# LECTURE 12: ARTIFICIAL BLADDER

## 12.1 Introduction

The urinary bladder is a hollow, muscular organ located in the pelvic floor and is part of the lower urinary tract. Other anatomical structures of the lower urinary tract are the urethra, internal urethral sphincter, external urethral sphincter, and ureters. The ureters drain the urine from each kidney into the bladder. The urethra is the outflow tract connecting the bladder to the exterior. The urethral sphincter enables the tight closure of the urethra.

The bladder itself is composed of four layers. The transitional epithelium or urothelium, which lines the interior surface of the bladder, is in contact with the urine. Under the epithelium is the lamina propria, a layer of connective tissue, smooth muscle and blood vessels. The third layer is the muscularis propria of detrusor muscle that forms the wall of the bladder. The outermost layer consists of a fibrous adventitia and a visceral peritoneum.

## 12.2 The Artificial Bladder

Several implantable medical devices and (surgical) techniques are available for the treatment of bladder dysfunction. Some of these devices and techniques have proven to be successful. Far-reaching surgical procedures (e.g., rhizotomy), technical failures (in case of artificial urethral sphincters), and the lack of selective neural activation must be overcome before these implantable medical devices can gain more widespread use.

Several cell-based approaches for bladder repair, reconstruction and replacement are being explored worldwide. These approaches do not comprise the development of the bladder as a whole organ, but are focused on specific parts or diseases of the bladder:

I) Recovery of the urethral sphincter,

II) Treatment of vesicoureteral reflux

III) Recovery or replacement of the bladder wall.

Clinical trials have been performed or initiated in all of these groups.

- The two main methods for replacing bladder function involve either redirecting urine flow or replacing the bladder *in situ*.
- Standard methods for replacing the bladder involve fashioning a bladder-like pouch from intestinal tissue.
- An alternative emerging method involves growing a bladder from cells taken from the patient and allowed to grow on a bladder-shaped scaffold.

## 12.3 Bladder function: micturition and continence

The function of the bladder is urine micturition (periodic evacuation of urine) and continence (storage). The bladder can store approximately 500-600 ml of urine for 2-5 hours. Once the bladder contains 150-300 ml, the urge to micturate is developed and signaled. Although the choice when to urinate is under voluntary control, once decided to do so the external urethral sphincter is voluntary relaxed and the autonomic nervous system causes detrusor contractions in the bladder wall, resulting in micturition. When the bladder is empty, the detrusor relaxes and the sphincters contract to close the urethra.

Normal bladder function involves a unique combination and interaction of autonomic and somatic functions. It is mediated by neural circuitry located in the brain and lumbosacral spinal cord. The lower urinary tract is controlled by three sets of peripherals nerves: sympathetic (hypogastric), parasympathetic (pelvic), and somatic (pudendal) nerves. Together, this complex system regulates continence and micturition and protects the upper urinary tract.

### 12.3.1 Bladder dysfunction

Actual damage of the peripheral or central nervous system, or disruption of the finely tuned balance between inhibitory and excitatory stimuli, results in continence and/or micturition disorders. Neurogenic bladder refers to a malfunctioning bladder due to neurologic dysfunction. This is often associated with spinal cord diseases, brain diseases, or peripheral nerve diseases, but may also be caused from internal or external trauma. Affected patients will demonstrate symptoms of urinary frequency-urgency, urge incontinence, and urinary retention, and complete micturition is problematic.

The spinal reflexes are lost, the bladder has no muscle tone and does not contract to empty automatically. Instead, it continues to fill and micturition is usually inefficient.

## 12.4 Medical device-based approach for function recovery

Several medical devices and techniques have been developed to restore bladder function. Whereas mechanical medical devices are limited to treating symptoms of organ dysfunction, devices using electrical stimulation can exert control over muscles and their neural control systems restoring function to persons with neurological or sensory impairment. The basis of electrical stimulators or neural prostheses is the application of electrical current pulses which generate artificial action potentials in axons of (peripheral) nerve fibers or neurons in the spinal cord by depolarization of the cell's membrane.

Five primary locations can be identified where electrical stimulation is applied: on peripheral nerves, sacral roots, in the spinal cord itself, in/adjacent to the urethra, and on the skin. In general, two techniques can be distinguished: neurostimulation and neuromodulation.

### 12.4.1 State of development

An overview will be given of the state of development concerning electrical, hydraulic, mechanical and other types of medical devices for restoring bladder function.

Devices, stimulation techniques, and some surgical techniques that are likely to affect the field in the future are described.

### 12.4.1.1 Electrical medical devices for neurostimulation

#### *Sacral nerve root stimulation*

In the early/mid 1980s sacral nerve root stimulation was reported in patients with spinal cord injury to enable micturition. The sacral root stimulation system was developed by Brindley Bladder System. Since then, some 3000 of these devices have been implanted. In general, it has provided good results (in some cases for over 15 years) and achieved sustained clinical use in spite of a few drawbacks.

The implantable components of the Finetech-Brindley Bladder System include tripolar ‘book’ electrodes, leads, and a passive receiver/pulse generator. The implant has no batteries and the various components are encased in silicone. The external portable control unit consist of an antenna connected to an external transmitter/controller device which allows programming of the stimulation parameters by a clinician, and provides the power for nerve root stimulation.

However, in many spinal cord injuries subjects these reflexes are not adequately functional and can be restored by other techniques. In recent years, patients have often objected to this intervention, not only because of the above-mentioned drawbacks, but also because it is irreversible. In addition, researchers in the field of spinal cord repair proclaim means of curing spinal cord injury in the (foreseeable) future.

#### *Sacral nerve neuromodulation*

Sacral nerve neuromodulation is used as therapy for non-neurogenic bladder dysfunction. Techniques for accessing the sacral nerves through the sacral foramina were developed making the implant procedure faster and less invasive. Implantable Neurostimulators are marketed (Figure 1). InterStim® was first introduced in the early

1990s and presently more than 25.000 implants worldwide have been performed. The implantable system is comprised of a battery-powered electrical stimulator, an extension cable (not for the InterStim® II), and a lead with electrodes.

Subsequent adjustments of the stimulation parameters can be accomplished easily and noninvasively with an electronic programming device. The battery can run for about five years and can be replaced during an outpatient procedure. Sacral nerve neuromodulation is only effective in a subset of patients with lower urinary tract dysfunction; therefore all patients are initially evaluated with a percutaneous electrode connected to an external stimulator to assess their response to this treatment before permanent implantation.

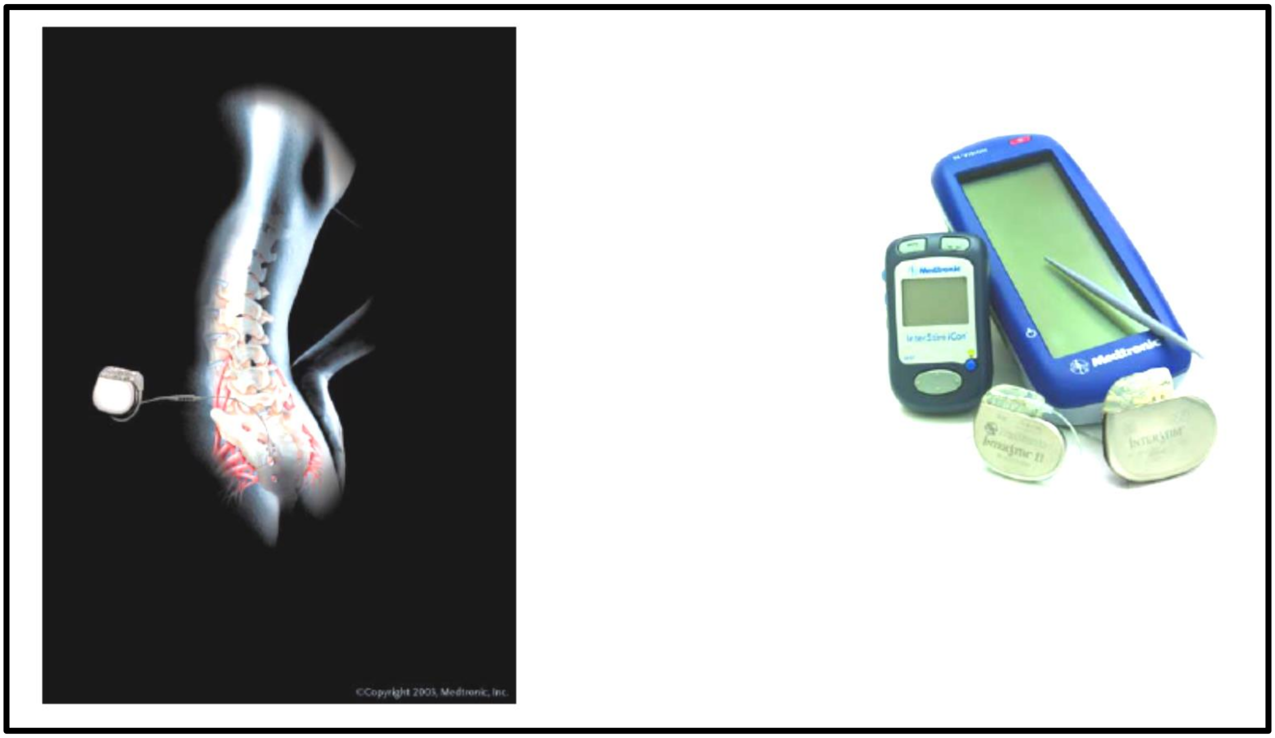

**Figure 1:** Anatomical position of the lead and the neurostimulator (on the left). consists of two implantable models

### 12.4.1.2 Hydraulic medical devices - artificial urethral sphincters

Artificial urethral sphincters are used primarily to treat stress urinary incontinence in male patients due to radical prostatectomy and in female patients due to intrinsic sphincter deficiency with or without hypermobility of the bladder neck or urethra. These devices are also successfully in managing incontinence with other aetiologias.

Artificial urethral sphincters simulate normal sphincter function by opening and closing the urethra under patient control.

The AMS 800™ Urinary Control System is an implantable, fluid-filled, solid silicone elastomer device. The basic concept of the system was a family of artificial urethral sphincters evolved. The system consists of an inflatable cuff, a control pump with lower squeezable part and upper hard part containing deactivation button, and a pressure-regulating balloon reservoir attached to each other with kink-resistant tubing. The pump deflates the cuff placed around the bladder neck or urethra by transferring fluid to the pressure-regulated reservoir.

Recently, a novel device with conditional occlusion has been clinically tested and may offer improved outcomes and decreased complication rates. This device, known as the Flowsecure®, UK), incorporates many characteristics in common with the AMS 800™ device. However, it also includes a number of innovative features, which aim to overcome some of the disadvantages of the AMS 800™.

## 12.4.1.3 Mechanical medical devices

### *Balloons*

A novel approach is the Adjustable Continence Therapy (ACT® for female patients). The system is a minimally invasive implant designed to treat stress urinary incontinence after other therapies have failed. It consists of two balloons placed para-urethrally just beneath the bladder neck. A titanium port, which is placed in the scrotum or labium, is connected to the balloons that allow incremental postoperative adjustments via percutaneous volume changes in the implant, so as to accommodate any individual responses to the altered outlet dynamic.

***Stents***

Obstruction of the urinary tract can be overcome by insertion of endoprosthesis devices. Urethral and ureteral stents can be used for the treatment of lower and upper urinary tract obstructions, respectively. Urethral stents are inserted into the urethra and mechanically support the duct wall to keep the lumen of the external urethral sphincter open. Ureteral stents are implanted into the ureter to restore urine flow from the kidneys to the bladder. Urethral stents were first developed to treat urethral strictures, but were also proposed as an alternative to sphincterotomies, the primary surgical treatment for patients with detrusor-sphincter dyssynergia.

Biodegradable stents are in an early stage of development but hold considerable promise for overcoming many of the limitations of permanent metallic implants. New configurations of bioabsorbable urethral stents are being developed to overcome sudden collapse of the stent in the terminal phase of bio absorption, urethral scarring, and periurethral fibrosis. Stents for treating urethral strictures in the anterior urethra are mostly bio absorbed, whereas those in the prostatic urethra biodegrade into small fragments which are washed out with urine.

## 12.4.1.4 Other types of medical devices

***Intraurethral pump***

The In-Flow™ Intraurethral Pump developed by SRS Medical Systems, Inc. (Billerica, MA, USA) incorporates a miniature valve and pump that can be inserted into the urethra to control both continence and micturition in women.

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. 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 patients when necessary.

Intraurethral Pump is designed to be replaced every month and is unsuitable for chronic use, but successful usage to an average of 90 days has been reported, at which time the device becomes fouled by salt deposits.

### *Catheters*

There are two types of urinary catheterization techniques employed clinically: indwelling catheterization and intermittent catheterization. The indwelling urinary catheter, as used today, was developed by F. Foley and first manufactured commercially in 1930s with the fundamentals of the design of the device remaining relatively unchanged since then. It is a hollow, sterile tube that is passed through the urethra, being retained within the bladder by the inflation of a balloon just below the drainage eyelets of the device. However, inherent flaws remain. Complications include urinary tract infection with device-associated blocking encrustations, biofilm formation, and bacterial adherence. Catheter-associated infections can be reduced if the catheter is removed as soon as possible. Patients can be taught to catheterize themselves within a few weeks after a spinal cord lesion. For selfRIVM report, catheterization good hand function is a prerequisite. Catheterization seldom stands alone.

## 12.4.1.5 Recent research efforts and future devices

Besides the above discussed devices, a large body of research is carried out, both on the development of new approaches and on the improvement of existing technologies. Specific areas of interest are the following:

- Sacral posterior and anterior stimulation: refinement and improvement of the Finetech-Brindley Bladder System

- Selective activation techniques: leading to a more physiological continuous micturition pattern, occurring at lower intravesical pressures.
- Bionic neurons (BIONs): injectable, wireless intramuscular microstimulators with integrated electrodes, indicated for urinary urge incontinence. In Europe BION3 is market-approved.
- Intraspinal microstimulation: possibility to achieve coordinated micturition through reductions in sphincter pressure and increases in bladder pressure.
- Control inputs to neural prostheses: enabling a closed-loop system which may replace surgical rhizotomy of sacral posterior nerve roots.
- Para-urethral neuromodulation: implantable system for the treatment of refractory interstitial cystitis; the miniaturo™-I device is undergoing clinical investigations for female patients.
- Percutaneous tibial nerve stimulation: alternative method of neuromodulation in the treatment of overactive bladder symptoms; the Urgent® PC Neuromodulation System is available; an implantable subcutaneous stimulation device is under clinical investigation.
- Optical stimulation of neural tissue: possible future alternative to electrical stimulation in certain situations.
- Artificial optical nervous system: future technology leading to e.g. less electromagnetic interference and more stability, resilience and biocompatibility of wiring.
- Urethral neo sphincter construction: surgical technique where the gracilize muscle is transposed from the inner thigh to construct an autologous neo sphincter in conjunction with electrical stimulation.
- Intradural nerve anastomosis: experimental technique to construct an artificial somatic central nervous system-autonomic reflex pathway in patients with spinal cord injury and

- in children with spina bifida.

## 12.5 Cell/tissue-based approach for function recovery

Gastrointestinal segments are commonly used as tissues for bladder replacement or repair. However, gastrointestinal tissues are designed to absorb specific solutes, whereas bladder tissue is designed to store urine with minimal solute transport across the urothelium. When gastrointestinal tissue is in contact with the urinary tract, many complications may ensue, e.g. infection, metabolic disturbances, urolithiasis, perforation, increased mucus production and malignancy. Because of the problems encountered with the use of gastrointestinal segments, numerous investigators are attempting to develop a tissue engineered bladder that approaches the mechanical and functional characteristics of the natural bladder.

### 12.5.1 State of development

The most common cell-based approaches currently under development for bladder repair or replacement are aimed at the following: recovery of the urethral sphincter, treatment of vesicoureteral reflux, and recovery or replacement of the bladder wall.

#### *Recovery of the urethral sphincter*

Stress urinary incontinence may occur in case of intrinsic sphincter deficiency, which means that the urethral sphincter (muscles to control the flow of urine from the urinary bladder) does not properly function. Cell-based therapies resulting in a stable and functional treatment of this deficiency have been proposed. One of the suggested approaches for the recovery of the external urethral sphincter of people suffering from incontinence is injecting adult stem cells with the potential to differentiate in muscle cells in the sphincter or bladder neck. Adult stem cells may be derived from striated muscles, fat tissue or as mesenchymal cells from bone marrow. These cells can differentiate in functionally normal smooth or striated muscle cells and thereby have the potential to increase the urethral closure pressure. Favorable findings of trials in animal models and in vitro results are encouraging to start clinical trials in humans and hold a promising future for the treatment of urinary incontinence.

### *Treatment of vesicoureteral reflux*

Vesicoureteral reflux is an abnormal movement of urine from the bladder into ureters or kidneys. Urine normally travels from the kidneys via the ureters to the bladder. In vesicoureteral reflux the direction of urine flow is reversed (retrograde). Vesicoureteral reflux is most commonly diagnosed in infancy and childhood after the patient has a urinary tract infection (Figure 2).

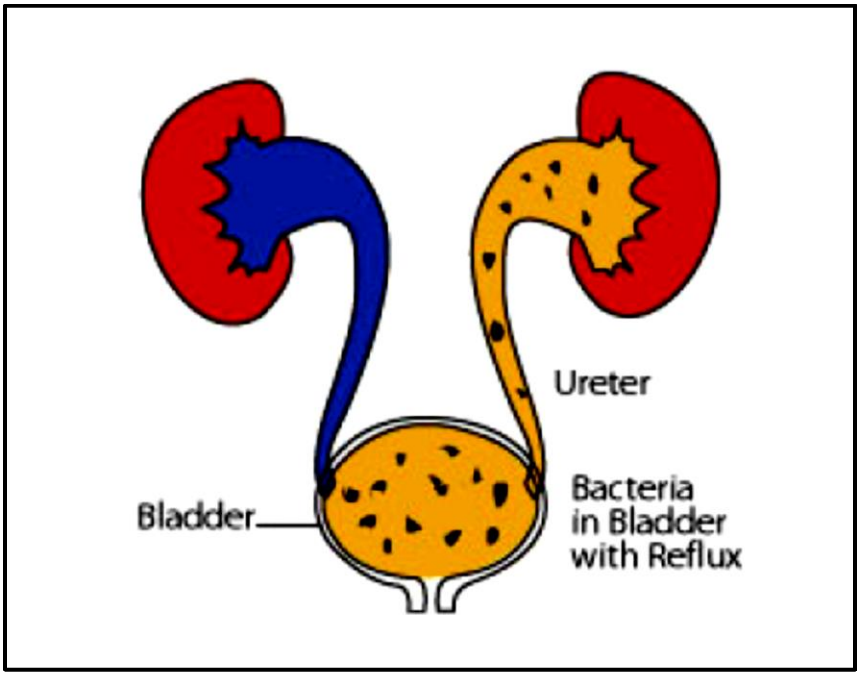


**Figure 2:** Urinary system with vesicoureteral reflux.