



# Newsletter

## Invitation to Berlin

### 31st Congress of the Société Internationale d'Urologie

### October 16-20, 2011

With the success of SIU 2010 still fresh in our minds, it is with much excitement that we begin to look forward to the next SIU Congress in Berlin.

Planning for SIU 2011 has been underway for quite some time now, and we are proud to present to you a one-of-a-kind scientific and social programme.

With the help of a global programme committee covering all the subspecialties, Scientific Chairs Drs. Gerald Jordan and Michael Marberger have assembled some of the biggest names in urology to share their expertise on the hot topics of today and the trends for tomorrow. We are grateful to those experts who have graciously agreed to contribute of their time and join us in Berlin.

Topic-wise, SIU 2011 will offer comprehensive coverage of areas of interest in current urology. The main plenaries will cover prostate cancer, bladder cancer and BPH, while

parallel plenary sessions will present the latest in pediatric urology, testis cancer, male and female incontinence, infections, urinary diversion, trauma from minimally invasive surgery (MIS), global perspectives on urethral reconstruction, stones, kidney cancer, diagnosis of urothelial tumors, neuro-urology, laparo-endoscopic single-site (LESS) surgery and urogenital fistula.

Other popular sessions, such as surgical tips and a full-day live surgery component, have also been scheduled. SIU Consensus & Education Chair Dr.



*Prof. Joachim W. Thüroff*  
SIU President

Richard Santucci has developed a varied and thought-provoking series of Instructional Courses - chaired by key opinion leaders - which will be offered on three consecutive mornings.

On October 15 and 16, SIU 2011 will also welcome the World Urological Oncology Federation (WUOF), chaired by Dr. Laurence Klotz and covering the topic of geriatric urooncology – an issue of tremendous relevance that will be tackled by a world-class faculty.

And finally, the International Consultation on Urologic Diseases (ICUD) is working in conjunction with the SIU to

produce a Consultation on prostate cancer. Chaired by our esteemed colleagues, Prof. Manfred Wirth and Dr. Gerald Andriole, this Consultation will provide an extremely valuable update for our clinical practices.

I also encourage those of you who have not done so already to submit your abstract for presentation in Berlin. All submissions must be made online ([www.siucongress.org](http://www.siucongress.org)) by midnight EDT, April 1, 2011.

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Remember to visit the  
SIU booth (Y72) in  
Vienna, March 18-22,  
2011, at the European  
Association of Urology  
Annual Meeting!



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Of course, SIU Congresses are known for more than just their quality scientific programmes. Local Organizing Chair Prof. Margit Fisch and her committee have done a fantastic job selecting activities that are sure to appeal to both visitors and locals.

On Monday, October 17, the LOC will welcome you to Berlin Station for an Oktoberfest-themed party. The following evening, guests will be able to purchase an optional activity suited to their interests and budget. The final formal event is the ticketed SIU Gala Banquet, held at the elegant Schlüterhof German Historic Museum.

While it is no easy task to condense all of German culture into a few evening events, I am sure that the activities on offer will inspire many visitors to explore our country on their own! To find out more about SIU 2011, and to register, visit the Congress website at [www.siu-congress.org](http://www.siu-congress.org)

I hope to see you all in Berlin!

*Prof. Joachim W. Thüroff, SIU President  
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## The New Ice Era

### Prostate Cancer Cryoablation

#### Introduction

Cryoablation therapy has gained interest for the treatment of prostatic adenocarcinoma since the American Urological Association recognized the procedure as a viable surgical treatment modality. The development of new cryotechnology i.e.; cryoprops with precise isotherm delineation, the employment of active thawing cycles, and argon and helium gas-induced freezing and warming and creation of urethral warmers have allowed surgeons to better control the application of extremely low temperatures to the tissues targeted for ablation. Long-term oncological outcomes have not been established but the continuous evolution of cryotechnology and improved understanding of the disease may allow the advancement of focal ablative therapy.



*Dr. Fernando J. Kim*

that apoptotic induction can be facilitated in prostate cancer cells through an extrinsic pathway involving tumor necrosis factor-related apoptosis-inducing ligand.<sup>2</sup>

Successful cryodestruction results from procedural factors that maximize malignant cell death, which includes the freeze rate, end-temperature, time, and freeze-thaw repetition.<sup>1</sup>

Tatsutani and colleagues studied thermal parameters associated with prostate cancer destruction in an ND-1 cell line. They demonstrated that temperatures less than -40°C were required for complete cell death.<sup>3</sup> In addition, the investigators noted that a faster freezing rate resulted in optimal cellular destruction, a finding reported by other groups.<sup>4</sup>

The second cycle has demonstrated an increased area of necrosis and effectiveness of the local ablation relative to the first cycle. Implementing a second freezing cycle also lowers the lethal temperature of the tissue to -20°C. The optimal freezing and thawing rates are still in discussion.

Contemporary cryosurgical technique provides precise temperature management of the targeted tissue with the combination of intra-operative real-time ultrasound imaging of the prostate with adjacent structures and temperature monitoring. Throughout the frozen prostate, the cancer cells not destroyed by intracellular ice undergo either necrotic or apoptotic cell death depending on the extent of the stress experienced and the cell-cycle stage.<sup>5</sup>

Immediately post-thaw, some cancer cells will have experienced partial physical damage and will then undergo a bout of primary necrosis within one hour. This event, along with the presence of cell fragments resulting from freeze rupture, is responsible for the inflammatory cascade. Between 6 to 12 hours post-ablation, surviving cancer cells experience the onset of apoptosis. A secondary

#### Cryotherapy cell injury mechanism

The mechanism of cell injury from cryotherapy is well understood. Cellular responses to freezing induce cell death, which includes freeze rupture necrosis and apoptosis. With the onset of ice formation, water is extracted from the extracellular solution as pure ice, leaving an increasingly hyperosmotic solution. This hyperosmotic extracellular solution causes cell shrinkage and damage to the intracellular matrix due to high salt content. The extracellular osmolality of the prostatic tissue increases to approximately 8,000 mOsm by -15°C. As the temperature approaches -15°C and below, lethal intracellular ice begins to form. In a structurally encapsulated organ, the expanding ice destroys the capillary endothelial lining, causing vascular impairment after thawing.<sup>1</sup> Apoptosis has recently been linked with thermal injury causing mitochondria-induced intrinsic damage. Clarke et al. have demonstrated

cascade of tissue necrosis occurs due to the vascular stasis resulting in local hypoxia approximately 24 to 48 hours after the “freeze rupture” effects.<sup>5</sup>

### Patient selection

According to the AUA guidelines, “the consensus opinion of the Panel concluded that primary cryosurgery is an option, when treatment is appropriate, to men who have clinically organ-confined disease of any grade with a negative metastatic evaluation. High-risk patients may require multi-modal therapy.”<sup>1</sup> Eligible prostate cancer patients include those who have clinically organ confined disease.

Although cryosurgery is an option for low-, intermediate-, and high-risk patients, gland volume is a factor; the larger the prostate, the more difficult to achieve a uniformly cold temperature throughout the gland. Prostate volume less than 50cc is a good candidate for cryotherapy and requires a single session. A prostate volume between 50 and 100cc may require more than one session for successful treatment. In larger glands, hormone therapy can be implemented to reduce the prostate size and obtain a manageable prostate volume for cryotherapy although there are no data to suggest that this improves outcomes. In our institution, we also consider the use of 5  $\alpha$ -reductase inhibitors to shrink the prostate.

### Advantages of cryoablation

Compared to external beam radiation therapy which requires months of continuous treatment, the minimally-invasive nature of cryoablation allows patients to be treated as outpatients, thus decreasing costs and improving patient satisfaction. Recently Kimura et al. demonstrated that cryoablation potentially improves urinary function after salvage prostate cryoablation.<sup>6</sup>

According to the AUA cryotherapy panel, cryosurgery is a minimally-invasive option when treatment is appropriate for men who either do not want or are not good candidates for radical prostatectomy because of comorbidities, including obesity or a prior

history of pelvic surgery. Cryosurgery may also be a reasonable option in men with a narrow pelvis or who cannot tolerate external beam radiotherapy (EBRT), including those with previous nonprostatic pelvic radiation, inflammatory bowel disease, or rectal disorders.<sup>1</sup>

### Surveillance after cryotherapy

As with other therapies for prostate cancer, post-treatment PSA measurements are an integral part of follow-up. At Denver Health Medical Center, patients post-cryoablation are monitored every 3 months with PSA levels for the first 3 years and every 6 months afterwards. PSA measurements are expected to be minimal but not undetectable because of the preservation of tissue surrounding the urethra.

Currently there is no universally established definition of biochemical failure after cryoablation. One method to determine biochemical failure is a comparison to a set PSA threshold. The American Society for Therapeutic Radiology and Oncology (ASTRO) proposed that 3 consecutive PSA increases post-treatment constitute biochemical failure. More recently, the new Phoenix criteria have been used, which define biochemical recurrence when the PSA is greater than nadir plus 2 ng/mL, since this is an “organ-preserving” procedure.<sup>1</sup>

These definitions are still experimental, requiring long-term studies. The uncertainty associated with these definitions suggests prostate biopsy may be the best method of surveillance for recurrence. However, the reported incidence of negative biopsy after one or more treatments is high, ranging from 87% to 98%.<sup>7</sup>

### Summary

In summary, prostate cryoablation is a minimally-invasive surgical modality that may benefit patients with localized prostate cancer, offering low morbidity, especially after the development of new generation cryoprobe, urethral warmers, and freezing/thawing techniques. The surgeon must carefully select patients, as well as address and discuss

patients’ expectations at length. Recent reports of focal cryotherapy of the prostate have shown potential application for a very well-selected group of men with localized, low-grade and low-volume prostate cancer.

### Conclusion

The new “Ice Era” in minimally-invasive technology has allowed organ-sparing surgery in patients with prostate, kidney and other pelvic and abdominal organ cancers. Although the long-term oncological results must be reported to validate this procedure, we cannot ignore the advances in cryotechnology, from liquid nitrogen to the argon/helium, urethral warmers, temperature probes, smaller probes, high definition real-time ultrasound imaging and the relative short learning curve to perform this procedure safely. There is room to improve the technology but cryoablation of the prostate and kidney tumors seems to be a safe and effective method of organ-sparing surgery for cancer, allowing repetition of the procedure and/or staged surgery. ■

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# How to Select the Right Antimuscarinic

## Evidence-Based Medical Treatment for the Overactive Bladder

Overactive bladder (OAB) is characterized by urgency, with or without urge incontinence, usually associated with frequency and nocturia. It is a highly prevalent condition and there have been numerous publications over the last decade regarding different treatment modalities.

### Mainstream: pharmacological treatment

Pharmacological treatment is the mainstream treatment of this condition, and antimuscarinic (anticholinergic) drugs are by far the most prescribed products. The rationale for their use is to block muscarinic receptors at detrusor and non-detrusor sites to prevent OAB symptoms and bladder hyperactivity without depressing bladder contraction during voiding. Although most commercially available products have proven efficacy with level 1 evidence and grade A recommendation for use, there are differences between them in terms of selectivity, pharmacokinetics and side-effects (Table 1).

Patients suffering from OAB may also have specific characteristics because

of age, underlying diseases, associated conditions and use of co-medications. For these reasons, it is sometimes difficult to decide which antimuscarinic to prescribe. By using available evidence from the 4th International Consultation on Incontinence (Paris 2008) and recent publi-



Luc Valiquette, MD

**1-Safety concerns:** All products are safe when used at recommended dosage in healthy patients. However, these drugs have different pharmacokinetics and some clinical conditions may favour use of a specific product. **With severe renal impairment**, maximum dosage must

be reduced for Fesoterodine, Solifenacin, Tolterodine and Trospium and this may favour use of Darifenacin, Oxybutynin or Propiverine. **With moderate to severe liver impairment**, caution and a reduced dosage are recommended for all antimuscarinics. When patients are taking other medications metabolized through the Cytochrome P450 system, caution is recommended with Darifenacin, Fesoterodine, Oxybutynin, Propiverine, Solifenacin and Tolterodine. This may favour Trospium. Precaution is required with Tolterodine, Trospium and Solifenacin in patients with congenital or acquired QT interval prolongation as seen sometimes with concomitant use of cardiovascular drugs. This may favour use of Darifenacin or Fesoterodine.

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**2-Tolerability:** All antimuscarinic drugs are associated with anticholinergic side-effects, mainly **dry mouth and constipation**. Oxybutynin has the highest incidence of dry mouth, while Oxybutynin and Darifenacin are associated with higher incidence of constipation: these considerations may favour use of

	Darifenacin hydrobromide	Fesoterodine fumarate	Oxybutynin chloride	Propiverine hydrochloride	Solifenacin succinate	Tolterodine tartrate	Trospium chloride
Type of drug	tertiary amine	tertiary amine	tertiary amine	tertiary amine	tertiary amine	tertiary amine	quaternary amine
Pure antimuscarinic	yes	yes	also muscle relaxant and anesthetic	also calcium channel blocking agent	yes	yes	yes
M3 receptor selectivity	highest	no	no	no	high	no	no
CyP450 metabolism	yes	yes	yes	yes	yes	yes	no
Half life	16h	7.3h	IR: 2-3h ER: 12-14h	IR: 14-20h	45-68h	IR: 2-3h ER: 8h	IR:18h ER: 35h
CNS side-effects	no	not clinically significant	yes (highest)	not clinically significant	not clinically significant	not clinically significant	no
Cardiac side-effects	no	not clinically significant	not clinically significant	not clinically significant	not clinically significant	not clinically significant	no
Dry mouth and constipation	yes	yes	yes (highest)	yes	yes	yes	yes
Hepatic metabolism	yes	yes	yes	yes	yes	yes	yes
Renal elimination	no	yes	yes	yes	yes	yes	yes up to 60%
Recommended initial dosage	7.5 mg q.d.	4 mg q.d.	IR 5 mg t.i.d. ER 10 mg q.d.	IR 15 mg b.i.d. ER 30 mg q.d.	5 mg q.d.	IR 2 mg b.i.d. ER 4 mg q.d.	IR 20 mg b.i.d. ER 60 mg q.d.
Dose escalation	to 15 mg	to 8 mg	ER to 30 mg	to 60 mg	to 10 mg	no	no

Table 1

# Bladder Replacement

## A Moroccan Experience

### Summary

**Objective:** We report 11 years' experience with 123 patients who underwent radical cystectomy for bladder cancer and orthotopic bladder substitution using a modification of the Studer pouch.

**Patients and Methods:** From 1998 to 2009, 120 men and 3 women, mean age 62 years (range 45 to 78), underwent bladder substitution after radical cystectomy. The pouch was constructed from 50 cm of isolated terminal ileum. The ureters were implanted in the proximal end of a 10 cm afferent tubular segment according to the Wallace technique. The distal 40 cm of the ileal segment was folded in a double "U" shape, opened along its antimesenteric side and closed with a continuous seromuscular suture, thus forming a spheric reservoir with low pressure.

**Results:** The mean operative time was 240 minutes. Early complications were ureteric obstruction in 5 cases requiring reoperation, 10 cases of urine leakage requiring prolonged hospital stay and 3 cases of peri-operative mortality. Late complications requiring surgery were neobladder outlet obstruction in 7% and incisional hernia in 8%. Based on our 11 years' experience and a median follow-up of 48 months, our results are encouraging: 98% of patients could void spontaneously, 95% had daytime and 82% had night-time continence with 3-4 hourly voiding intervals. Urodynamic evaluation showed an increased bladder capacity with low bladder pressure.

**Conclusions:** Our experience shows that ileal orthotopic bladder substitution gives good long-term functional results with a low pressure and high compliance reservoir which achieves continence in more than 90% of patients.

other products. All antimuscarinics have been studied for CNS related side-effects. Oxybutynin has the highest incidence of CNS symptoms. Darifenacin, because of its high M-3 receptor selectivity, and Trospium, because it is a quaternary amine, have the lowest incidence of CNS effects and may be preferred.

**3-Efficacy:** All products are superior to placebo and are recommended based on level 1 evidence. There are few published head-to-head comparisons, except against Oxybutynin IR, and all antimuscarinics show relative equivalence at recommended initial dosage. As a general rule, extended release (ER) formulations have demonstrated equivalence or superiority when compared to their immediate release (IR) formulations. For some products, dose escalation is possible at specific higher dosages (Darifenacin, Fesoterodine, Oxybutynin and Solifenacin), and this may prove useful for patients with difficult-to-control OAB symptoms.

**4-Price:** This may be a significant factor for drug access and compliance. Drug availability and price vary widely from country to country, and this has important consequences for patients and health care payers. Older products are often available in **generic formulations**, and this may favour Oxybutynin, Propiverine and Trospium.

**5-Simplicity of use:** Food interaction affects mainly Trospium IR but has limited impact for all other antimuscarinics. **Once-a-day formulations** are easier to take and improve compliance. This favours use of Darifenacin, Fesoterodine, Oxybutynin ER, Propiverine ER, Solifenacin, Tolterodine ER and Trospium ER.

**Conclusion:** Use of antimuscarinics is the recommended initial treatment for OAB symptoms. All commercially available formulations are effective, but differences exist between products. Selection of the right drug depends on patient and product-specific criteria. ■

Luc Valiquette, MD  
SIU General Secretary  
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### Introduction

Orthotopic neobladder replacement has proven to be the most elegant and accepted mode of urinary diversion because of its good functional results that are close to the preoperative state.

From 1988 to 2009 we performed 123 bladder substitutions in 120 men and women who underwent radical cystectomy for invasive bladder cancer. This procedure was performed only in patients who had invasive bladder cancer (T2,T3) with normal kidney function and a negative biopsy of the prostatic urethra.

### Technique

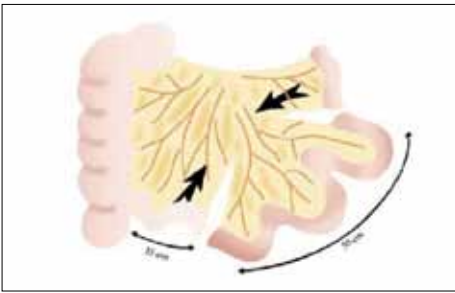
After bowel preparation the day before, we performed radical cystectomy with lymphadenectomy: cystoprostatectomy for men and anterior exenteration with preservation of the urethra for women.

Bladder substitution was performed by isolating an ileal segment 50 cm in length, preserving the last 25 cm of terminal ileum. The distal 40 cm of the ileal segment was shaped in a double "U" form. It was then detubularised by making an incision in the antimesenteric side. The free edges were sutured together, taking the full thickness of the wall, thus producing a spheric reservoir. The proximal 10 cm were kept intact for reimplantation of the ureters according to the Wallace technique.

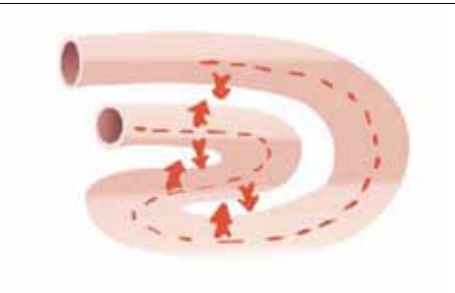
The site of urethro-neobladder anastomosis was chosen by introducing a finger into the neobladder so as to locate the lowest point. An incision (about 8 mm) was performed. A 3-way Foley catheter was then placed via the urethra into the pouch and the anastomosis was performed by 7 stitches of PDS 2/0. Ureteric catheters were exteriorized through the neobladder and the abdominal wall to protect the uretero-ileal anastomosis.

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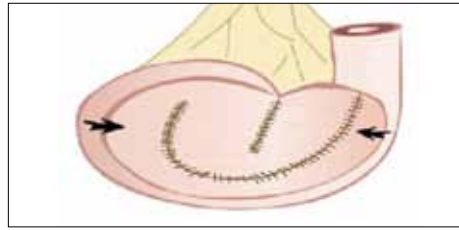
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Isolating the ileal segment



Ileum in double "U" configuration



Final aspect of double "U" configuration of orthotopic neobladder

## Results

The mean operating time was about 4 hours (range 3 to 6 hours) including the time necessary for performing the cystectomy prior to bladder replacement.

The average blood loss was 400 ml (range 300 to 900 ml). The average hospital stay was 12 days (range 8 to 22 days).

In our series the perioperative mortality was 4.6% (3 cases, 2 due to pulmonary embolism and one to myocardial infarction). Early complications occurred in 10

patients, 10 cases of urinary fistula and 5 cases of occlusion.

With an average follow-up of 6 years (range 4 to 10 years) the diurnal continence rate was 95% and the night-time continence rate 85% (32 cases). The neobladder average capacity was 500 ml. Urinary retention occurred in 2 cases and erectile dysfunction was present in all male patients. There was no ureteroileal stenosis. Urodynamic studies showed a good bladder capacity with low bladder pressure.

## Conclusion

Our orthotopic neobladder substitution has a good capacity with low pressure, which protects the upper urinary tract, and it has a high rate of continence. ■

Abdennabi Joual, MD, PhD

Ibn Rochd Hospital, Casablanca, Morocco

# An Unprecedented Success

## SIU 2010 World Meeting on Lower Urinary Tract Dysfunction

The SIU 2010 World Meeting on Lower Urinary Tract Dysfunction was an unprecedented success, attracting more participants than any previous SIU topical meeting.

While SIU 2010 was originally projected to welcome around 1,200 participants, the final count revealed that there were more than 2,400 attendees, representing over 90 countries, with delegates from Europe (68%), Africa (12%), Asia (12%), North America (5%), South America and Oceania (3%). The top five countries in attendance were Germany, Italy, Morocco, Poland and Turkey.

A number of factors contributed to this impressive showing: first and foremost, the strong scientific programme assembled by Dr. Paul Abrams, the late Dr. Dick Williams and their committee. The programme covered a range of topics relevant to a variety of settings and all geographical regions. Coupled with the fact that these topics were presented by key opinion leaders from all over the world, this programme was truly state-of-the-art.



SIU Moroccan Night at Dar Soukkar

In addition to the SIU programme, delegates also had the opportunity to attend special symposia presented by the Pan-African Urological Surgeons' Association (PAUSA) and the Association Marocaine d'Urologie (AMU). Both sessions were very popular and proved to be important venues for address-

ing urological issues facing African nations.

Other popular sessions included the two International Consultations on Urologic Disease (ICUD) plenary sessions, which presented the recommendations of the joint SIU-ICUD Consultations on Urethral Strictures and Vesico-Vaginal

Fistula. All ICUD subcommittee members deserve our thanks for their hard work and expertise. Publications from each consultation are scheduled to be released in 2011.

Of course, SIU 2010 was not only popular for its scientific aspects, but also for its location. Marrakech is a beautiful city, with a wealth of history and culture to share with visitors. Our generous hosts, led by Local Organizing Committee Chairs Drs. Redouane Rabii and Abdennabi Joul, organized a spectacular social programme that highlighted the best the city has to offer. The first off-site event, the SIU Moroccan Night, was held at breathtaking Dar Soukkar, and the Farewell Dinner took place at the remote and exotic Palm Grove. Both events were uniquely Moroccan and highlighted many exciting aspects of local culture and tradition.

In addition to the social programme, many extracurricular activities were organized for delegates by the SIU's local partner, Activ'Travel. The pre- and post-Meeting tours gave guests a chance to



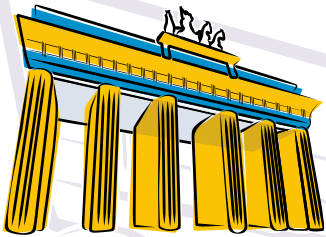
*Oulad Sidi Ahmed Ou Moussa perform during Opening Ceremonies.*

experience the spectacular geography of some of the most interesting parts of the country.

We hope that everyone who joined us in Marrakech enjoyed their experience at SIU 2010, and we are excited to in-

vite you all to Berlin, October 16-20, 2011 for the SIU's 31st Congress. To stay up-to-date on SIU Congress activities, visit [www.siucongress.org](http://www.siucongress.org)

See you in Berlin!



# SIU2011 berlin



**31st CONGRESS OF THE SOCIÉTÉ INTERNATIONALE D'UROLOGIE**

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# Medical Treatment of Erectile Dysfunction

## What Have We Learned in the Last Decade?

At the 91st AUA meeting in Orlando, in 1996, I was attending the podium session on erectile dysfunction (ED) when, suddenly, the room was filled with cameras from three major American TV networks. The paper to be presented, which was creating so much anticipation, was titled "Sildenafil: an orally active type 5 cyclic GMP-specific phosphodiesterase inhibitor for the treatment of penile ED", to be published later that year.<sup>1</sup>

In June 1998, 4 months after the launch of Viagra® in the US, the Brazilian Health Minister persuaded Pfizer to introduce the medication in the country because of the negative economic impact of illegal importation. I attended a patient who paid US \$70 for 1 pill of Viagra 50 mg in March 1998!

A search in PubMed using the terms "erectile dysfunction" or "impotence" indicated that 6,775 papers had been published until June 1996 (when the first paper on sildenafil was published). From July 1996 to December 2010, another 11,109 were published.

These facts give us a small idea about the impact from the launch of this new class of drugs, the phosphodiesterase type-5 (PDE5) inhibitors. For the first time in human history there was a non-invasive effective oral drug that could positively influence penile erection.

### One of the most successful pharmacological products ever

More than ten years have passed and there are at least five medications from the same group commercially available, including the 3 pioneers – sildenafil, tadalafil and vardenafil – the new ones – lodenafil and udenafil – and others which are still being researched.

Those medications can be used on demand or daily, depending on patient preference, and are currently the first

option of treatment adopted by most physicians and patients due to their high efficacy rates and favorable safety profiles.<sup>2,3</sup>

The PDE5 inhibitors can be considered one of the most successful products in the history of the pharmaceutical industry; millions of men have taken them during the last 10-12 years. However, their introduction in clinical practice brought some unexpected findings.

Despite being effective and safe drugs, their use is followed by a dropout rate of more than 50%.<sup>3</sup> There are several possible reasons for this. In some men with severe organic disease (e.g. diabetic neuropathy or pelvic surgery) the PDE5 inhibitors are not effective in promoting a rigid erection. Others try them to improve libido or even to treat premature ejaculation, most of the time not obtaining a good result.

Many men who do have a good erectile response do not persist using the medication due to emotional issues. Some patients do not enjoy the prospect of planning sex, claiming that it is not natural to take a pill and have to wait a specific length of time to engage in sexual activity. For others an erection, even as rigid as if they had become "young again", does not solve all relationship issues. A patient of mine told me once that although he got a wonderful response, his wife changed her mind and did not want to have sexual intercourse; he concluded that he had found a good medication for his erection problem, but was still married to the same wife.

### Recreational use of PDE5 inhibitors

In recent years, recreational use of PDE5 inhibitors as a sexual performance enhancement aid among some men without ED has become an issue. Korkes et al. related that almost 10% of

men who considered themselves as having perfect erectile function reported previous use of PDE5 inhibitors, among which 70% thought the drug had potential to facilitate condom use.<sup>4</sup> Other healthy men use the medication to reduce the post-orgasmic refractory time. The recreational use or abuse is facilitated in countries where prescription by a physician is not a firm requirement for purchasing, and worldwide by commerce through the internet. It has been estimated that up to 2.5 million men in Europe are exposed to illicit sildenafil.<sup>5</sup>

The recreational use of PDE5 inhibitors is associated with risks when they are taken together with other drugs. Furthermore, I have seen many young patients who had become psychologically addicted to these medications and could not try to have sex without taking them because of the fear of not getting a good erection and disappointing their partners.

### Counterfeit drugs: A growing problem

The "free" access to drugs for sexual performance enhancement leads to other situations. Counterfeit drugs are a growing problem; in Singapore, the Health Sciences Authority found that almost 80% of the natural sexual enhancement products were adulterated, 90% of them with PDE-5 inhibitors.<sup>6</sup>

The introduction of sildenafil and its successors was accompanied by a change in social behavior; probably never before in history was sexual dysfunction talked about so much. In the last decade, a great amount of time and money has been spent on public and physician education. Soon it was noticed that physicians in general were not prepared to deal with sexual issues, since there were very few medical schools worldwide with sexuality in their curriculum. While for many doctors ED is not a disease ("to treat real diseases such as cancer and diabetes is more important!"), others do not feel



Sidney Glina, MD



comfortable with the subject. In current medical practice, where medical fees are progressively lower, doctors do not have time to deal with a presumably time-consuming condition such as ED. Although we have much to improve, a great leap has been taken, and now in many parts of the world, general practitioners ask their patients about their sexual life and treat their dysfunctions.

What have we learned from the experience gained in the last 12 years with PDE5 inhibitors? Although we have found an effective and safe way to facilitate erection, we learned (or rediscovered) that sexual behavior is a little bit more complex than just an erection.

Nevertheless, men are eager to increase their confidence and guarantee their performance, even exposing themselves to risks and illicit drugs. Those men need to be better educated about their sexual function and understand that normal, healthy individuals do not need any enhancement to have good performance.

Lastly, cost is still an issue, preventing a more democratic use of PDE5 inhibitors. Reimbursement is still not very common all over the world. In Brazil, the launch of the sildenafil generic was followed by an increase in 50% on the PDE5 inhibitors' market performance. ■

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# In Memoriam: Richard Olivier Fourcade

1944-2010

On Christmas Day, the SIU lost a close friend and staunch supporter, Dr. Richard O. Fourcade.

During his medical studies, a meeting with the remarkable René Kuss at the Hopital Foch drew him decisively to urology. As early as 1974, he joined the recently-created Department of Urology at Pitié Hospital as an intern, later to become its Head. In 1979, Dr. Fourcade left for Auxerre, where his career as Chief of Urology flourished until his retirement in 2009. Under his tutelage, the institution gained wide recognition for its exacting standards and quality of patient



*Dr. Richard O. Fourcade*

debates featuring over 100 French experts crisscrossed the country, effectively demystifying the specialty and underscoring the wealth of expertise in France.

Dr. Fourcade is also to thank for the consolidation of continuing medical education for urologists, particularly through the creation of regular activities dedicated to exchange of medical knowledge and self-evaluation (Journées d'Échanges et d'Auto-Évaluation en Urologie--JEAU). In 1997, he published *La Prostate*, a monograph acclaimed by his colleagues, and was President of the 98th

French Congress of Urology in 2004.

On the international scene, Dr. Fourcade was active on several fronts, whether as Treasurer of the SIU (2000-2006), Local Organizing Committee President of the SIU Centennial Congress in Paris (2007), or organizing the annual AFU symposia



*Staff at the Pitié in April 1980 (Prof. Fourcade on left in blue jacket)*

care, and his innovative management strategies yielded strong results.

As of 1986, Dr. Fourcade was instrumental in bringing about a regeneration within the Association Française d'Urologie (AFU). During his tenure as its Treasurer, he carefully crafted balanced and lasting partnerships with the pharmaceutical industry, and thus succeeded in building and consolidating a healthy financial situation for the Association.

He also paved the way for ongoing communication and dialogue between urologists and the general public, increasing awareness of urologic diseases and the role of the urologist in patient care. Most notably, on the occasion of the Felix-Guyon Centenary in 1990, Dr. Fourcade developed a nationwide showcase for urology. For ten weekends, a travelling exhibition accompanied by lectures and

during the AUA (inaugurated at the San Francisco Meeting in 2004). Through his long and varied career, he made many friends and established long-standing relationships with colleagues all over the world, based on cooperation and mutual respect.

Professionally, Dr. Fourcade was known for his diligence, his intellectual rigor, his integrity, his dedication to fostering international cooperation in urology, and his keen organizational skills. All of us will remember with great fondness his unique personality, his great heart, his courage, aplomb and generosity – great human qualities that are seldom all seen in one individual.

Our dear friend and colleague will be deeply missed. Our most sincere condolences to his family and colleagues on their great loss.

# How to Manage Urologic Chronic Pelvic Pain Syndrome

## Plenary Session at the SIU World Meeting on Lower Urinary Tract Dysfunction

Urologic chronic pelvic pain syndrome (UCPPS), traditionally referred to as chronic prostatitis (CP) and interstitial cystitis (IC), is now acknowledged as an important worldwide clinical problem in terms of prevalence, morbidity, cost (both to patient and society) and, admittedly, poor treatment outcomes.

This problem has been – and continues to be – exacerbated by continued lack of a unifying etiologic mechanism, variations in clinical definitions and diagnoses and, until the last decade, poor therapeutic evidence from randomized placebo controlled trials. That has changed over the last decade or so and the two-hour conference in Marrakech, Morocco in October 2010 was an opportunity to illustrate our progress over the last 10 years and develop some form of consensus determination of where we are going.

Our understanding of CP and IC has evolved over the last decade or so from a simple traditional concept of inflammation and organ centrality to that of a more complicated pelvic pain syndrome involving possible infection, inflammation, peripheral and central neuropathy, immunologic change, muscular discomfort, voiding abnormalities and sexual dysfunction modulated by psychosocial influences. The changes in nomenclature and definitions for these syndromes have confused many in clinical practice, but in reality the evolution has been quite straightforward and makes sense.

As far as IC is concerned, we have progressed from Hunner's 1917 definition of IC as a "peculiar form of bladder ulcerations whose diagnosis depends ultimately on its resistance to all ordinary forms of treatment... in patients with frequency and bladder symptoms..." to the rigorous NIDDK criteria which proved to be useful for epidemiological and some clinical therapeutic trials.

However, it was soon recognized that the NIDDK criteria for the definition of IC

were too rigorous and missed many patients. Over time, a number of groups including NIH consensus panels, the European Society for the Study of IC/Painful Bladder Syndrome, the International Continence Society and the Asian IC Guidelines Committee proposed an evolving definition of IC. Presently, most of these associations



*J. Curtis Nickel, MD*

and societies agree that IC, now referred to as painful bladder syndrome (PBS) or bladder pain syndrome (BPS), can be diagnosed on the basis of chronic pelvic pain, pressure or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom such as persistent urge to void or frequency.

Confusable diseases such as urinary tract infection, malignancy, etc. as the cause of these symptoms must be excluded. The European and Asian societies further formalized the classification of this condition according to findings at cystoscopy with hydrodistension and morphologic findings in bladder biopsies.

In the case of CP it was recognized over a decade ago that for many patients, pelvic pain may not be related to the prostate but to other pelvic organs. Thus the term chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is now widely accepted worldwide as the major cause of prostate and/or pelvic pain in men. This condition can be diagnosed in men with chronic pelvic pain or discomfort in the perineum, penis, external genitalia and suprapubic area (often associated with ejaculation) in whom other confusable diseases (specifically infection) are ruled out with standard clinical evaluation (e.g. cultures).

As important as defining the diagnosis and classification and agreeing on nomenclature, the development of validated system questionnaires that can be used for epidemiologic studies, clinical trials and clinical practice has driven the field forward. For IC (or PBS or BPS), the use of the O'Leary-Sant IC Symptom Index and Problem Index as well as the Pain

Urgency Frequency (PUF) scoring system has been very helpful. For CP/CPPS the National Institutes of Health CP Symptom Index (NIH-CPSI) has been the key to the development of an evidence-based approach to this condition.

### Evidence-based management of male UCPPS

Michel Pontari from the US illustrated the major issues in management of CPPS in his presentation. He outlined that the most important diagnostic considerations in men with CP/CPPS were to rule out alternative diagnoses that cause pain and recognize associated conditions. The major treatment considerations that he reviewed were the appropriate use of antibiotics and alpha-blockers as well as other medications, treatments other than medication and the use of multi-modal therapy.

Data are available to show that, compared with age-matched controls, men with CPPS have 6 times the prevalence of cardiovascular diseases, 5 times the prevalence of neurologic disease, and 2 times the prevalence of sinusitis and depression/anxiety. There is evidence that CP/CPPS may be part of an evolving systemic pain syndrome with 21% of men reporting a history of musculoskeletal, rheumatic or connective tissue disease, 19-79% reporting irritable bowel syndrome (IBS) or IBS symptoms, and twice as many with CPPS reporting chronic fatigue syndrome.

The data suggest that antibiotics may be used in antibiotic naïve inflammatory prostatitis, alpha-blockers in selected patients, perhaps those with voiding dysfunction, anti-inflammatories including NSAIDs, phytotherapies (quercetin and pollen extract) for those with pain and inflammation, tricyclic anti-depressants (amitriptyline or nortriptyline) and/or gabapentinoids (gabapentin or pregabalin) for those with neuropathic pain.

Non-medical therapy such as physiotherapy for myofascial trigger points and pelvic floor dysfunction seems to be beneficial, perhaps along with skeletal muscle relaxants. It is important to recognize other

associated medical conditions, including vertebral disc disease, fibromyalgia, IBS and chronic fatigue syndrome, as these associated conditions certainly impact quality of life (QoL) and do need to be addressed.

Dr. Pontari concluded that a single treatment does not fit all and that patients should be clinically phenotyped and specific treatment should be directed towards each clinical phenotype. He suggested the use of UPOINT (Urinary, Psychosocial, Organ specificity, Infection, Neurologic/associated conditions, Tenderness of muscles) as a new and reasonable approach to individualized therapy for this patient population.

### Evidence-based management of female UCPPS (IC/BPS)

Dr. Jorgen Nordling from Denmark covered this particular topic in the Symposium and based his presentation on the 2009 International Consultation on Incontinence, which included a consensus document on IC/BPS.

The general considerations important in the treatment of female UCPPS are the high incidence of remission unrelated to specific treatment and the fact that almost all our treatments are empiric, since the cause of IC/PPS is unknown. However, symptoms can be controlled with one or a variety of treatments in most patients. Furthermore, there is little evidence that treatment does more than influence symptomatic expression of IC.

Dr. Nordling acknowledged that many of the treatments employed in clinical practice are based on small, uncontrolled, usually single center studies which appear to show significant benefit. However, when these treatments (which include nifedipine, cimetidine, immunotherapy, pentosan polysulfate, L-arginine, hydroxyzine, amitriptyline) were subjected to large multi-center properly powered randomized placebo-controlled trials, the benefits of therapy were either extremely modest or non-existent. This is similar for intravesical therapies (DMSO, the heparinoid therapies including hyaluronic acid and chondroitin sulfate, BCG).

It was stressed that conservative therapy, which includes education, behavioural modification, physiotherapy in selected patients, stress reduction and dietary manipulation, provides significant amel-

ioration of symptoms in real clinical practice, although most of these have not been subjected to large multi-center placebo-controlled trials.

In regard to surgery, there are only a few uncontrolled studies, and results are conflicting. The recent literature reports only a minority of patients experiencing a small improvement of symptoms for a relatively short period after bladder hydrodistension. However, there are numerous reports of patients with Hunner's lesions showing an improvement after resection or destruction of the lesions. Surgery on the nervous system (cystolysis or de-innervation) has not been very successful, although sacral nerve modulation may help some patients, particularly those

with irritative voiding symptoms. Cystectomy with a simple or continent urinary diversion is indicated only for end-stage IC. Surgical options should only be considered when all conservative treatment has failed. Novel pain related medications are presently being tested in clinical trials.

### Debate: Are male and female UCPPS the same condition?

The symposium included an interesting and provocative debate in an attempt to answer the long asked question – is CP in males and IC in females really the same condition?

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## Research Fellowship

The California Urology Foundation, in association with the Société Internationale d'Urologie, announces the availability of a Research Fellowship for a fully-trained Urologist from Africa to do research for one year in a medical laboratory of the University of California in San Francisco (UCSF).

This award is intended to prepare the candidate for an academic career in his or her home country; a firm commitment to return will be a material consideration in the evaluation of candidates. This fellowship carries a stipend of \$50,000 USD, of which \$14,000 is used to cover medical insurance and administrative fees.

Applications for this fellowship will be evaluated by a joint SIU/UCSF Committee and should include a proposed area of study, a detailed CV, and professional references.

The deadline for the 2011 Fellowship will be March 30, 2011. Application forms are available on the SIU website [www.siu-urology.org](http://www.siu-urology.org) under the Training Scholarships tab.

Applications can be submitted by mail, fax or e-mail to:

### UCSF-SIU Research Fellowship

c/o SIU Central Office  
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[central.office@siu-urology.org](mailto:central.office@siu-urology.org)

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Dr. Karl Kreder was able to show that there were many similarities between the proposed etiologies for CP and IC. Patients present clinically in a similar fashion (pelvic pain) and the diagnosis is one of exclusion. The clinical presentation of a male with IC/BPS and male chronic pelvic pain syndrome is almost identical, except for the perception that the pain is either in the prostate or blad-

### The steps to successful therapy

#### Step 1

- Make the diagnosis (determine bio-psycho-social associations - pain generators, associated conditions and impacting factors)
- Determine realistic patient-orientated goals for therapy

#### Step 2

- Treat main pain generator (prostate, bladder or other)

#### Step 3

- Multimodal therapy
- For main pain generator
- For associated pain generators and other symptoms/conditions (UPOINT)

#### Step 4

- Follow up closely
- Periodic completion of validated questionnaires may be most effective follow-up strategy
- Change therapy when required

#### Step 5

- Long-term follow-up (recurrences are common)

der area (diagnosis of IC/BPS is probably more frequent in males who also present with frequency/urgency or if they volunteer that their pain is associated with bladder recycling).

Although it has always been assumed that there are 9 females for every male diagnosed with IC, prevalence of pelvic pain in patients likely to be diagnosed with IC/PPS based on reported pelvic pain, urinary urgency and frequency is closer to 1:2 male:female. The QoL of males diagnosed with CP is similar to that with a male diagnosed with IC and the impact on activities is basically the same. Dr. Kreder cited a number of studies that show that the response to stress in males with CP is similar to that observed in patients with IC.

Dr. Anthony Schaeffer from the US argued the opposite, that male and female UCPPS are not the same condition. He based that on his recent findings that the brain activity measured by functional magnetic resonance imaging was different in males diagnosed with IC than those with CPPS. His group used functional resonance imaging to examine brain regions that were activated by spontaneous pain in these patients. He was able to show that patients with IC (albeit mainly females - only 1 male in the group) showed different activity patterns compared to that in males with a diagnosis of CP.

Dr. Schaeffer believes that these unique brain signatures for CP and IC suggest that they are distinctly different clinical syndromes. It was suggested by the chairperson, Dr. J. Curtis Nickel, after further discussion, that male CP/ CPPS and female IC/PBS are similar conditions, yet different.

### What have we learned and where are we going?

Dr. Nickel summarized and elaborated on the major question posed by this discussion. We all now realize that the pain (plus the voiding, sexual and psychosocial dysfunctions related to UCPPS) are not necessarily organ centric (not completely related to the prostate or bladder).

The etiology is likely multifactorial, meaning that although patients may present similarly, they may have one or more different etiologic mechanisms or pathogenic pathways. Heterogeneity of these two populations is reflected in the clinical evidence from therapeutic trials. Many patients respond to our treatments, but not all. Patients have clinical phenotypes that can be determined clinically and perhaps in the future with specific biomarkers. The UPOINT phenotype classification system had been presented and was judged to be a reasonably logical and valid approach to classifying patients with UCPPS.

Finally, new evidence shows that UCPPS is not a static condition. Some patients early on in their condition resolve spontaneously, while others follow a progression pathway that could lead from an organ centric pain syndrome to a regional pain syndrome (IBS, vulvodynia, pelvic floor

dysfunction) and finally a systemic pain syndrome (fibromyalgia, chronic fatigue syndrome) all modulated by supratentorial central nervous system mechanisms.

Before treatment is implemented, all the bio-psycho-social associations in that particular patient must be determined. This would include the pain generators (e.g. prostate, bladder, bowel, uterus, ovaries or pelvic floor) associated conditions (fibromyalgia, chronic fatigue syndrome, IBS) and impacting factors (stress, anxiety, depression, poor coping mechanisms). While it is important to treat the main pain generator (e.g. the prostate in CP/ CPPS and the bladder in IC/PBS) multimodal therapy should be considered for associated pain generators and other symptoms/conditions.

UPOINT allows a phenotypically driven therapeutic strategy. In clinical practice, periodic completion of the validated questionnaires described previously is probably one of the most effective follow-up strategies. Above all, physicians and patients must realize that contemporary medical knowledge does not allow for "cure" of UCPPS. The goals of therapy are to ameliorate the pain, reduce any voiding or sexual dysfunction, increase activities and generally improve the QoL of each individual patient.

Empathetic physicians interested in helping patients with UCPPS should embrace these new concepts in clinical practice. The future continues to lie in basic science research, which is attempting to determine the etiology and pathogenesis of this condition. Biomarker research holds great promise in allowing us to better clinically phenotype patients. Psychosocial investigations allow us to understand the impact of stress, anxiety, social interactions, depression, adaptive coping behaviours, etc. Collaborative scientific investigation will continue to develop and test novel pain therapies.

At the present time, a multi-disciplinary approach to the management not only of the organ centric pain and symptoms, but the other associations that make up the clinical picture of patients with UCPPS is essential. We do have a plan for our way forward. ■