Topical Review

Neural prostheses

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Assuming that neural regeneration after spinal cord injury (SCI) will eventually become a clinical reality, functional recovery will probably remain incomplete. Assistive devices will therefore continue to play an important role in rehabilitation. Neural prostheses (NPs) are assistive devices that restore functions lost as a result of neural damage. NPs electrically stimulate nerves and are either external or implanted devices. Surface stimulators for muscle exercise are now commonplace in rehabilitation clinics and many homes. Regarding implantable NPs, since 1963 over 40 000 have been implanted to restore hearing, bladder control and respiration. Epidural spinal cord stimulators and deep brain stimulators are routinely implanted to control pain, spasticity, tremor and rigidity. Implantable NPs have also been developed to restore limb movements using electrodes tunnelled under the skin to muscles and nerves. Spinal cord microstimulation (SCμstim) is under study as an alternative way of restoring movement and bladder control. Improvement in bladder and bowel function is a high priority for many SCI people. Sacral root stimulation to elicit bladder contraction is the current NP approach, but this usually requires dorsal rhizotomies to reduce reflex contractions of the external urethral sphincter. It is possible that the spinal centres coordinating the bladder–sphincter synergy could be activated with SCμstim. Given the large and growing number of NPs in use or development, it is surprising how little is known about their long-term interactions with the nervous system. Physiological research will play an important role in elucidating the mechanisms underlying these interactions.

The Symposium on Spinal Cord Function and Rehabilitation brought together physiologists, pharmacologists, researchers in the fields of neural regeneration and neuroprostheses (NPs) and rehabilitation clinicians. Numerous strategies to promote regeneration and restore motor function after spinal cord injury (SCI) were discussed.

Researchers in widely ranging fields often tend to focus on the details of their specialities and it is easy to lose track of the urgent questions uppermost in the minds of people with SCI and their support groups: (1) is a 'cure' possible? (2) which strategy is the most likely to succeed? (3) when will the research produce significant clinical results?

For people with SCI, the order of priority of the functional deficits they must deal with can also surprise neurophysiologists. For example, restoration of bladder and bowel control is often ranked higher than restoring locomotion. Clearly a 'cure' in the form of complete neural regeneration of the injured spinal cord with a restoration of normal bodily functions including bladder and bowel control as well as voluntary movement of the trunk and extremities is the ideal. Much interest and optimism was generated in the 1980s when it was shown that portions of peripheral nerve could be used as tissue grafts with the potential to 'bridge the gap' of a complete spinal transection (Richardson *et al.* 1980). In the last 6 years there have been several reports of successful regeneration of certain spinal pathways in rats, apparently resulting in improvements of motor function after partial or even complete spinal transections (Bregman *et al.* 1995; Cheng *et al.* 1996; Olson, 1997; Kim *et al.* 1999; Brosamle *et al.* 2000; Ramon-Cueto *et al.* 2000). However, though neural regeneration through or around tissue bridges can certainly be achieved, it is far from clear whether *functional* connections are made between descending axons and neurones caudal to the lesion. Restored function, when it occurs, may result from a facilitated recovery of local neuronal circuits rather than a restored flow of commands in descending pathways (see reviews by Jones *et al.* and

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Pearson in this issue of *The Journal of Physiology*). Taking the optimistic view that some combination of tissue bridging, stem-cell implants (Ribotta *et al.* 2000; Slawinska *et al.* 2000) and pharmacology (Marcoux & Rossignol, 2000) will become a clinical reality in the next few years, it remains almost certain that the functions of daily life will only be partially restored. In the light of this, there is clearly a continuing need for assistive technologies. NPs can not only provide limited restoration of function in the short term, but also have the potential to augment the outcome of regeneration techniques in the future.

Types of neuroprostheses

Most existing NPs are devices that electrically stimulate peripheral nerves, either through surface electrodes attached to the skin over nerves or through electrodes implanted in close proximity to nerves. On this broad definition, 'exercise' stimulators such as those sold to the public by mail order are in fact NPs. These stimulators are often used by people with hemiplegia for therapeutic electrical stimulation to maintain muscle bulk, reduce spasticity and to 'retrain' the nervous system (Kraft *et al.* 1992). The myotrophic effect of regular exercise, whether naturally or electrically evoked, has been extensively studied, whereas the neural 'retraining' effect, though well accepted clinically (Nudo, 1997; Taub, 2000), is poorly understood physiologically. One could also argue that transcutaneous electrical nerve stimulators (TENS stimulators) for pain relief, which have also been sold to the public in large numbers, are NPs as well. The physiological basis of the analgesic action of TENS stimulators has been explained in terms of the gate theory of pain, which posits that activity elicited in large sensory axons is transmitted via interneurones with an inhibitory action on nociceptive second-order neurones (Melzack & Wall, 1984).

The basic idea of restoring movement to paralysed limbs with electrical stimulation dates back to studies in the mid-19th century (Duchenne, 1867). For the next 100 years muscle stimulation was used by clinicians as much to impress patients as to provide any therapeutic effect. The advent of transistors in the early 1960s provided the basis for portable *functional* electrical stimulation devices designed to activate muscles phasically during the course of complex movements. The first of these was a stimulator that activated the peroneal nerve with surface electrodes to counteract footdrop (Liberson *et al.* 1961). Over the last three decades footdrop stimulators designed for daily use have been fitted to several thousand hemiplegic people, notably in Yugoslavia (Kralj & Bajd, 1989), Denmark (Dr Benny Klemar, University of Aarhus, personal communication) and more recently in the UK (Taylor *et al.* 1999). Standard physiotherapy stimulators are now often fitted with underheel sensors so they can be used as footdrop stimulators by therapists. Stimulators triggered by voluntary EMG activity have also been available commercially for quite some time (Hansen, 1979) and have recently been used as an adjunct to motor retraining (Chae *et al.* 1998; Francisco *et al.* 1998).

Implanted NPs are more complex devices that must fulfil several criteria in order to achieve clinical acceptance. They must be safe, durable, efficacious and cost-effective. In view of the numerous barriers and risks involved, it is therefore very interesting that implanted NPs have seen such a tremendous growth in numbers recently. Over one-million cardiac pacemakers have been implanted since the 1960s. Though it is debatable whether pacemakers should be classed as NPs, they are electronic stimulators that remain implanted in the body for many years and so the technology developed to ensure their functionality in this hostile environment is applicable to many types of implantable NPs. It is therefore no coincidence that the stimulator portions of most such NPs *look* like pacemakers.

Over 1500 Medtronic dorsal column stimulators have been implanted since the 1970s (Waltz, 1997) for control of intractable pain and spasticity. With some modifications, these stimulators have been pressed into action as deep-brain stimulators also for the treatment of intractable pain (Kumar *et al.* 1997) and more recently for the treatment of extrapyramidal disorders (Benabid *et al.* 1991, 2000). Several thousand deep-brain stimulators have been implanted in patients around the world. Over 1500 phrenic nerve stimulators for respiration have also been implanted (Glenn *et al.* 1973; Elefteriades & Quin, 1998) and more than 2000 sacral root stimulators for bladder control (see below). The biggest success story, however, is the implantable multichannel cochlear stimulator (Clark *et al.* 1977). Over 35 000 multichannel cochlear stimulators have been implanted in the last decade alone (Clark, 1999; Kessler, 1999).

Regarding implantable NPs for motor rehabilitation, the difficulties are arguably greater and the numbers implanted so far are therefore smaller. Radio-frequency-controlled stimulators of the detrusor muscle of the bladder were implanted in small numbers of patients in the 1960s (Bradley *et al.* 1963; Stenberg *et al.* 1967). Peroneal nerve stimulators to counteract hemiplegic footdrop were also implanted in small numbers in the 1970s and 1980s (Jeglic *et al.* 1970; Waters *et al.* 1975; Strojnik *et al.* 1987).

In relation to the upper extremity, after several years of trials with percutaneous multi-electrode systems, the fully implanted Neurocontrol Freehand stimulator (Peckham & Keith, 1992) received regulatory approval in the USA in 1997. About 150 of these systems have now been implanted in C4–C5 quadriplegic people. External sensors of either shoulder or wrist movement are used by an external control unit that selects and transmits commands percutaneously

by radio-frequency transmission. The implanted receiver then stimulates combinations of muscles to produce different types of hand grasp. In a parallel development, about 150 surface stimulators for hand function have been tested in people with C6–C7 quadriplegia or hemiplegia (Prochazka *et al.* 1997; Weingarden *et al.* 1998; Popovic *et al.* 1999).

In spite of the growing number of implantable NPs and, in some cases, excellent clinical outcomes, some technical and physiological concerns remain. For example, difficulties and risks are involved in implanting multiple electrodes to activate widely distributed peripheral nerves. The long-term effects of chronic stimulation of populations of neurones in the brain, spinal cord or peripheral nerves remain to be fully explored.

Spinal cord microstimulation

Over the last few years SCμstim has been investigated as a possible alternative to peripheral nerve stimulation. The rest of this review will be devoted to this emerging field. Studies so far have focused primarily on improving two main functions adversely affected by SCI: bladder control (Nashold *et al.* 1971; Carter *et al.* 1995; Woodford *et al.* 1996; Grill *et al.* 1999) and limb movements (Giszter *et al.* 1993; Tresch & Bizzi, 1999; Tai *et al.* 1999, 2000; Grill, 2000; Mushahwar *et al.* 2000*a*; Mushahwar & Horch, 2000*a*,*b*). SCμstim offers some potential advantages over conventional implantable NPs. First, the spinal cord is far away from the contracting muscles, so electrodes can be implanted in a relatively localized, mechanically stable environment. Second, the spinal column provides a protected region for implanted electronics. Third, the compact lumbosacral region of the spinal cord (~5 cm long in humans) contains interneuronal modules involved in the generation of important functions such as standing, walking and bladder voiding. Tapping into the spinal circuits that coordinate these functions may improve the quality of control and reduce the number of independent control channels needed (Nashold *et al.* 1971; Giszter *et al.* 1993; Tresch & Bizzi, 1999; Grill, 2000).

Control of limb movements using SCμstim

Detailed electrophysiological mapping of the lumbosacral region of the spinal cord controlling leg movements in deeply anaesthetized adult cats demonstrated that SCμstim can produce smooth and graded single joint movements, with a nearly normal order of recruitment of motor units (Mushahwar & Horch, 2000*a*,*b*). Distributed stimulation through two or more intraspinal electrodes could reduce muscle fatigue significantly (Mushahwar & Horch, 1997). More recently, Mushahwar *et al.* (2000*a*) demonstrated that SCμstim through chronically implanted electrodes can generate coordinated whole-limb synergies in the awake, intact cat. Figure 1*A* illustrates the electrode implantation procedure used in these experiments. The microwires (platinum–iridium, 30 μm in diameter) were individually inserted through the dorsal surface of the spinal cord, their exposed tips targeting the ventral horn. The fixation technique, developed originally for chronic single cell recordings (Prochazka, 1984) has been successful in maintaining the implanted microwires securely in place. On average 80% of the implanted electrodes in all animals ($n = 12$) elicited the same muscle responses throughout the period of implantation as they did immediately after recovery from surgery. Figure 1*B* shows a 6 μm thick cross-section of the spinal cord with a visible electrode track. Figure 1*C* and *D* shows close-ups of the same track. The damage induced by the microwire implantation appears to be minimal and the absence of lymphocytes and macrophages indicates the absence of an enduring inflammatory response.

SCμstim through as few as two electrodes in each side of the cord allowed the synthesis of bipedal locomotor stepping in anaesthetized animals (Mushahwar *et al.* 2000*b*). Given the complexity of the locomotor network in the spinal cord, this was not anticipated. Furthermore, in awake animals, low-level SCμstim was found to augment weak voluntary contractions by as much as threefold (Prochazka & Mushahwar, 2000). This suggests a possible application of SCμstim in people with incomplete SCI who retain some voluntary, though weak, control over their limb movements: subliminal SCμstim could be used to facilitate their residual voluntary movements.

Though the generation of movements using SCμstim seems promising, the safety, long-term stability and durability of such a system in humans with SCI is unproven. Most of the testing of SCμstim to date has been performed in anaesthetized or chronically implanted normal adult cats. We have recently begun to investigate the types of movement that could be generated by SCμstim after a complete spinal transection in rats (Mushahwar & Prochazka, 2001). Preliminary results indicate that smooth and graded movements can be generated with SCμstim 4–6 days after transection, but more trials, including those involving more rostral lesions affecting the limbs, are required.

We have found that the motor responses elicited by microwires during deep surgical anaesthesia are not necessarily the same as those elicited after recovery (e.g. flexion during surgery even changing to extension). Human implantation would only be justified if there were a high probability that basic flexion and extension movements could be restored. With our current technique, it would be necessary to implant at least 20 microwires to provide a sufficient choice of micro-stimulation sites to fulfil this requirement. Alternatively, a smaller number of multi-port electrodes might suffice (Mushahwar & Horch, 1997) but there are technical difficulties in fabricating multiple electrodes of an acceptably small overall diameter. Electrodes larger than 50 μm in diameter would probably cause neural damage

during insertion. Their lack of flexibility could result in further damage during relative movements of the vertebral column and spinal cord in daily life. Finally, manual insertion of microwires is currently accurate only to within about 1 mm of the intraspinal target. A more reliable method of insertion is required.

On a more positive note, SCμstim could be used to complement other SCI rehabilitation approaches such as neural regeneration, neuropharmacology and locomotor training. SCμstim may act as a neuromodulator of membrane properties and synaptic transmission. For instance, we are currently exploring different waveforms of SCμstim to reduce spastic hypertonus. It is also

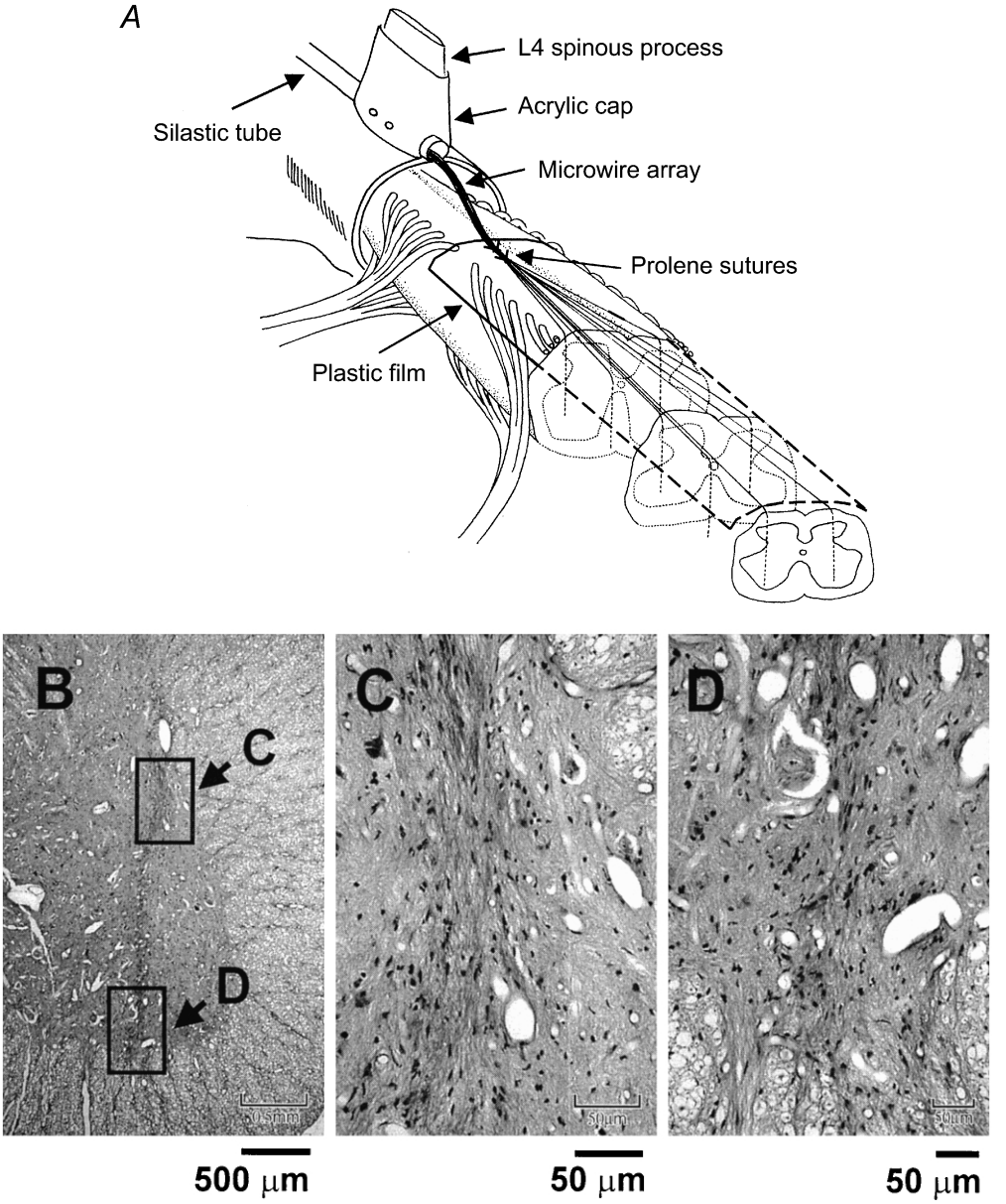

Figure 1. Microwire implantation technique and histology

A, 6–12 microwires were implanted in each side of the spinal cord with their tips targeting the ventral horn (1.7–2.1 mm from the midline, 3–4.2 mm deep). The microwires were spaced 2–3 mm apart along the rostral–caudal length of the lumbar enlargement. *B*, visible electrode track in a 6 μm cross-section of the spinal cord, stained with haematoxylin and eosin and embedded in paraffin. Boxed regions are shown at higher magnification in *C* and *D*. *C*, close-up of the microwire track. Note that the tissue capsule is only about 50 μm in diameter (microwire occupying 30 μm) and does not include any signs of an enduring inflammatory response (i.e. no astrocytes or lymphocytes are present). *D*, detail of the area around the microwire tip. No signs of electrically induced neural damage are seen and nearby motoneurone seems intact.

conceivable that SCμstim could enhance axonal regeneration or growth within the spinal cord by inducing the release of neurotrophic factors (Al-Majed *et al.* 2000). Finally, it could be used to reinforce a pharmacologically induced locomotor pattern (Marcoux & Rossignol, 2000).

Bladder control using SCμstim

In humans and in other mammals, the storage and release of urine are mediated by neural circuits located in the brain and the lumbosacral spinal cord (see review by Shefchyk in this issue). Micturition is effected by the coordinated action of the smooth muscles of the bladder and the striated muscles of the external urethral sphincter (EUS). Transection of the spinal cord rostral to the lumbosacral enlargement results in the loss of voluntary control of voiding and an areflexive bladder (Wheeler & Walter, 1995; de Groat *et al.* 1997). This is followed by bladder hyper-reflexia. Micturition is purely reflexive, mediated by spinal neural circuits. However, voiding usually is inefficient in patients with SCI due to the simultaneous contraction of the bladder and the EUS; the phenomenon of bladder–sphincter dyssynergia.

Implanted NPs have helped some people with SCI recover control of their urinary bladders (Nashold *et al.* 1971). The Brindley-Finetech system (Brindley *et al.* 1982) has been implanted on the ventral (anterior) sacral roots of over 2000 people, in some cases for over 15 years. It has provided generally good results and in spite of a few drawbacks (e.g. van der Aa *et al.* 1999), it has served as a model for the benefits that this type of intervention can provide. The two prerequisites for this system are intact preganglionic parasympathetic neurones to the bladder and a bladder detrusor that is able to contract (Creasey, 1993; Madersbacher & Fischer, 1993). Continuous electrical stimulation of the ventral sacral roots produces a sustained increase in bladder pressure with little voiding, due to the simultaneous contraction of the EUS (Schmidt, 1986). This is due to the composition of the sacral ventral roots which contain the large somatic fibres that innervate the pelvic floor and the EUS via the pudendal nerve, and smaller preganglionic parasympathetic fibres which innervate the bladder via the pelvic nerves (De Araujo *et al.* 1982). Since larger fibres have a lower threshold for electrical stimulation, excitation of the preganglionic parasympathetic axons will be accompanied by contraction of the EUS, thus obstructing the flow of urine. The Brindley-Finetech system partially circumvents this problem by utilizing the difference in the relaxation time of the bladder detrusor and the striated sphincter (Brindley *et al.* 1982). Electrodes are implanted (usually intradurally) upon the ventral (anterior) components of the S_2, S_3 and S_4 spinal roots. The procedure usually is combined with rhizotomy of the sacral dorsal (posterior) roots in order to avoid spontaneous reflex contractions of the bladder, to improve continence, and to avoid pain in patients with incomplete lesions. A train of electrical stimuli is applied for 3–9 s, allowing bladder pressure to rise behind the closed sphincter. Upon cessation of stimulation, the striated sphincter relaxes quickly and the delayed relaxation of the bladder detrusor allows transient 'poststimulus voiding' (Brindley *et al* 1982). This system has been implanted into hundreds of people (Rijkhoff *et al.* 1997*b*) and with generally good results, but it does have a few drawbacks. Voiding occurs in spurts at supranormal bladder pressure, and when the 'on' phase of the stimulus is too long, bladder pressure can become very high with the attendant risk of damage to the upper urinary tract (Rijkhoff *et al.* 1997*a*). The sacral nerve roots also contain fibres innervating the musculatures of the legs, and movement of the legs during stimulation can be cumbersome for some patients. The technique is applicable to patients with incomplete spinal lesions and preserved pain sensation only if they are willing to accept posterior sacral root rhizotomy (Madersbacher & Fischer, 1993). In these patients, it is essential to weigh the advantages of the implant and of posterior rhizotomy against any loss of function that it may cause (Creasey, 1993).

Various modifications of ventral root stimulation have been attempted in order to achieve a more normal voiding pattern. These include selective microrhizotomy of the somatic component of the ventral rootlets as they emerge from the spinal cord (Probst *et al.* 1997) or by fatiguing the somatic component by high-frequency, low-amplitude electrical stimulation (Shaker *et al.* 1998). A promising approach is anodic blocking of the large somatic nerve fibres in order to obtain selective activation of the small parasympathetic fibres innervating the bladder (Fang & Mortimer, 1991; Accornero, 1977; Grunewald *et al.* 1998). The anodic blocking technique also has been demonstrated in humans (Rijkhoff *et al.* 1995, 1997*a*,*b*).

The segregation of the neural elements mediating micturition and continence affords an opportunity to induce micturition by intraspinal microstimulation. Within the sacral spinal cord, the preganglionic parasympathetic neurones innervating the bladder detrusor are located in the intermediolateral cell column, while the somatic motoneurones innervating the EUS are located in the ventral (anterior) horn, in the nucleus of Onuf. The anatomy is essentially identical in humans and cats, but with slight differences in the anatomical levels (Morgan *et al.* 1979; de Groat *et al.* 1981; Blok and Holstege, 1998).

Carter *et al.* (1995) demonstrated that microstimulation within and near the feline preganglionic parasympathetic nucleus (PPN) of the S_2 spinal cord could induce an increase in bladder pressure without concomitant activation of the EUS. This study also demonstrated that continuous microstimulation at a moderately low pulsing rate ($20\ s^{-1}$) would induce a sustained, non-fatiguing increase in bladder pressure. Grill *et al.* (1999) monitored bladder and intraurethral pressure during a systematic

investigation of microstimulation throughout the feline sacral cord. They elicited increases in bladder pressure in excess of 20 cmH_2O when stimulating in and ventral to the PPN. They also found that stimulating at sites dorsal and medial to the PPN could induce an increase in bladder pressure.

In another study, arrays of four individual iridium microelectrodes were implanted chronically into the sacral spinal cord of 10 cats for 3 months (Woodford *et al.* 1996). The microelectrodes were designed to float on the dorsal surface of the spinal cord and were directed towards the intermediolateral cell column, as illustrated in Fig. 2*A* and *B*. Increases in bladder pressure of at least 40 cmH_2O were elicited by pulsing the individual microelectrodes or various combinations thereof (Fig. 2*C*). When the pressure-monitoring catheter was removed, the microstimulation frequently produced micturition.

We have been developing an integrated array of stimulating microelectrodes that can be implanted into the sacral spinal cord (Fig. 3). Similarly to the individual microelectrodes described above, the array is designed to float on the dorsal surface of the spinal cord, an approach

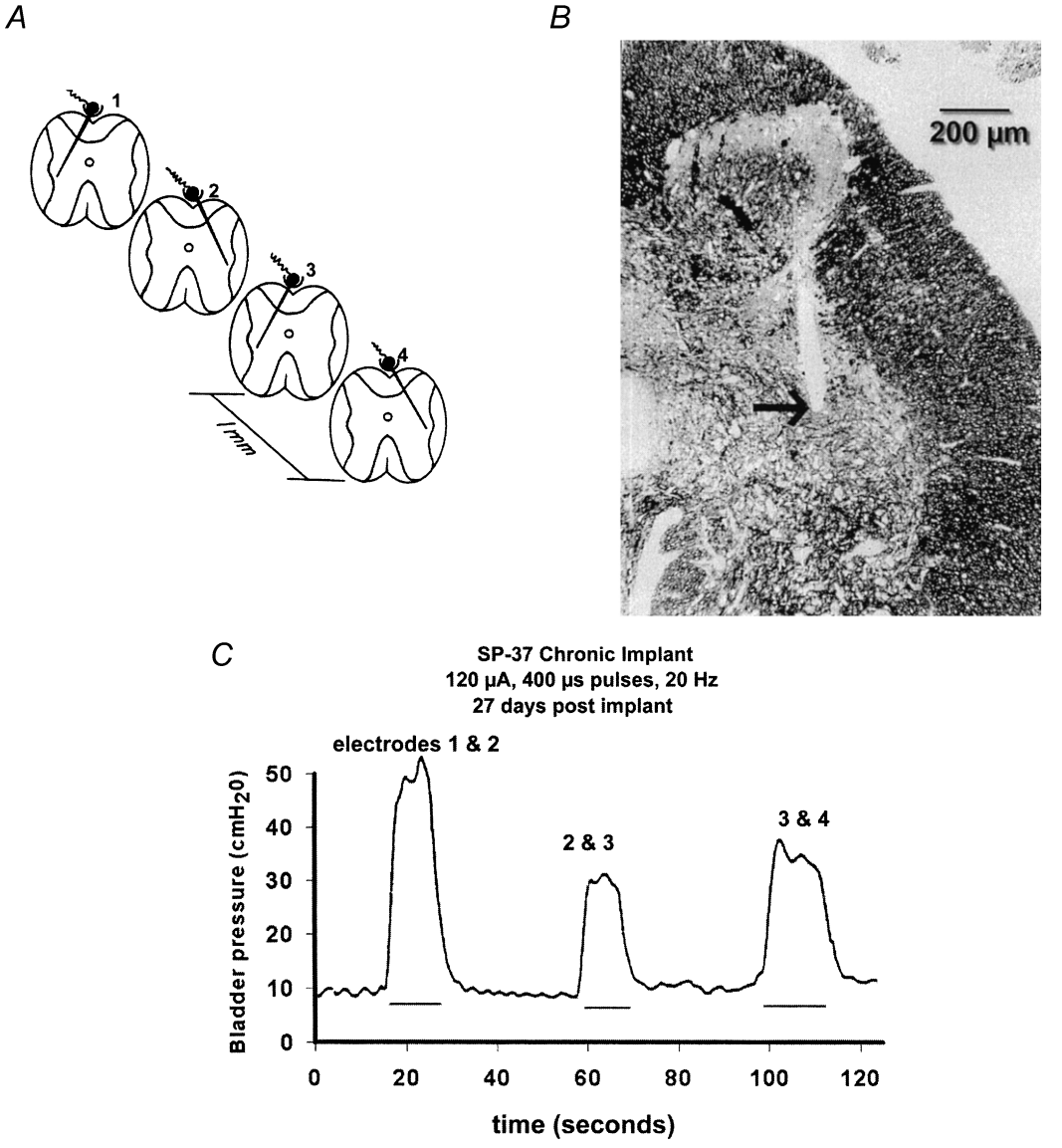

Figure 2. Scheme for chronic microstimulation in the feline sacral spinal cord

A, the arrays of 4 individual iridium microelectrodes were implanted at rostro-caudal intervals of approximately 1 mm, and directed towards the intermediolateral cell column and the preganglionic parasympathetic nucleus. *B*, site of the tip of one of the microelectrodes (arrow), close to the PPN (1 μm section of epoxy-embedded spinal cord, stained with Toluidine Blue and Azure II). *C*, hydrostatic pressure within the urinary bladder induced by stimulating with various pairs of microelectrodes. The stimulus pulses were applied to the 2 electrodes in an interleaved manner. (Modified from Woodford *et al.* 1996, with permission.)

that should be well adapted to the large subdural space above the human sacral cord. In order to expedite and standardize implantation, the array is implanted with the aid of a customized tool, and the electrodes penetrate into the cord at a moderately high velocity (~1 m s^{-1}). However, in most cases there has been minimal tissue injury adjacent to the electrode tracks (Fig. 3*C*) and the histological changes are comparable to those produced by individual microelectrodes implanted manually (Fig. 2*B*).

The activated (oxidized) iridium microelectrodes used in this system have a high charge capacity and very low rate of dissolution during pulsing (Robblee *et al.* 1983), making

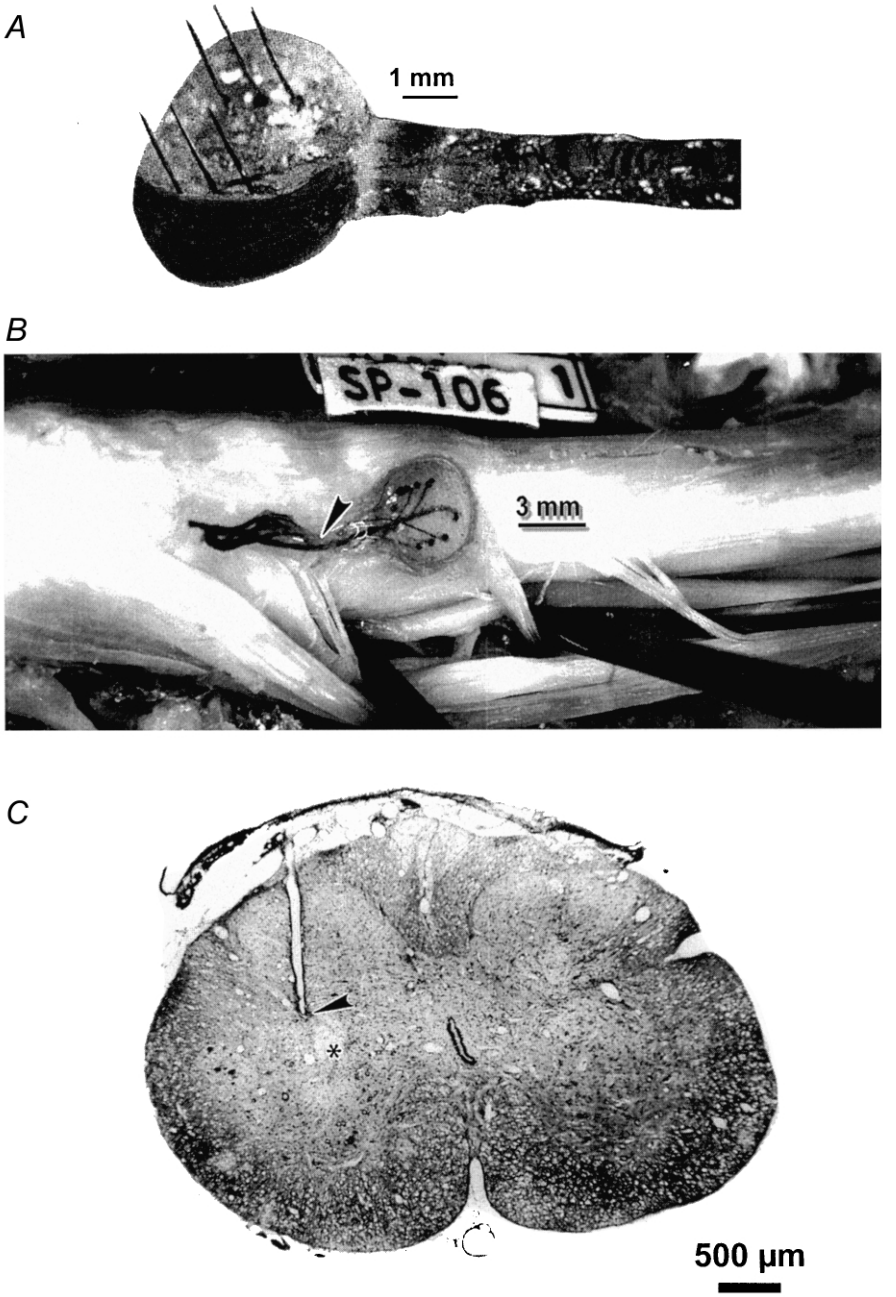

Figure 3. Integrated microelectrode array for chronic implantation in the sacral spinal cord

A, the array of 6 iridium microelectrodes, each approximately 50 μm in diameter, extends from an epoxy button whose underside is contoured to approximate the curvature of the dorsal spinal cord. *B*, an array *in situ* in a cat's sacral spinal cord, 35 days after implantation. *C*, histological section through the cat's sacral spinal cord, and parallel to one of the electrode tracks. The tip of the track (arrowhead) is slightly dorsal to the centre of its target, the intermediolateral cell column (asterisk). (D. B. McCreery, A. S. Lossinsky, W. F. Agnew & L. A. Bullara, unpublished observations.)

them suitable for long-term clinical applications. It has been demonstrated that prolonged microstimulation in the mammalian CNS can be implemented with these electrodes, without tissue injury (McCreery *et al.* 1992, 1994, 2000). Iridium or iridium oxide also can be deposited onto other metals, including the platinum alloy microwires described above, rendering these suitable for very long-term stimulation.

Because of the tendency for people with SCI to develop bladder–sphincter dyssynergia, it is likely that intraspinal microstimulation could achieve efficient voiding in such individuals only if excitation of the bladder efferents could be combined with efficient inhibition of the motoneurones innervating the EUS. During normal micturition, descending axons from the pontine micturition centre activate GABAergic neurones located near the dorsal grey commissure (DGC) at the S_1 and S_2 levels and these neurones then inhibit the motoneurones of Onuf's nucleus (Shefchyk, 2001). Blok *et al.* (1998) demonstrated in the cat that microstimulation within the DGC would induce a decrease in intraurethral pressure. In a clinical system, it is likely that several microelectrodes would have to be implanted throughout the rostro-caudal extent of the DGC in S_1–S_3 in order to activate a sufficient number of inhibitory neurones, and thus produce nearly full relaxation for the EUS.

In the future, the capability of controlling the bladder by intraspinal microstimulation might be integrated with a system of microelectrodes implanted into the somatic motor nuclei of the lumbar spinal cord, as described in the first part of this review.

Concluding remarks

Given the widespread use of NPs it is interesting that their basic physiological actions are often poorly understood. For example, trains of electrical stimuli applied to a muscle nerve excite both sensory and motor axons. The motor axons activate muscle fibres directly while the sensory input enters the spinal cord where it activates not only local neural circuitry but also ascending pathways. The net result in clinical functional electrical stimulation applications is an interplay between the direct motor and indirect reflex actions. Our incomplete understanding of the mechanisms of electrical stimulation of the nervous system is sometimes seen as a fundamental barrier between those whose primary interests are physiological mechanisms and those involved in developing clinical applications (for a forceful statement of this view see the review by Loeb in this issue). Yet electrical stimulation can often produce useful clinical and functional outcomes. In this regard it is no different from many drug treatments, the basic scientific understanding of which has often lagged far behind successful clinical application. The same could be said of the other clinical approaches discussed at the symposium: regeneration, neuropharmacology and intensive training.

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