Dear friends,

This is the first issue that is published in The Netherlands under my direct supervision as the new Editor-in-Chief. The ISSIR Executive Office (Robert Kessler, Renée van der Maesen and Sieka van Essen) will help us improving the quality of the Newsbulletin. Dr Buvat will remain a necessary help in my important job.

As mentioned by Dr Buvat in issue 9, we will try to cover all major events on sexual function and dysfunction. We will publish quickly the reports from important meetings and we will display these reports even earlier on the ISSIR website. Thanks to a good collaboration with the website committee and the newsbulletin committee, the exchange of information between the two groups will improve the quality of the newsletter. A report on the 7th Asian Congress of Sexology by Dr K. Gauthaman and on the 2nd Pan-Arab Congress of Sexual Dysfunction by Dr L. Incrocci have been displayed only some weeks after the meeting on the ISSIR website, and are now published in the present issue. We look back with pleasure and interest to the Montreal meeting, while Dr E. Becher is working hard to prepare the 11th ISSIR World Meeting in Buenos Aires in 2004. In this issue you will read more reports on the 10th ISSIR meeting in Montreal, and also shortly on the ESSIR meeting in Hamburg, last December 2002.

Thanks to an unrestricted grant by Pfizer, it has been possible to award 5 excellent research projects, while a 6th one has been funded by the Zorgniotti Research Fund. These young grant winners present their projects in the present issue and will keep us informed in the coming issues on their research developments. The quality of the submitted projects was very high, and it has been very difficult for the educational committee chaired by Dr G. Wagner to make a decision on the winners. Three interesting papers review the epidemiology of erectile dysfunction (Dr A. Martin-Morales), the hormones in male sexual functioning (Dr J. Buvat) and the treatment of premature ejaculation (Dr D. Rowland).

We are making our efforts to keep the quality of the Newsbulletin high, and we invite everybody to send us comments, reviews, papers.

Enjoy reading this issue.

Lucas Incrocci, MD, PhD
Chief Editor

Jacques Buvat, MD
Associate Editor

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To contact us:

Dr. Luca Incrocci
Department of Radiation Oncology
Erasmus MC - Daniel Den Hoed
PO Box 5201
3008 AE Rotterdam
The Netherlands
Tel. +31 10 4391 421
Fax +31 10 4391 013
Email. lucaincrocci@cs.com

ISSIR Executive Office
PO Box 97
3950 AB Maarn
The Netherlands
Tel. +31 343 442 043
Fax +31 343 443 888
Email. secretariat@issir.org

Website: www.issir.org
Sexual dysfunction is easier to overcome when you have a partner who cares.

Introducing...

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Dear members of the ISSIR,

Several important events have recently marked the life of our Society. The first one is the finalization of the contract binding our 3 Quality Partners (Pfizer, Lilly-Icos and Bayer, which we thank here) to the ISSIR and its Regional Affiliated Societies in the framework of the Global Business Plan. To summarize its broad outline, this renewable 3 years plan had been mainly elaborated under the presidency of Dr Sidney Glina and consists in Quality Partners (QPs) and Quality Sponsors (QSs) from the industry donating to ISSIR an annual grant subsequently shared with the Regional Affiliated Societies (RAS). In exchange the ISSIR and the RAS must have full meetings with scientific papers submission only every other year (even year for the ISSIR, odd for the RAS). Each Society may have a meeting on the following year, but in the form of subject oriented symposia, without paper submission. This intends to reduce the number of meetings, a request from most of our members, while maintaining at the top level the scientific interest of the biennial meetings in that more new papers will be presented during these meetings, leading to more attendance and thus more possibility of direct exchanges between researchers and clinicians. In addition the QPs and QSs obtain different advantages including free space for their exhibition and free time for their symposia in a proportion based on the level of their sponsorship. This Global Business Plan has been approved by the ISSIR, the APSIR, the ASSIR, the SLAIS and the SMSNA, but not for the moment by the ESSIIR (note that the ESSIIR has just changed its name in ESSM, European Society for Sexual Medicine during its last and successful meeting in Hamburg, under the able chairmanship of Pr Hartmut Porst). There was still to finalize the contract with industrial partners and especially their legal departments which has just been done, allowing the first signatures and grant’s payments. This is going to alleviate the burden previously linked to a permanent quest of money for supporting our research and educational activities, on which we will therefore now have more possibilities to concentrate.

Early April the African Society for Sexual and Impotence Research held its 4th biennial meeting in Marrakech, Morocco. This ASSIR meeting was associated (and preceded) with a full day ISSIR meeting made of 3 topic oriented symposia: Education, Priapism, and impact of Life Style on Erectile Dysfunction. This was the first meeting held according to the framework of the Global Business Plan, the financial support of which has been especially important to build this meeting which promises to be a great one. The Marrakech meeting was also one of the very first meetings of the ISSIR constellation with simultaneous translation (in French), in order to avoid neglecting the very large French speaking community of Africa (about half of the continent). This year 2003 is also going to see the biennial meetings of the SLAIS (Cathagena, Columbia, in August) and the APSIR (Cebu, Philippines, in October), as well as meetings of the SMSNA in Denver, Colorado, also in October, and of the ESSM in Istanbul in November. Lastly the preparation of the next biennial meeting of the ISSIR is progressing very actively, under the dynamic and very able chairmanship of Dr Edgardo Becher, strongly helped by our Executive Office. A first announcement is going to be mailed very soon. Announcements of all these meetings can also be found in the Newsbulletin and on our Website at www.issir.org.

The agreement between the ISSIR and the ESSIIR/ESSM about a common membership and the International Journal of Sexual and Impotence Research becoming the Journal of both Societies (as well as that of other RAS) has also been finalized. Dr John Pryor played a very active role in this achievement and has to be thanked. From now any member from the European area is going to pay a single annual membership fee which will make him member of both the ESSM and the ISSIR in the same time, allowing him to receive the International Journal of Impotence Research (IJJR), the ISSIR Newsbulletin, to have access to the private area of the ISSIR website with free access on line to the IJJR and different other very useful functionalities and to benefit from significant discounts on the registration fees at the ISSIR meetings. The ESSM will also have the possibility to pay itself for its members. In a first time the money will be collected by the ESSM but in the future it may be so by the ISSIR which has the capacity of registration on line through its website, reducing the administrative expenses. We hope this agreement will serve as an example for a common membership of the ISSIR and other RAS.

Since the Montreal meeting several ISSIR Committees have been completed or expanded, and new Committees have been formed. Their present state can be found in this issue. In order to speed the transmission of information on important events in Sexual Medicine the Newsbulletin and Website Committees have been linked with several members becoming simultaneously members of both. The Development Committee is now under the chairmanship of Dr Francesco Montorsi, President Elect of the ESSM. Its tasks have been updated, and include now the development of both the financial resources, the membership and the educational tasks of the ISSIR in close relationship with the Educational Committee as concerns the later. A Presidents’ Committee has been created, putting together the Presidents and Presidents-Elect of the 5 RAS and the board of the ISSIR. By regularly meeting physically, and keeping the contact in the meantime through a specific mailing list, this Committee is going to make easier the communication between the ISSIR and the RAS, to facilitate the evolution of their relationships, and to give the opportunity for debates on major topics as the Future of Sexual Medicine which is going to be one of the main topics discussed by this Committee in Chicago and Paris. A Standard Committee has been created, aiming at the establishment of standards for clinical trials and scientific studies, as well as for Evidence Based Medicine applied to Sexual Medicine. In the future it may also have to deal with the validation of investigations, and the Nomenclature of Sexual Medicine. The overall aim of this ambitious project is to gradually promote the ISSIR as the main reference in the field of Sexual Medicine. Lastly the Prizes Committee is going to revive in order of better organize the collection and assessment of the manuscripts submitted for the prizes, as well as their subsequent publication in the IJJR.

Among the other news being worth a mention: our Journal has just entered a new phase of its life with a new Chief Editor (Dr Irwin Goldstein), a new Editorial Board, and a new name: The International Journal of Impotence Research: a Journal of Sexual Medicine. Lastly we are thinking about a change of the name of our Society at the time of our next Business Meeting in Buenos Aires, for the “International Society of Sexual Medicine”.

Jacques Buvat
ISSIR President
ISSIR Committees

Executive Committee
Jacques Buvat - President ..........France
Jacques-Buvat@wanadoo.fr
P. Ganesan Adaiak - President Elect ....Singapore
obgadaik@nus.edu.sg
Ira Sharlip - Secretary General ........USA
isharlip@aol.com
Eric Meuleman - Treasurer ....The Netherlands
e.meuleman@uro.umcn.nl
Sidney Glin - Past-President ........Brazila
ginas@tena.com.br

Members at large
Young Chan Kim........................Korea
youngkim2004@kornet.net
Francesco Montorsi .......................Italy
montorsifrancesco@mail.hsr.it
Yoram Vardi .........................Israel
yvard@rambam.health.gov.il
Craig Donatucci ..............USA
donat001@mc.duke.edu
Edgardo Becher ..................Argentina
ebecher@cdu.com.ar

Representatives of the affiliated Organizations
Dimitrios Hatzichristou - ESM ..........Greece
Abrie Schmidt - ASSI R .............South Africa
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Culley Carson - SMSNA ...............USA
Fernando Ugarte y Romano - SLAIS....Mexico

Ex-Officio members
Irwin Goldstein - Editor IJIR ............USA
igoldst@bu.edu
Luca Incrocci -
Editor Newsbulletin ............The Netherlands
lucaincrocci@cs.com

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ISSIR meeting 2004 - Buenos Aires, Argentina

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Ganesan Adaikan

News from the Committees

Educational Committee
Six grant winners were presented in Montreal
Out of 21 excellent applications, 6 were outstanding. The ISSIR/Pfizer grants were awarded to 6 applicants from England, China, Venezuela, USA and Canada. The 6th winner was given a grant from the Zorgniotti Fund.
Even though all winners are from different nations most are working in the USA. It was discussed within the committee that this was unfortunate. However, the committee decided not to compromise the quality level of the research. The following researchers each received USD 10,000:
Dr. Derek Bochinski, University of California, San Francisco
Dr. Kelvin P. Davies, Albert Einstein College of Medicine, Bronx
Dr. Jas Kalsi, Wolfson Inst. for Biomedical Research, London
Dr. Steven R. King, Baylor College of Medicine, Houston
Dr. Guiting Lin, University of California, San Francisco
Dr. Ricardo Munarriz, University School of Medicine, Boston

Main Purpose of the committee
To create a proposal for a multidisciplinary teaching course for undergraduate medical students in Sexual Medicine, and to have this introduced in the formalized curriculum in medical schools, globally. Ideally this effort should be undertaken in collaboration with the WHO and WFME (World Federation of Medical Education) with support from them and support to them in their goals within education at university level.
At the committee meeting in Hamburg (Dec. 2002) the following objectives were decided upon:

Objectives
1. To ensure that any medical graduate has sufficient basic knowledge about human sexual function and disorders, in order to be able to identify the most common sexual problems in women and men and in these as couples.

2. To ensure that any medically qualified person is aware of the co-existence of sexual problems with commonly occurring diseases and their treatment.
3. To ensure that basic knowledge of existing “EBM-treatment modules” have been acquired.
4. To ascertain that the “basic” doctor has awareness in general terms of globally existing differences in sexual behavior and perception.
5. To ascertain that the manner in which teaching is provided shall make the student aware of own attitudes.

Final Goal
After collecting information of existing literature, teaching courses and plans to work out a proposal build-up as modules for simple application and integration into any curriculum.
Ideally the final step should be to produce an electronically available low-cost teaching package, which should make it possible for uncustomed university teachers to formulate a program in accordance with local demands.
A questionnaire to the existing 1600 Medical Schools will be mailed in January 2003 and an abstract for a poster presentation has been sent to the World Conference on Medical Education in March 2003 in Copenhagen (www.wfme2003.ics.dk), where the chairman will participate.

Gorm Wagner, Chairman

Executive Committee
I’m pleased to inform you that an agreement between the European Society for Sexual Medicine ESSM (former ESSIR) is in progress, which may result in a slight reduction of the present membership fees. Of course you will be updated when the agreement is finalized.

Eric Meuleman, treasurer
The effect of insulin-like growth factor-1 and insulin-like growth factor binding protein-3 in cavernous nerve cryoablation

References

Diabetes is a major, and still growing, health problem in the United States, and affects more than 100 million people throughout the world. There are several pathologies caused by diabetes, one of the commonest, occurring in approximately 60% of patients, is a detectable neuropathy. One of the corollaries of peripheral neuropathy is that patients with diabetes mellitus develop urogenital pathologies, such as diabetic cystopathy (associated with decreased bladder sensation and increased residual volume or detrusor instability) or erectile dysfunction.

Diabetic urogenital pathologies are almost certainly associated with alterations in gene expression. Several studies have focused on how diabetes affects the expression levels of neuroreceptors. For example, since it is believed that contraction of the normal human detrusor muscle is mediated primarily by stimulation of muscarinic (Mx) receptors by acetylcholine, the expression of these genes has been extensively studied. The findings from one study on rats with streptozotocin (STZ)-induced diabetes suggest that there is up-regulation of M2 biosynthesis in the diabetic urinary bladder. Another study determined that experimental diabetes elevated the density of endothelin receptors, 8 and 16 weeks following onset of diabetes compared to age-matched controls. When compared to normal human cavernosal tissue, diabetic corpus cavernosum from humans with erectile dysfunction also have higher levels of arginase II gene, an enzyme that competes with nitric oxide synthase (NOS) for arginine, the precursor of NO. There is also a report describing diabetes related alterations in membrane lipid composition. Diabetes can also result in changes in the regulation or activity of ion channels in bladder smooth muscle. In this regard we have recent evidence that there is a concomitant change in the type of Maxi-K splice variant expressed in the diabetic compared to non-diabetic rat corpora (presented at the 2002 ISSIR meeting in Montreal). Overall, these studies lead to the conclusion that the complications occurring in the urogenital system following the onset of diabetes are a result of changes in gene expression, although these changes are likely to involve changes in several, rather than a single, genes.

Previous approaches to understand the molecular events accompanying diabetic urogenital pathologies have necessarily been focused at the single gene level. However, the newly developed micro array technology has made it possible to simultaneously monitor thousands of genes in a single experiment, allowing efficient and global monitoring of gene expression from a single sample. We intend to use micro array gene chip analysis to understand the complete range of changes in gene expression that occurs following onset of diabetes in the urogenital smooth muscle tissue of animal models (STZ-induced diabetes in rats) and human patients. It is hoped that this genomic approach might lead to improved understanding and diagnosis of diabetic urogenital pathologies, as well as a more rational pharmacological or gene therapy treatment.

Aim: To investigate in vitro effects of a Rho-kinase inhibitor, soluble guanylate cyclase activator, PDE5 inhibitor and NO-releasing PDE5 inhibitor on human and rabbit corpus cavernosum.

Project: An important role for the nitric oxide (NO)-cGMP system in the physiology of penile erection has now been widely accepted. PDE5 inhibitors (e.g. sildenafil, VIAGRA) enhance erectile function by potentiating the NO-cGMP system in the physiology of penile erection via a nitric oxide-independent pathway. Nature Medicine 7:119-122.

References:

Role of the Steroidogenic Acute Regulatory Protein in Libido

Loss of sexual desire can manifest itself as erectile dysfunction and is a devastating and significant medical problem for many men, resulting in a diminished quality of life and many visits to the urologist. Reasons for this loss include aging and depression. While there has been progress in understanding and treating some sexual problems such as erectile dysfunction, a method for helping patients suffering from a loss in libido is more elusive.

Steroids are essential for reproduction including libido. The male sexual drive requires the synthesis of testosterone mediated by the steroidogenic acute regulatory (STAR) protein in Leydig cells. Through its actions in the brain, testosterone is critical for sexual and gender-typical (e.g., aggression and dominance) behavior. Conditions that reduce or eliminate testosterone production (castration, hypogonadism, and aging), result in a decline in sexual behavior. While this is neither the only hormone involved nor the only cause, testosterone replacement therapy is unfortunately the only practical option available today. The risks involved are substantial, especially in the elderly patient. Side effects include testicular atrophy, decreased ejaculate, erectile dysfunction, and possibly progression of prostate cancer and vascular disease. Worse, benefits gained can be disappointing. Thus, there is a need to understand the mechanism by which libido occurs and is maintained.

There is little information regarding the complex receptor pathways involved in libido in the human, where sexual desire and arousal are separable. Studies with rodents are simpler in that libido and potency are intimately linked. In the absence of physical problems of the testes and the penis, libido is manifested in successful breeding. It is difficult to separate erectile dysfunction due to loss of libido from local problems in the testes since loss of testosterone clearly causes both problems in rodents. While necessary, gonadal androgens are not sufficient for libido. Interestingly, STAR and the enzymes responsible for biosynthesis of steroids, such as testosterone, are also expressed in the brain. This leads to the possibility that other steroids, locally produced in the brain (neurosteroids), can regulate libido.

This potentially important class of hormones includes compounds such as progesterone, pregnenolone sulfate, dehydroepiandrosterone (DHEA), the androgenic hormone 3α-androstenediol, and pregnane steroids (e.g., allopregnanolone), and can be localized to areas essential for the regulation of sexual behavior (e.g., libido and erectile function). Studies have linked neurosteroids to the regulation of the hypothalamic-pituitary-gonadal axis, including both enhancement and suppression of sexual motivation and behavior. However, most of these observations have been correlative or made utilizing non-physiologic intracerebroventricular administration of steroids and focused on female behavior. Therefore, I propose a new approach to test the role of neurosteroids in libido, through generating mice that contain a brain-specific deletion in the gene for STAR, the protein required for hormone-regulated steroidogenesis.

STAR regulates the rate-limiting step in the production of all steroids, the delivery of cholesterol from the outer to the inner mitochondrial membrane and the P450scc enzyme, which converts cholesterol to pregnenolone. Mutations in STAR result in congenital lipid adrenal hyperplasia, a potentially lethal condition in which the body is unable to synthesize sufficient levels of adrenal and gonadal steroids and male patients are phenotypically female.

We have shown that STAR not only colocalizes with P450scc in the brain, but is synthesized in crucial regions for sexual behavior. Thus, STAR is probably instrumental in neurosteroid production. Unfortunately, the general loss of steroids in STAR-/ mice makes them unsuitable models to examine neurosteroid function. However, a conditional brain-specific targeted deletion of STAR will enable direct assessment of the role of neurosteroids in sexual behavior.

A Cre-LoxP strategy will be used to develop such a mouse model. A plasmid containing the STAR gene with LoxP sites has been introduced into introns I and III along with a selectable marker will be introduced through homologous recombination into the genome of an embryonic stem cell line, replacing the wild-type gene. These cells will be used for implantation and generation of mice carrying the altered “floxed” gene (STAR flo flo). These animals will be crossed with previously generated mice that express a truncated progesterone receptor fused to the p65 activation and GAL4 DNA-binding domains under the control of the prion promoter, and Cre recombine under the control of the minimal thymidine kinase (TK) promoter. Administration of RU486 will cause the fusion protein to bind the TK promoter and induce expression of Cre. Cre will then recognize the LoxP sites and excise exons II and III of the STAR gene, thus selectively eliminating STAR activity in the brain. This will be done at select timepoints in the lifespan of the mouse (i.e., development, puberty and aging). Techniques, such...
Background
Penile erection is a neurovascular event depending on neural integrity and functional blood vessels. Injury to or degeneration of the cavernous nerve from radical surgeries for prostate, bladder and rectal cancer or diabetes mellitus is one of the most common causes of erectile dysfunction (ED). Roughly 50% of patients with diabetes mellitus and more than 50% of patients after prostate cancer therapy developed ED. Neural injury or degeneration is a component of ED in many of these patients.

Currently, there is no cure for neurogenic ED. In the past few years, great stride has been made in the research of stem cells. Several institutions have reported successful induction of neurons from embryonic stem cells (ES) and applied them to neurologic diseases. Nevertheless, no research has been conducted to study the feasibility of implanting ES cell to treat neurogenic ED. In the past year, we have successfully isolated and cloned ES from rats and constructed a green fluorescence protein (GFP) positive ES cell model will also be suitable to study the feasibility of implanting rat embryonic stem cells to treat neurogenic ED. In this future, we will also study whether ES cells can be used to treat diabetic neuropathy.

Specific Aim
In this project, we propose to study whether embryonic stem cells can be induced to differentiate into neurons. The ES cells will be implanted to the dorsal-caudal region of the major pelvic ganglion (DCR-MPG) of rats after bilateral freezing injury to the cavernous nerves. It has been reported that “injury-conditioned” neurons produce many growth factors and gene promoters that are capable of inducing the injured neurons to regenerate. If the ES cells do not form neurons under this condition, we will transfec ES cells with BMP signal inhibitor Chordin to transform them to neurons and then implant them into the DCR-MPG. Successful completion of this study will provide a scientific basis for future study of embryonic stem cell therapy in impotence.

References
monitor intracavernous pressure. Electro-stimulation will be performed with a stainless-steel bipolar hook electrode attached to a multi-jointed clamp. Monophasic rectangular pulses (current of 1.5 mA, frequency of 20 Hz at a pulse width 0.2 m seconds) will be delivered to each cavernous nerve for 50 seconds. A 23G needle will be inserted into the right crus and connected to a pressure monitor. Arterial blood pressure will be continuously monitored via a catheter inserted into internal carotid artery. Both intracavernous and systemic blood pressure will be measured and recorded. Both intracavernous and systemic blood pressure will be measured and recorded. Both intracavernous and systemic blood pressure will be measured and recorded.

A recent report suggests that testosterone treatment prevented this decrease in penile cavernosal PDE 5-enzyme activity that penile cavernosal PDE 5-enzyme activity. Our preliminary data suggest that penile cavernosal PDE 5-enzyme activity remains unclear if steroid hormones, apart from the effects on growth and development and libido, androgens have been shown to exert local effects on the regulation of penile trabecular smooth muscle contractility. Most studies to date have focused on the effects of androgens on nitric oxide synthase. Furthermore, recent studies demonstrate that steroid hormones can activate intracellular signalling pathways via immediate, non-genomic mechanisms involving cyclic nucleotides.

A recent report suggests that testosterone may influence penile erection in the rat, in an acute fashion, by a mechanism independent of nitric oxide yet involving the cGMP pathway (Reilly CM et al., 1997). Furthermore, in human granulosa luteinizing cells, androstenedione has been shown to increase Ca2+ through a phospholipase C mediated mechanism (Machelon V et al., 1998). Other steroid hormones have also been shown to exert non-genomic effects in specific cell systems. Estrogens induced mobilization of Ca2+ from intracellular stores in chicken granulosa cells within seconds of exposure (Morley P et al., 1992). In addition, the effects of estradiol on estrogen-responsive genes (LIV-1 and pS2) have been demonstrated to be modulated by increases in cAMP. These findings indicate many potential interactions between classical G-protein-mediated signalling pathways and steroid hormones. To date, there have been no studies on the effects of steroid hormones on transcriptional regulation of phosphodiesterases and it remains unclear if steroid hormones, apart from their trophic effects, have more immediate effects on penile corpus cavernosum smooth muscle. Our preliminary data suggest that penile cavernosal PDE 5-enzyme activity is decreased in castrated rabbits while testosterone treatment prevented this decrease.

The studies in this proposal represent a novel approach in which regulation of human penile trabecular smooth muscle PDE 5 by hormones and second messengers will be investigated. It is expected that understanding of the cGMP/cAMP pathways and the potential role of steroid hormone action and their influence on PDE 5 will increase the current knowledge of the extensive nature by which distinct signalling pathways can interact and provide an integrated regulation of penile trabecular smooth muscle tone.

We propose to investigate the effects of the androgens and estrogens on cyclic nucleotide levels and PDE 5 phosphorylation, activity or expression in human penile corpus cavernosum smooth muscle cells. In addition, we will investigate the requirement for estrogen or androgen receptors in mediating the observed effects of these hormones. We have developed specific antibodies to phosphorylated and non-phosphorylated PDE type 5, which will allow us to assess PDE 5 expression and phosphorylation. Determination of PDE 5 activity in cell homogenate will be carried out after extensive washing of the intact cells to remove the inhibitor.

References

We have previously demonstrated that the incidence of occult coronary artery disease is higher in a selected group of men with vasculogenic erectile dysfunction (ED) (J Urol 1998;159:159:30) when compared to the general population.

The purpose of this current investigation was to define the risk of having obstructive coronary artery disease (CAD) on non-invasive cardiac assessment for patients with documented vasculogenic ED who were asymptomatic for CAD. Patients presenting for the evaluation of ED to our clinic without any history suggestive of CAD underwent duplex Doppler Penile ultrasonography (DUS) in a vasoactive agent redosing fashion. Those patients who had vascular insufficiency documented were sent for interview and examination by a cardiologist. Following this, patients without indicators of CAD underwent exercise stress echocardiography (SE) using a Bruce protocol.

Thirty-two patients completed DUS and SE. The proportion of patients with 1, 2, 3 and 4 vascular risk factors was 22%, 44%, 22% and 11% respectively. Thirty-three percent of patients had a first degree relative with known CAD; 97% patients had cavernosal artery insufficiency and 31% of patients had venogenic ED on DUS. The mean PSV was 22 ± 4 and mean EDV was 5 ± 3 cms/sec; 22% of men had an abnormal SE suggestive of obstructive CAD. This ongoing preliminary analysis of patients with vasculogenic ED is highly suggestive of a significant correlation between documented abnormalities on DUS and abnormal stress echocardiography. The small number of currently enrolled patients precludes analysis of any potential predictors of SE abnormalities. Further enrollment and analysis if confirmatory will present further data supporting ED as a harbinger of systemic disease processes and will encourage non-ED clinicians to assess ED patients in a more formal and comprehensive fashion.

John Mulhall
Department of Urology
Weill Medical College
of Cornell University,
The New York Hospital
525 E 68th St, New York, NY 10021
Tel: +1 212 746-5653
Fax: +1 212 746-0403
E-mail: jpm2005@med.cornell.edu

Study Methods

- Patients (18-60 years) presenting for the evaluation of ED who underwent duplex Doppler Penile ultrasonography (DUS)
- DUS performed in a vasoactive agent redosing fashion
  - CAI = PSV < 30 cms/sec
  - CVOD = EDV > 5 cms/sec
- Those patients who had vascular insufficiency documented were sent for interview and examination by a cardiologist
- Patients without indicators of CAD underwent exercise stress echocardiography (SE) interpreted by cardiologist

Comorbidity Profile

<table>
<thead>
<tr>
<th>Patients Age (years)</th>
<th>57 ± 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED duration (years)</td>
<td>3.5 ± 3</td>
</tr>
<tr>
<td>Diabetes</td>
<td>22%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>56%</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>41%</td>
</tr>
<tr>
<td>Cigarette smoking history</td>
<td>75%</td>
</tr>
</tbody>
</table>

DUS Data

| Mean PSV | 22±4 |
| Mean EDV | 5±3  |
| % with CAI | 97% |
| % with CVOD | 31% |

No difference in mean PSV between those with normal and those with abnormal SE

IIEF Data

| Mean total IIEF | 54±16 |
| Mean EF domain | 16±9  |

- No difference in EF domain between those with normal and abnormal SE
- No difference in Viagra response between 2 groups
Blue film-coated, rounded diamond-shaped tablets containing sildenafil citrate equivalent to 25mg, 50mg and 100mg sildenafil.

**Indications:** Erectile dysfunction. Sexual stimulation is required for efficacy. Not for use by women.

**Dosage:** Adults: 50mg approximately one hour before sexual activity. Adjust dose based on efficacy and tolerance. Maximum dose is 100mg. Single dose per day is recommended. If taken with food, the onset of activity may be delayed.

**Caution:** Elderly, a first dose of 25mg should be used.

Hepatic impairment, severe renal impairment: 25mg initial dose should be considered; adjust dose based on efficacy and toleration. Maximum dose is 100mg. One single dose per day is recommended. If taken with food, the onset of activity may be delayed.

Hepatic impairment, severe renal impairment: 25mg initial dose should be considered; adjust dose based on efficacy and toleration.

**Elderly:** A starting dose of 25mg should be considered, except for ritonavir (see Warnings and precautions).

Co-administration of sildenafil with ritonavir is not advised.

**Drug Interactions:** In combination with inhibitors of CYP3A4 e.g. ketoconazole, erythromycin, cimetidine, a 25mg starting dose should be considered. Ritonavir – see Warnings and precautions. Potentiates the hypotensive effects of nitrates (see Contra-indications). No potentiation of the increase in bleeding time caused by acetyl salicylic acid (150mg) or the hypotensive effects of alcohol. No data on non-specific phosphodiesterase inhibitors such as theophylline or diprydiamole.

**Side-effects:** Clinical study experience: headache, flushing, dizziness, dyspepsia, nasal congestion, altered vision (color tinge, increased perception of light or blurred vision). Dyspepsia and altered vision more common at 100mg. Muscle aches when sildenafil administered more frequently than recommended. Post marketing experience: Hypersensitivity, including skin rash. Prolonged erection and/or priapism. Serious cardiovascular events, including: myocardial infarction, angina pectoris intermediate syndrome, sudden cardiac death, ventricular arrhythmia, cerebrovascular haemorrhage, transient ischaemic attack, hypertension, hypotension, syncope, tachycardia and palpitations. Eye pain and red eyes / bloodshot eyes. Vomiting.

Driving and operating machinery: Caution if affected by dizziness or altered vision.

**Legal category:** POM. **Basic NHS cost:** Packs of 4, 25mg tablets [EU/1/98/077/002] £16.59; Packs of 8, 25mg tablets [EU/1/98/077/003] £33.19; Packs of 4, 50mg tablets [EU/1/98/077/006] £19.34; Packs of 8, 50mg tablets [EU/1/98/077/007] £38.67; Packs of 4, 100mg tablets [EU/1/98/077/010] £23.50; Packs of 8, 100mg tablets [EU/1/98/077/011] £46.99.

**Marketing Authorization Holder:** Pfizer Limited, Sandwich, Kent, CT13 9NJ, United Kingdom.

**Further information on request:** Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey KT20 7NT Last revised: November 2001 Ref: VI 5_0.

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**Predictors of Abnormal SE**

<table>
<thead>
<tr>
<th></th>
<th>Normal SE</th>
<th>Abnormal SE</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean EDV</td>
<td>5±3</td>
<td>7±2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>% with abnormal EDV</td>
<td>26%</td>
<td>60%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diabetes</td>
<td>11%</td>
<td>40%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>% with 1st degree relative with CAD</td>
<td>33%</td>
<td>60%</td>
<td>0.02</td>
</tr>
</tbody>
</table>

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**Study Limitations**

- Small study population size
- No multivariate analysis
- Absence of a control group
- Debate among cardiologists as to what represents the most reliable and reproducible non-invasive cardiac stress test

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**Univariate Analysis**

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>3.2</td>
<td>1.9-4.0</td>
</tr>
<tr>
<td>Abnormal EDV</td>
<td>2.2</td>
<td>1.6-4.3</td>
</tr>
<tr>
<td>1 st degree relative with CAD</td>
<td>1.8</td>
<td>1.5-2.9</td>
</tr>
</tbody>
</table>

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**Univariate Analysis**

**Conclusions**

- Ongoing analysis demonstrates that the presence of vascu-logenic ED is associated with a significant risk of having an abnormal stress echocardiogram
- The factors in this population most likely to be associated with an abnormal SE - Diabetes - CVOD - Family history of CAD
- Future study is aimed at increasing patient enrollment and recruiting control patients

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**Odds Ratio 95% CI**

<table>
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<td>1.8</td>
<td>1.5-2.9</td>
</tr>
</tbody>
</table>

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**VIAGRA Tablets (sildenafil citrate)**

**ABBREVIATED PRESCRIBING INFORMATION**

Please refer to the SmPC before prescribing VIAGRA 25mg, 50mg or 100mg.

**Presentation:** Blue film-coated, rounded diamond-shaped tablets containing sildenafil citrate equivalent to 25mg, 50mg and 100mg sildenafil.

**Dosage:** Adults: 50mg approximately one hour before sexual activity. Adjust dose based on efficacy and toleration. Maximum dose is 100mg. One single dose per day is recommended. If taken with food, the onset of activity may be delayed. Elderly: a first dose of 25mg should be used.

**Side-effects:** Clinical study experience: headache, flushing, dizziness, dyspepsia, nasal congestion, altered vision (color tinge, increased perception of light or blurred vision). Dyspepsia and altered vision more common at 100mg.

Driving and operating machinery: Caution if affected by dizziness or altered vision.


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Regularity, studies among media are performed in order to better specify the frequency of sexual difficulties and their incidence on quality of life and also the influence of various factors upon sexual function like age, cardiovascular problems, metabolic problems.

During the ISSIR meeting many data concerning this topic have been collected.

Gott and coll. (C1.3: How important is sex to the quality of life of older people?) have interviewed 69 persons (34 men, 35 women) aged 30 to 92 in a general practice of Great Britain. Although the importance of sexual function was lower among the aged people, data concluded that age by itself has not such an influence on prioritization of sex. The stereotype of “asexual” older people has little empirical grounding and it is important to take account of sexual life in elderly.

Cardiovascular problems occur more frequently with age and many studies have pointed out that erectile dysfunction (ED) can be a marker of cardiovascular problems.

Roumeguere and coll. (CP1.0: Coronary heart disease risk in patients with erectile dysfunction) have quantified the marker of cardiovascular risks among patients consulting for ED. They assessed lipids profile in 200 consecutive patients and using a multivariate analysis, they calculated the risks of coronary heart disease according to the Framingham reference table. Hyperlipemia was observed among 72.5% of the patients and 55% have another risk factor. They concluded on multivariate analysis that patient having ED and dyslipemia has a 58.5% probability to develop a cardiovascular incident within 10 years. We can wonder if hyperlipemia can alter smooth muscle content.

Schwartz and coll. (CP1.18: There is no association between serum lipids and corpora cavernosal smooth muscle content) have studied intracorporal smooth muscle content arguing the fact hyperlipemia is associated with atherosclerosis. Thirty-one healthy men, without ED have had a penile biopsy and lipids assessment. They did not find any correlation between lipid profile and intracorporal smooth muscle content. Although they cannot say lipids do not affect the corporeal ultrastructure, “it appears their role in affecting the corporeal arterial supply may be greater”.

Effectively, the association hypercho-

lesterolemia - atherosclerosis - vascular damage is now well known.

Badayan and coll. (CP2.24: The effect of increased plasma lipids on penile blood flow) have studied the effects of plasma lipids on penile vasoelasticisation; they conclude that systolic velocity is inversely correlated with plasma cholesterol level but not with triglycerides. If a high cholesterol level induce vascular problems, these are disseminated and sometimes the cause of coronary heart diseases.

Francesco Montorsi and coll. (CP1.09: May erectile dysfunction predict ischemic heart disease?) assessed the correlation which might exist between ED and a coronary heart disease. Forty-eight per cent of the patients with a coronary heart disease also complained of ED. In 32.5% of the cases, ED occurred before the coronary heart disease. The association ED + dyslipemia was present in 35% of the patients and the association ED + dyslipemia + hypertension among 21 % of the cases. They also notice the association ED + hypertension in 35% of the cases and no risk factors in 8% of the cases. Among patients with ED, 46% have stenosis on 3 coronary arteries. This trend to confirm the high prevalence of ED among patients with cardiovascular pathology.

These data are corroborated by Man and coll.: (CP1.53: Relationship between erectile dysfunction and coronary artery disease in men undergoing elective diagnostic cardiac catheterisation”). They assessed the relation between ED and coronary arteries damages among patients having a coronographic; 105 patients out of 145 had a dyslipemia and 103 out of 130 had ED. The author concludes that ED is a predictor and a marker of coronary disease. Very often, damages of coronary arteries are assessed among patients suffering of ED and having to undergo this investigation.

Next to hyperlipemia, diabetes is known as a major cause of ED. An international survey was presented by Gingell and coll. (GSSAB investigators group) (CP1.24: Diabetes and sexual problems in men and women between 40 and 80 years of age: an international survey). Sexual dysfunction is more frequent among diabetics than among non-diabetics. Thirty-four per cent of diabetic males and 24% of diabetic females reported to have been more anxious about their sexual functioning during the 12 previous months versus 17 and 14 % of non-diabetic males and females. This confirm the high prevalence of sexual dysfunction among diabetics but, still now, very few patients seek help.

The same investigator group (CP1.26: Sexual problems reported by men and women in 28 countries: results of the global study of sexual attitudes and behaviours) have studied the behaviour and attitudes of medical team. In an international survey performed in 28 countries, 17% of the interviewed men recognized to have ED but among them only 1/5 spoke to the GP. Among 26000 interviewed persons only 8 to 10 % have been asked by their GP about their own sexual function. The ENIGMA study was presented by De Boer (CP1.34: ED in primary care practice: prevalence and patient characteristics; the enigma study). He concluded that ED is frequent among men (17 % out of 2117 men included in an epidemiological study). ED is positively correlated with age, depression, relational conflict, diabetes, way of life (alcohol, tobacco).

Considering all these recent data, can we propose a systematic cardiovascular assessment among every patient consulting for ED?

Solomon and coll. (CP2.23: The value of Routine cardiovascular assessment in patients with erectile dysfunction) have probed 178 men suffering of ED. 37% had uncontrolled hyperlipemia (2/3 diagnosed for the first time) 17% an uncontrolled hypertension (1/3 diagnosed for the first time). They concluded that taking care of sexual dysfunction include the assessment of cardiovascular risks factors.

So erectile dysfunction is an indicator of general health as said by Burgess and coll. (CP1.36: Erectile dysfunction as an indicator of general health). A retrospective study of 6000 patients consulting the Keogh Institute has discovered a significant percentage of organic disorders that could have been the causes of ED. Thus 28% of the patients with a so called idiopathic ED presented such anomalies. This indicates that ED may be the first indicator of general health problems.

A. Lemaire, M.D.
CETPARP
3 rue Carolus, 59000 Lille, France
Eighteen papers were read during the Basic Science Sessions on Tuesday, 24 September 2002. The meetings were well attended and presentations were often followed by lively discussions. This is a summary of all presentations. It is very difficult to single out any presentations, due to the large variation in the field of research.

McKenna et al from Northwestern University Medical School, Chicago, reported direct spinal pathways and brainstem projections from the para-ventricular nucleus (PVN), as demonstrated with the aid of retrograde and antegrade neuro-anatomical techniques in male and female rats. They concluded that PVN control of sexual function may be mediated directly by these projections and that oxytocin is only one of the PVN neurotransmitters. Son et al from Seoul, Korea, observed a synergistic effect of apomorphine and sildenafil on erection in the rabbit.

Inhibition of the cavernous smooth muscle contracting effects of Rho-Kinase with topical application of the Rho-Kinase inhibitor, Y-27632, in rats suggested that topical application may be effective in increasing intracavernous pressure, according to Mills et al from Medical College of Georgia. Musicki et al from Johns Hopkins University suggested that intracavernous injected VEGF promotes penile erection by activation of Akt and eNOS in mice. Silverstein et al from Duke University had previously reported that high dose bFGF resulted in an improved, but not a durable effect on erectile function and increased arteriosclerosis in a hypercholesterolemic rabbit model. The authors reported now that low dose bFGF does not increase arteriosclerosis, but also does not restore corporal function both in-vivo and in-vitro and is not likely to be an effective administration system.

Christ, on behalf of Lagaud from Albert Einstein College of Medicine, eloquently presented, and also demonstrated on video, how the shape of freshly isolated rat corporal myocytes change with changes in intracellular calcium during modulation of the KATP channel. Genetic modulation of the KATP channel may soon become available as a therapeutic option for erectile dysfunction (ED). Behr-Roussel et al reported an imbalance in extra cellular matrix (decrease in collagen type I and increase in collagen type III), in ageing spontaneous hypertensive rats in comparison to wild type rats. This is reflected in the fibrotic changes of the penis. These structural changes may explain the mechanical properties of erectile tissue contributing to ED in spontaneous hypertensive rats. They concluded that changes are already present at 6 weeks of age and may be hereditary. Srilatha et al from Singapore reported that chronic estrogenic and phytoestrogen exposure leads to ED in rabbits. This may reflect a sexual and ED hazard, during chronic exposure to estrogens and phytoestrogens. Uckert et al from the Hannover Medical School, Germany, reported a possible role for NO in the control of seminal function in men and suggested that this may be therapeutically applied in hyperekitory disturbances of ejaculation. In another study on oxytocin levels in systemic and cavernous blood in healthy male volunteers, Uckert et al reported an increase in oxytocin levels during tumescence, in both systemic and cavernous blood. This is followed by a further increase in cavernous blood oxytocin levels, but not in systemic levels, during erection. During detumescence a decline in cavernous blood levels and an increase in systemic levels were noticed. They concluded that these observations support the role of oxytocin in male sexual arousal and erection and the rationale for using apomorphine in treatment of ED.

Wayman et al, Pfizer Global Research, reported that inhibition of neutral endopeptidase inhibitors enhanced genital blood flow in the anaesthetized female rabbit during, but not in the absence, of pelvic nerve stimulation. This may be applied as treatment in female sexual arousal disorder. Adams et al, Queen’s University, Kingston found that endothelin receptor antagonism in conscious rodents prevented NOS blockade hypertension and restored erections to 75% and 81% of controls with respectively ETA and ETA/B antagonism. This may offer an alternative strategy for different causes of endothelial dysfunction, for instance in diabetics.

Azadzoi et al, Boston University, reported that cavernosal ischaemia induced molecular changes compatible with a demand for angiogenesis and NO production in the rabbit. Endothelial cell content does not change, but dysfunction was observed after a short period of ischemia. Initially VEGF and nNOS expressions were up regulated, but decreased with prolonged ischemia. This suggests that prophylactic measures to protect penile vasculature and nerves must be taken at an early stage.

Usta, Tulane University, New Orleans, reported an increase in Advanced Glycation End Product (AGE) and iNOS in rat penile tissue, when uremia was induced, and glucose containing peritoneal dialysis fluids aggravated the situation. These products may affect erectile function during uremia and peritoneal dialysis. Sicca et al from the same institute, reported that extraneous oxidative stress, induced by reactive oxygen and nitrogen species, at low doses lead to cellular proliferation and at high doses to apoptosis in an established cavernosal cell line. The apoptotic responses may be reversed by vitamin E. Zheng et al, University of Pennsylvania, developed a phenotypically stable corpus cavernosum smooth muscle cell line that retains smooth muscle contractile proteins and contractility. This may be valuable to study intra cellular molecular changes, transcription mechanisms, including effects of PDE 5 inhibitors.

Yonover et al, Loyola University reported that anti-apoptotic elements in fibroblasts derived from Peyronie’s disease plaques are up regulated. Martin et al from the same institute reported up regulation of both the pro-apoptotic agent P53 and the pro-proliferative agent cyclin D1. They concluded that the up regulated P53 may be due to a non functional protein and the up regulated cyclin D1 as an indication that cellular over proliferation in Peyronie’s disease is depending on more than one pathway.
The Congress took place in beautiful Montreal from the 22nd to the 26th of September, 2002. There were two thousand delegates from all corners of the world. It was a warm autumn and the delegates shirt-sleeved the cavernous conference center’s lecture and exhibition halls. It was essentially a relaxed and uncomplicated congress program.

“Daddy, what do you do?”
“I teach art. I teach people how to paint.”
“What kind of people daddy?”
“I teach adults how to paint.”

I would like to transpose this entire conversation into our own world of Sexual and Impotence research.

“What do you do Daddy?”
“I teach men how to love.”

Listening intently to the papers read at the 10th World Congress for Sexual and Impotence Research, it seemed to me that there are an overwhelming number of men who have “forgotten” how to make love. The massive complexities of life and survival have made loving a deeply convoluted hazardous experience. No, it wasn’t the complexities of loving that was placed under the microscope, not even man himself, but his penis. We were listening to the rise and fall of the modern-day massively pressurized penis. The neuropharmacological magic of resuscitating a penis overcome with 21st century grief...

There was a review of an enormous number of men who had prosthesis implanted into their moribund penises. They now had a permanent erection flapped upwards out of harms way by their underpants. In bewilderment the speaker told us that 30% of these men reported that they were still not making love! No one, it appeared, had examined their relationship with their women. No attempts had been made to demilitarize the bedroom or ponder the psyche of the man behind the penis.

The occasional paper that actually suggested treating the patient as part of a couple dilemma was received in a hushed surprise. I particularly enjoyed the unusual suggestion that prescribing medication for an erectile dysfunction was the beginning of therapy and not the end.

There are always sessions on the lengthening, thickening or straightening of the penis. The major concern in this congress was the new world of oral medications for erectile dysfunction. Sildenafil, of course, had established itself with a user base of over 20 million patients. Pfizer had profoundly set the stage for all further research in the area of PDE5 inhibitors.

It is now clear that the penis at rest is in a state of contraction. Erection can only occur when the muscles of the corpora cavernosa relax and allows blood under pressure to pour in. This relaxation is mediated by nitric oxide elevating levels of cyclic Guanosine Monophosphate (cGMP). This is hydrolysed by phosphodiesterase (PDE5). Any chemical that increases the amount of cGMP available or prevents the destruction of cGMP will increase the possibility of a normal erection. Sildenafil is the first of the inhibitors of PDE5. Both Eli Lilly and Bayer (tadalafil and vardenafil) presented symposia on their new inhibitors. The half-life of these inhibitors differs, offering a longer window of opportunity for an erection, with seemingly similar safety and ease of treatment.

Abbott presented the first centrally acting oral preparation apomorphine (Uprima). The paraventricular nucleus of the hypothalamus is responsible for initiating the erection. It synthesizes the entire complex input of visual, auditory, olfactory, tactile and imaginary stimuli balancing it against fear and depression. The neurotransmitter dopamine is released in the paraventricular nucleus. The released dopamine stimulates dopamine receptors leading to the transmission of erectile signals through the mid-brain to the descending parasympathetic pathways of the sacral spinal cord. These signals culminate in the activation of pelvic nerves supply the penis, causing relaxation of the muscle fibers in the corpora cavernosa. Apomorphine directly activates dopamine receptors in the brain to enhance natural sexual responses. The medication is placed under the tongue and is absorbed by the buccal mucosa bypassing hepatic metabolism. It is effective within 10 minutes of taking the pill and has a half-life of 2 - 3 hours.

There is a massive surge of energy and activity in the entire field of erectile problems. More Pharmaceutical Reps will be out there in the market place talking sex to Doctors. There is little doubt that this increase in interest will generate more and more awareness in the general community. The erectile dysfunction pie will get bigger. There will be a greater ease in all our patients talking about sexual problems. More men will ultimately call for help.

I am always interested in the brave new world of computer power point slide presentations. In the beginning the spectacular shock creations were hard to resist. Particularly the Latin-American groups. Kaleidoscopic multicolored words cartwheel and explode on the screen. These have all thankfully vanished. The slides are more sober and conservative. In many presentations we are still sadly exposed to reading exactly what the speaker is saying. The slides don’t augment the talk. They are the talk.

It was nice to know that people are still making love. This varied from the surprising global study of sexual attitudes and behavior in men and woman between 40 and 80 years of age (26,000 men and women in 29 countries). The majority reported that sex was moderately, very or extremely important to them. To a paper read to us by a Mexican delegate who conceded that while the Mexicans sang erotic songs and performed erotic dances, the rest of the world was probably making love.

The next meeting of the African Society of Sexual and Impotence Research (ASSIR) will take place in Marrakech, Morocco, April 2003.
The 7th Asian Congress of Sexology was held from November 14-17, 2002 at the Raffles City Convention Centre, Swissotel, Singapore. The meeting was organized by the National University of Singapore and the Society for the Study of Andrology and Sexology, Singapore (SSASS). The congress was well supported by other societies such as AFS, APSIR, ISSIR and WAS. Nearly 400 delegates from over 30 countries participated in this scientific event. The ISSIR President Elect, Dr P Ganesan Adaiakan, was the congress president. He was instrumental in providing this platform of scientific endeavor for Asia by bringing in all eminent scientists in the field of sexual medicine from around the world to participate in the congress. This window of opportunity was well exploited by scientists in this discipline and scientific information from East to West, traditional to modern was highly discussed.

The opening ceremony on the 14th evening, marked with a cultural performance to welcome the delegates reflected the multiracial concept of Singapore. Following this social event, the scientific crescendo began which included four plenary lectures, 11 symposia, 7 podia and 25 poster presentations with over 130 papers covering almost all areas of sexual medicine. The first day of the scientific program was almost fully dedicated to ED research/management.

In his plenary, Dr Emil Ng (Hong Kong) emphasized the need for bridging the sexual education gap in Asia and also identified the possible means of overcoming the deficiencies by effectively carrying out web-based courses to improve awareness and recognition of sexual rights. Dr Ronald Lewis (USA) categorically went through the developments in the management of ED in the past 25 years, providing insights into current research targeting both peripheral and central mechanisms.

Dr Beverly Whipple (USA) rightly questioned the existing definitions and classifications that lack adequate criteria (such as pleasure and satisfaction) in assessing female sexual dysfunction. In order to overcome these inadequacies she put forth a new classification system that could be considered hitherto. Dr Tan Hui Meng (Malaysia) explained growing concern in men’s health following the advent of safe oral medications to treat ED. Various portals available to gain information and education on ED both to the public and professionals were highlighted and he also stressed on the need for a holistic approach towards the aging males.

The Pfizer sponsored symposium embarking on the real experience for nearly five years with sildenafil citrate in the management of ED clearly brought out the distinct advantages of Viagra over the other newer agents such as vardenafil and tadalafil. Dr Li Man Kay (Singapore), Dr Edward Kim (USA) and Dr Ajay Nehra (USA) shared and discussed their clinical experiences with Viagra and finally concluded that although the new agents have much to offer in the coming years, extrapolation of data on all these compounds can rightly be done only after adequate clinical experience with newer compounds.

The ISSIR sponsored special symposium on “management of ED - novel concepts and new horizons” began with much emphasis on how the quality of life is affected in both the patients suffering from ED and their partners (Dr Sidney Glina, Past President, ISSIR). Discussing on the advancements in molecular mechanisms and signal transduction pathways in relation to ED, Dr Ronald Lewis (USA) suggested the development of chemical agents that might cause direct activation of cGMP as an alternative in future. The ISSIR President Dr Jaques Buvat (France) highlighted the current perspectives in clinical management of ED while Dr Eric Meuleman (Netherlands) spoke of the efficacy of sublingual apomorphine and its excellent safety profile based on the phase I/II/III clinical trials carried out in more than 5000 men with ED. Regarding the future pharmacotherapy for ED, Dr Ira Sharlip (Secretary General, ISSIR) who coordinated the ISSIR symposium, put forward various agents in the pipeline, some of them undergoing phase I/II/III clinical trials belonging to different categories such as rhokinase inhibitors, new PDE5 inhibitors, potassium channel openers, melanocortin receptor agonists and also identified the possibility of gene based therapy.

The Bayer-GSK sponsored symposium on vardenafil was represented by Dr Ian Eardley (UK), Dr Jay Young (USA), Dr Eric Meuleman (Netherlands), Dr Harin Padma-Nathan (USA) and Dr Li Man Kay (Singapore). The symposium highlighted various studies on how this new PDE5 inhibitor significantly improved all aspects of ED and also went on to explain that it is safe and efficacious even at a lower dosage level compared to other PDE5 inhibitors.

WAS sponsored symposium emphasized on new goals for sexual health and education; simple and efficient diagnostic criteria (Dr Kothari, India); the various levels of counseling measures to overcome sexual problems (Dr Emil Ng, Hong Kong); and the need for protected sex to thwart the rising incidence of HIV/AIDS (Dr Yamanaka, Japan).
In the symposia on sex education were discussed the Chinese sexuality in the past, present and future (Dr Peicheng Hu, China); the initiation of a new training programme by Dr Judy Kuriansky, USA; the rise of adolescent sexuality in Singapore (Dr Annaporna Venkat, Singapore) and the importance of sex education to begin in schools were highlighted (Mr Vasavan, Singapore). Discussing on sexuality and the aging male, the need for holistic therapeutic approach in treating male sexual dysfunction (Dr Louis Gooren, The Netherlands) and the fact that there will be an increase in the aging population and the necessity of understanding their sexual needs (Dr KK Chew, Australia) were highlighted. Sexual abuse – incidence, prevention and treatment, the management updates in ED, the role of complementary medicines were also highly discussed.

In addition, female sexuality was presented with equal importance and enthusiasm. The symposium on erotic spots in female sexuality highlighted the role of ‘G spot’ and the pain blocking effect by anterior vaginal wall stimulation (Dr Beverly Whipple, USA). Information on an ancient Sanskrit citation of a pleasure spot that coincides with the ‘G spot’ (identified in later years) and also an ejaculatory spot named as ‘P spot’ (Dr Shashank Samak, India) were interesting facts. The sexual profile in menopause (Dr WW Kim, Korea), HRT – indications and controversies (Dr FH Loh, Singapore) and sexuality in the aging female (Dr J Black, USA) were some of the other topics on female sexuality.

Podium sessions were marked with 62 papers covering wide range of topics such as male and female sexual concerns; ED – scientific studies & management; adolescent sexuality and education; gender identity concerns and alternative approaches. Qin et al. (Japan) compared the sex culture in China and Japan and found to be mostly identical. Kato et al. (Japan) videographically demonstrated the use of hypnotherapy to relax patients and to facilitate behaviour therapy to overcome frigidity. Sexual exploitation and violence against women in Thailand and Indonesia were highlighted by Suparp et al. (Thailand) and Tafal et al. (Indonesia). Padma-Nathan et al. (USA) found the new PDE5 inhibitor vardenafil to improve erectile function following nerve sparing radical prostatectomy and more so, it was found efficacious irrespective of aetiology or severity as reported by Eardley et al. (UK) following randomized double blind trials in men. Bischoff et al. (Germany) reported the NO-independent stimulating effect of BAY 41-2272, which is a direct soluble guanylyl cyclase stimulator. It was observed to induce weak penile erections in conscious rabbits and also that the dose levels could be considerably reduced when combined with NO donor such as SNP. The role of phytoestrogens in the causation of impaired corpus cavernosal function as demonstrated in rabbits (Srilatha et al., Singapore) emphasized the necessity to identify and avoid diets containing phytoestrogens in excess. The possibility of genetic links for transexuality was put forth based on a study on female monozygotic twins concordant for male gender identification by Harima Katsuki (Japan). Petkar (India) identified the need for physical fitness, calmness and concentration of mind by practicing yoga for better sex.

The poster sessions though limited, adequately displayed new scientific information in ED research. Joyce Lim et al. (Singapore) presented a case report to explain that Turner mosaic males with normal phenotypes may have compromised sexual function. The use of infrared spectrum to study the functional components in cells can be utilized to identify the changes that happen in the cell following disease/treatment was proposed by Neviliappan et al. (Singapore). A rare case of vaginal laceration leading to haemorrhagic shock was reported by Liang et al. (Taiwan). Kato et al. (Japan) reported hypnotherapy as a means of overcoming female orgasmic problems. Coffee drinking may facilitate erection (Adebiyi et al., Singapore); androgens increase the responsiveness of CC to nitroglycerin and sildenafil (Chen et al., Singapore) were additional interesting facts.

The 7th ACS ended on a successful note encompassing professionals from various disciplines who shared their vast experience and knowledge covering almost all areas of sexual medicine research, with a promise to continue and contribute to science at large.

Huge number of attendants

From left to right, Drs J. Buvat, ISSIR President, G. Adaikan, ISSIR President-Elect, I. Sharlip, ISSIR Secretary, R. Lewis, ISSIR Past-President, S. Glna, ISSIR immediate Past-President
Although sildenafil is an effective and well-tolerated drug for the treatment of erectile dysfunction (ED), its pharmacokinetics has been a matter of discussion in recent papers. In three open-label, randomized crossover studies to determine the effects of food on the pharmacokinetics of single oral dose of sildenafil, food slowed the rate of absorption, delaying mean Tmax by approximately 1 h and reducing Cmax by 29%. In spite of that, the authors suggested that these reductions are unlikely to be of clinical significance.

Another aspect is that sildenafil is a drug with extensive first-pass metabolism, and oral bioavailability reaches only 40%. Recent evidence supports the cytochrome P450 (CYP) isoenzymes CYP3A4 and to a lesser extent CYP2C9 as the enzymes responsible for the metabolism of sildenafil. In fact, 75% of metabolism of the drug is mediated by hepatic CYP3A4, and N-demethylation to N-desmethylsildenafil is the main route for sildenafil metabolism. Clinically important CYP3A4 inhibitors include itraconazole, ketoconazole, clarithromycin, erythromycin, nefazodone, ritonavir and grapefruit juice. At the meeting, the interaction between grapefruit juice and sildenafil was discussed. Grapefruit contains inhibitors of intestinal CYP3A4 enzyme. In a randomized crossover study with 24 healthy white male volunteers receiving a single 50-mg dose of sildenafil, grapefruit administration increases sildenafil bioavailability and delays sildenafil absorption. Maximum plasma concentrations of sildenafil was not different. A great interindividual variability was demonstrated, and sildenafil pharmacokinetics may become less predictable. Although patients usually will not be endangered by concomitant use of grapefruit juice, it seems advisable to avoid this combination.

Phosphodiesterase Type 5 Inhibitors for Erectile Dysfunction

When a sexual stimulation occurs, there is generally inside the penis a smooth muscle relaxation. It occurs because the nitric-oxide (NO), released from nerves and endothelium, stimulates the guanylate cyclase to convert GMP in cGMP, which leads to decrease of the intracellular calcium concentration and results in sinusoidal muscle relaxation.

In 1998, sildenafil citrate (Viagra, Pfizer) emerged to facilitate the erectile dysfunction (ED) treatment. This is a drug, as we know, that inhibits phosphodiesterase type 5 (PDE5). PDE5 is an enzyme, which inactives cGMP and therefore the muscle relaxation finishes, during the penile erection process. This discovery promoted a revolution in ED management, because after that we generally do not do perform anymore expensive evaluations. We use this treatment as a first option and a large number of patients will experience an erection. This drug can be used in all kinds of ED, obviously with different rate of response based on the severity of the dysfunction.

After almost 5 years using sildenafil to manage these patients we actually perceive the safety of this drug. There are lots of papers reporting on its security. We are expecting two new PDE5 drugs for next year (tadalafil, Lilly/Icos and vardenafil, Bayer/GSK). The 3 compounds demonstrated potent and selective PDE5 inhibition when compared their selectivity profiles. The onset of action is very similar in all drugs. There is a big difference in half-time of the tadalafil and a greater biochemical potency of the vardenafil. In spite of the pharmacological differences between the 3 drugs, the clinical efficacy probably will be the same. And the cardiovascular security of these novel drugs seems to be the same, as we can perceive in some preliminary studies.

Dr Stanley Althof said during the congress that the PDE5 discontinuation occurs because inadequate education, fear of serious adverse events and/or unacceptable ratio of benefit to side effect of the patients.

Dr Irwin Goldstein reported that the patients will judge these three PDE5 drugs and will say what is the best for each specific case. The physician’s option will be based on previous experience, preferences, patient satisfaction and pharmacodynamic and pharmacokinetic profiles.

We have to wait for extensive clinical experience with these phosphodiesterase type 5 inhibitors and the time will judge them.

References


References:


The 2nd Pan-Arab Congress of Sexual Dysfunction, organized by the Pan-Arab Society of Genital Surgeons, follows the first successful meeting two years ago, also in Cairo. Under the patronage of the Ministry of Health and Population and of Tanta University, Dr Khaled Lofty Dabees organized a very interesting meeting giving the opportunity to Arab countries to enrich knowledge about recent aspects of urogenital surgery, sexual dysfunction and infertility. About 300 colleagues of whom 70 from countries other than Egypt participated in vivid discussions. Guest speakers from Europe completed the program.

The meeting started with a workshop on erectile dysfunction (ED) granted by Pfizer, held by Egyptian colleagues which purpose was to update information on all aspects of ED. Dr Mettawae reported on the recent survey on sexual health that was worldwide conducted by Pfizer in 28 countries on 26,000 men and women, 40-80 years old. Eighty-two per cent of men and 64% of women were sexually active and about 70% weekly. About 40% of men and women reported sexual difficulties such as ED or lubrication problems in the previous 2 months. This survey also indicated that few doctors ask their patients about sexual problems. Although country differences were encountered, about 40% of the interviewed population expressed satisfaction with their sexual life; this percentage was higher in healthier people.

Dr Foda presented an extensive overview of the anatomy, pathophysiology and hemodynamics of erection, while Dr Sharaf, internist, stressed the relation between ED and dyslipidemia, recalling that per each mmol/L increase in total cholesterol the risk for ED increases 1.32 times. Dr Fayek, cardiologist, presented the American Consensus on ED and Cardiovascular Disease and the use of sildenafil. He concluded that sildenafil is safe, having no effect on cardiac contractility, heart rate, central hemodynamics and on platelets. The only contraindication remains the use of nitrates and unstable angina. This topic raised interesting discussions on the safety of sildenafil in different cardiovascular diseases. Dr Anis presented an extensive overview of the different evaluation methods for the patient with ED, even mentioning the obsolete penile brachial index testing. Dr Ghanem emphasized how often such tests are overdone and useless, stressing the importance of a good anamne-
sis, history taking, evaluation of the used drugs. He suggested a treatment-oriented approach starting giving an oral erectogenic agent, eventually together with sexual therapy, or a vacuum device, and proceeding to intracavernosal injections (ICI) and even penile implants, if necessary. I was impressed by the excellent quality of the lectures that reached the goal of the workshop.

The second day opened with a lecture on the prevalence of ED among Egyptian men over 40 years presented by Dr Khalaf. By performing a survey on prostate diseases, Egyptians were also asked about sexual functioning using three questions (IIEF 3, 4, 7). Among 5,069 men, almost 51% complained of some form of sexual dysfunction. From this survey it became clear that many religious misconceptions were present as well confusion between ejaculation disturbances and ED, and lack of sexual education. This survey showed as expected a correlation of ED with hypertension, heart diseases, diabetes mellitus and rheumatic disease but no correlation with smoking. Dr Khalaf pointed out that of the interviewed men only 50% were smokers, though further statistical analyses did not show any correlation of ED and smoking. Dr Khalaf also presented the different experimental drugs being evaluated at the moment in phase I-II trials. His take-home message was to first eliminate risk factors before any therapy is started. Dr Dabees also presented the different experimental drugs being evaluated at the moment in phase I-II trials. His take-home message was to first eliminate risk factors before any therapy is started. Dr Tritto presented the futuristic, but possible use of bio-engineering and microtechnology for male reconstructive surgery while he sceptically addressed gene therapy for ED that does not seem to be easy (and maybe even safe) to perform.

Peyronie’s Disease (PD) was addressed in two state-of-the-art lectures; after an excellent overview on the etiology, pathophysiology, evaluation and medical therapy of PD by Dr El-Behnasawy, Dr Incrocci presented a critical overview on radiotherapy for PD still debatable but effective.

Female Sexual Dysfunction (FSD) was an important topic at the meeting. Dr Graziottin presented interactive case studies on evaluation and therapy of dyspareunia, chronic vestibulitis and other FSDs. She also addressed the topic of the overactive bladder and sexual dysfunction. She stressed that incontinence is still a taboo, because it is the failure of control and of physical integrity. Women with urine incontinence have an impairment of their body image because of fear of urine leak and smell. This situation impairs sexual functioning, specifically orgasm because of urine incontinence at the climax. Dr Graziottin also said that topical estrogen-androgen combination is very useful in post-menopausal women for local application when the clitoris is not functioning anymore while it can be systemically used in case of libido and orgasm disturbances. Sildenafil seems to improve arousal in pre-menopausal women (Dr Drettas). The meeting presented also state-of-the-art lectures and podium presentations on fertility/-infertility, addressing advantages and disadvantages of new techniques. Also interesting podium presentations on ED completed the program.

In conclusion, the meeting was an excellent opportunity for Arab colleagues to be updated on evaluation and treatment of sexual dysfunction in males and females. The organization was very good, the location was great in a beautiful hotel overlooking the pyramids so everybody enjoyed the atmosphere. I am looking forward to the 3rd meeting in 2004.
Digest of recent discussions on ISSIR mail (July-December 2002)

Hussein Ghanem, M.D.

Several interesting cases were recently discussed on ISSIR mail. Dr. Kevan Wylie inquired about the significance of a double peak with Doppler ultrasound of the penis post I.C.I. Drs. Juhana Piha and Chris G McMahon suggested atrial fibrillation or ventricular bigeminy. Dr. Gregory Broderick pointed out that very often we pick up arrhythmias on penile Doppler. Dr. Kurt Lehmann mentioned that incomplete closure of the aortic valve (aortic valve insufficiency) produces double peak in larger arteries. Whether this is also true for penile vessels is known. Dr. Francisco Costa Neto noted that in his experience, even having lower PSV peaks in the presence of extra-beats most of the patients had a Response 3 to I.C.I. with Trimix.

Dr. Carlos Moreira presented another case of stuttering priapism. Dr. Broderick suggested confirming that these cases are ischemic by drawing a blood gas from the penis or performing a Doppler study, if erection persists 2-4 hours. He also advised excluding sickle cell or sickle cell trait; teaching the patient how to self-inject phenylephrine 200mcg if erection persists one hour after he awakens or after climax; or try a daily anti-androgen.

Dr. Giuseppe La Pera presented a case of post-traumatic high flow priapism with persistent slight tumescence after successful embolization. Drs. Edgardo Becher, Jack-Charles Tremeaux, Andik Wijaya, Sidney Glina, and Chris G McMahon contributed many useful treatment options. Suggestions included: waiting for spontaneous resolution; super selective angiogram and see whether it is possible to re-embolize the defect (if still present) with microparticulae as distal as possible; a sapheno-cavernous anastomosis if the corpora cavernosa are still smooth and the penis is still painful; a slow release form of pseudoephedrine. Suggestions if fibrosis/ED resulted were penile prosthesis implantation after doppler ultra-sound of the cavernosal arteries, or a vacuum device.

Dr. Frederick Snoy presented a case of a 70 years old patient that has had pain on erections in the right side of the glans penis since he was a teenager. Dr. Emre Akkus & Dr. Shedeed A Shedeed suggested MRI & US evaluation while Hussein Ghanem suggested evaluation regarding a psychosomatic disorder if a physical lesion is ruled out.

The detailed discussions may be read on www.issir.org under ISSIRList/Discussions.

The list of topics and responses includes:

• Double peak with penile Doppler
• Stuttering priapism
• High-flow priapism
• Pain with erection

The International Society for Sexuality and Cancer (ISSC)

One of the ‘hidden’ areas in relation to cancer, particularly breast, prostate and gynaecological cancers, is sexuality and associated sexual problems. Patients often feel unable to communicate with their clinical team about sexual matters, and even when they do, there may be a lack of appropriately trained personnel to work with them. This can have a hugely negative impact on their quality of life, even when the cancer has been treated successfully.

As a response to such observations, a new multidisciplinary international society has been formed to focus on this important area of clinical care, the International Society for Sexuality and Cancer (ISSC).

Membership will include cancer clinicians, experts in sexual medicine, social workers, nurses and psychologists. The principal aim of the society is to heighten awareness about sexuality in cancer by fostering research, encouraging training and increased service provision, and providing a forum at international meetings for discussion.

The inaugural board is:

Peter Heintz, Gynaecological Oncologist, The Netherlands, President
Susan Carr, Consultant in Family Planning and Reproductive Health Care, Scotland, Vice President
Luca Incrocci, Radiation Oncologist, The Netherlands, Secretary-Treasurer
Wout Gianotten, Medical Sexologist, The Netherlands, Chair Education Committee
Michael Quinn, Gynaecological Oncologist, Australia, Chair Scientific Committee.

To find out further details and to register interest, please write to the secretariat: International Society for Sexuality and Cancer (ISSC)
Luca Incrocci, M.D., Ph.D.
Department of Radiation Oncology
Erasmus MC-Daniel den Hoed
P.O. Box 5201
3008 AE Rotterdam, The Netherlands
Tel. +31 10 43 91 421
Fax +31 10 43 91 013
Email secretariat@issc.nu
Website www.issc.nu

The membership fee for 2003 + 2004 is 50 Euro.
If you want to join us now, please make a payment by bank transfer for the amount of netto 50 Euro (+ voluntary donation) to:
L. Incrocci, ISSC Secretary. Account number 46 56 48 592, ABN-AMRO Bank, Rotterdam, The Netherlands. Please indicate your name and address.
Significant effects of hormones on sexual function in men have been proved only as regards androgens and prolactin (PRL).

Erectile Dysfunction (ED) and low sexual desire are for a long time the only presenting symptoms of Male Hyperprolactinemia (HPRL), a condition often resulting from a pituitary tumor. HPRL inhibits the sexual function not only by lowering the testosterone secretion, through central inhibition of the LH release, but also by non androgen-deendant mechanisms. This is confirmed by the fact plasma Testosterone (T) is within the normal range in up to 50% of the HPRL males referred for ED, which emphasizes that screening for HPRL may not rely only on T determination. However the very low prevalence of HPRL (0.7%) and prolactin-secreting pituitary tumors (0.32%) in ED questions the validity of a systematic determination of plasma prolactin (PRL).

Testosterone (T) is the main hormonal stimulus of sexual function. It acts directly or via 5 alpha-reduction into dihydrotestosterone (DHT). There is no evidence for a role of aromatization in the human male. Double blind placebo controlled studies in hypogonadal men have shown that sexual desire and spontaneous erections (morning, nocturnal) are clearly testosterone-deendant, while psychic erections are only partly testosterone-deendant. The testosterone effects upon male sexuality are dose dependent until a ceiling level close to the lower limit of the normal adult range, but varying from 2 to 4 ng/ml according to the individuals. According to different studies, nocturnal erections seem always impaired under 1.5 ng/ml, sexual activity is always impaired under 2 ng/ml and is optimum over 4 ng/ml, though several studies have found it may be slightly stimulated by increasing the testosterone level within the normal adult range. Between 2 and 4 ng/ml sexual activity may or may not be optimum, according to the sensitivity to androgens of the individual. In human males most of the testosterone effects are exerted at the level of the brain. A peripheral impact also exists, at least in animals, through modulation of the Nitric Oxide Synthase in parasympathetic neurons, possibly explaining the pattern of Veno-Occlusive Dysfunction occurring following castration. Some studies have also found correlations between testosterone and parameters of penile vascular function in men.

The mean prevalence of low T values in ED (<3 ng/ml) was of 8.3% in a compilation of 9 large series with a total of more than 2700 patients. However the effects of androgen therapy are rather disappointing in the ED patients with low T level: definite improvement in 36% of a personal series of 44 cases (including full recovery in only 25%) and in 36.4% of a compilation of 6 series with a total of 162 cases.

Several hypotheses may explain this low success rate. Plasma total testosterone (TT) may be a little reliable index of androgenicity. TT circulates in the blood mainly bound to proteins, Sex Binding Protein and Albumin. The protein bound fraction is thought not to be bioavailable (able to enter the target cells and to exert its androgenic effect in it). The bioavailable fractions of T would be only the free (unbound) T (FT) and the albumin-bound T, because of its loose binding, allowing for a quick dissociation and replacement of the FT having entered the target cell. Determining these bioavailable fractions could detect patients with androgen defect at the receptor’s level despite normal total testosterone, and could select the patients with actual hormonal cause among those with low testosterone levels. We have determined FT and bioavailable T (BT, the sum of FT + albumin bound T) in more than 400 ED patients. Their level was low more often than that of TT (respectively 31.5% and 14.6% vs 6.6% for TT), especially after 50 (37% and 25% vs 9%). However we were not able to prove the advantage of substituting the determination of these bioavailable fractions for that of TT. Especially the success rate of androgen therapy was very poor in 33 patients with normal TT and electively decreased FT or BT (definite improvement in respectively 5 and 13%).

These poor results have been recently confirmed in a new personal study including assessment of the results with the IIEF.

Such low success rates of androgen therapy may question the reality of androgen deficiency as a cause of ED. However testosterone replacement in young hypogonadal males proves to improve not only sexual desire and the frequency of sexual activity, but also the quality of the erections. In addition this reality has been confirmed by a meta-analysis of the trials of testosterone supplementation for ED. The response rates of testosterone and placebo were significantly different (respectively 65 and 17%). However the response rate was significantly higher in the cases with primary hypogonadism (64%) than in those with secondary hypogonadism (44%), who are older and more representative of the ED patients with low T. Unlike studies in young hypogonadal males, until now no study in elderly males has found really significant correlations between androgens, including their bioavailable fractions, and the sexual parameters.

Another possible explanation of the low success rate of androgen therapy in ED patients is that in certain cases the low testosterone would not be the real, or at least, the only cause of ED. Because of the liability of serum testosterone, a single low T result is not enough for a diagnosis of hypogonadism. The test must be repeated in every case. In our experience a second determination following a first subnormal result is normal in 40% of the cases. In addition, in many cases the low T may be only one of several consequences of aging contributing to a plurifactorial ED. In a personal series of men with ED and low T, 42% were found evidence of significant penile arterial obstruction sufficient to prevent the improvement of the erections following T replacement. Lastly the low T may also be a consequence rather than the cause of ED: because of the reduced sexual activity, since sexual activity is followed by an increase in T secretion; because of the stress and/or depression very often associated with ED, since many studies have shown that both these conditions may be associated with low T level, due to central inhibition of the LH secretion. Recent data from Jannini et al support this hypothesis. The significant
decrease of TT and FT they found in ED patients disappeared following successful non-hormonal treatment of their ED (i.e sex therapy, intracavernosal injections) while it remained identical in case of failure. In a subsequent study, they found clues supporting an hypothalamic mechanism for this impact of ED on the T secretion, since the bioactivity of LH (ratio bioactive / immunactive LH), which depends on the frequency of the GnRH pulses, was significantly decreased in ED patients, and improved on successful non hormonal treatment in the same way as T.

The exact relationship between T and sexual function therefore remains to clarify. However even if the success of androgen therapy in ED patients with low T is limited, these patients must be screened for T deficiency since in that case, T administration is one of the very few therapies able to restore “natural” erections, avoiding the necessity of planning sexual activity as with Sildenafil or the ICI. In addition, because it is the only therapy active on sexual desire, and it may also have extra-sexual beneficial effects, T may be useful even if it fails to restore erections. Many physicians restrict T determination to those ED patients with low sexual desire and / or clinical evidence of hypogonadism, and restrict that of PRL to those ED patients with low T. We have shown that this strategy would miss 40 % of the patients with low T subsequently improved with androgen therapy, as well as a significant proportion of the ED patients with HPRL and even pituitary adenoma. According to our experience, we recommend determining T in every ED patient except, before 50 years, in those with normal sexual desire and no physical sign of hypogonadism, and PRL in all those with low sexual desire, as well as in those with low or low borderline T levels.

Epidemiology of Erectile Dysfunction. A worldwide prevalence overview

Introduction

Impotence, now more accurately termed, Erectile Dysfunction (ED), is a dramatic condition that goes along men all over the time. The up to date relatively low efficacy rate of treatments, made sexual dysfunctions a marginal matter, with very few physicians interested in the field. Things became different in the early 70’s with penile prosthesis availability. A dramatic change occurred in mid 1980s with intracavernosal injection therapy (ICI), but the revolution accounted when oral therapy was available by the end of 90’s. Findings in physiology and mechanism of erectile function during the most recent past decades, has enabled the launching of very effective and friendly users treatment options.

Interest in epidemiology arises and increases when a health problem become, precisely a “problem”, because of its magnitude or severity. ED although a non life-threatening condition, has the potential to constitute a health problem due to:
- Prevalence, incidence
- Impact on quality of life
- Emerging evidence of being a predictor of cardiovascular life-threatening conditions.

Besides, the aging process of the population, related to the increase in life expectancy, together with the close and direct relationship between ED and age, constitutes the last call for epidemiological research and knowledge on ED.

Epidemiology render us two kinds of data:

- Descriptive
  - Prevalence (number of subjects suffering the condition in a given time)
- Analytic
  - Incidence (new cases of the condition in a given period)
  - Risk factors (relationship of the condition with given factors)
  - Health correlates (relationship of the condition with given health correlates)

Coming from two kinds of sources:

- Specific populations (convenience samples):
  - Men seeking care for another disease
  - Men as a part of a physician patient group
  - Men with a given condition, etc.

- General population (representative samples):
  - In home interview
  - Phone interview
  - Mail questionnaire

The first ones offer the possibility of collect and publish data on specific and carefully monitored biologic and physiologic data but offer little insight at the problem as it affect the population at large. Until recently the most published belongs to the first category.

To be valid, the community sample must be representative of the population studied including the cultural, racial, ethnic and health status available and well pondered.

The NIH Consensus Conference on Impotence encouraged investigators to research the epidemiology of ED in order to provide a better understanding of the prevalence, incidence, health correlates and risk factors for this condition. This knowledge could enable us to delineate prevention strategies, being these desirables as long as the population shows a consistent aging trend and ED is strongly age-related, as mentioned before.

Epidemiological studies: a review

Kinsey et al in a historical survey conducted in 1948, reported that ED was an age-dependent disorder with a prevalence of 0.1% at 20 years of age, 0.9% at 30, 1.9% at 40, 6.7% at 50, 18.4% at 60, 27% at 70, 55% at 75 and 75% at 80 years of age. However, since only 5% of the population evaluated were older than 55 years, data for men above that age must be interpreted with caution.

A more recent study, constituted as a reference for the modern approach to the field of ED, is the Massachusetts Male Aging Study (MMAS) which measured several health related variables in 1290 men aged 40 to 70 years. ED was very common. Fifty two per cent of the men reported some degree of impotence-mild in 17.1%, moderate in 25.2%, and complete in 9.6%. Complete impotence was reported by 5% of men at 40 years of age and 15% at 70 years of age; however, a higher prevalence of complete impotence was seen in men with concomitant illnesses. ED is more common with advancing age, and since the aged population will incre-
ase, its prevalence will continue to rise.

No validated questionnaire addressing ED has been used in epidemiological surveys till the ‘Epidemiologia de la Disfuncion Erectil Masculina’ (EDEM) study. Moreover, to our knowledge, no one but the EDEM study has used two instruments to define ED in a population based setting. This approach allows the comparison between both tools that in turn results in interesting considerations. With an overall participation rate of 75% the prevalence of ED according to the "simple question" (a single self-assessment question about erectile capacity, reported by the interviewed) was 12.1%. According to the Erectile Function domain of the International Index of Erectile Function the overall prevalence was 18.9%. Several independent risk factors were significantly associated with the probability of ED. Some differences arose according to the tool used to define the condition. However, there was a strong relationship of patient age with frequency or severity no matter which instrument was used to define ED. Diabetes (age adjusted odds ratio 4), high blood pressure (odds ratio 1.58), high cholesterol (1.63), peripheral vascular disorder (2.63), lung disease (1.79), rheumatism (2.37) and allergy (3.08) were significantly associated with ED. Drug intake, which respondents called medication for nerves and sleeping pills, correlated strongly (odds ratio 2.78 and 4.27, respectively), as did tobacco use (2.5) and alcohol consumption (1.53).

Contemporary with these studies and in response to the call of the NIH Consensus Conference on Impotence to researchers all over the world, to find out prevalence and other significant correlates of ED in their own countries, a considerable number of papers has been published and presented at different meetings, addressing these issues.

Unfortunately, the use of different definitions of ED from study to study, the existence of subtle cultural influences in different societies, in addition with different study designs, methodologies and subject demographics have yielded a wide variety of prevalence rates of ED among countries and world regions.

Tables 1, 2 and 3 summarizes ED surveys, roughly grouped accordingly to the source of data: 1- Specific populations studies, 2- Community based studies which attempt to represent the whole country, and 3- Population based surveys.

To note the differences in study design, samples’ age range and even outcome measures.

Table 1. Specific population studies

<table>
<thead>
<tr>
<th>ED criterion</th>
<th>Sample size</th>
<th>Sample source</th>
<th>Age range</th>
<th>Prevalence</th>
<th>Country (Year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH definition</td>
<td>2010</td>
<td>143 GPs</td>
<td>&gt;18 years</td>
<td>12.8%</td>
<td>Italy(^{(6)}) (2000)</td>
</tr>
<tr>
<td>FE-IIEF</td>
<td>256</td>
<td>15 GPs</td>
<td>50-69 years</td>
<td>14% 50-54 years 30% 55-64 years</td>
<td>Italy(^{(7)}) (2000)</td>
</tr>
<tr>
<td>Questionnaire</td>
<td>1182</td>
<td>49 GPs</td>
<td>&gt;40 years</td>
<td>20% moderate 13% complete</td>
<td>Norway(^{(8)}) (2001)</td>
</tr>
<tr>
<td>Mailed questionnaire (IIEF modified)</td>
<td>789</td>
<td>4 GPs</td>
<td>18-75</td>
<td>26%</td>
<td>UK(^{(9)}) (1998)</td>
</tr>
<tr>
<td>Single self-assessment question</td>
<td>1240</td>
<td>62 GPs</td>
<td>&gt;18 years</td>
<td>39.4%</td>
<td>Australia(^{(10)}) (2000)</td>
</tr>
<tr>
<td>Self-administered questionnaire</td>
<td>917</td>
<td>Assist to a GP office</td>
<td>35-70 years</td>
<td>50.7%</td>
<td>Niger(^{(11)}) (2000)</td>
</tr>
<tr>
<td>Self-administered questionnaire</td>
<td>585</td>
<td>Men seeking PHC in two cities</td>
<td>25-70 years</td>
<td>70.6%</td>
<td>Pakistan(^{(12)}) (2000)</td>
</tr>
<tr>
<td>Self-administered questionnaire</td>
<td>594</td>
<td>Men seeking PHC</td>
<td>30-70 years</td>
<td>54.9%</td>
<td>Egypt(^{(13)}) (2000)</td>
</tr>
</tbody>
</table>

Table 2. Community based studies

<table>
<thead>
<tr>
<th>ED criterion</th>
<th>Sample size</th>
<th>Sample range</th>
<th>Age (year)</th>
<th>Prevalence</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q3 y Q4 of IIEF Mailed questionnaire</td>
<td>1983</td>
<td>Tampere &amp; 11 municipalities</td>
<td>50-70 years</td>
<td>74%</td>
<td>Finland(^{(14)}) (2000)</td>
</tr>
<tr>
<td>KEED questionnaire</td>
<td>4889</td>
<td>Representative sample “Cologne”</td>
<td>30-80 years</td>
<td>19.2%</td>
<td>Germany(^{(15)}) (2000)</td>
</tr>
<tr>
<td>Self administered questionnaire</td>
<td>1650</td>
<td>Randomly selected Rural NY state</td>
<td>50-76 years</td>
<td>46.3%</td>
<td>USA(^{(16)}) (2000)</td>
</tr>
<tr>
<td>IIEF Japanese version (mailed)</td>
<td>1517</td>
<td>Employees and fathers of 11 companies</td>
<td>23-71 years</td>
<td>1.8% 23-29% 64.3% 70-79 y Mod/severe</td>
<td>Japan(^{(17)}) (2001)</td>
</tr>
<tr>
<td>Single self-assessment question</td>
<td>1233</td>
<td>Random sample (Boxmeer)</td>
<td>40-79 years</td>
<td>13%</td>
<td>Netherlands(^{(18)}) (2001)</td>
</tr>
<tr>
<td>Mailed questionnaire: Erections adequate for intercourse</td>
<td>427</td>
<td>Probability sample (men who agreed to participate)</td>
<td>&gt;40 years</td>
<td>3% 40-49 years 64% 70-79 years</td>
<td>South Australia(^{(19)}) (1999)</td>
</tr>
<tr>
<td>Self-administered questionnaire</td>
<td>646</td>
<td>Random sample in Casablanca</td>
<td>&gt;25 years</td>
<td>53.6%</td>
<td>Morocco(^{(20)}) (2000)</td>
</tr>
<tr>
<td>Single self-assessment question</td>
<td>1290</td>
<td>Random sample in Boston area</td>
<td>40-70 years</td>
<td>52.1%</td>
<td>USA(^{(21)}) (1994)</td>
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<tr>
<td>IIEF</td>
<td>799</td>
<td>Randomly selected Ghent &amp; Charleroi</td>
<td>40-70 years</td>
<td>61.3%</td>
<td>Belgium(^{(22)}) (2002)</td>
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</table>
18. Meuleman EJ H, Donkers LHC, Robertson C,
The Treatment of Premature Ejaculation: Selecting Outcomes to Determine Efficacy

The Defining Criteria for Premature Ejaculation

Critical to the study and treatment of any sexual dysfunction is the application of criteria that reliably discriminate men with the dysfunction from those without it. With respect to premature or rapid ejaculation (PE), DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, American Psychiatric Association, 1994, p. 509) essentially specifies three criteria that define the problem. (1) Ejaculation occurs persistently with minimal stimulation. (2) The man experiences a lack of self-efficacy regarding the condition, that is, he ejaculates before he wishes, feeling incapable of affecting the process. And (3), the condition is a source of distress to the man and/or his partner.

Each of these three criteria is readily operationalized (Rowland et al., 2001). The first—recurrent ejaculation upon minimal stimulation—is typically operationalized by an intravaginal ejaculatory latency time (IELT), defined by the number of minutes/seconds between vaginal intromission and ejaculation, averaged over a number of attempts. Latencies of less than about 1 minute are considered normal, and men who ejaculate before 2 minutes or less typically show only minor overlap with those of men without PE, which range from about 2 to 10 minutes.

The second criterion—self-efficacy or the patient’s ability to control the dysfunctional response—distinguishes men who ejaculate rapidly because they are incapable of any other response from those who do so for any number of willful reasons, including ones related to the situation or the partner. In recent research, a 7-point Likert-type item of self-reported “control over ejaculation” has been used successfully as a self-efficacy measure that differentiates PE men from sexually functional men (Rowland, Cooper et al., 1997; Strassberg et al., 1999). Men with PE rate their ejaculatory control around 2 to 4 (1 = not at all; 7 = complete control), whereas functional men typically rate their control at 4 or higher.

The third criterion—concern or distress about the condition—is usually satisfied by the mere fact that the man (often with his partner) comes to the clinic seeking help for the sexual problem. In situations where participants are recruited into an experimental or clinical investigation, several questions might be included in a screening questionnaire that directly address the issue of concern or distress. Most commonly these items query the man (and when possible his partner) about his general level of sexual satisfaction, with further elaboration about anxiety surrounding the sexual problem and about the quality of the sexual relationship. Standardized measures of general anxiety or dyadic distress might also be included to further operationalize this criterion.

The Nature of the Defining Variables

Satisfying all three criteria—recurrent ejaculation with minimal stimulation, lack of self-efficacy, and distress about the condition—is essential for a PE classification. Because these characteristics are clustered in PE men, they also tend to show a moderate association within the general population (r = .35; Grenier & Byers, 2001). That is, men with a lack of control over the timing of ejaculation tend to have short IELTs and express dissatisfaction about sexual interactions with their partner (Rowland et al., 2000). Nevertheless, within the general population,
these three dimensions are independent of one another, since each can occur in the absence of the others. For example, a man might have a short ejaculatory latency because he chooses, not because he lacks control over its timing; or a man could have little control over ejaculatory timing yet have a long IELT, as with inhibited ejaculation; and so on.

On the surface, the foregoing PE classification scheme suggests that successful treatment of PE should affect all three defining characteristics—ejaculatory control should improve, with subsequent lengthening of the IELT, and ultimately greater sexual satisfaction. However, the set of variables used to define a PE classification may not necessarily serve as the best set of outcome measures to determine successful treatment. As was mentioned previously, the criterion variables used to define a PE classification are independent of each other within the general population. But once the PE group has been defined as such, these same variables—ejaculatory control, latency, and satisfaction—assume an ordered and dependent arrangement within PE men. Specifically, as illustrated in Figure 1, "sexual satisfaction" represents a final endpoint, which is influenced by ejaculatory latency, which in turn is influenced by ejaculatory control. This ordered and dependent arrangement has clear implications for the selection of appropriate outcome measures in determining the efficacy of a PE treatment procedure.

Selection of Outcome Measures Depends on the Type of Treatment

Because different types of treatment intervene at different stages in the dysfuntional response sequence (Figure 1), the choice of outcome measures depends partly on the specific treatment that is implemented. A treatment plan for PE, for example, may primarily address the endpoint of sexual satisfaction; alternatively, it could address ejaculatory latency, which in turn affects sexual satisfaction, or it might address ejaculatory control, which subsequently affects both ejaculatory latency and sexual satisfaction.

Consider the following example based on another male sexual problem, erectile dysfunction (ED). Before the advent of effective pharmacotherapy for ED in 1980’s, little could be done to overcome erectile insufficiency (short of penile implants) due to organogenic causes. As a result, sex therapy for organic ED was often limited to decreasing the distress associated with the dysfunction by addressing issues of “satisfaction.” This approach included education aimed at de-stigmatizing the problem, changing the man’s (or couple’s) expectations, increasing communication and intimacy with the partner, identifying alternative strategies for mutual gratification, and so on. In this approach, although erectile dysfunction was the major cause for sexual dissatisfaction, because erectile response itself could not be modified, treatment was directed toward other factors that might influence sexual satisfaction. In assessing the efficacy of this treatment, only "satisfaction" would be considered a relevant outcome variable, as genital response (in this case, erectile capacity) would not have changed.

Consider a second example, the treatment of PE using cognitive-behavioral strategies. This approach instructs patients in the use of mental imagery and behavioral techniques (e.g., adjusting intercourse position, using pauses, etc.) to develop greater control over the timing of ejaculation. In achieving such control, IELT would be lengthened and greater satisfaction attained. In this treatment, all three measures—ejaculatory control, IELT, and satisfaction—might be considered relevant endpoints, as the focus of the intervention is on developing better ejaculatory control, which, in turn, affects IELT and ultimately satisfaction. Indeed, in using all three measures, the researcher or clinician is better able to verify the specific processes through which sexual satisfaction, the ultimate endpoint, is affected.

Outcome Assessment When Using Pharmacological Treatment for PE

Because a great deal of attention has recently focused on the treatment of PE using pharmacological agents, outcomes salient to this treatment approach are important to specify. Pharmacotherapeutic treatment of PE is aimed at inhibiting the ejaculatory reflex—increasing the IELT in turn increases sexual satisfaction. In contrast with cognitive-behavioral therapy, pharmacotherapy does not necessarily enable greater control over the timing of ejaculation. But, as with any medical treatment in which the patient is a "passive" recipient of a treatment procedure, pharmacotherapy—delaying the ejaculatory reflex—may give the man with PE a greater sense of control over his sexual problem.

As a result, assessment of self-efficacy by using a measure such as "ejaculatory control" is perhaps less germane to pharmacotherapy studies than assessment of the other two characteristics of PE—ejaculatory latency and general sexual satisfaction. Indeed, our own research indicates that while men who respond positively to the ejaculatory-inhibiting effects of clomipramine show substantial increases in both IELT and satisfaction, the effect on self-reported "ejaculatory control" tends to be more modest (e.g., Haensel et al., 1996; Strassberg et al., 1999).

Nevertheless, assessment of self-efficacy in pharmacotherapy studies may be warranted, as increased feelings of self-efficacy are undoubtedly related to overall satisfaction with the treatment procedure. However, self-efficacy in such studies might be better assessed with re-worded items asking about "the ability to delay ejaculation" or "the ability to control/avoid rapid ejaculation" than with one that specifically assesses "ability to control ejaculation (or its timing)." This difference, though subtle, is an important one that will help ensure more adequate assessment of pharmacotherapeutic treatments aimed at inhibiting the ejaculatory reflex.

Conclusion

Premature ejaculation is typically defined by three characteristics: short latency to ejaculation, lack of self-efficacy regarding the rapid ejaculation, and distress or dissatisfaction with the condition. The selection of outcome measures used to assess the efficacy of a PE treatment procedure may not always include the same set of measures used to define the PE condition, but rather depends on the specific type of treatment procedure implemented. Pharmacotherapeutic studies, which typically use agents that inhibit the ejaculatory reflex, should include outcome measures of ejaculatory latency and sexual satisfaction, but may also include measures of self-efficacy. However, in such studies the wording of items used to assess self-efficacy might focus more on the ability to delay ejaculation or avoid rapid ejaculation than on the ability to control ejaculation.

References


Figure 1. Relationship between defining characteristics of premature ejaculation, their operationalization, and various treatment strategies.

<table>
<thead>
<tr>
<th>(1)</th>
<th>(2)</th>
<th>(3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSM-IV criterion:</td>
<td>lack of self-efficacy</td>
<td>minimal stimulation</td>
</tr>
<tr>
<td>Operationalized:</td>
<td>lack ejaculatory control</td>
<td>short IELT</td>
</tr>
<tr>
<td>Intervention Points:</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Treatments:</td>
<td>cognitive-behavioral techniques</td>
<td>pharmacotherapy</td>
</tr>
</tbody>
</table>

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Meetings Calendar

Luca Incrocci: lucaincrocci@cs.com

2003

April 2-4, Marrakech, Morocco
4th Biennial Congress of the African Society of Sexual & Impotence Research (ASSIR)
14 Syria St., Mohandeseen, Cairo, Egypt
Phone: +20 2 33 68 304
Fax: +20 2 33 68 304
E-mail: assircongress@congress-center.org
Web: www.congress-center.org/assir
ASSIR organizes one symposium

April 15, London, UK
The First European Symposium on Female Sexual Dysfunction
Event Management, "Shoregate"
Quayside, Berwick Upon Tweed
Northumberland, TD15 1HE, UK
E-mail: info@sfrgatucl.org.uk
Web: www.sfrgatucl.org.uk/fdsSYMposium

April 26-May 1, Chicago, USA
98th Annual Meeting of the American Urological Association (AUA)
1120 North Charles Street
Convention Department
Baltimore, Maryland 21201-5559, USA
Phone: +1 401 22 34 308
Fax: +1 401 22 34 372
E-mail: convention@auanet.org
Web: www.auanet.org

May 8-10, Toronto, Canada
Comprehensive Review of Sexual Medicine
Venue West Conference Services, Ltd.
645-375 Water Street
Vancouver, BC, Canada V6B 5C6
Phone: +1 604 68 15 226
Fax: +1 604 68 12 503
E-mail: congress@venuewest.com
Web: www.venuewest.com/crsm

June 29-July 1, Paris, France
2nd International Consultation on Erectile Dysfunction
Prof. S. Khoury
Hôpital de la Pitié, Clinique Urologique
83 Boulevard de l’Hôpital
75634 Paris Cedex 13, France
Phone: +33 1 42 17 71 20
Fax: +33 1 42 17 71 22
E-mail: consulturo@aol.com
Web: www.congress-urology.org

July 16-19, Bloomington, USA
29th Annual Meeting of the International Academy of Sex Research (IASR)
J. Michael Bailey, Secretary-Treasurer IASR
Department of Psychology
2029 Sheridan Rd., Northwestern University
Evanston, IL 60208-2710, USA
Phone: +1 847 49 17 429
Fax: +1 847 49 17 859
E-mail: jm-bailey@northwestern.edu
Web: www.iasr.org

August 20-23, Cartagena de Indias, Colombia
7th Congress of the Latin American Society for the Study of Impotence & Sexuality (SLAIS)
Dr Mauricio Delgado
Transversal 17 No. 121- 12 Office 507
Bogotá, Colombia
Phone: +57 1 63 72 811
Fax: +57 1 62 03 430
E-mail: info@slais2003.com
Web: www.slais2003.com

October 1-4, Cebu, The Philippines
9th Congress of the Asia Pacific Society for Impotence Research (APSIR)
PUA Secretariat
3/F, PCS Building, 992 EDSA
Quezon City 1105, The Philippines
Phone: + 632 92 56 740
Fax: + 632 45 44 439
E-mail: pua@info.com.ph
Web: www.puanet.org

October 16-19, Amsterdam, The Netherlands
3rd meeting of the International Society for the Study of Women’s Sexual Health (ISSWSH)
1111 N. Plaza Drive, Suite 550
Schaumburg, IL 60173
Phone: +1 847 51 77 225
Fax: +1 847 51 77 229
E-mail: isswsh@wjweiser.com
Web: www.isswsh.org

November 16-19, Istanbul, Turkey
6th Congress of the European Society for Sexual and Impotence Research (ESSIR)
CPO Hanser Service
P.O. Box 1221
22882 Barsbüttel, Germany
Phone: +49 40 67 08 820
Fax: +49 40 67 03 283
E-mail: essir@cpo-hanser.de
Web: www.essir2003.org

2004

May 12-16, Brighton, UK
7th Congress of the European Federation of Sexology (EFS)
Intemarket, Gordon House, 14a Ship Street
Brighton BN1 1AD
Phone: +44 12 73 32 53 15
Fax: +44 12 73 32 38 82
E-mail: Intermkt@pavilion.co.uk
Web: www.efs2004.com

June, Istanbul, Turkey
3rd Mediterranean Congress of Sexual Dysfunction
BROS Tourism & Travel
Halaskargazi Cad. 53/4 Harbiye
Istanbul, Turkey
Phone: +90 212 29 66 670
Fax: +90 212 29 66 671
E-mail: info@brostourism.com
Web: www.brostourism.com

October 17-21, Buenos Aires, Argentina
11th World Congress of The International Society for Sexual and Impotence Research (ISSIR)
ISSIR Executive Office, P.O. Box 97
3950 AB Maarn, The Netherlands
Phone: +31 343 44 38 88
Fax: +31 343 44 20 43
E-mail: secretariat@issir.org
Web: www.issir2004.org

December 5-8, London, United Kingdom
7th Congress of the European Society for Sexual and Impotence Research (ESSIR)
CPO Hanser Service
2 Zum Ehrenhain 34
22885 Barsbüttel, Germany
Phone: +49 40 67 08 820
Fax: +49 40 67 03 283
E-mail: essir@cpo-hanser.de
Web: www.essir2004.org

2005

July 3-8, Montreal, Canada
17th. World Congress of Sexology
Dr. Pierre Assalian
Human Sexuality Unit, Montreal General Hospital
1650 Cedar Avenue
Montreal, Quebec H3G 1A4
Phone: +1 51 49 34 19 34
Fax: +1 51 49 34 82 37
E-mail: pierre.assalian@mhuc.mcgill.ca
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and the Representatives of the Collaborating Organisations

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Pr. Saad Khoury
Clinique Urologique (Pr. Richard) Hôpital de la Pitié
83 bld de l'Hôpital 75634 Paris Cedex 13 - France
Tel: +33 1 42 17 71 20 or 21
Fax: +33 1 42 17 71 22
E-mail: consulturo@aol.com

Pr. Tom F. Lue
Pr and Vice Chairman - Dpt of Urology, UCSF
400, Parnassus Avenue, A-633
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The use of Viagra and organic nitrates in any form, at any time, is contraindicated. The most common side effects of Viagra were headache (13%), flushing (11%), and dyspepsia (5%). Adverse events, including visual effects (2%), were generally transient and mild to moderate. Before treating ED, physicians should consider the impact of resuming sexual activity and the mild and transient vasodilatory effects of Viagra on blood pressure. Physicians should carefully consider whether patients with underlying cardiovascular disease or other more unusual conditions could be adversely affected by vasodilatory effects, especially in combination with sexual activity.

Please see full prescribing information for Viagra (25-mg, 50-mg, 100-mg) tablets on accompanying page.

Reference: I. NDC Data. The blue diamond tablet shape is a registered trademark of Pfizer Inc.