent data suggest that there is a threefold risk of having diabetes in 514 patients with carpal tunnel syndrome compared with a normal control group (28). Among the cranial nerves, those supplying the external ocular muscles are most commonly involved. Thoracolumbar radiculoneuropathies may present with girdle-like pain, occasionally with motor weakness of abdominal wall muscles. Proximal motor neuropathy (amyotrophy) may be unilateral or asymmetrically bilateral with pain, wasting, and weakness that may be relatively acute in onset. All of these focal/multifocal neuropathies are discussed in greater detail below.

It seems probable that *chronic inflammatory demyelinating polyneuropathy* (CIDP) occurs more commonly in people with diabetes (24,29), although a case-control study has not been performed. Its features, differential diagnosis, and management will be discussed in more detail below.

Table 2—*Stages of DPN

Stage of neuropathy†	Characteristics
No neuropathy	No symptoms or signs
Clinical neuropathy	
Chronic painful	Burning, shooting, stabbing pains with or without "pins and needles"; increased at night; absent sensation to several modalities; reduced/absent reflexes
Acute painful	Severe symptoms as above (hyperesthesiae common), may follow initiation of insulin in poorly controlled diabetes, signs minor or absent
Painless with complete/partial sensory loss	Numbness/deadness of feet or no symptoms, painless injury, reduced/absent sensation, reduced thermal sensitivity, absent reflexes
Late complications	Foot lesions, neuropathic deformity, nontraumatic amputation

*Types of DN: frequent, sensorimotor symmetrical neuropathy (mostly chronic, sensory loss, or pain), autonomic neuropathy (history of impotence and possibly other autonomic abnormalities); rare, mononeuropathy (motor involvement, acute onset, may be painful), diabetic amyotrophy (weakness/wasting usually of proximal lower-limb muscles). †Staging does not imply automatic progression to the next stage. The aim is to prevent, or at least delay, progression to the next stage.

C. Consensus statements and staging of neuropathy

There have been a number of consensus and committee reports relating to DN in the last two decades, the best known of which is probably the San Antonio Conference (20), which discussed definitions, measurements, and classification primarily for clinical research. The use of standardized measurement techniques was recommended, and a further development conference was convened in 1992 to review the standardization of procedures and approaches used for epidemiological and clinical studies (30). Both of these meetings were jointly sponsored by the American Diabetes Association and the American Academy of Neurology.

An international group of experts in DN held a consensus meeting to develop guidelines for the management of diabetic peripheral neuropathy by the practicing clinician (19). The agreed clinical stages of DPN are shown in Table 2. This clinical staging is in general agreement with that proposed by Dyck (21,31), for use in both clinical practice and epidemiological studies or controlled clinical trials. Thus, the clinical "no neuropathy" is equivalent to Dyck's N0 or N1a; "clinical neuropathy" is equivalent to N1b, N2a, or N2b; and "late complications" is equivalent to Dyck's N3 (Table 3).

There have been a number of other relevant reports, including two on measures for use in clinical trials to assess symptoms (32) and quantitative sensory testing (QST) (33). Most recently, a committee of the American Academy of Neurology reported on the use of QST for clinical and research purposes (34).

SECTION 3: PATHOGENESIS OF DN— This section will focus predominantly on the pathogenesis of DPN. Studies in animal models and cultured cells provide a conceptual framework for the cause and treatment of DN (35). However, limited translational work in diabetic patients continues to generate much debate and controversy over the cause(s) of human DN, and to date we have no effective treatment.

Table 3—*Staging severity of diabetic polyneuropathy*

- N0: No objective evidence of DN
- N1: Asymptomatic polyneuropathy
  - N1a: No symptoms or signs but neuropathic test abnormalities
  - N1b: Test abnormalities* plus neuropathy impairment on neurological exam
- N2: Symptomatic neuropathy
  - N2a: Symptoms, signs, and test abnormality
  - N2b: N2a plus significant ankle dorsiflexor weakness
- N3: Disabling polyneuropathy

Adapted from Dyck (21,31). *Nerve conduction, QST, or autonomic test abnormalities.

A. Hyperglycemia

Longitudinal data from the Rochester cohort support the contention that the duration and severity of exposure to hyperglycemia are related to the severity of neuropathy only (36). Similarly, in a study of newly diagnosed patients with type 2 diabetes followed up from baseline and at 5 and 10 years, the overall severity, and not the development of neuropathy, was related to the degree of hyperglycemia (8). Recent studies in patients with impaired glucose tolerance (IGT) provide important insights into the role of the degree of glucose dysmetabolism and the development of neuropathy. In a study of patients with IGT, the sural nerve amplitude and myelinated fiber density do not differ significantly from those with normal glucose tolerance, suggestive of a glycemic threshold for the development of neuropathy (37). However, of 121 patients with a painful neuropathy and electrodiagnostic evidence of axonal injury together with epidermal nerve fiber abnormalities, 25% had IGT (38). The neuropathy associated with IGT is milder than the neuropathy associated with newly diagnosed diabetes, and small nerve fiber involvement may be the earliest detectable sign of neuropathy (39). Improving hyperglycemia by more intensive insulin therapy (7) or pancreatic transplantation (40) improves electrophysiology in patients with type 1 diabetes. However, the evidence is not clear in type 2 diabetes. In the VA Cooperative Study on Type 2 Diabetes Mellitus (VACSDM), 153 patients randomized to intensive versus conventional therapy achieved a 2.07% difference in HbA_{1c} over 2 years, but failed to demonstrate a significant difference in the progression of either somatic or autonomic neuropathy (41). Similarly, the more recent Steno-2 Study failed to demonstrate a benefit of multifactorial intervention, including glycemic control, on measures of somatic neuropathy (42). The U.K. Prospective Diabetes Study (UKPDS) represents the largest interventional study in type 2 diabetes that has assessed the effects of improved glycemic control, but the

neuropathy data have not yet been reported (26).

B. Other pathogenetic mechanisms

Polyol pathway. Animal models of diabetes consistently demonstrate an association between increased flux through the polyol pathway and a reduction in nerve conduction velocity (NCV), both of which can be ameliorated with aldose reductase inhibitors (ARIs) (43). However, in humans the situation is not clear. A recent study has demonstrated enhanced aldose reductase (AR) but minimal sorbitol dehydrogenase expression in the peripheral nerve of diabetic patients (44). In one of the earliest clinical studies, sorbitol and fructose levels were increased in only one-third of the sural nerve biopsies studied and could not be related to clinical, neurophysiological, or pathological severity of neuropathy (45). Postmortem sciatic nerves from diabetic patients demonstrated a significant increase in glucose, fructose, and sorbitol compared with normal subjects (46). In nerve obtained at amputation, glucose, fructose, and sorbitol were significantly higher in diabetic patients than in nondiabetic patients (47), but concentrations differed markedly from those in postmortem samples (46). In a recent study of patients with normal glucose tolerance, IGT, and type 2 diabetes, only the diabetic patients demonstrated an elevation in nerve sorbitol, indicating a glycemic threshold for activation of this pathway (37). Linear regression analysis has demonstrated a significant inverse correlation between nerve sorbitol and myelinated fiber density (48). Moreover, it would appear that those at greatest risk of developing the complications are those with a higher set point for AR activity (49). Polymorphisms in the promoter region leading to a highly significant decrease in the frequency of the Z+2 allele have been demonstrated in patients with overt neuropathy compared with those without neuropathy (50).

With regard to intervention, a meta-analysis of all randomized controlled trials of ARIs identified 19 trials, testing four different ARIs for 4–208 weeks (median 24 weeks). It demonstrated a small but statistically significant reduction in decline of median (0.66 m/s, 95% CI 0.18–1.14 m/s) and peroneal (0.53, 0.02–1.04) motor NCV without benefit in sensory nerves (51). The clinical relevance of an effect on motor but not sensory nerve function is questionable, especially as the latter is primarily responsible for the most common manifestations of human DN: severe pain and the insensate extremity, leading to ulceration and eventual amputation (52).

Possible reasons for this marginal benefit may be related to the lack of a targeted approach identifying those most genetically susceptible to alterations in AR activity and, therefore, those most likely to benefit from AR inhibition (50). Furthermore, the degree of AR inhibition may determine the improvement observed. Thus, in a randomized, placebo-controlled, double-blinded, multiple-dose, clinical trial with zenarestat, dose-dependent increments in sural nerve sorbitol suppression were accompanied by significant improvement in NCV, and in doses producing >80% sorbitol suppression, there was a significant increase in the density of small-diameter myelinated fibers of the sural nerve (53). More recently, fidarestat, a potent ARI, significantly improved median nerve F-wave conduction velocity and minimal latency, as well as symptoms of numbness, spontaneous pain, paresthesiae, and hyperesthesia, in 279 diabetic patients (54).

Myoinositol. While myoinositol deficiency has been proposed to play a role in the pathogenesis of DN, there is little evidence to support this contention. In a sural nerve biopsy study, myoinositol levels did not vary among patients with normal glucose tolerance, IGT, and type 2 diabetes (37).

Glycation. Hyperglycemia results in the formation of advanced glycation end products (AGEs), which in turn act on specific receptors (RAGEs), inducing monocytes and endothelial cells to increase the production of cytokines and adhesion molecules (55). Glycation has also recently been shown to have an effect on matrix metalloproteinases (MMPs), in particular MMP-2, which degrades type IV collagen, but also on membrane type 1 MMP, tissue inhibitors of MMPs (TIMP)-1 and -2, and transforming growth factor-β (TGF-β) (56). Other effects include prevention of epidermal growth factor–induced autophosphorylation and activation of extracellular signal–regulated kinases (ERKs) (55). In experimental diabetes, these changes can be prevented by AGE inhibitors, such as the nucleophilic compounds pyridoxamine, tenilsetam, 2,3-diaminophenazone, or aminoguanidine (56,57). Alternatively, the administration of recombinant RAGE hinders the AGE-RAGE interaction (56,57). Human sural nerves obtained from diabetic and nondiabetic amputation specimens demonstrate normal furosine, an early reversible glycation product, but significantly elevated pentosidine levels in both cytoskeletal and myelin protein (58). Enhanced staining for carboxymethyllysine in the perineurium, endothelial cells, and pericytes of endoneurial microvessels, as well as myelinated and unmyelinated fibers, has been shown to correlate with a reduction in myelinated fiber density in peripheral nerve from five patients with type 2 diabetes compared with five nondiabetic control subjects (59). Pyrraline, an AGE, is also increased in postmortem samples of optic nerve from diabetic patients (60). Intervention trials have focused on nephropathy, and no trial data are currently available for human DN.

Oxidative stress. An increasing body of data supports the role of oxidative stress in the pathogenesis of DN in animal models (35). Again, there is emerging evidence that single-nucleotide polymorphisms of the genes for mitochondrial (SOD2) and extracellular (SOD3) superoxide dismutases may confer an increased risk for the development of neuropathy (61). This may partially explain the lack of benefit observed with a number of antioxidants. However, benefits have been observed with α-lipoic acid (LA), a powerful antioxidant that scavenges hydroxyl, superoxide, and peroxyl radicals and regenerates glutathione. In the ALADIN II study, diabetic patients with symptomatic polyneuropathy were randomly assigned to 5 days of intravenous LA followed by oral treatment for 2 years and demonstrated a significant improvement in sural sensory NCV, sensory nerve action potential (SNAP), and tibial motor NCV but not neuropathic disability score (NDS) (62). ALADIN III randomized 509 diabetic patients to LA intravenously for 3 weeks, followed by oral treatment compared with placebo. It showed no change in the total symptom score, but did show an improvement in the neuropathy impairment score after 3 weeks of intravenous therapy, which was maintained until the end of the study (63). Most recently, the SYDNEY study has demonstrated a significant improvement in the neuropathy symptom score, neuropathy impairment score, and one attribute of nerve conduction after daily intravenous

treatment with racemic LA for 5 days/week for 14 treatments (64).

Vascular factors. The most direct evidence that improving tissue blood flow may improve DN is derived from large-vessel revascularization studies, which have shown an improvement in NCV in one study (65) but not in another (66). However, a longer-term follow-up of the latter study did show a prevention of worsening of peroneal NCV (67). There are of course a number of pharmacological treatments that can achieve a similar effect. Angiotensin-converting enzyme (ACE) inhibitors mediate increased flow-dependent release of endothelium-derived relaxing factor (EDRF) and endothelium-dependent vessel relaxation. In a double-blind, placebo-controlled clinical trial of trandalopril over 12 months, peroneal motor NCV, M-wave amplitude, F-wave latency, and sural nerve amplitude improved significantly (68). Recently, the Appropriate Blood Pressure Control in Diabetes (ABCD) trial assessed the effects of intensive versus moderate blood pressure control with either nisoldipine or enalapril and surprisingly failed to prevent progression of DN, retinopathy, and neuropathy (69).

1,2-Diacylglycerol (DAG) induced activation of protein kinase C (PKC); in particular, PKC-β has been proposed to play a major role in DN (35). However, even in nerve from diabetic animals, a fall in DAG levels and a consistent pattern of change in PKC activity has not been observed (70). Despite this, inhibition of PKC-β in diabetic rats appears to correct reduced nerve blood flow and NCV (71). Based on the findings of a phase II clinical trial demonstrating some benefit in diabetic patients with neuropathy (72), multicenter, randomized, double-blind, placebo-controlled trials are under way and are due to complete in 2005.

An increasing body of evidence suggests that conventional risk factors for macrovascular disease (such as deranged lipids) are also important in the pathogenesis and progression of human DN (73). Recent studies show that hydroxymethylglutaryl CoA reductase inhibitors may enhance endothelial cell nitric oxide bioavailabilty (76), prevent AGE-induced nuclear factor (NF)-κβ–induced protein-1 activation and upregulation of vascular endothelial growth factor (VEGF) mRNA (75), and thereby ameliorate experimental DN (74). Simvastatin has shown a trend toward slower progression of neuropathy measured by vibration perception threshold (VPT) but no change in the status of clinical neuropathy (76). Paradoxically, as a cautionary note, recent observational data suggest a link between chronic statin use and an increased risk of peripheral neuropathy (77).

Growth factors. Neurotrophins promote the survival of specific neuronal populations by inducing morphological differentiation, enhancing nerve regeneration, stimulating neurotransmitter expression, and altering the physiological characteristics of neurons. Initially, the skin of diabetic patients with sensory fiber dysfunction demonstrated a depletion of nerve growth factor (NGF) (78). However, subsequent studies have shown a significant increase in skin NGF mRNA (79) and neurotrophin-3 concentrations (80) and normal sciatic nerve ciliary neurotrophic factor (CNTF) levels (81). In situ hybridization studies have also demonstrated an increased expression of both trkA, the high-affinity receptor for NGF, and trkC, the receptor for NT-3, in the skin of diabetic patients, which has been proposed to reflect a compensatory response (82). Despite these apparently contradictory findings, a phase II clinical trial of recombinant human NGF in 250 diabetic patients with symptomatic diabetic polyneuropathy demonstrated a significant improvement in the sensory component of the neurological examination, in two quantitative sensory tests, and in a rather vague end point, "the clinical impression of most subjects that their neuropathy had improved" (83). However, a phase III trial in 1,019 diabetic patients with sensory polyneuropathy failed to demonstrate a significant benefit (84). More recently a randomized, double-blind, placebo-controlled study of brain-derived neurotrophic factor (rhBDNF) in 30 diabetic patients demonstrated no significant improvement in nerve conduction and quantitative sensory and autonomic function tests, including the cutaneous axon reflex (85).

Insulin-like growth factors. In cultured Schwann cells and the streptozotocin (STZ)-induced diabetic rat, insulin-like growth factor (IGF)-1 demonstrates a protective effect via phosphatidylinositol (PI) 3-kinase in preventing glucose-mediated apoptosis (86). Both the STZ-diabetic and the BB/W rat develop severe hyperglycemia and a deficiency in circulating IGF-1 levels and reproducibly develop neuroaxonal dystrophy (NAD) in nerve terminals of the prevertebral sympathetic ganglia and the distal portions of noradrenergic ileal mesenteric nerves. In contrast, the Zucker diabetic fatty (ZDF) rat, an animal model of type 2 diabetes, also develops severe hyperglycemia comparable to that in the STZ- and BB/W-diabetic rats but maintains normal levels of plasma IGF-1 and fails to demonstrate NAD in sympathetic ganglia and ileal mesenteric nerves as assessed by quantitative ultrastructural techniques (87). However, IGF-1 and IGF-1 receptor mRNA levels have not been shown to differ in the sural nerve of diabetic patients compared with control subjects (88).

C-peptide. Impaired insulin/C-peptide action has emerged as a prominent pathogenetic factor. Preclinical studies have demonstrated a range of actions that include effects on Na(+)/K(+)-ATPase activity, endothelial nitric oxide synthase, expression of neurotrophic factors, regulation of molecular species underlying the degeneration of the nodal apparatus in type 1 diabetic nerves, as well as DNA binding of transcription factors and modulation of apoptotic phenomena (89,90). These findings have recently been effectively translated into benefits in patients with type 1 diabetes with the demonstration of a significant improvement in sural sensory NCV and vibration perception but without a benefit in either cold or heat perception after 12 weeks of daily subcutaneous C-peptide treatment (91).

VEGF. VEGF was originally discovered as an endothelial-specific growth factor with a predominant role in angiogenesis. However, recent observations indicate that VEGF also has direct effects on neurons and glial cells, stimulating their growth, survival, and axonal outgrowth (92). Thus, with its potential for a dual impact on both the vasculature and neurons, it could represent an important therapeutic intervention in DN. Both the STZ-induced diabetic rat and the alloxan-induced diabetic rabbit have demonstrated restoration of nerve vascularity, blood flow, and both large- and small-fiber dysfunction 4 weeks after intramuscular gene transfer of plasmid DNA encoding VEGF-1 or VEGF-2, with confirmed constitutive overexpression of both transgenes in tissue (93). In contrast, immunohistochemistry of sciatic nerves

and dorsal root ganglia from STZ-induced diabetic rats demonstrates intense VEGF staining in cell bodies and nerve fibers, whereas controls express no or very little VEGF, and animals treated with insulin or NGF show significantly lower immunostaining for VEGF (94). Thus, there is an intrinsic capacity to upregulate VEGF, but this appears insufficient and may require exogenous delivery possibly via gene therapy. A phase I/II, single-site, dose-escalating, double-blind, placebo-controlled study to evaluate the safety and impact of phVEGF165 gene transfer on sensory neuropathy in patients with diabetes with or without macrovascular disease involving the lower extremities is currently under way and will involve 192 patients over a period of 4 years (95).

Immune mechanisms. Studies suggest that sera from type 2 diabetic patients with neuropathy contains an autoimmune immunoglobulin that induces complement-independent, calcium-dependent apoptosis in neuronal cells (96). The expression of these cytotoxic factors has been related to the severity of neuropathy and the type of neuronal cell killed (97). Thus, it has been suggested that such toxic factors may contribute to DN by acting in concert with hyperglycemia to damage sensory/autonomic neurons (97).

SECTION 4: FOCAL AND MULTIFOCAL NEUROPATHIES

A number of rare neuropathies referred to as the focal and multifocal neuropathies will now be discussed in detail, particularly with regard to clinical presentation and management.

Factors leading to the development of the compression neuropathies relate to either the peripheral nerve itself or the structures surrounding it at the point of compression. Many of the animal models of entrapment are based on acute compression, the mechanics of which differ considerably in terms of nerve stretch, tethering, and associated ischemia involved in entrapment. Therefore, translation of these experimental findings to entrapment neuropathies in diabetic patients should be interpreted with caution.

A. Mononeuropathies

Carpal tunnel syndrome. This is the most common entrapment neuropathy encountered in diabetic patients and occurs as a result of median nerve compression under the transverse carpal ligament. Idiopathic carpal tunnel syndrome (CTS) occurs in patients with rheumatoid arthritis, hypothyroidism, and obesity. In 20–30% of diabetic patients, it can be demonstrated electrophysiologically but presents as a clinically relevant problem in ~5.8% (98). Painful paresthesiae of the fingers may progress to a deep-seated ache, which radiates up the forearm or, very rarely, the arm. This occurs primarily at night but may be initiated during the day by repetitive flexion and extension of the wrist. Motor weakness is uncommon but thenar muscle wasting occurs particularly in the elderly. Two common clinical tests include the Phalen (forearms held vertically and hands held in complete flexion for 1 min; positive if paresthesiae develop in the median territory within 30 s) or Tinel (percussion at the wrist and palm induces paresthesiae in the median nerve territory) tests, but they have a high false-positive rate. Electrophysiological studies measure the speed of conduction across the carpal tunnel, and median sensory nerve conduction studies are compared with radial and/or ulnar sensory latencies. Their interpretations are made difficult if there is a coexisting peripheral neuropathy affecting the upper limbs or if there are no symptoms of CTS. Demyelination is thought to be the primary pathological abnormality. Treatment options include wrist splints, which have limited application because they cannot be worn during the day, but can be effective for nocturnal symptoms. Injections of cortisone into the carpal tunnel may provide short-lived relief, and in the majority of cases, repeat injections are required. Surgical sectioning of the transverse carpal ligament provides variable degrees of pain relief but does not particularly benefit muscle wasting or sensory loss.

Ulnar neuropathy. The second most common entrapment neuropathy (2.1%) occurs as a result of ulnar nerve compression immediately distal to the ulnar groove beneath the edge of the flexor carpi ulnaris aponeurosis in the cubital tunnel. It may develop as a result of deformity at the elbow joint secondary to fracture or as a consequence of prolonged pressure during surgery, and it has been most commonly associated with alcoholism. Typical symptoms include painful paresthesiae in the fourth and fifth digits associated with hypothenar and interosseous muscle wasting. The pathology is a combination of demyelination and axonal degeneration. The key electrophysiological findings include low amplitude ulnar sensory nerve action potentials, reduced sensory NCV, and fibrillation potentials in the interossei (99). Management of patients is primarily conservative, with advice to avoid pressure to this area, as the results of surgery are very poor. However, if symptoms and signs progress, then a number of approaches may be used: medial epicondylectomy, transaction of the flexor carpi ulnaris aponeurosis, and ulnar nerve transposition (100).

Radial neuropathy. Radial neuropathy is rare (0.6%), occurring as a consequence of radial nerve compression in the spiral groove. It presents with the characteristic motor deficits of wrist drop with very occasional sensory symptoms of paresthesiae in the dermatomes supplied by the superficial radial nerve. Causes of idiopathic radial neuropathy include humeral fracture, blunt trauma over the posterolateral aspect of the arm, and external compression. Electrophysiological assessment demonstrates a predominant effect on amplitude rather than the conduction velocity, suggestive of predominantly axonal degeneration associated with secondary demyelination (101). Management is conservative with pressure relief.

Common peroneal neuropathy. This is the most common of all limb mononeuropathies. Involvement of the motor fibers in the common peroneal nerve results in weakness of the dorsiflexors and "foot drop," but loss of the motor supply to the tibialis anterior muscle also leads to weakness in eversion. This is accompanied by a sensory deficit but characteristically no pain or paresthesiae. Diabetes is a relatively uncommon cause (5–12% of cases) of peroneal nerve palsy (102). Common causes include external compression at the fibular head during anesthesia (in bed-ridden patients) and inappropriately placed plasters following lower-limb fractures. An important differential is a radiculopathy involving the L5 root. Features that define L5 involvement include pain in the lower back and additional loss of inversion. Electrophysiological studies suggest demyelination with conduction block in mild lesions with a marked loss of amplitude presumably secondary to axonal degeneration in more severe lesions (103). Because the majority

of these lesions are caused by external pressure that, if relieved, will result in resolution of the motor deficit within 3–6 months, a conservative approach is advocated with removal of pressure and a foot brace in the interim.

Lateral femoral cutaneous neuropathy. Compression of the lateral femoral cutaneous nerve (meralgia paraesthetica) is uncommon and results in pain, paresthesiae, and sensory loss in the lateral aspect of the thigh (104). Obesity is the most common cause, followed by trauma due to external injury of the nerve, as it runs down the lateral aspect of the thigh. Most will resolve spontaneously and are therefore managed conservatively.

Other nerves that may be involved include the sciatic and obturator nerves. They can be a cause of significant motor deficit; however, they are extremely rare and their management is conservative.

B. Cranial neuropathies

Cranial neuropathies in diabetic patients are extremely rare (0.05%) and occur in older individuals with a long duration of diabetes (105).

Ocular neuropathies. Cranial nerves III, IV, and VI are affected, and among diabetic patients, the relative frequency is oculomotor (3.3%) and abducent (3.3%) nerve occurring with equal and greater frequency than the trochlear nerve (2.1%) (106). The classical presentation of oculomotor nerve palsy is that of an acute-onset diplopia with ptosis and pupillary sparing associated with ipsilateral headache. While pupillary sparing is often quoted as a means of differentiating diabetic from other structural (aneurysm, tumor, or mass) ophthalmoplegias, 14–18% of diabetic patients do develop pupillary dysfunction (107). Resolution of neurological deficits occurs over ~2.5 months and recurrence can occur in 25% of patients (107). A clear understanding of the underlying pathology and pathogenesis of this condition is limited due to the difficulties in obtaining tissue in such patients. Based on four single postmortem case reports demonstrating centrofascicular pallor of myelin staining in paraffin-embedded sections, it is assumed that focal demyelination occurs secondary to ischemia (108). This is supported by more recent studies in plastic sections offering clearer pathological detail (109). However, this conclusion should be interpreted with caution as acute ischemic injury should result in axonal degeneration. Furthermore, pallor in staining should not be interpreted as demyelination, as this has not been confirmed using teased fiber analysis. A recent study of oculomotor nerve specimens from 8 diabetic patients without oculomotor nerve palsy compared with 15 nondiabetic patients has shown subperineurial as opposed to centrofascicular alteration. Microfasciculation has been demonstrated and suggests chronic injury due to ischemia (110). Management is expectant with strong reassurance to the patient for recovery. Maintaining optimal glycemic control as well as minimizing the other stronger risk factors for ischemia, including hypertension and hyperlipidemia, may aid recovery.

Facial neuropathy. In most series of idiopathic facial neuropathy or Bell's palsy, diabetes is well represented, ranging from 6% (111) to 48.8% (112). The main neurological findings are those of acute-onset unilateral weakness of facial muscles, widening of the palpebral fissure, and secondary corneal irritation. This is accompanied by varying degrees of disturbance in taste and hyperacusis. The presence of hypertension and severity of paralysis at onset, but not diabetes, determines the degree of recovery at 1 year (113). Neurophysiological studies demonstrate reduced or absent compound muscle action potentials (CMAPs) in the nasalis muscle, which can actually be used to determine outcome. Thus, CMAP >30% results in 90–100% recovery, CMAP 10–30% results in <50% recovery, and CMAP <10% results in virtually no recovery. This is associated with prolongation of the R1 and R2 latencies of the trigeminal "blink reflex" (114). If the presentation is acute for <1 week, 7–14 days of prednisone may be administered but with attention to optimizing glycemic control.

Other cranial nerves. Other cranial nerves may be affected in diabetes. However, their relatively infrequent involvement warrants an awareness of their occurrence but will not be discussed in detail. Thus, olfactory and optic nerve involvement has been described. More recently, corneal confocal microscopy has been used to show significant degeneration of small myelinated and unmyelinated fibers in the cornea of diabetic patients with increasing neuropathic severity (115). There are also reports of an increased frequency of trigeminal neuralgia in diabetic patients. Hearing loss as a result of VIII nerve involvement has also been described (116). Vagal nerve involvement manifests as part of diabetic autonomic neuropathy. Vocal cord paralysis has also been attributed to recurrent laryngeal nerve involvement.

C. Diabetic amyotrophy

Clinical features. Diabetic amyotrophy typically occurs in patients with type 2 diabetes aged 50–60 years and presents with severe pain and uni- or bilateral muscle weakness and atrophy in the proximal thigh muscles (117).

Pathogenesis. Factors contributing to the development of diabetic amyotrophy (proximal motor neuropathy) (118,119) are poorly understood. Somewhat polarized views have evolved. One proposal has implicated ischemia based on an early case report that demonstrated infarcts in the proximal femoral, sciatic, and obturator nerves and lumbosacral plexus (120); other investigators have proposed a metabolic basis for a more subacute, symmetrical disorder affecting the distal branches of the proximal motor nerves (121). A conciliatory view is derived from reports of patients with an initial rapid evolution with subsequent slow progression of symptoms and signs over several months, indicating a combination of both vascular and metabolic factors (117,122).

Neurophysiology. Needle electrode sampling reveals different responses depending on the stage of this condition. In the early stages, spontaneous fibrillation and reduced motor unit recruitment occur, suggestive of denervation. In later stages, there is an increase in amplitude of the motor unit potential, indicating reinnervation via collateral sprouting. Electrophysiological studies demonstrate a reduction in femoral NCV (123). Additionally, however, femoral nerve stimulation produces an attenuated compound muscle action potential of the quadriceps muscle, supporting the occurrence of axonal pathology (124).

Pathology. Recent reports have demonstrated an epineurial vasculitis in the intermediate cutaneous nerve of the thigh (ICNT) in a proportion of patients with amyotrophy (124–126). Centrofascicular degeneration of the ICNT has been observed in association with an inflammatory infiltrate and occlusion of epineurial blood vessels (124,125). These studies have highlighted the heterogeneous na-

ture of myelinated and unmyelinated fiber damage as some patients showed an almost complete loss of fibers, whereas others demonstrated a moderate reduction with regeneration both proximally in the ICNT and distally in the sural nerve (124,125). Another study demonstrated a reduction or absence of CMAPs in the tibial and peroneal nerves and also in the sensory action potential of the sural nerve, with relative preservation of NCVs, suggestive of axonal degeneration rather than demyelination (127). This was confirmed on pathological examination of the sural nerve, which demonstrated multifocal fiber loss and dystrophic fibers with predominantly axonal degeneration and secondary demyelination associated with abortive regeneration represented by the formation of microfasciculi and perineurial scarring (125). One may question the relevance of distal findings in the sural nerve for a condition that affects proximal lumbosacral nerve segments. Thus, in contrast, a recent study in the intermediate cutaneous nerve of 15 patients with diabetic amyotrophy has shown multifocal fiber loss, but teased fiber studies have primarily demonstrated demyelination (128).

The other major finding that has provided a novel perspective on the pathogenesis of this condition has been derived from immunohistological studies. In the study by Said et al. (126), all ICNT biopsies demonstrated an inflammatory infiltrate composed of B- and T-cells and occasional macrophages. In another study, which included 12 patients with diabetic amyotrophy, the sural nerve demonstrated a mononuclear cell infiltrate in 4 patients and a perivascular infiltrate of activated T-cells expressing both interleukin (IL)-2 and major histocompatibility complex class II antigens in 6 patients (129). There was, however, no evidence of infiltration with B-cells or polymorphonuclear cells. The majority of nerves from patients also showed staining for tumor necrosis factor (TNF)-α, IL-6, and IL-1β. Furthermore, C3d and C5b-9 complement protein was found within endoneurial and epineurial blood vessel walls in all patients (129). Dyck et al. (127) demonstrated epineurial vascular and perivascular mononuclear inflammatory infiltrates, which stained positive for leukocytes. There were also additional features of a necrotizing vasculitis (arteriolar, venular, and capillary wall infiltration with inflammatory cells) with hemosiderin deposition. Together these changes suggested a microscopic vasculitis, and levels of IL-1β and IL-6 were increased in these patients (127). A recent study has demonstrated a polymorphonuclear vasculitis with transmural infiltration of postcapillary venules with IgM deposition along the endothelium as well as in the endoneurium and subperineurial regions, indicating increased permeability and immune-mediated nerve damage (128). There was additional deposition of activated complement (C5b-9) in the same areas, indicating an active immune-mediated vasculitis.

Management. Current therapies lack a robust evidence base to support the use of any therapy, because the rarity of this condition precludes controlled clinical trials. The main aim of therapy is to control pain, and this can be achieved through nonsteroidal antiinflammatory agents (ibuprofen and naproxen), opioids (codeine phosphate and morphine elixir), or tricyclic antidepressants (amitriptyline and imipramine). Other agents that may be useful include tramadol and gabapentin (see Section 5*B*, no. 8). Measures that putatively affect the underlying pathology include an improvement in glycemic control. This has been particularly advocated in patients on oral hypoglycemic agents who are recommended for conversion to insulin therapy. Based on the observations of vasculitis in a proportion of patients, immunosuppressive therapy has been recommended using initial intravenous, followed by high-dose oral corticosteroids, or intravenous immunoglobulin. Reports of a dramatic improvement in neurological function (130) have resulted in the initiation of a multicenter clinical trial of immunotherapy in the U.S., due to report in 2004 (131).

D. Diabetic truncal radiculoneuropathy

Clinical features. Diabetic truncal radiculoneuropathy affects middle-aged to elderly diabetic patients and appears to have a predilection for men. Pain is a primary feature and is acute in onset but may evolve over several months. It is aching or burning in quality, may be superimposed with lancinating stabs, and demonstrates nocturnal exacerbation with cutaneous hyperesthesia. It occurs in a girdle-like distribution over the lower thoracic or abdominal wall, usually unilateral but sometimes bilaterally. On rare occassions, it may result in motor weakness with bulging of the abdominal wall (11). Profound weight loss may accompany the onset of symptoms. Clinical examination demonstrates heterogeneous neurological findings ranging from no abnormality to sensory loss and hyperesthesia in a complete dermatomal pattern, but may sometimes just involve the distribution of the ventral or dorsal rami (132). Resolution of symptoms generally occurs within 4–6 months.

Pathogenesis. Clinically, this condition bares strong similarities to diabetic amyotrophy, but due to the lack of pathological studies, its pathogenesis is based more on inference than on actual evidence. The acute onset suggests a vascular cause, although its occurrence in patients with generally poorer glycemic control suggests a metabolic basis.

Electrophysiology. Electromyography demonstrates denervation potentials in the intercostal, anterior abdominal wall, and paraspinal muscles (133). There are no reported conduction studies of the intercostal nerves in this condition.

Pathology. There are no pathological studies on this condition. Therefore, one may only infer the site of the lesion. In those patients demonstrating denervation of the paraspinal muscles, a lesion of the dorsal primary rami is probable (134). However, those who do not demonstrate this feature may demonstrate lesions more distally in the intercostal or subcostal nerves. From the sensory deficits, it is clear that the lesions may vary and involve posterior primary rami of the spinal nerves or intercostal nerves (132). The cause may be ischemia, and the contiguous dermatomal involvement may be explained by the occlusion of a single intercostal artery supplying several truncal nerves.

Management. There is no evidence to support the use of any therapy. Because the natural history is for spontaneous resolution within 4–6 months, and as there are strong similarities to diabetic amyotrophy, the approach to management is very similar to that for the latter. The main aim of therapy is to control pain. Again, an improvement in glycemic control has been advocated, as has immunosuppressive therapy with corticosteroids or intravenous immunoglobulin.

Table 4—*Contrasts between acute sensory and chronic sensorimotor neuropathies*

	Acute sensory	Chronic sensorimotor
Mode of onset	Relatively rapid	Gradual, insidious
Symptoms	Severe burning pain Aching: weight loss usual	Burning pain, paresthesiae, numbness; weight loss unusual
Symptom severity	+++	0 to ++
Signs	Mild sensory in some: motor unusual	Stocking and glove sensory loss: absent ankle reflexes
Other diabetic complications	Unusual	Increased prevalence
Electrophysiological investigations	May be normal or minor abnormalities	Abnormalities unusual in motor and sensory nerves
Natural history	Complete recovery within 12 months	Symptoms may persist intermittently for years: at risk of foot ulceration

E. CIDP

Diabetic patients occasionally develop clinical and electrodiagnostic features suggestive of CIDP (29). It is important to recognize that this subgroup, unlike those with diabetic polyneuropathy, is treatable (135). Many of the clinical, electrophysiological, and nerve biopsy criteria are not sufficiently helpful in the differential diagnosis of these two conditions. However, when an unusually severe and progressive polyneuropathy develops in diabetic patients, one must consider CIDP.

Although electrodiagnosis is an important element in the diagnosis of CIDP, current electrodiagnostic criteria alone appear to be insufficient for defining many cases of CIDP and therefore certainly should not be relied on to differentiate from diabetic polyneuropathy (136).

Nerve biopsies in CIDP demonstrate segmental demyelination and remyelination, onion bulbs, and inflammatory infiltrates, but they are also present in diabetic polyneuropathy (137). The presence of increased numbers of macrophages indicating a macrophage-associated demyelination may be helpful, as this is a characteristic feature of CIDP not observed in diabetic polyneuropathy (137).

Treatment of CIDP requires long-term immunomodulatory therapy with combinations of corticosteroids, azathioprine, plasmapheresis, and intravenous immune globulin but does produce relatively rapid and substantial improvement in neurological deficits and electrophysiology (138,139).

SECTION 5: DISTAL SYMMETRICAL POLYNEUROPATHY

A. Acute sensory neuropathy

Acute sensory (painful) neuropathy is a distinctive variant of DPN that warrants a separate discussion (23,24,140). Although many of the symptoms of acute sensory and chronic sensorimotor neuropathy are similar, there are clear differences in the mode of onset, accompanying signs, and prognosis, which are summarized in Table 4 (140–142). Pain is the outstanding complaint in all patients, who also experience severe weight loss, depression, and, frequently in males, erectile dysfunction. Common complaints include constant burning discomfort (especially in the feet), severe hyperesthesiae, and deep aching pain, and many experience sudden, sharp, stabbing, or "electric shock"–like sensations in the lower limbs. All symptoms are prone to nocturnal exacerbation, with bed clothes irritating hyperesthetic skin. Clinical examination is usually relatively normal, with allodynia on sensory testing, a normal motor exam, and occasionally reduced ankle reflexes.

Acute painful neuropathy is associated with poor glycemic control and may follow an episode of ketoacidosis; it has also been associated with weight loss and eating disorders (143).

Conversely, it may develop after sudden improvement of glycemic control; the term "insulin neuritis" is unfortunate, as it may follow improvement of glycemic control induced by oral hypoglycemic agents. Both of these observations are in keeping with the hypothesis that blood glucose flux is important in the genesis of neuropathic pain (10).

Sural nerve biopsies have been performed in patients with acute painful neuropathy (141,144) and show active degeneration of both myelinated and unmyelinated fibers. No correlations were demonstrated between pain and either active degeneration of myelinated fibers or regenerative activity in myelinated or unmyelinated axons. Thus, it is difficult to reconcile these findings with the suggestion that acute painful neuropathy is an example of a "small-fiber neuropathy." Indeed, a recent review concluded that painful neuropathy is not restricted to selective involvement of small or large fibers (145). There is also a suggestion that acute painful neuropathy may be related to neural ischemia precipitated by sudden improvement of glycemic control. Using in vivo epineurial vessel photography and fluorescein angiography, Tesfaye et al. (146) demonstrated severe abnormalities of epineurial vessels in acute painful neuropathy, with arteriovenous shunting and proliferating neural "new vessels" that resembled new vessels seen in retinopathy. One hypothesis for the genesis of neuropathic pain in such cases is that sudden changes in blood glucose control result in alterations in their blood flow, leading to a "steal" effect with arteriovenous shunting thus rendering the endoneurium ischemic.

In the management of this condition, achieving stable blood glucose control is most important: stability may well be the key feature as blood glucose flux (as assessed by the "M" value) is associated with pain (10,147). Additionally, most patients require medications for their neuropathic pain (these medications are detailed below). The natural history of this condition is very different from the much more common chronic sensorimotor neuropathy: its onset is acute or subacute, but the severe symptoms resolve in less than a year (140,141).

B. Chronic sensorimotor neuropathy (DPN)

Chronic sensorimotor neuropathy is the most common manifestation of the DNs that is usually insidious in onset and may be the presenting feature in people with type 2 diabetes (10,26). Many patients are asymptomatic, and a neurological deficit may be discovered by chance during a routine neurological exam, although they

may even present with a neuropathic complication such as a painless foot ulcer. It is a length-dependent process, and its sensory manifestations are most pronounced in the lower limbs and, in more severe cases, in the fingers and hands.

The following subsections will focus on the clinical presentation and assessment of chronic sensorimotor neuropathy; methods of quantitative sensory testing, electrophysiological study, and other methods of assessment; and treatments of chronic sensorimotor neuropathy.

1. Clinical presentation of chronic sensorimotor neuropathy (DPN).

Symptoms. DPN occurs in both type 1 and type 2 diabetes and is more common with increasing age and duration of diabetes. These symptoms tend to be intermittent and of similar character but with lesser intensity than those described under painful neuropathy. In a large population survey, Harris et al. (148) reported that 30% of type 1 diabetic patients and 36% of male and 40% of female type 2 diabetic patients experienced neuropathic symptoms. However, 10% of males and 12% of females in the nondiabetic population reported similar symptoms.

As in acute sensory neuropathy, painful symptoms tend to be more pronounced at night, but in addition, patients with DPN may experience "negative" symptoms such as numbness or "feet feel dead." Patients often find it difficult to describe the symptoms as they are different than the pain that they have previously experienced. Though not often mentioned in older texts, unsteadiness is increasingly being recognized as a manifestation of DPN, due to disturbed proprioception and possibly abnormal muscle sensory function (149). Such unsteadiness has been quantified (150–152) and may result in repetitive minor trauma or falls and in late complications such as trauma or Charcot's neuroarthropathy.

Signs. On clinical examination, there is usually a symmetrical sensory loss to all modalities in a stocking distribution. In severe cases, this may extend well above the ankle and also involve the hands. The ankle reflexes are usually reduced or absent, and the knee reflexes may also be absent in some cases. Motor weakness is unusual, although small muscle wasting in the feet and also the hands may also be seen in more advanced cases. Any pronounced motor signs should raise the possibility of a nondiabetic etiology of the neuropathy, especially if asymmetrical (1,19).

In more severe cases, with loss of proprioception, patients may demonstrate a positive Romberg's sign.

As DPN is often accompanied by distal (sympathetic) autonomic neuropathy (140), signs of autonomic dysfunction are often apparent on examinations: these might include warm dry skin (in the absence of peripheral vascular disease) and the presence of plantar callus under pressure-bearing areas. The "at-risk" foot for neuropathic ulceration might also have a high arch (pes cavus) and clawing of the toes (153). However, it must be emphasized that all patients with DPN with or without obvious foot deformities must be considered as being at risk of neuropathic complications, such as Charcot's neuroarthopathy or foot ulceration (27,153).

2. Clinical assessment of DPN.

Symptoms. As noted above, many patients have difficulty in describing the symptoms of neuropathy. Pain and paresthesiae are personal experiences, and there is marked variation in the description of symptoms between individuals with similar pathological lesions. This has important implications for the assessment of symptoms: Huskisson (154) clearly stated that "[p]ain is a personal psychological experience and an external observer can play no part in its direct measurement." When recording symptoms in clinical practice, physicians must therefore avoid the temptation to "interpret" or "translate" patient reports; instead, they should record the patient's description verbatim.

A number of simple symptom screening questionnaires are available to record symptom quality and severity. A simplified neuropathy symptom score that was used in the European prevalence studies could also be useful in clinical practice (2,4). The Michigan Neuropathy Screening Instrument (MNSI) is a brief 15-item questionnaire that can be administered to patients as a screening tool for neuropathy (155). Other similar symptom scoring systems have also been described (156).

Simple visual analog or verbal descriptive scales may be used to follow patients' responses to treatment of their neuropathic symptoms (156–158). However, it must always be remembered that identification of neuropathic symptoms is not useful as a diagnostic or screening tool in the assessment of DN, as shown by Franse et al. (159).

It is well recognized that both symptoms and deficits may have an adverse effect on quality of life (QOL) in DN (160). The NeuroQol, a recently developed and validated QOL instrument, also includes a symptom checklist and may be used as an outcome measure in future clinical studies (161).

Signs. The use of composite scores to assess clinical signs was pioneered by Dyck and colleagues (21,162), who first described the NDS and later the Neuropathy Impairment Score (NIS). A modified NDS has been used in several large studies (2,4,52) and can also be used in the community by a trained nonspecialist (Fig. 1). It has been shown to be the best predictor of foot ulceration and the best neuropathic end point in a large prospective community study (52). The maximum NDS is 10, with a score of 6 or more being predictive of foot ulcer risk.

Similarly, the Toronto group (163) have described a number of simple screening tests for the diagnosis of neuropathy in outpatient clinics. They have recently validated this clinical scoring system (164) and concluded that it can be used to document and monitor neuropathy in the clinic. Looking to the future, Dyck et al. (165) recently reported electronic case-report forms for the recording of symptoms and signs of neuropathy that might be useful in the longitudinal follow-up of neuropathic patients.

Whatever methodology is used in the assessment and documentation of neuropathic signs, it should be noted that the neurological exam of the lower limbs is the important aspect in the clinical diagnosis of DN (166).

Simple devices for clinical screening. The dividing line between simple devices used in daily clinical practice and QST is difficult to define. For the purposes of this review, QST will be defined as procedures requiring a power source where the intensity and characteristics of the stimuli are well controlled and where the detection threshold is determined in parametric units that can be compared with established "normal" values (167).

Although the simple handheld screening devices are less sensitive than the more sophisticated QST devices described below, they have the advantage of being relatively inexpensive, easy to oper-

NDS

		Right	Left
VPT 128 Hz tuning fork; apex of big toe: normal = can distinguish vibrating/not vibrating	Normal = 0; abnormal = 1		
Temperature perception on dorsum of the foot Use tuning fork with beaker of ice/warm water			
Pin prick Apply pin proximal to big toenail just enough to deform the skin; trial pair = sharp, blunt; normal = can distinguish sharp/not sharp			
Achilles reflex	Present = 0 Present with reinforcement = 1 Absent = 2		
	NDS total out of 10		

Figure 1—*The modified NDS.*

ate, and easily portable; therefore, their use in clinical practice is increasing.

The most widely used device in clinical practice is the Semmes-Weinstein monofilament (168,169). The filament assesses pressure perception when gentle pressure is applied to the handle sufficient to buckle the nylon filament. Although filaments of many different sizes are available, it is the one that exerts 10 g of pressure, the value most commonly used to assess pressure sensation in the diabetic foot. It is also referred to as the 5.07 monofilament because, during calibration, the filaments are calibrated to exert a force measured in grams that is 10 × log of the force exerted at the tip; hence, 5.07 exerts 10 g of force.

A number of cross-sectional studies have assessed the sensitivity of the 10-g monofilament to identify feet at risk of ulceration. Sensitivities vary from 86 to 100% (170–172), although there is no consensus as to how many sites should be tested. The most common algorithm recommends four sites per foot: generally the hallux and metatarsal heads 1, 3, and 5 (169). However, the most recent study (172) suggested that there is little advantage gained from multiple site assessments. There is also no universal agreement as to what constitutes an abnormal result (i.e., one, two, three, or four abnormal results from the sites tested). Despite these problems, the 10-g monofilament is widely used for the clinical assessment of neuropathy.

A final caution on the use of the filaments: Booth and Young (173) identified that filaments manufactured by certain companies do not actually buckle at 10 g of force. Indeed, several tested filaments buckled at <8 g. Thus, care must be taken when selecting suppliers of filaments.

The graduated Rydel-Seiffer tuning fork is used in some centers to assess neuropathy (174,175). This fork uses a visual optical illusion to allow the assessor to determine the intensity of residual vibration on a 0–8 scale at the point of threshold (disappearance of sensation). Hilz et al. (174) reported that results with this instrument correlated well with other QST measures.

The tactile circumferential discriminator assesses the perception of calibrated change in the circumference of a probe (a variation of two-point discrimination). Vileikyte et al. (176) reported a 100% sensitivity in the identification of patients at risk of foot ulceration. Similarly, this device also demonstrated good agreement with other measures of QST.

Finally, the recently reported Neuropen is a clinical device that assesses pain using both a Neurotip at one end of the "pen" and a 10-g monofilament at the other end. This was shown to be a sensitive device for assessing nerve function when compared with the simplified NDS (177).

3. QST. The progressive loss, or change, in sensation is the hallmark of DPN. QST measures can be used to identify the sensory modalities affected and to estimate the magnitude of the deficit. In the diabetic population, vibration, thermal, and pain thresholds have proven valuable in the detection of subclinical neuropathy (178,179), in tracking the progression of neuropathy in large cohorts (180,181), and in predicting patients "at risk" for foot ulceration (182,183). In addition, QST measures have played a key role as primary efficacy end points in a series of multicenter clinical trials evaluating the prevention or treatment of diabetic polyneuropathy (74,91).

The strengths of QST are well documented (rev. in 167) and include *1*) the accurate control of stimulus characteristics; *2*) the ability to assess multiple modalities; *3*) the use of well-established psychophysical procedures to enhance sensitivity; *4*) the capacity to measure function over a wide dynamic range of intensities, thus supporting the evaluation of multiple degrees of neuropathy; *5*) the ability to measure sensation at multiple anatomical sites, enabling the exploration of a potential distal-to-proximal gradient of sensory loss; and *6*) for most

measures, the availability of data from large, age-matched, "normal" comparison groups. The limitations of QST are also clear. No matter what the instrument or procedure used, QST is only a semiobjective measure, affected by the subject's attention, motivation, and cooperation, as well as by anthropometric variables such as age, sex, body mass, and history of smoking and alcohol consumption (184,185). Expectancy and subject bias are additional factors that can exert a powerful influence on QST findings (186). Further, QST is sensitive to changes in structure or function along the entire neuroaxis from nerve to cortex; it is not a specific measure of peripheral nerve function (167).

There have been several reviews of QST procedures (167,187–189) and several "consensus expert panels" have considered the value of QST as a method of assessing sensory neuropathy (20,30, 33,34). A discussion of the merits of specific instruments or testing algorithms is beyond the scope of this review. However, it is noteworthy that a recent study comparing VPTs using two very different instruments and procedures reported similar sensitivity to mild DPN and consistent correlation of each VPT measure with sural NCV (190).

Recently, a consensus subcommittee of the American Academy of Neurology (34) stated "QST testing for vibratory and cooling thresholds receives a Class II rating as a diagnostic test. Further, QST is designated as safe, effective and established, with a type B strength of recommendation. However, QST is unacceptable as the sole criteria to define diabetic neuropathy."

Vibration thresholds. The relationship between elevated VPT and DN has been documented for almost 100 years. When tested in the 50- to 300-Hz range, VPT reflects the activation of mechanoreceptors (i.e., Pacinian and Meissner corpuscles), conduction in large-diameter myelinated peripheral axons, and transmission through the dorsal column spinal pathways.

Multiple studies have documented the relation between loss of vibration sensation and the progression of a variety of indicators of DPN (191,192). Dyck et al. (193) used computer-assisted QST to evaluate three large cohorts and identified a "strong and consistent correlation" between sensory loss and other markers of DN. These studies confirmed that vibration thresholds are especially sensitive to mild or subclinical neuropathy. Davis et al. (194) also demonstrated that vibratory thresholds can detect subclinical neuropathy in children and adolescents with type 1 diabetes. Boulton et al. (195) documented that vibration thresholds provided a strong indication of "risk" for future ulceration across a wide range of ages and durations of diabetes. In a 4-year prospective study (182), patients with baseline threshold elevated above a fixed value (i.e., 25 V with the biosthesiometer) were seven times more likely to develop foot ulcers. This observation is supported by the recent evaluation of 187 type 2 diabetic patients that used multivariate logistic regression to document that an elevated VPT score was the strongest predictor of foot ulceration (i.e., relative risk of 25.4) (183). The strength of the relationship between elevated VPT and foot ulceration is illustrated by the finding, in 1,035 type 1 and type 2 diabetic patients, that each 1-unit increase in vibration threshold (voltage scale) at baseline increased the hazard of foot ulceration by 5.6% over a 1-year study period (196).

Thermal thresholds. Although most mechanoreceptors and free nerve endings can be stimulated by thermal energy, true cutaneous thermoreceptors are orders of magnitude more sensitive to shifts in temperature. Separate cold and warm thermoreceptors have been identified (197) and generally characterized by small receptor fields. Thermal energy is conducted in thinly myelinated Aδ or unmyelinated C fibers and is principally transmitted in the crossed anterolateral tracts of the spinal cord. The sensation of pain can also be driven by high-intensity stimulation of thermoreceptors, especially those sensitive to warming; this activation can be assessed by measuring heat-pain thresholds (198).

As is the case with vibration, altered thermal thresholds have been well documented in patients with DN defined by other criteria (179,191,193), and their elevation has been associated with progression of neuropathy and ultimately with foot ulceration (199). Abnormal thermal thresholds have been reported in 75% of subjects with moderate-to-severe DPN, and elevated heat-pain thresholds were detected in 39% of these subjects (200). Generally, there is a high correlation between elevated thermal and vibration thresholds, but these measures can be dissociated, suggesting a predominant small- or large-fiber neuropathy in individual patients. The symptoms of neuropathic pain have been associated with altered thermal thresholds (201), but, as stated earlier, painful neuropathy likely involves both small- and large-diameter neurons (145). Lowered heat-pain thresholds have been reported in patients with DN, and this condition may be an important indication of hypersensitivity associated with early changes in distal nerve segments (193).

It is technically more challenging to measure thermal thresholds compared with vibration thresholds; the evaluation generally takes longer and the smallest detectable difference has been reported as approximately double that of vibration (201). Computer-assisted procedures may be especially valuable in examining thermal thresholds (202).

4. Electrophysiology. Whole nerve electrophysiologic procedures (e.g., NCV, F-waves, sensory, and/or motor amplitudes) have emerged as an important method of tracing the onset and progression of DPN (203). Multiple consensus panels have recommended the inclusion of electrophysiology in the evaluation of DPN, as well as the use of these procedures as surrogate measures in multicenter clinical trials (20,33). These procedures have also been used extensively to explore the mechanisms of dysfunction and the value of various therapeutic interventions in chemical and genetic animal models of hyperglycemia.

An appropriate battery of electrophysiologic tests supports the measurement of the speed of both sensory and motor conduction, the amplitude of the propagating neural signal, the density and synchrony of muscle fibers activated by maximal nerve stimulation, and the integrity of neuromuscular transmission (rev. in 204,205). These are objective, parametric, noninvasive, and highly reliable measures. However, "standard" procedures, such as maximal NCV, reflect only a limited aspect of neural activity and then only in a small subset of large-diameter and heavily myelinated axons. Even in large-diameter fibers, NCV is insensitive to many pathologic changes known to be associated with DPN. For example, there is strong evidence linking DPN with a reduction in Na^+/K^+ adenosine triphosphatase activity (206). This deficit would primarily diminish the ability of neurons to rapidly reestablish appropriate trans-

membrane ion gradients after activation. Standard NCV, which essentially evaluates single pulses, could be unaffected at a time point when assessment of refractory cycles and axonal recovery would document altered function (207).

A key role for electrophysiological assessment is to rule out other causes of neuropathy or to identify neuropathies superimposed on DPN. Unilateral conditions, such as entrapments, are far more common in diabetic patients (208). Sharma et al. (209) report that the odds of occurrence of CIDP were 11 times higher among diabetic than nondiabetic patients. The symmetry of electrophysiological measures, and the nature and magnitude of the deficits, can help identify additional causes for neurological deficits and can be valuable in selecting appropriate subjects for clinical trials.

Mechanisms of NCV slowing. The principal factors that influence the speed of NCV are *1*) the integrity and degree of myelination of the largest diameter fibers, *2*) the mean cross-sectional diameter of the responding axons, *3*) the representative internodal distance in the segment under study, and *4*) the microenvironment at the nodes, including the distribution of ion channels.

Functional deficits. The responsiveness of the neuron and its ability to propagate neuroelectric signals are ultimately dependent on the distribution of transmembrane ion channels. In myelinated axons, the nodal region is characterized by a high density of voltage-sensitive channels permeable to Na^+, K^+, or both, as well as a nonspecific channel likely responsible for nodal "leakage currents." Factors that may contribute to the anchoring of specific Na^+ channels to the nodal region include suppression of Na^+ channels in the internodal regions or select binding of channels to portions of the extracellular matrix (rev. in 210). DPN has been reported to alter the nodal/paranodal distribution of ion channels and to widen the nodal gap. These changes may reflect "functional" deficits that could underlie acute and rapidly reversible slowing of NCV (200,201).

Early structural deficits. Demyelination can have a profound effect on NCV, but this mechanism appears to be only a minor factor in slowing of NCV in DPN (127). A recent study of 57 patients with diabetes reported an amplitude-independent slowing of NCV in intermediate, but not distal, nerve segments, consistent with some contribution of demyelination (211). The initial structural deficit responsible for slowing of NCV in DPN is likely a diminished "length constant" of large-diameter axons due to altered cross-sectional volume (i.e., early stages of a distal axonopathy). This early structural pathology could reasonably be due to a diminished production of endoskeletal and growth-associated proteins (212).

Chronic deficits. The impact of changes in ion distributions and axonal diameters continues to be present in chronic DPN, but in addition, NCV is altered by Wallerian degeneration, a consequent reduction in axon density, and a gradual but relentless shift in the fiber diameter histogram toward smaller-diameter fibers.

Specific electrophysiologic measures in DPN.

NCV. In the past 5 years, there have been more than 100 published articles discussing the link between NCV and DPN, and this builds on decades of previous research. A thorough discussion of this literature is beyond the scope of this review; however, several key findings have emerged:

- NCV is only gradually diminished by DPN, with estimates of a loss of ~0.5 m $\cdot s^{-1} \cdot year^{-1}$ (204). In a 10-year natural history study of 133 patients with newly diagnosed type 2 diabetes, NCV deteriorated in all six nerve segments evaluated, but the largest deficit was 3.9 m/s for the sural nerve (i.e., 48.3 to 44.4 m/s); peroneal motor NCV was decreased by 3.0 m/s over the same period (8). A similar slow progression of change in NCV was detected in the Diabetes Control and Complications Trial (DCCT) (7), in which the sural and peroneal nerve velocities in the conventionally treated group diminished by 2.8 and 2.7 m/s, respectively, over the 5-year study period.
- NCV provides a sensitive but nonspecific index on the onset of DPN and can be valuable in detecting subclinical deficits. The earliest reports of altered NCV in patients without clinical symptoms or signs of DPN date back for more than 40 years and have been confirmed in recent studies (204,205).
- NCV can trace the progression of DPN and can provide a valuable measure of the severity of DPN and "quality of life related to peripheral nerve involvement" (213).
- Changes in NCV are related to glycemic control (214). In the DCCT, subjects who were "free of confirmed neuropathy at baseline" had a 40.2% incidence of abnormal NCV in the conventionally treated group and only 16.5% in the group receiving intensive therapy after a period of 5 years (7). This was associated with a between-group difference of 4.0 m/s for the peroneal nerve and 3.9 m/s for the sural nerve. A previous study in 45 type 1 diabetic patients utilized a regression analysis to document that a 1% change in HbA_1 was associated with a 1.3 m/s change in maximal nerve conduction (215).
- Changes in NCV can reflect underlying structural pathology in large-diameter axons, including atrophy, demyelination, and loss of fiber density (205).
- NCV can improve with effective therapy (51) or with transplantation (216).

Amplitudes, area, and duration. Peak amplitude of either the SNAP or the CMAP driven by maximal stimulation reflects the number of responding fibers and the synchrony of their activity. There is a strong correlation ($r = 0.74$; $P < 0.001$) between myelinated fiber density and whole-nerve sural amplitude (217) in DPN. Russell et al. (218) calculated that a change of 1.0 μV in sural nerve SNAP amplitude is associated with a decrease of ~150 fibers/mm^2, while a loss of 200 fibers/mm^2 is associated with an approximate 1.0-mV reduction in the mean amplitude of the CMAP from the ulnar, peroneal, and tibial nerves. Longitudinal studies suggest an average loss of SNAP amplitude at a rate of ~5% per year in DPN over a 10-year period (8).

Measuring the total area of the SNAP and CMAP has been suggested as a means of assessing the contribution of slower conducting fibers, but these measures are severely limited by variability. Area alone, or in association with peak amplitude, can also be used to estimate the degree of temporal dispersion and conduction block.

F-waves. F-waves reflect the antidromic conduction of the compound neural volley to the ventral spinal cord, the activation of a subpopulation of spinal motor neurons, the orthodromic conduction of the newly established volley, and

the postsynaptic activation of a portion of the muscle fibers in the innervated muscle. Because of its "long-loop" nature, this measure is sensitive to factors that alter the speed of conduction, especially those widely distributed along the nerve. A subtle change affecting each node may not be detected in measures focused on an isolated distal segment, but may accumulate and become evident in the long latency F-wave response.

F-wave procedures have been reported as a sensitive and reliable tool in patients with axonal polyneuropathy (219). However, changes limited to the distal segment of the axon, including possible therapeutic benefits, may be poorly represented in F-wave measures. Minimal latency is the most frequent measure of F-wave activity. However, the addition of chronodispersion, duration, persistence, and amplitude can add sensitivity to slower conducting axons (219).

Distribution of velocities. Several procedures have been developed to analyze the distribution of conduction velocities as a means of measuring activity in small-diameter axons (220). The original studies of an altered distribution of conduction velocities in DPN are approximately two decades old, but the technique is rarely used in current clinical studies. The fusion of a collision technique and an analysis of the distribution of velocities is promising as a practical and valuable electrophysiologic procedure to explore the effects of DPN on slower fibers. Caccia et al. (221) demonstrated that a computer-assisted collision procedure was both capable of examining velocities in slower conducting fibers and sensitive to the presence of subclinical neuropathy in insulin-dependent diabetic subjects. Bertora et al. (222) examined 138 patients with subclinical DPN and reported sensory nerve deficits were detected in 58% of the subjects using the distribution of conduction velocities data compared with only 11% of subjects using standard procedures.

Excitability. In addition to measuring the speed of conduction or the size of the activated signal, the magnitude and nature of the current necessary to establish the electrophysiologic response can be an important parameter in assessing neuropathy (rev. in 223). For instance, one computer-assisted measure of excitability, termed "threshold electrotonus," examines the effects of prolonged hyperpolarizing and depolarizing subthreshold currents (224) to explore differences in excitability between sensory and motor axons and fluctuation of excitability during the refractory period. Excitation studies have indicated that the diabetic nerve has less accommodation to hyperpolarization (i.e., inward rectification), which may limit its ability to follow rapid stimulus trains (225). At the cellular level, changes in excitability may be related to alterations in intracellular levels of cyclic adenosine monophosphate (cAMP) that have been reported with DPN (225).

5. Other methods of assessment. The majority the methods included in this section are relatively invasive, requiring biopsy of a whole nerve or fascicle or a skin biopsy to assess small-fiber structure. More recent noninvasive techniques include magnetic resonance imaging (MRI) and corneal confocal microscopy.

Nerve biopsy. The nerve biopsy, typically of the sural nerve posterior to the lateral malleolus, has been used for many years in the study of peripheral neuropathy (226–228). When undertaken at a center with sufficient expertise, it is a useful diagnostic procedure in patients with neuropathy of a known origin or in diabetic patients with atypical neuropathies (228). However, this is an invasive procedure with recognized sequelae that might include persistent pain at the biopsy site, cold intolerance, unpleasant though mild mechanically elicited sensory symptoms, and sensory deficits in the sural distribution (229,230). These prolonged sensory symptoms and sensory loss appear to occur more commonly in diabetic than in nondiabetic subjects (229). Thus, with the widespread availability of accurate QST and electrophsiological techniques, biopsies are rarely required for the routine diagnosis of DPN. For clinical diagnostic purposes, a fascicular or subtotal biopsy should suffice; if the nerve is left in continuity, a greater possibility of regeneration across the gap exists (228).

The use of morphological measures of neuropathy from biopsies as end points in trials of potential pharmacological therapies for DPN is a more controversial area. Whereas several trials of ARIs have used myelinated fiber density and other morphological measures as end points (51,53), concerns have been expressed about the use of such measures as end points (228). These concerns not only include the invasive nature of having two nerve biopsies on separate occasions, but also relate to a number of uncertainties in relation to the interpretation of these findings (228,231,232). The Peripheral Nerve Society (PNS) consensus report on DPN in controlled clinical trials suggested that the use of biopsy findings in assessing response to therapy needs further validation (33). In addition to the above list of concerns, the PNS also suggested that there is insufficient information as to how well neuropathological measures predict the severity and course of neuropathy and questions the validity of such assessments as axonal atrophy and axo-glial dysjunction, which require electron microscopy. The PNS did report that, of all the pathological measures, the myelinated fiber density is probably most useful as it correlates with the clinical deficit and electrophysiological findings (33,217).

In addition to assessing responses to therapy, nerve biopsies have also been used to help determine the etiopathogenesis of neuropathy. Examples of this include studies of diabetic amyotrophy (125) and the importance of glycemic control in DPN (233).

Nerve exposure. A number of published studies investigating the pathogenesis of neuropathy have studied the sural nerve in vivo without actually biopsying it. These have included using microelectrodes to measure endoneurial oxygen tension (234) and the use of epineurial vessel photography and fluorescein angiography to study the neural microvasculature (235). More recently, the same group used a new minimally invasive technique of microlight-guide spectrophotomety to measure blood flow and oxygen saturation in the sural nerve (236). However, these techniques are only used in specialist research units investigating the etiopathogenesis of DPN.

Skin biopsy. The significance and usefulness of immunohistochemically quantitated cutaneous nerves in the morphological assessment of DPN is increasingly being recognized (237, 238). It was the discovery of the panaxonal marker, protein gene product 9.5, that allowed the direct visualization of epidermal nerve fibers. This technique, though still invasive, only requires a 3-mm skin biopsy and enables a direct study of small nerve fibers, which are difficult to assess electrophysiologically (238). Much of this work has been developed by researchers who use the

technique to study three main groups of patients: DN, HIV-associated neuropathy, and idiopathic small-fiber sensory neuropathy (238). Recently this method was used to assess early neuropathic changes in diabetes and IGT (38). The assessment of cutaneous nerve pathology, including nerve regeneration, has also been recently advocated by other groups (239).

Noninvasive assessment. MRI has been used to assess involvement of the spinal cord in neuropathy. In an exploratory study, Eaton et al. (240) used MRI of the cord and demonstrated that patients with DPN had a lower cross-sectional cord area than healthy control subjects in the cervical and thoracic regions, leading them to suggest that DPN is not simply a disease of the peripheral nerves.

More recently, Malik et al. (115) reported the technique of corneal confocal microscopy in the assessment of DPN. This is a completely noninvasive technique that offers the future potential of assessing nerve structure "in vivo" without the need for biopsy. This technique is able to accurately define the extent of corneal nerve damage and repair, which seems to correlate with peripheral nerve function. This may provide the opportunity in future studies to act as a structural surrogate measure of nerve function in diabetes.

6. Epidemiology and natural history of DPN.

Background. This section will specifically examine data that pertain to manifestations of DPN. Some liberty has been taken to use the DPN "label" since this term is not used in some of the referenced studies.

A number of studies have produced extensive data regarding epidemiologic aspects of DPN. Despite this, there are still areas in which knowledge is deficient. This seeming paradox is at least partially explained by the pathological complexity of DPN. The number of peripheral nerves that can be affected, their differing compositions of sensory and motor fibers, and the varying extent of pathology of the nerve fibers account for this complexity. Thus, although there are similarities in clinical presentations, the manifestations of DPN can be quite heterogeneous.

This heterogeneity has led to multiple kinds of assessments and multiple end points in studies of DPN, including symptoms, signs, QST, and electrophysiology. Because epidemiologic studies have used a variety of these assessments, singly or in combination, it is difficult to evaluate these studies for consistency of findings and to draw firm conclusions. This is even further complicated by differences in characteristics of the study populations.

Table 5—*Descriptions of positive neuropathic sensory symptoms*

Nonpainful	Painful
Thick	Prickling
Stiff	Tingling
Asleep	Knife-like
Prickling	Electric shock-like
Tingling	Squeezing
	Constricting
	Hurting
	Burning
	Freezing
	Throbbing
	Allodynia
	Hyperalgesia

*Allodynia: the perception of pain from a nonnoxious stimulus. Adapted from ref. 32.

Given the above considerations, this review will examine epidemiologic studies of DPN according to the specific assessments and end points that have been used. This discussion will at times draw from findings from clinical trials, since these studies can contribute useful epidemiologic information pertaining to DPN.

Positive sensory symptoms and painful neuropathy. The importance of distinguishing positive sensory symptoms from negative sensory symptoms has been emphasized (32). Positive sensory symptoms arise spontaneously or as a response to stimuli. In contrast, negative sensory symptoms represent decreased responsiveness to stimuli. There is an abundance of types of positive sensory symptoms, and it has been suggested that they should be divided into painful and nonpainful categories (32). This classification is somewhat arbitrary, since there is little evidence that it relates specifically to neuropathology; however, for certain purposes, such a classification may be useful.

Table 5 presents a listing of positive sensory symptoms compiled by a committee that examined end points for painful neuropathy (32). Although painful and nonpainful symptoms were separated, "prickling" and "tingling" appeared in both categories. This overlap underlies the difficulty in developing symptom criteria for painful neuropathy.

The discussion below will mostly focus on painful neuropathy. However, it should be emphasized that studies of painful neuropathy have often required evidence of DPN from other neurologic assessments for the inclusion of individuals. Although this strategy helps to confine studies only to individuals who truly have painful neuropathy, it carries the implicit assumption that pain in itself does not occur as a sole manifestation of DPN. Also, as discussed above, it is difficult to determine the specific symptoms that should constitute painful neuropathy. It is clear that care must be taken in interpreting studies of painful neuropathy.

Prevalence. There have been few epidemiologic studies that have specifically examined the prevalence of painful neuropathy. The large population-based study of Harris et al. (148) utilized questionnaires of both diabetic and nondiabetic individuals to ascertain information about sensory symptoms. Symptoms were categorized according to pain and tingling, numbness, and the inability to feel hot or cold. Of interest was an appreciable prevalence of painful symptoms in the nondiabetic individuals. The basis for their symptoms is unclear, but the differences in the prevalence estimates between those with and those without diabetes can be used as an estimate of the prevalence of symptoms due to diabetes. The overall prevalence estimate for painful symptoms in the diabetic individuals was 27%, but the difference in the prevalence rates between those with and without diabetes was smaller and tended to decrease with age.

Other studies (8,241,242) have examined the prevalence of painful symptoms in clinical settings, and estimates have varied from 3 to >20%. This variation probably is a function of the differing criteria used for painful neuropathy and the characteristics of those studied.

Because some studies suggest that painful neuropathy can remit (see below), its prevalence could be much lower than its cumulative incidence over the full course of diabetes. Unfortunately, there are no such cumulative incidence data available.

Natural history. There is limited information regarding the natural history of painful neuropathy. A decrease in the intensity of painful neuropathy with worsening of quantitative measures of sensory function has been observed (243). The

findings of this study are consistent with the hypothesis that pain can decrease with the pathological progression of DPN. It should be noted that a number of the study participants were on treatment for painful symptoms, and this could have affected the findings. The observed improvement of pain with decreasing sensory function in that study appears to contrast with another study (147) that found a coupling of improvement of pain with improvement of sensory function in individuals treated with continuous subcutaneous insulin infusions.

There have been inconsistent data regarding how commonly painful neuropathy remits. Studies in this area must carefully differentiate those with chronic painful symptoms from those who develop painful symptoms more acutely early in the course of diabetes. These patterns may represent different pathological processes. In a study of 36 diabetic patients with chronic, painful symptoms who were followed for an average period of 4.7 years, there was no overall change in the severity of pain scores over time, and there were no full remissions in any of those followed (244). However, other studies have observed an appreciable occurrence of remissions (243,245).

Risk factors. Despite the large number of studies that have examined risk factors for DPN, there are few that have addressed painful neuropathy per se. In analyses of risk factors in their study, Harris et al. (148) combined positive and negative sensory symptoms together as end points. They found that the combined sensory symptoms were related to years since diagnosis, reported degree of hyperglycemia and glycosuria, and hypertension. In a study of a clinic population, painful neuropathy was found to be associated with diabetes duration but not with HbA_{1c} levels (8). In an uncontrolled intervention study, pain levels improved in individuals treated with continuous subcutaneous insulin infusions (147).

Negative sensory symptoms and hypoesthetic neuropathy. Much more information has been accrued for hypoesthetic neuropathy than for positive sensory symptoms and painful neuropathy, possibly as a result of the ability to more objectively quantify sensory function through QST. Because it is well recognized clinically that patients tend to underestimate their degree of insensitivity, there has been more reliance on QST than on symptomatology in studies of hypoesthesia. Thus, the discussion below will mostly pertain to QST assessments rather than those based on symptomatology. Although studies have examined different sensory modalities with a number of quantitative sensory methodologies, much of the available data pertain to VPTs. The sensory modalities and the methodologies utilized for their assessments should be considered in interpreting the data presented below, since nerve fibers may be differentially affected, and as indicated above, techniques can vary considerably. Also, it should be emphasized that quantitative sensory measurements are not fully objective because they are dependent on the understanding and cooperation of the individuals studied.

Prevalence. The prevalence of hypoesthesia that has been reported in studies varies greatly according to the above considerations and to the criteria used to define abnormality. In a study that utilized three quantitative sensory measurements in the same individuals, the prevalence of abnormalities varied from 8 to 34% (246). The location of measurement is also an important factor. The presence of hypoesthesia increases substantially as measurements become more distal (247). Also, the prevalence can vary greatly according to the characteristics of the population under study. For example, age requires careful consideration, since normal values increase markedly with age (248).

Relatively few studies using QST have provided specific estimates of the prevalence of decreased sensory function alone. However, perhaps because of the above considerations, there appears to be a rather wide variation (242,246,247,249). In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), a prospective cohort study, the 10-year incidence of the symptoms of loss of tactile sensation and loss of temperature sensitivity varied from 19 to 25% and from 11 to 19%, respectively, depending on the age of onset and the use of insulin (250).

Natural history. Quantitative sensory measurements lend themselves to studies of natural history. In a study of children and adolescents, there was a small but statistically significant elevation of VPTs (251). A recent study of adults revealed that the presence of decreased sensation at diagnosis appears to vary according to diagnostic criteria for diabetes (252). Those who fulfilled the ≥126 mg/dl fasting glucose criterion, on average, had elevated vibration and thermal thresholds at screening for diabetes. In contrast, those who fulfilled the ≥200 mg/dl 2-h oral glucose tolerance test criterion, but not the ≥126 mg/dl fasting glucose criterion, had normal thresholds.

In a study of type 1 diabetic patients who were followed from diagnosis, thermal thresholds tended to increase more than vibration thresholds in the first 5 years after diagnosis. The increase in thermal thresholds was particularly evident in those with higher glucose levels. Nerve conduction was also found to be affected in that interval (253).

The progression of hypoesthesia has been examined early in the course of type 2 diabetes. In one study, individuals were found to have small but statistically significant increases of vibration and thermal thresholds over an average follow-up interval of ~2 years (254). Findings from a study that utilized 10-g monofilament testing suggested that there is little progression of neuropathy in the first few years of diabetes (255). However, the 10-g monofilament may not be sufficiently sensitive to detect a small change in loss of sensation.

Progression appears to be more rapid once decreased sensation appears. In a study that followed a control group participating in a clinical neuropathy trial for 18 months, there was marked worsening of vibration and thermal thresholds (256). A similar rate of progression was observed over a 2-year period in another study of individuals with an appreciable degree of hypoesthesia at baseline (257). In this study, the changes of the various sensory modalities paralleled each other. In another study that followed individuals initially considered to have normal vibration thresholds for an average interval of 12 years, there was marked progression in those who eventually developed decreased sensation (181).

Risk factors. Diminished sensory function was consistently related to diabetes duration in a number of studies (242,247,249,255). Decreases in sensory thresholds have been found to be related to the degree of hyperglycemia (181,242, 249,253) and height (181,242,247, 249,255) in both cross-sectional and follow-up studies. In the WESDR, the development of symptoms of the loss of tactile and temperature sensation tended to be

related to HbA_{1c} (250). Studies have revealed variable findings for the relations of hypoesthesia with alcohol consumption (247,249,255) and cigarette smoking (249,255).

Combined assessments. Included in this section are studies that have utilized various combinations of positive symptoms, negative symptoms, QST, abnormalities of the neurological exam, and electrophysiological testing for end points of neuropathy. Although substantial information has been obtained from large epidemiologic studies and clinical trials that have utilized such combined assessments as criteria for neuropathy, these studies can be difficult to interpret in pathophysiological terms. For example, it is problematic to discern the specific functions that are actually related to the risk factors identified with this approach. The interpretation of findings is also complicated by differences between studies in the choice of the combined assessments.

Prevalence and incidence. In a large epidemiologic study that utilized combined end points, Pirart (258) followed a number of patients for the development of neuropathy over many years. The criteria were quite broad and some of those considered neuropathic could have had other forms of DN instead of DPN. The findings revealed that the prevalence of neuropathy was >40% after 25 years of known duration.

The EURODIAB IDDM Complications Study (9) has examined a large number of participants from clinical centers over a broad geographical area. The overall prevalence of neuropathy was 28%; however, among the 27 centers included in the study, the prevalence ranged from <20% in several centers to >50% in two centers. In the Epidemiology of Diabetes Complications (EDC) Study (259), a prospective study of patients with type 1 diabetes, there was an overall prevalence of DPN at baseline of 37% in those >18 years of age with substantial variation according to age (18% for those 18–29 years and 58% for those who were older). After an average length of follow-up of 5.3 years for that cohort, the incidence rate for DPN was 2.8 per 100 person-years with a cumulative probability of 29% (260). In the San Luis Valley Diabetes Study (SLVDS) (261), a population-based study of type 2 diabetic patients, there was an overall prevalence of 28%. In an analysis of baseline data from the DCCT (262), "clinically detectable" neuropathy was found in 39% of the participants.

Natural history. There is a lack of data on the progression and regression of DPN in studies of combined end points. This information is difficult to ascertain since such end points are not optimal for quantitative assessments of severity. However, these types of studies could still be useful for identifying individuals with a substantial change in neuropathic status.

Risk factors. The Pirart study (258) revealed strong associations of neuropathy with duration of diabetes and with the degree of hyperglycemia (according to certain clinical indicators); however, only univariate associations were reported and no other risk factors were discussed. The EURODIAB IDDM study (9) identified associations of neuropathy with a number of factors. Although the degree of association was to some extent dependent on the multivariate modeling, neuropathy was consistently related to age, duration, HbA_{1c}, and severe ketoacidosis. Factors for which statistical significance was model dependent were weight, height, and current cigarette smoking. The prevalence of neuropathy was related to elevated diastolic blood pressure, triglyceride, and decreased HDL cholesterol.

The DCCT utilized combined end points in its baseline prevalence estimate and in the trial itself (7). However, in its baseline report, the DCCT specifically examined associations of nerve conduction indexes with characteristics of participants. Nerve conduction impairment was found to have some association with age, diabetes duration, HbA_{1c}, male sex, and C-peptide deficiency. The DCCT definitively showed a decrease in the rate of development of DPN with intensive treatment of hyperglycemia.

In the EDC Study (259), DPN at baseline was observed to be related to a number of variables with varying degrees of association according to age. In the overall analysis, DPN was associated with diabetes duration, HbA_1, HDL cholesterol, hypertension, and cigarette smoking. Prospective data revealed associations of DPN with duration, height, HbA_1, cigarette smoking, and hypertension.

The SLVDS (261) found that DPN was related to age, diabetes duration, HbA_{1c}, and insulin use. Several studies observed associations of DPN with other complications of diabetes (9,259,261).

In a case-control study, DPN was observed to be associated with lifetime cigarette smoking in individuals with type 1 diabetes, but not in those with type 2 diabetes (263).

Conclusion. This section has discussed the epidemiology of DPN according to the end points that were utilized in studies rather than according to risk factors. Although it might appear that this is a tedious approach, the end points should be considered separately in order to make etiologic and pathogenetic sense of the literature. Also, this approach can help to explain the seeming inconsistencies of findings in studies.

Despite the many different end points, study populations, and methodologies described, some definitive conclusions can still be made. First, it is clear that DPN is a very common condition. Although the prevalence estimates of its various manifestations are clearly study dependent, it appears that at least one manifestation of peripheral neuropathy is present in well over 20% of individuals with diabetes. However, the prevalence of painful neuropathy appears to be appreciably lower.

Second, regarding natural history, studies suggest that some evidence of abnormality can occur relatively early in the course of diabetes. Studies also show that once DPN is present, there is a tendency toward rapid pathological progression. The frequency of the remission of painful neuropathy and other manifestations of neuropathy is still unclear.

Finally, DPN is clearly associated with certain risk factors. The degree of hyperglycemia has been identified as a risk factor in both epidemiologic studies and clinical trials. Diabetes duration has also been a consistent risk factor. Height has been observed to be a risk factor in a number of studies, but it may be dependent on location and the sensory modality assessed. Certain conventional cardiovascular disease risk factors, including lipid and blood pressure indexes, have been identified as risk factors for DPN. Several studies have observed associations of DPN with other complications of diabetes. Other risk factors such as alcohol consumption and cigarette smoking have been less consistent in their associations with DPN.

The definitive risk factors that have been identified have biological plausibility for involvement in the pathogenesis of DPN. Duration and degree of hyperglyce-

Table 6—*Trials of ARIs*

Drug	Results	Status	Ref.
Alrestatin	Minor benefits (Sy)	Withdrawn (toxicity)	270
Sorbinil	Benefits (Sy, Ep, M)	Withdrawn (toxicity)	43
Tolrestat	Minor benefits (Sy, Ep)	Withdrawn (toxicity)	271
Ponalrestat	No efficacy	Withdrawn	272
Zenarestat	Minor benefits (Ep, M)	Withdrawn (toxicity)	53
Epalrestat	Minor benefits (Sy, Ep)	Marketed (Japan)	269
Fidarestat	Minor benefits (Sy, Ep)	Under investigation	54

Ep, electrophysiology; M, motor; Sy, symptoms.

mia can be viewed as being indicative of the extent of overall exposure to hyperglycemia. Height, as a proxy for nerve length, appears to be an across-individual expression of the intraindividual dependence of nerve length for the occurrence of DPN. A hypothesis can be entertained that longer nerves are more susceptible to the metabolic consequence of diabetes. Indeed, one study has shown an association of vibration perception with an interaction of height and degree of hyperglycemia (254). Blood pressure and lipid indexes could indicate that vascular abnormalities contribute to the development of DPN. Finally, the relation between DPN and other complications could mean that they have common pathogenetic pathways.

It is clear that epidemiologic findings already provide some clues for mechanistic research; yet, there is a potential for the accrual of much more epidemiologic information with regard to occurrence, etiology, and natural history. This will be especially enhanced with attention to the end points and methodology utilized, both with regard to designing new studies and the interpretation of studies already performed.

7. Pathogenetic treatments and prevention. This section will discuss those treatments that may prevent the onset or modify the natural history of DPN by targeting known pathogenetic mechanisms. In general, treatments in this category do not treat symptoms and are mostly experimental and not therefore available for clinical usage at present. The discussion of most of these approaches will be brief, as mention is also made in SECTION 3: PATHOGENESIS OF DIABETIC NEUROPATHY.

Near normoglycemia. In addition to the DCCT (7), three much smaller but long-term prospective studies have confirmed that maintained near-normal glycemia prevents the development and retards the progression of DPN as assessed electrophysiologically. These include the Stockholm Diabetes Intervention Study (7.5 [264] and 10 [265] years), the Oslo Study (8 years) (266), and, in type 2 diabetes, the Kumamato Study (6 years) (267).

The most reliable method of achieving and maintaining near-normal glycemia is by pancreatic or islet cell transplantation. However, as in most published series that assess nerve function, the transplant was in combination with renal transplants, and the recipients generally had long duration of diabetes and established neuropathy. Thus, in the series from Minneapolis, Minnesota (40,268), only modest improvements in measures of neuropathy were seen after several years of normoglycemia. Nevertheless, achieving near-normoglycemia should be the aim in both the prevention of and the first step of managing DPN.

ARIs. The first clinical trials of ARIs in DN took place 25 years ago, and currently only one agent is available in one country (Epalrestat in Japan) (269). Most of the early trials can be summarized as:

- Too small. The effect of the drug was inadequate in terms of inhibiting nerve sorbitol accumulation.
- Too few. Inadequate numbers of subjects were included.
- Too short. Many trials were for only weeks or months for a chronic disease of many years' duration.
- Too late. No drug targeting a pathogenetic mechanism is likely to be effective when the complication is well established.

A summary of some of the drugs that have been studied in clinical trials are listed in Table 6: further details are provided in Section 3*B*.

Antioxidants. As discussed in section 3, there is accumulating evidence to support the role of oxidative stress in the pathogenesis of neuropathy. Studies with the antioxidant α-LA have provided evidence of potential efficacy for this agent, which may well be beneficial for both neuropathic symptoms and modifying the natural history of DPN (62–64). Two large North American/European clinical trials of the efficacy of α-LA are in progress and should report in 2005.

γ-LA. γ-LA (GLA) is a component of evening primrose oil and can prevent abnormalities present in diabetes and in essential fatty acid and prostanoid metabolism (273). GLA treatment for 1 year in a randomized trial resulted in improvement in electrophysiology and deficits (276).

The use of a conjugate of LA and GLA was proved to be effective in improving both electrophysiological and neurochemical correlates of experimental DN (275). To date, this conjugate has not been sited in clinical neuropathy.

Neutrophins. As a result of contradictory results from clinical trials, the clinical development of NGF was halted, and no further studies are planned at the time of writing (276).

Inhibitors of glycation. Studies of aminoguanidine, which inhibits the formation of AGEs, have mainly focused on nephropathy (54). Few data are available on aminoguanidine or other inhibitors of AGE formation in clinical neuropathy (277).

PKC inhibition. Intracellular hyperglycemia increases DAG levels, which activates PKC formation, leading to multiple pathogenetic consequences including altered expression of endothelial nitric oxide synthetase and VEGF. Preliminary data suggest that treatment with a PKC-β inhibitor might ameliorate measures of nerve function in DPN (278). Multicenter trials are currently in progress and should report in 2004 or 2005.

Vasodilators. Treatment with ACE inhibitors has been shown to improve electophysiological measures of nerve function in mild neuropathy (68). The short-acting vasodilator isosorbide dinitrate has been shown to improve painful symptoms, but its effect on deficits and electrophysiology are unknown (279).

8. Symptomatic management of DPN. This section will discuss the management of neuropathic symptoms. Most of the pharmacological and other interventions that will be described have no effect on the natural history of neuropathy, which

Table 7—*Initial management of symptomatic neuropathy*

1) Exclude nondiabetic causes
   - Malignant disease (e.g., bronchogenic carcinoma)
   - Metabolic
   - Toxic (e.g., alcohol)
   - Infective (e.g., HIV infection)
   - Iatrogenic (e.g., isoniazid, vinca alkaloids)
   - Medication related (chemotherapy, HIV treatment)
2) Explanation, support, and practical measures (e.g., bed cradle to lift bed, clothes off hyperesthetic skin)
3) Assess level of blood glucose control profiles
4) Aim for optimal stable control
5) Consider pharmacological therapy

is of progressive loss of nerve function. The initial management of patients with symptomatic neuropathy is summarized in Table 7.

Control of hyperglycemia. A number of small open-label uncontrolled studies have suggested that achieving stable near-normoglycemic control is helpful in the management of painful neuropathic symptoms. In one such study (147), patients with painful neuropathy were treated with continuous subcutaneous insulin infusion for a period of 4 months. As well as resulting in relief of neuropathic symptoms, improvements were noted in QSTs and electrophysiological investigations. Improvement of glycemic control was assessed by glycated hemoglobin as well as regular home blood glucose monitoring. The fact that blood glucose flux was reduced in this early study might explain the symptomatic benefit of this treatment in light of more recent observations (10). In this later study, when patients with painful neuropathy were compared with those with painless neuropathy, those with painful symptoms had poorer control, more excursions to hyper- and hypoglycemic levels, and greater blood glucose flux as assessed by a number of measures. Thus, it may be the stability of glycemic control that is equally important to the level of achieved control. Despite the lack of appropriately designed controlled studies in this area, it is generally accepted that intensive diabetes therapy aimed at near normoglycemia should be the first step in the treatment of any form of DN.

Pharmacotherapy. A large number of therapeutic agents have been used in the management of painful symptoms; some of the more commonly used ones are listed in Table 8. Although some have advocated the use of nonsteroidal anti-inflammatory drugs in symptomatic neuropathy, there is little evidence to support their use. Moreover, these agents should be used with caution in neuropathic diabetic patients, many of whom may have renal impairment, a contraindication to nonsteroidal drugs in most cases.

Tricyclic drugs. Several randomized clinical trials have supported the use of these agents in the management of neuropathic pains. Putative mechanisms by which these drugs relieve pain include inhibition of norepinephrine and/or serotonin reuptake at synapses of central descending pain control systems and, more recently, the antagonism of *N*-methyl-D-aspartate receptors, which mediate hyperalgesia and allodynia (280). The rapid onset of pain relief with these agents, together with the fact that they seem to be equally effective in relieving pain in patients with normal and depressed moods, suggests a mode of action that is not primarily relief of depression. Although these agents remain the first-line treatment for symptomatic neuropathy in most centers, their use is restricted because of the frequency and severity of side effects.

Most experience has been achieved with amitriptyline and imipramine. The dosage of either one of these two drugs required for symptomatic relief is similar (25–150 mg daily); to avoid undue drowsiness, the dose can be taken once a day in the evening. Desipramine is also a useful drug that may be better tolerated than amitriptyline in many patients (280). The usefulness of these agents was confirmed in a systematic review performed by McQuay et al. (281). As noted above, the major problem remains the frequency of side effects, which are predictable. Although drowsiness and lethargy are common, the anticholinergic side effects, particularly dry mouth, are the most troublesome.

In cases of very severe painful neuropathy that are partially resistant to tricyclic drugs, a combination of the tricyclics with other agents, such as major tranquilizers, may be useful (282). More recently, the combination of amitriptyline and transcutaneous electrotherapy has been described in those who failed on tricyclic monotherapy. In a controlled trial, this combination was superior to that of tricyclic monotherapy plus sham electrotherapy (283).

Selective serotonin-reuptake inhibitors. Selective serotonin-reuptake inhibitors (SSRIs) inhibit presynaptic reuptake of serotonin but not norepinephrine. Studies suggest that treatment with paroxetine (284) but not fluoxetine (280) is associated with significant pain relief. Similarly, citalopram 40 mg/day was confirmed to be efficacious in relieving neuropathic pain, but was less effective than imipramine (285). These drugs should, however, be used with caution in diabetic patients who may be on other medications, as there is a suggestion that SSRIs might increase the risk of upper-gastrointestinal bleeding (286). However, troublesome side effects are in generally less common with SSRIs.

Table 8—*Oral symptomatic therapy of painful neuropathy*

Drug class	Drug	Daily dose (mg)	Side effects	Ref.
Tricyclics	Amitriptyline	25–150	++++	280,281
	Imipramine	25–150	++++	280,281
SSRIs	Paroxitene	40	+++	284
	Citalopram	40	+++	285
Anticonvulsants	Gabapentin	900–1,800	++	290,291
	Lamotrigine	200–400	++	292
	Carbamazepine	Up to 800	+++	289
Antiarrhythmics*	Mexilitene	Up to 450	+++	293,294
Opioids	Tramadol	50–400	+++	295,296
	Oxycodone CR†	10–60	++++	297,298

All medications in the table have demonstrated efficacy in randomized controlled studies. *Mexilitene should be used with caution and with regular EKG monitoring; †oxycodone CR may be useful as an add-on therapy in severe symptomatic neuropathy.

Anticonvulsants. Anticonvulsants have been used in the management of neuropathic pain for many years (287,288). Limited evidence exists for the efficacy of phenytoin and carbamazepine for DN (287,289). Gabapentin is now widely used for neuropathic symptoms (this agent is structurally related to the neurotransmitter γ-aminobutyric acid [GABA]) and was introduced some years ago as an anticonvulsant for complex partial seizures. In a large controlled trial of gabapentin in symptomatic neuropathy, significant pain relief together with reduced sleep disturbance was reported using dosages of 900–3,600 mg daily (290). In a recent review of all the trials of gabapentin for neuropathic pain, it was concluded that dosages of 1,800–3,600 mg per day of this agent were effective; the side-effect profile also seems superior to that of the tricyclic drugs (291).

Lamotrigine is an antiepileptic agent with at least two antinociceptive properties. In a randomized placebo controlled study, Eisenberg et al. (292) confirmed the efficacy of this agent in patients with neuropathic pain.

Antiarrhythmics. Mexilitine is a class 1B antiarrhythmic agent and a structural analog of lignocaine. Its efficacy in neuropathic pain has been confirmed in controlled trials and reviewed by Dejgard et al. (293) and Jarvis and Coukell (294). The dosage used in trials (up to 450 mg daily) is lower than that usually used for the treatment of cardiac arrhythmias; however, regular electrocardiogram (ECG) monitoring is necessary, and the long-term use of mexilitine cannot be recommended.

Other agents. Tramadol is an opioid-like, centrally acting, synthetic nonnarcotic analgesic. Its efficacy in the management of patients with painful neuropathy was confirmed in a randomized controlled trial (295). Although this first trial was only of 6 weeks' duration, a subsequent follow-up study suggested that symptomatic relief could be maintained for at least 6 months (296). Side effects, however, are relatively common and similar to other opioid-like drugs. Similarly, two randomized trials have confirmed the efficacy of controlled-release oxycodone for neuropathic pain in diabetes (297,298). Opioids such as oxycodone may be considered as add-on therapies for patients failing to respond to nonopioid medications.

Topical and physical treatment.

Topical nitrate. A recent controlled study suggested that the local application to the feet of isosorbide dinitrate spray was effective in relieving overall pain and burning discomfort and the burning discomfort of DN (279). If confirmed by larger randomized studies, this could offer a very useful alternative and local pharmacological treatment for relieving neuropathic symptoms.

Capsaicin. This alkaloid, which is found in red pepper, depletes tissue of substance P and reduces chemically induced pain. Several controlled studies combined in meta-analyses seem to provide some evidence of efficacy in diabetic neuropathic pain (299). However, true blinding of these studies has been questioned because of the local hyperalgesia experienced when applying the active drug. Its use is only recommended for up to 8 weeks of treatment, and it seems to be most useful in those with localized discomfort.

Acupuncture. A number of unmasked studies support the use of acupuncture. In the most recent published report, benefits of acupuncture lasted for up to 6 months, and reduced use of other analgesics was reported (300). The conduct of potential blinded studies of acupuncture is problematic; although a placebo response is possible with acupuncture, this response should not detract from its use, which is generally without side effects.

Other physical therapies. Many other physical therapies have been proposed. Controlled evidence has been provided for the use of percutaneous nerve stimulation (301) and, most recently, static magnetic field therapy (302).

Electrical spinal cord stimulation. A case series of patients with severe painful neuropathy unresponsive to conventional therapy suggested efficacy of using an implanted spinal cord stimulator (303). However, this cannot be generally recommended except in very resistant cases, as it is invasive, expensive, and unproven in controlled studies.

SECTION 6: NEUROPATHY AND ITS LATE SEQUELAE — The late sequelae of DPN are recognized to be foot ulceration (which may occasionally result in amputation) and, less commonly, Charcot's neuroarthropathy (27,153,304). The importance of DPN in the etiopathogenesis of foot ulceration has been confirmed in several prospective studies (50,182,196). Both large- and small-fiber somatic as well as sympathetic autonomic dysfunction have been implicated in the pathway to ulceration (153,182,196,305). However, it must be remembered that the neuropathic foot does not ulcerate spontaneously; it is the combination of neuropathy with either extrinsic factors (e.g., ill-fitting shoe gear or foreign body in shoe) or intrinsic factors (e.g., high foot pressures or plantar callus) that results in ulceration. In an observational study, Reiber et al. (306) applied Rothman's model of causation to the pathogenesis of foot ulceration and reported that the most common pathway to diabetic foot ulceration comprised the combination of neuropathy, trauma, and foot deformity. Although it is generally believed that education and preventative foot care should reduce the risk of ulceration in high-risk individuals, a recent systematic review could find few data to support this contention (307). However, one large randomized study of a screening and protection program reported a nonsignificant trend to reduced ulceration; significantly, those in the intervention group who developed ulcers were less likely to proceed to amputation (308). This suggests a potential benefit of screening and education. For a more extensive discussion on the relation between neuropathy and foot ulceration, please consult the technical review on this topic (153).

Charcot neuroarthropathy is a rare and disabling condition affecting the bones and joints of the foot. It particularly affects patients with both somatic and autonomic neuropathy who have intact peripheral circulation (27). Although the overall prevalence of Charcot neuroarthropathy in the diabetic population is low, a study of a randomly selected neuropathic population reported radiological evidence of Charcot neuroarthropathy in 16% of patients (309), suggesting a key role of neuropathy in the pathogenesis of this condition. For further discussion of Charcot neuroarthropathy, consult the review by Sanders and Frykberg (310).

SECTION 7: CONCLUSIONS — DPN, which may be asymptomatic in up to 50% of cases, is one of the most common complications of diabetes. Every diabetic patient, regardless of type, should undergo a careful clinical examination of the lower extremities and feet at least once

a year (18). A number of simple screening methods that are applicable to clinical practice, including the MNSI (153), the 10-g monofilament (165), and the modified NDS (Fig. 1) (52), have been developed. Of these screening tests, the modified NDS (Fig. 1) has been proven in a large prospective study to be predictive of insensate foot ulceration: those with NDS ≥6 have a sixfold increased risk of developing an ulcer (52). Those patients with foot ulcer risk require more frequent review, regular podiatric care, and footcare education, as there is a suggestion that these steps might result in earlier presentation when ulcers develop (308). In those patients with atypical presentations (e.g., rapidly progressing motor deficits), alternative diagnoses, such as CIDP, should be considered.

Rarer somatic neuropathies associated with diabetes comprise the focal and multifocal neuropathies, including amyotrophy.

A number of therapeutic choices are available for the management of symptomatic DPN, although few if any of these will influence the natural history of neuropathy. Several pathogenetic therapies are currently under investigation. Surrogate end points for such trials include electrophysiology and QST of large- and small-fiber function. It is anticipated that newer, noninvasive techniques to assess directly nerve fiber damage will be developed and that these will replace biopsies of nerve or skin.

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