Control of urinary bladder function with devices: successes and failures

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Abstract: The management of urinary tract dysfunction is crucial for the health and well-being of people with spinal cord injury. Devices, specifically catheters, play an important role in most patients' daily regime of bladder management. However, the high incidence of complications associated with the use of catheters, and the fact that the spinal segments involved in lower urinary tract control remain intact in most patients, continue to motivate research into devices that could harness the nervous system to provide greater control over lower urinary tract function. Mechanical devices discussed in this review include catheters, artificial urethral sphincters, urethral stents and intraurethral pumps. Additionally, many attempts to restore control of the lower urinary tract with electrical stimulation have been studied. Stimulation sites have included: inside the bladder, bladder wall, thigh, pelvic floor, dorsal penile nerve, pelvic nerve, tibial nerve, sacral roots, sacral nerves and spinal cord. Catheters and sacral root stimulators are two techniques whose efficacy is well established. Some approaches have proven less successful and others are still in the development stage. Modifications to sacral root stimulation including posterior root stimulation, anodal blockade and high frequency blockade as well new techniques including intraspinal microstimulation, urethral afferent stimulation and injectable microstimulators are also discussed. No single device has yet restored the control and function of the lower urinary tract to the pre-injury state, but new techniques are bringing this possibility closer to reality.

Introduction

People with spinal cord injury face many challenging medical problems. Inadequate post-injury management of lower urinary tract dysfunction can lead to many complications including renal failure. This used to be the leading cause of death after spinal cord injury, but has dropped to fourth position in recent decades (Frankel et al., 1998) with improved treatment methods (Jamil, 2001). However, complications of the genitourinary system, primarily urinary tract infections, are the most common cause of rehospitalization after spinal cord injury and account for the second highest number of bed-days for readmitted patients (Savic et al., 2000; Middleton et al., 2004). While management of lower urinary tract dysfunction with devices, primarily catheters, has reduced mortality after spinal cord injury, the high incidence of complications is primarily due to the limited success that these devices or other treatment modalities have had in restoring normal function to the neurogenic bladder. In addition to these clinical considerations, effective management of lower urinary tract dysfunction is generally outranked in its importance to patients only by the desire for hand function in people with quadriplegia and sex function in people with paraplegia (Anderson, 2004). These factors provide an impetus to develop improved methods of

managing lower urinary tract dysfunction after spinal cord injury.

Lower urinary tract control

The lower urinary tract has two functions: storing urine (continence) and voiding urine (micturition). The lower urinary tract is innervated by the somatic nervous system and both the sympathetic and parasympathetic branches of the autonomic nervous system. Efferent parasympathetic innervation of the detrusor, the muscular layer of the bladder, arises from preganglionic neurons in the sacral parasympathetic nucleus in spinal segments S2-S4. The preganglionic neurons send axons via the pelvic nerve to the pelvic plexus where they synapse with ganglionic neurons. Afferent innervation of the bladder is also primarily via the pelvic nerve. Efferent somatic innervation of the external urethral sphincter arises from motoneurons in Onuf's nucleus in spinal segments S3-S4. These efferent axons as well as the afferents of the external urethral sphincter and urethra travel via the pudendal nerve. As the bladder fills during the storage phase, stretch sensitive mechanoreceptors in the bladder wall transmit a sense of fullness to both spinal and supraspinal centers. Once the decision to void is reached, the external urethral sphincter is voluntarily relaxed and parasympathetic activity causes detrusor contractions. This synergistic activity, coordinated by the pontine micturition center, results in micturition (Barrington, 1921; Barrington, 1925). More details on the anatomy and physiology of the lower urinary tract can be found in de Groat (1993) and de Groat et al. (2001).

After spinal cord injury, supraspinal coordination from the pontine micturition center is lost leading to lower urinary tract dysfunction. Sacral spinal cord or cauda equina lesions

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generally lead to an areflexive bladder and sphincter paralysis. Suprasacral lesions however, spare sacral spinal reflexes, and after a period of shock, reflexive bladder contractions often occur at low bladder volumes. This condition, called detrusor hyperreflexia or neurogenic detrusor overactivity (reviewed in Yoshimura, 1999), is often accompanied by reflexive co-contractions of the external urethral sphincter. This combination, termed detrusor-sphincter dyssynergia (Andersen and Bradley, 1976; Blaivas et al., 1981) leads to incontinence, inefficient voiding with high residual volumes and high intravesical pressures which in turn leads to ureteric reflux and upper urinary tract deterioration.

Why devices?

Any treatment for lower urinary tract dysfunction after spinal cord injury should create a bladder capable of storing large volumes of urine at low pressure, prevent incontinent episodes, and allow periodic evacuation of urine at low pressure. Surgical treatments, such as bladder augmentation using a section of intestine, ameliorate the problem of hyperreflexia and low storage volume (Hollander and Diokno, 1993), while sphincterotomies (cutting into the external urethral sphincter) improve detrusor-sphincter dyssynergia (Reynard et al., 2003). Anticholinergic medications are frequently used to relax the hyperreflexive bladder but have undesirable side effects including a dry mouth and blurred vision (Wein, 1998). These treatments address the symptoms of the neurogenic bladder so that storage and evacuation of urine is achieved without upper urinary tract damage, but they do not address the fundamental loss of control associated with spinal cord injury.

Devices present attractive alternatives to the management of lower urinary tract dysfunction after spinal cord injury as they attempt at least partly to restore the control of the neurogenic bladder. Additionally, while devices are locally invasive to varying degrees, they do not generally cause systemic complications as do pharmacological treatments. Surgical procedures such as the ones described above are usually irreversible and subsequently limit patients to a specified course of treatment while possibly excluding new techniques. The devices described in this review, and those under development do not cause irreversible changes and therefore do not prevent patients from taking advantage of improved treatments in the future.

Many review articles have been published that focus on devices for bladder control (Schmidt, 1983; Talalla et al., 1987; Lee, 1997; Rijkhoff et al., 1997b; Grill et al., 2001; Groen and Bosch, 2001; Jamil, 2001; Jezernik et al., 2002; Van Kerrebroeck, 2002; Middleton and Keast, 2004; Rijkhoff, 2004b; van Balken et al., 2004), so no attempt will be made to provide detailed descriptions of each of these methods here. Rather, we will summarize the methods that have been devised over the years for device-based management of the neurogenic bladder secondary to spinal cord injury and summarize current research on those devices and methods that are likely to affect the field in the future. Additionally, we will attempt to identify the reasons that many methods and devices have ultimately been unsuccessful, sometimes in spite of good clinical results. Finally, we will summarize the problems that we feel should be addressed to improve the effectiveness and adoption of devices in the management of the neurogenic bladder. Both mechanical and electrical devices will be described as they have met with different levels of success and failure and have the potential to offer solutions to a variety of the problems faced by people with spinal cord injury.

Mechanical devices for control of the lower urinary tract

Catheters

The use of catheters to manage urinary retention dates back to ancient Egypt (reviewed in Nacey and Delahunt, 1993). During World War I, up to 80% of patients with spinal cord injury died shortly after injury due of complications arising from the neurogenic bladder (Kennedy, 1946). However, improved management of the lower urinary tract using catheters during World War II (Kennedy, 1946) and especially Guttmann's technique of sterile intermittent catheterization (Guttmann and Frankel, 1966) helped reduce this figure significantly. Sterile intermittent catheterization was eventually modified to non-sterile clean intermittent catheterization for reasons of practicality (Comarr, 1972; Lapides et al., 1972), and this technique, along with generally improved medical care, has caused urinary tract dysfunction to fall from the primary cause of death (22%) for patients injured between 1943-1972 to the fourth most common cause of death (9%) for patients injured between 1973-1990 (Frankel et al., 1998).

Chronically indwelling urethral and suprapubic catheters, condom catheters and clean intermittent catheterization are common forms of catheterization currently used in the management of spinal cord injury patients. Each method has its own advantages and disadvantages (reviewed in Selzman and Hampel, 1993), but clean intermittent catheterization is the form of bladder management least likely to lead to complications (Weld and Dmochowski, 2000). Clean intermittent catheterization is generally the most prescribed form of bladder management at hospital discharge (Cardenas et al., 1995), and although a number of reports suggest that there is a trend for some patients to switch to other methods (Cardenas et al., 1995; Weld and Dmochowski, 2000), a more recent study suggests that this trend may be reversing (Hansen et al., 2004). However, only 30% of patients using clean intermittent catheterization remain free of urinary tract infections. Clean intermittent catheterization requires good hand function, preventing people with tetraplegia with impaired hand function and some people with paraplegia

from performing this procedure themselves (Selzman and Hampel, 1993; Dahlberg et al., 2004).

The critical role of catheter technology and techniques in the management of lower urinary tract dysfunction after spinal cord injury cannot be overstated. The simplicity and clinical efficacy of catheters in increasing life expectancy in patients make them arguably the single most important device for patients with spinal cord injury. However, the high incidence of urinary tract infections and other complications associated with catheter use presents a continuous burden on patients and the medical system. This, and patient desire for improved methods (Anderson, 2004), is a motivation for new device development.

Artificial sphincters

The concept of an artificial urethral sphincter was first proposed by Foley (1947) to treat urinary incontinence. The artificial urethral sphincter developed by Scott, Bradley and Timm (Scott et al., 1974; Timm et al., 1974) has developed into the commercially available AMS 800 artificial sphincter (American Medical Systems, Minnetonka, MN, USA) (reviewed in Hajivassiliou, 1998). The AMS 800 uses a pump to deflate a cuff placed around the bladder neck or urethra by transferring fluid to a pressure-regulated reservoir. The cuff re-inflates automatically over a period of several minutes. Of reported studies using the AMS 800 including 2606 patients, 73% achieved full continence, 14% experienced device failure, 4.5% experienced infections and 11.7% experienced urethral erosion from excessive pressure placed on the urethra by the cuff (Hajivassiliou, 1998). Artificial urethral sphincters are primarily used to treat patients with post-prostatectomy incontinence, but they can be successful in managing incontinence with other etiologies as well (Petrou et al., 2000). It was originally suggested that detrusor hyperreflexia was a contraindication for artificial urethral sphincter implantation as high intravesicular pressures may cause deflation of the pressure-regulated cuff (Scott et al., 1974). However, artificial urethral sphincters have been implanted in spinal cord injury patients with an overall success rate of 70% (Light and Scott, 1983), though device removal due to infections was high (24%). Currently, artificial urethral sphincters are not commonly used to manage incontinence after spinal cord injury, but they can be useful in patients with lesions leading to a flaccid bladder and sphincter.

Urethral stents

Urethral stents were first developed to treat urethral strictures, but shortly after, their use in spinal cord injury patients with detrusor-sphincter dyssynergia leading to hydronephrosis and vesicoureteric reflux was described (Shaw et al., 1990). Urethral stents were proposed as an alternative to sphincterotomies, the primary surgical treatment for patients with detrusor-sphincter dyssynergia. Sphincterotomies are generally irreversible and can cause

hemorrhage, erectile dysfunction, bladder neck stenosis or stricture (reviewed in Reynard et al., 2003). Urethral stents are inserted into the urethra and mechanically hold the external urethral sphincter open. After sphincterotomy, or implantation of a urethral stent, most patients must wear a collection device such as a condom catheter as the continence mechanism of the urethra is defeated.

Several different urethral stent designs have been tested in various trials including the UroLume® (American Medical Systems, Minnetonka, MN, USA) (Chancellor et al., 1999b), Memokath® (Doctors & Engineers A/S Ltd., Kvistgaard, Denmark) (Low and McRae, 1998; Hamid et al., 2003), Memotherm® (Bard Corp., Covington, GA, USA) (Juan Garcia et al., 1999) and Ultraflex® (Boston Scientific Corp., Natick, MA, USA) (Chartier-Kastler et al., 2000). The UroLume, Memotherm and Ultraflex are flexible wire mesh tubes while the Memokath is a helically wound wire. The devices are inserted into the urethra and positioned in the region of the external urethral sphincter where the wire becomes largely covered by urothelium over time. The UroLume is the most well studied of these devices and has similar results in terms of urodynamic parameters and incidence of urinary tract infection to sphincterotomies, but requires less hospitalization and is potentially reversible (Chancellor et al., 1999a). A 5-year multi-center trial of the UroLume in 160 patients showed that the treatment was successful in 84%, while 15% required explantation. Complications such as device migration were most common in the first 3 months (Chancellor et al., 1999b). Although explantation of the stent was possible, it has presented a variety of challenges (Chancellor et al., 1999b; Wilson et al., 2002). The Memokath has been found to be suitable for short-term implantation as most devices fail within two years (Hamid et al., 2003) and complications including migration, autonomic dysreflexia and stone formation on the stent can occur (Low and McRae, 1998). However, explantation of this device is much simpler than the UroLume due to its helical design and thermosensitive material which, when cooled with saline, becomes soft and uncoils, making this device useful for acute management of detrusor-sphincter dyssynergia (Hamid et al., 2003).

Urethral stents represent a clinically successful device for management of detrusor-sphincter dyssynergia in spinal cord injury patients. Although stents do not restore normal control of the sphincter, their efficacy, simplicity and potential reversibility makes them an attractive option for patients who would otherwise receive an irreversible sphincterotomy (Chancellor et al., 1999b).

Intraurethral pump

In 1997, Nativ et al. (1997) described a device incorporating a miniature valve and pump that could be inserted into the urethra to control both continence and voiding in women. The In-Flow™ intraurethral pump (SRS Medical Systems, Inc., Billerica, MA, USA) is designed to manage chronic

urinary retention caused by an atonic bladder or urethral dysfunction. The device secures itself in the urethra by means of flexible fins that open in the bladder and a flange at the external urethral meatus (see Figure 1). The device is controlled by a remote activator that is placed over the pubic area and is magnetically coupled to the pump. Once activated, the turbine actively pumps urine out of the bladder at a rate of 6-12 ml/s until the bladder is empty. The device is easily inserted by a physician and can be removed by the patients if they wish. The device is designed to be replaced every month, but successful usage to an average of 90 days has been reported, at which time the device can become fouled by salt deposits (Madjar et al., 1999).

In a study of 18 women with spinal cord injury and hyporeflexive bladders, only 6 continued to use the device at follow-up (mean 9.6 months) (Schurch et al., 1999). Discomfort, incontinence, urinary tract infections, technical
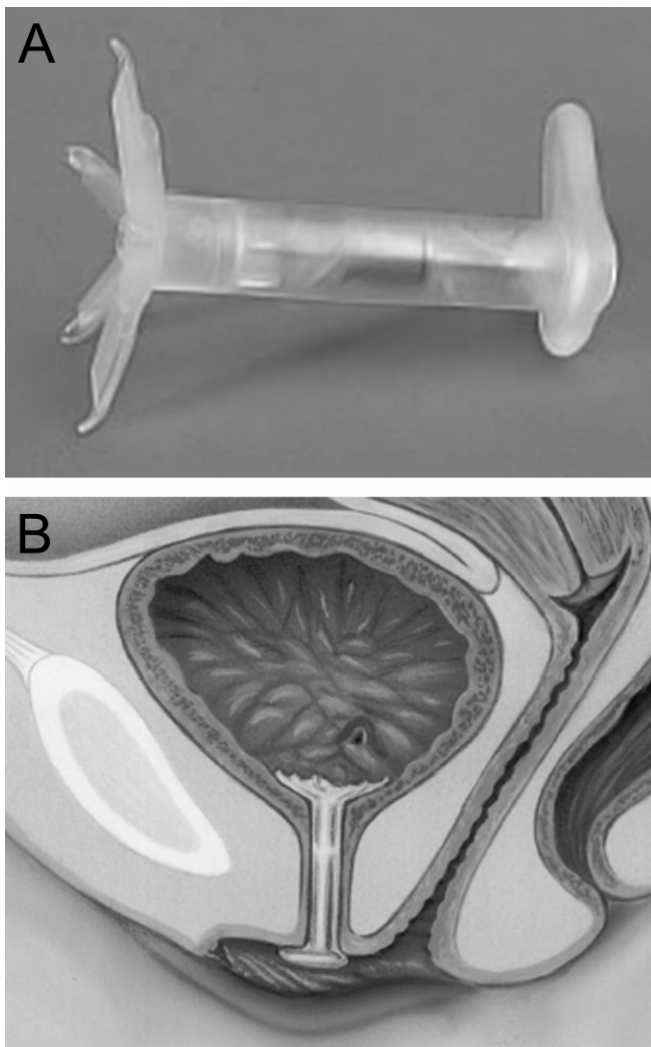

Fig. 1. The In-Flow™ intraurethral pump. (A) Photograph showing the unfolded petals that secure the device in the urethral and prevent migration. (B) Diagram showing the placement of the device in the urethra. Adapted from (Madjar et al., 1999; Schurch et al., 1999).

failures, urethral dilation and the possibility of long term urethral damage were cited as reasons why this device was unsuitable for chronic use. Studies in 60 (Mazouni et al., 2004) and 92 (Madjar et al., 1999) patients with voiding dysfunction from various etiologies reported success rates of 50% with average follow-up times of 3 and 7.6 months respectively. Most of those patients that adopted this device for long term usage were previously dependent on clean intermittent catheterization and preferred the convenience of this device. Intraurethral pumps are very interesting from a technical viewpoint and further investigation with clearer indications for use, such as complete spinal cord injury, atonic bladder and previous dependence on clean intermittent catheterization may improve the success rate among spinal cord injury patients.

Electrical stimulation devices for control of the lower urinary tract

While mechanical devices are necessarily limited to treating symptoms of the neurogenic bladder, electrical stimulation techniques allow devices to be created that can exert control over spared muscles and their neural control systems. Electrical current, passed between two electrodes, can be used to generate action potentials in surviving neurons in the spinal cord or peripheral nerve below the lesion in spinal cord injury patients. These artificially generated action potentials can lead directly to muscular contraction or they can modulate the activity of neuronal networks and reflex pathways (termed neuromodulation).

The discussion below of devices and techniques that have been developed to control the lower urinary tract is organized by the location of stimulation electrodes rather than by the neurophysiological mechanisms on which the devices operate or by their intended function. Five primary locations can be identified where electrical stimulation electrodes can be placed: on or in the bladder, on the skin, peripheral nerve, sacral roots, and in the spinal cord itself. Figure 2 shows the various stimulation locations for devices discussed throughout this review.

Electrical stimulation of the bladder

Intravesical stimulation

Intravesical electrical stimulation (IVES) was the first attempt at treating bladder dysfunction using electrical stimulation. In 1878, M.H. Saxtorph described a technique in which stimulation between a catheter-mounted electrode, passed into the bladder to act as the cathode (see Figure 2A), and a suprapubically placed indifferent electrode, were used to treat urinary retention caused by an underactive bladder (reviewed in Madersbacher, 1990). IVES is essentially a neuromodulation therapy intended to reinforce the weak functioning of existing neural micturition pathways by stimulating mechanoreceptors in the bladder wall to facilitate reflex bladder contractions and improved sensation.
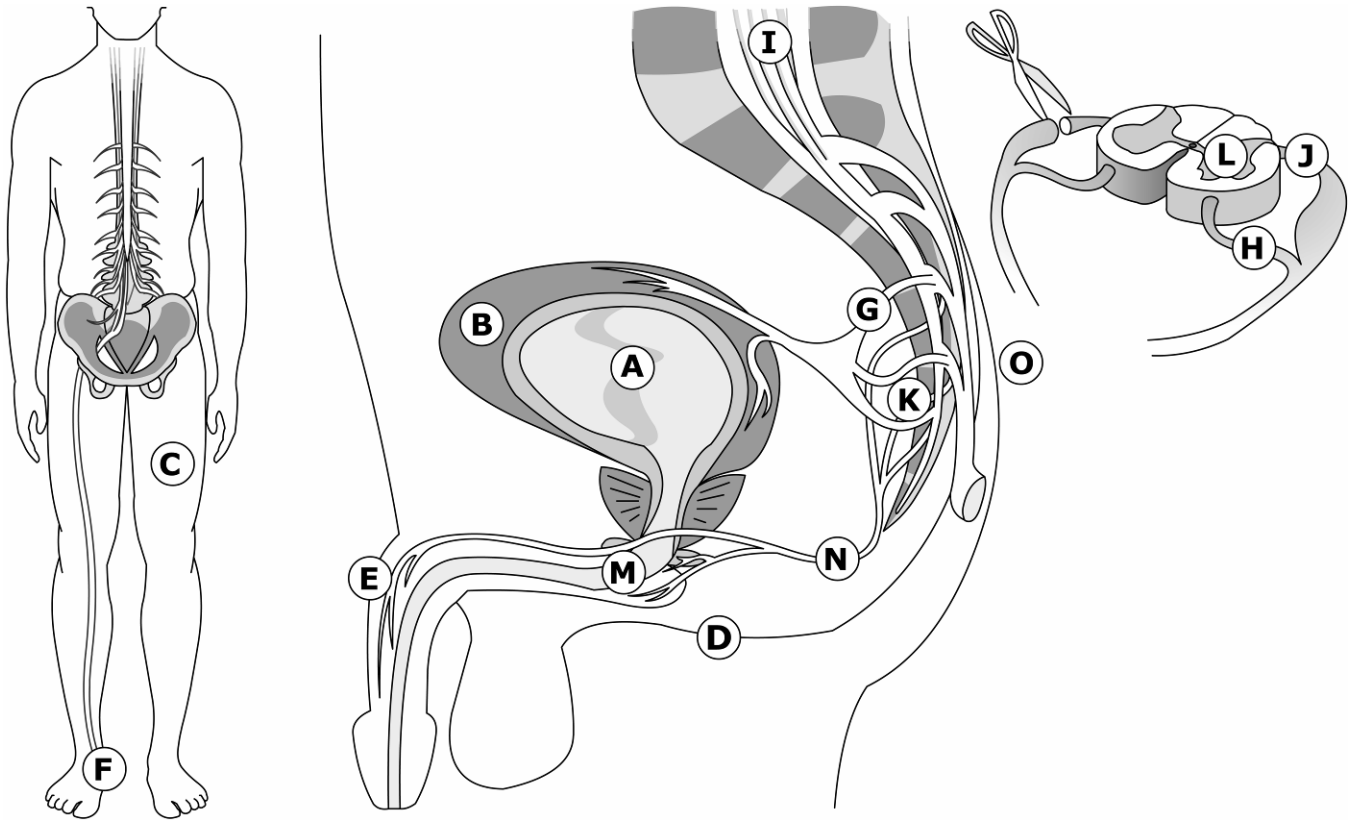
Fig. 2. Electrode locations for controlling the lower urinary tract. The locations are numbered primarily by the order in which they are discussed in the text. The location for a posterior rhizotomy is also indicated. (A) Intravesical, (B) Bladder wall, (C) Thigh, (D) Pelvic floor, (E) Dorsal penile nerve, (F) Tibial nerve, (G) Pelvic nerve, (H) Intradural sacral anterior root, (I) Extradural mixed sacral root, (J) Intradural sacral posterior root, (K) Sacral nerve, (L) Spinal cord, (M) Intraurethral, (N) Pudendal nerve, (O) Sacrum.

Electrical stimulation is below the threshold required to elicit bladder contractions directly via stimulation of the efferent portion of the pelvic nerve or of the detrusor myocytes themselves. Acute studies in rats and cats have confirmed the hypothesis that IVES acts by stimulating stretch-sensitive mechanoreceptors in the wall of the bladder that reflexively cause contractions of the bladder (Ebner et al., 1992).

Few reports of IVES studies in spinal cord injury patients exist, but one dealing specifically with incomplete spinal cord injury patients reported improvements in bladder sensation, detrusor contraction and residual volumes in almost all patients (Madersbacher et al., 1982). A retrospective study on the effectiveness of IVES for patients with spinal cord injury by the same author indicated that one third of the patients experienced improvements in sensation, detrusor contractility and voluntary control. This occurred only in patients with preserved pain sensation in the S2-S4 dermatomes (Madersbacher, 1990). This would seem to be the only predictor of the efficacy of this therapy. Additionally, patients require many hours of treatment before the effectiveness of IVES can begin to be evaluated and the positive results reported by some investigators (Kaplan, 2000) have not been repeatable by others (Decter,

2000). While IVES has been used to treat patients with spinal cord injury, recent studies have focused on children with underactive bladders (Gladh et al., 2003). IVES appears ultimately unattractive as a clinical technique to improve micturition in spinal cord injury patients as it only seems to work in some patients with incomplete spinal cord injury, requires long treatments before effectiveness can be evaluated and has not been repeatable amongst investigators.

Bladder wall stimulation

Electrical stimulation of the exterior surface of the bladder (see Figure 2B) was first studied in the early 1950's (Boyce et al., 1964). This marked the beginning of the development of electrical stimulation devices to elicit voiding directly, in response to the high morbidity and mortality associated with catheterization (Bradley et al., 1962). Several groups developed implanted stimulators inductively coupled to external transmitters with variations in the design, placement and number of electrodes (Bradley et al., 1962; Hald et al., 1967; Stenberg et al., 1967; Susset and Boctor, 1967; Merrill and Conway, 1974; Magasi and Simon, 1986). Initial animal experiments demonstrated that spinalized dogs were able to void regularly using the implanted stimulators without requiring additional procedures (Bradley et al., 1962; Bradley et al., 1963; Kantrowitz and Schamaun,

1963). However, results in spinal cord injury patients implanted with these stimulators were much less successful (Bradley et al., 1963; Hald et al., 1967; Stenberg et al., 1967; Susset and Boctor, 1967; Merrill and Conway, 1974). The primary reason that patients were unable to void was that stimulation currents high enough to generate useful bladder contractions spread to surrounding structures causing co-activation of the external urethral sphincter and pelvic floor musculature. It was noted that the canine bladder is primarily an abdominal organ, whereas the human bladder is
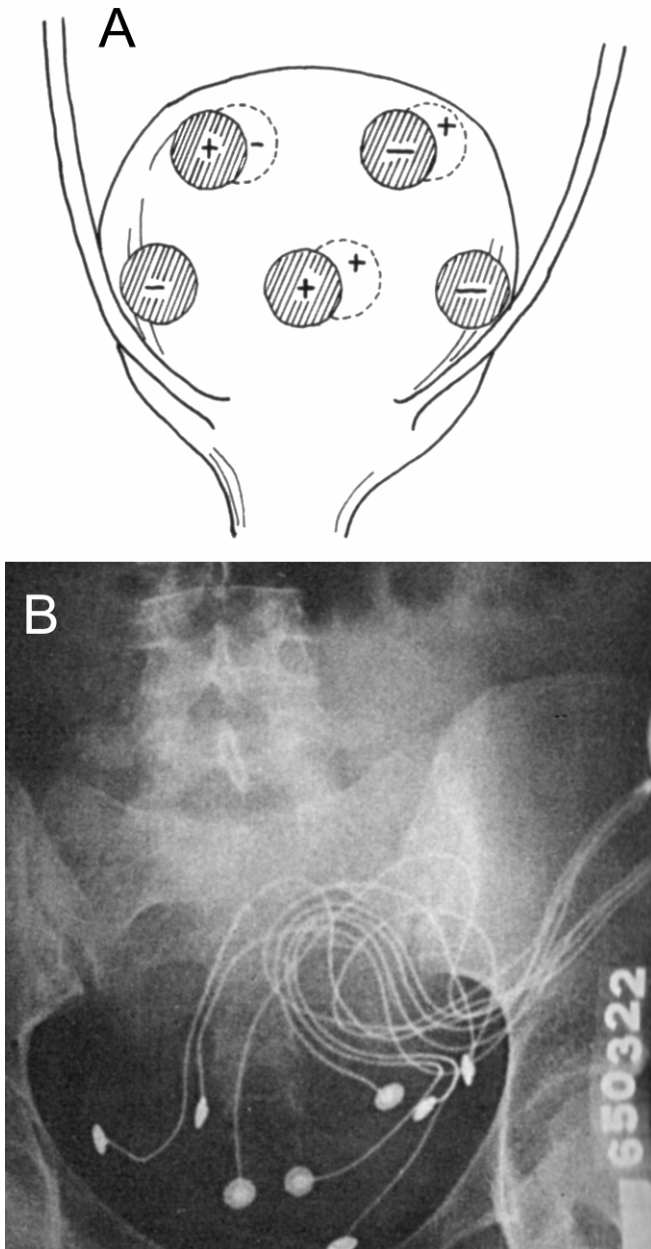

Fig. 3. The bladder wall stimulator used by Magasi and Simon (1986). (A) The intended positioning of electrodes on the bladder. (B) Stimulator implanted in a patient. The patient had just used her stimulator to empty her bladder. Adapted from (Magasi and Simon, 1986).

a pelvic organ and is in close proximity to the pelvic floor musculature, increasing its susceptibility to contraction by current spread (Bradley et al., 1963).

Because of this problem, experimental and clinical work was the directed towards obtaining sufficient contraction of the bladder while limiting current spread. Tape electrodes and more powerful stimulators successfully elicited micturition, but infection and technical failures prevented evaluation of their long-term effect (Bradley et al., 1963). Experience with the Avco stimulator, in which individual wires were embedded into the bladder wall, were also hampered by activation of urethral and pelvic floor musculature (Hald et al., 1967; Stenberg et al., 1967). Another stimulator design, the Mentor bladder stimulator, used two helical wire electrodes sewn into the bladder wall. This was successful in two of five patients with upper motor neuron lesions, but required subarachnoid injections of phenol to abolish electrically-induced detrusor-sphincter dyssynergia which otherwise prevented micturition (Merrill and Conway, 1974). Susset and Boctor (1967) reported a successful implant that incorporated 8 disc electrodes around the dome of the bladder in a patient with a complete lower motoneuron lesion. These investigators considered upper motoneuron lesions to be a contraindication for implantation of these systems due to the unwanted activation of sphincter and pelvic floor muscles. The most successful report of bladder wall stimulation was made by Magasi and Simon (1986) in which 29 of 32 patients with neurogenic bladder paralysis attained complete voiding with 8 disc electrodes implanted around the bladder (see Figure 3). However, the concomitant sphincter activation reported by most investigators, lead and electrode breakage, receiver malfunction, bladder perforation and pain caused failure in most human studies. With the success of sacral root stimulation (see below) for restoring micturition in patients with upper motor neuron lesions, and the multiple difficulties in achieving successful clinical results with bladder wall stimulation, recent work in this area has focused on patients with lower motoneuron lesions who cannot benefit from sacral root stimulation (Walter et al., 1999).

Transcutaneous electrical stimulation

Thigh stimulation

In 1986 it was reported that electrical stimulation through surface electrodes over the thigh muscles (see Figure 2C) could cause changes in the urodynamic parameters of spinal cord injury patients (Wheeler et al., 1986). Stimulation was applied through bilateral quadriceps surface electrodes on a daily basis for 4-8 weeks. Some patients exhibited persistent increases in bladder capacity and/or reductions in bladder pressure, while others experienced the opposite result. Another study, examining hamstring and quadriceps stimulation to reduce spasticity in spinal cord injury patients, noted that 16 of 32 patients became continent (Shindo and

Jones, 1987) perhaps indicating a suppression of detrusor hyperreflexia. A more recent study examining urodynamic changes in response to thigh muscle stimulation showed that 8 of 14 patients, including a single subject with spinal cord injury with neurogenic detrusor overactivity, increased their bladder volumes by >50% (Okada et al., 1998). However, no methods of identifying those patients likely to respond positively to treatment exist. None of these studies noted any adverse side effects from the treatment.

The effects of electrical stimulation of the thigh muscles on the bladder may be mediated by limb afferents known to inhibit bladder contractions to prevent leakage during physical activity (Fall and Lindstrom, 1991), although other mechanisms have been proposed (Okada et al., 1998). Carry-over, observed with thigh stimulation, has also been observed with other electrical stimulation techniques (Fall and Lindstrom, 1991), and may be at least partially explained by mechanisms such as those proposed by Vodovnik (1981). Despite the simplicity of this approach, efficacy in some patients and lack of adverse side effects, few studies of stimulation of the thigh muscles have been reported, and this technique does not appear to be widely used in practice. This is likely because many patients show no improvement, and those that may cannot be identified prior to treatment. Additionally, treatment requires a significant time investment and most patients can achieve effective suppression of hyperreflexive bladder contractions with anticholinergic medications.

Pelvic floor maximal functional electrical stimulation

On the basis of a previous observation, Moore and Schofield (1967) decided to test the effectiveness of electrically induced maximal contraction of the pelvic floor musculature (see Figure 2D) to treat female patients with stress incontinence. Some patients reported being cured after a single session and more reported a reduction in symptoms. Maximal functional electrical stimulation (MFES) may involve the use of surface, vaginal, anal, penile, percutaneous or a combination of such electrodes to stimulate the pelvic floor musculature and pudendal nerve at the maximum tolerable threshold for patients. This treatment can lead to long-lasting bladder inhibition in patients with non-neurogenic bladder overactivity (Fall and Lindstrom, 1991). While MFES is used in some clinical settings for treating incontinence in many patient groups (Geirsson and Fall, 1997), results in patients with spinal cord injury for suppressing hyperreflexive bladder contractions are mixed (reviewed in Previnaire et al., 1998). Given the side effects of MFES, including physical discomfort in incomplete spinal cord injury patients, possibly limiting the stimulation current to non-therapeutic levels (Previnaire et al., 1998), as well as psychological discomfort (van Balken et al., 2004), anticholinergic medications are often a more practical method to manage neurogenic detrusor overactivity.

Dorsal penile nerve stimulation

Stimulation of the dorsal penile nerve or clitoral nerve can inhibit detrusor activity. They form the most superficial branch of the pudendal nerve, and are therefore easily accessible. Detrusor inhibition by this means was first demonstrated scientifically using mechanical stimulation (penile squeeze) to suppress ongoing bladder contractions (Kondo et al., 1982). It has also been demonstrated using electrical stimulation with bipolar surface electrodes placed on the penis (Nakamura and Sakurai, 1984) (see Figure 2E). Given the success of this simple technique in inhibiting bladder contractions, its potential in treating subjects with detrusor hyperreflexia secondary to spinal cord injury has been examined by several groups. In one study of 6 spinal cord injury subjects with complete and incomplete cervical and thoracic lesions, inhibition of detrusor contractions during bladder filling was demonstrated in all subjects (Wheeler et al., 1992). Continuous stimulation at 5 pulses per second was sufficient to increase the volume at which reflexive bladder contractions first occurred during a cystometrogram by an average of 76% (range 26% to 150%) without side effects. Continuous stimulation of the genital nerves, however, may pose practical challenges for the design of a neuroprosthesis and would preclude measurement of bladder activity using peripheral nerve recording techniques (Jezernik et al., 2000). Kirkham et al. (2001) and Dalmose et al. (2003) therefore examined whether conditional stimulation of the dorsal penile nerve is sufficient to effect clinically useful inhibition of the detrusor. Stimulation lasting one minute was initiated by a rise in bladder pressure of 10 cmH$_2$0 during a cystometrogram and successfully inhibited bladder contractions while increasing bladder capacity by 144% (±127%) in all six spinal cord injury subjects studied (Kirkham et al., 2001). The effects of conditional stimulation on detrusor inhibition are robust amongst both male (Kirkham et al., 2001; Dalmose et al., 2003) and female (Dalmose et al., 2003) patients with a wide range of injury levels. In addition to inhibiting hyperreflexive bladder contractions, dorsal penile nerve stimulation can reduce blood pressure in spinal cord injury patients with high level injuries (Lee et al., 2003) which may reduce the risks associated with autonomic dysreflexia which is often triggered by a full bladder or bowel.
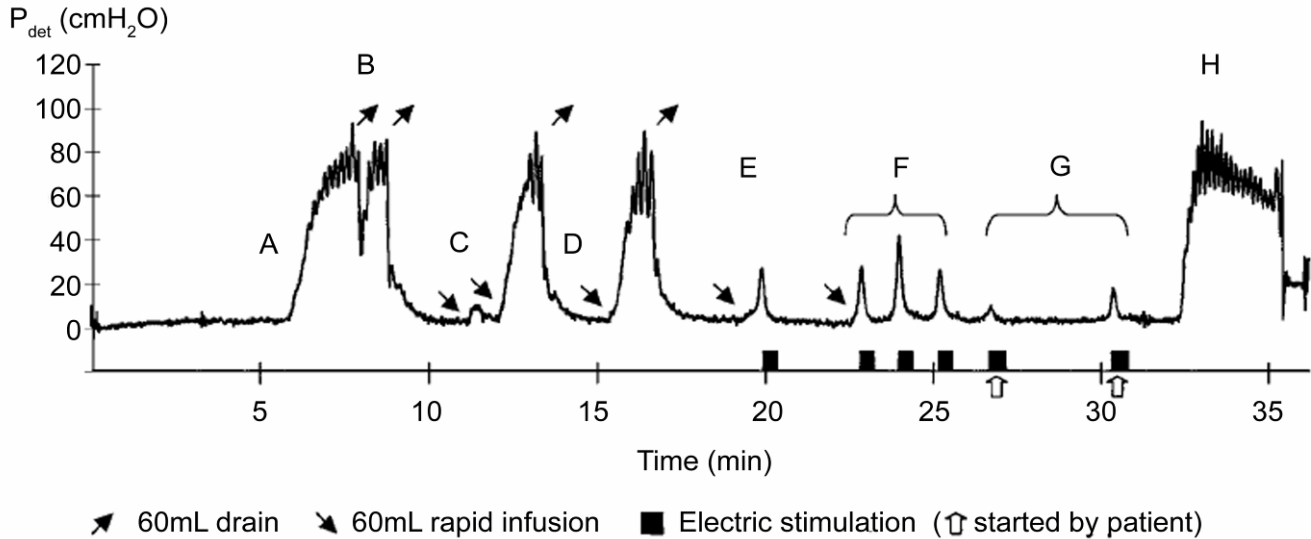
Fig. 4. Bladder pressure recording with and without stimulation during provocation of the bladder with rapid infusions of saline. Reproducible reflexive bladder contractions were caused by rapid infusions of 60 ml of saline (C and D) and were abolished by withdrawal of the saline. Further provocations (E and F) resulted in small reflexive bladder contractions that were immediately abolished by stimulation of the dorsal penile nerve. During F and G, bladder pressure increases are hyperreflexive contractions caused by the high volume. The two stimulation periods shown by open arrows at the onset of termination of G indicate patient-initiated stimulation in response to sensation of bladder fullness. These suppressions of reflexive bladder contractions were better than the previous ones. Without stimulation, bladder contractions are not suppressed (H). (Lee and Creasey, 2002).

Dorsal penile nerve stimulation is an active area of neuroprosthesis development due to the relative simplicity of the technique and its reliability and efficacy in patients with spinal cord injury. Two recent reports describe attempts at moving dorsal penile nerve stimulation from the laboratory to clinical use. Lee and Creasey (2002) describe the application of a surface stimulation system to an incomplete C6 patient who experienced episodes of incontinence after sensing his full bladder, but before he was able to catheterize himself. Figure 4 shows the effect that conditional dorsal penile nerve stimulation had on bladder contractions in this subject. During home use for 3 weeks, this patient applied stimulation when he sensed his bladder was full allowing him time to perform successful catheterization. He continued to use the system after the trial was over because of its success and his confidence in it. Additionally, Fjorback et al. (2003) developed a portable device that measured bladder pressure and automatically stimulated the dorsal penile nerve to inhibit bladder contractions. This device used a catheter to measure bladder pressure, and as such was impractical clinically, but did serve to demonstrate the feasibility of a closed-loop system to treat neurogenic detrusor overactivity.

Stimulation of peripheral nerve

Tibial nerve stimulation

In 1983, a report of investigations on nonhuman primates demonstrated that the amount of current required to cause detrusor inhibition with bipolar percutaneous anal sphincter stimulation could be reduced by changing the cathode to a surface electrode positioned over the posterior tibial nerve (McGuire et al., 1983). In the same study, similar results were observed with percutaneous tibial nerve stimulation alone (see Figure 2F). This target was chosen as it is the acupuncture point used to inhibit bladder contractions in Chinese medicine. This technique was successful in improving continence in 19 of 22 patients, including 4 with spinal cord injury, although bladder contractions returned immediately once stimulation ceased.

More recent work with tibial nerve stimulation includes evaluation of the commercially available Urgent PC device (CystoMedix, Andover, MN, USA), formerly the Urosurge SANS device given FDA approval in 2000 (Govier et al., 2001; van Balken et al., 2001; Vandoninck et al., 2003). Encouraging results were reported in patients with overactive bladders although no spinal cord injury patients were included in these studies. Two small-scale studies evaluating tibial nerve stimulation in patients with spinal cord injury also reported reductions in incontinence caused by neurogenic detrusor overactivity, although the results in the subset of patients with spinal cord injury are not stated in one study (Amarenco et al., 2003) and the other is a report from a single patient (Andrews and Reynard, 2003). Given the technical simplicity of this technique and its potential to suppress neurogenic detrusor overactivity, further experiments to determine efficacy in larger groups of spinal cord injury subjects would help determine if this technique should be pursued.

Pelvic nerve stimulation

Stimulation of the nerve supply to the bladder presents some potential advantages over bladder wall stimulation in spinal

cord injury patients. Stimulation of the pelvic nerve (see Figure 2G), which contains the preganglionic parasympathetic fibers innervating the detrusor, should cause contraction of the entire detrusor at a much lower current than bladder wall stimulation (Hald, 1969). Pelvic nerve stimulation was shown to elicit bladder contractions in dogs, but co-activation of the sphincters prevented good micturition, especially in male dogs (Holmquist and Olin, 1968a; Holmquist and Olin, 1968b). Sphincter activation was likely a reflex caused by stimulation of bladder afferents in the pelvic nerve. In addition, chronic stimulation was found to cause fibrosis of the pelvic nerve leading to reductions in bladder response over time (Hald, 1969). Application in humans was also frustrated because of the structure of the pelvic nerve. While a distinct pelvic nerve exists in the cat and dog, parasympathetic innervation of the human bladder is distributed from the pelvic plexus arising from the pelvic nerves shortly after their exit from the sacral foramina (Wozniak and Skowronska, 1967), making placement of electrodes very difficult (Susset and Boctor, 1967; Hald, 1969). Despite this, brief reports describing mixed results with pelvic nerve stimulation in humans appeared in the 1970's (Burghele, 1973; Kaeckenbeeck, 1979 cited in Rijkhoff et al., 1997b), but no further reports exist to our knowledge.

Stimulation of sacral roots and nerves

Sacral root stimulation

The first electrical stimulation technique to develop into a commercially available device for bladder emptying in spinal cord injured patients began with the work of Brindley (1977) as well as that of Tanagho and Schmidt's group (Heine et al., 1977; Schmidt et al., 1979). These investigators reported positive results using a sacral anterior root stimulator (SARS) to elicit voiding in spinalized animals. This was followed by successful outcomes in humans with spinal cord injury (Brindley et al., 1982; Tanagho et al., 1989). Brindley's device was commercialized as the Finetech-Brindley Bladder System (Finetech Medical Ltd., Welwyn Garden City, UK) and has been implanted in over 2,500 people, in some cases for over 20 years (Rijkhoff, 2004b). This system has been described and reviewed in detail in a number of articles, so only a summary of the device will be presented here (Brindley, 1977; Brindley et al., 1982; Brindley et al., 1986; Creasey, 1993; Egon et al., 1998).

The two prerequisites for implantation of SARS devices are intact parasympathetic preganglionic neurons and a detrusor that is able to contract (Creasey, 1993). Electrodes can either be implanted intradurally (see Figure 2H) on the S2-S4 anterior roots (Brindley et al., 1982) or extradurally (see Figure 2I) on the mixed sacral roots within the spinal canal (Sauerwein et al., 1990; Lee, 1997). In either case, the procedure is usually combined with sacral posterior rhizotomy to abolish hyperreflexive bladder and sphincter

contractions, autonomic dysreflexia triggered by bladder fullness and pain in patients with incomplete lesions (Creasey, 1993; Brindley, 1994). After electrode placement, leads are tunneled subcutaneously to an implantable receiver, activated by an external controller through a radiofrequency link (Brindley et al., 1982). Figure 5 shows the components of this system. After implantation and posterior rhizotomy, the majority of patients are continent, have increased bladder capacity, are able to void using their stimulator with residual volumes <30 ml and are freed from catheter usage leading to a great reduction in urinary tract
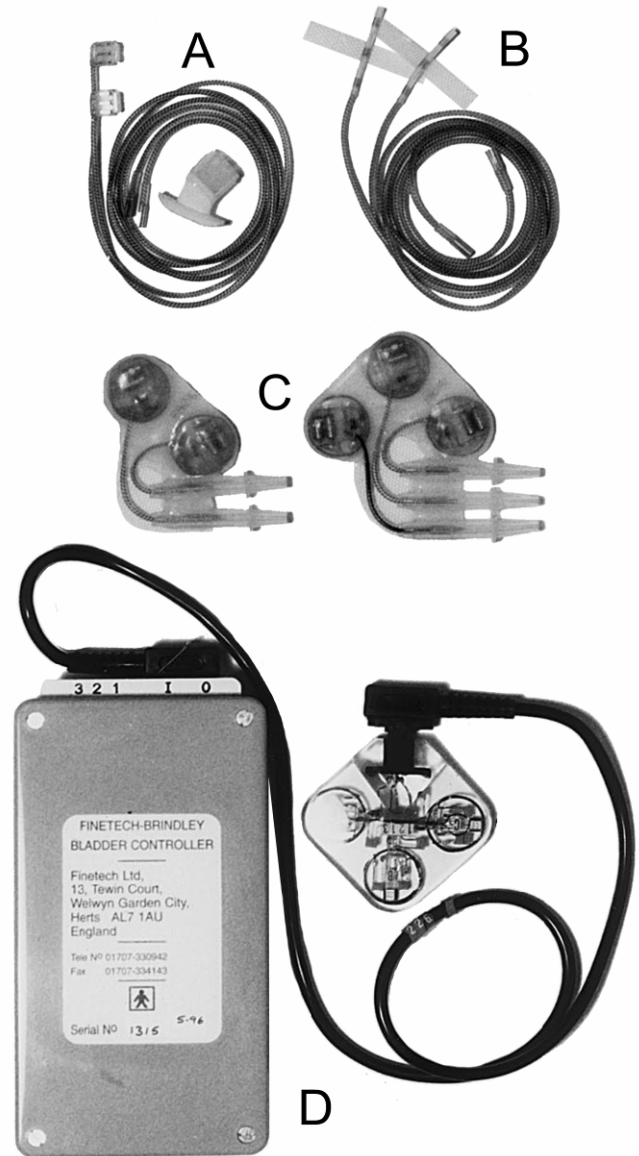

Fig. 5. The components of the Finetech-Brindley sacral anterior root stimulator. (A) Intradural electrodes and leads. (B) Extradural electrodes and leads. (C) 2 and 3 channel implantable receiver blocks. These components are implant subcutaneously and connect to the electrode leads. (D) The external components of the device including the stimulator and transmission block that is placed on the skin over the receiver block. Adapted from (Egon et al., 1998).

infections (Van Kerrebroeck et al., 1993). Additionally, patients have reported beneficial stimulator-driven erections and defecation (Brindley et al., 1986; Van Kerrebroeck et al., 1993; Egon et al., 1998).

One limitation of this device is that electrical stimulation of the sacral roots, in addition to producing sustained increases in bladder pressure, activates the external urethral sphincter due to the presence of both small parasympathetic preganglionic fibers and large somatic fibers in the sacral anterior roots (Brindley, 1977). Since large fibers have lower thresholds of electrical stimulation, excitation of the parasympathetic preganglionic fibers is accompanied by excitation of the somatic fibers, leading to external urethral sphincter contraction and urethral occlusion. The Finetech-Brindley SARS circumvents this problem by utilizing the difference in the relaxation time of the detrusor and the sphincter (Brindley et al., 1982). A train of electrical stimuli is applied for 3-9 seconds, allowing bladder pressure to rise behind the closed sphincter. Upon cessation of stimulation, the striated sphincter relaxes quickly while bladder pressure is transiently maintained allowing post-stimulus voiding (Brindley et al., 1982) (see Figure 6). Despite the supranormal bladder pressures that occur with this technique, no evidence of vesicoureteric reflux or hydronephrosis has been found (Creasey, 1993). Sacral roots also contain fibers innervating the musculature of the legs, and leg movement during stimulation can be cumbersome to some patients.

Given the proven benefits to patients and the large number of other neuroprosthetic devices implanted in patients (Rijkhoff, 2004b), one might ask why more Finetech-Brindley SARSs have not been implanted. This is likely due in part to patient unwillingness to undergo the irreversible posterior rhizotomy, which, in addition its very great benefits, abolishes reflex erection, defecation and micturition as well as any remaining perineal sensation. Implantation of this system is also technically demanding

and attempts to market the device in the United States as the Vocare™ Bladder System by NeuroControl Corp. (Cleveland, OH, USA) were ultimately unsuccessful for commercial and regulatory reasons (Hall, 2003), despite evidence that long term use could realize a reduction in costs for management of lower urinary tract dysfunction (Creasey and Dahlberg, 2001). Commercialization in the USA has recommenced through NDI Medical (Cleveland, OH, USA).

Sacral nerve neuromodulation

In the early 1980's, Tanagho and Schmidt began implanting extradural sacral root stimulators in patients (Tanagho and Schmidt, 1988; Tanagho et al., 1989). It was found that continence could be controlled by low-frequency, low-amplitude stimulation to maintain sphincter contraction without concomitant detrusor contraction (Tanagho and Schmidt, 1988). As contractions of the detrusor are inhibited by contractions of the sphincter, it was also noted that stimulation causing sphincter contraction could inhibit detrusor activity leading to improvements in continence in a range of neurogenic and non-neurogenic bladder conditions (Tanagho and Schmidt, 1988; Tanagho et al., 1989). This neuromodulatory aspect of these implants was pursued and techniques for accessing the sacral nerves though the sacral foramina were developed (Schmidt et al., 1990) making the implant procedure faster and less invasive than spinal implantation of extradural electrodes. Since this time, sacral nerve neuromodulation for treating non-neurogenic bladder dysfunction including incontinence, urgency-frequency and urinary retention have been well studied (Bosch and Groen, 2000; Siegel et al., 2000). A sacral nerve stimulator based on this work has been commercialized by Medtronic as the InterStim® (Medtronic, Minneapolis, MN, USA) and implanted in more than 10,000 people (Rijkhoff, 2004b). The InterStim consists of a battery-powered implantable stimulator connected to a single quadripolar electrode usually inserted through the S3 sacral foramen to lie next to
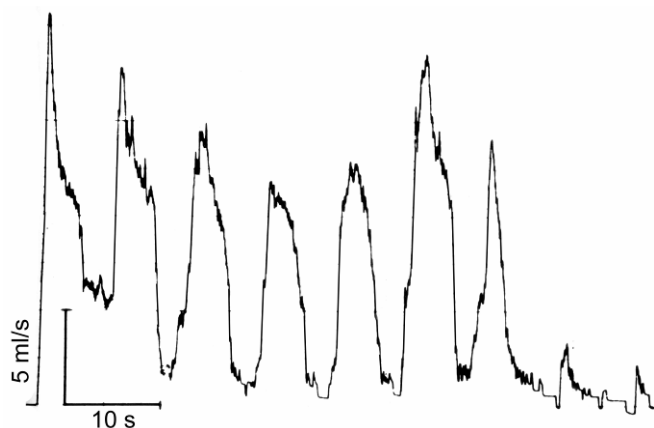

Fig. 6. Urine flow rate in a patient voiding his bladder using the post-stimulus voiding technique. During stimulation, the flow rate drops to nearly zero as contraction of the sphincter occludes the urethra. Adapted from (Brindley et al., 1982).
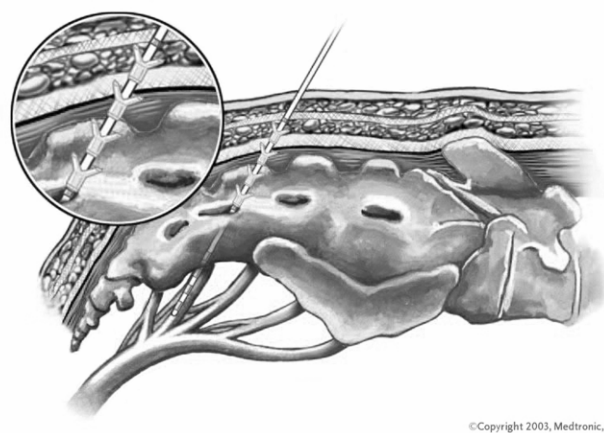

Fig. 7. Insertion of the quadripolar electrode through the S3 sacral foramen to lie next to the S3 nerve. This electrode insertion can be performed non-invasively to test the acute response of a patient to neuromodulation. Reprinted with the permission of Medtronic, Inc. © 2003.

the S3 spinal nerve (see Figure 2K and Figure 7). Sacral neuromodulation is only effective in a subset of patients with the above-mentioned bladder dysfunctions, so all patients are initially evaluated with a percutaneous electrode connected to an external stimulator to assess their response to this treatment before permanent implantation (Bosch and Groen, 2000; Siegel et al., 2000). Other reviews provide more detail about this technology and its history (Schmidt, 1988; Groen and Bosch, 2001; Jezernik et al., 2002; Van Kerrebroeck, 2002; Middleton and Keast, 2004; Rijkhoff, 2004b; van Balken et al., 2004).

With the effectiveness of sacral nerve neuromodulation, a number of investigators have examined this modality for treating neurogenic detrusor overactivity in small-scale studies of spinal cord injury patients. Improvements in incontinence and increases in maximal cystometric capacity have been demonstrated in incomplete spinal cord injury subjects (Ishigooka et al., 1998; Chartier-Kastler et al., 2001; Hohenfellner et al., 2001). However, S3 sacral nerve neuromodulation in complete spinal cord injury subjects has been generally less effective (Chartier-Kastler et al., 2001) or had no effect at all (Hohenfellner et al., 2001; Schurch et al., 2003) leading to the suggestion that intact spinobulbospinal pathways contribute to the success of sacral neuromodulation (Schurch et al., 2003). On the other hand, stimulation of the mixed S2 root extradurally using the Finetech-Brindley stimulator without posterior rhizotomy, has successfully suppressed hyperreflexive bladder contractions in complete spinal cord injury patients with neurogenic detrusor overactivity (Kirkham et al., 2002). The differing results observed using the S2 and S3 spinal nerves for neuromodulation in complete spinal cord injury subjects may indicate a fundamental difference in the neural pathways being excited in these two cases: namely that S3 neuromodulation has a larger supraspinal component than S2 neuromodulation.

These results suggest that the success of neuromodulatory techniques in spinal cord injury patients may depend on the completeness of the injury as well as the specific location of the electrodes. Given the commercial availability of the InterStim and the straightforward and well established evaluation techniques, sacral neuromodulation will likely continue to be investigated for its usefulness in treating spinal cord injury patients with neurogenic detrusor overactivity.

NeoPraxis Praxis/Minax

In 1983, a multi-channel implantable neuroprosthesis targeting sacral roots and nerves based upon existing cochlear stimulation technology from Cochlear Ltd. (Lane Cove, NSW, Australia) was proposed (reviewed in Davis et al., 2001). After successful implantation of a 22 channel system for standing (Davis et al., 1994; Davis et al., 1997) an FES 24-A stimulator (NeoPraxis Pty. Ltd., Lane Cove, NSW, Australia) that included electrodes intended to restore

bladder function was implanted in a T10 paraplegic (Davis et al., 1999). Three pairs of electrodes intended to elicit bladder contractions were inserted bilaterally through the sacral foramina targeting the S2-S4 spinal nerves. An epidural electrode, intended to suppress detrusor hyperreflexia, was implanted on the conus medullaris to obviate the need for dorsal rhizotomies (Davis et al., 2001). Increases in bladder pressure and some voiding was reported with intermittent stimulation, but little data were presented (Davis et al., 1999; Davis et al., 2001). Two additional patients were implanted with similar systems, but bladder contractions could not be elicited (Smith et al., 2002; Benda et al., 2003). However, in these patients, external urethral sphincter activity caused by low-frequency stimulation of the sacral nerves was reduced by selective high-frequency blockade of the large somatic fibers (Shaker et al., 1998; Benda et al., 2003). A conference report introduced the Minax system, a subset of the Praxis FES 24 stimulator specifically for bladder control (Houdayer et al., 2002), but no further reports have been published on either the Minax or Praxis systems and NeoPraxis as a company appears to have become inactive.

Stimulation of the spinal cord

During the late 1960's and early 1970's, experiments were performed by Nashold and Friedman in animals (Nashold et al., 1971) and humans (Nashold et al., 1972) to test the efficacy of deep stimulation of the spinal cord (see Figure 2L) to restore micturition after spinal cord injury. These experiments were conducted based on earlier studies demonstrating that electrical stimulation of the cut sacral spinal cord could elicit bladder contractions (Stewart, 1899). It was proposed that electrical stimulation of the presumed sacral micturition center (Kuru, 1965) would be capable of causing coordinated micturition after spinal cord injury. Two electrodes, forming a bipolar pair, were implanted in the intermediolateral gray matter of the sacral spinal cord (Nashold et al., 1971; Friedman et al., 1972). Optimal rostrocaudal electrode placement was determined by monitoring the change in bladder pressure during stimulation of the dorsal surface of the sacral spinal cord. The location causing the greatest increase in bladder pressure was selected as the location for implantation of the penetrating electrodes. Friedman et al. (1972) reported that 6 of 11 animals with intact spinal cords and 5 of 9 animals with transected spinal cords voided during acute experimentation. Additionally, in chronic experiments, stimulation in 5 of 6 animals with intact spinal cords and 5 of 10 animals with transected spinal cords produced voiding. In animals where voiding did not occur, bladder pressures elicited by electrical stimulation were low, possibly indicating poor electrode placement. While some reduction in pelvic floor EMG, suggesting coordinated sphincter inhibition, was occasionally noted, stimulus spread resulting in activation of the sphincter was also observed (Friedman et al., 1972). Studies conducted by another group, utilizing a variety of

electrode designs and stimulation parameters, concluded that sphincter motoneurons in the spinal cord were always stimulated with the sacral parasympathetic nucleus but that post-stimulus voiding could be used successfully to empty the bladder (Jonas et al., 1975; Jonas and Tanagho, 1975).

Based on these results, 27 patients, 17 in the USA, 9 in France and one in Sweden, were implanted with penetrating spinal cord electrodes (see Figure 8) beginning in 1970 (Nashold et al., 1981). These patients are believed to be the only people in the world implanted with electrodes targeting intraspinal structures. The implanted device consisted of two electrodes, connected to a subcutaneous radiofrequency receiver that could be activated by a handheld stimulator placed over the skin. The report on the initial four patients (3 male, 1 female) with electrodes implanted at the S1 level eventually showed good voiding in three patients (Nashold et al., 1972). Unlike some of the animal work, electrical stimulation did not generally cause concomitant relaxation of the urethra in these patients. Rather, a spastic external urethral sphincter prevented micturition in the male subjects even though large increases in bladder pressure were achieved. To overcome this, partial transurethral sphincterotomies were performed that allowed voiding in two of the male patients without causing incontinence. The female subject was able to void with an intact sphincter. This general pattern was reported in most patients in a 10-year review of the technique (Nashold et al., 1981). Good voiding was achieved in 10 of 13 females subjects, but in only 5 of 14 male subjects. Clinical results from Duke University, where the technique was developed, reported success in 6 of 7 female subjects and 4 of 7 male subjects (Nashold et al., 1981). Of the male subjects, two voided successfully after bladder neck resections or partial sphincterotomies but two others failed to void even after
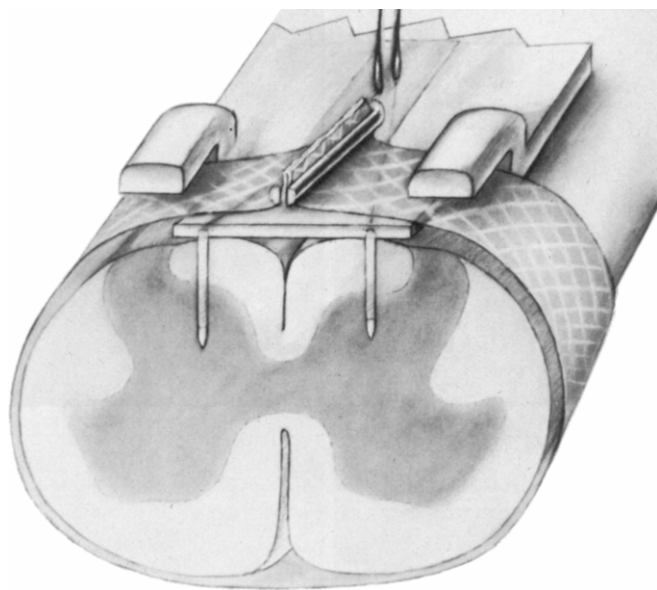

Fig. 8. Diagram showing the location of the penetrating electrodes implanted into the spinal cord. (Nashold et al., 1972).

these procedures were performed. However, two male subjects did achieve concomitant relaxation of the urethra leading to complete bladder evacuation without sphincterotomy, suggesting that at least in some patients, spinal cord stimulation can elicit coordinated voiding (Grimes et al., 1975). Ultimately, 60% of the subjects obtained clinically good micturition with low residual volumes, reductions in urinary tract infections, increases in bladder capacity and freedom from catheterization. Reductions in spasticity, as well as erections in some male patients, and defecation in some female patients were reported. However, autonomic and motor responses including sweating and lower limb movement often accompanied stimulation of the spinal cord (Nashold et al., 1981).

Despite these reasonably good clinical results, no further implants using this procedure were performed. There were several reasons for the abandonment of this approach. One reason is that the procedure, which involves highly invasive surgery, was unsuccessful in 40% of the subjects (Nashold et al., 1981) presumably due to ineffective electrode placement. Since neither coordinated micturition nor selective stimulation of the bladder were achieved in most patients, this procedure offered no advantages over Brindley's SARS system (1982) but added the complication of a more unpredictable electrode placement compared to sacral root electrode implantation. The inability to achieve stimulation of the bladder without concomitant sphincter activity was likely due to stimulus spread and the close proximity of the sacral parasympathetic nucleus and Onuf's nucleus (Kuru, 1965; de Araujo et al., 1982).

Future devices for electrical control of the bladder

Modifications of sacral root stimulators

The Finetech-Brindley SARS has proven to be the only commercially successful electrical stimulation device to restore voiding in spinal cord injury patients. Despite its proven efficacy (Van Kerrebroeck et al., 1993; Brindley, 1994) and low risk of complications and technical failures (Brindley, 1995), two issues exist, that if overcome, could help improve the function and acceptance of this device. The posterior rhizotomy that is performed in conjunction with the implantation of the Finetech-Brindley SARS eliminates neurogenic detrusor overactivity, detrusor-sphincter dyssynergia and autonomic dysreflexia triggered by bladder afferents, but irreversibly eliminates reflex erections, reflex defecation, reflex micturition and any remaining perineal sensation. The second issue is that both detrusor and sphincter efferent fibers are activated during stimulation, resulting in the functional, but non-physiological, post-stimulus voiding pattern associated with this implant. Rather than abandoning stimulation of sacral roots because of these limitations however, several

techniques are being developed to address these issues. Three promising techniques are discussed here. Additional techniques to reduce or eliminate stimulation-induced sphincter contractions are reviewed by Rijkhoff et al. (1997b).

Sacral posterior and anterior root stimulation

One of the primary benefits of posterior rhizotomy in spinal cord injury is the abolition of neurogenic detrusor overactivity allowing low-pressure storage of urine and an increase in bladder capacity. Since inhibition of reflexive bladder contractions has been demonstrated in some spinal cord injury patients using sacral nerve neuromodulation techniques (Ishigooka et al., 1998; Chartier-Kastler et al., 2001; Hohenfellner et al., 2001), neuromodulation of sacral roots was investigated in 5 patients with complete spinal cord injury and neurogenic detrusor overactivity who underwent implantation of a Finetech-Brindley system without the usual posterior rhizotomy (Kirkham et al., 2002). Electrodes were implanted extradurally on the mixed sacral roots in 4 subjects and intradurally on anterior, posterior (see Figure 2J) and mixed roots in the remaining subject. Since posterior rhizotomy was not performed, this system was referred to as a "Sacral Posterior and Anterior Root Stimulator" (SPARS) (Kirkham et al., 2002). In the three subjects that exhibited neurogenic detrusor overactivity after implantation, stimulation with small pulse widths successfully inhibited hyperreflexive bladder contractions and increased bladder capacity to a level similar to that obtained with anticholinergic medication. However, intermittent stimulation at larger pulse widths to induce voiding was unsuccessful, in spite of large increases in bladder pressure, because of detrusor-sphincter dyssynergia between stimulation periods. Less than 50% of the bladder volume was voided.

The SPARS system is an important next step in the development of sacral root stimulation in that neurogenic detrusor overactivity, previously abolished by posterior rhizotomy can be eliminated by posterior root neuromodulation. However, detrusor-sphincter dyssynergia, also previously abolished by posterior rhizotomy, prevents bladder voiding in this system. Clinical use of the SPARS system will require additional techniques to inhibit detrusor-sphincter dyssynergia without posterior rhizotomy to allow effective voiding.

Selective anodal block

Anodal blocking offers a method to block action potential propagation in large fibers, effectively allowing selective stimulation of the small parasympathetic fibers innervating the bladder. Selective stimulation of these fibers would reduce the concomitant contraction of the sphincter and lower limbs that presently occurs with the Finetech-Brindley SARS. This could restore a more physiological voiding pattern. Anodal blocking takes advantage of the fact that
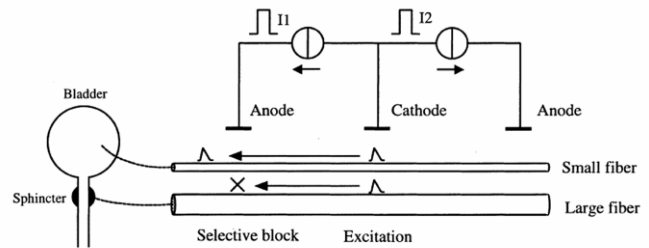

Fig. 9. Electrical current under the anode hyperpolarizes the membrane of large fibers at lower stimulation amplitudes than smaller fibers. This section of hyperpolarized membrane blocks the transmission of action potentials generated at the cathode preventing activation of the sphincter while allowing activation of the bladder. (Rijkhoff et al., 1997a).

axons are hyperpolarized under the anode, reducing their excitability. Since larger diameter axons have a lower threshold for electrical activation, they can be selectively hyperpolarized (Accornero et al., 1977; Rijkhoff et al., 1994a). Stimulation at the cathode excites both large somatic fibers and the smaller parasympathetic fibers, but action potential propagation in the somatic fibers is blocked at the hyperpolarized portion of membrane, allowing selective transmission in the parasympathetic fibers (see Figure 9). Brindley and Craggs (1980) successfully tested this technique in animals to achieve selective parasympathetic fiber stimulation with a SARS, but it did not work well enough in humans for regular use (Brindley et al., 1982). More recently, anodal blocking has been examined in modeling studies to determine stimulation parameters (Fang and Mortimer, 1991; Rijkhoff et al., 1994a). Additionally, both animal studies (Fang and Mortimer, 1991; Koldewijn et al., 1994; Rijkhoff et al., 1994b; Grunewald et al., 1998) and intraoperative humans studies (Rijkhoff et al., 1997a; Rijkhoff et al., 1998) of anodal blocking have demonstrated large decreases in sphincter and leg activity while producing bladder contractions.

Several issues remain with anodal blocking however. Anodal blocking waveforms being examined currently are monophasic and require pulse widths of approximately 600 μs in humans (Rijkhoff et al., 1998). Depending on the currents required, long duration pulses can lead to irreversible electrochemical reactions at the electrodes and eventual nerve damage (McCreery et al., 1990). However, methods to increase safety by reducing the charge per phase used to achieve anodal block are being examined (Vuckovic and Rijkhoff, 2004). Additionally, implantable stimulators capable of producing the waveforms generally required for anodal blocking do not exist, although they are under development (Bugbee et al., 2001; Rijkhoff, 2004a). Although anodal blocking allows selective activation of the bladder, posterior rhizotomies may still be required to allow voiding. In one animal study, anodal blocking without posterior rhizotomy never resulted in voiding because of reflexes that increased intraurethral pressure. In the same

experiment however, continuous voiding was achieved once a posterior rhizotomy was performed (Grunewald et al., 1998). In another animal study, complete voiding was achieved using anodal blocking without posterior rhizotomy (Koldewijn et al., 1994). Even if posterior rhizotomy is required to allow voiding when using anodal blocking, this technique may allow a more physiological continuous voiding pattern and may reduce unwanted leg movements that currently occur with SARSs.

High-frequency blockade

Another technique to prevent external urethral sphincter activation with SARSs uses high-frequency stimulation to block action potential propagation in somatic fibers. Sawan, Elhilali and colleagues have successfully stimulated mixed sacral roots with high-frequency (600 Hz), low-amplitude pulses to block urethral sphincter efferent activity while superimposing low-frequency, high-amplitude pulses to activate parasympathetic preganglionic effects that in turn generate bladder contractions (Shaker et al., 1998; Abdel-Gawad et al., 2001) (see Figure 10). High-frequency stimulation has been shown to block action potential propagation by hyperpolarizing axons and maintaining them in their refractory period (Solomonow et al., 1983). High-frequency, low-amplitude stimulation hyperpolarizes large fibers but the stimulation amplitude is not high enough to affect the smaller parasympathetic fibers. In a study of 12 chronically implanted dogs, 7 voided with <10% residual urine and the remaining 5 voided with <20% residual urine (Abdel-Gawad et al., 2001). This system represents a potential advantage over the current Finetech-Brindley SARS where the bladder and sphincter contract simultaneously and voiding occurs post-stimulus.

This device, including a proposed method of neuromodulation to inhibit the hyperreflexive bladder by stimulation of the sacral nerves, has been patented (Sawan and Elhilali, 2002). While this group has not published results regarding the proposed neuromodulatory action of their device, proof of principle has been demonstrated in spinal cord injury patients with a similar device (Kirkham et al., 2002). Neuromodulation could remove the necessity for posterior rhizotomy in sacral root stimulators, especially since successful voiding without posterior rhizotomy has been achieved with this stimulation paradigm, at least in animals (Abdel-Gawad et al., 2001). A brief report from another group using the same stimulation paradigm suggests that it is also effective in humans (Benda et al., 2003). Although no reports in humans exist from Sawan and Elhilali's group, Victhom Human Bionics (Saint-Augustin-de-Desmaures, Quebec, Canada) has licensed the technology and is continuing development of the device.

Intraspinal microstimulation

Since Nashold and Friedman's original work on spinal cord stimulation to evoke micturition (Nashold et al., 1971;
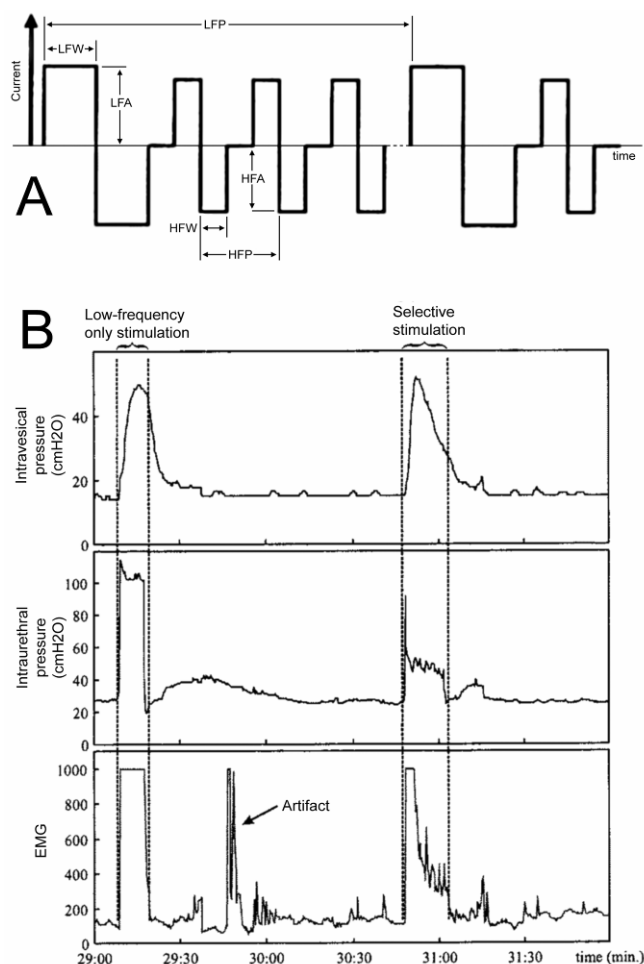

Fig. 10. High-frequency block of large fibers allowing selective activation of the bladder. (A) High-frequency, low-amplitude pulses superimposed on low-frequency, high-amplitude pulses. LFA – low-frequency amplitude, LFP – low-frequency period, LFW – low-frequency pulse width, HFA – high-frequency amplitude, HFP – high-frequency period, HFW – high-frequency pulse width. (B) Reduction in intraurethral pressure and sphincter EMG while maintaining bladder pressure when the selective stimulation (high-frequency, low-amplitude) waveform is utilized. Adapted from (Boyer et al., 2000).

Nashold et al., 1972), interest has persisted in this technique. In these experiments, electrodes were on the order of 0.3 – 0.4 mm in diameter with 0.5 – 1.0 mm long exposed tips (Nashold et al., 1971; Jonas et al., 1975) leading to geometric electrode surface areas of 0.5 – 1.4 mm^2 . Stimulus spread from these comparatively large electrodes between the adjacent sacral parasympathetic nucleus and Onuf's nucleus (Kuru, 1965; de Araujo et al., 1982) was the likely cause of observed concomitant bladder and sphincter contractions (Nashold et al., 1972). Electrode development has improved the ability to selectively stimulate specific regions within the spinal cord (Prochazka et al., 1976; Mushahwar et al., 2000; McCreery et al., 2004). Currently, electrode arrays for chronic intraspinal microstimulation (ISMS) use microwire electrodes (see Figure 11A) or silicon substrate microelectrodes manufactured using
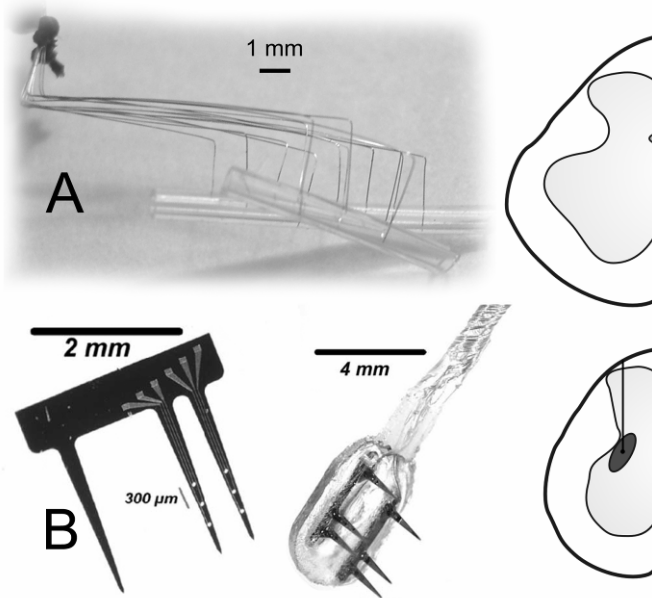
Fig. 11. Electrode designs and target locations (in the cat) for intraspinal microstimulation. (A) Microwire electrode array. (B) Multi-site penetrating silicon electrode array. (C) Electrode targets in the cat sacral spinal cord. Electrical stimulation in the dorsal gray commisure, which contains interneurons with inhibitory projections to sphincter motoneurons, can elicit relaxation of the external urethral sphincter. Electrical stimulation photolithographic processes (see Figure 11B). Microwire-based electrodes use iridium and platinum-iridium alloy wires 20 – 30 μm in diameter with 20 – 100 μm long exposed tips resulting in geometric electrode surface areas of 1,600 – 10,000 μm^2 (Mushahwar et al., 2000). Silicon substrate microelectrodes used for chronic ISMS implants can have multiple stimulation sites at various depths per penetrating shank with electrode surface areas around 2000 μm^2 (McCreery et al., 2004). These electrode surface areas are 50 – 300 times smaller than the smallest electrodes used in the first spinal cord stimulation experiments (Nashold et al., 1971; Jonas et al., 1975) and allow selective stimulation of the sacral parasympathetic nucleus without concomitant sphincter activation (Carter et al., 1995; Grill et al., 1999). Although electrode arrays can cause inflammatory reactions, glial scarring and neural death around the implantation site, this can be minimized (McCreery et al., 2004) and would presumably be just as safe or safer in long term use as the larger electrodes implanted in humans (Nashold et al., 1981).

If ISMS is to be clinically useful, clear advantages over sacral root stimulation must be offered, especially since an ISMS implant would likely be at least as difficult to perform as a SARS implant. One advantage of ISMS is that bladder contractions can be evoked without concomitant sphincter contractions (Carter et al., 1995; Grill et al., 1999). However, more importantly, ISMS allows the possibility of activating sacral interneuronal networks that produce coordinated micturition or some part thereof (Nashold et al., 1971; Grimes et al., 1975; Grill, 2000).

Networks of interneurons responding to pelvic and pudendal afferents and receiving projections from the pontine micturition center exist in various regions around the central canal, in the dorsal gray commissure and in the intermediolateral cell column of the sacral spinal cord (reviewed in de Groat et al., 1996; Shefchyk, 2001) and are active during micturition (Grill et al., 1998; Buss and Shefchyk, 2003). One group of interneurons, located in the dorsal gray commissure, is of particular interest in relation to inhibition of the external urethral sphincter as the interneurons contain inhibitory neurotransmitter, receive direct projections from the pontine micturition center and are believed to project to Onuf's nucleus (Blok et al., 1997; Sie et al., 2001). Since Onuf's nucleus does not receive projections from supraspinal centers, inhibitory interneurons in the dorsal gray commissure may mediate voluntary relaxation of the sphincter (Blok, 2002). This view is supported by the finding that electrical stimulation in the dorsal gray commissure produced active and sustained decreases in urethral pressure in spinally intact cats (Blok et al., 1998; McCreery et al., 2004). Additionally, some voiding can occur when electrodes around the central canal are stimulated (Grill et al., 1999). The ability to actively inhibit urethral activity is not currently possible with sacral root stimulation. These results demonstrate the potential of ISMS to achieve coordinated micturition through bladder excitation and sphincter inhibition.

Current research on ISMS is therefore focused on simultaneous stimulation of the sacral parasympathetic nucleus to produce bladder contractions and the dorsal gray commissure to actively relax the urethra (see Figure 11C). This approach has produced sustained high-pressure bladder contractions, coordinated increases in bladder pressure and decreases in urethral pressure, and occasional incomplete voiding (Prochazka et al., 2003b), but so far it has proven unreliable. One possible reason, is that in addition to the interneurons in the dorsal gray commissure that inhibit sphincter motoneurons, there are other interneurons in this same region have been shown to decrease their firing rate during micturition, and may be part of pathways with excitatory connections to sphincter motoneurons (Buss and Shefchyk, 2003). If this is the case, electrical stimulation in parts of the dorsal gray commissure may in fact activate more excitatory interneurons that inhibitory interneurons, and thereby cause contraction, rather than relaxation of the external urethral sphincter. It is also unknown whether ISMS can affect the activity of the smooth muscle internal urethral sphincter, which is the primary mechanism to maintain continence until the bladder is very full or at high pressure. These results were obtained in an awake animal, suggesting that previous results in anesthetized animals may also hold true in the absence of anesthesia. Additionally, electrodes targeting the sacral parasympathetic nucleus produced similar increases in bladder pressure using the same stimulation parameters, before and after complete
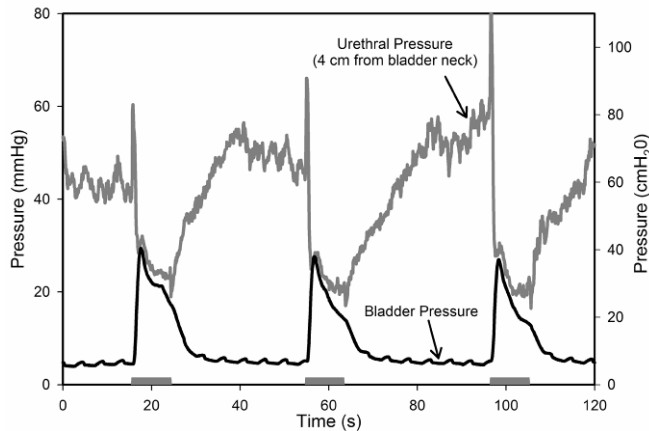
Fig. 12. Bladder and urethral pressure changes in response to electrical stimulation through three electrodes: 2 targeting the sacral parasympathetic nucleus and 1 targeting the dorsal gray commissure. During stimulation, immediate increases in bladder pressure and decreases in urethral pressure were achieved. The pressures measured in the bladder and urethra became essentially equal during stimulation indicating that voiding should occur in the absence of the urethral catheter. However, once the catheter was removed to unblock the urethra, stimulation through the same electrodes did not induce voiding. (Prochazka et al., 2003a).

spinalization. However, even when bladder pressure is increased by stimulation in the sacral parasympathetic nucleus and urethral pressure is decreased by stimulation in the dorsal gray commissure, this may not be sufficient to produce micturition. In some cases, simultaneous intraurethral pressure recordings in the vicinity of the external urethral sphincter and bladder pressure recordings, have indicated that voiding should occur (Prochazka et al., 2003a) (see Figure 12), but once the urethral pressure catheter was removed to unblock the urethra, stimulation through the same electrodes did not elicited voiding. In this case, high pressure in the bladder neck or distal urethra may have prevented voiding.

Urethral afferent stimulation

Electrical stimulation of afferent branches of the pudendal nerve, specifically the dorsal penile nerve, has been shown to inhibit hyperreflexive bladder contractions occurring after spinal cord injury. However, electrical stimulation of urethral afferents, also forming part of the pudendal nerve, has been shown to elicit bladder contractions as well as relaxation of the sphincter. This spinal reflex was first described by Barrington in spinalized cats (Barrington, 1914; Barrington, 1941), and more recently they have been investigated in spinalized cats (Shefchyk and Buss, 1998; Gustafson et al., 2003) and humans with spinal cord injury (Gustafson et al., 2003; Gustafson et al., 2004). These reflexes are presumed to facilitate voiding by positive feedback from afferents sensitive to urethral dilation (Shafik et al., 2003a; Shafik et al., 2003b). In humans, urethral afferents were electrically stimulated using a catheter-mounted electrode (Gustafson et al., 2003) passed into the urethra (see Figure 2M). In complete spinal cord injury

subjects, bladder contractions reaching 70 cmH₂O as well as voiding could be achieved if the bladder volume was above a threshold value (Gustafson et al., 2004). Below this threshold, bladder contractions could not be generated and voiding was therefore incomplete. Despite the fact that only incomplete voiding has been demonstrated, this stimulation technique is very intriguing from the perspective of neuroprosthesis device development as it is so far the only way in which bladder contractions can be generated without invasive implantations of electrodes targeting the bladder, sacral roots or spinal cord itself. However, even more interesting is the apparent ability of urethral afferent stimulation to evoke coordinated micturition after complete spinal cord injury (Shefchyk and Buss, 1998).

Microstimulators

Implanted neuroprostheses discussed in this review have all used the same basic set of components. An implanted stimulator, either battery powered or inductively coupled to an external power source, is implanted subcutaneously in a convenient location such as the abdominal or chest region and long leads connect the electrodes to the stimulator. This design can lead to time-consuming surgical procedures as well as technical failures including lead breakage and connector failure (Brindley, 1995). Microstimulators such as the BION (Advanced Bionics, Valencia, CA) provide an alternative approach. BIONs are self-contained, injectable microstimulators that are programmed and powered by inductive coupling. A single external transmitter coil can communicate with up to 256 BIONs, each of which can deliver current controlled pulses with a pulse width range of 4 – 512 μs and amplitude range of 0 – 30 mA up to frequencies of 50 pulses per second in a package 2 mm in diameter and 16 mm long (Loeb et al., 2001) (see Figure 13). A more recent version of the BION includes a lithium-ion battery to power the device during normal use, but is programmed and recharged using the external coil. This device is larger (3.3 mm diameter, 27 mm long) (Groen et al., 2004), but allows subjects to be free of the external coil and associated hardware during daily activities, at least in applications not requiring phasic control.

Two studies have evaluated the use of BIONs for treating bladder dysfunction using the inductively powered (Buller et al., 2002) and battery powered (Groen et al., 2004) systems. Although final reports have yet to be published, both studies have shown positive results using pudendal nerve (see Figure 2N) stimulation to treat overactive bladder incontinence. BIONs have not been clinically tested in spinal cord injury patients for bladder control, but a number of the stimulation techniques presented in this review could be adapted to use BIONs.

MiniatURO

The miniatURO (Biocontrol Medical Ltd., Yahud, Israel) is a closed-loop implantable electrical stimulation system for

TABLE 1

Summary of mechanical devices used for lower urinary tract management.

Device	Efficacy	Advantages	Disadvantages	Current Status
Catheter	Very good	Simple, Inexpensive	Urinary tract infections, inconvenient	Clinical
Artificial urethral sphincter	Mixed	Proven design	Infection, Urethral erosion	Limited use
Urethral stent	Good	Reversible alternative to sphincterotomy	Not for long-term implantation	Some clinical
Intraurethral pump	Good	Simple implant	Regular replacement, Discomfort	Investigational

treating mixed urinary incontinence. The device consists of an intra-abdominal pressure sensor, pelvic floor stimulation electrode and a stimulator with integrated control system. Stimulation is triggered by increases in intra-abdominal pressure. This device has been tested in short-term settings where abdominal pressure was measured rectally, stimulating electrodes were introduced percutaneously, and the stimulator was worn externally. All patients in a group of 16 with stress incontinence responded positively and became dry or had reduced episodes of incontinence (Nissenkorn et al., 2004). While this device has not been tested in spinal cord injury patients, there is reason to believe that this kind of device might be effective in the spinal cord injury population (Fjorback et al., 2003).

Transcutaneous magnetic stimulation

Transcutaneous magnetic stimulation of the nervous system is a noninvasive method of activating neural tissue and has therefore become a useful technique for human experimentation and clinical diagnostics. Two studies have examined the ability of magnetic stimulation to exert control over lower urinary tract function in spinal cord injury patients but have arrived at very different results (Lin et al., 1997; Bycroft et al., 2004). In the first study it was concluded that repetitive magnetic stimulation (15 – 30 Hz) of the sacral nerves, achieved by placing the stimulation coil over the sacrum (see Figure 2O), caused direct activation of parasympathetic preganglionic neurons innervating the bladder leading to increases in bladder pressure. Fatigue of the external urethral sphincter and intermittent stimulation to allow post-stimulus voiding were the two methods postulated to explain the voiding that occurred, even though many subjects had received sphincterotomies (Lin et al., 1997). The more recent study suggests that magnetic stimulation of the sacral nerves causes direct inhibition of bladder contractions in spinal cord injury patients with neurogenic detrusor overactivity. It also stated that the previously described bladder contractions were rebounds occurring at the end of stimulation as a result of releasing the detrusor from direct inhibition (Bycroft et al., 2004).

Whatever the effect of magnetic stimulation on bladder function in spinal cord injury patients, this technique holds promise for a device-based therapy for bladder control. Current magnetic stimulation systems are large and would

not be suitable for chronic use in patients. However, the potential benefits of this completely noninvasive technique, and its demonstrated efficacy for treating neurogenic detrusor overactivity and/or eliciting partial voiding, deserve further investigation.

Successes and failures of devices for bladder control

A wide variety of techniques and devices have been developed to manage the significant problems associated with lower urinary tract dysfunction after spinal cord injury. While devices such as the Finetech-Brindley SARS can truly be said to exert control over the lower urinary tract, other devices, including catheters merely manage the symptoms associated with lower urinary tract dysfunction after spinal cord injury. However, the ultimate goal of any treatment modality, including pharmacological and surgical methods, is to create a bladder capable of storing large volumes of urine at low pressure, while preventing incontinent episodes and allowing periodic evacuation of that urine at low pressure. If a treatment achieves its intended function, then the merits of one technique versus another depend on issues such as adverse side effects, procedural reversibility, device cost, ease of use and ease of implantation.

Device efficacy, advantages and disadvantages

Two classes of devices have been described in this review: mechanical devices and electrical stimulation devices. The mechanical devices discussed range from the very simple to the very complex and address voiding dysfunction, incontinence and detrusor-sphincter dyssynergia. A brief summary of the efficacy, main advantages and disadvantages, and current status of these devices is presented in Table 1. Several general comments about the use of mechanical devices can be made. Catheters and the In-Flow intraurethral pump do not require implantation. They are also commercially available, allowing easy adoption by clinicians. Artificial urethral sphincters and urethral stents do require surgery, but this is relatively simple. However, none of these devices offers the potential to restore lower urinary tract function to the pre-injury state. There are significant side effects the chronic presence of foreign materials in the lower urinary tract. Finally, no mechanical device is able to affect neurogenic detrusor

overactivity, so pharmacological or surgical treatments must be used to establish a high-volume, low-pressure bladder.

Electrical stimulation devices, while not curative, offer the unique potential to restore normal function to the lower urinary tract after spinal cord injury. Many techniques have been presented in this review that vary significantly in their ability to establish a high-volume, low-pressure bladder and to produce low-pressure voiding. Improving continence, storage volume and storage pressure by inhibiting hyperreflexive bladder contractions has been the specific aim of a number of devices. A brief summary of the efficacy, main advantages and disadvantages, and current status of these devices is presented in Table 2, while a similar summary for devices intended to evoke bladder emptying is presented in Table 3. Of the electrical stimulation techniques intended to inhibit hyperreflexive bladder contractions, both dorsal penile nerve stimulation and tibial nerve stimulation have shown promising results. However, these methods require additional study with the use of more practical devices that are suitable for chronic use. Bladder wall, pelvic nerve and spinal cord stimulation are all methods to elicit voiding that were tested in human patients with spinal cord injury, and subsequently were abandoned clinically. However, bladder wall stimulation and spinal cord stimulation continue to be explored in the laboratory setting.

Clinical success of devices in managing dysfunction after spinal cord injury

Catheters and urethral stents, as well as dorsal penile nerve, tibial nerve, spinal cord and sacral root stimulation have all been shown to be effective in managing various aspects of lower urinary tract dysfunction after spinal cord injury in some patients. However, the success of these devices from a clinical perspective varies significantly. The clinical success of catheters remains foremost. Of the other effective techniques, only the Finetech-Brindley SARS could be considered a proven clinical success with over 2,500 systems implanted (Rijkhoff, 2004b). This system is successful

TABLE 2

Summary of electrical stimulation devices used to control continence.

Device	Efficacy	Advantages	Disadvantages	Current Status
Pelvic floor maximal functional electrical stimulation	Mixed	Long-lasting improvements	Physical and psychological discomfort Inconsistent results	Limited use
Thigh stimulation	Mixed	Non-invasive Long-lasting improvements	No predictors for success Time consuming treatment	Limited use
Dorsal penile nerve surface stimulation	Promising	Non-invasive	Not well studied	Investigational
Tibial nerve stimulation	Promising	Simple treatment procedure	Permanent device required Not well studied	Investigational
Sacral neuromodulation	Mixed	Minimally-invasive Proven design and implant procedure Commercially available	May not work in complete injuries Inconsistent results, Not well studied	Investigational

TABLE 3

Summary of electrical stimulation devices used to control voiding.

Device	Efficacy	Advantage	Disadvantages	Current Status
Intravesical electrical stimulation	Mixed	Long-lasting results Can improve voluntary voiding in incomplete injuries	Ineffective in many patients No predictors for success Time consuming treatment	Limited use
Bladder wall stimulation	Mixed	Simple surgical approach	Sphincter and pelvic floor contraction Electrode-bladder interface failure	Abandoned
Pelvic nerve stimulation	Poor		Sphincter and pelvic floor contraction Difficult surgical approach Nerve unsuitable for stimulation	Abandoned
Sacral root stimulation	Very good	Voiding without catheterization Low residual volume Proven design and implant procedure Long term usage with few failures Commercially available	Posterior rhizotomy required Demanding surgical implant Unphysiological voiding	Clinical
Spinal cord stimulation	Good	Voiding without catheterization Low residual volume Long-term usage	Sphincter contraction Sphincterotomy required in males Difficult electrode placement 40% failure rate	Abandoned

because it is the only device that reliably evokes complete bladder evacuation, significantly reducing the complications associated with catheterization. When combined with sacral posterior rhizotomy, as it nearly always is, the Finetech-Brindley SARS provides a complete system for lower urinary tract control after spinal cord injury. However, the consequences of irreversible rhizotomy, the technically demanding implant procedure and commercial and regulatory issues have limited the availability of this device as well as the acceptance of it by patients and clinicians. With this in mind, given the large number of patients that could benefit from such a device, and a generally increasing clinical acceptance of neuroprostheses in general, the Finetech-Brindley SARS has had a limited impact on the spinal cord injury population throughout most of the world.

The future of devices for bladder control

Progress is being made on regeneration of the spinal cord, but a complete biological cure for spinal cord injury is unlikely to be developed in the near future (Fawcett, 2002). In light of this, and the fact that eventual regenerative therapies will likely be combined with neuroprostheses to maximize functional recovery (Prochazka et al., 2002b), new and improved device are required to restore control of the lower urinary tract after spinal cord injury. The feasibility and efficacy of a number of mechanical and electrical devices for treating lower urinary tract dysfunction has been clearly demonstrated in spinal cord injury patients. However, no clinical device can be said to have solved the problem of bladder control as low-pressure physiological voiding can not yet be produced and no device has successfully incorporated methods to produce both voiding and suppression of neurogenic detrusor overactivity. While future improved biomaterials will undoubtedly reduce some of the side effects associated with the use of mechanical devices (Beiko et al., 2004), these are unlikely ever to achieve complete control over the lower urinary tract. Electrical stimulation devices on the other hand have demonstrated the ability to achieve significant control over neurogenic detrusor overactivity and voiding. Adaptations of the Finetech-Brindley SARS, including posterior root stimulation and anodal blocking or high frequency blockade of somatic fibers, offer the possibility of inhibiting hyperreflexive bladder contractions and producing physiological voiding without the currently requisite posterior rhizotomy. Combining such methods may significantly improve future electrical stimulation devices for bladder control.

Other electrical stimulation techniques currently under investigation also show promise. ISMS has the potential to utilize remaining spinal cord networks and can achieve selective stimulation of the bladder as well as active inhibition of the sphincter, albeit not reliably enough to produce consistent voiding. ISMS research has yet to address the problem of neurogenic detrusor overactivity.

Surgical implantation of ISMS devices in their current form is even more difficult than implantation of sacral root stimulators. Unless simpler electrode configurations are developed, this may limit clinical use of ISMS even if it can be shown to be reliable and effective in animals. Stimulation of the dorsal penile nerve and urethral afferents are among the most interesting techniques currently being investigated to restore control of the lower urinary tract from a neuroprosthetic device development perspective. They offer the potential of a minimally invasive implant to suppress neurogenic detrusor overactivity and produce voiding, perhaps using microstimulators. If these techniques are to have an impact on the clinical management of lower urinary tract dysfunction after spinal cord injury, they must provide clear improvements in treatment over what can be currently accomplished with catheters, pharmacological therapies and surgical intervention.

An ideal device for controlling lower urinary tract function after spinal cord injury can be postulated based on the material presented in this review. Above all, the device must suppress neurogenic detrusor overactivity and allow user-controlled, continuous, low-pressure voiding with a low residual volume. The device should not require additional pharmacological or surgical procedures to operate successfully and would ideally require only minimally invasive surgery. Although not discussed in this review, an implant to restore lower urinary tract function should ultimately provide means to restore bowel and sex function as well. Finally, any procedure must be completely reversible so that patients are not committed to a particular device for the rest of their lives and are able to take advantage of future devices.

Conclusions

In this review we have discussed devices and techniques aimed at restoring normal function to the lower urinary tract after spinal cord injury. Some of these devices and techniques have ultimately proven to be unsuccessful for reasons such as insufficient efficacy, unacceptable treatment procedures, side effects and technical failures. Other devices, most notably catheters and sacral root stimulation, have been successful. Over 20 years of experience with sacral root stimulation to restore voiding clearly indicates the advantages that spinal cord injury patients can expect to achieve with neuroprostheses. However, detrusor-sphincter dyssynergia must be overcome before neuroprostheses can gain more widespread use. Electrical stimulation techniques to suppress neurogenic detrusor overactivity, allowing efficient bladder filling and storage, have been demonstrated in some spinal cord injury patients. But relatively few studies have been conducted and many details regarding these techniques have yet to be elucidated. These, or other similar techniques, must be successful if a neuroprosthesis for complete control of lower urinary tract function is to be developed. Perhaps the most difficult and crucial problem is

achieving relaxation of the sphincter to allow physiological voiding. It has been said that "The key to control of the bladder lies in control of the sphincter" (Schmidt, 1986). While this comment was originally made in reference to the ability of sphincter activity to modulate bladder contractility, it is equally true that the ability to control the sphincter and eliminate unwanted activity remains the final piece of the puzzle that must be put in place for bladder control neuroprostheses to be completely effective. A number of techniques are being investigated to accomplish this, but no single one has completely achieved this goal. In conclusion, while many devices and techniques have been tried but ultimately abandoned, the successes clearly show the immense benefits that can in principle be achieved with the use of devices in the control of the dysfunctional bladder.

Acknowledgements

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