## TEAM NEURO-UROLOGY — BASICS

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## NEURO-ANATOMY AND NEUROPHYSIOLOGY

Urinary continence requires controlled bladder storage and timely emptying. Much has been discovered about the human experience of bladder storage and voiding in recent years and an attempt will be made here to review those findings, both neurophysiological and neuroanatomical. Current thinking highlights the importance of the afferent innervation of the bladder, providing as it does information as to the state of bladder fullness as well as the stimulus for bladder emptying in several pathological conditions. This review will travel with the afferent innervation of the urinary tract from urothelium to the brain.

Once urine reaches the bladder, the process of distension activates the dynamic properties of the urothelium and recent discoveries about the urothelium and its innervation point to it as being a critical sensory organ. The urothelium may have secretory properties, it is metabolically active and naked axons may be seen penetrating its basal lamina possibly providing its sensory innervation. Within the lamina propria of the urothelium there is a rich plexus of presumptive afferent nerves and ultra structural studies have shown these fibres have numerous clear and dense cored vesicles contained within axonal varicosities. Immunohistochemical studies in animals and man have shown vanilloid and purinergic receptors on the unmyelinated nerves in this layer of the bladder and their precise role in causing disorders of detrusor overactivity as well as bladder hypersensitivity remains to be discovered. The findings of increased purinergic innervation in women with idiopathic DO and the clinical response of patients with neurogenic as well as idiopathic detrusor overactivity to intravesical vanilloids suggests that the afferent innervation is of critical importance in the initiation of detrusor contractions in these conditions.

Afferent fibres are thought to travel to the spinal cord together with the somatic, parasympathetic and sympathetic nerves and enter the cord through the dorsal roots. There have been no recent developments in methods for studying human spinal cord function and much of what we know of the pathways that convey lower urinary tract sensory information dates back to the careful clinical studies of patients before and after cordotomy. However in addition to its conduit functions between the periphery and cerebrum, the cord is also the site of many complex segmental reflexes. It seems highly likely that the action of neuromodulation, an intervention that may be so effect in treating disorders of detrusor overactivity, is at this level.

The advent of functional brain imaging techniques to study the neurology of human bladder control has provided fascinating new insights. It was known from animal experiments that the periaqueductal grey matter is an important sensory relay centre for bladder afferents and PET imaging studies have now confirmed its central role in humans. Separate analysis of the sensations of bladder fullness and of urgency have shown both processes involve different and complex networks of neuronal activity and amongst the sites activated by bladder filling are regions in the frontal lobes. It may be here that on the basis of information about bladder fullness and an assessment of the appropriateness of the situation, the decision to void is made, so achieving social continence.

## TEAM NEURO-UROLOGY — PRESENT

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## DIAGNOSIS AND THERAPY

**Helmut Madersbacher**

During the past two decades concepts and understanding of neurogenic lower urinary tract (LUT) dysfunction have undergone important changes. The introduction of urodynamics and sophisticated neurophysiological investigatory techniques paved way for more precise and detailed evaluation of the functional status of the lower urinary tract. They allow to define the underlying pathophysiology and the pattern of detrusor and sphincter dysfunction associated with. The concept of adequate storage at low intravesical pressure being necessary to maintain urinary tract integrity in patients with LUT dysfunction stresses the need for urodynamics.

However, experience has shown that the consequences of identical urodynamic findings may vary according to the underlying pathophysiology. Beside sophisticated urodynamic and neurophysiological tests history taking and clinical investigation still play an important part especially in regards to treatment strategies: the social situation and other disabilities determine the treatment strategy. Fortunately enough, nowadays the neurourologist is in the position to offer several treatment options for one and the same dysfunctional pattern.

The aim of treatment in neurogenic lower urinary tract dysfunction still is (1) preservation of kidney function, based on a bladder with sufficient capacity, filling at low pressure, emptying completely without hyperpressure

and without outflow obstruction, which is important for life expectancy, and (2) to manage urinary incontinence or possible to restore continence, which is important for quality of life of these patients.
Neurogenic LUT dysfunction is not a static condition, functional and morphologic changes occur over time. Therefore expert and regular urological surveillance is crucial to achieve the goals mentioned above. New techniques like magnetic resonance urography (MRU) could replace ultrasonography or IVU, mostly used for routine controls, in patients with severe deformities, chronic obstipation and presence of internal fixation devices.
The discussion on therapy of neurologic LUT dysfunction will comprise three aspects: intermittent catheterisation, botulinum-A toxin therapy and operations for neurogenic detrusor overactivity. In regards to intermittent catheterisation the important question „aseptic intermittent catheterisation" versus „hygienic (clean) intermittent catheterisation" will be discussed as well as the question which catheter, which lubricant or which technique are best according to evidence based medicine. The part on pharmacotherapy will mainly focus on botulinum-A toxin therapy. The efficiency of botulinum-A toxin injections into the detrusor muscle to treat major neurogenic detrusor overactivity and neurogenic incontinence has been recently established. This minimal invasive procedure offers a new therapeutic option between ineffective or incompatible anticholinergic drug therapy and surgery. However, also possible changes of the bladder wall properties in long-term, caused by mini-lesions through repeated botulinum-A toxine injections, should be considered.
Many operations were designed for neurogenic detrusor overactivity, only sacral deafferentation and bladder augmentation have stood the test of time. The differential indication for both operations, which are rather complementary than competitors, their advantages and disadvantages, as well as future developments in this field are presented.
An important innovative field, especially for neuro-urology, is electrical neuromodulation and electrical neurostimulation, which will be the topic of the next speaker.

**Udo Jonas**

This part will focus on electrical stimulation of neural structures as the currently most promising approach for treatment of lower urinary tract dysfunction. For better understanding of the different techniques and their indications it is essential to distinguish between sacral anterior root stimulation (SARS) and sacral nerve stimulation (SNS) or „neuromodulation.
SARS is used to induce a bladder contraction for bladder evacuation in the sense of a real „bladder pacemaker" in spinal cord injured (SCI) patients with an intact lower motor neuron. In this case the effect of electrical stimulation is caused by electrical activation of small non-myelinated efferent parasympathetic-visceromotoric nerve fibers directly inducing a contraction of the detrusor smooth muscle. The current amplitude to achieve this needs has to be high enough to activate non-myelinated nerve fibers and is thus far beyond the pain threshold, therefore limiting clinical application to spinal cord injured patients with a complete lesion or few selected SCI-patients with residual sensibility. Currently sacral nerve root stimulation is clinically only used in combination with complete sacral deafferentation (SDAF), meaning the complete surgical transsection of all afferent dorsal nerve roots providing afferent input to the sacral segments S2-S4. Only this posterior rhizotomy leads to a conversion of a low compliant hyperreflexic detrusor to a high compliant areflexic state, allowing storage of large amounts of fluid at low bladder pressure consecutively achieving continence and protection of the upper urinary tract.
Based on experimental work in baboons, the group of G.S. Brindley developed a stimulation system, using electrodes, placed on the bilateral S2-S4 sacral anterior or ventral nerve roots intradurally. In this concept, the deafferentation is also performed intradurally. Electrical energy is transmitted to the electrodes by an external impulse generator via radio transmission from a sending to a receiving subcutaneously implanted antenna.
The concept of sacral anterior root stimulation in combination with sacral deafferentation has become an ideal way for rehabilitation of lower urinary tract function in SCI patients. Stimulator driven micturition, continence and improvement of compliance can be achieved in about 90% of patients with a very limited amount of complications. The promotors of SARS and SDAF today are D. Sauerwein and Ph. V. Kerrebroek. Their data clearly demonstrated excellent efficacy ( 87 % continence) combined with a low incidence of AE's.
The effect of SNS is predominantly caused by electrical activation of delta myelinated afferent nerve fibers contributing afferent input to the sacral spinal cord segments S2-S4 and/or to the pontine mesencephalic micturition center. Therefore SNS predominantly is used in idiopathic voiding dysfunction in patients with intact sensory input to the central nervous system (CNS), such as motor urge incontinence, sensory urge incontinence, detrusor hypocontractility and detrusor sphincter dyssynergia.
Neuromodulation for treatment of lower urinary dysfunction has been used for more than 30 years. In 1981, the group of E.A. Tanagho and R.A. Schmidt introduced a chronic neuromodulation technique using an unilateral sacral foramen electrode connected to an implanted battery driven impulse generator, allowing chronic stimulation and therefore achievement of a sustained clinical effect. Clinical response rates both to temporary external neuromodulation techniques and chronic techniques using implants are in the range of about 70-90% for patients with motor urge incontinence. In patients with urinary retention, similar effects are accomplished in restoring voiding function .
Today, double channel implantable systems are available, allowing bilateral or doublesegmental electrical

stimulation of the sacral spinal nerve afferents in order to even enhance clinical efficacy. Current research is predominantly focussing on adapted current characteristics or different electrode design fur further outcome-improvement.

## TEAM NEURO-UROLOGY — FUTURE FORUM — PAEDIATRICS

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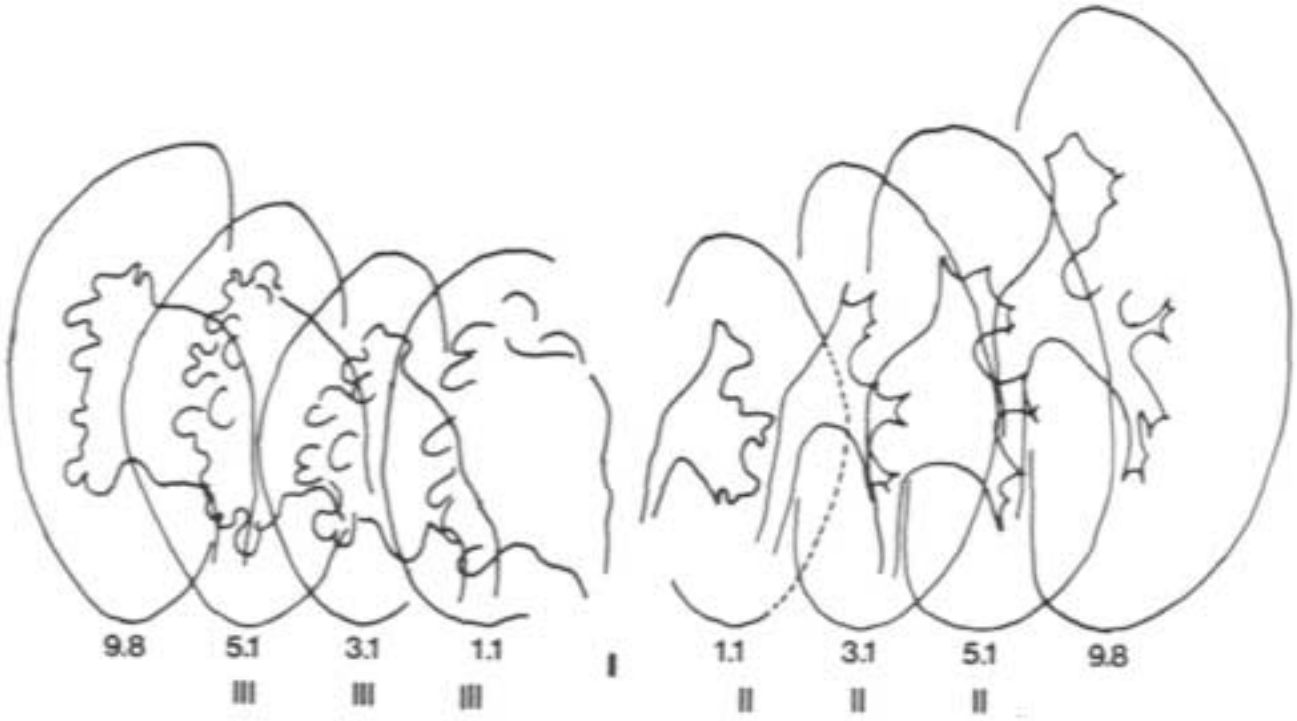
## KIDNEY DAMAGE IN CHILDREN WITH SPINA BIFIDA IS PREVENTABLE

**Introduction**

Very few published data are available on the incidence of acquired kidney damage in children with myelo-meningocele (MMC), but we do know that in 30% of adults with MMC end-stage renal failure is the cause of death.

Since the early seventies, In Utrecht, urological management of children with MMC consists of regular screening and low-dose chemoprophylaxis for urinary tract infection, periodic imaging of kidneys and bladder, and periodic urodynamic investigations (pressure/flow/EMG). In children with detrusor-sphincter dyssynergia and obstructive uropathy with/without vesicoureteral reflux, the aim was and is to restore complete bladder emptying and combat detrusor overactivity.

As of 1969, this was achieved first with careful endoscopic sphincterotomy or urethral dilatation.




These surgical measure were gradually replaced by clean intermittent catheterization (CIC), combined with anticholinergic drugs in cases with detrusor overactivity. As of 1984, treatment with CIC and oxybutynine-HCl is used exclusively.

Because of the promising results of this management we introduced CIC and oxybutynine-HCl in all infants with MMC and detrusor-sphincter dyssynergia, in the 90's.

**Methods**

Renal growth has been evaluated in 238 subjects with MMC, all followed in Utrecht, and born between 1965 and 1990.

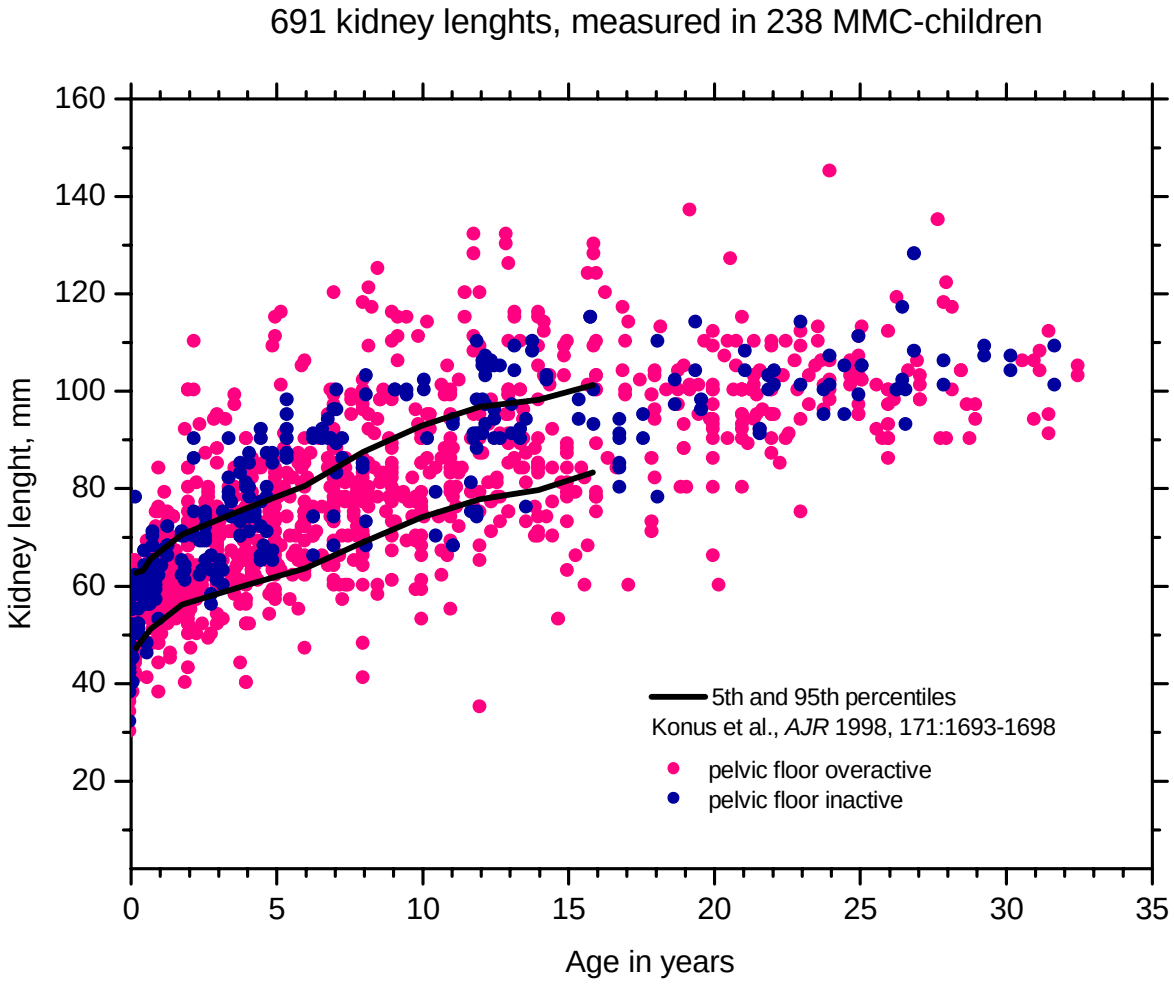
In children with MMC, parenchymal damage will result in measurable loss of kidney mass and kidney function at adolescence or later. Kidney length was the only parameter available to document substantial loss of kidney parenchyma over such a long time.

Before the era of ultrasound, intravenous urograms were made of all patients, and kidney lengths could be measured on the tracings made from these urograms (see illustration). After 1984, all data on kidney length were obtained directly with ultrasonography.

**Results**

Before age 2-3 years, all individual kidney lenghts are within the normal range for age. After age 2 years,

some individual kidney lengths start to deviate from the 5-95 centiles for normal children: they can be above the 95th centile, indicating upper tract dilatation and obstructive uropathy, or below the 5th centile, as a consequence of retarded growth and/or scarring.
The prevalence of kidney parenchymal scars in the Utrecht population is 15%, about half the incidence reported in the literature. As yet, there are no cases of renal failure in this population.




Abnormal kidney lenghts as well as scarred kidneys occur predominantly in the MMC-children with overactive pelvic floor muscles due to detrusor-sphincter dyssynergia.
**Hypothesis** It seems clear that children with MMC are born with normal kidneys, and that even with up-to-date management scarring and upper tract dilatation do occur, predominantly in the presence of detrusor-sphincter dyssynergia.
Both the incidence of scars in the very young and the progression of scarring to renal failure can and should be avoided, by introducing CIC with antimuscarinics, as early as possible, in the management of children born with MMC.

## TEAM NEURO-UROLOGY — FUTURE FORUM — GERIATRICS

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## POPULATION AGEING: DO WE NEED GERIATRIC UROLOGY?

**Aims of Study**
The purposes of this study are to investigate characteristic changes in the population pyramid and to find an answer to the self-imposed question of “Do we need Geriatric Urology?”
**Methods**
Data and documents were looked for in the domestic, international and WHO publications which dealt with ageing, the world population, and medical treatments of the lower urinary tract.
**Results**

As early as 1988 a consensus development conference of NIH reported that urinary incontinence was not part of normal ageing, but age-related changes predisposed to its occurrence, and that monetary costs of managing urinary incontinence among nursing home residents was approximately 3.3 billion US dollars (USD) annually.

Basic and clinical experiments reported that bladder function deteriorates as a function of age in rats (Saito; 1993) and in men. Resnick demonstrated that the elderly were urodynamically characterized by detrusor hyperreflexia with impaired contractile function (DHIC) (1987). The urethral sphincter was compromised by a decrease of the volume of the striated muscle and blood vessels and by an increased volume of connective tissue (Carlile; 1988). Strasser reported that apoptosis was responsible for loss of muscle cells of the rhabdosphincter which would lead to urinary incontinence (1999). The number of those suffered from urinary incontinence sharply increased in both men and women after 60 years of age except women suffered from stress incontinence (Kondo; 1992).

Urinary incontinence in the frail, elderly is frequently associated with impairment of cognitive and physical functioning and with overactive bladder (OAB). These people could be dealt with behavioral and/or pharmacological treatments or with surgery in case of stress urinary incontinence. In one of nursing homes in Japan urinary incontinence was prevalent in 87% of 400 residents with a mean age of 81 (Ueda; 1988). In 6 European countries OAB symptoms were present in 17% among 16,700 people over 40 years of age, and the symptoms were characterized by the fact that only 16% of presumable patients have been medically treated (Milsom; 2001).

During the past 50 years the world population has considerably increased in the absolute and relative numbers of older people in both developed and developing countries, which is referred to as “population ageing”. The population ageing is the result of less fertility, less mortality, and developments of new drugs and innovative medical technologies, which, in turn, elongates life expectancy and increases the population especially in the developing countries (WHO information, 1998).

The total fertility rate has been decreasing in the developed and developing countries alike. In 1950’s and 1960’s this number was over 3.0 in US and Holland, 2.8 UK and France, 2.5 in Denmark, Germany and Sweden, and 2.3 in Japan. However, after 1980 the ratio started to decline to a point less than 2.0 in the majority of developed countries and was only 1.36 in Japan in the year of 2000, suggesting that developed countries have been really losing their population.

Average life expectancy has continuously elongated in both developed and developing countries. In Japan it was 70 and 65 years for women and men in 1960, respectively, however, 40 years later, Japanese were enjoying the longest life expectancy in the world, i.e., 85 and 78 years in 2000. In more than 20 developing countries life expectancy is currently 72 years or above, that include Cuba, Malaysia and Republic Korea.

The population of 65 years and over has been also increasing. By 2025 there will be more than 1 billion people over 65 years in the world; two-thirds of them reside in developing countries. The ratio of the elderly will reach 31% in Japan, followed by 28% in Italy, Greece and Switzerland, 22% Germany, 20% UK, 19% US. Europe will be the oldest region in the world, i.e., 25%. The medical expenditure for these people will inevitably and immensely increase. In Japan, for instance, this value was 28% of the total medical expenditure in the year of 1990, but will be 41% in 2010.

Quality of life in those with urinary incontinence is substantially impaired. Namely avoiding social activity, absenteeism from works, sleep disturbance, lack of energy, and interference with sexual intercourse are pointed out as impairments (Kobelt; 1998).

The cost of drugs for treating BPH has increased 2.7 times in 10 years in Japan, namely from 2.8 billion USD in 1989 to 7.4 billion USD in 1998. In the US the cost to manage urinary incontinence in individuals 65 years of age or older was estimated 26.3 billion USD in 1995. In Sweden the estimated national costs of free incontinence aids accounted for 0.5% of the total costs of her healthcare, including the care and nursing of older and disabled people (Samuelsson; 2001).

Taking into consideration a rapid increase in the elderly in the whole world, urologists and urogynecologists alike must take positive attitudes towards the treatment of LUTS, ultimately helping improve the confidence of those people suffering and contributing to a decrease in healthcare costs. We must be aware of the fact that urinary incontinence can be cured or improved provided the etiology and the environment are appropriately assessed and analyzed.

## Conclusions

The answer to the self-imposed question of “Do we need Geriatric Urology?” is yes.

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# TEAM NEURO-UROLOGY — FUTURE FORUM — SURGICAL APPROACHES

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## SURGERY IN NEUROPATHIC VESICO-URETHRAL DYSFUNCTION

Most neurological conditions give rise to bladder and urethral dysfunction, particularly detrusor over- or under-activity, detrusor-sphincter dyssynergia (DSD) causing obstruction, or sphincter weakness causing incontinence. Mixed lesions may results in a combination of effects on vesico-urethral function. The functional disorder may result in failure to empty, failure to store, or to a mixture of both. The place of surgery has changed with the advent of successful conservative stratagems to be discussed by Prof JJ Wyndaele. This presentation will discuss the possible surgical stratagems available to address each of the functional disorders based on full urodynamic workup.

Failure to empty may be due to detrusor underactivity (acontractile detrusor or impaired contractility), or to urethral resistance being too high. Intermittent self-catherisation (ISC) is often the treatment of choice, but may be precluded by tetraplegia or cognitive dysfunction.

When detrusor underactivity is the problem, augmentation of detrusor activity may be possible in patients with suprasacral SCI, by using sacral anterior root stimulation (Brindley-Finetech)[1,2,3] to drive electro-micturition, electro-erection (in men), and bowel function. An alternative stratagem has been the use of detrusor myoplasty with either latissimus dorsi[4] or rectus abdominis[5] with functional electrostimulation (FES).

In men, lowering urethral resistance by endoscopic sphincterotomy may be accomplished by diathermy knife or laser[6,7], but not without hazard[8,9], or by a trans-sphincteric stent ( e.g. UroLume), which on RCT[10,11] seems to yield equivalent results. There are a few reports of 150U of Botulinum-A toxin (BoTox) injected into the rhabdosphincter[12,13]. A condom catheter is used to manage the ensuing incontinence. In women, ISC or a suprapubic catheter (SPC) may be better options.

The future seems to lie with enhancement of electrostimulation techniques and myoplasty to enhance detrusor function when it is deficient. When DSD is the problem, UroLume or Bo-Tox injection into the sphincter may prove preferable to sphincterotomy by any technique.

Failure to store results from either detrusor overactivity (phasic contractions in hyperreflexia in suprasacral lesions, or low compliance in some infrasacral lesions), or from low urethral resistance. Incontinence results.

When elevated intravesical pressure is the cause there may benefit from antimuscarinics. When these fail, denervation techniques[14,15], neuromodulation[16,17], or intravesical BoTox (300IU)[18,19] have been used. Bladder augmentation by enterocystoplasty[20] or detrusor myomectomy[21] followed by ISC may be required.

When neuropathic sphincter weakness causes incontinence, urethral resistance can by augmented by the artificial urinary sphincter (AUS)[22,23], periurethral bulking agents[24,25], suburethral slings[26,27] or dynamic graciloplasty[28,29].

In the future we may see progress in the use of neuromodulation, now only in its infancy. The technique can reduce detrusor overactivity to enhance storage and can be applied to facilitate voiding as in the Fowler syndrome. Further development using multichannel (15-30) stimulators is underway. The poor durability of periurethral bulking with collagen will see this material replaced by other agents (Durasphere) or balloons (ACT device), or suburethral slings. The Prosthetic bladder, in development for 10 years, seems still be a long way from providing SCI patients with a long term solution to their problem[30].

Catheter management of the neuropathic bladder is seldom a “fit and forget” solution to the problem. The underlying vesico-urethral abnormality (DO, low compliance, sphincter weakness, loss of sensation) must still be managed appropriately. Only as a last resort, urinary diversion to a conduit or continent urinary reservoir may be appropriate. Management should aim to preserve renal function, restore continence, independence and sexual function where possible, and be compatible with the patient’s wishes and physical and cognitive abilities. This is especially true with progressive conditions.

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## TEAM NEURO-UROLOGY — FUTURE FORUM — NON-SURGICAL APPROACHES

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## NON-SURGICAL APPROACHES IN NEUROGENIC LOWER URINARY TRACT DYSFUNCTION

Therapy of neurogenic lower urinary tract (NLUT) is primarily a conservative one: regular and as complete as possible bladder emptying, controlled fluid intake, avoidance of urinary tract infection and incontinence are the prerequisites for successful treatment.

The actual treatment possibilities are behavioural techniques, intermittent catheterisation, drugs, electrical stimulation and external appliances. Indwelling catheters are more rarely used especially in the long term but can find indications in specific patients.

In every form of treatment more research is necessary to improve the success rate, to lower the complications and to gain a better socio-economic situation. Quality of life has become very important and has changed therapeutic decision making.

Intermittent catheterisation is actually considered as the mainstay of treatment in many patients with NLUT. So far not one best catheter and not one best technique have been determined. But several specific developments in catheter types occur including the hydrophilic reusable, antibiotic coated etc. It remains to be seen if these bring the solution. So far patients' compliance, good education of all involved and the following of the undisputed basic rules of catheterization seem the best ways to success. Many abandon IC after a while and it will be necessary to find out which the reasons are for this.

Behavioural training and physiotherapy have been and still are in full evolution. Suprapubic tapping and Crédé manoeuvre which used to be the most applied techniques 20 years ago have been greatly abandoned for unsafety unless patients meet special requirements. For detrusor hyperactivity scheduling regimens, detrusor inhibition with pelvic floor contraction, biofeedback, TENS and maximal electrical stimulation are studied. For detrusor hypoactivity maximal electrical stimulation is evaluated. The techniques will probably work better in patients with mild and moderate symptoms. The advantage is the lack of morbidity.

Pharmacological treatment is aimed more at controlling neurologic bladder overactivity and improving deficient urethral closing function. Peroral drugs have been used for many years with some success. The bothersome side effects as dry mouth, worsened constipation have been reasons to search for more specific and better tolerated drugs. Most drugs are $M_3$ (+ other M's) relaxants. Intravesical application has been tried out

and trials are been done with other types such as alpha-adrenolytics or drugs influencing the sensory system in the LUT.
Intravesical instillations with capsaicin and resinoferatoxine have been studied.
Sphincter spasticity and later on detrusor overactivity have been treated with Botulinum Toxin injections. These techniques seem promising but longterm effects and socioeconomic data need to be evaluated.
With increasing disability DDAVP (Desmopressin) has been added to treat daytime frequency. Sublingual cannaboid medicine extract is under investigation.
Non invasive modulation of the neurogenic bladder by electrical stimulation comprises ano-genital stimulation of the pudendal afferents, intravesical stimulation and transcutaneous stimulation. Good results and unrewarding experiences by other groups have been reported. For sure, intravesical stimulation depends on technical details as recent data have shown. This has to be further studied as IVES is the only available technique to induce/improve bladder sensation and to enhance the micturition reflex in incomplete cerebral or peripheral nerve damage. Industry is busy with research on other minimal invasive techniques permitting more easy access to stimulation in different part of LUT innervation.
External appliances seem to undergo an evolution in form regularly in a search to overcome problems with retractile penis, skin pathology et al. The development of an easy and effective external appliance for women has not succeeded yet.