INTRODUCTION

Pain is probably the most distressing symptom of diabetic neuropathy (1). The features of pain in diabetic neuropathy were clearly documented by Pavy (2), who observed, that it was of burning and unremitting quality often with a nocturnal exacerbation. Indeed the quality of neuropathic pain has been described as burning, shooting, lancinating, prickling, and aching in character, often with many of these symptoms manifesting in the same patient (3). Some patients describe these symptoms as the feeling of walking barefoot on hot sand or pebbles. Others describe an odd sensation of their legs feeling swollen. The intensity of neuropathic pain is also variable among different individuals and often varies with time in the same individual. Some patients may have mild paresthesia in one or two toes; others may have intolerable unremitting pain involving both legs (4). Most patients with chronic, painful neuropathy have a moderate background pain with relatively short intervals of peak neuropathic pain. Sleep is often disturbed because of the nocturnal exacerbation of these symptoms, in addition to allodynia (contact hypersensitivity to bed clothes) (4). In some patients, neuropathic pain can be so disabling as to lead to loss of employment, reduction in exercise tolerance, and hence interference with daily activities, a reduction in recreational activities, and depression (4,5).

Pain is not only a feature of acute and chronic symmetrical sensorimotor neuropathy occurring in a stocking distribution, but may also develop in relation to focal and multifocal neuropathy such as isolated lesions of cranial-nerve palsy, proximal lower-limb motor neuropathy affecting thighs, and truncal neuropathy (6). Conventional treatment for painful diabetic neuropathy is largely symptomatic and frequently ineffective (7). Although significant pain relief can be achieved in some patients by the use of tricyclic agents, the use of these compounds is frequently complicated by unacceptable side
effects (7). In this chapter, we look at the possible mechanisms involved in the generation of neuropathic pain, and review the methods available for the assessment of pain in diabetic neuropathy. Finally, we discuss nonpharmacological treatments of painful diabetic neuropathy.

MECHANISMS OF PAIN IN DIABETIC NEUROPATHY

Pain is an unpleasant, subjective sensory and emotional experience. Neuropathic pain is caused by dysfunction of the peripheral or central nervous system, that does not require any receptor stimulation. Painful symptoms are relayed by nociceptive, afferent small myelinated A-delta, and unmyelinated C fibers. Unmyelinated C fibers are thought to transmit the slower component of pain, whereas myelinated A-δ fibers relay the faster component.

The exact pathophysiological mechanisms underlying pain in diabetic neuropathy are not known (8), although several workers have tried to provide a neuro-structural correlate for neuropathic pain (9-11). Brown et al. (12), found a predominant loss of small myelinated and unmyelinated fibers on nerve biopsy of patients with chronic painful diabetic neuropathy. Said et al. (13), also found similar pathological changes in some of their patients with painful neuropathy. However, other workers have demonstrated degeneration of all nerve fiber sizes, both myelinated and unmyelinated, in subjects with painful neuropathy (14-17). Some observers have suggested that a clear relationship between selective degeneration of fibers of certain size and the presence of neuropathic pain is unlikely by virtue of the fact that neuropathic pain is variable in intensity and may remit for variable periods (18). This does imply that biochemical or vascular factors that are likely to vary with time, may be important in the generation of neuropathic pain, in the context of an already damaged nerve. As nerve biopsy studies do not give a dynamic view of nerve function, the author and colleagues have attempted to study human sural nerve in vivo, in subjects with relatively sudden-onset painful neuropathy (18), by employing the techniques of nerve photography and fluorescein angiography. This study has suggested that vascular factors may be important contributing factors in the generation of neuropathic pain (18). The following are some of the hypotheses put forward as possible mechanisms of neuropathic pain generation based on studies in humans and animal models with nerve injuries.

Ectopic Impulse Formation by Regenerative Sprouts

Asbury and Fields (19) suggested that spontaneous ectopic impulse generation in regenerative sprouts (Fig. 1) could be the cause of neuropathic pain. The sprouting was thought to occur in small-diameter primary afferent fibers. Dandona et al. (20), have also suggested that regenerative sprouts initiated by strict glycemic control may provide the explanation for treatment-induced painful neuropathy that occurs in previously poorly controlled diabetic subjects with asymptomatic small-fiber neuropathy. Fowler and Ochoa (21) demonstrated that when primary sensory afferents are damaged in rats, they develop axonal sprouts (Fig. 1). Animal experiments have shown that these regenerative sprouts have heightened mechano sensitivity (22-24). This may be the explanation for Tinell's sign in which paresthesia in the distribution of peripheral nerve is elicited by a gentle tapping of a damaged regenerating nerve. Increased adrenergic chemosensitivity has also been found in axonal sprouts (25). This may be secondary to the development to alpha receptors by neuroma sprouts (25).