Pain past, present and future: the unhappy paradox of scientific advances and therapeutic standstill

Apart from those rare individuals with an inability to feel pain, and those who are indifferent to it—and they suffer in different ways—all of us will experience pain. How fortunate, then, we are to be living now: it is almost beyond one’s comprehension to envisage what tortures were experienced by those at the sharp end of the sword or the surgeon’s knife, or during childbirth, when there was so little to offer in the way of pain relief. At the end of life, too, what suffering was endured—and all too often still is—by those in the terminal and often painful stages of their existence, before the need for alleviating pain became accepted as something of unsurpassed importance.

The story of ‘The fight against pain’, the subtitle of Dormandy’s book, is the story, or more accurately the very many stories, of attempts to grapple with pain and its prevention, abolition and management. In the stories are reflected too the virtues and imperfections of man when making these attempts. The virtues include humanity, fortitude, energy, ingenuity and optimism; the imperfections include ignorance, laziness, greed and arrogance; and these human qualities are amply demonstrated in Dormandy’s absorbing account.

One might have expected the relief of suffering would always have been an endeavour of mankind, but this is not so. Thus, although in 17th century England the poet John Milton expressed in Paradise Lost that ‘Pain is perfe[c]t misery, the worst Of evils, and, excessive, overturns All patience’, it remained a commonly held view, at least until the 20th century, that ‘the worst Of evils’, the book’s title, was often beneficial: an opportunity for fortitude, and an ordeal that God had provided for man to endure. Doctors often acquiesced in this view, and as a result, buttressed by the hazards that pain relief undeniably could pose, a nihilistic approach to pain relief appeared justified. Dormandy reminds us that, as recently as 150 years ago, amputations were still often performed in America on conscious patients due to the risks of anaesthesia; and, despite the highly successful and well-known use of chloroform during Queen Victoria’s confinements, it is just 70 years since the ‘messianic’ obstetrician Grantly Dick Read was asking ‘Why is labour so often painful?’. In passing, even more recent has been the acknowledgement that, as every mother always knew, even very young infants can feel pain, and it is now accepted that, whenever possible, painful procedures should not take place without an anaesthetic. At what stage a foetus can feel pain is a debate that continues to rage, with strongly held views based...
on semantic (‘what is pain?’), biological, ethical and legal considerations.

Dormandy charts in exuberant detail many of the developments in 'The fight against pain', and what emerges particularly striking is the often authoritarian approach of the medical profession. Doctors in the past have so often decided what is good or bad for their patients, and even today one wonders whether doctors sometimes make unwarranted assumptions. For instance, doctors may judge a treatment to be effective if pain is relieved by, say, 30% or 50%. But do patients really agree, or do we deceive ourselves about our perceived successes? How content is the patient whose post-herpetic neuralgia has been reduced from 9/10 to 6/10 on some pain scale?

This story of pain relief is much concerned with quests for the therapeutic Holy Grail, and the history of drugs ranging from opium to COX-2 inhibitors is explored at length. The developments both of local anaesthetics, and in particular cocaine and its derivatives, and of general anaesthetics, provide rich sources for the story-teller that Dormandy is. For example, the rivalry of those claiming priority for the introduction of nitrous oxide into clinical practice makes an intriguing narrative, as do the development and marketing of aspirin. And to bring the anti-inflammatory drug story up to date, Dormandy reports the punitive damages awarded in 2005 against the pharmaceutical company, Merck, in respect of its analgesic preparation Vioxx.

In a volume of over 500 pages, it is only possible to select a very few examples such as these to illustrate how pain represents a fascinating, multifaceted subject. The book, which paints a historical picture of enormous dimensions and encompasses a breathtaking journey from China and the Greeks and Romans to the gate control theory and beyond, is certainly easy, but ominously perhaps too easy, to read. The caution is necessary, partly because pain is a subject of limitless complexity, and partly because the book itself is unsatisfactory in a number of ways. It is too long, wanders into excessive background historical and other peripheral byways, and inevitably leans heavily on the hundreds of mainly secondary sources. Irritations include the numerous unnecessary footnotes reporting the age and date of death of many of the players, lots of the author’s asides, and various minor errors that should have been dealt with by proper editing.

What is unforgivable, however, is the discussion of the ‘sensory or afferent fibres’ whose extensions ‘...enter the grey matter in the spinal cord as the so-called ‘anterior nerve roots’’. Later on the same page 482, the position is restated: ‘The anterior nerve roots make for the anterior horns where they synapse with a second set of neurons’, and to make matters worse, a few lines later, Wall and Melzack are attributed as having ‘...showed in the 1960s...that pain messages can be drastically modified at the level of the anterior horn cells.’ The anterior and posterior horns in the spinal cord too are confused.

The problem is not only that such a major and repeated error reveals either considerable ignorance or carelessness, but that it inevitably makes the reader nervous about what other errors, major or minor, may have crept in. One’s confidence is shaken. It is a relief, therefore, to turn to books which deal with the study of pain in a more rigorous fashion.

Thus, in contrast, Snow’s monograph Operations without pain is a meticulously written book that also deals largely with historical aspects of pain. Her aim is very different. She tells the story of the introduction of anaesthetic gases into surgical practice, including the pros and cons of ether versus chloroform, from the perspectives of the patient, the surgeon, and the ‘administrator’ of the gas, and she sheds fascinating light on the medical scenes in America and Victorian Britain. For example, even when anaesthetic gases had been introduced into surgical practice, the often unpleasant and sometimes fatal complications of ether and chloroform led patients to be very cautious and indeed sometimes refuse to undergo surgery, just as surgeons would sometimes refuse to operate using general anaesthesia. Snow points out that certain patients’ natures were thought to make them more susceptible to adverse reactions, an interesting reflection on the influence of psychological factors on pain and its relief. Her text, fully annotated with numerous primary and secondary sources, is less racy but more scholarly, an approach which to the present reviewer is more satisfactory albeit less entertaining.

For the neurologist, neither Dormandy’s all-embracing account, nor Snow’s focused study, sheds new light on the mechanisms subserving pain or its treatment. Written for the layman, these books are, after all, largely works of history, and should be viewed in that context. However, they demonstrate that in two very important fields, ‘The fight against pain’ has been won, or should have been. These fields are surgical anaesthesia together with management of acute pain, which are touched on above, and pain in terminal care. Skilful management of terminal pain, whether in the patient’s home, or in a hospital or hospice, is nowadays accepted without discussion to be essential, and a patient with a terminal disease who dies in pain is generally thought to be a patient whose management has been less than successful.

But if these fights against pain ‘should have been’ successful, they are often not. Thus management of acute pain is commonly suboptimal. Patients suffering from an acute painful illness or recovering from surgery all too often experience pain, and huge numbers of patients around the world experience pain that remains partially or entirely untreated. Sometimes this is due to factors that could easily be remedied, such as lack of opiates resulting from failure of supply, cost considerations, or misplaced fears of addiction. As for adequate palliative care, effective symptom control is often elusive, and even now perhaps half of terminally ill patients experience moderate to severe pain (Weiss et al., 2001). In the Western world, pain.
management in terminal care is often patchy and, quirikly, often reliant for its provision on the voluntary sector. In deprived parts of the world, the end of life is even more often a story of unmitigated pain and suffering.

At least in the management of acute pain and pain in the terminal stages of life we have an effective therapeutic armamentarium at our disposal, but it is in the field of chronic pain that treatment has been dismally unsuccessful, particularly in the case of neuropathic pain. As an aside, pain in relation to neurological disease appears to be of little interest to many neurologists now. This lack of interest is puzzling, because pain is a manifestation of function and dysfunction of the somatosensory system, albeit invariably with cognitive and emotional components, which one might have thought would be subjects of considerable fascination for neurologists. However, pain is a subject that clinical neurologists find too subjective or nebulous for their liking.

In mitigation, neurologists also need to be practical. For instance, notwithstanding the pain community’s seeming obsession with measurement of pain, and the necessity of measurement for the production and licensing of pain-relieving drugs by pharmaceutical companies, neurologists will recognize that, as discussed earlier, measurement itself is not the answer: the patient is simply concerned with whether their pain becomes better or worse, or remains unchanged.

Understandably and rightly, neurologists too may well be concerned about the paucity of data and lack of rigour in many studies of pain and its management. Two examples will suffice. First, and very surprising given most neurologists’ experience, the evidence that carbamazepine is effective in trigeminal neuralgia is supported by just three randomized controlled trials comprising 161 patients (Zakrzewska and Lopez, 2005). Second, the British Pain Society’s current recommendations on the use of spinal cord stimulation for complex regional pain syndromes (discussed below) and painful peripheral neuropathy are based on randomized controlled studies consisting of only 52 patients with the former condition and 10 patients with the latter (British Pain Society, 2005). It is disquieting that guidelines on a major invasive procedure are based on so few patients. It could reasonably be argued that pain relief for the individual patient is all that matters, but anecdote is not necessarily the hallmark of the respectable scientific approach, neither should it be the basis for therapeutic guidelines.

But where are studies and management of pain going now? Emerging strategies for the treatment of neuropathic pain, ‘the outcome of a novel think-tank conference’ held in 2005, is a book comprising 23 chapters written by 49 internationally renowned contributors who report on and summarize the very latest neuroscientific developments in four extensive areas: both peripheral and central nervous system targets, disease-specific targets, and measurement and new technologies. And developments are sometimes surprising. For instance, who would have thought until recently that immune mechanisms may be crucial in various injury-induced pain states, and a field ripe for pharmaceutical innovation (Manning, 2006)? It is true that very chronic inflammatory changes have been found in the dorsal horn of the spinal cord in post-mortem studies of patients with post-herpetic neuralgia (Watson et al., 1991), but cytokine involvement and the contribution of glial cells in chronic pain are areas only now being intensively studied, together with the therapeutic implications. In retrospect, however, immune disturbances may explain the efficacy of steroids reported half a century ago in the treatment of the shoulder–hand syndrome (Steinbrocker and Argyros, 1958). This syndrome, an example of what has been dubbed ‘...a “funny” pain in a “funny-looking” limb’ (Jadad et al., 1995), is one form of the condition previously known as reflex sympathetic dystrophy and which has now been given the long and remarkably unhelpful new label of ‘complex regional pain syndrome, type I’. Terminological squabbles notwithstanding, there is a promising, single-case report of the benefit of intravenous gamma globulin in a patient bearing this latter diagnosis (Goebel et al., 2005).

Surely the greatest challenge ahead will be for the fruits of the tree of knowledge cultivated in the laboratory to mature into effective pain-relieving therapies and preventative measures (Oxman et al., 2005). There is a long way to go. We all know that menthol and other cold applications can sometimes be transiently helpful in treating pain, and perhaps can now explain this on the basis of dorsal horn gating mechanisms mediated by activation of TRPM8 receptors (Proudfoot et al., 2006), but we can rarely help patients with burning feet. Similarly, we now know more about abnormalities of the Na1.7 sodium channel, the genetic bases and the electrophysiological consequences, in patients with the pain of erythromelalgia (Dib-Hajj et al., 2005), than we do about how to treat painful diabetic peripheral neuropathy. We now know that the spinal cord is a major site of central sensitization (Salter and Woolf, 2005), and that there are not only the well-known descending inhibitory circuits but also descending circuits that initiate and maintain pain (Porreca et al., 2002), yet we have little to offer the patient with pain from spinal cord injury or from myelopathy in multiple sclerosis. We now know that phantom limb phenomena, and possibly specifically when painful, are associated with remarkable plasticity changes in the sensory cortex (Flor et al., 1995; Ramachandran and Hirstein, 1998), but, despite the ingenious concept of mirror box therapy, treatments for phantom pain are nearly always unsuccessful.

Whilst scientific advances in understanding pain mechanisms have been extraordinarily impressive, when it comes to management of pain, retreats have been similarly impressive. For pain relief we no longer usually amputate a limb, not least because a painful phantom is likely to develop. We rarely interrupt nerves in the brain, spinal
cord or periphery now, not only because such procedures may be ineffective and even cause different pain, but even if surgery is effective, very curiously the pain often recurs. Similarly, we rarely interrupt the sympathetic nervous system for complex regional pain syndromes, and, shamefully, it is only relatively recently that we bothered to do the trials which showed that sympathetic procedures including regional intravenous guanethidine infusions are no better than placebo (Kingery, 1997). Only recently, too, have there been proper evaluations of those physical forms of treatment that are particularly used for musculoskeletal pains, such as low back pain. Again it is difficult not to be disillusioned. For example, acupuncture at best provides only ‘small’ long-term benefits (Thomas et al., 2006), and routine physiotherapy is no better than one session of assessment and advice from a physiotherapist (Frost et al., 2004). With drugs, whilst benzodiazepines and phenothiazines are no longer prescribed for chronic pain, remarkably few drugs are left that have withstood proper evaluation. According to various Cochrane Library reports and reviews (e.g. Finnerup et al., 2005), these drugs simply include tricyclic antidepressants; carbamazepine, gabapentin and perhaps now pregabalin; opioids, notably tramadol and oxycodone; and topical lidocaine.

Perhaps apart from the contributions of psychologists that are discussed below, and despite widespread pain clinics and the best intentions of those in the multidisciplinary pain team, there is little effective for the treatment of chronic pain, particularly when neuropathic. This impotence doubtless accounts for the large numbers of sometimes invasive procedures which continue to be performed, perhaps repeatedly and often uncritically—presumably more out of desperation than realistic chance of success.

What of the future? Borderlands are often fruitful territories to explore, and one of the most exciting borderlands is where neurologists, psychiatrists and psychologists meet over the interactions between the somatosensory and affective components of pain. Successes in psychological management of pain preceded advances in neuroscientific understanding of the mechanisms, and it is now accepted that psychological interventions, especially cognitive and other behavioural therapies, are particularly valuable in treating chronic pain. This conclusion has been confirmed in a number of randomized controlled trials (Morley et al., 1999), albeit not yet specifically for neuropathic pain. But what are the underlying mechanisms, and how do they relate to the somatosensory elements comprising the location and quality of pain?

In the past year alone, research has provided some fascinating insights. For example, recent experimental findings demonstrate changes in functional connectivity between specific laser evoked, pain-related cortical structures, the changes depending upon whether the subject attends to, or is distracted from, their pain (Ohara et al., 2006); here may be an objective handle on the sensory—psychological interactions in pain that perhaps underpin the different techniques employed by the psychologist.

Another emerging clue concerning these interactions is the disruption of the placebo response in patients with Alzheimer’s disease, a phenomenon attributable to impairment in prefrontal connectivity (Benedetti et al., 2006); these findings chime with the relief of pain after old-fashioned frontal lobotomy and leucotomy. And returning to the beginning of this review and to those with congenital insensitivity to pain, rather unexpectedly these individuals who cannot feel pain can still perceive the pain of others, even if sometimes to a variable and attenuated degree (Danziger et al., 2006).

Do such leaps in knowledge augur well for the future? If the three books discussed here reflect the perspectives of the layman, the historian, and the neuroscientists, the missing perspective is that of the clinician. But finally it is the clinician who must advise, support, and sometimes comfort the patient with pain. Knowledge about pain is only useful in medicine when it helps the sufferer. Judging from the past, we would do well to be realistic and very humble—the nervous system seems to be extraordinarily resistant to switching off pain.

**References**


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