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EDITORIAL

Spinal cord stimulation

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The gate hypothesis of pain of Melzack and Wall, published in 1965,[1] prompted a revisiting of the centuries-old therapeutic application of electrical stimulation. Peripheral nerve stimulation was re-examined by Wall and Sweet[2] and the first "dorsal column stimulator", targeting the ascending collaterals of the large gate-closing A beta fibres, was implanted in a patient in March 1967.[3] Spinal cord stimulation (SCS), as it should more properly be called, then followed an undistinguished career for 12–15 years. Seventy per cent were implanted for back pain, against which it was not very effective. The few large series were heterogeneous in every respect and attempts to identify the keys to good patient selection were unsuccessful. The significance, even the existence, of neuropathic pain was not widely appreciated. The hardware was so unreliable that consistent results were elusive and meaningful outcomes difficult to identify. Whilst most of these shortcomings have changed for the better, allowing clear indications and high success rates to emerge, the field remains dominated and distorted by the "failed back surgery syndrome" (FBSS) and the search for the economic holy grail of a "cure" for low back pain. This is particularly so in the USA with its high incidence of FBSS; the European practice has evolved differently, the pain of peripheral vascular disease (PVD) now equalling deafferentation pain as the joint main indication across Europe.

Approximately 5000 units are implanted in Europe per annum (four times the number of intrathecal drug pumps) with wide variations between countries. Belgium has the highest rate at around 25 per million per annum (four times that of the UK) followed by Switzerland, Sweden, Italy and Spain; the UK ranks ninth in Europe. The numbers are small compared with other implantable devices; in the UK 13,000 cardiac pacemakers are implanted per annum, but fewer than 400 spinal cord stimulators. At present PVD exceeds neuropathic pain as the commonest indication in Italy, Spain and Germany. The proportion implanted for PVD is increasing in Belgium. Neuropathic pain is gaining ground in Germany and Holland. Belgium is the only European Union (EU) country with a full official reimbursement system (for approved indications), and Germany and Holland have limited official reimbursement. Switzerland, the main non-EU implanting country, also has official reimbursement. Elsewhere, reimbursement depends on local arrangements or private insurance. In EU countries, devices are strictly regulated by federal legislation expressed in the 'CE mark' system.

Two categories of electrode can be employed, those that can be inserted percutaneously via a Tuohy needle and flat plate electrodes which require an open operation. They are all placed epidurally and must lie neurologically rostral and (if the pain is unilateral) ipsilateral to the area of pain. It is well established that the evoked paraesthesiae must cover at least the majority of the painful area. The great advantage of percutaneous placement is that the implanter does not need to be a surgeon; most pain specialists are anaesthetists. It also allows optimal placement, being performed in the awake patient. The disadvantages include a greater positional specificity than the more "forgiving" plate electrodes and a greater risk of becoming dislodged than with electrodes that can be sutured in position (although modern designs have reduced this tendency). There is also considerable current "wastage" around most of the circumference of the electrode compared with plates which are insulated except at the area of contact with the dura. Most systems employ four electrodes (usually referred to inappropriately as "channels"), but there is a trend towards greater complexity with eight, 16 and even more electrodes, fuelled mainly by a desire to target the low back.[4,5] The 50 active combinations possible with four electrodes pale into insignificance when compared with the 6050 available with eight and more than 40 million provided by 16! For most purposes four electrodes are adequate, particularly now that we know more about optimal parameters, configurations and placement.[6–9] The computer modelling and biophysical studies of Holsheimer's group in the Netherlands have provided several very useful insights, following the earlier pioneering work of Coburn.[10] Thus, the dorsal roots, stimulation of

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which can be unpleasant, generally have a lower threshold than do the dorsal columns but the difference is a factor of electrode configuration[11] and of the thickness of the CSF layer; where the latter is thinnest, in the mid-cervical region, the relationship is (favourably) reversed,[12-14] the dorsal columns having the lower threshold. The problem is greatest in the mid-thoracic spine where the kyphosis takes the cord away from the electrode. The need is not only to target the stimulation appropriately but also to create as large a window as possible between the perception threshold and the discomfort threshold, in order to give robust, clinically useful stimulation. The advent of truly multi-channel systems, in which the stimulation parameters (amplitude, pulse width and frequency) can be varied independently for each electrode or group of electrodes, should greatly increase the effective targeting and "usability" of SCS.

Stimulators can be powered either by a totally intracorporeal pulse generator or by radio-frequency (RF) coupling from an external transmitter. The former is unobtrusive and uncluttered, but requires an operation and further significant expenditure every time the power source expires; RF systems use rechargeable batteries and, of great importance in the present climate, incur very much lower recurring costs. The greater operant input of the patient with chronic pain using an RF system is also attractive, although this has been recently matched to some extent by the introduction by one manufacturer of a small individual telemetry system that can be used by the patient with an implanted pulse generator. This also overcomes the previous problem of the lack of fine control available to the patient which was inherent in totally implanted systems, provided the programmer is kept close to hand. Intracorporeal pulse generators would be convenient for patients with motor disorders (see below), but cannot generate the high frequencies usually needed.

By far the commonest application of SCS is in the treatment of intractable pain. In recent years a pattern has finally emerged. It is most effective where there is deafferentation, particularly if accompanied by autonomic disturbance, and against ischaemic pain, both cardiac and peripheral.[15] It is not generally effective against nociceptive pain as in arthritis, cancer pain and postoperative pain. It does not seem to help in brachial plexus damage in segments relating to total root avulsion but can be extremely effective in partial brachial plexus damage. It does not usually relieve the end-zone pain in painful paraplegia, but can certainly relieve the phantom pain. Phantom limb or digit pain following amputation can also be effectively controlled and the paraesthesiae can be felt in the phantom. The 'battered root' element of the FBSS responds much better than the back pain and the analogous position obtains in the cervical region. Although patients with complete cord lesions usually do not respond, a few do; similar comments apply to perineal pain.

Nashold and Friedman recognized in 1972 that the best results were in patients with burning pain and with evidence of sensory neurological damage[16] (i.e. neuropathic pain), but this and other clues went largely unheeded for many years. Similarly, success in causalgia was noted in the early 1970s;[17,18] the complex regional pain syndromes (CRPS), i.e. reflex sympathetic dystrophy and causalgia, have since been found to be excellent indications.

Dooley commented in 1977 that the best subgroup was those with vasospastic disease[19] and it had already been observed that SCS caused warming of the cold extremities of patients with multiple sclerosis (MS).[20] The efficacy of SCS in relieving obstructive ischaemic limb pain and in promoting the healing of small cutaneous ischaemic ulcers has since become firmly established although the possible limb salvage effect is more controversial.[21-26] Considerable research has demonstrated that the effect is via the microcirculation[25-27] and has thrown light on the possible neural substrate.[28,29] The clinically useful response in vasospastic conditions such as Raynaud's disease has also been confirmed.[30,31] As already noted, PVD has become a major indication for SCS in Europe, but not in North America.

The extraordinary efficacy of SCS in intractable angina pectoris was first reported in 1984.[32] It soon became apparent that the effect was consistently reproducible to the extent that this indication has the highest success rate of all.[15] Glyceryl trinitrate intake falls and mobility increases, with less shortness of breath. Thorough physiological studies have demonstrated that SCS reduces cardiac ischaemia, probably prevents or delays the catecholamine-mediated vicious circle of pain-induced sympathetic hyperactivity and, very importantly, does not mask the vital warning of infarction which angina can provide.[33-37] Whereas a large number of Scandinavian patients with intractable angina have been treated with SCS—a Swedish trial has recently closed after recruiting more than 300 patients (L. E. Augustinsson, personal communication)—this indication has gone largely unnoticed by most of the rest of the world.

SCS has only a small role in the treatment of movement disorders. The "striking" benefit in MS[20] proved to be a false dawn[38,39] except for the reduction of the miserable features of the "upper motor neurone" neurogenic bladder, a consistent and often very useful effect which has been largely ignored.[40-43] Flexor spasms in MS and in other conditions are much more effectively controlled by intrathecal baclofen infusion than by SCS. Cord stimulation, via high cervical electrodes, undoubtedly helps some patients with dystonia and with titubation or torticollis,[15,44,45] but probably only

those who are relatively mildly affected. The beneficial effects on the bladder and in some cases of extrapyramidal disorder are achieved at the same frequency of stimulation as in pain control (33–80 Hz), but much higher frequencies (1100–1400 Hz), which must act by inhibition, being too fast for neurones to follow, have uniquely been effective in other cases of extrapyramidal disorder and in spasticity.

The results of SCS probably depend more upon case selection than upon any other factor and this has been, and continues to be, the subject of much research and debate. Assistance has long been sought from psychological testing and psychiatric assessment; in Belgium this remains a prerequisite for reimbursement. In general, this avenue has not proved helpful and whilst few would deny the relevance of psychological factors to the management of intractable pain, the interpretation of their significance may often be flawed.[15] A failure to recognize that depression, anxiety, obsessiveness and a degree of drug dependence might be quite normal in someone who has lost the ability to work and their independence and mobility, who may have become socially isolated, who suffers constant malaise due to drug intake and sleep deprivation and whose severe constant pain dominates every waking moment, has almost certainly led to over-zealous exclusion.

Similarly, temporary trial cord stimulation is widely used as a rigorous excluder of unsuitable candidates yet it is actually not a particularly good predictor of outcome and virtually nothing is known of the patients who are rejected. Only its efficacy in "screening in" patients has been reported; its reliability in "screening out" potential failures has gone almost untested. In a rare study in which 28 "rejects" from a trial were implanted, six enjoyed a good outcome.[46] In heterogeneous series and in those containing a high proportion of FBSS cases and other "mixed bag" diagnoses, even where the rejection rate has been high the success rate from permanent implants has rarely been higher than around 50% overall.[15] The key lies in the very low rejection rate now seen in certain *specific* conditions which are already known to respond in a high proportion of cases, such as angina, PVD and CRPS (reflex sympathetic dystrophy and causalgia). A growing number of implanters, including the author, now dispense with trial stimulation in such cases. Despite its low efficacy in the more complex, multifactorial cases (e.g. FBSS), the use of trial stimulation is easier to justify in these. Those who advocate the blanket use of trial stimulation, of whom there are many, imply that all conditions are similarly likely or unlikely to respond and this is patently not correct; the diagnosis can be a much more powerful indicator. Transcutaneous electrical nerve stimulation (TENS) has little or no practical predictive power for SCS.

In the context of intractable pain the assessment of outcome is not as straightforward as one might think although, if SCS works well, complicated or subtle methods should not be required to gauge this—the patient will tell you. A marked (but not necessarily complete) reduction in analgesic drug intake and increase (if physically possible) in activity are reliable indicators. Failure to return to work by middle-aged disabled people who have not worked for a long time in a society with a high unemployment rate means absolutely nothing. In successful cases the relief from the debilitating side effects of the medication is often cited voluntarily by the patient. This, in turn, enables him or her to cope better with any residual pain; a good outcome reflects more than a simple analgesic measurement. A large majority of reports run the risk of distortion by relying upon the notation "percentage pain relief". The first erroneous assumption is that chronic pain is both quantifiable (what are the units?) and linear. The second is that all patients understand the concept of percentages. The third is that memory for chronic pain is accurate. In fact very little is known about memory for chronic pain in general and virtually nothing about memory for *neuropathic* pain in particular. The fourth implication is that patients can make the appropriate calculation. Many studies then content themselves with referring only to "more than 50% relief" and "less than 50% relief" which does nothing to justify the method. This way of expressing outcome also over-simplifies; the original pain and its effects may have varied over time and the degree of relief may be different in different circumstances and at different times. Even a change on contemporaneous visual analogue scales from, say, eight out of ten to four out of ten does not necessarily indicate a 50% reduction in pain. Williams discusses the complexity of pain measurement in chronic pain management in her recent review.[47]

Blind trials are impossible in SCS for pain syndromes because of the need to evoke paraesthesiae. Whilst few would now suggest a placebo effect (the high success rate in certain conditions, the failure of many previous treatments to work, the lack of pain relief if the paraesthesiae are topographically inappropriate), almost no well-structured trials have been performed which compare SCS with other therapies. A notable exception comes from North at Johns Hopkins who has focused upon improving methods of selection and assessment in this field and has instigated the first prospective, randomised comparison of SCS with another treatment (re-operation) for the FBSS.[48] Clearly, more studies of this nature are needed.

The tarnishing of the reputation of SCS has been contributed to by the frequently reported phenomenon of "late failure", i.e. a reduction or loss of effectiveness after months or years. This can be explained to some extent by equipment failure and

a lack of the essential proper follow-up. Simple misunderstandings or a lack of coaching can easily result in the patient failing to obtain full advantage from the use of the stimulator. A single postal or telephone follow up at, say, one year asking whether the stimulator is still working, or what percentage pain relief is currently being obtained, is simply not adequate. Another possible explanation, at least in part, relates to the question of memory for chronic pain alluded to above. Patients' perceptions appear to change over the years in the presence of effective SCS. Anecdotally, sudden true failure of the stimulator, i.e. failure of a component, is frequently accompanied by pressure to rectify it quickly and, by the volunteered statement, "I had forgotten just how bad the pain used to be". Thus, patients may well underestimate the effectiveness of SCS with the passage of time. True tolerance may occur, but is probably not common. It seems more likely if continuous, 24 h per day, stimulation is used;[49] patients should be advised to "switch off" for a few hours in each 24-h period if they use their stimulator every day. It should be emphasized at this point that large numbers of patients continue to enjoy effective pain relief after very many years of SCS.

The outcome in motor disorders can be problematical because of difficulty in knowing what to measure and in appreciating the significance of the results of those measurements. A change which is modest to an observer can be extremely welcome to, and appreciated by, a physically disabled person.

A complete explanation of the mechanism of action of SCS is not yet available. Biochemical and pharmacological studies have generally contributed little, with the exception of the animal studies of Linderoth, Meyerson and colleagues at the Karolinska Hospital and Institute, Stockholm. In the periphery, they have examined the vasodilator effect[50] and centrally they have found different changes in GABA, serotonin and substance P in the dorsal horn of the spinal cord and in the periaqueductal grey matter.[50] However, these are acute studies in previously normal animals; the dorsal horn is probably not normal in chronic pain states, particularly those involving deafferentation.* There is no strong evidence for the involvement of opioids.

Neurophysiological studies have demonstrated that dorsal column stimulation activates inhibitory interneurones in the dorsal horn[51] and can inhibit spinothalamic neurones which respond specifically to noxious stimulation, both cardiac and somatic in the areas to which cardiac pain is referred.[52] Whilst it is not yet known how much of the clinical effect of SCS on ischaemic pain is actually antinociceptive, it is now well known that SCS is ineffective against wound pain, arthralgia, etc., but can be extremely effective against neuropathic pain. A shortcoming of much neurophysiological investigation into the action of SCS is that it addresses nociception rather than neuropathic pain. Studies of supraspinal interactions are perhaps more likely to produce relevant, useful information. An effect at thalamic level has been shown in monkey[53,54] and human,[55,56] but particularly promising is the work of Roberts and colleagues in Cardiff on the anterior pretectal nucleus (APtN) of the rat,[57] and of Meyerson and colleagues on the rat mononeuropathy model.[58] The APtN has a rich excitatory input from the dorsal column nuclei and although it appears to have a major role in the suppression of acute, nociceptive pain (see Roberts' review[57]), its stimulation also has an anti-aversive effect via higher centres.[59] Furthermore, the onset of autotomy, the behaviour exhibited by animals subjected to peripheral nerve damage and which may be a good model for human neuropathic syndromes, is accelerated by bilateral destruction of the APtN.[57,60] The APtN, and the equivalent in the human, may therefore normally prevent or limit neuropathic syndromes following peripheral nervous system injury and its action may be enhanced by SCS. Animal studies of chronic pain, are of course, limited by ethical considerations and modern legislation.

The antisympathetic effect of SCS which is apparent in its effect in peripheral ischaemia, possibly in cardiac ischaemia and in at least some cases of CRPS I (reflex sympathetic dystrophy) and II (causalgia) seems to be the opposite of its relaxing effect on the spastic bladder, which should be sympathomimetic, and this has yet to be explained. Although dorsal column stimulation is undoubtedly central to the therapeutic effects of SCS, other pathways will also be stimulated including the intermediolateral grey column sympathetic pathway and the corticospinal motor pathway; hence it should not be referred to as "dorsal column stimulation" in the clinical context.

Looking to the future, better recognition is needed of the fact that the present applications of SCS for pain fall into two groups. First are specific conditions in which a success rate of 70–90% of cases can be achieved, including angina, ischaemic limb pain, CRPS (reflex sympathetic dystrophy and causalgia), brachial plexus damage (cf. complete avulsion), phantom limb and digit pain, and battered root syndrome. Second, is the group with a variety of pain mechanisms, permeated by psychosocial, cultural, occupational and other contaminating factors, i.e. mostly back pain sufferers including those with FBSS. The former group will be better served by dissemination of knowledge amongst the medical profession, by the provision of meaningful cost-effectiveness data (of which very few are so far available, angina being almost the only exception[61]) and by the

*Since this editorial was written, the Karolinska group has published work on SCS-induced GABA release in the dorsal horn of rats which have a deafferented limb and allodynia. [Stiller C-O, Cui J-G, O'Connor WT, Brodin E, Meyerson BA, Linderoth B. Release of γ-aminobutyric acid in the dorsal horn and suppression of tactile allodynia by spinal cord stimulation in mononeuropathic rats. *Neurosurgery* 1996; 39: 367–75].

continuing improvement in hardware. Multichannel systems will make topographical targeting more reliable and predictable and new electrodes will resist dislodgement better. The thoracic spine is relatively forgiving but the far more mobile cervical spine requires new approaches such as surgically-implanted electrodes mounted in small "paddles".[62] The latter are proving reliable in more than 90 patients, nearly one third with cervical placements, implanted by the author (unpublished data). This gives access to effective SCS to large numbers of patients, many of them relatively young, with upper limb intractable pain. The second group (mostly back pain), in whom success rates vary widely from less than 30% to rarely more than 60%, will be better served by fundamentally more enlightened methods of assessing outcome which in turn should lead to improvements in case selection. Much could probably be learned from investigating failures, including those rejected from trials of stimulation, an area of potential research that has been singularly ignored. The reasons for individual cases of therapeutic failure in generally good indications are not known.

Possible new applications comprise mainly cerebral ischaemia and coma. The former has been examined for more than a decade, both in humans and experimentally, following Hosobuchi's original observation.[63,64] Although improvement after stroke is far from proven, the possibility that the brain behaves like the ischaemic foot or hand offers exciting and potentially valuable possibilities. These include temporary high cervical stimulation via percutaneous leads for persistent vasospasm following subarachnoid haemorrhage. A possible coma-limiting effect has received attention in recent years, particularly in Japan where a recent conference included no fewer than five papers on cervical SCS in prolonged coma and persistent vegetative state.[65] Fifty-five patients were included overall, but obviously very large numbers would be needed to demonstrate an effect. Further new indications, including certain visceral disorders, will emerge in the near future.

Finally, the areas of research which may prove especially fruitful for the practice of SCS include: the neuropharmacology of the supraspinal mechanisms of its action, which may lead to effective pharmacological enhancement of SCS; the pathophysiology of CRPSs, their relationship to autonomic pathology and why only some people develop them; and memory for chronic pain which, apart from being of interest in its own right, might lead to a more enlightened assessment of the outcome of treatment.

Appropriately practised in appropriate patients, SCS can be dramatically effective where all else has failed. Its efficacy is such, in certain specific and dreadful conditions, that it should not necessarily be regarded as a last resort.

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