

been planted by constructive multidisciplinary teamwork in an environment pursuing high-quality clinical research backed by basic sciences and thus generating novel ideas. Centres of research excellence need to be preserved at all costs, particularly at this time of devolution of care into an environment where treatment is often protocol driven with the potential to stifle the generation of new ideas. Yet it is in the everyday routine clinics attended by so many people with diabetes where the detection of 'absorbing variations on an unchanging theme' provides the crucial seed for innovation.<sup>24</sup>

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### CURRENT KEY DEVELOPMENTS

## Advances in the management of painful diabetic neuropathy

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Diabetic distal symmetrical polyneuropathy (DSP) affects approximately 30–50% of all diabetic patients.<sup>1</sup> The two main clinical consequences of DSP are foot ulceration because of insensitivity to trauma and painful diabetic neuropathy (PDN) that can be very distressing. There is little doubt that glycaemic control and duration of diabetes are major determinants of DSP.<sup>2</sup> In addition, a major European prospective study has recently shown that potentially modifiable, traditional markers of macrovascular disease such as hypertension, hyperlipidaemia and smoking are also independent risk factors for DSP.<sup>3</sup>

Pain is the most distressing symptom of DSP and prompts the patient to seek medical advice.<sup>4</sup> There has been little advance in the description of PDN; the features of pain in DSP were documented by Pavy in the latter part of the 19th century, who observed that it was of burning and unremitting quality often with a nocturnal exacerbation.<sup>5</sup> Sufferers may be so disabled by the pain as to experience a reduction in their daily activities, profound depression and a poor quality of life.<sup>4</sup>

### Mechanisms of neuropathic pain

Unlike nociceptive pain, neuropathic pain is caused by dysfunction of the peripheral or central nervous system, and does not require any receptor stimulation.<sup>6</sup> The exact pathophysiological mechanisms of neuropathic pain in diabetes remain unknown although several mechanisms have been postulated.<sup>6</sup> In the 1970s and 1980s researchers tried to provide a neurostructural correlate for PDN.<sup>7</sup> Asbury and Fields suggested that spontaneous ectopic impulse generation in small-diameter regenerative sprouts could be the cause of neuropathic pain.<sup>8</sup> However, Llewellyn *et al*<sup>9</sup> and Britland *et al*<sup>10</sup> were unable to detect any correlation between PDN and morphologic indicators of regeneration in sural nerve biopsies. More recently, based on experiments in animal models of neuropathic pain, a number of peripheral and central mechanisms have been put forward (Table 1).<sup>11</sup>

### Managing neuropathic pain

Although the case for good blood glucose control in preventing/delaying the onset of DSP is strong, there are no controlled studies that show efficacy in reducing pain perception.<sup>12</sup> There have been significant advances in the pharmacological management of PDN over the past 30 years. Tricyclic compounds such as amitriptyline have been used as first-line agents for many years but many patients fail to respond to them and side effects (drowsiness, dry mouth etc) are frequent.<sup>13</sup> Serotonin and norepinephrine reuptake inhibitors (SNRIs), such as duloxetine, appear better tolerated with reasonable efficacy.<sup>14</sup> The anticonvulsant gabapentin,<sup>15</sup> and more recently pregabalin,<sup>16</sup> have also been shown to be effective in relieving neuropathic pain. Other drugs include anticonvulsants, in particular carbamazepine; opiates, such as tramadol and oxycodone; membrane stabilisers including mexiletine and intravenous lignocaine; the antioxidant,  $\alpha$ -lipoic acid and the substance-P depletor, topical capsaicin. Despite these, however, the treatment scenario remains less than satisfactory, with many sufferers having sub-optimal pain relief.<sup>17</sup>

**Table 1. Mechanisms of neuropathic pain.** With kind permission of Springer Science and Business Media.<sup>11</sup>

Peripheral mechanisms	Central mechanisms
Changes in sodium channel distribution and expression	Central sensitisation
Altered neuro-peptide expression	A $\beta$ fibre sprouting into lamina II of the dorsal horn
Sympathetic sprouting	Reduced inhibition of descending pathways
Peripheral sensitisation	
Altered peripheral blood flow	
Axonal atrophy, degeneration or regeneration	
Damage to small fibres	
Glycaemic flux	

Lack of response and unwanted side effects of conventional drug treatments force many sufferers to try alternative therapies such as acupuncture, transcutaneous electrical stimulation and as a last resort, implantation of electrical spinal cord stimulator.<sup>18</sup> Pain could, however, get better spontaneously.

Although there has been significant advances in the management of PDN, targeted studies comparing those with and without painful symptoms are required to explore further the underlying mechanisms of pain in DSP, particularly the extent of the pathology in the central nervous system, in order to develop more effective treatments.

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