

NEWSLETTER

EUROPEAN SOCIETY for IMPOTENCE RESEARCH

N° 6 MARCH 1999

EDITORIAL:
**Welcome to the XIVth Congress of the
European Association of Urology
Stockholm International Fairs
April 7-11 1999**



In 1999, as in 1998 in Barcelona, the ESIR wants to give full institutional support to this major event in the medical calendar.

This year our participation goes a little further as the EAU organisers have been kind enough to invite us to have our own focussed scientific session, scheduled for the 7th April from 9:00 to 14:00. We have put together what we consider to be a stimulating programme covering an ample spectrum within the new areas in the pharmacological treatment of erectile dysfunction.

It only remains for me to stress our Society's wish that all of you join us and partake of what promises to be a lively, informative and, we hope, entertaining warm-up to the great scientific programme of the rest of the Congress. (Programme overleaf)



Aerial view of Stockholm

In this issue:

- *Editorial: The ESIR scientific programme at the XIVth Congress of the European Association of Urology Stockholm*
- *EANOSD - The Italian centre*
- *More news and updates of international events in Edoardo Pescatori's calendar section*
- *Interview with A. Jardin and S. Khoury by Dimitrios Hatzichristou*
- *Therapeutic targets for erectile dysfunction along the NO-cGMP pathway by Javier Angulo*
- *Highlights from the 8th World Meeting on Impotence Research. Amsterdam 25-28 August 1998 (PART II) by Hartmut Porst*

**VISIT OUR WEBSITE
www.esir.com**

ESIR PROGRAMME FOR THE EAU MEETING IN STOCKHOLM

I. Nitric Oxide in penile erection

1. Central Nitric Oxide pathways in the regulation of penile erection
F. Giuliano (Le Kremlin, Bicêtre) France
2. Regulation of penile smooth muscle contractility by Nitric Oxide
R. Pickard (Newcastle Upon Tyne) UK
3. Evidence for disruption of the NO/cGMP pathway in systemic diseases associated with high prevalence of erectile dysfunction
U. Simonsen (Aarhus) Denmark
4. Role for NO precursors and NO donors in the treatment of erectile dysfunction
G. Letts (Bedford) USA

II. Phosphodiesterases as pharmacological targets for the treatment of erectile dysfunction

1. Classification and molecular biology of PDEs
K. Ferguson (Seattle) USA
2. Regulation of PDE activity
A. Naylor (Sandwich) UK
3. Pharmacology and physiology of PDEs in human penile tissue
I. Sáenz de Tejada (Madrid) Spain
4. Clinical experience with PDE5 inhibitors in the treatment of erectile dysfunction
C. Gingell (Bristol) UK
5. Precautions on the use of PDE5 inhibitors on patients with cardiovascular risk factors and/or ischemic heart disease.
E. Pescatori (Modena) Italy

III Use of Alpha Adrenergic blockers in the treatment of erectile dysfunction

1. Classification, function and regulation of alpha adrenergic receptors in human penile tissue
K-E. Andersson (Lund) Sweden
2. Clinical experience with the use of alpha blockers in the treatment of erectile dysfunction
R. Rosen (New Jersey) USA

Iñigo Sáenz de Tejada
President ESIR

ESIR-Newsletter Editorial Board

- Iñigo Sáenz de Tejada
Editor
- Dimitrios G. Hatzichristou
Associate Editor
- Milagros Lemos
Associate Editor

Section Editors:

- Edoardo Pescatori
(Meetings: calendar and reports)
- Francesco Montorsi
(In my country... contributions from the advisory board)
- Hartmut Porst
(Don't miss... Literature review)
- Yoram Vardi and Clive Gingell
(Clinical highlights)
- Karl-Erik Andersson and François Giuliano
(Basic research highlights)
- John Pryor, Eric Wespes, Michael Sohn
(Clinical cases - questions and answers)

- Gorm Wagner
(Freelance contribution)

- Hans Hedlund and Dimitrios Hatzichristou (Interviews)

Other sections:

- Editorial
- New products
- What's up doc! (Humour)
- Letters to the Editor

ESIR Secretariat

Antonio Robles nº4 (9°C)
Madrid 28034, Spain
Tel: +34 91 358 38 54
Fax: +34 91 358 50 45
E-mail:
esir@coronadoserv.com
Contact person:
Milagros Lemos

Deposito legal M-9891/1998
Título: NEWSLETTER-ESIR
Editor:
IÑIGO SAENZ DE TEJADA
I.S.S.N.: 1029-2861
Imprime: Gráficas Mar. España

European Alliance of National Organisations for Sexual Dysfunction (ITALY)

Vincenzo Mirone

Impotence sufferers often feel they have nobody to turn to for help and support. They generally lack information as to the causes and the therapies available for their medical problem. This often leads to months and even years of waiting in silence before approaching a doctor. They risk frustration, irritability, anguish and depression rather than voice their problem. Unfortunately sexual difficulties transcend the individual domain when the person is in an ongoing relationship, spilling onto their partner and damaging the relationship, sometimes irreparably.

From March 19th 1998, the date of the launch of this free-phone number supervised by the Italian Andrological Society (SIA), we have received many requests for information and help. Many callers have tried to contact us and although we were only able to answer a proportion of those calls, the operators (specialised medical staff) have worked non-stop during the four hours that the line is available, from 4 p.m. to 8 p.m. Monday to Friday. It is clear that more facilities are needed to deal with the bulk of people trying to get through the switchboard. The difficulty of getting to grips with such a widespread problem as erectile dysfunction, which affects 13% of the male population, has led us to reach agreements with other scientific societies in order to set up an ad hoc task force. The main objective of this unit will be to provide multidisciplinary scientific information through the Centro Uomo & Donna in Salute (The Man and Woman's Health Centre).

Andrologists will now have a close working relationship with the general practitioners of the SIMG (The Italian General Practitioners Society) and the FIMMG (The Italian Federation of Family Physicians) as well as the SISS (The Scientific Sexology Society) and the gynaecologists of SIGO (The Italian Gynaecological and Obstetric Society). The centre will not just answer telephone requests for advice, it will evaluate symptoms, identify risk factors and provide information on diagnostic enquiries and therapies. It will also educate patients and encourage those who suffer in silence to seek help, given that there are now more effective diagnostic tools and methods to cure this ailment. There are various paths to follow: the distribution of educational material for patients and their partners through general practitioners,

the organisation of meetings with the press, the creation of an Internet site. A double strategy has been designed to reach those who decide to go to a physician's surgery and those who have not, as yet, been able to overcome the various taboos that prevent them from talking to a specialist about their problem. In these cases the anonymity of dialling a phone number or the click of the mouse can open doors to a future solution.

Referral to the family doctor or specialist can also help to highlight other problems that go beyond the strict definition of impotence, "the incapacity to reach and/or maintain an erection sufficient for satisfactory sexual activity". Erectile dysfunction is often associated to other common pathologies. The data collected via the SIA free-phone service confirms the psychogenic nature of the causes afflicting predominantly young men (up to 44 years of age), while organic or psychogenic/organic causes apply to men over the age of 45. Such causes are often associated with hypertension, diabetes, arteriosclerosis, depression, prostate hypertrophy, smoking and alcohol.

In general terms being better informed means being better equipped to come to terms with the problem within the couple relationship by eliminating feelings of guilt, all too common in these cases. Such questions as "is it my fault?, am I no longer attractive?, is he betraying me? Etc. can be laid to rest. The free-phone service receives many calls from wives and companions anxiously looking for an answer to their doubts. We are certain that the Centro Uomo & Donna in Salute will be able to help by providing a much-needed service hitherto unavailable.





Dear
Colleagues,

The Andrologic agenda for 1999 is full of exciting events, as you will see below. The first major European Convention will be the XIVth Congress of the European Association of Urology, to be held in Stockholm. People involved in the field of Erectile Dysfunction will find multiple sessions devoted to the subject each day of the Congress. The first of such events will be an ESIR pre-congressional session, addressing such hot off the press topics as the new oral treatments for E.D. See you soon in Stockholm!

1999

March 10-12, 1999 **Oviedo, SPAIN**
9th SPANISH CONGRESS of ANDROLOGY
Contact: Dr. C. Garcia-Ochoa
Tel +34 939 949898
Fax +34 85347070
Email andro@netcom.es
Website <http://www.netcom.es/andro>

March 29-30, 1999 **London, GREAT BRITAIN**
Exploiting the Market Potential and Product Development Opportunities in the Treatment of Erectile Dysfunction
Contact: Catherine Warren
Tel +44 (0) 171-4535496
Fax +44 (0) 171-6366858
Email cust.serv@ibcuk.co.uk
Website www.ibc-uk.com/IX176

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.nl



April 7, h. 09.00 - 14.00:
Pre-Congress Session of the ESIR
Erectile dysfunction
Chairman: I. Saenz de Tejada

- I. NitricOxide in penile erection
- II. Phosphodiesterases as pharmacological targets for the treatment of E.D.
- III. Use of Alpha Adrenergic blockers in the treatment of E.D.

April 7, h. 14.30 - 16.30:
Satellite Symposium 3
Recent advances and treatment of male erectile dysfunction
April 8, h. 08.00 - 08.30:
State of the Art Lecture 1
Modern management of erectile dysfunction - I. Eardely
April 8, h. 11.30 - 12.30:
Focused Discussion 2
Erectile dysfunction: risk factors / results of surgery?
April 9, h. 06.30 - 08.00:
Post Graduate Course 7
Diagnosis and management of erectile dysfunction
April 9, h. 10.00 - 11.30:
Poster session 16
Erectile dysfunction: Therapeutic aspects
April 9, h. 11.30 - 12.30:
Contemporary Issues 1
Penile enlargement
Poster session 24
April 9, h. 14.00 - 15.30:
Erectile dysfunction: Basic research
April 10, h. 12.30 - 14.00:
Oral session 16
Penile disorders, cancer and Peyronie's disease
April 10, h. 15.30 - 17.30:

Satellite Symposium 13
Erectile dysfunction: recent advances
April 11, h. 10.30 - 12.00:
Oral session 19
Erectile dysfunction: Therapeutic aspects

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

Annual Scientific Meeting of the SOCIETY FOR THE STUDY OF IMPOTENCE
June 9-12, 1999 Copanello (Catanzaro), ITALY
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
Tel +33 1 42 177120
Fax +33 1 42 177122

September 2-4, 1999 **Giessen, GERMANY**
11th Meeting of the GERMAN SOCIETY OF ANDROLOGY
Contact: Prof. W. Weidner
Urologische Klinik der Justus-Liebig-Universität Giessen
Klinikstrasse 29, D-35385 Giessen
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

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,
Istambul -TURKEY
Tel. +90 212 2305535
Fax +90 212 2304923
Email serpilb@antmarin.com.tr

* Abstracts will be accepted via internet.
For more information consult our website
(www.esir.com)



See you in
Stockholm

ESIR

Interview with Professor A. Jardin and Professor S. Khoury

Dimitrios Hatzichristou

The 1st International Consultation on Erectile Dysfunction will take place in Paris July 1- 3, 1999 under the patronage of the World Health Organisation. Although urologists are aware of similar WHO initiatives on BPH, prostate cancer, and more recently, urinary incontinence, many physicians from other specialities have not had the opportunity to participate in such activities. Today, it is a great pleasure to host interviews with two distinguished European academicians leading this effort.

Prof. A. Jardin, President and Prof. S. Khoury, a representative of WHO and Secretary for the Consultation.

Last year WHO decided to patronise the 1st International Consultation on Erectile Dysfunction. Could you give us some details on the background to this decision?

Current medical practice requires the clinician to make a balanced choice when considering treatment options for the management of the various diseases. This must take account, not only of the growing complexity of new technology and medical knowledge, but also of the economic restraints which are now unavoidable, even in the richest countries. It has become extremely difficult for medical practitioners to make objective decisions within the multiple facets of their clinical practice. It is also difficult for health organisations to define the most widespread policy. Expert recommendations are invaluable, so that the essential is not sacrificed in favour of the marginal, in order to provide the most effective health care at the most reasonable cost.

Since 1990 the World Health Organisation has been sponsoring many Consultations in Urology on such widespread diseases as BPH, Prostate Cancer, Incontinence and now Erectile Dysfunction.

Does that mean that WHO activities have expanded to include medical conditions that influence quality of life issues?

That is correct. As potentially lethal diseases continue to be eradicated, and as the population matures in many developing nations as well as in the developed world, conditions which substantially affect quality rather than the quantity of life are on the increase and are becoming major health issues. WHO is more and more compelled to address these new health issues so that people can live longer, healthier, productive lives and this outlook has shaped its new strategy.

Could you give us some more details of the structure of the Consultation?

Each Consultation is a long process lasting about 18 months conducted under the supervision of a steering committee composed of urological associations such as the American Urological Association (AUA), and the European Association of Urology (EAU).

The participation of associations related to the specific disease as the International Society for Impotence Research (ISIR), the European Society for Impotence Research (ESIR) and others, will be fundamental to the success of this Consultation.

How has the ED Consultation been planned?

The subject of E. D. was divided into 18 main topics covering the major areas: basic research, diagnosis and treatment (Table 1).

An international multidisciplinary committee of about 7 well-known experts headed by a chairman has reviewed each topic throughout the 18-month period. Each committee has had to:

- Update current knowledge on the subject assigned to it
- Give recommendations and conclusions for clinical practice.

After several preparatory meetings, a plenary session is planned in Paris, July 1-3 1999 during which the chairman of each committee will discuss his recommendations with an audience of about 1000 participants before finalising his report.

The reports of the 18 committees will be published shortly after the Paris plenary meeting in the proceedings book which will become an excellent and authoritative reference book on ED.

The first meeting will take place in Paris, June 29, 1999. What are your expectations for that meeting?

This first meeting has several main objectives:

- To update present data on E. D.
- To define a widely accepted strategy for the diagnosis and treatment of E. D., taking into account the risk / benefit factor of the different approaches in order to produce a decision tree adaptable to various settings.
- Propose an International Symptom Intensity Score, and Quality of Life Score to help standardise the assessment of the disease all over the world. (Previous Consultations on BPH proposed the International Prostate Symptom

Score (IPSS) which is widely used today around the world. A similar scale for incontinence is in preparation.

- To define the criteria of response to treatment and propose guidelines for conducting clinical studies in the field of E. D.

Is this a meeting for the experts only or will it be useful for both basic scientists and clinicians too?

Although the committees are composed of well-known experts on ED, the recommendations of the committees are aimed at helping the practitioner in the every day course of his work.

The plenary session, which will take place in Paris 1-3 July 1999, is an excellent opportunity for all those working in the field of ED, scientists and clinicians from many specialities, to update their knowledge on the subject.

You are no doubt aware that there is, as yet, no generally accepted diagnostic and treatment algorithm for impotence. As we noted earlier, all the major scientific associations have been invited to contribute to this united effort. Are you confident that the WHO guidelines will be adopted by the scientific community and the medical societies?

Erectile dysfunction is a complex and multi-faceted medical condition, implicating many systems of the organism and several medical disciplines. It is my belief that only an international multidisciplinary task force could hope to construct a valid, solid and widely acceptable strategy for the management of this disease. In order to achieve this objective we have invited the major associations representing the main disciplines involved in E. D. and asked them to pool their resources and produce comprehensive guidelines, taking into consideration somatic, psychological and socio-economic aspects. We are especially looking forward to collaborating with the ESIR and we hope that ESIR participant members will be numerous.

This approach has proved effective with the guidelines of our previous Consultations on other diseases (BPH, Prostate Cancer, Incontinence) which have been widely adopted by the medical community around the world and we are confident that the formula will also work for E. D.

Let me expand a little on my previous question. Several scientific societies have already published, or are working on the development of their own guidelines. The AUA, the ESIR and the British have already done so, and the EAU is currently preparing a document. Could you comment on this?

Although the basic aspects of E. D. are universal, various countries and cultures may have differences in their approach to the management of this disease, because of variations in their social, cultural and economical settings. It is natural that they should each seek to produce guidelines tailored to their realities and needs.

The WHO Consultation on E. D. does not aim to propose universal guidelines to be considered as "cook book recipes" or "one size fits all". We know from previous experience that there are no valid "universal guidelines" for such a complex disease as ED, where influences from social, cultural and economic parameters are so high. What the WHO Consultation will try to provide are "basic pragmatic reflections" on E. D. from a group of experts that may be of help to those people responsible for establishing health care policies in a given context or country. This should help them to make their choices without having to start their work from scratch saving time and money.

On the other hand, it is important to note that the Consultation is constantly enriched by all the efforts and progress achieved internally by the various individual associations participating. The WHO Consultation acts as a platform for debate, helping to bring emerging new ideas into focus and as a melting pot to produce the final blend.

In such a fast-changing field there is a constant need for follow-up of scientific advances. How will the WHO Consultation address the issue of producing rapidly outdated information?

Medical knowledge doubles every 5 to 6 years and recommendations and guidelines are only valid for a short period. The Consultation is an on-going process. It updates its findings every 3 years. If in the meantime some important breakthrough emerges, the scientific committee of the Consultation reacts by modifying, if needed; the recommendations before the 3-year period is up.

So, when and where will the next meeting take place?

The next Consultation on ED will be held in Paris in June 2002.

My last question refers to Female Sexual Dysfunction (FSD), which has attracted attention lately, as many new drugs are under phase II and III clinical trials. Will the Consultation on Erectile Dysfunction include FSD? And if so, is it appropriate to include female sexual problems under the title "erectile dysfunction"?

The status of the sexual activity of the male is constantly influenced by "real time" interactions with the status of the sexual activity of his female partner (and vice versa). Sexuality is a bipolar "action and reaction" phenomenon. Erectile function (and dysfunction) can only be accurately assessed in reference to the sexual activity status of the female partner. We should note that research in the psychological and in pharmacological aspects of FSD is still in its infancy and urologists along with those working in the field of sexuality are very active in this area. That is why the scientific committee came to the conclusion that "female sexual dysfunction" is a parameter that simply cannot be ignored when assessing "male erectile dysfunction" and decided to include this topic in the program.

Therapeutic targets for erectile dysfunction along the NO-cGMP pathway

Javier Angulo



Penile erection is brought about by relaxation of arterial and trabecular smooth muscle. Release of nitric oxide (NO) by nerves within the trabecular and penile arterial tissues as well as the endothelia that line lacunar spaces and the intima of penile arteries, promotes cGMP accumulation and relaxation of penile smooth muscle. Since the NO-cGMP pathway plays a prominent role in erectile function, therapeutic efforts for the treatment of impotence have been and will be in the future guided towards preserving or enhancing this pathway, with the development of drugs to modulate this vasodilator mechanism.

The enzymatic activity responsible for NO generation is NO-synthase, which has been detected in human penile tissue. Logically, the potentiation of NO-synthase activity could result in improvement NO-mediated responses. NO-synthase uses L-arginine as substrate, promoting its oxidation with oxygen consumption and yielding L-citrulline and NO as products of the reaction. Although, theoretically, L-arginine concentration is not a limiting step in NO formation, administration of high doses of L-arginine has been shown to improve NO-mediated relaxations, mainly in diseases involving impairment of endothelial relaxations, such as diabetes. This fact supports the rationale for the use of NO synthesis precursors for the treatment in erectile dysfunction. Indeed, L-arginine has been tested for the treatment of impotence, obtaining discretely encouraging results (1).

Another precursor of NO which has been proposed as a candidate agent for stimulation of NO synthesis is N-hydroxy-L-arginine, which carries an atom of oxygen bonded to the guanidine group of L-arginine, forming a hydroxyl group. NO generation from N-hydroxy-L-arginine could be faster and more effective than from L-arginine. N-hydroxy-L-arginine has also shown more potent relaxant properties than L-arginine in several vascular preparations, although its ability to facilitate penile smooth muscle relaxation and erection is still being tested.

More recently, gene therapy has been proposed as a possible treatment for erectile dysfunction, transfecting the gene of NOS (inducible or constitutive isoforms) to regain reduced expression or to achieve over expression of the NOS activity in penile tissue.

Stimulation of nitrergic nerves promotes NO-release to the surrounding penile smooth muscle, producing erection. The release of NO from these nerves is down-regulated by presynaptic α_2 -adrenergic receptors, suggesting the possibility of the use of α_2 -adrenergic blockers, such as yohimbine (pure α_2) or phenolamine (α_1 and α_2) for the potentiation of NO-cGMP pathway.

Direct administration of NO to the smooth muscle could activate the NO-cGMP pathway regardless of NOS activity, but NO is a free radical with a very short half-life, hindering its therapeutic use. In this way, synthesis of compounds with capacity for NO release from its structure to the tissues is of great interest for the treatment of erectile dysfunction. Sodium nitroprusside and linsidomine (SIN-1) are two NO-donors that have been evaluated for the treatment of impotence, obtaining less effectiveness than PGE1 but showing advantages such as absence of local pain and decreased risk of priapism (2, 3).

Nitrosothiols are a type of nitrovasodilator that bear the NO radical attached to a sulfhydryl group and are present in human blood, playing a role in the regulation of vascular tone and platelet aggregation. These compounds are potential tools for the treatment of erectile dysfunction and are now being studied for this purpose. Furthermore, the nitrosylation of α -blockers permits the combination, in one molecule, of the vasodilator activity of nitric oxide together with α -adrenergic blocking activity. These drugs are at a pre-clinical development stage.

One way to make the release or administration of NO more effective might be by increasing its half-life and thus enhancing its action. Oxidative environments and the presence of high levels of superoxide anions inactivate NO, decreasing its availability. Antioxidants and superoxide scavengers preserve NO and are therefore candidate drugs for the potentiation of NO-cGMP pathway.

The result of the action of NO is the generation of cGMP by guanylyl cyclase, which causes relaxation of smooth muscle. cGMP is rapidly hydrolysed to the inactive GMP by cGMP-phosphodiesterases (PDE), mainly PDE5 in penile tis-

sue. Extension of the action of cGMP may produce a potentiation of the smooth muscle relaxation, transforming PDE5 into a therapeutic target for the pharmacological enhancement of NO-pathway in impotent patients. An inhibitor of PDE5, sildenafil, has been successfully evaluated in clinical trials for erectile dysfunction (4) and is now commercially available for use in impotent patients. This drug possesses the advantage of oral administration, making it a more comfortable medication for the patient.

As discussed above, there are several potential targets for the pharmacological manipulation of the NO-cGMP pathway. Better understanding of the mechanisms of how diseases alter the NO-cGMP pathway will help us to select the best approach and the best tools to reverse or prevent erectile dysfunction.

References

1. Zorngiotti AW, Lizza EF. Effect of large doses of the nitric oxide precursor, L-arginine, on erectile dysfunction. *Int J Impot Res*, 6: 33-5, 1994.
2. Martínez-Piñeiro L, Cortés R, Cuervo E, Lopez-Tello J, Cisneros J, Martínez-Piñeiro JA. Prospective comparative study with intracavernous sodium nitroprusside and prostaglandin E1 in patients with erectile dysfunction. *Eur Urol*, 34: 350-4, 1998.

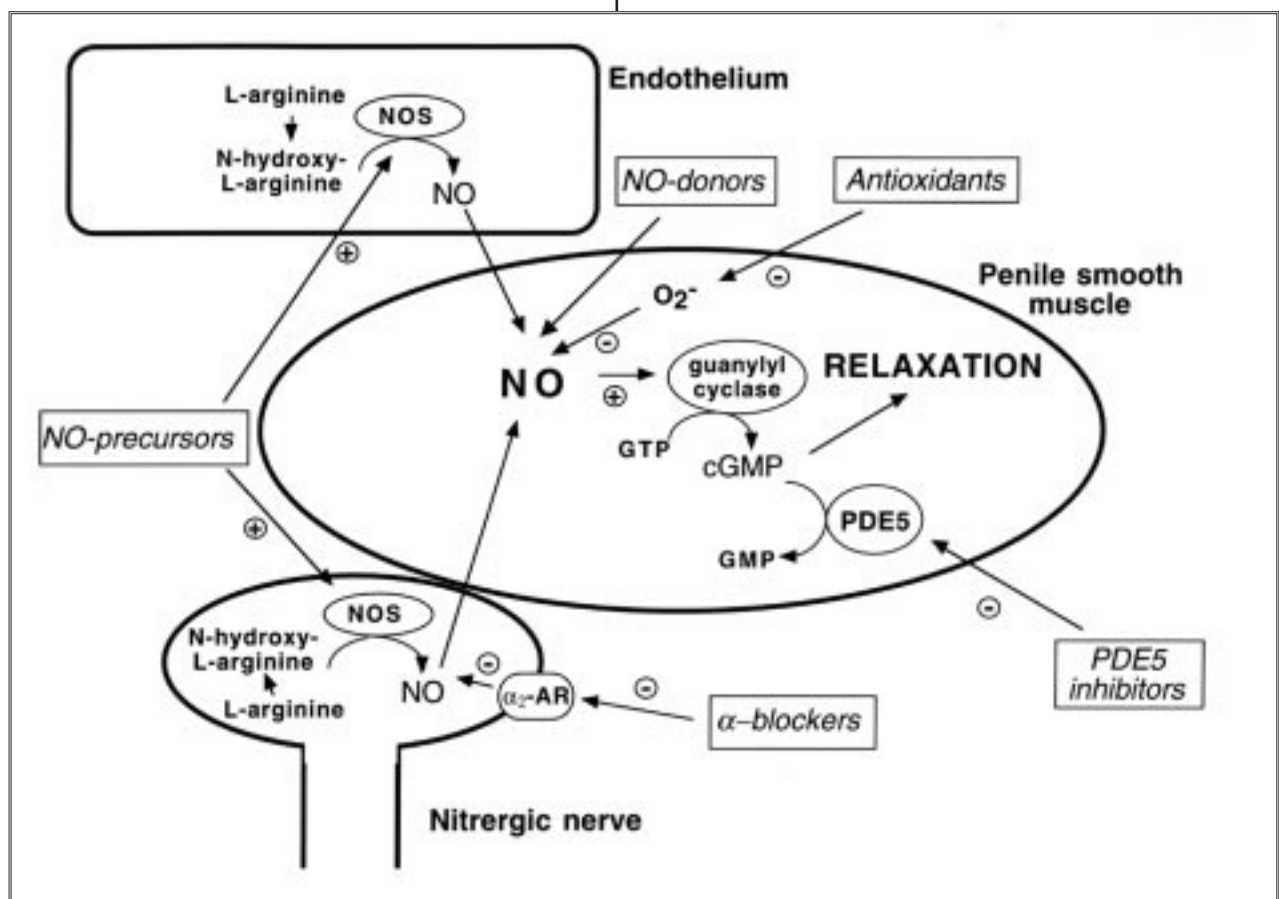
3. Truss MC, Becker AJ, Djamilian MH, Stief CG, Jonas U. Role of the nitric oxide donor linsidomine chlorhydrate (SIN-1) in the diagnosis and treatment of erectile dysfunction. *Urology*, 44: 553-6, 1994.

4. Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA. Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. *N Engl J Med*, 338: 1397-1404.

Javier Angulo

Head of the research laboratory

Fundación para la Investigación y el Desarrollo en Andrología (FI + DA) Madrid, SPAIN



Highlights from the 8th World Meeting on Impotence Research

Amsterdam 25-28 August 1998 - PART II

Diagnosis, Therapy, Ejaculatory Disorders, Female Sexual Dysfunction

Diagnosis

Redosing of vasoactive drugs in a subset of 17 patients with proven veno-occlusive dysfunction did not result in significant changes of enddiastolic flow, peak systolic velocity and resistance index in color duplex evaluation and seems therefore dispensable (Chen et al).

- The comparison of the IIEF with the results of the diagnostic work-up (PGE₁-Test, duplex-sonography, hormone-levels) provided evidence that the IIEF does not represent a valid instrument in distinguishing severe organic from severe psychogenic etiologies of erectile dysfunction (Porst).

Oral Drug Therapy

- An overview on the safety-profile of Sildenafil in 18 double-blind, placebo-controlled, clinical trials with a total of 4274 men resulted in the following most frequently observed adverse events (Sildenafil to Placebo): headache 20,8 % vs. 5,4 %, flushing 14 % to 1,3 %, dyspepsia 9,5 % vs. 1,9 % (Osterloh).

- In more than 15 papers the varied results of the different Sildenafil (**Viagra**[®]) studies were presented resulting in impressive success and satisfaction-rates (60 – 80 %) and significant improvements in quality of life parameters. Dosage increase above 100 mg and up to 200 mg did not lead to higher success but to higher adverse event-rates.

- In a prospective multicenter trial with 317 patients enrolled, **Apomorphine LS** up to 6 mg resulted in 65 % rigid erections (Padma-Nathan et al). The most commonly reported adverse event was nausea in 27 %. In a further prospective multicenter trial with **Apomorphine SL** in 457 patients with psychogenic ED 60 % of the attempts in the active group (6mg) resulted in sexual intercourse compared to 34 % (p < 0.01) after placebo (Padma-Nathan et al.)

- In a 5 month US-trial with **oral phentolamine (Vasomax**[®]) 40 mg dosages resulted in 36 % success-rates vs. 26 % placebo-rates (p<0.01) out of 312 patients (Goldstein) Adverse events were mild with rhinitis??? 3,7 % headache 2,9 % tachycardia 1,4 % and dizziness 1,9 %.

Vacuum Therapy

- After discussion of all treatment options 323 out of 1236 patients (27 %) opted for vacuum

therapy but after a two-week trial period only 74 (23 %) out of these 323 patients requested a prescription indicating a low acceptance rate (74 out of 1236 patients = 6 %) of vacuum devices (Graham et al).

- The beneficial effects of vacuum devices in terms of minimisation of corporeal fibrosis after removal of penile prosthesis, was reported by Hakim et al.

Transurethral Therapy

- A comparative trial between transurethral Alprostadil (MUSE[®]) and intracavernous injections of PGE₁ in 125 males resulted in efficacy-rates of 48 % for MUSE[®] and 79 % for i.c. PGE₁ (Ghuzi et al). At the end of this study 47 % preferred self-injection therapy and 33 % MUSE[®] whereas 20 % used both methods alternatively.

- A further comparative trial between intracavernous Alprostadil (Viridal[®], Edex[®]) in doses of up to 40 µg and MUSE[®] up to 1000 µg (Shabsigh et al) resulted in responder rates of 60 – 66 % (positive Buckling-test) vs. 22 – 27 %. Both comparative trials provide convincing evidence of the superiority of intracavernous Alprostadil.

- Both the application of an adjustable penile constriction band (Actis[®]) (Lewis et al) and the addition of Prazosin (Melman et al) resulted in the enhancement of MUSE[®] efficacy up to 75 % compared to 63 % after MUSE[®] alone.

Self-injection Therapy

- A review of the English language medical literature from 1987 to 1997 covering 15 publications with a total of 2877 patients and considering the issue of improved natural erectile function following long-term self-injection therapy, revealed only 9,2 % prevalence of adequate natural erection function (Sharlip) indicating that the overwhelming majority of the patients show long-term dependence on self-injection therapy.

- In a self-injection trial with VIP/Phentolamine (Invicorp[®]) in 311 patients suffering from ED, 241 (77 %) responded with a grade 3 erection (Hackett et al) . Two priapisms corresponding to an incidence of 0,1 % were observed.

- In a prospective multicenter long-term trial with Alprostadil (Caverject[®]) 22 % (147 out of 683 patients) completed the trial after 5 years (Linnet) Incidence of penile fibrosis ranked between 2 % and 10 % in the different study periods, and priapisms > 6 hours were only encountered in 5 cases (< 1 %) and exclusively in the initiation period.

Penile Prosthesis

- Due to the well-known cylinder problems and decreased cylinder survival of the AMS Ultrex prosthesis, Montague et al, recommend the exclusive use of AMS CX or CXM when corporeal dilation is limited in men with long penises,

Peyronie's disease or in implant redoings.

Penile Deviation

- The so-called Essed plication method for correction of penile deviations was burdened with high failure rates both in congenital (25 %) and acquired (42,9%) curvatures due to Peyronie's disease (Schultheiss et al). In addition 1/3 of all patients complained about discomfort from the non-absorbable sutures. Manning et al also reported also high unsatisfactory results (> 50 %) with the Essed technique in acquired penile deviations.

Ejaculation/Orgasmic Disorders

- Dysorgasmia after radical prostatectomy was successfully treated with the alpha-adrenoceptor blocking agent Terazosin in 75 % out of 20 patients (Mulhall et al).
- The combination of fluoxetine and local lidocaine in premature ejaculation showed total improvement rates of 82 % and was somewhat superior to fluoxetine alone with 73 % successes (Atan et al).
- Treatment of premature ejaculation with paroxetine 20 mg daily or on demand, precoital administration resulted in impressive success rates with prolongation of the mean ejaculatory interval from 0,4 min to 4,5 min if given daily, and success-rates of 68 % (36 out of 53) if given on demand (Mc. Mahon et al).

Female Sexual Disorders

- In the female rabbit animal model, chronic clitoral ischemia resulted in subsequently clitoral fibrosis and decrease of smooth muscle content (Park et al), a phenomenon proven in the male cavernous bodies more than a decade earlier. Human cadaver studies in 15 fresh female cadavers (11 to 90 years) revealed marked histologic changes in clitoral erectile tissue with age (Tarcan et al). In female rabbits, Azadzoj et al were able to prove that contraction of clitoral cavernosal and vaginal smooth muscle is regulated by adrenergic nerves and relaxation predominantly by the NO-pathway. Therefore from the biological and biochemical point of view male and female erectile tissue are comparable. Systemical administration of **Apomorphine** increased clitoral and vaginal arterial inflow in rabbits (Tarcan et al). In a pilot study of six postmenopausal women with lubrication and sexual arousal disorders **oral phentolamine** (Vasomax® 40 mg) improved lubrication with pleasurable sensations in the vagina (Rosen et al). The National Health and Social Life Survey of 1511 men and 1921 women between the ages of 18 and 59 revealed sexual problems (desire, arousal or orgasm) in 31 % of the men and 43 % of the women (Laumann et al) indicating that both sexes are at high risk of sexual disorders.