

Considerations for Safety with Chronically Implanted Nerve Electrodes

William F. Agnew and Douglas B. McCreery

Neurological Research Laboratory, Huntington Medical Research Institutes, Pasadena, California, U.S.A.

Summary: Electrical stimulation of cranial and peripheral nerves has been used to ameliorate a variety of neurologic disease states and neural injuries over the past 20 years. In this review, clinical applications and the histopathologic results of chronic implants in animals and humans are discussed, and the results of neural damage models developed at Huntington Medical Research Institutes are summarized. Chronically implanted electrode arrays may produce neural injury by either mechanical factors or by

continuous, high-frequency electrical stimulation. The margin of safety to avoid electrically induced injury may be increased by minimizing the frequency or total stimulation time, and by the use of an intermittent duty cycle. The protocols presently being used for the stimulation of the vagus nerve to effect inhibition of seizures appear to have an adequate margin of safety. **Key Words:** Epilepsy—Seizures—Vagus nerve—Electric stimulation—Safety—Pathology—Peroneal nerve—Sciatic nerve.

INTRODUCTION

It has been 40 years since Sarnoff et al. (1950) introduced the modern era of nerve stimulation with their report of electrophrenic respiration. Only in the past 20 years, however, have technological advances in materials science, biostimulators, and electrodes made possible completely implantable systems for functional electrical stimulation (FES) of peripheral nerves. Present clinical applications of FES include respiratory pacing for ventilatory insufficiency (Kim et al., 1976; Glenn and Phelps, 1985; Thoma et al., 1987), lower extremity neuromuscular-assist devices (Waters et al., 1975, 1985; McNeal et al., 1976, 1977; Cybulski et al., 1984; Holle et al., 1984; Strojnik et al., 1987), upper extremity neuromuscular-assist (Kiwinski, 1983), control of intractable pain (Burton, 1975; Sweet, 1976; Nashold et al., 1982), electromicturition, and control of incontinence (Brindley, 1977, 1982; Schmidt and Tanagho, 1979; Tanagho and Schmidt, 1982; Thuroff et al., 1982), and inhibition of epileptic seizures (Penry and Dean, 1990; Uthman et al., 1990).

This paper is an overview of the literature pertaining to nerve stimulation in animals and humans

and presents a summary of our work with peripheral nerve neural-damage models.

HISTOPATHOLOGY OF CLINICAL FES

Despite the rapidly increasing number of clinical FES applications, there have been relatively few postimplant pathologic evaluations. Waters et al. (1975) reported on a peroneal nerve stimulation device for the correction of footdrop in 16 hemiparetic patients. In a follow-up study 10 years later (Waters et al., 1985), the authors reported six failures among the 16 implants, one due to electrical failure of the system, two due to lack of acceptance by the patients on the basis of "gadget intolerance," and three due to infection and the accompanying nerve damage. Of the remaining patients, seven used the system successfully for periods of 10.1–12.3 years. Interestingly, some of the patients recovered dorsiflexion during the swing phase of the gait and, ultimately, no longer required stimulation. McNeal et al. (1976, 1977) reported results with 31 patients treated for footdrop by peroneal implants using a commercially available circumneural cuff electrode. Six patients died due to causes not related to the stimulation, and the implant had to be removed from seven patients, primarily due to inflammatory reactions attributed to the Silastic matrix of the electrode array. Most of the nerves were not available for examination. Of the 18 units remaining, the long-

Address correspondence and reprint requests to Dr. W. F. Agnew at Huntington Medical Research Institutes, Pasadena, CA 91105, U.S.A.

est implant time was 7.3 years and the mean implantation time was 4.6 years at the time of the study. At least one patient still has a functioning implant after 18 years (D. R. McNeal, personal communication).

One of the most extensive and successful applications of FES is diaphragm pacing for ventilatory insufficiency. Glenn and Phelps (1985) reported on results from 77 patients who had Silastic circum-neural cuff electrodes or "half cuffs" implanted on the phrenic nerve. Kim et al. (1976) summarized the postmortem histologic findings from seven of Glenn's patients. They reported a heavy buildup of fibrous connective tissue, inflammation, and focal axonal demyelination and degeneration at most of the electrode sites. Although the damage was attributed to mechanical rather than electrical factors, these could not be clearly delineated. Two cases showed no significant axonal degeneration after 2 years.

RESULTS OF ANIMAL STUDIES

There have been a few animal studies directed at determining the relative contribution of mechanical and electrical factors to neural damage, which is often incurred with chronic stimulation of nerves. Kim et al. (1983) stimulated the phrenic nerves of dogs for periods of 4–374 days. They used an interrupted stimulus with an interpulse interval varying from 28 ms (36 Hz) to 140 ms (7 Hz). The current amplitude was usually 1.5 mA, but occasionally was increased to 5 mA. In most cases, the animals were stimulated for 6 weeks followed by 6 weeks of rest, whereas others were stimulated continuously for 52 weeks. There was minimal neural damage in the form of focal demyelination in two nerves, and this was attributed to mechanical rather than electrical effects.

For the past 10 years, we at Huntington Medical Research Institute, have conducted histologic and physiologic evaluations of the extent of neural damage following electrode implants on various peripheral nerves of dogs and cats (Yuen et al., 1984; Agnew et al., 1989a,b, 1990; McCreery et al., 1990; Naples et al., 1990). Early studies were designed to assess for neural damage during duplication of clinical FES protocols for electromicturition for periods up to 9 months. Yuen et al. (1984) studied the histopathologic effects of chronic electrical stimulation to effect micturition. Three types of electrode arrays (two cuff and a helical configuration) were evaluated. To effect bladder evacuation, pulses of 0.5–5.0 V (0.25–2 mA) and 200 μ s in duration were used at 20 Hz for approximately 1 min/day for up to 9

months. No neural damage attributable to electrical stimulation and minimal mechanically induced injury was observed. More recently, we have developed a neural damage model that is designed to delineate mechanically induced from electrically induced neural damage following implantation of the electrode for up to 6 weeks and with stimulations for 4–16 h. Several variations of the Huntington Helix Electrode (Agnew et al., 1989a) were implanted bilaterally on either the peroneal or sciatic nerves of cats. One nerve was stimulated and the contralateral nerve was not stimulated to determine the component of neural damage due to mechanical factors (surgical trauma, effects of the electrode cable and the mere presence of the electrode).

Mechanically induced damage

Mechanically induced neuropathology of nerve includes thickened epineurium due to accumulation of connective tissue beneath the electrode, increased subperineurial and endoneurial connective tissue, and, in more severe damage, endoneurial edema, demyelination, axonal degeneration, and frank axonal loss. In our animal studies, severe neural damage was observed only in those cases in which a nerve had been compressed or constricted due to excessive tension on the cable. A mild but common form of mechanically induced injury in these studies was subperineurial crescents that are most frequently observed on the outer (epineurial-facing) side of fascicles, suggesting an abrasive rather than a compressive-type injury (Fig. 1A, B). These structures resemble Renaut bodies, which have been reported in human nerve, particularly at limb joints, and appear to increase with age (Asbury, 1987).

The evolution of the Huntington Helix Electrode has included reduction of the number of turns comprising the array (from 7 to 3), improved flexibility and routing of cables, and the addition of an application tool that minimizes mobilization and handling of the nerve. Consequently, we have reduced mechanically induced injury considerably. In a recent series of implants of this type of electrode array on 30 nerves (containing 222 fascicles), minimal neural damage in the form of subperineurial crescents of connective tissue was observed on only five fascicles (Agnew et al., 1989b). This electrode is presently being used in clinical trials for electromicturition, control of urinary incontinence, and for the suppression of epileptic seizures by vagal stimulation.

Naples et al. (1990) reviewed the extant data on the various types of electrodes that have been used for chronic peripheral nerves and the factors in-

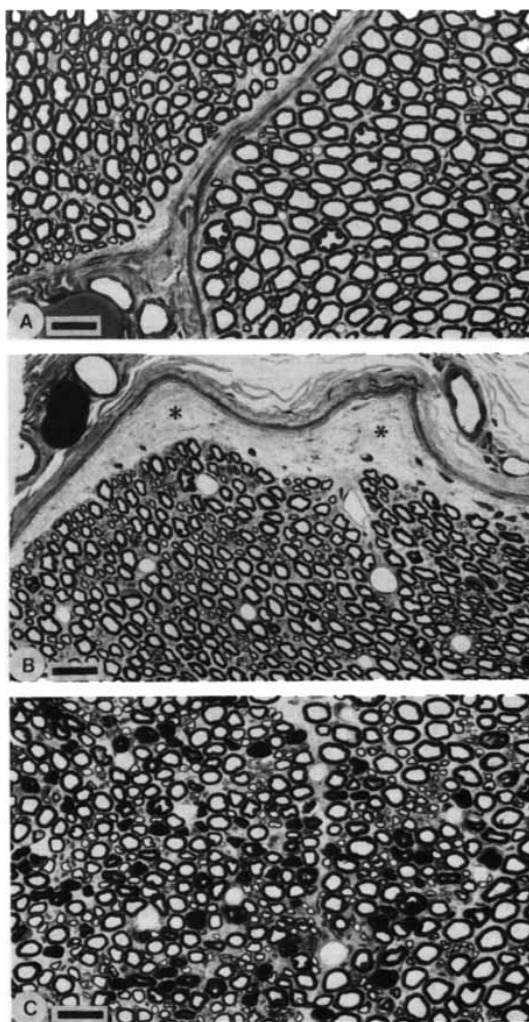


FIG. 1. Cross sections (1 μm thick) of common peroneal nerve of the cat. **A:** Cross section showing portions of 2 fascicles of an unstimulated (no array) nerve. Bar = 30 μm . **B:** Cross section through the nerve beneath an unpulsed helical electrode array. The mechanically induced subperineurial "crescents" (asterisks) of connective tissue contains a few fibroblasts. A normal population of myelinated axons is shown. Bar = 30 μm . **C:** Cross section taken beneath the proximal electrode on a nerve pulsed with 1,500 μA at 50 Hz for 16 h. Numerous myelinated axons showing EAD (dark profiles) are uniformly dispersed throughout the nerve. Bar = 30 μm .

involved in the induction of passive neural damage in nerve implants (damage not associated with electrical stimulation). Although the mechanisms responsible for neural damage due to surgical implantation and residence of electrodes on nerves are the subject of some debate, the following principles

were emphasized: the electrode should fit snugly around the nerve while avoiding compression to allow the electrode to move with the nerve, and thereby minimize abrasion from relative movement of the nerve and electrode (particularly during the first week to 10 days). Subsequently, the nerve and electrode are bound together by connective tissue. The electrode should be soft and flexible, allowing self-sizing to accommodate possible postimplantation edema. Finally, the design and placement of the electrode cable should permit slack at the terminal end of the cable to minimize traction on the array, which could result in torquing or compression of the nerve. The latter is of particular importance for implant sites in which the relative movement between nerve and surrounding muscles is appreciable.

Electrically induced damage

Continuous stimulations of the cat peroneal or sciatic nerves for 8–16 h at high frequency (50–100 Hz) and with pulse amplitudes of 2,500 μA (charge-balanced, biphasic pulse pairs, 100 μs per phase) result in irreversible axonal injury (Agnew et al., 1989a). The neural damage is characterized by endoneurial edema at 48 h after the end of stimulation and by early axonal degeneration (EAD), which is manifested at 1 week following stimulation. The EAD occurs in the medium to large fibers and is rather uniformly distributed throughout the fascicles (Fig. 1C). The nerves from animals sacrificed at 2–3 weeks after damaging stimuli, showed large numbers of macrophages, advanced axonal degeneration, fiber loss, and also axons undergoing remyelination, indicating that at least some of the myelinated axons undergoing EAD were irreversibly damaged. When the frequency was reduced to 20 Hz, using the same pulse amplitude and stimulation time, no damage was observed. In the same study, we also showed that the damage could be markedly reduced when an intermittent (5 s of stimulation, then 5 s of no stimulation) duty cycle was employed. Damage could also be reduced by reducing the total stimulation time. These factors are summarized in Fig. 2.

Recent experiments also indicate that stimulations with 50 Hz and a shorter pulse duration (50 μs rather than 100 μs per phase) were protective, that is, there was an elevation of the neural damage threshold (unpublished observations). If the objective of the stimulation is to excite large fibers (which can be accomplished efficiently with the short-pulse waveform), then a short-pulse waveform would be preferred because of the additional margin of safety. On the other hand, for applications such as stimu-

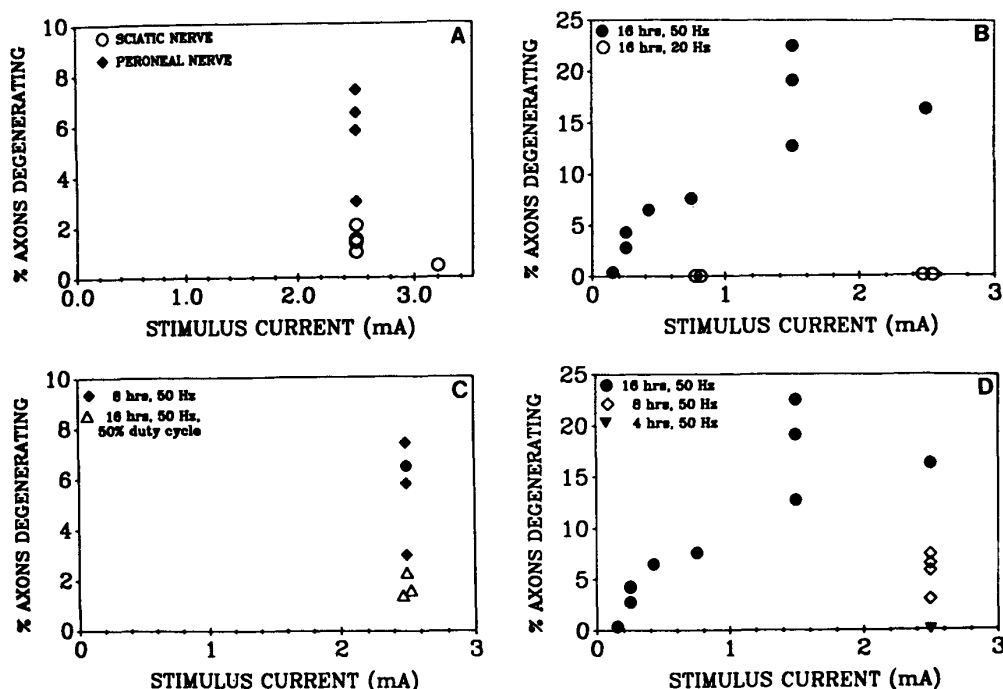


FIG. 2. The role of various stimulation parameters in stimulation-induced injury in cat common peroneal and sciatic nerves. **A:** The importance of the size of the nerve being stimulated (8 h of stimulation at 2,500 μ A and 50 Hz). **B:** The role of the stimulus frequency. **C:** The importance of the temporal pattern of stimulation. **D:** The effect of stimulus amplitude and duration of stimulation. Data for B, C, and D were from cat peroneal nerve.

lation of the vagus nerve for suppression of epileptic seizures, excitation of a broader spectrum of fibers is desirable (Woodbury and Woodbury, 1990). Consequently, the longer pulse duration would be preferable.

In addition to the pathologic alterations, elevation of the electrical threshold of the evoked nerve action potentials was observed during, immediately after, and at 1 week following damaging stimuli (2,500 μ A, 50 Hz for 8–16 h). However, stimulating at 20 Hz with the same parameters did not produce an elevation of the electrical threshold of myelinated fibers.

It is unlikely that the data from the cat peroneal nerve can be quantitatively extrapolated to other nerves or to nerves of other species. For example, we have shown that, with a given set of damaging parameters and using the same type of helical electrode fit to the nerve, smaller nerves appear to be more vulnerable to damaging stimuli than are larger nerves. The peroneal nerve of the cat, approximately 2 mm in diameter, underwent three to four times the amount of EAD as did the larger sciatic (approximately 3 mm in diameter). (This is probably

due to the greater longitudinal current density induced in the smaller peroneal nerve by the circum-neural, bipolar electrode array.) In general, however, the principles discussed above should apply to human peripheral and cranial nerves such as the vagus nerve. As demonstrated in these studies, the cat's peroneal nerve, which is approximately the same size as the human vagus nerve, may be stimulated *continuously* for 4 h at 50 Hz and 2,500 μ A with no neural damage. Although we have not yet assessed the effects of short bursts of high-frequency, high-amplitude stimulation, it appears likely that an adequate margin of safety exists for the vagal FES protocols currently in use. Additional animal studies to evaluate particular vagal stimulation protocols, as well as the mechanical effects of electrodes and cables on the vagus nerve, would be highly desirable.

Mechanisms of electrically induced damage

The neural damage model described above has also been used in recent studies to investigate the mechanisms underlying electrically induced damage. Understanding the mechanisms involved is im-

portant in extrapolating data between nerves of differing diameters and functions and is fundamental in the formulation of protocols for FES.

Several lines of evidence from the studies discussed previously indicate that axonal injury during electrical stimulation is due to neuronal hyperactivity. The morphologic pattern of injury shows a rather uniform distribution of EAD over the cross section of the nerve affecting primarily the medium to large myelinated axons, whereas the smaller myelinated and nonmyelinated axons are spared (Fig. 1C). The damaged axons are the ones that were excited by the electrical stimulation, whereas the smaller myelinated axons are not recruited and are spared (Agnew et al., 1989a). This morphologic pattern of axonal injury supports stimulation-induced hyperactivity of individual fibers, rather than toxic products from an electrochemical reaction at the electrode-tissue interface, as the cause of the damage.

In further experiments, a local anesthetic (2% lidocaine) was topically infused on the nerve adjacent to stimulating electrodes implanted on the cat peroneal nerve in order to effect a block of the action potentials evoked by the electrical stimulation. Although only 60–70% of the fibers were blocked by the anesthetic, the axonal injury was completely abolished (Agnew et al., 1990). This finding suggests that high-frequency, stimulation-induced neuronal hyperactivity is at least part of the cause of the damage and also suggests that the damage to individual axons is related to the totality of the induced neural activity as *all* axons can be spared from damage by blocking the activity in *most* but not all of the axons. Such a global effect could be explained by the elution of a toxic substance into the endoneurial fluid or by depletion of a vital substrate.

In summary, it is quite clear from the results described above that peripheral nerves are vulnerable to injury, both from mechanical factors and electrical stimulation. Judging by our own neural damage model and from the results of other studies of long-term implants of peripheral nerve electrodes, it appears that mechanically induced damage is a more formidable problem than is damage from electrical stimulation. Mechanically induced damage can be minimized by using snug-fitting, self-sizing electrodes with flexible cables and with provision for slack in the distal segment to avoid tension on the electrode array and nerve. Electrically induced injury of peripheral nerves is dependent upon several of the stimulus parameters, but particularly upon the stimulus frequency. It appears most prudent to use frequencies that are as low, and pulse durations as short, as are commensurate with the

desired clinical effect. Because neural damage appears to be closely associated with hyperactivity of fibers, intermittent rather than continuous stimulation should be utilized whenever possible.

Acknowledgment: The authors acknowledge the contributions of their colleagues, Dr. Ted Yuen and Mr. Leo Bullara, in this work. We thank Ms. Julie Jensen for typing the manuscript. This work was supported in part by NIH Research Contracts N01-NS-62397 and N01-NS-92320.

REFERENCES

- Agnew WF, McCreery DB, Yuen TGH, Bullara LA. Histologic and physiologic evaluation of electrically-stimulated peripheral nerve: considerations for the selection of parameters. *Ann Biomed Eng* 1989a;17:39–60.
- Agnew WF, McCreery DB, Yuen TGH, Bullara LA. *NIH Quarterly Progress Report #1 Contract # N01-NS-9-2320* Jan. 1, 1989b.
- Agnew WF, McCreery DB, Yuen TGH, Bullara LA. Local anesthetic block protects against electrically-induced damage in peripheral nerve. *J Biomed Eng* 1990;12:301–8.
- Asbury AK. Renault bodies. A forgotten endoneurial structure. *J Neuropathol Exp Neurol* 1987;22:334–43.
- Brindley GS. An implant to empty the bladder or close the urethra. *J Neurol Neurosurg Psychiatry* 1977;40:358–69.
- Brindley GS, Polkey CE, Rushton DN. Sacral anterior root stimulators for bladder control in paraplegia. *Paraplegia* 1982;20:365–81.
- Burton C. Implanted devices for electronic augmentation of nervous system function. *Med Instrum* 1975;9:221–33.
- Cybulski G, Penn R, Jaeger R. Lower extremity functional neuromuscular stimulation in cases of spinal cord injury. *Neurosurg* 1984;15:132–46.
- Glenn WWL, Phelps ML. Diaphragm pacing by electrical stimulation of the phrenic nerve. *Neurosurg* 1985;17:974–84.
- Holle J, Frey M, Gruber H, Kern H, Stohr H, Thoma H. Functional electrostimulation of paraplegics. Experimental investigations and first clinical experience with an implantable stimulation device. *Orthopedics* 1984;7:1145–55.
- Kim JH, Manuelidis EE, Glenn WWL, Kaneyuki T. Diaphragm pacing-histopathological changes in the phrenic nerve following long-term electrical stimulation. *J Thorac Cardiovasc Surg* 1976;72:602–8.
- Kim JH, Manuelidis EE, Glenn WWL, Fukuda Y, Cole DS, Hogan JF. Light and electron microscopic studies of phrenic nerves after long-term electrical stimulation. *J Neurosurg* 1983;58:84–91.
- Kiwerski J, Weiss M, Pasniczek R. Electrostimulation of the median nerve in tetraplegics by means of implanted stimulators. *Paraplegia* 1983;21:322–26.
- McCreery DB, Agnew WF, Bullara LA, Yuen TGH. Partial pressure of oxygen in brain and peripheral nerve during damaging electrical stimulation. *J Biomed Eng* 1990;12:309–15.
- McNeal DR, Reswick J. Control of skeletal muscle by electrical stimulation. *Adv Biomed Eng* 1976;6:209–56.
- McNeal DR, Waters R, Reswick J. Experience with implanted electrodes at Rancho Los Amigos Hospital. *Neurosurg* 1977;2:228–29.
- Naples GG, Mortimer JT, Yuen TGH. Overview of peripheral nerve electrode design and implantation. In: Agnew WF, McCreery DB, eds. *Neural Prostheses: Fundamental Studies*. Englewood Cliffs, New Jersey: Prentice Hall, 1990:107–45.
- Nashold BS Jr, Goldner JL, Mullen JB, Bright DS. Long-term pain control by direct peripheral nerve stimulation. *J Bone Joint Surg* 1982;64-A:1–10.
- Penry JK, Dean JC. Prevention of intractable partial seizures by

- intermittent vagal stimulation in humans: preliminary results. *Epilepsia* 1990;31(suppl 2):S40-3 (this issue).
- Sarnoff SJ, Gaensler EA, Maloney JV. Electrophrenic respiration: The effectiveness of contralateral ventilation during activity of one phrenic nerve. *J Thorac Surg* 1950;19:929.
- Schmidt RA, Tanagho EA. Feasibility of controlled micturition through electric stimulation. *Urol Int* 1979;34:199-230.
- Strojnjk P, Acimovic R, Vavken E, Simic V, Stanic U. Treatment of drop foot using an implantable peroneal underknee stimulator. *Scand J Rehab Med* 1987;19:37-43.
- Sweet WH. Control of pain by direct electrical stimulation of peripheral nerves. *Clin Neurosurg* 1976;23:103-11.
- Tanagho EA, Schmidt RA. Bladder pacemaker: Scientific basis and clinical future. *Urol* 1982;20:614-19.
- Thoma H, Greener H, Holle J, et al. The phrenic pacemaker: substitution of paralyzed functions in tetraplegia. ASAIO, 33rd annual meeting, New York, NY, 1987.
- Thuroff JW, Bazeed MA, Schmidt RA, Wiggin DM, Tanagho EA. Functional patterns of sacral root stimulation in dog micturition. *J Urol* 1982;127:1031-33.
- Uthman BM, Wilder BJ, Hammond EJ, Reid SA. Efficacy and safety of vagus nerve stimulation in patients with complex partial seizures. *Epilepsia* 1990;31(suppl 2):S44-50 (this issue).
- Waters RL, McNeal DR, Perry J. Experimental correction of foot-drop by electrical stimulation of the peroneal nerve. *J Bone Joint Surg* 1975;57A:1047-54.
- Waters RL, McNeal DR, Faloony W, Clifford B. Functional electrical stimulation of the peroneal nerve for hemiplegics. *J Bone Joint Surg* 1985;67:792-93.
- Woodbury DM, Woodbury JW. Effects of vagal stimulation on experimentally induced seizures in rats. *Epilepsia* 1990;31(suppl 2):S7-19 (this issue).
- Yuen TGH, Agnew WF, Bullara LA. Histopathological evaluation of dog sacral nerve following chronic electromicturition. *Neurosurgery* 1984;449-55.