

# NEWSLETTER

## EDITORIAL:

### European Alliance of National Organisations for Sexual Dysfunction (EANOSD)

The ISIR Meeting in Amsterdam in August was successful in many ways, not least in convincing this Society that there was a real need for patient support centres/helplines to be set up across Europe to help impotence sufferers.

Some countries already have these services and one of these "The Impotence Association" in London was kind enough to share its experiences with other European delegates at a meeting to discuss the feasibility of a European-wide initiative.

These reference centres would provide a totally confidential route for Impotence sufferers and their families to access reliable and objective information about their condition, delivered in a professional and supportive manner.

The telephone operators are trained to have extensive knowledge of Impotence and its treatments and more importantly, a knack for handling these sensitive queries in a warm and efficient manner. This support service does not and cannot offer a "diagnosis", nor is it intended to provide on-going therapeutic support. Its aim is to be a reliable source of clear and medically correct information regarding the current treatment modalities for Impotence and to inform about new ones as and when they become available. A range of guides and leaflets will back up this telephone information service on Impotence and other sexual disorders of the male.

Many doctors, in particular GPs and nursing staff, are also expected to request information on guidelines for treating impotent patients especially since the arrival of sildenafil. In this sense the European Society for Impotence Research is keen for its guides for both patients and doctors to be translated into various languages to make them readily available through these centres, and has asked the Advisory Board to begin work on translating these educational materials.

## In this issue:

- *Editorial: The European Alliance of National Organisations for Sexual Dysfunction, a network of patient support centres and helplines throughout Europe with one common aim, to inform and encourage impotent patients to seek medical help.*

- *An interesting freelance contribution from the UK concerning the complications of penile prostheses implants by Christine Evans.*

- *Events of major importance in the field of Erectile Dysfunction in our Calendar section.*

- *The EANOSD: information on the Spanish centre.*

- *Highlights from the 8th World Meeting on Impotence Research in Amsterdam by Hartmut Porst.*

- *Basic Research Highlights: Gene Therapy, a new approach by Hunter Wessells of the University of Arizona*

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The next step has been to define a global strategy for the implementation of this ambitious project.

A meeting held recently in London paved the way forward by outlining the structure of this future initiative. A Steering Committee comprised of members of the ESIR will take responsibility for making headway on this project. The EANOSD will have its co-ordinating office in the UK, with the ESIR Headquarters in Madrid expanding its activities to include the future publication of a patients' Newsletter in an electronic format designed to be adapted to different languages across Europe. This publication would consist of a core of common articles with the flexibility to accommodate articles on local issues set against different cultural backdrops and published in the local language. These were the other main points agreed on:

■ There should be only one of these associations / centres per country, approved by the steering committee of the European body.

■ National organisations / centres should be charitable or have a non-profit making status, and funding should be through donations and educational grants.

■ The chairman of national associations / centres should be a member of the ESIR.

■ A telephone helpline is the core communication instrument with the general public. In addition a web site and a newsletter will provide further lines of communication.

The activities of this new European body (EANOSD) would be clearly aimed at patients and the general population and as such would be separate from the scientific activities of the ESIR as they stand at present. Although affiliated to the ESIR, the EANOSD would have its own identity with a logo and stationery and all the materials produced by the organisation would be approved by a steering committee and be available to all the centres across Europe, ready for translation into the local language.

The objectives of the EANOSD will be to co-ordinate and promote the activities of the national associations and to provide core materials for use throughout the Alliance. This will guarantee the standard and prestige of the educational information available.

As President of the ESIR, I would strongly urge as many European countries as possible to join in this initiative. It is the feeling of this society that this project will have an enormous influence on the general public and will bridge the existing gap between the increased awareness brought about by recent media coverage and access to high quality medical information and care.

Although the issue of funding is still at the negotiation stage, we foresee the possibility of central funds being available to help countries with initial start up costs and materials until they can secure local funding through educational grants in their own countries. Those of you who are interested in joining should contact the ESIR headquarters for further information. We look forward to making this a truly unified effort to provide a network of much needed support and updated information to ED sufferers in Europe.

*Iñigo Sáenz de Tejada*

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(Don't miss... Literature Review)

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(Basic research highlights)

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Other sections:

• Editorial

• New products

• What's up doc! (Humour)

• Letters to the Editor

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IÑIGO SAENZ DE TEJADA

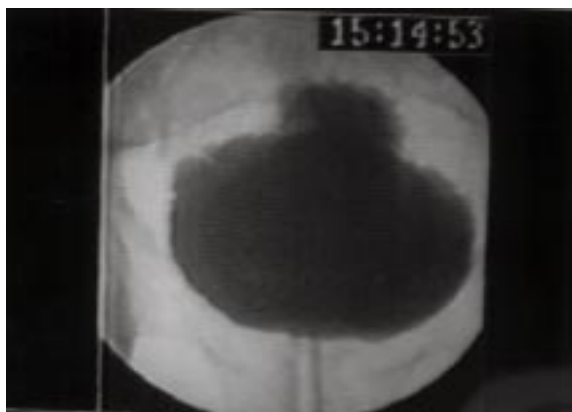
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# The man who could not pass urine after penile prosthesis

*Christine Evans, GLAN CLWYD HOSPITAL*

A man aged 59 was admitted for implantation of an inflatable penile prosthesis following complete impotence lasting 10 years. During those ten years he had been an insulin-dependent diabetic and had had a pan proctocolectomy for ulcerative colitis in 1976. He had tried intracorporal pharmacotherapy with Alprostadil that had worked for a while and a vacuum device which his wife had not liked.



At the time of admission a routine flow rate was done, which was found to be normal, 55 ml/second for a voided volume of 493 ml. The patient denied having any problems with voiding. A bladder scan to measure residual urine was not done as it was not working properly. An AMS (American Medical Systems) Ultrex prosthesis was inserted under spinal anaesthetic through a transverse infrapubic incision on 31st October 1996. It was noted that at the beginning of the operation that the bladder was distended, it was emptied and 500 ml drained. The operation itself was very straightforward.

Following the operation he was unable to void and commenced clean intermittent catheterization on which he has remained since.

Video urodynamics were performed on 14th January 1997 which showed a hugely trabeculated bladder (plate) with reduced sensation which did not generate any pressure and he was unable to void.

The patient was extremely disgruntled that he could not void, to the extent that he wished he had not had the operation. This was partly aggravated by the fact that he was not using his prosthesis as his marriage had fallen apart at the time of his surgery, information which he had not shared with the surgeon! However at

subsequent follow ups he has revealed that he has found another partner and that his prosthesis works well so he is a little happier.

## **Discussion**

This bladder had long-term neuropathic problems which were not recognised. How much investigation should we have performed pre-operatively? The presence of a post-voiding residual if done, would have alerted us to the fact that he had a problem, but he would probably have proceeded with the operation even with a neuropathic bladder as he was so anxious to have something done. At this stage his hospital admission had already been expedited.

Why did he not void? It is likely that he voided, unknowingly, by abdominal straining which was compromised by the lower abdominal incision. Spinal anaesthesia can cause post-operative voiding problems. Twenty-five per cent of patients undergoing spinal anaesthesia for leg and foot surgery experienced urinary retention as compared with seven per cent who had a general anaesthetic (1), and further studies show epidural and spinal anaesthesia can cause voiding problems although these are mostly temporary (2,3,4) .

This case is a salutary lesson for us all to investigate patients properly before surgery and warn these patients with previous pelvic surgery or neuropathic bladders that they may not void satisfactorily afterwards.

## **Mahan KT. Wang J.**

Spinal morphine anaesthesia and urinary retention

Journal of the American Podiatric Medical Association. 1993 Nov. 83 (11):607-14.

## **Williams A. Price N. Willett K.**

Epidural anaesthesia and urinary dysfunction: the risk in total hip replacement (see comments). Journal of the Royal Society of Medicine 1995 Dec. 88 (12): 699-701.

## **Tammela T.**

Postoperative urinary retention - why the patient cannot void?.

Scandinavian Journal of Urology & Nephrology. Supplementum. 1995. 175: 75-7.

## **Kerdraon J. Amarenco G. Denys P.**

(Bladder-sphincter complications after peridural anaesthesia. 8 cases (see comments). Presse Medicale. 1993 Mar. 13, 22 (9): 410-2.



Dear Colleagues,

*Below you will find a list of the main events of andrological interest, in Europe and the world, until the end of 1999. It gives me special pleasure to announce that our sister association, the African Society of Impotence Research (ASIR) is growing, and will hold its 2nd Continental Meeting in February 1998. Our sincere congratulations.*

## 1998

November 13-15, 1998 **Athens, GREECE**  
**3rd Congress of the HELLENIC SOCIETY OF ANDROLOGY**  
Contact: Congress Secretariat  
MEDLINE, 114 Zan Moreas str., 15231  
Athens - GREECE  
Tel +3 1 6773316 or 6755473  
Fax +3 1 6722849

December 10-12, 1998 **Pisa, ITALY**

### **VI International Congress on THERAPY IN ANDROLOGY**

Contact: Prof. F. Menchini-Fabris, Pisa University

Via Roma 67, 56126 Pisa - ITALY

Tel +39 50 553404

Fax +39 50 550033

## 1999

February 10-12, 1999 **Cairo, EGYPT**

### **2nd Continental Meeting of the AFRICAN SOCIETY OF IMPOTENCE RESEARCH (ASIR)**

Contact: Congress Service Center  
14 Syria St., Mohandeseen Guiza - EGYPT

Tel +20 2 3371482

Fax +20 2 3368304

Email [cscasf@pacc.com.eg](mailto:cscasf@pacc.com.eg)

March 10-12, 1999 **Oviedo, SPAIN**

### **9th SPANISH CONGRESS of ANDROLOGY**

Contact: Dr. C. Garcia-Ochoa

Tel +34 939 949898

Fax +34 8 5347070

Email [andro@netcom.es](mailto:andro@netcom.es)

Website <http://www.netcom.es/andro>

April 7-11, 1999 **Stockholm, SWEDEN**

### **XIVth Congress of the EUROPEAN ASSOCIATION OF UROLOGY**

Contact: EAU Congress Office - P.O.  
Box 204

6600 AE Wijchen - THE NETHERLANDS

Tel +31 24 6452510

Fax +31 24 6450769

Email [urocom@bpc.n](mailto:urocom@bpc.n)

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April 11-13, 1999 **Louisville, Kentucky, USA**  
**24th Annual Meeting of the AMERICAN SOCIETY OF ANDROLOGY**  
Contact: ASA Executive Offices  
Tel +1 415 7644823  
Fax +1 415 7644915  
Email 105037.1120@compuserve.com

May 1-6, 1999 **Dallas, Texas, USA**  
**96th Annual Meeting of the AMERICAN UROLOGICAL ASSOCIATION**  
Contact: AUA - 1120N Charles St.  
Baltimore, MD - 21201 USA  
Tel +1 410 2234308  
Fax +1 410 2234372  
Email convention@AUAnet.org  
Please note: abstracts on Erectile Dysfuntions will be presented on Monday, May 3, and on Tuesday, May 4.

June 16-19, 1999 **Copanello (Catanzaro), ITALY**  
**12th Congress of the ITALIAN SOCIETY OF ANDROLOGY**  
Contact: Divisione Urologia Ospedale "Pugliese"  
88100 Catanzaro - ITALY  
Tel +39 961 863248  
Fax +39 961 863386

July 1-3, 1999 **Paris, FRANCE**  
**1st INTERNATIONAL CONSULTATION ON ERECTILE DYSFUNCTION**  
Contact: Prof. Saad Khoury  
Email khoury@pratique.fr

September 2-4, 1999 **Giessen GERMANY**  
**11th MEETING OF THE GERMAN SOCIETY OF ANDROLOGY**

Contact: Prof. W. Weidner  
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Giessen, GERMANY  
Tel. +49 641 99 44501  
Fax +49 641 99 44509  
Email W. Weidner@chiru.med.uni-giessen.de

September 6-9, 1999 **Cairo, EGYPT**  
**6th Congress of the MEDITERANEAN UROLOGICAL ASSOCIATION**

Contact: M. El-Dimiri  
Email Domery@link.com.eg

October 3-6, 1999 **Istanbul, TURKEY**  
**3rd Meeting of the EUROPEAN SOCIETY FOR IMPOTENCE RESEARCH (ESIR)**

Contact: Congress Secretariat PERA Organization  
Rumeli cad. 124/5, 80260 Osmanbey, Istanbul -TURKEY  
Tel. +90 212 2305535  
Fax +90 212 2304923  
Email serpilb@antmarin.com.tr



# EANOSD - The way forward in Europe

Feedback from different European countries after the meeting in August in Amsterdam has provided us with an update on the state of affairs with respect to the future European Alliance of National Organisations for Sexual Dysfunction:

## Countries which already have a national association or are setting up at present:

- **Germany:** has already begun work on setting up a non-profit making organisation and are in the process of contacting sponsors.
- **Greece:** has set up a helpline and is in the first stages of organising the day-to-day running of the association.
- **Norway:** a private helpline was set up some time ago and is expecting to receive government support. Would like to know more about the Alliance project.
- **Spain:** is in the process of setting up and should be operating by the end of November.

## Countries that have shown interest in the project of the EANOSD:

- **Belgium:** is finding some problems with regard to the three languages spoken. A national representative will be talking to the institutions involved and will be reporting back on policy decisions.
- **France:** has shown interest in joining the Alliance and will probably be arranging a visit to the UK office in the near future.
- **Netherlands:** contact will soon be made with the Dutch-Flemish Society for Impotence Research and with the UK office to discuss a possible set up.
- **Portugal:** is looking into the possibilities of setting up with the support of the Portuguese Society of Andrology. Guidelines are being translated at present.
- **Turkey:** has shown much interest in joining the Alliance and is keen on ESIR support to help them organise the project.
- **Switzerland:** very positive about the central co-ordination of the Alliance and willing to participate.



Countries which already have a national association or are setting up at present



Countries that have shown interest in the project of the EANOSD



## EUROPEAN ALLIANCE OF NATIONAL ORGANISATIONS FOR SEXUAL DYSFUNCTION

### *The Spanish centre*

The Foundation for Research and Development in Andrology (FI+DA), is launching a telephone helpline for Impotence sufferers, from its headquarters in Madrid, Spain. This service aims to provide ED sufferers with clear and concise information on the different treatments available for Impotence, as well as general support and guidance for a population which totals more than two million in Spain alone. The project is part of the ambitious initiative to set up and coordinate such centres throughout Europe with the collaboration of the European Society for Impotence Research. The ESIR will act as an umbrella organisation, providing administrative back up and literature through a new office in the United Kingdom, and a Website and European Newsletter publication aimed at patients, via the existing ESIR head office in Madrid.

FI+DA, is a non-profit making organisation and is concerned with all aspects of male sexuality but more specifically with those of erectile and ejaculatory dysfunction.

Recent developments in the area of new treatments for Impotence have had a tremendous impact on the media. This has opened the door for a great number of sufferers to come forward and seek help for impotence, whereas they would otherwise have continued to suffer in silence. These changes in public awareness, together with the results of a recent campaign to inform the public about sexual impotence in Spain convinced us of the demand for more information about treatments from the general public. Information of this type is not easy for them to access due to the misconceptions that still exist with regard to Impotence, both within the community at large and a part of the medical profession. Some GPs are uncomfortable dealing with the subject of erectile dysfunction or see it as a minor pathology that they would prefer not to address.

We hope to launch the helpline by the end of November. The information provided to callers through this helpline will be solely informative. There will be no diagnosing or attempts at medical or psychological treatment offered by the

operators (physicians and psychologists/sexologists). In this sense the clear objective is to guide the caller towards using the services that exist in the community and to be informed about how to access them. The final message will always be for the caller to consult with his GP or be referred to a specialist who will evaluate and supervise his treatment. Factsheets will be available on the different treatments for impotence and other sexual dysfunctions such as prema-



ture ejaculation, Peyronie's disease etc. The ESIR guides presented in Amsterdam in August for both patients and physicians will also be available in translated versions to send out to callers promptly and free of charge. At present we are trying to establish a communication network with the primary care sector in Spain to distribute the Erectile Dysfunction guidelines for physicians to as many centres as possible throughout the country.

The Spanish helpline will be roughly modelled on that of the Impotence Association in London which was set up three years ago. We hope this Spanish initiative can learn from their experience to date, taking advantage of the European network which will support the national centres.

# Highlights from the 8<sup>th</sup> World Meeting on Impotence Research

*Hartmut Porst*

AMSTERDAM

25–28 AUGUST 1998

## Part 1: Epidemiology, Risk Factors, Basic Research.

Epidemiologic data from China revealed that in the age group 40 – 70 years prevalence of erectile dysfunction was at 73 % showing that this condition is also a major issue in the emerging countries (Jing et al). According to a European Nations Survey more than half of the patients (53 %) were of the opinion that erectile dysfunction is an inevitable sequelae of growing older and therefore only 20 % considered seeking medical help for this disease (Gingell).

In a study, erectile dysfunction in **diabetes** was shown to be mainly arteriogenic (64 %) proven by duplex sonographic measurements. In an animal model of diabetic rats, investigators Broderick et al, showed a significant decrease in NOS-containing nerve fibers (El-Sakka). From a clinical point of view, an association between poor glycemic control (increase of HbA1C) and impaired sexual function was reported by Seftel et al, stressing the importance of a strict diabetes control. In this sense early administration of insulin was shown to prevent or inhibit diabetic nerve damage (Sik et al) or improve erections by regulating the translation of nitric oxide synthase (Abdel-Baky et al). Also in the rat-model, Srilatha et al provided evidence, that the **antihypertensive drugs** propranolol and clonidine influence sexual function negatively whereas the ACE-inhibitor captopril was devoid of such negative effects.

**Chronic renal failure** is widely associated with erectile dysfunction. In a group of 89 patients with the need of regular dialysis, 69 % reported erectile failure (Botturi et al). The most common pathological hormonal findings contributing to the onset of erectile dysfunction were, elevated prolactin in 55 % and decreased testosterone in 70 % of patients. In **uremic rats** the intracavernosal pressure (ICP) rise after cavernous nerve stimulation was significantly reduced but the tissue levels of nNOS in the major pelvic ganglia (MPG) and cavernous tissue were high, sug-

gesting the presence of systemic or cavernous NOS-inhibitors (Abdel-Gawod et al). After **renal transplantation**, 30 % of 121 men reported increased coitus frequency, 24 % an improvement of penile rigidity and 17 % a better orgasm (Yamanaka et al). In another series of transplanted males 33 % of a population of 170 patients reported improved sexuality, 28 % a deterioration and 39 % no change (Giuliano et al).

**Basic research: Hypercholesterolemic** rabbits exhibited a functional impairment especially of the eNOS which resulted in impairment of cavernous smooth muscle relaxation (Seo et al). Open biopsies on the occasion of penile prosthetic surgery in 60 patients with organic impotence revealed a significant reduction of smooth muscle and elastic fibers and a significant increase in collagen fibers **in veno-occlusive and mixed vascular impotence** (Metaweia et al). In female rats, activation of the **cerebral 5HT<sub>1A</sub>-receptors** facilitated female sexual behaviour which was comparable to the males (Marson et al). In the cat, intracavernosal injection of the **PDE 3,4 and 5 – inhibitors**, milrinone, rolipram or zaprinast, respectively, induced erections with the PDE3 – inhibitor milrinone and PDE 5 – inhibitor, zaprinast, resulting in nearly two fold higher ICP than rolipram (Hellström et al). In the **paraplegic rat animal model**, a threefold increase in the level of nNOS mRNA both in the penis and major pelvic ganglia (MPG) was found, whereas the eNOS was not affected (Abdel Baky). As the response to EFS was attenuated in the paraplegic rats, the authors presume an impaired translation or increase in proteolysis of the enzyme could explain the reduced responses. The same investigators were also able to demonstrate a 30 – 40 % impairment in the expression of IGF-I-mRNA in the penis and MPG in the paraplegic rat model.

**Whereas unilateral occlusion of the internal pudendal artery** in the rat did not impair erectile response, acute occlusion of both internal pudendal arteries dramatically decreased ICP with partial restoration of erectile response after 1 and 3 months (Droupy et al). In studies in vivo with rats the **potassium channel blockers**, Glibenclamide and TEA, resulted in a significant decrease in the nerve-stimulated ICP responses whereas the **calcium channel blockers**, Verapamil and Nifedipine, caused a dose –dependent increase in ICP suggesting that both potassium and calcium channels are important modulators of the corporal smooth muscle tone (Melman et al).

In the rabbit **phentolamine** relaxed corpus cavernosum smooth muscle strips precontracted with KCL or Endothelin suggesting an activation of non-adrenergic mechanisms by phentolamine besides the alpha 1 and 2 adrenergic receptor antagonism (Gupta et al). Human in-vitro studies on cadaver penile dorsal arteries revealed that **Vasopressin** constricted penile arteries via V<sub>1</sub>-receptors and potentiated the contraction to NA and EFS (Domenech et al). In the rabbit animal model, contractile responses were mediated via both ET<sub>A</sub> and ET<sub>B</sub>-receptors (Mumtaz et al). **In rat experiments** heptanol, a **gap-junctional uncoupling agent**, significantly and reversibly attenuated ICP responses to neurostimulation, emphasizing the role of gap-junctions in the erectile mechanism (Zhao et al).

By means of autoradiography, Canning et al, provided evidence for the first time that 5-HT<sub>1</sub> receptors are also located in the penis although the importance of this finding for the erectile mechanism remains to be defined.

In the rat, Giuliano et al, found that **NOS positive cell bodies** are very close to **Oxytocin** (OT) containing nerve fibers in the spinal erectile centers. The proerectile effects of Oxytocin were suppressed by the injection of the NOS inhibitor L-NAME or the guanylate cyclase inhibitor methylene blue, suggesting that the proerectile effects of OT are NO-cGMP pathway dependent.

Moreland et al. demonstrated the **expression of EP<sub>2</sub>, EP<sub>3</sub> and TP - receptors** in human trabecular smooth muscle cells by RNase protection assays. The relaxant or contractile effects of the varied Eicosanoids are mediated through G-protein coupled receptors. In vitro studies in human cavernosum tissue revealed the following ranking of contractile prostanoids according to their potency: U496619 (TP-receptor agonist), >>PGF<sub>2α</sub> >>Fluprostenol (FP-receptor agonist) >Sulprostone (EP<sub>1</sub> and EP<sub>3</sub>-receptor agonist) (Sáenz de Tejada et al). In relaxant prostanoids the ranking was as follows: PGI<sub>2</sub> >PGE<sub>1</sub>=PGE<sub>0</sub> in penile arteries and PGE<sub>2</sub> > PGE<sub>1</sub> > butaprost (EP<sub>2</sub>-agonist) >>> PGI<sub>2</sub> in trabecular tissue.

In the rabbit animal model, the **content of cavernous smooth muscle cells** was significantly reduced after **castration** (Traish et al). This decrease of smooth muscle cell content was reversed by testosterone replacement the-

rapy but not by estrogen treatment. The expression of nNOS was not influenced by castration or testosterone therapy. In **castrated rats NOS activity** and the amount of **nNOS mRNA** were considerably reduced but recovered through testosterone and dihydrotestosterone-therapy (Kim et al). Therefore it was concluded that androgens play an important role in NOS activity by enhancing nNOS gene expression with DHT representing the most potent androgen. After castration, levels of **eNOS** decreased considerably in rat erectile tissue, whereas the levels of **Vascular Endothelial Growth Factor (VEGF)** increased (Henry et al). Testosterone replacement therapy was able to reverse these effects. In the rat-brain **testosterone replacement therapy** led to a significant increase of the NOS-containing cells compared to non-treated rats (Horita et al).

Intracavernous injection of **TGF-β<sub>1</sub>** induced corporal fibrosis in rabbits suggesting that TGF-β<sub>1</sub> plays an active role in ischemic induced-corporal fibrosis (Nehra et al).

Regeneration of NOS-containing nerve fibers in the cavernous tissue after cavernous neurotomy was accompanied by a significant increase of mRNA expression of bNOS, IGF-1 and TGF-β<sub>2</sub> suggesting a key-role of the aforementioned substances in restoration of NOS-activity (Jung et al).



*Hartmut Porst*

# GENE THERAPY: NEW FRONTIER IN ERECTILE DYSFUNCTION RESEARCH

*Hunter Wessells*



Karl - Erik Andersson and  
François Giuliano

Gene therapy to correct erectile dysfunction (ED) was announced amid great excitement at the VII World Meeting on Impotence in 1996. The corpus cavernosum is particularly amenable to site specific gene augmentation: the syncytial nature of the corporal smooth muscle suggests that not every cell would need to be genetically altered in order to see improvements in erectile function (1). In addition,

the ease of injection, interconnection of the two sides, and potential for repeated injections make the penis unique.

Two genes have been investigated in attempts to alter the corporal environment: the inducible nitric oxide synthase (iNOS) and the human maxi K channel. Garban et al at UCLA infused iNOS inducers and liposomal encapsulated iNOS cDNA into the penises of 5 and 20-month old rats. This led to increased iNOS expression, NOS activity, and increased intracavernous pressure (ICP) in response to cavernous nerve stimulation (2). Around the same time investigators at Albert Einstein in New York injected naked NOS cDNA into the rat penis and found similar increases in erectile function and NOS expression (3).

Christ et al subsequently injected plasmid hSlo cDNA into the corpus cavernosum and documented enhanced intracavernous pressure to neurostimulation (1). This gene encodes the human maxi-K<sup>+</sup> channel, and increased expression increases the resting potential of the cavernous smooth muscle cell, enhancing smooth muscle relaxation. The effects on ICP were maintained for up to 4 months.

These animal studies represent exciting preliminary reports. But before clinical gene therapy trials can be considered, a number of fundamental questions need to be answered. These include:

1. Which cells are being transfected by the cDNA.
2. What is the efficiency of gene transfer.
3. How can efficiency of transfer be optimized.
4. What is the ideal gene for transfer.
5. How will the genes be regulated once they are taken into the cell.
6. What is the consequence of repeat injections.

### **Gene transfer techniques**

Gene transfer methods influence the efficiency of gene therapy. Naked cDNA infusion allows only low levels of gene transfer but may work well in a tissue dependent fashion; because the

transgene is not incorporated into the cell's replicating DNA, only short-term gene expression is usually possible (4). Paradoxically, the quiescent state of the corporal endothelium and smooth muscle, which divide only rarely, may allow incorporated genes to persist in the penis for long periods of time. Plasmids have highly charged surfaces, and lipid based delivery systems can protect the DNA from digestion and drive it into the cell.

Adenoviral mediated gene transfer allows high efficiency gene transfer into non-dividing cells, but short-term gene expression and inflammatory response to infection are drawbacks. "Gutless" adenoviruses are a modified version with less immunogenicity and less durable gene expression. Adeno-associated virus is a non pathogenic single strand DNA that leads to site specific infection of non-dividing cells, but is not integrated into the genome. Perhaps most appealing of all, from a theoretical perspective, is the Lentivirus. A retrovirus related to HIV, it can contain many more genes and is integrated into non-dividing cells.

Retroviruses integrate into the DNA of the recipient cell, allowing prolonged expression of the gene, a desirable trait for penile gene therapy for ED, where long-term gene augmentation makes sense. Retroviral vectors appear to require a dividing cell, making it unlikely to be effective as an infusion. Insertional mutagenesis is a potential risk of retroviral gene transfer. Transduction of cells in culture, with subsequent transplantation into the corpus cavernosum, would overcome the hurdle of low cell turnover and ensure that mutagenesis does not occur (5). Cells expressing high levels of the gene could be selected using an antibiotic resistance gene co-transferred with the selected gene. The combination of ex vivo retroviral transduction and cell transplantation appears to provide stable gene expression for more than 6 months (4). Gene transfer of eNOS and iNOS into endothelial cells has been developed to alter endothelial response to injury, reduce apoptosis, and enhance penile erection(2);(6-8). We have transplanted microvessel endothelial cells transduced with retroviral iNOS into the corpus cavernosum of the rat, and at the University of Pittsburgh a similar technique has been used with myoblasts (9), (10). Of concern to us is how the gene will get turned on or turned off; finding a tissue-specific promoter may be an important requirement for successful gene expression.

Shotgun gene therapy approaches with iNOS may not prove beneficial to all models of ED. In future studies we will use a variety of techniques and models, rather than a single methodological approach. The biggest challenge facing impotence researchers is to identify underlying mechanisms of dysfunction which can be specifically corrected with gene therapy. The ultimate goal remains the same: to correct erectile dysfunction so that on-demand therapy is no longer necessary.

### ***References***

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