Andrew J.M. Boulton
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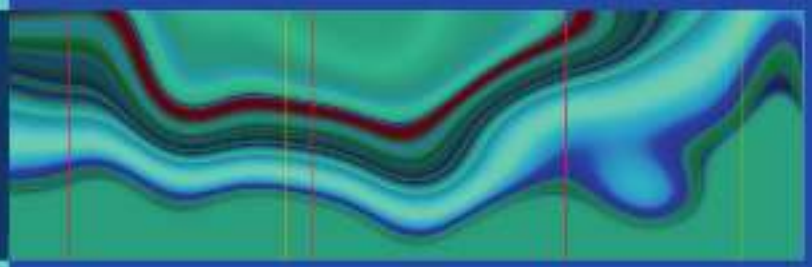

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Springer

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About the Authors

Andrew J.M. Boulton, MD, FRCP, is Professor of Medicine at the Manchester Royal Infirmary and Visiting Professor at the University of Miami, USA. Among his many awards, his contribution to worldwide care of the diabetic foot was honoured by receiving the American Diabetic Association's Roger Pecoraro Lectureship and the European Association for the Study of Diabetes (EASD) Camillo Golgi prize, and he was the first recipient of the international award on diabetic foot research. In 2008 he was awarded the Harold Rifkin prize of the ADA for distinguished international service in the cause of diabetes and the first outstanding achievement award of the American Professional Wound Care Association. Professor Boulton was the founding Chairman of the Diabetic Foot Study Group and was previously Chairman of Postgraduate Education and then programme chair for the EASD. He is renowned worldwide as a leading educator and lecturer on neuropathy and the diabetic foot. He is the global chairman of the Diabetes Lower Extremity Research Group (DIALEX). Professor Boulton chaired the ADA's expert group on diabetic neuropathy that resulted in the April 2005 ADA statement on diabetic neuropathy, and was chair of the ADA Foot Council 2005–2007. He is a member of the editorial review board for *Diabetes/Metabolism: Research and Reviews*, *Acta Diabetologica*, *Diabetes Care*, *The Diabetic Foot* and *International Diabetes Monitor*. Professor Boulton has authored more than 350 peer-reviewed manuscripts and book chapters, mainly on diabetic neuropathy and foot complications.

Loretta Vileikyte, MD, PhD., is Senior Lecturer at the University of Manchester and visiting Assistant Professor of Medicine at the University of Miami, USA. Her main research interests lie in the psychosocial aspects of the lower limb complications of diabetes and she developed the first neuropathy-specific quality-of-life scale that has been used in several clinical trials of new medications for painful diabetic neuropathy. She previously held the first joint American and British Diabetes Association grant to develop a scale to assess patients' cognitive and emotional representations of neuropathy and is currently funded by the National Institutes of Health (NIH) to study the effects of stress on wound healing in diabetic neuropathic foot ulceration.

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Chapter 1
Introduction to Diabetic Neuropathies

The neuropathies are among the most common long-term complications of diabetes mellitus, affecting up to half of patients. Diabetic neuropathies are characterised by a progressive loss of nerve fibres and may involve both autonomic and somatic divisions of the nervous system.

The early recognition and appropriate management of neuropathies in diabetic patients are important for a number of reasons:

- Non-diabetic neuropathies may be present in patients with diabetes;
- Many patients with diabetic neuropathy are asymptomatic and thus at risk of insensate damage to their feet;
- Both symptoms and deficits in patients with diabetic neuropathy have an adverse effect on quality of life;
- Autonomic neuropathy causes substantial morbidity and mortality, particularly if the cardiovascular system is involved; and
- Effective symptomatic treatments are available.

Definition

In 1998, an international consensus group agreed the following simple definition for use in clinical practice: 'Diabetic neuropathy is the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes'.[1]

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The same group agreed that neuropathy cannot be diagnosed without a careful clinical examination, and that an absence of symptoms must not be equated with absence of neuropathy. The definition also conveys the importance of excluding non-diabetic causes, which account for around 10% of peripheral neuropathies in diabetic patients.[2]

It is also widely accepted that diabetic neuropathy should not be diagnosed on the basis of one sign, symptom or test alone; a minimum of two abnormalities (to include a clinical or quantitative test) is recommended.[3]

Care must be taken to distinguish between the diagnosis of early diabetic neuropathy and that of 'loss of protective sensation' (LOPS), which is used to identify the foot at risk of ulceration. Whereas two simple clinical tests may be used for the latter,[4] the diagnosis of early neuropathy may require more investigation and the exclusion of non-diabetic causes.

The most recent discussion on definitions of the diabetic neuropathies is to be found in the report of the 2009 Toronto Diabetic Neuropathy Expert Group meeting.[5]

Epidemiology and Natural History

The epidemiology and natural history of diabetic neuropathies are poorly understood. This reflects variations in diagnostic criteria, biased patient selection in observational studies, the asymptomatic nature of many neuropathies and the large pool of patients with undiagnosed diabetes mellitus.

Incidence and Prevalence

Despite the limitations noted above, it is known that diabetes mellitus is the leading cause of neuropathy in the western world,[6] and that neuropathies are the most common long-term microvascular complication of diabetes.[7] Based on several large studies, the annual incidence of neuropathy in

patients with type 2 diabetes is believed to be around 2%.[8] The prevalence of symptomatic neuropathy may be as high as 21%,[9] while neuropathic deficits are found on examination in up to 50% of all patients with diabetes.[10,11] A recent German population-based study[12] reported a prevalence of neuropathy of 28% in the diabetic population, whilst also highlighting that neuropathy also occurs in impaired glucose tolerance (IGT; 13%) and that the non-diabetic population may have signs of neuropathy (7%) which needs to be taken into account in any future epidemiological studies. Indeed, the neuropathy of IGT affects predominantly small fibres, and neuropathic pain is common is these patients (see below[13]).

Risk Factors

Diabetic neuropathy has a multifactorial origin, and numerous metabolic and vascular factors have been implicated in the pathogenesis of the disease. Of all the proposed mechanisms, however, the strongest evidence exists for chronic hyperglycaemia. Indeed, it is clear that the development and progression of neuropathy are related to glycaemic control in both type 1 and type 2 diabetes.

In the Diabetes Control and Complications Trial, the annual incidence of neuropathy in type 1 diabetes was around 2% in conventionally treated patients versus just 0.56% in individuals with intensive glycaemic control.[14]

In the landmark UK Prospective Diabetes Study, the progression of neuropathy in type 2 diabetes was dependent on glycaemic control.[15]

In addition, longitudinal data from follow-up studies suggest that the duration and severity of hyperglycaemia are related to the severity of neuropathy.[16,17]

Recent studies in patients with IGT provide further insights into the role of glucose metabolism and the development of neuropathy. In a study of patients with idiopathic painful neuropathies, IGT was significantly more common than it is in the general population.[18] Interestingly,

neuropathy associated with IGT is milder than that associated with diabetes, and small nerve fibre involvement may be the earliest detectable sign of neuropathy.[19]

The large EuroDiab prospective study in Europe has demonstrated the importance of vascular risk factors in the pathogenesis of diabetic neuropathy, including cigarette smoking, history of cardiovascular disease, hypertension and hypercholesterolaemia,[20-22] in addition to height, alcohol consumption and duration of diabetes.

Natural History

In contrast to the many published reports on the prevalence of diabetic neuropathy, there are few on the natural history of the condition. The disease course is one of gradual progression. Although symptoms may wax and wane, and even resolve entirely, this does not imply improvement of the underlying pathology. Typically, the disappearance of symptoms reflects a worsening of the condition, with the resulting insensate foot at risk of ulceration.[23]

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Chapter 2
Classification and Clinical Features

Classification

Several classification systems for the neuropathies have been proposed. Some are based on presumed aetiology whereas others refer to topographical features or disease pathogenesis. However, the inter-relationship of aetiology, mechanisms and symptoms is complex and poorly understood, and, as such, this traditional classification is of little use in clinical practice (Fig. 2.1).

Until the underlying pathophysiology of diabetic neuropathies has been elucidated, the most useful systems for practising physicians are those based on clinical manifestations. Three classification systems are presented in Fig. 2.2. This book follows the system used in the 2005 American Diabetes Association statement,[3] which discusses diabetic neuropathies under three headings: sensory neuropathies; focal and multifocal neuropathies; and autonomic neuropathy.

The clinical features associated with each type of neuropathy are discussed in detail on the following pages. Pain terminology, as defined by the International Association for the Study of Pain, is summarised in Fig. 2.3. The definition and classification of symptoms are described in more detail in Chap. 3.

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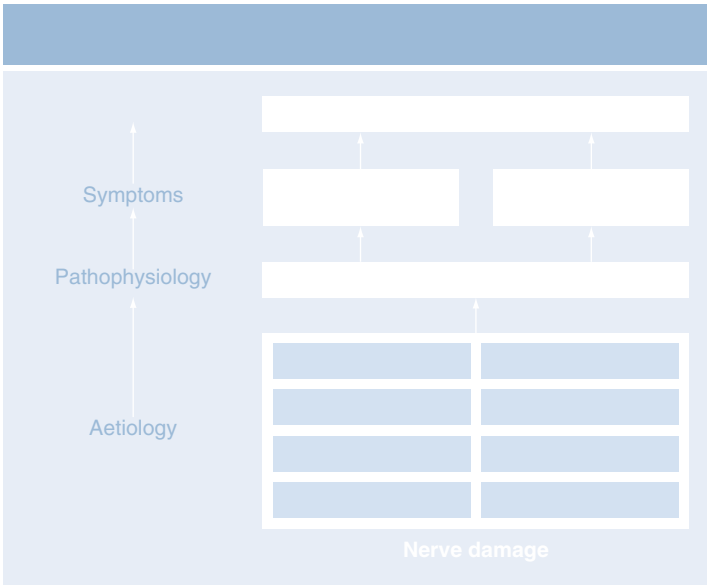

FIGURE 2.1 Inter-relationship of aetiology, mechanisms and symptoms in neuropathic pain (Reproduced with permission from Woolf and Mannion[1])

Sensory Neuropathies

Chronic Sensorimotor Distal Symmetrical Polyneuropathy

Chronic sensorimotor distal symmetrical polyneuropathy (DPN) is the most common form of diabetic neuropathy, being present in more than 10% of patients at the diagnosis of type 2 diabetes.[5] DPN occurs in both type 1 and type 2 diabetes and becomes more common with increasing age and duration of diabetes. In a large population survey, neuropathic symptoms affected 30% of type 1 diabetic patients and 36% and 40% of male and female type 2 diabetic patients,

Three classification systems for diabetic neuropathies

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

Length-dependent diabetic polyneuropathy • Distal symmetrical sensory polyneuropathy • Large fibre neuropathy • Painful symmetrical polyneuropathy • Autonomic neuropathies
Focal and multifocal neuropathies • Cranial neuropathies • Limb neuropathies • Proximal diabetic neuropathy of the lower limbs • Truncal neuropathies
Non-diabetics neuropathies more common in diabetes • Pressure palsies • Acquired inflammatory demyelinating polyneuropathy

Rapidly reversible • Hyperglycaemic neuropathy
Generalised symmetrical polyneuropathies • Sensorimotor (chronic) • Acute sensory • Autonomic
Focal and mutifocal neuropathies • Cranial • Thoracolumbar radiculoneuropathy • Focal limb • Proximal motor (amyotrophy)
Superimposed chronic inflammatory demyelinating neuropathy

FIGURE 2.2 Three classification systems for diabetic neuropathies (Copyright © 2004 American Diabetes Association from Boulton et al.[2] Reproduced with permission from the American Diabetes Association)

Allodynia	Pain caused by stimulus that does not usually provoke pain. May be static (produced by single, non-moving stimulus) or dynamic (ie, produced by a moving stimulus)
Analgesia	Absence of pain in response to a painful stimulus that would normally be painful
Central pain	Pain initiated or caused by a primary lesion or dysfunction in the central nervous system
Dysaesthesia	An unpleasant abnormal sensation, whether spontaneous or evoked
Hyperalgesia	Increased pain response to a painful stimulus
Hyperaesthesia	Increased sensitivity to non-painful stimuli (e.g., temperature, touch)
Hyperpathia	Pain syndrome characterised by abnormally painful reaction to a stimulus, especially repetitive stimulation
Hypoalgesia	Reduced pain response to a painful stimulus
Hypoaesthesia	Decreased sensitivity to non painful stimuli (e.g., temperature, touch)
Neuritis	Inflammation of a nerve or nerves
Neurogenic pain	Pain initiated or caused by a primary lesion, dysfunction or transitory perturbation in the peripheralor central nervous system
Neuropathic pain	Pain initiated or caused by a primary lesion or dysfunction in the nervous system
Neuropathy	A disturbance of function or pathological change in a nerve: in one nerve, mononeuropathy; in several nerves, mononeuropathy multiplex; if diffuse and bilateral, polyneuropathy
Paraesthesia	An abnormal sensation, whether spontaneous or evoked

FIGURE 2.3 IASP pain terminology (Adapted with permission from Merskey and Bogduck[4])

respectively.[2,6] However, 10% of men and 12% of women in the non-diabetic population reported similar symptoms.

Around half of patients with DPN experience symptoms, most often burning pain, electrical or stabbing sensations, paraesthesia, hyperaesthesia, and deep aching pain. Neuropathic pain tends to be intermittent and is typically worse at night. Symptoms are most commonly experienced in

the feet and lower limbs but may extend to the hands and fingers in more severe cases.

DPN tends to have an insidious onset and many patients are truly asymptomatic, putting them at risk of foot ulceration and other late sequelae including Charcot's neuroarthropathy and even amputation.[2,7] Often, a neurological deficit is discovered by chance during a routine examination; patients may not volunteer symptoms, but on enquiry admit that their feet feel numb or dead.[3]

Recently, unsteadiness has been recognised as a manifestation of DPN, reflecting disturbed proprioception and possibly abnormal muscle sensory function.[6,8] This unsteadiness has been quantified and may result in repetitive minor trauma or falls, as well as late complications including neuroarthropathy.[8] In most severe cases, with loss of proprioception, patients may demonstrate a positive Romberg's sign.[8]

Examination of the lower limbs usually reveals a symmetrical sensory loss of vibration, pressure, pain and temperature perception (mediated by small and large fibres), and absent ankle reflexes. Sensorimotor neuropathy is often accompanied by autonomic dysfunction, signs of which include a warm or cold foot, sometimes with distended dorsal foot veins (in the absence of obstructive peripheral vascular disease), dry skin and calluses under pressure-bearing areas.[3] Any pronounced motor signs should raise the possibility of a non-diabetic aetiology, especially if asymmetrical.

Acute Sensory Neuropathy

Acute sensory (painful) neuropathy is a rare, distinct variety of the symmetrical polyneuropathies. It is characterised by severe sensory symptoms similar to those associated with DPN but with few neurological signs on examination. Differences between acute sensory and chronic sensorimotor neuropathies are summarised in Fig. 2.4.

The overriding symptom reported by all patients is pain. This may be described as constant burning pain, discomfort

Contrasts between acute sensory and chronic sensorimotor neuropathies

Mode or onset	Relatively rapid	Gradual, insidious
Symptoms	Severe burning pain, aching: weight loss usual	Burning pain, paraesthesia, 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

FIGURE 2.4 Contrasts between acute sensory and chronic sensorimotor neuropathies (Copyright © 2004 American Diabetes Association from Boulton et al.[2] Reproduced with permission from the American Diabetes Association)

(especially in the feet), severe hyperaesthesia, deep aching pain or sudden, sharp, stabbing or electric shock-like sensations in the lower limbs. Symptoms tend to be worse at night and bedclothes may irritate hyperaesthetic skin.

Other symptoms of acute sensory neuropathy include severe weight loss, depression and, in men, erectile dysfunction.[2] Clinical examination is usually relatively normal, with allodynia on sensory testing, a normal motor examination and, occasionally, reduced ankle reflexes.

Acute sensory neuropathy tends to follow periods of poor metabolic control (e.g. ketoacidosis) or a sudden change in glycaemic status (e.g. insulin neuritis), including an improvement in glycaemic control induced by oral hypoglycaemic agents. It has also been associated with weight loss and eating disorders.[9]

The natural history of acute sensory neuropathy is very different from DPN: its onset is acute or subacute but symptoms improve gradually with stabilisation of glycaemic control, and typically resolve in less than 1 year.[10]

The Effects of Painful Neuropathic Symptoms on Negative Affect and Quality of Life

As noted above, the symptoms of the sensory neuropathies (both acute and chronic) vary from the extremely painful at one end of the spectrum to the painless at the other. The painful symptoms, especially the burning discomfort, electrical sensations and other uncomfortable but very difficult to describe sensory experiences, frequently cause severe physical and mental dysfunction as well as sleep disturbance,[11,12] thereby negatively impacting on individuals' quality of life. The increasingly recognised symptom of neuropathic unsteadiness as a consequence of impaired proprioception can also be incapacitating.[12,13] Whereas most studies, including the recent German Diabetic Microvascular Complications Study,[14] have demonstrated that symptomatic neuropathy markedly diminishes patients' quality of life, such studies have invariably used generic instruments to assess health-related quality of life.[15] As the content of such instruments is imposed by the investigators and did not emerge from patients affected by neuropathic pain and other somatic experiences of neuropathy, the findings from these studies left a gap between painful neuropathy, as abstractly defined, and the patient's experience of pain, which is essential for framing effective interventions. In view of the more recent observation that only 65% of a community-based diabetes population with painful diabetic neuropathy had ever received treatment for their symptoms despite almost all reporting pain to their physician,[16] the adverse effect on quality of life is likely to be even greater than previously reported. In an attempt to overcome these shortcomings, several questionnaires have recently been developed to assess quality of life from the perspective of an individual affected by diabetic neuropathy. One such measure, a neuropathy and foot ulcer-specific quality of life scale, the NeuroQoL,[17] is increasingly being used in trials of new agents for the treatment of painful neuropathy in which quality-of-life measurement is an integral part of the assessment of efficacy.