

EDITORIAL: The arrival of Sildenafil

Sildenafil, a selective phosphodiesterase 5 (PDE5) inhibitor, has been on the market for weeks in the USA, having undergone an expedited review by the FDA and received its approval as an oral therapy for impotence. The reaction of the media and the general public has been explosive. Never before, it seems, has a new treatment/medication received so much attention from the media, and within just a few weeks hardly anyone on the street is impervious to the VIAGRA® phenomenon, the commercial name for sildenafil, what it is, and what it is used for. In the USA patients have rushed to clinics en masse requesting prescriptions, and it is estimated that one million males and an unknown number of females have already taken this medication. Europe, where sildenafil is not yet available, has not fallen short in terms of media coverage. In Spain, for example, countless television programmes handed their prime time over to sildenafil, despite the fact that there was no experience of using this medication. One can only begin to imagine the Byzantine discussions that took place in such forums that brought together writers, politicians, musicians, and other "experts" in the field of erectile dysfunction.

Why has the appearance of sildenafil produced this reaction? For several reasons, one can guess. Firstly, sex is important in the life of many, if not most people. Secondly, sildenafil is an effective treatment that is easy to administer and if need be, conceal. It is important to keep in mind that before sildenafil, there were very effective but less user-friendly treatments for impotence. Thirdly, sildenafil is not only used by impotent men but also by men who want better erections. This reveals that many men feel insecure about the quality of their erection and the argument that most women are more interested in love and affection than in harder erections seems of little consolation to the average man who insists on more "potency".

(continues overleaf)



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The biannual meeting of the International Society for Impotence Research brings together experts from around the world as well as state-of-the-art updates on research in the area of erectile dysfunction.

More information inside

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EDITORIAL: The arrival of Sildenafil

Iñigo Sáenz de Tejada

European Union authorities have recently given a favourable review to sildenafil and it is therefore expected to become available in most European countries before the end of 1998. In the meantime, herds of patients are flocking to International pharmacies in many countries such as Switzerland, Andorra and Gibraltar, regulation-free havens where they can already purchase sildenafil.

Enthusiasm for sildenafil was somewhat shaken by reports of some deaths of patients who had taken sildenafil. While the exact medical relationship between the medication and these deaths is yet to be determined, it is important to remember that a specific and very dangerous drug interaction has been identified with the use of nitrates or any kind of nitric oxide donors while using sildenafil. Thus, any patient taking nitrates should not be prescribed sildenafil. This is clear. The problem however, lies in the management of the patient who has taken sildenafil and is currently not taking nitrates, but who develops ischemia of the heart and requires emergency treatment. Current protocols usually applied in situ by emergency medical personnel, use nitrates as first line treatment in such situations and alternative therapies have not yet been designed. To date, cardiologists and emergency departments have not been faced with the need to treat ischemia of the heart in patients whose phosphodiesterase type 5 activity had been knocked-out by another medication. This is a medical challenge that will require rethinking current therapy and finding alternatives for this important emergency situation, since millions of patients will foreseeably take sildenafil and future generations of PDE5 inhibitors.

Finally, the introduction of sildenafil will change the initial management of many ED patients, since it will be first line therapy for most, and physicians who did not previously treat this pathology (problems of erectile dysfunction of their patients) will probably prescribe it. As a medical and scientific society, the ESIR, faces the need to convey clear and important messages to the medical community. The first and foremost of these is that a simple, minimal, but indispensable diagnosis of erectile dysfunction should be done on every patient, with the goal of identifying forms of impotence that can be cured (e.g. hypogonadism or psychogenic impotence). Treatment with sildenafil or any other drug should never be initiated without taking this necessary step. The second is that if sildenafil fails, other effective therapies are available and can be implemented, step-wise, in the treatment of erectile dysfunction. Specialists in the field, who will undoubtedly manage more complicated or severe forms of erectile dysfunction from now on, will provide these treatments.

For those of you who wish to contact us:

New ESIR Secretariat

Address:

Antonio Robles nº4 (9^oC)

Madrid 28034, Spain

Tel: +34 1 358 38 54

Fax: +34 1 358 50 45

E-mail: esir@coronadoserv.com

www.esir.com

Contact person:

Milagros Lemos

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IÑIGO SAENZ DE TEJADA

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Selective inhibitors of cyclic nucleotide phosphodiesterases as a new class of drugs in the treatment of male erectile dysfunction

Stefan Ückert



Phosphodiesterase enzymes (PDE) play a key role in the metabolism of cyclic nucleotide monophosphates (cNMP) cAMP and cGMP. Many agents modulate smooth muscle function via stimulation of adenylyl or guanylyl cyclase activity and via elevation of intracellular levels of cAMP and cGMP. cNMP are degraded by PDE by hydrolytic cleavage of the 3'-ribose-phosphate bond. Because of the central role in smooth muscle tone regulation and the considerable variation of PDE isoenzymes regarding tissues and species, PDE have become an attractive target for drug development. Since the distribution and functional role of PDE-isoenzymes varies in different tissues, selective inhibitors of the isoenzymes have the potential to exert at least a partially specific effect on the target tissue. With respect to their kinetic and molecular genetic characteristics, 6 families of PDE can be distinguished: Ca²⁺/calmodulin dependent PDE (PDE I), cGMP-stimulated PDE (PDE II), cGMP-inhibited PDE (PDE III), cAMP-specific PDE (PDE IV), cGMP-specific PDE (PDE V), and the cGMP-hydrolyzing PDE of mammalian rods and cones (PDE 6). Stief et al. have demonstrated the presence of PDE III, IV and V in cytosolic supernatants of human cavernous smooth muscle homogenates while, later, others reported the presence of PDE II, III and V in cavernous tissue. Regarding the functional importance in the regulation of cavernous muscle tone, inhibition of PDE III and V was proved to be most effective in inducing cavernous smooth muscle relaxation in vitro.

Nitric oxide (NO) is supposed to be released from nerve endings and endothelial cells during sexual arousal. NO then stimulates the cytosolic guanylyl cyclase to produce cGMP which, via activation of cellular protein kinase enzymes, results in a decrease in cytosolic Ca²⁺ and leads to relaxation of smooth muscle cells. cGMP is mainly degraded by PDE I and PDE V. Therefore, in cavernous tissue, a pharmacological agent which inhibits PDE V should enhance the action of NO/cGMP on penile erectile activity and have the potential to amplify the cGMP dependent relaxation mechanism during sexual stimulation. Recently, the PDE V inhibitor sildenafil (VIAGRA®) was introduced into clinical studies as a novel orally-efficacious drug for the treatment of male erectile dysfunction and has again brought cavernous intracellular signal transduction to the attention of the general

scientific public. In patients without an established organic cause of erectile dysfunction, sildenafil was found to enhance the duration and rigidity of erection in about 60% - 80% of the patients. This might emphasize the pronounced role of PDE V in human penile erection. Nevertheless, cGMP- and cAMP-dependent signal transduction pathways are not generally parallel or independent in smooth muscle tissue.

Since intracavernous injection of PDE III inhibitor milrinone was reported to induce good erectogenic effect in patients with erectile dysfunction, a possible functional relevance of cAMP-hydrolyzing PDE III in human corpus cavernosum should also be considered. cGMP and cAMP either appear to have similar physiological effects in cavernosal smooth muscle and work synergistically in this tissue or an increase of cGMP by inhibition of PDE V may exert an inhibitory effect on PDE III leading to an elevation of cellular cAMP and, finally, to cavernous smooth muscle relaxation. A comparable mechanism has already been assumed by Maurice and Haslam from experiments on rat aortic smooth muscle.

In conclusion, all present studies on the role of PDE-isoenzymes in cavernous signal transduction provide a rational possibility for the use of PDE-inhibitors as an innovative new class of selective drugs in the treatment of erectile dysfunction.

Stefan Ückert, Hannover Medical School, Department of Urology, 30625 Hannover, Germany

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The ESIR Secretariat notice board

The past 5th May saw the launch of an interesting campaign to raise public awareness of the problem of Erectile Dysfunction in Spain. Like other European countries Spain has a large population of men who suffer from erectile dysfunction of different degrees. As a result, The Foundation for Research and Development in Andrology with the patronage of The National Urological Association and the National Andrological Association set about co-ordinating a nation-wide campaign to bring this medical problem to light.

A telephone service has been set up where the general public can get information about specialists in their geographical area who are qualified to deal with this problem and are members of the two National Associations therefore guaranteeing professional expertise and standard medical practice.

This campaign is based on two main objectives:

First and foremost to bring relief to all those silent ED sufferers and make them aware of the wide range of effective treatments available through their urologist/andrologist.

Secondly, to counteract the negative effects of a growing number of "cow-boy outfits" which have sprung up over the last few years offering miraculous treatments at often exorbitant prices, with no medical guarantees, and which may be operating outside the laws that govern the ethics and standards of medical practice.

Elections were held in the month of April to choose the new representatives of the Advisory Board of the European Society for Impotence Research. This Board of the ESIR is renewed with each incoming Term. Members from countries with more than four members were asked to vote for one to represent them on the Advisory Board and the results were as follows:

Italy	Vincenzo Mirone
The Netherlands	Eric Meuleman
France	François Giuliano
Turkey	Halim Hattat
Spain	Antonio Allona Almagro
Portugal	Alexandre Moreira
Germany	Hartmut Porst
Norway	Hans Hedlund
United Kingdom	David Ralph
Greece	Konstantinos Hatzimouratidis
Austria	Hans Christoph Klinger
Belgium	Benny Verheyden

ELECTIONS

3rd Meeting of the European Society for Impotence Research

We can also offer you updated information about the next ESIR 99 meeting in Istanbul under the supervision of the Turkish Association of Andrology. This meeting will take place between the 3rd and 6th of October 1999 at the Istanbul Convention and Exhibition Centre. Professor Halim Hattat has been elected Chairman for this event, with Associate Professor Ates Kadioglu Co-chairman and Associate Professor Emre Akkus Secretary General. The Honorary President will be Professor Sedat Tellaloglu.

The Scientific Committee of the meeting will be composed of the following members:

John Pryor - Chairman
Olivier Rampin
Yoram Vardi
Halim Hattat - Local Representative
Iñigo Sáenz de Tejada - President ESIR
Francesco Montorsi - Secretary General ESIR

The meeting will be officially opened on Sunday and will run through to Wednesday 13:00 approximately, when it will be officially closed.

The dreaded abstract deadline is June 15th 1999 and in the interests of the smooth running of this event we would request that you adhere to it.

We look forward to seeing all the ESIR members and to welcoming new members to make this European Chapter of the ISIR the leading scientific forum for Impotence Research in Europe and neighbouring countries.

All enquiries regarding ESIR 99 should be forwarded to the Congress Secretariat:

Mrs. Serpil Bagriacik
Tel: +90 212 230 55 35
+90 542 210 1449
Fax: +90 212 230 4923
Email: serpil@antmarin.com.tr



PSEUDOHERMAPHRODITISMUS MASCULINUS:

Indication for penile reconstruction.

Michael Sohn



fig 1

Penile and urethral reconstruction by using an extended free forearm flap has emerged as a standard procedure in sex-reassignment surgery in female-to-male transsexualism.

The penile shaft and penile urethra are formed following the "tube-in-a-tube" principle. The epigastric artery and vena saphena have to be prepared for microsurgical vessel-anastomoses. Subcutaneous nerves from the flap may be anastomosed to the transected clitoral nerves, which have an ideal diameter for micro-anastomoses. As an alternative, the neurovascular bundle of the hypertrophical clitoris may be isolated, the corpora of the clitoris resected and the glans clitoridis reimplanted into the skin of the neo-penis shaft. In transsexualism the vaginas must be completely resected during the procedure, isolating an anterior vaginal flap to reconstruct the missing distance of the bulbar urethra. Neoscrotum formation can be done by inverted U-incision and dissection of the labia majora from the pubic bone.

In our case the situation differed from this technique in various details:

The young thirty year old man had been operated on at the age of 16, when the diagnosis of pseudohermaphroditismus masculinus was confirmed by hormonal and chromosomal work-up. This first operation included the complete resection of the blind-ending vagina, a neo-urethra formation by local flaps to the base of the hypertrophical clitoris and the implantation of testicular prosthesis into the reconstructed scrotum. The right testicle remained in its original position in the right former labium majoris, which now became part of the scrotum (see figure 1).

The boy was brought up as a man and now requested penile augmentation, because he wanted to marry his girlfriend.

We decided to perform a forearm-flap transplant for urethral and penile reconstruction following the "tube-in-a-tube" principle (see fig. 1).

The length of the hypertrophical clitoris was only 3 to 4 cm in the erect state.

Because the patient insisted on maintaining his original clitoris and consequently refused clito-



fig 2

rectomy and nerve anastomoses, we decided to resect the corpora cavernosa and to implant part of the glans clitoridis into the penile shaft relying on its blood and nerve supply via the preserved dorsal neurovascular bundle. Defect covering of the left forearm was facilitated by mashed split-skin-grafting from the right buttock.

The result of the procedure can be seen in figs. 3 and 4.



fig 3

The glans clitoris was well vascularised and maintained its sensitivity during follow-up. After one year the patient is now awaiting the implantation of a single cylinder hydraulic penile prosthesis covered by a Dracon® sock.

This example may show, how innovative free-flap procedures in transsexual surgery may be applied for penile reconstruction in other situations. Currently, another patient with pseudohermaphroditismus masculinus and a patient with penile amputation after penile cancer are awaiting a similar reconstruction at our institution.



fig 4

Michael Sohn, Prof. M.D.
Department of Urology
St. Markus-Hospital
Wilhelm-Epstein-St. 2
D-60431 Frankfurt a. M.
Germany

A contribution from the United Kingdom

Wallace Dinsmo



In the United Kingdom erectile dysfunction is managed by urologists, venereologists (genitourinary physicians), psychiatrists and a wide range of other specialists including endocrinologists and geriatricians as well as family doctors who have developed a special interest.

The products with a licence in the United Kingdom for the treatment of erectile dysfunction are Alprostadil which is available either as Caverject® or Viridal®. Caverject® is available at 10 and 20 microgram doses and Viridal® is available as 5, 10 and 20 micrograms doses. Both have different devices to facilitate injections. Prostaglandin has also been available intraurethally as MUSE® at dosages of 125, 250 500, 1000 micrograms since January 1998 and is produced by VIVUS and marketed by Astra.

Although much research has been carried out in the UK on sildenafil (Viagra®) this is not available and there is no definite date for availability. Erecnos®, marketed by Fournier, has also become available within the past few months in the United Kingdom.

A very successful conference on erectile dysfunction was held at the Royal Society of Medicine on 13th March 1998. This was also the first meeting of the British Society for Sexual and Impotence Research (BSSIR). This society was formed following a preliminary meeting on 1st December 1997. At this meeting a Steering Committee was formed and provisional office bearers were elected being Clive Gingell, President, Geoff Hackett, Treasurer, Wallace Dinsmore, Secretary, and John Green, Assistant Secretary. These positions were confirmed at the Royal Society of Medicine Erectile Dysfunction Conference pending a formal constitution and more formalised arrangements.

In the United Kingdom there have been a number of groups with speciality interests in erectile dysfunction, which have included the Genito Urinary Physicians Study Group on Sexual Dysfunction, The British Erectile Dysfunction Society and the Impotence Association. All of these groups have had some overlap with each other but have been formed by different sectional interests and it is hoped that the new British Society will draw these groups together in a stronger organisation. The impetus for this new society was the highly successful conference in Madrid 1997, during which it became obvious that there was a need within the United Kingdom for a body which would have a similar remit to the ESIR and it is hoped that close links may be formed between these organisations.



IN MY COUNTRY
Contributions from the
advisory board

ESIR

Dispelling the Wince Factor

Terry R. Payton and Irwin Goldstein

In a recent article published in Newsweek magazine (October 1997 - pills for impotence) one segment devoted to self-injection was headlined the "wince factor". While this may be true as an initial reaction by many men considering this therapy, what is equally true is that this treatment remains the most effective with the least amount of side effects. To date, thousands of men in all age categories utilise this form of therapy, despite the wince factor.

Since the mid-eighties, self-injection treatment has unquestionably met some resistance by potential consumers, some men even opting to do nothing rather than rely on a needle. However, it is clear from the men who practise intracavernosal injection therapy that the benefit from an injection far outweighs the minor pin-prick it produces.

The needle

The past fifteen years have witnessed an interesting learning curve regarding what gauge needle should be used and what length is most appropriate and effective. From the start, the standard insulin type syringe with a 28 gauge 1/2 inch needle has been used with an excellent track record. Patients receiving proper instruction including varying injection sites and religiously practising post injection compression rarely encounter side effects. Some patients have also reported using the 29 gauge 1/2 inch needle with good results.

In an effort to reduce the wince factor, manufacturers produced spring-loaded injector pens of every size and shape to please the customer. Although the somewhat subtle punch of these devices has helped some, their acceptance has not been overwhelming. The introduction of the 30 gauge needle has, for some men, almost entirely eliminated the wince factor. This needle, available in 1/2 and 5/16 inch, has proven very effective, but each has a drawback. The 1/2 inch 30 gauge needle can actually bend if used to aspirate medication from a vial, so its use should be restricted to the actual injection. The 5/16 inch 30 gauge needle can function very nicely as an aspirant and penile injector, but its length may be too short for some men. In fact, some of our patients have opted to return to the 1/2-inch needle due to its reliability.

Enter Schwarz Pharma who, with FDA approval for their injectable EDEX®, ingeniously incorporated a two-needle injection kit. One needle, a 27 gauge, is used for mixing EDEX®. A simple manoeuvre and off comes the 27 gauge, to be replaced with a 30 gauge 1/2 inch needle. This system has worked very well. Patients report barely feeling this 30 gauge injection and welcome this advancement.

Alleviating the wince factor

At our clinic in Boston new patients are routinely injected for a variety of reasons. When indicated, patients undergoing duplex ultrasonography receive an intracavernosal injection. For most, this is their first exposure to a penile injection. This is an inter-office procedure where all patients are encouraged to check out the injecting needle first. Also, patients view an instructional video on proper injection technique. Other patients receive their first injections while undergoing dynamic infusion cavernosometry /cavernosography. This is a diagnostic procedure generally performed in a radiology suite. Patients are informed that multiple injections are required and interestingly enough, almost all report the insignificance of the injection versus the significance of the test findings. Injections are also given as part of a standard in-office diagnostic evaluation. A simple test dose of Edex® or other vasoactive drugs can be used to assess vascular integrity and to assess any degree of curvature in patients with Peyronie's disease. Aside from the diagnostic value, this approach serves two very important objectives. First, the patient experiences first hand the minimal discomfort of a needle injection. Secondly, the patient is able to realise the positive erectile results from this simple and practically painless procedure. Injection therapy, despite the required needle insertion, is practised as an effective therapy by thousands of men. Unquestionably it represents the most effective treatment with the least amount of side effects.

Terry R. Payton, R.N.C.
Irwin Goldstein, M.D.
Boston University
Medical Center

Countdown to theth 8th World Meeting on Impotence Research

This month we provide you with further information about one of the most important forthcoming events concerning this Society and the field of Erectile Dysfunction. The 8th World Meeting on Impotence Research AMSTERDAM 24th-28th August 1998.

The Congress President is Eric Meuleman and the scientific programme is under the supervision of the local Scientific Committee made up of the following people:



Michel Hengeveld
Guus Lycklama à Nijeholt
Eric Meuleman
Koos Slob
Dirk Vanderschueren
Eric Vrijhof

The Congress venue will be the Free University and information regarding the congress can be obtained from the Congress Office:

Status Plus Conferances
Robert von Hinke Kessler
P.O. Box 97, 3950 AB Maarn
The Netherlands

Tel: +31 - 343 443888
Fax: +31 - 343 442043
Email: statusplus@compuserv.com

* Among the many social activities planned by the organising committee in Amsterdam we recommend you do not miss the Amsterdam pub-crawl. This is a popular tradition which gives people from different nationalities and cultures the

opportunity to bridge the gaps that divide them whilst joining the natives in a friendly drink at their local.



**The 8th World Meeting
on
Impotence Research**

AMSTERDAM



8th World Meeting
on Impotence Research

Interview with Drs. Adaikan and Ishii

Dimitrios Hatzichristou

In the first 2 issues of ESIR Newsletter, we hosted the interviews of Dr Gorm Wagner and Ronald Virag, two of the pioneers in the field of erectile dysfunction (ED).

This issue hosts two colleagues outside Europe, who are definitely to be included among the pioneers; Dr. Adaikan from Singapore and Dr Ishii from Tokyo, Japan. Coming from countries with a vastly different cultural background, they give us their own very important views on several issues within the field of erectile dysfunction.

Almost twenty years have elapsed since papaverine was first introduced as a diagnostic and therapeutic tool in male erectile dysfunction (ED). Today, there is world-wide experience with self-injection programmes. On the other hand, intraurethral application is already in the market, and very soon oral therapy will be available to patients and doctors. How much has pharmacological development changed our attitude and consideration for impotent patients, and how much will the global aspect of ED change, when oral therapy comes on the market?

Dr. Adaikan: With our limited understanding of human sexuality, the last three decades have seen us move from an "it is all in the head" era to often confusing diagnostic procedures and development of pharmacologic approaches for the treatment of impotence. In this regard, intracavernosal injections provided simplicity of treatment for the doctors and patients and somehow minimized and retarded further interest for the diagnostic work-up or understanding of the clinical presentation. Oral therapy will further enhance the ease of treatment and will also introduce a flood of "borderline" patients who may want to use this as an "aphrodisiac". However, there will always be a definite group of patients who will need the specialist's diagnostic work-up and treatment procedures, including all the existing methods.

Dr. Ishii: We cannot perform intracavernous autoinjections because it is judicially prohibited in Japan. In addition to this situation, the Japanese attitude towards sex is extremely conservative and the number of individuals who desire implantation of penile prosthesis is very limited. If intraurethral PGE1 or oral drugs became available, it would be possible to treat those patients who had given up treatment for impotence, and PGE1 could be used in more than 100.000 candidates in Japan. The problem is the extent of indications for the new treatments. If this drug is used without sufficient studies on erectile function, then such use is not con-

sidered correct.

The Japanese Society for Impotence Research plans to assess this point more specifically. However, we welcome widened options for the treatment of erectile dysfunction.

We have accepted a high drop-out rate in men following self-injection programmes, specifically during the first treatment period. Based on your experience do you have any practical advice to help reduce the number of drop-outs?

It has been reported for example, that the use of more "friendly" application systems such as autoinjectors have considerably reduced the early drop-out rate. What is your view on this?

Dr. Adaikan: A certain drop-out rate in men following self-injection programs will continue to exist; this may be so even with other forms of treatment for impotence. The difficulty and fear of using intracavernosal injections (storage problems, dilution, stability, self-injection, hiding from partner etc.) may play a role in the drop-out rate. The main reasons in my opinion however are the personal expectations and the needs of the individuals that are not being met which contributes most to this drop-out rate.

Dr. Ishii: I cannot answer your question because intracavernosal autoinjections are not available in Japan. Recently, since the Japanese Ministry of Public Health and Welfare has authorized the use of VCD, this type of therapy is the primary choice of treatment in Japan, while intracavernosal injections have a wide application in vascular studies of erectile dysfunction.

Intracavernosal injection therapy is now accepted as the gold standard treatment for ED. Do you believe, we run the risk of forgetting the deeper and main aspects of sexual disturbances and become more concerned with creating erectile athletes?

Dr. Adaikan: Yes, as mentioned earlier, we have not only inadvertently reduced our enthusiasm for diagnostic approaches but also other aspects of individuals and their interpersonal relationships with partners and their needs. The end-user of the intracavernosal injection therapy is not just the man. It involves two people: he and his partner.

Dr. Ishii: I do not clearly understand the meaning of erectile athletes. Intracavernous injections are considered to have many problems, such as the injection per se, medical waste and misuse. I look forward to future developments of oral medication and more easy-to-use VCD products.

Within a wider perspective, the results of vascular surgery for ED are not encouraging, although some young patients with insufficient arterial inflow may restore their erectile function with revascularization. Should we try to treat such patients medically - with intracavernosal or intra-urethral alprostadil today and with oral medication such as sildenafil tomorrow - without any work-up, or shall we refer them directly to national centres with a certain surgical expertise?

Dr AdaiKAN: Pharmacotherapy (intracavernous, intraurethral or oral) may be the first choice. If this approach is not satisfactory to the patient, partner and doctor, further work-up may be necessary. Identifying the root cause of vascular insufficiency is also important.

Dr Ishii: We do not perform vascular surgery. One reason is that we have found that our impotence patients do not wish their erectile failure to be treated by surgery. Other reasons are poor long-term results of this type of treatment and our resistance to vascular surgery in young patients because new kinds of therapy are expected to be available in the future. We are anticipating good results from oral medication and we are extremely confident of establishing an information centre for impotence in Japan in the future.

There is still variation and discrepancy between groups handling ED, as far as diagnostic and therapeutic strategies are concerned. Do you think that we are still far from reaching a consensus?

Dr AdaiKAN: We have reached a milestone in our diagnostic and therapeutic strategy. However, this situation is far from perfect or satisfactory. In this respect, our international and continental organizations will continue to work together in their efforts to reach a satisfactory consensus. This is an on-going process which will evolve from further research in the area of physiology, pathology, diagnosis and therapy. We should also include and place greater emphasis on the preventive approach to ED.

Dr. Ishii: The methods and criteria for the diagnosis and treatment of ED vary from country to country and from group to group, which leads to controversy in presenting papers at medical meetings. Drafting unified diagnostic criteria, such as that used by the AUA, may solve this issue. Now more than ever, when the new oral medication is launched on the market, common examination and indication criteria will be considered essential.

Dimitrios Hatzichristou