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“Sexual Dysfunction for the New Millennium”

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ABSTRACTS

ORAL PRESENTATIONS

OR 1-1

Penile enhancement for implant patients: outpatient vein-ligation technique

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Introduction: Penile implantation has been accepted as a cornerstone of impotence solution for fifty years. However the postoperative penis is always reduced both in girth and in length. Here we develop a method of penile enhancement to meet the ultimate expectation of those patients.

Patients and methods: From May 1992 to November 2000 a total of 95 patients had undergone penile implantation with a variety of implants under local anesthesia on outpatient basis. Thirty-seven returning patients complained that their penis became shorter or smaller postoperatively. Of them 21 men underwent additional procedures of penile enhancement which included ligation of the retrocoronal plexus, deep dorsal vein, cavernosal vein and para-arterial veins and two 90 de-

gree Z-plasty under local anesthesia of epinephrine-rinsed lidocaine solution in order to enlarge the penis.

Results: With a mean follow-up period of 4 years 3 months (range 3 months to 8.5 years), the penile length increased in all by a mean of 2.5 cm. All the patients experienced a significant penile enlargement during coitus with an increase in penile girth and length. The glans is always felt flushed rather than cold and ischemic before.

Conclusion: The procedure of ligation of the retrocoronal plexus, deep dorsal vein, cavernosal vein and para-arterial veins and two 90 degree Z-plasty is a potential solution for reduced penile size in penile implantation patients.

OR 1-2

Revision in failed dermal graft in the management of Peyronie's disease

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In the management of Peyronie's disease, many kinds of grafts with vascular, dermal or synthetic materials are acceptable. We found several cases of delayed complication with fibrosis of the graft after plaque excision and dermal graft. We repaired the condition with saphenous vein graft and partial excision of the dermal graft or penile prosthesis implantation.

From March 1999 to February 2001, 16 cases of the Peyronie's disease were treated by plaque excision and dermal graft procedures. During the follow-up periods (average 8 months), a delayed complication of cur-

vature development due to fibrosis of graft was found in 4 cases.

We repaired 3 cases with saphenous vein graft and partial excision of the dermal graft. Partial excision of the previous graft site was possible because the fibrosis was partially along the graft margin. One case with fibrosis of most of the graft site was managed with penile prosthesis implantation.

In conclusion, delayed fibrosis of dermal grafts in Peyronie's disease may be repaired with saphenous vein graft and partial excision of the dermal graft.

OR 1-3

Surgical treatment of congenital penile curvature and Peyronie's disease

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Aim: We experienced 16 patients with congenital penile curvature and 14 patients with Peyronie's disease. We herein report these cases with regard to surgical procedures.

Methods: Congenital penile curvature was treated with plication. As J. Rehmanet undertook shaving to prevent recurrence, we also devised our own shaving technique. Peyronie's disease can be treated by either conservative or surgical procedure. Surgical treatment of this disease includes plication, lump removal and vein

grafting, and penile prosthesis implantation.

Results: No recurrence or complications were observed after treatment of congenital penile curvature and plication for Peyronie's disease.

Conclusion: Congenital penile curvature was treated with plication and shaving was additionally performed to prevent recurrence using our own technique. This shaving procedure seems to be an effective therapeutic modality in the treatment of Peyronie's disease with severe penile curvature.

OR 1-4

Comparison of cadaveric pericardium, dermis, vein and Gore-tex grafts in the surgical treatment of Peyronie's disease using a rat model

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Introduction and aim: Peyronie's disease is a connective tissue disorder of the tunica albuginea of the penis. When less invasive modalities fail to correct the penile deformity, surgical excision of the plaque and coverage with various grafting materials, *e.g.* dermis, vein, Gore-Tex, and recently, cadaveric human pericardium, has been advocated. The aim of this study was to evaluate the long-term efficacy of cadaveric pericardium comparing with dermis, vein and Gore-Tex as a grafting material in the surgical correction of Peyronie's disease using an animal model.

Methods: One hundred male Sprague-Dawley rats (300-325 g) constituted the study population. The animals were divided into 5 groups: group 1 consisted of control rats ($n=20$), and group 2-5 consisted of rats who underwent wedge excision of tunica albuginea and replacement with cadaveric pericardium, dermis, vein and Gore-Tex grafts ($n=20$ in each group), respectively. Ten rats each underwent electrical stimulation of the cavernous nerve to assess erectile function 4 and 6 months after the surgery. The sacrificed tissues were fixed in 10% formalin, paraffin-embedded, and stained with trichrome and Verhoff's van Giesen for collagen and elastic fibers.

Results: Erectile function, as studied by cavernosal

nerve stimulation at 4 and 6 months, were not statistically significant different in all groups ($P>0.05$). However, histological studies of penile cross-section revealed minimal fibrosis surrounding the patch in the dermal and vein graft groups at 4 and 6 months. In the cadaveric pericardium group, histological studies revealed moderate degree of fibrosis at 4 months and minimal fibrosis at 6 months. In Gore-Tex graft group, severe fibrosis was evident at 6 months and moderate fibrosis at 4 months.

Conclusion: We found that cadaveric pericardia allow for penile expansion and are strong enough to withstand normal intracorporeal pressures. Histological studies of the pericardial graft at 4 months revealed more fibrosis comparing with the dermal and vein grafts; this might be caused by the difference in antigenicity between human pericardial graft and rat tunica albuginea. However, at 6 months histological studies revealed a mild degree of fibrosis similar to the dermal and vein graft groups. Therefore, pericardium as a grafting material is satisfactory for tunica albuginea replacement in the surgical treatment of Peyronie's disease.

Source of funding: An educational grant from Mentor Corporation.

	Control		Pericardial		Dermal		Vein		Gore-Tex	
ICP	5 V	7.5 V	5 V	7.5 V	5 V	7.5 V	5 V	7.5 V	5 V	7.5 V
(4 mo)	59±7	76±8	50±6	52±6	63±8	68±7	56±8	70±8	57±4	75±5
ICP										
(6 mo)	51±5	58±5	55±4	60±5	52±5	55±6	53±5	63±4	52±4	62±4

$P>0.05$ in all cases, Compared with controls

OR 1-5

Biomechanical engineering – based computer – assisted surgery in LA Peyronie's disease

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At the Inaugural Congress of the International Society for Simulation Surgery, held in Tokyo, December 9-11, 1992, the first simulation model of the human penis for male genital reconstructive surgery was presented (G. Tritto *et al*, Computer Aided Surgery, vol.1, n.1, 52-54, 1994). Three basic computer – generated modules are developed and applied for modelling the human penis for simulation surgery: CASMeD Computer-Aided Skin Meshes' Design, PEN – FEM Finite Element Method, PEN – FLOW Analog Electrical Model of the penile vascular system. (Proceedings AMBER '95, IASTA Ed, Paris, 5-7 July, 281-283, 1999).

On La Peyronie's disease surgical procedures, biomechanical impairment interferes with the hemodynamics of the corpora: biomechanical correction must solve not only the structural problems of a consistent deformation, but also redistribute the hemodynamic parameters to guarantee the maintenance of erection. Solving on the FEM model with the potential energy method, using Lagrange's equations, it is possible to evaluate pre-operatively in simulation environment the best solution that can accomplish the minimum energy loss distribution into the structure, evaluating the elasto-plastic stress-strain relationships into the time-space domain.

OR 1-6

The management of priapism in western Australia: a 15 year audit

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Aim: We conducted an audit of priapism presenting to the emergency departments of the major teaching hospitals in Perth, Western Australia, from 1985 to 2000.

Methods: Hospital data bases were searched by diagnostic code. We recorded date, patient's age, clinical history, cause, use of intracavernosal injection, dosage, duration and management.

Results: There were 82 episodes of priapism reported in 63 patients. Of these, 62 episodes occurred after the use of ICI. 15 patients experienced a total of 20 episodes of priapism from other causes, predominantly psychotropic medication.

The majority of ICI priapisms occurred with papaverine (39) or papaverine containing combinations such as the double (5) and the triple or quad mix (2). The incidence of priapism fell after the institution of PGE1 monotherapy as the treatment of choice (9). Time from onset to presentation ranged from 4 to 96 h (mean 16.5 h).

Treatment included blood aspiration alone, aspiration with ICI of alpha-adrenergic agents and surgical shunts. Medical therapy was effective in most cases of priapism and no serious consequences of alpha-adrenergic drugs were documented. Priapism occurring outside the setting of ICI was more likely to require surgical intervention with 7 of 20 cases requiring shunts. After ICI therapy, 6 required shunts and the rest being managed successfully with medical therapy. If the priapism had lasted beyond 36 hours, medical therapy was less likely to be effective.

Conclusion: Priapism is a major side effect of ICI and a minor, although important, side effect of other conditions. The best approach is education for each patient embarking on an ICI programme, or on other medication with a risk of priapism. If the patient is well informed about the condition and the urgency required for treatment there should be a better chance of successful medical therapy.

OR 1-7

Penile prosthesis in Thailand: an option for treatment of ED

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Penile Prosthesis was the first primary treatment of erectile dysfunction for a long period of time. For the urologist, a good candidate for penile implant is a young diabetic or those with hypertension, ischemic heart disease or Peyronie's disease. In the process of surgery in King Chulalongkorn Hospital and two nearby private hospitals, we have discovered that the Thai male corpora are approximately 16.8 cm in length. This was never known before except during surgery of penile prosthesis.

A review of penile prosthesis implantation in 108

cases in the past 10 years showed an average age of 56 years old, the shortest size of 12 cm, and the longest of 21 cm. There were 3 wound infection cases and 5 cylinder leakage, and the degree of pain is at tolerable degree. Most patients are fascinated with the 3 piece equipment of both AMS 700 or Mentor's Alfa 1, but the decision to choose depends on the patients and their budgets.

We have an equal number of patients with malleable and inflatable prosthesis and patients are quite happy with what they have.

OR 1-8

The necessity of curvature correction in patients with tunical rupture

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Introduction: Rupture of the tunica albuginea is not uncommon in urologic practice. It is generally agreed that emergent repair of the ruptured tunica and possible associated urethral injury is feasible. For its ultimate postoperative result we recommend that simultaneous curvature correction may be critical and mandatory for those patients.

Patients and methods: From November 1987 to August 2000 a total of 11 men who suffered tunical rupture consulted us and 10 of them had undergone emergent repair. Before 1992 simple tunical repair were made in the first 3 patients, however in the following 7 patients whose penis was curved with artificial erection underwent simultaneous curvature correction with 6/0 nylon.

Results: In the first 3 patients who underwent simple tunical repair with 3/0 Vicryl or Dexon was uneventful

initially. Unfortunately the third case suffered a second tunical rupture which was ascribed to penile curvature 5 months postoperatively. Then we performed additional curvature correction in the following 7 consecutive patients with 4/0 Vicryl or 6/0 Nylon satisfactorily.

The most recent man was unusual who presented with a contracted glans which was solved with reattached distal ligamentous structure to the outer longitudinal layer of the tunica albuginea with 6/0 Nylon.

Conclusion: Rupture of tunica is a hazardous accident which is a nightmare for the couple. Although coital position may be important, but penile curvature may be contributed and should be corrected simultaneously. The rupture nidus may vary from proximal tunica to the glanular ligamentous structure.

OR 1 - 9

Stimulation of testosterone production on PADAM

Promptly reduce symptoms, achieve younger appearances and minimal side effect

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The study was carried out based on the experience on treating male infertility patients that suffer from symptoms of PADAM. From March 1999 to March 2001, 290 patients, aged 30-74 years (48.3 ± 11.4) suffering from PADAM. The PSA and the liver and renal function were normal and the blood pressure ≤ 160 mmHg. The testicular volume, Doppler vasculoscope for spermatic vein, leukocyte of expressed prostatic fluid (EPF), prolactin (PRL), PSA, and blood FSH, LH, and total testosterone (T) were examined before treatment. Only patients with hypergonadotropic-hypogonadism (H-H) were checked before and after treatment. After treatments of possible prostatitis and/or varicocelelectomy for H-H patients, all patients received 5000 IU of LH injection, twice a week for 1 month. During treatment, 2 patients were excluded due to side effects that disappear soon after cessation. Changes in symptoms were qualitatively assessed.

Low T levels (<270 ng/dl) were seen in 74 patients (25.6%), while high LH (>3.7 mIU/ml) was found in 99 patients (34.3%). A combination of high LH and low T

was found in 30 patients (10.4%), while H-H found only in 13 patients (12 with notable varicocele). It was noticed that high prolactin (>16.5 ng/ml), varicocele (Doppler +), and prostatitis (EPF > 40 leukocytes/HPF) were found in high frequencies, being as much as 164 (56.6%), 176 (61.1%), and 47 (16.3%) respectively. They might have an important role in declining T.

Various rejuvenation effects were seen. Libido improvement was reported uniformly by all patients, while erectile function was also improved in various degrees. Other results, such as developing younger appearance (decreasing face wrinkle), increasing well being, improving work performance, endurance, and physical fitness, as well as decreasing anxiety, insomnia, and disappearance of flushing (2 patients) were also reported. Interestingly, an increasing size of the penis was also noticed by some patients and their spouse. On the other hand, the T concentration in 21 patients with H-H was significantly increased ($P<0.01$). Side effects encountered: gynecomastia and pitting edema found in 2 patients and slight darkening of the skin in many patients.

OR 2-1

Treatment with sildenafil and partners' sexual function

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Aim: Sexual life is an important issue not only for patients with erectile dysfunction, but greatly affecting their partners as well. A questionnaire research was conducted in patients treated with Sildenafil and their partners to assess the treatment and also to investigate the actual state of female sexual function.

Subjects and methods: A questionnaire was distributed to 40 couples, consisting of patients (mean age 51.1 years) who had a satisfactory response to Sildenafil treatment during a period of 1 year and 8 months, at the Reproduction Center, Toho University Omori Hospital, and their partners (mean age 45.8 years). Sixteen couples desired to have a child (40%). Patients were asked to fill out the questionnaire at the hospital and their partners were asked to send the questionnaire by mail after filling out. Items investigated included satisfaction with the treatment and other concerned matters.

Results: Treatment was evaluated to be effective in all 40 patients. As side effects, hot flushes, heartburn, palpitation, seeing a light as if it was a red object and nasal obstruction occurred in 3, 2, 2, 1, and 1 patient,

respectively. Patients were all satisfied with the treatment; 70% of the partners were satisfied with the treatment, satisfaction seemed to be undeterminable in 15% and slightly dissatisfactory in 6%. In regard to related matters, 5%, 5%, 5%, 20%, and 20% of the patients reported premature ejaculation, sexual desire disorder, ejaculation disorder, worry about side effects, and others, respectively. Painful intercourse, sexual desire disorder, arousal disorder, orgasmic disorder, worry about side effects, and others were reported from 22.5%, 17.5%, 12.5%, 12.5%, 72.5%, and 17.5% of the partners, respectively. Painful intercourse and sexual desire disorder were reported from 16.7% and 4.2% of 24 premenopausal partners and 28.6% and 31.3% of 16 postmenopausal partners, respectively. It seems that there are higher incidences of painful intercourse and sexual desire disorder after menopause.

Conclusion: Although both patients and partners were highly satisfied with Sildenafil treatment, the satisfaction tended to decrease in the partners with female sexual dysfunction and worry about side effects.

OR 2-2

Characterization of prostaglandin E receptor subtypes in human corpus cavernosum

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Introduction and aim: Prostaglandin E (EP) receptors have been classified into four subtypes through pharmacological studies. Our aim was to determine the EP receptor subtype involved in the relaxing effect of the human corpus cavernosum using selective agonists and to search for an alternative to prostaglandin E1 (PGE1).

Methods: Human corpus cavernosal tissue (HCC) was obtained at penile biopsy with patients' permission. The preparations were mounted in Krebs solution in an organ bath and the isometric tension recorded. The drugs used were PGE1, ONO-DI-004 (EP1 agonist), ONO-AE1-259 (EP2 agonist), ONO-AE-248 (EP3 agonist) and ONO-AE1-329 (EP4 agonist). We evaluated the relaxation induced by cumulative additions of each EP agonist in norepinephrine (Nor) - contracted HCC strips.

Results: EP1 and EP3 agonists showed no relaxant response in HCC strips. PGE1, EP2 agonist and EP4 ago-

nist caused concentration-dependent relaxation of HCC precontracted with Nor. The degree of relaxation was EP2 agonist > PGE1 > EP4 agonist. Following Nor-induced contraction, the maximum relaxation response by PGE1 (10-5M) was 32.9mg 4.5% ($n=8$), versus 40.5mg 4.9% ($n=8$) for EP2 agonist and 20.0mg 3.7% ($n=8$) for EP4 agonist. There was a significant difference in the degree of relaxation between EP2 agonist and EP4 agonist. The concentration required for 20% of maximum relaxation was approximately 1:13.

Conclusion: Both EP2 and EP4 agonists produce relaxation of the HCC with that by EP2 significantly greater than by EP4 agonist. These results suggest that PGE1 relaxes HCC mainly by interacting with the EP2 receptor. In the future, through studies of the EP2 agonist, an alternative drug to PGE1 with fewer side effects may be possible.

OR 2-3

Treatment for erectile dysfunction in patients with treated prostate cancer

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Aim: We evaluated the sexual activity in patients with prostate cancer and their desire for treatment for their erectile dysfunction (ED).

Materials and methods: 36 patients who underwent treatment for prostate cancer surgically or non-surgically (radical retropubic prostatectomy [RPP] 18, radiation therapy 3, androgen ablation 15) were evaluated. We retrospectively evaluated the sexual activity, the acceptance and the efficacy of the ED treatment with sildenafil and intracavernous PGE1.

Result: Only 3 of the 36 patients (8%) had sexual

intercourse. However, of the 33 patients who did not have intercourse, 11 (33%) accepted ED treatment. The treatment was effective for 6 of 8 patients who underwent RPP. However none of the 3 patients who underwent androgen ablation therapy responded to ED treatment.

Discussion: Results suggested that most of the patients were still interested in sexual life and treatment for ED. Thus it is important that urologists should provide information about ED treatment for patients with treated prostate cancer.

OR 2-4

The effect of intrinsic and extrinsic factors on the pharmacokinetic properties of tadalafil (IC351)

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Aim: Tadalafil (IC351) is a potent and selective phosphodiesterase type 5 inhibitor being investigated in phase 3 clinical trials for the treatment of erectile dysfunction (ED). Several studies were designed to evaluate the effect of intrinsic and extrinsic factors (age, gender, diabetes, renal and hepatic insufficiency, and food) on the pharmacokinetic properties and tolerability of tadalafil.

Methods: Appropriately designed studies were conducted in healthy subjects aged 19-45 years using tadalafil 10 or 20 mg. Elderly subjects (aged 65-78 years) and subjects with renal insufficiency (creatinine clearance 31-80 mL/min), hepatic insufficiency (Child-Pugh class A and B), or diabetes were also dosed to assess the impact of these factors on tadalafil pharmacokinetics.

Results: Systemic exposure (AUC) to tadalafil was 25% greater in elderly compared with young subjects, indicating a slight reduction in oral clearance with age. In addition, steady-state concentrations were slightly higher (13%) in women than in men. Tadalafil AUC was 19% lower in subjects with diabetes than in healthy age-

and-gender-matched controls. In subjects with mild or moderate renal impairment, tadalafil AUC was higher than in healthy controls, whereas systemic exposure in subjects with mild or moderate hepatic impairment was similar to that in age-matched controls. Food (FDA standard high-fat breakfast) did not alter the rate and extent of absorption of tadalafil from a single 20-mg dose. The most common drug-related adverse events were back pain and headache, which were mild to moderate in intensity.

Conclusion: Tadalafil was well tolerated in these studies. There were no statistically or clinically significant effects of age, gender, or diabetes on tadalafil pharmacokinetics. Hence, adjustment of tadalafil dosing should not be warranted. Likewise, tadalafil dose adjustment is unlikely warranted in patients with hepatic insufficiency. Tadalafil can be administered without regard to food. These pharmacokinetic characteristics should allow for uncomplicated dosing of tadalafil in men with ED. (Funding provided by Lilly ICOS, LLC)

OR 2-5

Tadalafil (IC351) enhances NO-mediated relaxation of human arterial and trabecular penile smooth muscle

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Aim: The NO/cGMP pathway plays a central role in the neurogenic relaxation of penile smooth muscle needed to achieve and maintain erection. Inhibition of cGMP degradation by PDE5 inhibitors is useful for treatment of erectile dysfunction (ED). This study evaluated the selectivity of the novel PDE5 inhibitor tadalafil (IC351). The compound's effect on NO-mediated relaxation, and cGMP accumulation in human trabecular penile smooth muscle were also assessed.

Materials and methods: Tadalafil's selectivity for various human PDEs was determined using human recombinant PDEs and PDE6 from human retinas. Human corpora cavernosa tissues were collected from men with ED during penile prosthesis implantation. Penile arteries were mounted on Halpern-Mulvany myographs. Strips of cavernosal smooth muscle were placed in organ baths. Sodium nitroprusside was used to activate the endogenous guanylyl cyclase. Transmural electrical stimulation (0.5-12.0 Hz) was used to evaluate neurogenic relaxation of trabecular smooth muscle.

Results: Tadalafil potently and selectively inhibited PDE5 activity (IC_{50} 0.9 nM). A 780-fold greater concentration was needed to inhibit the retinal enzyme PDE6 (IC_{50} 730 nM). Still greater concentrations were needed to inhibit other human PDEs. Neurogenic relaxation of trabecular smooth muscle was enhanced by 30 nM tadalafil ($67.4 \pm 10.8\%$ versus $42.4 \pm 8.2\%$ at 6 Hz). Tadalafil (30 nM) produced significant potentiation of cGMP accumulation induced by sodium nitroprusside (1mM) in human cavernosal tissue (cGMP; 0.99 ± 0.18 versus 0.47 ± 0.12 pmol/mg protein, $n=6$). Tadalafil also potentiated the relaxation of penile smooth muscle induced by acetylcholine.

Conclusion: Tadalafil demonstrated potent and selective inhibition of PDE5. Tadalafil potentiated responses mediated by exogenous and endogenous sources of NO in human penile smooth muscle by promoting cGMP accumulation. Tadalafil is being evaluated as an oral therapy for ED. (Funding provided by Lilly ICOS, LLC)

OR 2-6

Dose-normalized pharmacokinetics of tadalafil (IC351) administered as a single dose to healthy volunteers

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Objectives: Tadalafil (IC351) is a potent and selective phosphodiesterase type 5 inhibitor currently being developed for the treatment of erectile dysfunction. In a clinical trial, tadalafil showed a clinical response in erectile function for up to 24 hours postdosing. This integrated statistical analysis was designed to assess the pharmacokinetics of tadalafil 20 mg when administered to healthy volunteers.

Methods: Noncompartmental pharmacokinetic parameters for single 10- or 20-mg doses administered to 237 healthy subjects in the fasted state were pooled across 13 studies. The dose-dependent parameters for the 10-mg dose were normalized to 20 mg. Parameters analyzed included the area under the plasma-concentration-time curve (AUC), maximum observed plasma drug concentration (C_{max}), time to C_{max} (t_{max}), half-life ($t_{1/2}$), apparent oral clearance (CL/F), and the apparent volume of distribution (V_z/F).

Results: The geometric means (CV%) of the parameters measured are listed in the table below.

In most subjects, adverse events were mild or moderate in severity and generally transient. The most common adverse event was headache.

Parameters	Geometric mean (CV%)
AUC ($\mu\text{gh/L}$)	8066 (39.3) ^a
C_{max} ($\mu\text{g/L}$)	378 (27.6) ^a
$t_{1/2}$ (h)	17.5 (32.3)
t_{max} (h)	2.0 ^b
CL/F (L/h)	2.48 (39.3)
V_z/F (L)	62.6 (25.4)

^a Normalized to 20 mg, ^b Median

Conclusion: Tadalafil is rapidly absorbed, is a low hepatic clearance drug, and is distributed in tissues. The 17.5-hour $t_{1/2}$ of tadalafil supports results from clinical trial that indicated a period of responsiveness for up to 24 hours postdosing. Moreover, there have been no apparent consequences of half-life on safety or tolerability in clinical trials to date. (Funding provided by Lilly ICOS, LLC)

OR 2-7

The effects of sildenafil as an intracavernosal agent

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Aim: Despite the development of Sildenafil, intracavernosal injection of vasoactive substance is still the most effective therapy for severe organic impotence patients. However, the side effects of intracavernosal injection, e.g. pain and priapism, require a more comfortable approach of therapy. We performed this study to assess the feasibility of Sildenafil citrate as a intracavernosal agent.

Materials and methods: In New Zealand white male rabbits ($n=11$), the relaxation of precontracted cavernosal smooth muscle strips was studied after administration of Sildenafil citrate, acetylcholine and sodium nitropruside (SNP). In *in vivo* experiment in adult male cats ($n=25$), changes in intracavernosal pressure (ICP), duration of increased ICP and changes in systemic arterial blood pressure after retrograde selective internal puden-

dal arterial administration of four separate doses (0.1mg, $n=5$; 0.3mg, $n=6$; 0.5mg, $n=7$; 1.0mg, $n=7$) of Sildenafil citrate were monitored.

Results: Acetylcholine, SNP and Sildenafil citrate effectively relaxed the precontracted strips in a dose-dependent manner (10-8-10-3 M). Maximal relaxation of strips to acetylcholine, SNP and sildenafil citrate were 50.11 %, 98.65%, and 68.32%, respectively.

Conclusion: Sildenafil citrate was effective in relaxing the precontracted cavernosal strips *in vitro* and in erecting feline penis after local administration *in vivo*. These results suggest that phosphodiesterase inhibitor has a potential to be developed into a new, safe and effective intracavernosal agent for the treatment of impotence patients.

OR 2-8

Tadalafil (IC351) provides prompt response and extended period of responsiveness for the treatment of men with erectile dysfunction

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Aim: The time to onset (TTO) and period of responsiveness to tadalafil (IC351; a potent and highly selective PDE5 inhibitor) in men with erectile dysfunction (ED) was assessed in two phase 2 studies.

Methods: In a double-blind, crossover, RigiScan™ study, 61 men received tadalafil 10 mg or placebo. Immediately postdosing, patients underwent RigiScan evaluations during visual sexual stimulation. Endpoints included TTO of response ($\geq 55\%$ penile rigidity for ≥ 3 consecutive minutes), percent responders, and cumulative time of rigidity $\geq 55\%$. In an at-home study, 223 men received tadalafil 10 or 20 mg or placebo with instructions to take study drug every 8-10 days (4 doses total) when ready to engage in sexual activity. No instructions restricting food or alcohol consumption were given. TTO (elapsed time from dosing to attainment of first erection resulting in successful intercourse) and multiple attempts within 24 hours were recorded in diaries.

Results: In the at-home study, response to tadalafil 20 mg was significantly greater than placebo as early as

16 minutes postdosing ($P=0.012$). The mean time for achievement of erection among responders was 17 minutes. Twenty-nine, 38, and 26 patients in the tadalafil 10-mg, 20-mg, and placebo groups, respectively, attempted intercourse ≥ 2 times within 24 hours of dosing. Among these patients, tadalafil 10 and 20 mg resulted in significantly more successful additional intercourse attempts versus placebo ($P=0.025$ and $P<0.001$, respectively). In the RigiScan study, tadalafil provided a trend within 30 minutes and a statistically significant response versus placebo at 45 minutes ($P = 0.034$) and 24 hours ($P < 0.001$). In both studies, tadalafil was well tolerated and there were no treatment-related serious adverse events.

Conclusion: In this research, tadalafil 20 mg enabled the onset of erection sufficient for completion of intercourse as early as 16 minutes postdosing. The period of responsiveness of tadalafil extended to at least 24 hours postdosing, enabling multiple successful intercourse attempts. (Funding provided by Lilly ICOS LLC)

OR 2-9

Male erectile dysfunction in patients with medications for benign prostatic hyperplasia

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To investigate the prevalence of erectile dysfunction (ED) among the patients treated with long term medication for benign prostatic hyperplasia (BPH), we reviewed the erectile function domain scores according to the BPH medications. We also investigated the responsiveness to sildenafil citrate according to the BPH medication,

From March 2000 to June 2001, 485 patients taking BPH medication longer than 6 months were enrolled for the analysis of International Index of Erectile Function (IIEF) and for the erectile function domain scores. The data were analyzed for the severity of ED and for the responsiveness to sildenafil citrate.

ED prevalence according to BPH medication was 43% with doxazosin (age 62 ± 15.5), 48% with terazosin (age 65 ± 13.8), 51% with tamsulosin (age 68 ± 19.1), 64% with doxazosin plus finasteride group, 72% with terazosin plus finasteride and 75% with tamsulosin plus finasteride. 178 patients with ED were treated with sildenafil citrate 50-100mg/day, and the responsiveness appeared to be not significantly different between different drug groups.

ED prevalence among the patients taking BPH medication is significantly higher in the group combined with finasteride. However the responsiveness to sildenafil citrate was not significantly different between the alpha-blocker groups or combined with finasteride groups.

OR2-10

Dhant or jaryan, a cultural sexual dysfunction incidence and treatment in conservative muslim living in prowestern social setup like Pakistan

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Dhant or Jaryan is the name given to a sexual dysfunction in which young male gets white semen drop before or after urination or on visual sexual stimulation, excessive erection and more night ejaculation. This sexual dysfunction is thought to be a serious sexual defect locally in Pakistan. This dysfunction results from the Islamic restrictions of pre-marriage sexual activity and sexual stimulation of younger in non-Islamic Culture that leads to guilty feeling and sexual neurosis. A total of 290

patients, aged 22-30 years, were treated at the Nasim Fertility Centre, Faisalabad, Pakistan during last year for sexual dysfunction. 27% complained of Dhant or Jaryan. 90% were unmarried. Diagnostic work up included detailed history and basic laboratory tests. 90% patients attributed the dysfunction to excessive masturbation and premarriage sexual activity. Effective psychotherapy and drugs achieved 100% success in treatment.

OR2-11

Female sexual dysfunction in conservative Muslim society like Pakistan

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Introduction: Pakistanis are conservative Muslims where sex education is not common. Marriage is arranged by parents. Females mostly do not disclose any sexual dysfunction and attend the doctor for psycho-somatic therapy.

Material and methods: 47 patients of female sexual dysfunction were treated at Nasim Fertility Center, Pirmahal, Faisalabad (Pakistan) from June 1996 to May 1998. 31% complained of vaginismus, 9% of very early

orgasm during sexual intercourse and 11% did not have experienced orgasm and had no idea about orgasm. Effective psychosexual counseling, anxiolytics and antidepressant were used in treating these patients.

Results: 1. All the female sexual dysfunctions are the result of inadequate sex education and low educational standard of population. 2. All the dysfunction was effectively treated with 100% cure.

OR 3-1

Comparison between vardenafil and sildenafil in facilitating pelvic nerve-mediated penile erection in the rabbit model

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Aim: Phosphodiesterase type 5 (PDE 5) is the predominant enzyme responsible for cGMP hydrolysis in trabecular smooth muscle. Activation of PDE type 5 terminates NO-induced and cGMP-mediated smooth muscle relaxation, resulting ultimately in restoration of basal smooth muscle contractility and penile flaccidity. Sildenafil citrate and vardenafil hydrochloride have been shown to be potent, reversible and selective PDE 5 inhibitors in penile smooth muscle cells with $K_i(s)$ of 14.7 nM and 4.5 nM, respectively. The differences in the inhibition constants suggested that sildenafil and vardenafil may have different efficacy in facilitating penile erection in response to sexual stimulation. The objective of this study was to compare the time of onset and efficacy of vardenafil and sildenafil in facilitating/enhancing penile erection in an anesthetized rabbit model.

Methods: Penile hemodynamics were assessed in male New Zealand White rabbits (3.5-4.0 kg) by intracavernosal pressure (ICP) monitoring before and after administration of varying doses of vardenafil or sildenafil. Drugs were administered intravenously or

intracavernosally. Penile erections were elicited by submaximal electrical stimulation (2.5 or 6 Hz) of the pelvic nerve. ICP recordings were normalized to mean systemic systolic arterial pressure.

Results: Intravenous administration of 1, 3, 10 or 30 mg/kg of vardenafil or sildenafil facilitated pelvic nerve mediated penile erection in the anesthetized rabbits. ICP increased in a dose dependent fashion with both agents and reached the peak response at about 5 min and lasted over 30 min at all doses tested. Intracavernosal injection of 10 mg/kg of vardenafil or sildenafil enhanced pelvic nerve mediated erection at 2.5 Hz. At all doses investigated, vardenafil was more effective than sildenafil in facilitating pelvic nerve mediated penile erection. Vardenafil had a significant effect on changes in systemic blood pressure when compared to sildenafil.

Conclusion: In this report, we demonstrate that vardenafil is more effective than sildenafil in potentiating penile erection at equivalent doses as indicated by the maximal increase in ICP over time.

OR 3-2

Vardenafil, a new highly selective PDE5 inhibitor, improves erectile function in patients with diabetes mellitus

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Vardenafil is being evaluated extensively as treatment for erectile dysfunction (ED). Patients with diabetes mellitus have a high prevalence of ED, but seem to be less responsive to available oral ED therapies. This randomized, double-blind, placebo-controlled trial was designed to determine the efficacy and tolerability of vardenafil in ED patients with diabetes mellitus.

Patients aged 18 years and older with Types 1 or 2 diabetes mellitus and erectile dysfunction >6 months were eligible. 452 patients were randomized to placebo, 10mg or 20mg of vardenafil, taken as needed, for 12 weeks. Patients were evaluated after a 4-week baseline period and at the end of 12 weeks. Primary efficacy variables were the erectile function domain of the International Index of Erectile Function (IIEF-EF) and the per-patient success rates both for penetration and maintaining erections to complete intercourse. Responder rates of improved erections were derived from the Global Assess-

ment Question (GAQ). We used ANCOVA for analyzing the primary variables and logistic regression for the GAQ responder rates.

The responder rate for improved erections at 12 weeks was 72% for the 20mg group, statistically greater than the 13% for placebo ($P<0.01$). Both vardenafil doses significantly improved IIEF-EF (for 20mg: 19.0 vs 12.6 for placebo, $P<0.01$), as well as the rates of successful penetration ($P<0.01$) and maintenance to intercourse completion ($P<0.01$) compared to placebo. The success rates were dose-related with 64% for penetration and 54% for maintenance to completion for the 20mg group (36% and 23% for placebo, respectively). Adverse events were generally mild or moderate.

In conclusion, vardenafil was well tolerated and highly effective in improving erectile function in the diabetic population.

OR3-3

Vardenafil, a new selective PDE5 inhibitor, significantly improved all IIEF-domains and showed a favorable safety profile over 12 weeks

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In a recent Phase II study in patients with erectile dysfunction (ED) vardenafil significantly improved erectile function. This report further evaluates the changes in efficacy and tolerability that occurred over time.

In a double blind at-home study 601 men with ED were randomized to on-demand oral doses of placebo, 5 mg, 10 mg, or 20 mg of vardenafil for 12 weeks. Efficacy was measured by the International Index of Erectile Function (IIEF) at 4, 8 and 12 weeks. Rates of adverse events (AE) were calculated for 4 week-intervals.

Erectile function mean baseline scores ranged from 13.8 to 14.2. By 4 weeks, placebo increased only to 15.9 while scores for 5mg, 10mg and 20mg increased to 20.3, 21.5, 23.2 ($P < 0.001$). This improvement was maintained for the 12-week period. While the maximum effect was already reached by 4 weeks at the 10-and 20-

mg dose levels, results for the 5-mg dose showed a trend to continue to improve from 4 to 12 weeks.

Throughout the study monthly rates for headache and dyspepsia were low (1% to 4% and 1% to 3% for 5- and 10-mg vardenafil respectively). For the 20-mg dose, initial headache and dyspepsia rates were 11.5% and 5%, decreasing to 8% and 2% respectively. Rates for flushing were between 6% and 10% throughout the study. There were no drug-related serious AEs.

Vardenafil significantly improved all aspects of erectile dysfunction by 4 weeks. This benefit was maintained or even improved. AEs were either decreasing after 4 weeks or remained stable throughout. Vardenafil provides both an early and sustained benefit for patients with erectile dysfunction and is well-tolerated.

OR3-4

A double-blind, cross-over study for the evaluation of the efficacy of Korean red ginseng in patients with erectile dysfunction

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Aim: This study was performed to investigate the efficacy of Korean red ginseng (KRG) on erectile dysfunction (ED) using the international index of erectile function (IIEF), Rigiscan and penile duplex ultrasonography with audio-visual sexual stimulation.

Methods: After measuring the baselines of the hormonal levels, lipid profiles, IIEF, Rigiscan and duplex ultrasonography for each patient, a total of 45 patients with clinically diagnosed ED were enrolled in a randomized, double-blind, cross-over study (4 weeks, 2-week of washout, 4 weeks). KRG (900mg *t.i.d*) or placebo were randomly administered over the period and all the parameters were checked after the treatment of each regimen.

Results: The mean IIEF scores were higher significantly in KRG treatment than placebo (baseline: 28.0 vs. 16.7, KRG: 38.1 vs. 16.6, placebo: 30.9 vs. 15.7, $P < 0.01$).

The mean scores of erectile function, sexual desire and intercourse satisfaction domain in KRG treatment were significantly higher as compared with the placebo group. The scores of Q3 and Q4 (penetration and maintenance ability) were significantly higher in KRG treatment than in placebo (Q3: $P < 0.01$, Q4: $P < 0.01$). In response to global efficacy question, 60% of patients reported that KRG improved their erections ($P < 0.01$). Among other variables, the penile tip rigidity of Rigiscan showed significant improvement in KRG treatment compared with that of placebo.

Conclusion: KRG is effective for the treatment of ED. The effect was proven subjectively and objectively by the global efficacy question, IIEF scores and Rigiscan study of the penile tip rigidity.

Keywords: Korean red ginseng; erectile dysfunction, IIEF; rigiscan

OR3-5

The effect of medical or surgical castration on erectile function and sex organs, and the efficacy of vardenafil in castrated rabbit model

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Aim: This study was designed to delineate the effect of medical or surgical castration on the erectile function, and to clarify whether vardenafil, a new PDE5 inhibitor, has a beneficial effect on the castrated model.

Methods: In the New Zealand male white rabbits (3.5–4.0 kg), surgical castration was done by bilateral orchiectomy via scrotal skin incision under ketamin/xylazine intramuscular anesthesia and medical castration by intramuscular injection of LHRH analogue (Lupron depot, TM) 0.375mg/kg (per 4 weeks). The animals were divided into 5 groups [control, Ox (bilateral orchiectomy), LHRH 2W, LHRH 4W and LHRH 8W]. Penile hemodynamics were assessed by intracavernosal pressure (ICP) monitoring after penile erection induced by pelvic nerve stimulation (PNS: 2-32 Hz) before and after intravenous administration of vardenafil (10 mg/kg). ICP recordings were normalized to systemic systolic arterial pre-ssure.

Results: The mean weights of penis (mg) of the 5 groups (control, Ox, LHRH 2W, LHRH 4W and LHRH 8W) were 2.99±0.14, 1.85±0.36, 2.31±0.19, 2.07±0.28

and 2.56± 0.26, respectively, the mean weights of prostate (mg) were 0.95± 0.08, 0.37± 0.11, 0.51± 0.06, 0.57 ±0.11 and 0.63± 0.18, respectively, the mean weights of seminal vesicles (mg) were 1.99± 0.23, 0.56±0.15, 0.92 ± 0.20, 0.93± 0.33 and 2.00± 0.58, respectively, and the mean weights of testis (mg) were 3.33 ±0.62, 1.94 ± 0.38, 2.24 ±0.49 and 3.14 ±0.45, respectively. PNS (2.5-32Hz) caused significant frequency-dependent increases of ICP/SAP in all the control and the castrated groups. The ICP/SAP to maximal PNS (32Hz) were 0.92 ± 0.03, 0.62 ± 0.09, 0.69 ± 0.09, 0.72±0.18 and 0.52± 0.11, respectively, but after intravenous administration of vardenafil (10 mg/kg), they were 1.02±0.11, 0.59±0.20, 0.70±0.12, 0.66±0.09 and 0.60±0.12, respectively.

Conclusion: The erectile function and the weights of sexual organs decreased significantly after medical or surgical castration compared to the controls. Vardenafil had limited beneficial effects on erectile function in the medically or surgically castrated model.

OR3-6

Efficacy and safety of uprima (apomorphine SL) in patients with documented co-morbidity of hypertension, coronary artery disease (CAD) and diabetes

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Introduction and Aim: Patients with hyper-tension, CAD and diabetes are more likely to develop erectile dysfunction (ED) than the general male population. The objective of this analysis is to evaluate the efficacy and safety of Uprima in patients with documented evidence of these co-morbidities.

Materials and methods: A subgroup meta-analysis of four multicenter, double blind, randomized, placebo-controlled, 2-period crossover studies, was performed to assess the efficacy and safety of Uprima in patients with hypertension, CAD, and diabetes. Of the 704 patients in the four crossover studies who had at least one dose of 2 or 3 mg Uprima, 42% of patients had one or more of the three co-morbidities. Thirty three (33%) had hypertension, 13% had CAD and 11% had diabetes. The percentage of attempts resulting in intercourse was analyzed, for Uprima 2, 3 and 2-3 mg combined, in the co-morbidity subgroup of patients.

Results: In the co-morbidity subgroup, Uprima resulted in significantly greater percentage of erections firm enough for intercourse than did placebo ($P<0.001$). The percentage of all attempts resulting in an erection firm

enough for intercourse was 43.3% for patients taking 2 mg vs. 31.3% for placebo ($n=151$, $P<0.001$) and 25.8% at baseline; and 43.4% for patients taking 3 mg vs. 32.1% for placebo ($n=84$, $P=0.001$) and 20% at baseline. Uprima 3 mg produced a 2.2 fold improvement from baseline compared to a 1.7 fold improvement recorded with 2mg. For 2 and 3 mg combined, 43.4% of administrations resulted in erections firm enough for intercourse vs. 31.9% for placebo ($n=235$, $P<0.001$) and 23.7% at baseline. Overall only 17.1% of patients reported adverse events at the 2 and 3 mg doses. The following adverse events occurred in >2% of patients for all three subgroups combined compared to patients without organic disease: yawning, 5.4% vs 3.0%; dizziness, 3.3% vs 3.7%; headache 2.7% vs 2.7%; and nausea 2.3% vs 3.7%.

Conclusion: Uprima significantly improves the erectile function of patients with hypertension, CAD or diabetes who have ED, with a safety profile that is similar to that observed in patients without co-existing organic disease.

OR3-7

Long-term efficacy of Uprima (apomorphine SL) in men with erectile dysfunction (ED)

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Introduction and aim: The efficacy of Uprima, for the treatment of men with ED, has been established in clinical trials over 4 to 8 week periods. The maintenance of the effect over time is important to patients who will be taking Uprima on a long-term basis. This analysis assesses the long-term efficacy in patients who elected to continue taking Uprima 2 mg up to 18 months.

Materials and methods: A meta-analysis of the long-term phase III clinical studies was performed to assess the efficacy of Uprima 2 mg in patients who had completed the short-term, placebo-controlled, phase II/III studies and elected to continue into long-term, open label, phase III studies. Efficacy was measured as the percentage of attempts resulting in an erection firm enough for intercourse with Uprima, according to patient and partner diary assessments.

Results: Eighty-two percent of all eligible patients in Uprima phase II/III studies (2, 4, 5, and 6 mg) elected to continue into four long-term, open label studies. In patients who opted to stay on Uprima 2 mg for at least 6 months ($n=55$), 92% (2320/2534) of all attempts over

this period of time resulted in an erection firm enough for intercourse. Continued success was observed in patients who stayed on Uprima 2 mg for 12 months ($n=22$) and 18 months ($n=16$). During the 12th and 18th month, 97% (164/170) and 91% (95/104) of all attempts resulted in an erection firm enough for intercourse, respectively. In the entire study, the overall percentage of attempts resulting in an erection firm enough for intercourse, for all patients who had taken Uprima 2 mg for at least six months, was 92%. The average percentage of attempts resulting in an erection firm enough for intercourse according to partner responses was 96%, which is consistent with patient responses.

Conclusion: The results of this analysis indicate that in those patients with erectile dysfunction who are successfully treated with Uprima 2 mg and continue therapy, a consistent response with a high rate (92%) of erections suitable for intercourse can be expected with long-term use. There is no apparent development of tolerance to the efficacy of Uprima with long-term use.

OR3-8

Safety and efficacy of Uprima (apomorphine SL) 2 and 3 mg for erectile dysfunction (ED) in hypertensive men concurrently taking anti-hypertensive medication

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Introduction and aim: The efficacy, tolerability and safety of Uprima (2 and 3 mg) have been established in men with ED for which hypertension and its treatment are well-recognized risk factors. This analysis examines the effect of Uprima in the important subgroup of hypertensive men concurrently taking antihypertensive medication.

Materials and methods: A subgroup meta-analysis of four multicenter, double blind, randomized, placebo-controlled, 2-period crossover studies, was performed to assess the efficacy of Uprima 2 and 3 mg in patients with hypertension concurrently taking antihypertensive medication. A further meta-analysis of all phase II/III Uprima clinical studies was performed to assess the safety and tolerability of the 2 and 3 mg doses of Uprima in this subgroup of patients.

Results: In the placebo-controlled crossover studies, 33% of patients (234/704) were men with hypertension treated with antihypertensive agents. The percentage of attempts resulting in an erection firm enough for inter-

course in hypertensive men was 44.3 % compared to 33.1 % for placebo ($P = 0.001$) and 26.0 % at baseline for Uprima 2 mg; and 44.4% compared to 31.2% for placebo ($P=0.001$) and 19.8% at baseline for Uprima 3 mg respectively. Of 2919 men who received at least one dose of 2 or 3 mg in all phase II/III clinical studies, 1028 were enrolled with hypertension treated with one or more antihypertensive agents. The incidence of treatment-related adverse events in these patients concurrently taking antihypertensives was 12.9%, which was similar to the 15.7% incidence observed in the study population as a whole. Nausea occurred in 2.3% vs. 4.0%, headache in 1.8% vs. 2.9%, dizziness in 2.0% vs. 3.1% and yawning in 2.6% vs. 2.0% of the hypertensive patient subgroup compared to non-hypertensive patients respectively.

Conclusion: Uprima 2 and 3mg is an effective, safe and well-tolerated treatment for erectile dysfunction in hypertensive men concurrently receiving antihypertensive medication.

OR4-1

Erection related venous distribution in human penis

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Aim: The venous system of human penis has been widely studied. Unfortunately its description is not exactly true. We report a revolutionary finding of penile veins based on 9 cadavers and 41 postoperative patients.

Methods: Forty-one returning patients who underwent venous stripping surgery and complained nonresponsiveness 3 months to 5 years postoperatively received cavernosography again. Of them 5 patients received spongiosography and 3 cases underwent intra-operative cavernosography. Nine male cadavers were carefully dissected and examined.

Results: Deep dorsal vein served as a common channel for corpora cavernosa and corpus spongiosum. A prominent cavernosal vein with emissary ones was noted in all the 41 returning patients without exception.

Of them 21 cases were found to have two cavernosal systems which we would referred to as residual ones. In 7 cadavers, a cavernosal vein was found coursing along each corpus cavernosum distal to the glans, while the reported description was that it was a short segment (the cavernous vein) at the penile hilum. All cadavers were found to have 2 sets of para-arterial veins, which sandwiched the dorsal artery. Six cadavers were found to have independent cavernosal drainage directed to the Santorini's plexus.

Conclusion: A long and independent cavernosal vein was found in at least 66.7% of human penis. An independent para-arterial vein was noted in 55.6% of cadavers. These findings may be the explanation to those patients who do not respond to venous operation.

OR4-3

Feasibility of CT angiography in the diagnosis of arteriogenic erectile dysfunction

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Introduction: Multi slice CT is a newly developed minimally invasive method of imaging. The purpose of this study is to compare CT angiography (CTA) obtained by multi slice CT with the current standard of arterial imaging, digital subtraction angiography (DSA), in the diagnosis of arteriogenic erectile dysfunction.

Methods: Twenty-one patients with suspected arteriogenic erectile dysfunction (ED) underwent DSA and CTA after providing informed consent. CTA was performed with AsteionTR (TOSHIBA Medical, JAPAN). We injected prostaglandin E1 into the penile cavernous body and then rapidly infused nonionic contrast medium into the antecubital vein. CTA was performed on an out-patient basis, but DSA required hospitalization.

Results: In the 42 internal pudendal arteries, DSA represented 28 normal arteries and 14 impaired arteries.

On the other hand, CTA showed 21 normal arteries and 21 occlusions. The CTA image had a good correlation with the diagnosis of stenosis or occlusion in internal pudendal arteries with a sensitivity of 93%, specificity of 71% and accuracy of 79%. In the cavernous arteries, the CTA image had a good agreement with the diagnosis of stenosis or occlusion in cavernous arteries with a sensitivity of 96%, specificity of 43% and accuracy of 79%.

Conclusion: CTA images correlate with DSA images. At present DSA is superior to CTA in the visualization of stenosis in fine arteries. However, CTA is less invasive and relatively inexpensive and in the future will probably show even greater improvement in graphic quality. We believe that CTA would be an adequate replacement for DSA in the evaluation of internal pudendal arterial stenosis.

OR 4-4

Effects of apomorphine and amantadine on the behavior of pigeons

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It has been reported that both apomorphine and amantadine are centrally effective on male sexual dysfunction, putatively via dopaminergic receptor stimulating and dopamine releasing actions, respectively. In their clinical applications, it is noticed that both drugs have adverse effects of nausea and emesis. This study was aimed at comparing their behavioral effects in pigeons.

We observed the behavior of conscious pigeons with a video-monitoring system. Apomorphine and amantadine were intravenously and the other drugs were intramuscularly injected.

Apomorphine (1 mg/kg) induced pecking response without emesis in all pigeons tested and chlorpromazine (3 mg/kg) completely abolished the pecking response. Amantadine (3, 10 and 30 mg/kg) induced emesis without pecking in 0%, 10% and 100% of the pigeons, respectively. Amantadine (30 mg/kg)-induced emesis was attenuated by reserpine and chlorpromazine. However, it was not affected by haloperidol, methysergide,

granisetron, disulfiram or bilateral vagotomy. Intracerebral injection of amantadine (0.15, 0.3, 1.5 and 3 mg/kg) induced emesis in 10%, 20%, 60% and 70% of the pigeons, respectively, and the emetic response to amantadine (3 mg/kg) was suppressed by reserpine and propranolol, but not by chlorpromazine. Plasma levels of noradrenaline and adrenaline were decreased and dopamine and 5-hydroxyindoleacetic acid levels were increased after amantadine (30 mg/kg). These results demonstrate that amantadine-induced emesis is partially associated with the release of catecholamines and serotonin.

In conclusion, dopamine receptor stimulation causes not only pecking but also emesis. The mechanisms of distinctively different behavior of pecking and emesis putatively based on dopamine receptor stimulation remain to be elucidated. It is suggested that pigeons may be used for animal models of screening test of sexual dysfunction-improving agents as well as emetic and/or antiemetic agents.

OR 4-5

Clinical investigation of ejaculatory dysfunction

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Among male sexual dysfunctions, the treatment of ED became considerably easy after the development of Sildenafil, but for ejaculatory dysfunction, common next to ED, there are still many cases with difficulty in treatment. We examined 277 patients with ejaculatory dysfunction in the past 16 years. The patients were 17 to 90 (mean 34) years old, and 220 patients (79%) had no children. The underlying diseases included spinal cord injury in 99 patients, psychiatric disease in 20, diabetes mellitus in 19 and after surgical operation such as retroperitoneal lymph node excision in 12. 99 patients were with no particular underlying disease. There were 20 patients with natural and 172 patients with secondary disability of both masturbation-induced and intravaginal

ejaculation, 49 patients with disability of intravaginal ejaculation only, 24 patients with premature ejaculation, 3 patients with ejaculation retardation, 2 patients with insufficient force of ejaculation, 3 patients with headache at ejaculation and 4 patients with insufficient orgasm. Disabled ejaculation is a critical cause of male infertility. Thirty-three patients underwent subarachnoidal injection of neostigmine, 89, electro ejaculation, 62, treated with vibrator and 38 underwent the training of ejaculation. Using the semen obtained by these methods, AIH was conducted in 29 patients, among whom 6 had their children. In the patients undergoing unsuccessful AIH, the partner of 1 patient undergoing electro ejaculation is pregnant after ICSI using frozen sperm.

OR4-6

Low dose of bisphenol A affects the erectile tissues and erectile responses

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Aim: Previously, we reported the changes of erectile tissues by intraperitoneal administration of BPA at a toxic dose (cumulative dose of 900mg) in the rabbit. We performed this study to investigate the changes of erectile tissues by intracavernosal administration of BPA at low doses.

Materials and methods: New Zealand white rabbits were treated intracavernosally with 1 mg, 1 μ g, 1 ng and 1pg of BPA. Four weeks after treatment, the contraction and relaxation of precontracted cavernosal smooth muscle strips were studied after the administration of norepinephrine, acetylcholine, sodium nitropruside (SNP) and L-arginine. Histological changes were studied and tunical thickness was measured at the proximal, middle, and distal ends of the penis. The ratio of trabecular smooth muscle content to connective tissue

was measured histomorphometrically.

Results: Four weeks after administration of BPA, the contraction and relaxation of cavernosal tissue strips were significantly suppressed in BPA-treated animals at a dose dependent manner compared with the controls. Histologically, thickening of the tunica albuginea with increased collagen fibers and subtunica fat, and decreased sinusoidal space with consequent increase in trabecular smooth muscle content were noted. Histological changes by BPA were more prominent in animals receiving high doses of BPA compared to those receiving low doses.

Conclusion: Xenoestrogen BPA at low doses may affect the erectile function through evident histological changes of the penis. Further studies to clarify the details of BPA effects on human erectile tissues and its mechanism of action are necessary.

OR4-7

Butea Superba (red Kwao kreu): basic investigation and clinical trial on thai men with sexual dysfunction

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Butea Superba has been known in Thai traditional medicine for the treatment of impotence, but no basic research and clinical trial are so far available. This is a preliminary report on the basic investigation and clinical trial of this drug. Butea Superba was shown to contain key chemicals as flavonoid and flavonoid glycoside with a potent cAMP phosphodiesterase inhibitory action. Subchronic toxicity test in mice and rats exhibited no

significant toxic effects in the physiology, blood chemistry and histology of the vital organs including liver, kidney and testis. A double blind clinical trial in a group of 47 Thai men with DM, hypertension, and heart diseases, aged 20-65 years, for a period of 3 months was carried out. Hormonal level, renal and liver function and ECG were monitored. Overall results of 87 % improvement were obtained.

OR4-8

The reasons why patients with erectile dysfunction hesitate to seek medical help

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Aim: To investigate the reasons why patients with erectile dysfunction (ED) hesitate to seek medical help.

Materials and methods: Patients with the chief complaint of ED visited our OPD were requested to fill out a questionnaire regarding reasons why they hesitate to seek treatment. This questionnaire included personal factors, influence of sexual partner, medical factors and other factors. Patients were also asked to answer further questions about the treatments they had received and what they would receive later.

Results: A total of 71 patients with ED was enrolled in this study. The mean age was 69.9 years (range 36 to 91). In the first domain, the personal factor, 24 patients (33.8%) thought that the treatment may be useless and embarrassment was felt in 22 patients (31.0%). In the second domain, sexual partners of 19 patients (26.8%)

thought that the treatment may be useless. In the third domain, the medical factor, 27 patients (38.0%) did not know what department they should seek help, and 17 patients (23.9%) could not find the proper doctor for help. In the fourth domain, the other factors, only 11 patients (15.5%) hesitated for treatment due to economic cause. Nine patients (12.7%) even visited herbal doctors for help and only 12 patients (16.9%) visited the urologists. After visiting our OPD, 39 patients (54.9%) will visit an urologist for further treatment but 9 patients (12.7%) will visit an herbal doctor for help.

Conclusion: About one third of the patients still felt embarrassed for seeking treatment for impotence. Another one third did not know the right department that they should seek. We should do more for the public education rather than treating patients in the hospital only.

OR4-9

Incidence and treatment of impotence in sexual dysfunction patients in conservative Muslim living in prowestern social setup like Pakistan

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Aim: To find out the incidence of impotence in sexual dysfunction patients and the treatment most suitable in conservative Muslim society like Pakistan.

Material and methods: 195 patients of sexual dysfunction were treated at the Nasim Fertility Center, Faisalabad & Lahore, Pakistan from 01/10/1999 – 20/04/2000. Diagnostic work up included detailed history, blood and urine complete examination, blood sugar, and I/C tests to differentiate psychogenic from organic impotence. 33% of patients complained of impotence and 52% of early ejaculation. Among impotence, 58% had psychogenic and 48% organic impotence. Age of psychogenic impotence patients ranged from 25-35 years and those of organic impotence from 30-60 years. High incidence of psychogenic impotence is due to sexual

neurosis developed as a result of sexual stimulation in prowestern social setup, where religious prohibition of sex and Islamic norms on sexual behavior are not observed. Any sexual activity, even masturbation led to guilty feeling and sexual neurosis. Effective psychotherapy and drugs used in different combinations achieved 100% success in psychogenic patients. In organic impotence, spontaneous erection is restored in 40% of patients, while 20% left the treatment and others were advised I/C injection or vacuum therapy.

Conclusion: High incidence of psychogenic impotence among impotent patients is the effect of interaction of two opposite social setups. 58% psychogenic and 40% organic impotence patients were cured by psychotherapy and drugs used in different combinations.

OR5-1

Time to erection with Uprima (apomorphine SL) 2 and 3 mg in men with erectile dysfunction (ED)

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Introduction and aim: Oral pharmacotherapy has become the appropriate first-line therapy for most men with ED. Oral treatments are however associated with a delay in onset of erections that limits spontaneous sexual activity. Uprima is a novel therapy for ED that has been proven to be a safe, well-tolerated and efficacious treatment option that employs a unique sublingual method of delivery.

Materials and methods: A meta-analysis of four multicenter, double blind, randomized, placebo-controlled, 2-period crossover studies of Uprima was performed to assess the time to onset of an erection in 554 men, mean age 55 (to 9.2) years who received the recommended doses of Uprima (2 and 3 mg). Patients in these studies were asked to record the time to erection when an erection occurred after administration of the study drug.

Results: Uprima 2 and 3 mg resulted in a total of 2511 erections compared to 1849 with placebo. The median time to erection with Uprima 2 mg was 17.5 minutes (95% CI = 15.6 – 19.0) and 18.8 minutes (95% CI

= 16.4 – 21.1) with Uprima 3 mg compared to 16.7 (95% CI = 15.0 – 18.0) and 20.0 (95% CI = 17.1 – 21.7) minutes for placebo respectively. This implies that the onset of erections achieved with Uprima in men with ED is similar to the natural normal erectile response. Combined analysis of the time to erection with Uprima 2 and 3 mg shows that 33.8% of erections were achieved within 10 minutes and 71.1% within 20 minutes of administration of Uprima. Erections occurred for up to 2 hours after administration. There were no significant differences in the time to erection with Uprima 2 and 3 mg when analyzed by age group. The percentage of erections occurring within 20 minutes of receiving Uprima was 75.3%, 69.9%, 72.4% and 61.6% for the age groups <45, 46-55, 56-65 and >65 years respectively.

Conclusion: Uprima 2 and 3 mg resulted in a rapid onset of erection that is not affected by age, which may allow for more spontaneous sexual activity for the patient seeking treatment for erectile dysfunction.

OR5-2

Reduced incidence of nausea with continued use of apomorphine SL in men with erectile dysfunction (ED)

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Introduction and aim: The efficacy, tolerability and safety of Uprima (2 and 3 mg) have been established in men with ED. The most frequently reported adverse event with the use of Uprima is nausea. The objective of this analysis was to determine if the incidence of nausea decreases with continued use.

Materials and methods: A meta-analysis of four multicenter, double blind, randomized, placebo-controlled, 2-period crossover studies, was performed to assess the incidence of nausea per dose with Uprima 2 and 3 mg in patients who received at least 8 doses.

Results: In the placebo-controlled crossover studies, nausea occurred in 2.1% and 5.8 % of patients with the 2 and 3 mg doses, respectively, in patients who had at least one reported incidence of nausea. For patients who had at least 8 doses, the incidence of nausea by dose was more common with the first dose and decreased

with subsequent doses. In patients receiving Uprima 2 mg ($n=360$), the incidence of nausea decreased from 1.39 % with the first dose to 0 % with the eighth dose. Similarly, in patients receiving Uprima 3 mg ($n=218$), the incidence of nausea was 2.75 % with the first dose and decreased to 0.46 % with the eighth dose. In the same group of patients, no incidence of nausea was reported after the eighth dose. Discontinuation due to nausea occurred in 0.2% and 1.5% of patients for the 2 and 3 mg doses, respectively, and in 0.7% of patients for the 2 and 3 mg doses combined.

Conclusion: The incidence of nausea related to Uprima 2 and 3 mg decreases with continued use, indicating that a tolerance to this effect develops with repeated doses. Nausea was generally dose related, transient and mostly mild in severity for the recommended doses.

	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	Dose 8
2 mg	1.39%	0.56%	0.28%	0.28%	0.56%	0%	0.28%	0%
3 mg	2.75%	0%	0.92%	0%	0.92%	0%	0%	0.46%
2&3mg	1.90%	0.35%	0.52%	0.17%	0.69%	0%	0.17%	0.17%

OR5-3

Efficacy and safety of sublingual apomorphine for male erectile dysfunction: a multicenter, double-blind, placebo-controlled, crossover, flexible-dose study

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Aim: To investigate the efficacy and safety of sublingual apomorphine for male patients with erectile dysfunction (ED).

Methods: A total of 71 male patients (mean age: 63.8 years) with ED were randomized to either group 1 (period I: apomorphine, II: placebo) or group 2 (period I: placebo, II: apomorphine). The durations of run-in, period I and period II were 4-week, 6-week and 6-week, respectively. In each period I or II, sublingual apomorphine 2 mg was administered for initial 2 weeks, and escalated to 4 mg or maintained on 2 mg adjusted by the efficacy and safety for the remaining 4 weeks. The primary endpoint of efficacy was percentage of achieving and maintaining sufficient erection. The secondary endpoints were international index of erectile function (IIEF), number of patients with successful intercourse and glo-

bal efficacy assessment. The adverse events (AE) were also evaluated.

Results: There was a statistically significant increase of patients achieving (45%) and maintaining (38%) erection after apomorphine (vs. placebo, 34% and 23%, respectively). In the apomorphine group, an increase of score in each of the 5-domains of IIEF was noted and the orgasmic function even improved significantly. The side effect was mild and tolerable. The most common AE were nausea (apomorphine 19%, placebo 7%) and dizziness (apomorphine 13%, placebo 12%). No treatment-related serious AE was noted.

Conclusion: Sublingual administration of apomorphine 2 mg and 4 mg provides an effective treatment with mild side effect for male patients with erectile dysfunction.

OR5-4

DA-8159, a new PDE5 inhibitor, does not influence fertility function in male rats

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The effect of DA-8159, a new phosphodiesterase-5 inhibitor, on reproductive system and fertility function was investigated in rats. DA-8159 (0, 17.5, or 70 mg/kg) was gavaged to albino rats daily for more than 4 weeks before mating. After confirmation of the mating by vaginal smear, pathological changes of reproductive organs and the number, motility and viability of epididymal sperm were examined. The time spent before mating, copulation index, insemination index and fertility rate were not changed by DA-8159 compared to the controls. DA-

8159 did not induce any abnormality in the number, morphology, viability and motility of sperm. The serum testosterone level was also unchanged by repeated administration of DA-8159. In addition, reproductive indices including implantation, number of corpus luteum and fetal mortality were not affected by DA-8159. These results clearly demonstrate that DA-8159, a new erectile dysfunction treatment, does not influence reproductive system and fertility.

OR5-5

Pharmacokinetics and metabolism of DA-8159, a new phosphodiesterase-5 inhibitor

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DA-8159 is a new phosphodiesterase 5 inhibitor, which is being developed for the treatment of male erectile dysfunction as an oral dosage form. The objective of this study was to investigate the absorption, distribution, metabolism and excretion of DA-8159 using HPLC. The metabolic pathways and various factors influencing the protein binding of DA-8159 were also evaluated. The extents of absolute oral bioavailability of DA-8159 and sildenafil in rats were 25% and 12%, respectively. The apparent volume of distribution at steady state was considerably large, 15048 ml/kg, suggesting that DA-8159 has a good affinity to tissues. This was proved by the following results that the tissue to plasma ratio (T/P) of

DA-8159 at 30 min, 2 h, and 6 h were greater-than-unity at each time in all tissues. The three metabolites of DA-8159 in human liver microsomes were identified by LC-MS/MS analysis: N-demethylation, N-hydrolysis and hydroxylation. CYP3A4 was primarily responsible for the formation of the three metabolites. 5.98% of intravenous dose of DA-8159 were excreted unchanged in 24-h urine. The protein binding of DA-8159 and sildenafil to human plasma was 93.95 and 95.1%, respectively. Based on the oral bioavailability data, the absorption of DA-8159 to the general circulation was approximately 2 times higher than that of sildenafil.

OR5-6

The oral efficacy of DA-8159, a new PDE5 inhibitor, for inducing penile erection in conscious rabbits

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Introduction: DA-8159 is a pyrazolopyrimidinone derivative showing potent and selective phosphodiesterase 5 inhibition. In the previous study, DA-8159 induced a dose-dependent increase in intracavernous pressure (ICP) in the anesthetized dog. The aim of this study was to investigate the oral efficacy of DA-8159 in a conscious rabbit model.

Methods: DA-8159 and sildenafil citrate (0.3 to 10 mg/kg) was given orally to awake male rabbits in the absence or presence of intravenous sodium nitroprusside, a nitric oxide donor. Erection was evaluated in a time-course manner by measuring the length of the uncovered penile mucosa.

Results: Both DA-8159 and sildenafil citrate induced a dose-dependent erection in conscious rabbits. The effective dose level and the duration of DA-8159 induced erection were comparable to those of sildenafil citrate. However, the onset time of erectile activity was significantly faster in DA-8159 treated than in the sildenafil citrate-treated rabbits. The oral efficacy of both drugs was potentiated and the effective doses were significantly decreased by intravenous sodium nitroprusside. Potentiation of the effect by a nitric oxide donor implies that DA-8159 would have enhanced activity during sexual arousal. These results clearly demonstrate that DA-8159 may be useful for treatment of erectile dysfunction.

OR5-7

Testosterone level before and after sildenafil treatment

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Testosterone level in ED patient is thought to be low. Sildenafil improves the erectile function, so we evaluated the serum testosterone level before and after Sildenafil treatment. 12 men attending the ED clinic were examined. The mean patients age was 60.3 (range 32 to 75). The serum testosterone level and IIEF5 was measured in the patients before and after Sildenafil treatment. Blood was drawn between 9:00 and 12:00. The serum testosterone

level before and after Sildenafil treatment were 356 and 354 and for IIEF5 were 6.8 and 17.3. There was no significant differences in serum testosterone level and no correlation with IIEF5 and serum testosterone level. Our series is small and more reserch is needed to define the serum testosterone level reflecting the erectile function.

OR5-8

Management of pre-mature ejaculation in male in Singapore

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Introduction: Premature ejaculation is not uncommonly seen in urology clinic in Singapore. Due to health awareness, there is about a 5-6 fold increase in the number of patients who seek treatemnt for premature ejaculation. The objective of this paper is to review the management of premature ejaculation in patients with and without erectile dysfunction and to determine the outcome of treatment.

Material and method: The study involved patients seen in the erectile dysfunction clinic and comon urology clinic from Jan 2000 to Jan 2001 with the minimum follow up of 6 months or more. The patients with premature ejaculation are divided into 2 groups: those with and without erectile dysfunction. The premature ejaculation is treated with conselling, medication and relax-

ation methods and the outcome of each is compared between the 2 groups.

Results: There is a total of 102 patients with premature ejaculation and 47 in the ED group and 55 in the non-ED group. There may be an under estimation of patients with PE in the ED group. However, the patients in the non-ED group seems to have better response in terms of treatment compared to the ED group. This could be due to the fact that the ED group is older, more comorbid factors and less responsive to medication. Those without ED response well to the medication with Zolof or seroxat.

Conclusion: There may be more problems in patients with ED and PE is the issue which should not be ignored and proper managment of these patients should be undertaken so that the sexual satisfaction would not be discounted.

OR5-9

A new comprehensive alternative approach in treating premature ejaculation in conservative Muslim society like Pakistan

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Aim : To find out alternative treatments for premature ejaculation in conservative Muslim society like Pakistan.

Materials and methods: Premature ejaculation is the most common sexual dysfunction in conservative Muslim society living in prowestern social setup like Pakistan, where it is recognised as surat-i-anzal. 440 patients of early ejaculation, aged 25- 35 years, were treated at the Nasim fertility center Faisalabad Pakistan. Diagnostic work-up included detailed history and basic lab tests. The patients attributed the dysfunction to excessive masturbation (35%) and to excessive intercourse and sodomy plus masturbation (65%). All the sexual activities were thought great sin and immoral religiously and were performed in great hurry and worry. The causes of early ejaculation are considered to be sexual frustration (due to late marriage), sexual stimulation in prowestern social setup where Islamic norms on sexual behavior are not observed, extramarital sexual activity, masturbation performed in great haste and worry and

guilty feeling, which is due to Islamic prohibition of such activity. These lead to sexual neurosis and hasty ejaculation resulting in premature ejaculation. Behavioral sex therapy approaches were not accepted due to the association of depression and anxiety to varying extents. Treatment with charlatanism by the quacks is a serious problem to be dealt with. Quick response was desired and over half of the patients had married only a few days to a few weeks and there was the fear of divorce from their wives. After full assent from the patient at the first visit, my new comprehensive alternative approach by using medicines and different ejaculation controlling techniques were applied for 8 weeks. Medicines were then tapered off and patients were advised to maintain control on ejaculation by the techniques as advised. All the 440 patients were treated with excellent results.

Conclusion: The new alternative treatment is the most effective and rapid solution to premature ejaculation in the conservative Muslim society.

OR5-10

Chemical hormone vs phytohormone substitution for aging male

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Accompanying the progress of age inevitable aging processes will occur. In the past, aging has clustered to myth that aging is associated with a specific disease. However current studies open a new horizon, that aging should not be equated with the decline of health or/and the susceptible to suffering diseases. Aging are caused by multiple processes, combining and interacting at many levels; proteins, cells, tissues and organ systems are all involved. Although several hormones have been promoted as having the potentials to rejuvenate. It is unrealistic to expect that a single agent can prevent or postpone aging as has been claimed for “nutritional food” or “health food” that can be easily bought over the counter.

Andropause in general is equalized to the decrease of androgens in the aging male. Recently it has been known that the so many clinical signs of hypogonadism are in general only a partial androgen deficiency of the aging male (PADAM). Testosterone compounds for hormonal substitution have been therefore promoted and revealed to have their benefits but also their drawbacks. Testosterone undecanoate (TU) seems to be preferred and most recommended oral testosterone, because it is non-hepatotoxic, and is esterifiable. Aromatization of testosterone to estrogen may play a vital role for the maintenance of bone mass and psychological sexual drive. However, androgen only cannot substitute and cover all health problems when men aged. Aging is a result of a multi factorial decrease of diverse hormone production and numerous physiological and biological processes. Sleep decrements in aging male cannot be substituted with androgen only. The decline of GH and GnRH may probably be responsible for some of the clinical signs also. Cardiovascular diseases and occurrence of osteoporosis appeared to be dependent to the decline of GH and GnRH. In analogy to menopause, therefore, the fall of GH is termed as *somatopause* and is incorrectly termed as *andropause*. Melatonin has been long a debate for playing a major role in insomnia when aging progresses. Hence

sleep decrements in the aging male would probably due to more bio-hormonal factors. The decline of IGF-I has been reported to be inversely related to the body mass index (BMI) and waist-hip ratio (WHR) in women. It also reflects the reduction of the lean body mass in aging men, parallel with the fall of the circulating IGF-I. Increasing age decreases the lean body mass and bone mineral density (BMD); parathyroid hormone (PTH) and osteoclast increase in both gender, however, BMI and WHR increase only in women. Interests should be the role of dehydroepiandrosterone (DHEA) in aging male. Substitution of DHEA in aging male has been reported to improve remarkably the physical strength as well as psychological performance and constant macho sex life. The augmentation of DHEAS of the old aged to young-aged serum levels have been shown to induce and increase bio-available IGF-I. Hence DHEA has ever been mentioned as “The Master Hormone” that may stimulate and balance other hormone production in man when life progresses. As for other chemical hormones, the route of administration and absorption of DHEA are other problems to be cautioned. Phytohormones, because of their minimal side effects, will therefore be preferred over chemical hormones. Protodioscin, an active component in *Tribulus terrestris L*, has been known to contain a pre-hormone compound that may be converted to DHEA. This phyto-prehormonal compound protodioscin has been proofed for its safety and efficacy use for treatment in aging male with sexual dysfunctions and other andropausal complains.

The terminology of andropause cannot clearly describe the complexity manifestation of all clinical aging phenomena. Andropause, viropause, testopause, penopause and ‘*male menopause*’ as well are just a limited description for sexual changes in the aging male. Therefore andropenia (Adamopoulos, 1998) was suggested to describe the over-all aging phenomena in the male.

OR6-1

Cavernous neurotomy causes hypoxia and fibrosis in rat corpus cavernosum

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Aim: The etiologies why the erectile function can not be preserved in some patients even with nerve-sparing technique are still not known. Most investigators believe that the erectile dysfunction (ED) post nerve-sparing radical prostatectomy can be caused from vascular, neurogenic, psychogenic or mixed etiologies. The aim of this study was to evaluate the effects of cavernous nerve injury to cavernous oxygenation and cavernous fibrosis, which may help to prevent the permanent damage of the cavernous tissues.

Methods: Twenty male Sprague-Dawley rats (300-325 gm.) constituted the study population. The animals were divided into 2 groups: group 1 consisted of sham-operated rats ($n=10$) and group 2, rats underwent incision of bilateral cavernous nerve ($n=10$). Three months later, intracavernous pressure response study was performed in the rats using intracavernous papaverine injection at 300 and 600 mg, respectively.

TGF- β_1 mRNA expression was studied from rat penile tissue using the RT-PCR method. Hypoxia-inducible factor-1 α (HIF-1 α), TGF- β_1 , Collagen I and Collagen III protein expression were determined by Western blot analysis and immunohistochemical staining. The rat pe-

nises were stained with Masson's trichome stain, which determines the relative proportion of collagen to stromal smooth muscle.

Results: Erectile function as studied by intracavernosal papaverine injection and histological observation of penile cross-sections at three months were similar in both groups. TGF- β_1 mRNA expression, and HIF-1 α , TGF- β_1 , Collagen I and III protein expression were significantly higher in the neurotomy group. Immunohistochemical staining for TGF- β_1 , HIF-1 α and Collagen III were more positive in the neurotomy group but the staining for Collagen I could not be subjectively differentiated.

Conclusion: The results of this study demonstrated an increase in TGF- β_1 , HIF-1 α and collagen synthesis in cavernous neurotomy rats, which were possibly caused from loss of nocturnal and normal erection. These results may explain why the recovery and response rate to therapies of post-radical prostatectomy ED patients is low. In theory, this fibrosis can possibly be down-regulated by PGE₁ or any other modalities, which could increase oxygenation to the corpus cavernosal tissue.

OR6-2

Involvement of estrogen in relaxation of rabbit cavernous smooth muscles

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Aim: Estrogen relaxes vascular smooth muscles via genomic and nongenomic mechanisms. It is well known that testosterone is involved in local and systemic reactions related with penile erection. However, the role of estrogens in penile erection has not been attended to so far, although hyperestrogenemia is known to cause erectile dysfunction. This study was aimed to determine whether the estrogen maybe involve in the relaxation response of cavernous smooth muscles and its action mechanism if yes.

Materials and methods: Relaxation responses of the rabbit ($n=5$ in each, 2.8 to 3.0 kg) cavernous smooth muscles to estrogen (10 ng/ml, 100 ng/ml, 1 µg/ml, and 10 µg/ml) were observed *in vitro*. The responses to estrogen of the strips after incubation with either actinomycin D (10 µM, transcription inhibitor) or L-NAME (10 µM, nonspecific NOS inhibitor) for 20 minutes were

also evaluated. Expression of estrogen receptor protein using an immunohistochemical staining method in the rabbit clitoral and cavernous smooth muscles was observed.

Results: Nuclear estrogen receptor was detected in the cavernous smooth muscles although the receptor number was 32% of that in the clitoral muscles. Estrogen caused a dose-dependent relaxation of the strips precontracted with norepinephrine. The onset of the response was about 10 min after treatment with estrogen. Estrogen-induced relaxation could not be prevented by actinomycin D or L-NAME, suggesting that the response was not mediated by gene transcription or NO.

Conclusion: Estrogen may be involved in relaxation of the rabbit cavernous smooth muscles via nongenomic mechanism.

OR6-3

Effect of saponin fraction from Korean red ginseng in intracavernosal pressure

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Introduction: Korean Red Ginseng is reported to have a potential to improve penile erection. It is also suggested that total the saponin (TS) of Red Ginseng has a dominant role over other extracts to directly relax cavernous smooth muscle. Present study was undertaken to investigate the principal extract from Korean Red Ginseng responsible for direct induction of penile erection in rats.

Materials and methods: We evaluated the intracavernosal pressure, latency to erection and tumescence time in Sprague-Dawley rats, following intra-cavernosal injection with 0.25, 0.5, 1, 2mg/0.1ml of the total saponin (TS), protopanaxadiol saponin (PD), protopanaxatriol saponin (PT), ginsenosides Rb1, Rb2, Rc, Rd, Re, Rg1 and Rg3.

Results: In the groups treated with TS, PD or PT, the intracavernosal pressure was increased in a dose-dependent manner ($P<0.01$) without any significant change in the systemic blood pressure. The order of potency to increase the intracavernosal pressure was $PT>$

$PD>TS$. In addition, the latency to erection was shortened and the tumescence time was prolonged within the saponin group in a dose-dependent manner ($P<0.05$). However, the erection induced by TS, PD or PT was only partial (increased intracavernosal pressure at the dosage of 2mg: 22.2 ± 9.8 , 24.0 ± 6.6 , 35.0 ± 1.4 cmH₂O, respectively) compared to that induced by electrical stimulation of cavernous nerve (increased intracavernosal pressure: 95.2 ± 20.4 cmH₂O). Both ginsenosides Rg1 and Rb1 also induced partial erection (increased intracavernosal pressure: 13.0 ± 6.2 cmH₂O with 2mg of Rg1 and 12.1 ± 4.0 cmH₂O with 1mg of Rb1). Other ginsenosides did not cause any significant change of intracavernosal pressure.

Conclusion: The major fractions of total saponin induce penile erection, although it is partial. The PT saponin is more potent to induce erection than the PD saponin. Ginsenosides Rg1 and Rb1 may account for direct action of those saponins on penile erection.

OR6-4

Effects of Icariin on cGMP formation and PDE5 isoenzyme activity

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Introduction: Penile erection is a hemodynamic procedure involving relaxation of corpus cavernosal smooth muscle and associated arteries and NO-cGMP signal pathway plays an important role in the regulation of penile erection. Icariin (C₃₃H₄₀O₁₅; W/M 676.67) is a flavonoids isolated from the natural drug, *Epimedium herba*, which is used for enhancing sexual activity traditionally and shown to have a dose-related relaxation effects on corpus cavernosal smooth muscle. We investigated the action mechanism of Icariin on penile erection by assessing its effect on the *in vitro* formation of cGMP in the corpus cavernosum of rabbit and determining its activity against PDE5 isozyme.

Materials and methods: Male New Zealand White rabbits (2.5kg) were killed and penises were rapidly excised and cut into segments and incubated with various concentrations of Icariin. The formation of cGMP was stimulated with sodium nitroprusside (SNP) and the ¹²⁵I

cGMP concentrations measured by radioimmunoassay. The PDE5 isozyme was isolated from human platelets and the effect of Icariin on PDE5 activities was evaluated by measuring the conversion of [³H]cGMP to their respective [³H]-5'-mononucleotides.

Results: Icariin significantly increased cGMP concentration in the corpus cavernosum of penis in a dose-dependent manner as measured by ¹²⁵I cGMP radioimmunoassay. The EC₅₀ of Icariin was 3.13 μM. The rates of cGMP hydrolysis catalyzed by human platelet-derived PDE5 were determined by across arrange of both the concentrations of cGMP and Icariin to characterize the mode of inhibition of PDE5 by Icariin which showed that Icariin significantly inhibited PDE5 activities in a dose-dependent manner, and the IC₅₀ was 0.43 μM.

Conclusion: Icariin enhances penile erection by inhibiting PDE5 activity, thus increasing the cGMP level in the corpus cavernosal smooth muscle.

OR6-5

Elicitation of penile erection after administration of NMDA into paraventricular nucleus of hypothalamus in the rat

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Aim: Our previous study has shown that administration of L-glutamate (excitatory amino acid, EAA) into paraventricular nucleus (PVN) of hypothalamus induces penile erection in the rat. N-methyl-D-aspartic acid (NMDA) is an ionotropic EAA. The aim of the present study is to investigate whether NMDA may activate the PVN and induce penile erection in the rat.

Methods: Male adult Sprague-Dawley rats anesthetized with pentobarbital were used. A 26-gauge needle was inserted into the corpus cavernosum to measure the intracavernous pressure (ICP). Four groups of study were conducted: 1) stereotaxically administration of NMDA (50 ng/500 nl) into PVN; 2) administration of a mixture (1 ml) containing NMDA antagonist - MK-801 (100 ng/500 nl) and NMDA (50 ng/500 nl) into PVN; 3)

saline 500 nl into PVN; and 4) intracavernous injection of NMDA (50 ng). The ICP was monitored after each administration of the chemicals.

Results: Upon administration of NMDA into PVN, there was a significant increase of ICP from the resting level of 8.7±1.8 mmHg to the peak at 60.7±9.1 mmHg. There was no change in the resting ICP after administration of the mixture of MK-801 and NMDA into PVN. Saline to PVN did not induce a change in ICP. Intracavernous NMDA failed to increase ICP. The site of stimulation was histologically verified to be at the PVN with frozen section of the rat brain.

Conclusion: The results of this study suggest that administration of NMDA may activate the PVN and induce penile erection in the rat.

OR6-6

Effects of four new selective prostanoid EP receptor agonists on isolated corpus cavernosum penis and vas deferens of rabbits

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The aim of this study was to investigate the effects of the new 4 agonists of prostanoid EP receptors (EP1: ONO-DI-004, EP2: ONO-AE1-259, EP3: ONO-AE-248, EP4: ONO-AE1-329) on the isolated corpus cavernosum penis (CCP) and vas deferens of rabbits in comparison with those of prostaglandin (PG) E1 and PGE2.

In CCP preparations precontracted with phenylephrine, all of the 6 agonists concentration-dependently relaxed the CCP and the relaxing efficacy of EP4 agonist was the strongest (potency order, EP4>EP2>PGE1=PGE2>EP1=EP2). At a high concentration (100 nM), EP1 agonist did not further relax but slightly contracted the CCP in 4 out of 5 preparations. Nitric oxide synthase inhibitor (*L*-NAME) did not affect the EP2- and EP4-induced relaxation. Adenylyl cyclase inhibitor (MDL

12330A) suppressed the EP4-induced but not EP2-induced relaxation. Both *L*-NAME and MDL12330A potentiated PGE1- and PGE2-induced relaxation. In vas deferens preparations, all 4 selective agonists did not affect the phenylephrine-induced contraction, but all the other 5 agonists, except EP2 agonist, partly suppressed the electrical field stimulation-induced contraction.

The above results indicate that relaxing prostanoid receptor subtypes in rabbit CCP may be EP4 and EP2 concerning Gs protein and that the EP receptors other than EP2 may partly participate in suppressing the release of contractile transmitters. The potentiative effects of *L*-NAME and MDL12330A on the PGE1- and PGE2-induced relaxation remain to be elucidated.

OR6-7

Oxytocinergic neurotransmission at hippocampus in central regulation of penile erection in the rat

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Aim: To investigate a possible oxytocinergic neurotransmission at hippocampus participated in central neural regulation of penile erection in the rat.

Methods: Male adult Sprague-Dawley rats anesthetized with pentobarbital were used. The intracavernous pressure (ICP), the systemic and mean arterial pressure (SAP and MAP) and the heart rate (HR) were measured simultaneously by inserting a 26-gauge needle into the corpus cavernosum. Four groups of study were conducted: 1) stereotaxical administration of oxytocin (3 pmol/100 nl) into the hippocampus; 2) microinjection of a mixture of the same amount (3 pmol/100 nl) of [d(CH₂)⁵-Tyr(Me)²-Orn⁸]-vasotocin and oxytocin into the hippocampus; 3) administration of saline into the hippocampus; 4) intracavernous application of oxytocin (3 pmol). The ICP, SAP, MAP and HR were monitored for

at least 2 hours after the administration of each experimental agent.

Results: There was a significant elevation of ICP from the resting level of 8.8 ± 1.7 mmHg to the peak at 49.6 ± 12.5 mmHg after microinjection of oxytocin into the hippocampus. But administration of both [d(CH₂)⁵-Tyr(Me)²-Orn⁸]-vasotocin and oxytocin into the hippocampus failed to induce a change of ICP. Furthermore, administration of saline to the hippocampus or intracavernous application of oxytocin were ineffective to induce an increase in ICP.

Conclusion: The results of this study suggest that oxytocinergic neurotransmission at the hippocampus may be participated in the central regulation of penile erection in the rat.

OR6-8

The effect of chemical androgen deprivation on apomorphine-induced penile erection through paraventricular nucleus of hypothalamus in rats

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Aim: To investigate the effect of chemical androgen deprivation on apomorphine-induced penile erection through the paraventricular nucleus (PVN) of hypothalamus in the rat.

Methods: Male Sprague-Dawley rats anesthetized with pentobarbital were used. Four groups of study were conducted: 1) stereotaxically delivery of apomorphine 0.1 nmol/100 nl into the PVN of adult rat; 2) leuprorelin (LHRH analogue) 62.5 µg/kg s.c to young rat (70 gm) every month for 3 times, then apomorphine into the PVN; 3) the same as group 2 study initially, followed by testosterone replacement with s.c tubing testosterone. Then apomorphine into the PVN 1 month later; 4) saline 100 nl into the PVN. A 26-gauge needle was inserted into the corpus cavernosum to measure the intracavernous pressure (ICP) during the experiment. The serum testosterone levels were determined.

Results: Upon the administration of apomorphine

into the PVN, there was a significant increase in ICP from the resting level of 12.7 ± 2.0 mmHg to the peak at 97.5 ± 2.1 mmHg. After leuprorelin injections, administration of apomorphine into the PVN failed to increase ICP. There was a significant increase in ICP, peaked at 45.2 ± 10.8 mmHg, after the initial leuprorelin injections and subsequent testosterone replacement. Saline to PVN was ineffective to induce an increase in ICP. The serum testosterone decreased after leuprorelin injections and recovered one month after testosterone replacement.

Conclusion: The present results suggest that chemical androgen deprivation with leuprorelin may eliminate the apomorphine-induced penile erection through the PVN in the rat. Testosterone replacement after androgen deprivation may recover, at least partially, the penile erection elicited by the administration of apomorphine into the PVN.

OR6-9

Expression of PDE5 and effects of icariin on cGMP formation in rabbit clitoris corpus cavernosum

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Introduction: Icariin (C33H40O15; W/M 676.67) is a flavonoids isolated from the natural drug, *Epimedium herba*, which was shown to have a dose-related relaxation effect on corpus cavernosal smooth muscle and an inhibiting effect on PDE5. We investigated the expression of PDE5 in the clitoris tissue and the effects of Icariin on the *in vitro* formation of cGMP in the clitoris corpus cavernosum of rabbit for the clarification of the effect of Icariin on female sexual function.

Materials and methods: Female New Zealand White rabbits (2.5 kg) were killed and the clitoris rapidly excised and cut into segments. One of the segments was used to extract RNA, followed by RT-PCR to detect the expression of PDE5, and others were incubated with various concentrations of Icariin or Sildenafil. The formation of cGMP was stimulated with sodium nitroprusside (SNP) and the ¹²⁵I cGMP concentrations measured

by radioimmunoassay.

Results: There was a lane around 800 bp on the agar electrophoresis, representing RT-PCRnM, which was as long as we expected according to the cDNA sequence of PDE5. Icariin and Sildenafil significantly increased the cGMP concentration in clitoris corpus cavernosum of female rabbits. EC₅₀ of Icariin and Sildenafil were 3.16 nM and 0.31 nM, respectively.

Conclusion: The result of agar electrophoresis showed the presentation of PDE5 in clitoris tissue. The mechanism of Sildenafil and Icariin on clitoris erection may involve the activation of the NO-cGMP signal pathway, which mediates the relaxation of corpus cavernosal smooth muscle, and Icariin may be also as a potential inhibitor of PDE5 increasing concentration of cGMP.

OR7-1

Laser oximetry: a novel non-invasive method to determine changes in penile hemodynamics in an anesthetized rabbit model

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Introduction: This study was designed to determine the validity and usefulness of laser oximetry in measuring changes in penile hemodynamics for assessment of erectile function.

Materials and methods: Anesthetized male New Zealand White rabbits (3.5–4.0 kg) were divided into two groups and penile hemodynamics were assessed by either laser oximetry (oxyhemoglobin, deoxyhemoglobin concentration and oxygen saturation) or intracavernosal pressure (ICP) monitoring before, during and after penile erection induced by pelvic nerve stimulation (PNS) or intracavernosal administration of phentolamine (0.05–1.0 mg/kg), nitroprusside (1–30 mg/kg), papaverine (0.1–1.0 mg/kg) or sildenafil (3–150 mg/kg). ICP recordings were normalized to systemic systolic arterial pressure.

Results: PNS caused significant frequency-dependent increases in penile ICP. PNS also caused significant increases in penile tissue oxyhemoglobin concentrations

and tissue oxygen saturation in a frequency-dependent manner. The changes in oxyhemoglobin concentrations and oxygen saturation correlated with frequency-dependent increases in ICP. The duration of recorded responses (changes in oxyhemoglobin concentration or ICP) increased with increasing frequency of nerve stimulation. Intracavernosal administration of phentolamine, nitroprusside, papaverine or sildenafil produced significant increases in ICP, tissue oxyhemoglobin concentration, oxygen saturation and duration of response as a function of increasing drug concentration.

Conclusion: Laser oximetry permits reproducible and valid assessment of changes in penile hemodynamics comparable to classical intracavernosal pressure measurements. Thus, we consider laser oximetry a reliable technique in evaluating penile hemodynamics. Its sensitivity in detecting small changes in oxyhemoglobin concentration and its non-invasive nature makes it advantageous over invasive methods such as intracavernosal pressure monitoring and laser Doppler flowmetry.

OR7-2

Three-dimensional structure of the internal pudendal artery and obturator artery using CT scanner

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Introduction: The internal pudendal artery (IPA) and the obturator artery (OA) supply blood to the penis. We evaluated the origin and course of these two arteries using 3-dimensional CT angiography (CTA).

Materials and methods: Thirty ED patients (mean age: 37 years) were study candidates. CTA was performed using Asteion TR (TOSHIBA Medical, Japan). We injected prostaglandin E1 (10 mg) into the cavernosum and then infused nonionic contrast medium (3 ml/sec) into the antecubital vein. Scanning was triggered by a predetermined Hounsfield unit of the external iliac artery.

Results: All internal pudendal arteries were visualized and classified into five types. Type 1: the IPA arose from the anterior division of the internal iliac artery (IIA) (12/30 bilateral, 12/30 unilateral, 36/60 hemipelvis). Type 2: the IPA arose from the anterior division of the IIA at

the ischial spine level (3/30 unilateral, 3/60 hemipelvis). Type 3: the superior gluteal artery, inferior gluteal artery and IPA arose separately from the IIA (1/30 bilateral, 7/30 unilateral, 9/60 hemipelvis). Type 4: the IPA arose from the proximal IIA prior to the bifurcation into the anterior and posterior divisions (2/30 bilateral, 7/30 unilateral, 11/60 hemipelvis). Type 5: the IPA was absent and the accessory pudendal artery was the major blood supply to the distal penile arteries (1/60 unilateral). The OA, visualized in 40/60, was classified into six types, the most common being from the anterior division of the IIA (11/40 hemipelvis).

Conclusion: CTA showed the complex three-dimensional structure of the internal pudendal artery and obturator artery. The variations of the IPA were classified into 5 types and the OA into six types.

OR7-3

Effect of endosulfan on sperm dynamics, plasma testosterone & testicular histology of albino rat

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Reproductive toxicity is a complex subject which besides birth defects, sexual dysfunction or sterility, includes adverse effects which may be less readily observed, but more relevant to chronic low level exposures. Ecologically pesticides have created life threatening health hazards to non-target species including man and animals. Endosulfan, (Thiodon 6,7,8,9,10,10-hexa chloro 1,5,5a,6,9,9a-hexahydro-6,9-methano-2,4,3- benzodioxathien pin-3 oxide) a broad spectrum organochlorine pesticide, is widely used in agriculture sector as a potent pesticide all over the world. The present work was therefore undertaken to evaluate the toxic effects of endosulfan on the mammalian reproduction.

Oral administration of endosulfan at 10 mg/kg/day

for two to four weeks caused a significant reduction in the weights of testes and accessory sex organs. The spermatozoal motility in cauda epididymides and spermatozoal density in cauda epididymides and testes were significantly decreased. The reduction in the plasma testosterone concentration were much pronounced at longer duration (30 days) of endosulfan exposure. Marked histologic changes were also observed in the seminiferous tubules of endosulfan treated rats. These degenerative changes include shrunken, disorganized and damaged seminiferous tubules with increased interstitial spaces and vacuolated Sertoli cells. Rupturing of basement membrane, spermatogenetic arrest and presence of cellular debris in the lumen of tubule were also common features.

OR7-4

Female sexual dysfunction and hysterectomy: results of mailed questionnaire

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A mailed questionnaire for female sexual dysfunction in 118 patients with hysterectomy, from January to December 2000 at this hospital was analyzed. The contents of the questionnaire were as follows; age, abdominal or vaginal approach, with or without male partner, key person for consulting sexual dysfunction and importance of sexual life. Also, comparisons were made before and after hysterectomy concerning sexual frequency, sexual desire, genital response, genital transformation, dyspareunia, genital pain and itching, and orgasms. Forty-eight of 118 (40.7%, mean age 57.8 years) patients returned the questionnaire. The mean age of 11 patients without male partner was 60.7 years old and they had no sexual intercourse, very low sexual desire and did not consider their sexual life of importance. The mean age of 37 patients with male partner was

57.0 years. Five of these 37 patients felt that the hysterectomy prevented good sexual intercourse and 54.1% of them considered that the sexual life is a very significant factor for their life. Results indicate the presence of female sexual dysfunction after hysterectomy, including decrease in sexual frequency in 37.9%, decrease in genital response in 60.9%, dyspareunia in 25.0%, and decrease in orgasm in 45.8%. These were observed in the patients with male partner. However, in some patients, the female sexual dysfunction symptoms were improved after hysterectomy, such as genital response in 4.3%, dyspareunia in 12.5% and orgasm in 8.3%. Accordingly, hysterectomy had unfavorable influence on female sexual function in several patients, but might relieved female sexual dysfunction symptoms in a few patients.

OR7-5

Effect of malathion on reproductive physiology of albino rat

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Pesticides are being widely used to control agricultural pests and pest causing public health problems all over the world. Ecologically pesticides have created life threatening health hazards to non-target species including man and animals. Malathion, an organophosphate compound, is widely used in the agricultural sector as a potent pesticide. The present work was therefore undertaken to evaluate the toxic effects of malathion on the mammalian reproductive.

Oral administration of malathion at a dose of 100 mg

/kg/d for 2, 4 or 7 weeks caused a significant reduction in the weights of testes and accessory sex organs. The spermatozoal motility in cauda epididymes and testes was significantly decreased. A sharp decline in fertility (50%) in malathion exposed rat was also observed. The testicular biochemistry showed depletion of glycogen, sialic acid and elevation of testicular protein and cholesterol. The plasma testosterone concentration was also found slightly decreased. These observations clearly showed the toxic interference of malathion on the reproduction of rat.

OR7-6

The penile nomogram in Korea

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Introduction: The definition of normal penile length is of considerable importance to urologists performing penile augmentation surgery. With an aim of constructing a better guideline regarding the patient selection for penile augmentation, we have recently completed a study designed specifically to investigate the relationship between penile sizes in the flaccid and the erect states.

Materials and methods: In 309 Korean potent males visiting our institution. A single examiner obtained the tape measurements of the flaccid and the erect penis. Measurements were made of flaccid length, flaccid circumference, depth of the prepubic fat pad and stretched penile length. Also, after self-stimulation or injection of prostaglandin E1, penile length and circumference were measured at full erection.

Results: Mean flaccid and erect penile length were 7.76 ± 1.19 cm and 11.88 ± 1.32 cm, respectively. The stretched length demonstrated a more predictable relationship with erect length than flaccid length ($R=0.648:0.549$). Subjects were classified into over- and under-40

year-old groups to study the effect of age on the fat pad depth, flaccid length, stretched length and erect length increase. Only erect length increase differed significantly, being greater in younger subjects ($P<0.05$). When the subjects were grouped by flaccid length as small (<6.5 cm), medium (6.5-9) and large (>9), we discovered that the erectile proportion (erect length-flaccid length/flaccid length) of the small group was greater than that of the large group ($0.72:0.38$, $P<0.01$). However, the mean erectile increase in the small group was not significantly greater than that of the large group ($4.5:4.3$, $P=0.24$).

Conclusion: Based on statistical considerations (less than mean-2SD), respective cut-off levels of 5 cm (flaccid) and 9 cm (erect) can be utilized for proper selection of patients for penile augmentation. Only 1.1% (3) of patients enrolled had values below this cut-off levels. Thus, it may be concluded that only a small number of patients are realistic candidates for penile augmentation in Korean males.

OR7-7

Relationship between psychological patterns and degrees of self-esteem on penile size in Korean men in early 20's

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Introduction: The penile augmentation operation is becoming popular in Korea, but so far data on actual degree of men's self-esteem on penile size and their psychological patterns have been scarce. We investigated the psychological patterns and the degrees of self-esteem on penile size in young Korean males as well as their flaccid and stretched penile sizes.

Methods: After expressing their formal consents, 123 Korean male in their early 20's who visit our institution were enrolled. We measured their pre-pubic fat pad depth, flaccid penile length, flaccid circumferences and stretched length. With the stretched penile length being closely correlated with the erect length, we did not measure the erect length. All subjects were asked to answer questions of Minnesota Multiphasic Personality Inventory (MMPI) and also another question on the self-esteem about penile size. Subjects were divided into 2 groups. Group I misperceived their penile size as small or very small in spite of their above-average stretched

penile size. Group II perceived their penile size in accordance with their above-average stretched penile sizes.

Results: The mean flaccid length, flaccid circumference, stretched length and fat pad depth were 6.9 ± 0.8 cm, 8.5 ± 1.1 cm, 9.6 ± 0.8 cm and 1.1 ± 0.4 cm, respectively. The distribution of the answers on penile size is as follows: 1 (0.8%) 'very small', 29 (23.6%) 'small', 86 (69.9%) 'normal', 6 (4.9%) 'large', and 1 (0.8%) 'very large'. Group I ($n=8$) showed significantly higher scores on the three subscales of the MMPI [Hypochondriasis (66.3 ± 9.5 v.s. 58.5 ± 10.1), Depression (63.4 ± 9.9 v.s. 53.11 ± 1.1) and Psychasthenia (59.9 ± 3.9 v.s. 49.5 ± 7.8)] than Group II ($n=43$) ($P < 0.05$).

Conclusion: In this study, more subjects think their penile size is rather small and this tendency was associated with some specific psychological patterns. In the selection of candidates for penile augmentation, urologist should not ignore the psychological aspects.

OR7-8

Development and evaluation of a new international index of erectile function-5 (IIEF-5) version as a diagnostic tool for erectile dysfunction in Korean male

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Introduction: Recently, an abridged five-item version of the International Index of Erectile Function (IIEF-5) has been developed as a brief diagnostic tool for erectile dysfunction (ED). In this study, we tried to newly select an optimal set of five items for Korean men and evaluate the validity of it.

Materials and methods: Patients with documented evidence of ED and control group completed the 15 items of Korean version of IIEF questionnaire. Then, the statistical program Classification and Regression Trees (CART) was used to newly select an optimal set of five items from 15 items of IIEF for discriminating between Korean men with and without ED. Also, the optimal cutoff score for the diagnosis of ED was determined using the receiver operating characteristics (ROC) with its sensitivity and specificity. The optimal cutoff score, sensitivity and specificity were calculated based on the original IIEF-5.

Results: A total of 307 Korean men (151 ED, 156 controls) completed this study. Our newly-developed version of IIEF-5 for Korean men consisted of items 15, 5, 13, 4 and 2 of the original 15-item IIEF. The Item 7 in the original IIEF-5 being replaced with item 13. The average IIEF-5 score for men with ED was 12.6 (range 5-22) which was significantly lower ($P < 0.01$) than that of the control group (22.6, range 10-25). The optimal cutoff score proved to be 21 with the corresponding sensitivity and specificity being 0.97 and 0.91, respectively. As for the original IIEF-5, the optimal cutoff score was 21, and the corresponding sensitivity and specificity were 0.94 and 0.90, respectively.

Conclusion: Our newly-developed IIEF-5 appeared to be more useful than the original as a diagnostic tool for ED in Korean men. The items included in the original IIEF-5 may be interpreted differently according to the different cultural backgrounds of various nations.

OR7-9

Effects of experimental renal failure on sexual behavior, penile erection and nitric oxide levels in corpora cavernosa

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Erectile dysfunction is common in chronic renal failure patients. This study assesses the impact of uremia on several indices of sexual and erectile function and NO release in the corpora cavernosa in a rat model.

Materials and methods: Two groups of 12 adult male Sprague-Dawley rats were compared: normal control and uremic. Chronic renal failure was induced by subtotal nephrectomy, the resulting serum creatinine was 1.6 ± 0.17 mg/dl (0.5 ± 0.04 mg/dl in the controls). Forty days later the animals were tested for mating behavior and penile reflexes. They were then anesthetized with urethane and the NO levels in their corpora cavernosa were monitored electrochemically using porphyrin micro-sensors prior and after cavernous nerve electrostimulation (SCN). The intracavernous (ICP) and arterial (AP) pressures were recorded simultaneously. The main NOS isoforms (nNOS, eNOS and iNOS) were

determined in corporeal homogenates by Western blot.

Results and conclusion: In the mating tests the uremic animals showed significantly longer latencies to mount, intromission and ejaculation. They also displayed less erections, flips and cups and longer erection latency in the reflexes test. Consistently with these findings they had lower NO levels in the corpora, both basal and following SCN, and a hindered ICP response to SCN. They also had higher AP values (130 ± 8 mmHg vs 105 ± 3 mmHg) and lower serum testosterone levels (0.6 ± 0.15 ng/ml vs 2.5 ± 0.48 ng/ml). There were no significant changes in any of the NOS isoenzymes protein content. These results suggest an impaired NO production due to post-translational factors as a main contributor to the sexual deficits observed in chronic renal failure. (Grant PM 99-0144)

OR7-10

Masturbation, a taboo and cause of different sexual dysfunction in conservative Muslim society like Pakistan

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Aim: This study is to find out the effect of masturbation on different sexual dysfunction in conservative Muslim society where masturbation is a taboo and religiously prohibited. There is wrong information in society by quacks and hakims (Unani medical practitioners) that masturbation destroyed the sexual health and weakens the muscles of penis. Due to this, masturbation is the most important cause (as perceived by patients) of different sexual dysfunctions in conservative Muslim society like Pakistan.

Material and methods: 240 Patients of sexual dysfunction were treated at Nasim Fertility Center Faisalabad, Pakistan from 01/10/1999 – 20/04/2000. The diagnostic work-up included detail history and examinations. The

patients suffering from early ejaculation, impotence and Dhant or Jaryan were 52%, 33% and 10%, respectively. 54% of patients of early ejaculation attributed the dysfunction to excessive masturbation, 58% of the impotence patients attributed the cause of dysfunction to excessive masturbation and 84% of Dhant or Jaryan patients were also the victims of excessive masturbation.

Conclusion: The guilty feeling of masturbation due to Islamic restrictions and the wrong information that masturbation destroys the sexual health and muscles of penis, lead to sexual neurosis and make it the major cause of most common sexual dysfunction (early ejaculation, impotence, Dhant or Jaryan) in conservative Muslim society like Pakistan.

OR8-1

Community based study about sexual life over 50's among Korean agricultural populations

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Aim: Even though the interest in sexual life increases with quality of life and increase in average life span, there is lack of relevant research. Therefore we have studied the sexual life and marital harmony in old married couples who have living in somewhat similar environment such as farming village.

Methods: In a rural area of 2500 people, 53 married couples of the age 50 to 72 years (average age: male 62.4 and female 58.8) were investigated by interviews questionnaires, in regard to the sexual pattern, sexual activity and sexual methods.

Results: In the last month, the cases having sexual relationship was 90.6% (48/53) and their average age was male 62.0 and female 58.5 years. The ages were lower than the couples [9.4%(5/53)] not having sexual relationship, which were 64.0 (male) and 61.8 (female) years, the difference being significant ($P<0.05$). With 92.3% (48/53) of male and 90.2% (46/51) of female, the frequency of sexual relationship was 4 times a month. Vaginal intercourse was the most common method of sexual relationship. In a few cases, the methods of petting the whole body, sexual foreplay, kissing and masturbation were accomplished for both the male and

female. The average number of sexual relationship were 11.0 times for petting whole bodies and sexual foreplay, 7.2 times for kissing, and 5.4 times for vaginal intercourses in one month. However, in female, there were 2.5 times for petting whole bodies and sexual foreplay, and 2.4 times for vaginal intercourses without any interests in masturbation, oral sex and anal sex. The frequency of sexual desire such as sexual imagination, fascination and dream was 5.9 times for male and 1.9 times for female in one month ($P<0.05$). For suggestion of sexual relationship by their partners, both the male and female accepted delightedly, but 19.5% (8/41) of male and 11.6% (5/43) of female refused. The number of sexual activity was significantly different between the male (62.3%) and female (37.7%) ($P<0.05$).

Conclusion: Last but not the least, the marital harmony and relationship has maintained by the positive attitude of sexual life in Korean agricultural population. It should be considered to perform more extensive epidemiologic research to investigate the sexual life and its accompanying sexual problems.

Keywords : sexual life; marital harmony; aging men

OR8-2

Effects of hypertension and antihypertensive drugs on sexual function in elderly men

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Introduction: Erectile dysfunction (ED) may be associated with peripheral vascular changes or adverse effects of medications used to treat the condition. This study investigated the sexual function in elderly men with hypertension.

Methods: A questionnaire from the International Index of Erectile Function (IIEF) was given to 1,207 non-institutionalized men of age 60 to 79 years along with a survey of their health status. The study was conducted from September 1999 to December 1999. The prevalence of men suffering from ED were determined from the scores of questions and 15 men who responded "Low" were classified as having moderate ED and men who responded "Very low" were classified as having severe ED. Statistical analysis was performed using the chi-square test.

Results: Complete responses were provided from 466 men (38.6%). The prevalence of men with hyper-

tension was 31.8% and 38.1% in men of 60s and 70s, respectively. The prevalence of ED was 60.4% in hypertensive men and 43.7% in normotensive men. Treatment with a calcium channel blocker, alpha-blocker or beta-blocker did not affect the scores for sexual function on the IIEF. In contrast, men taking an angiotensin-converting enzyme inhibitor had significantly better IIEF scores compared to other types of antihypertensives ($P < 0.05$).

Conclusion: There is no doubt that ED is associated with age, but the present study demonstrated the contribution of hypertension to the probability of ED development, and the efforts to prevent hypertension may lead to reduction in unnecessary ED. Results also showed that adequate selection of antihypertensives may bring favorable effects on the erectile function. Further control studies and analysis of individual risk factors are required.

OR8-3

Physician's and practitioner's attitude toward erectile dysfunction

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Aim: The physician's attitude to ED is very important to the diagnosis and management of this disease. We investigated the physician's and practitioner's attitude to ED in Beijing, China.

Materials and methods: Three hundreds and one physicians and practitioners completed a questionnaire. The subjects included urologists (Group A, $n=83$), non-urologist physicians (Group B, $n=132$) and community practitioners (Group C, $n=86$). The 15-item questionnaires included three domains: basic knowledge of ED, whether the physicians asked their patients about erectile function especially if the patient was exposed to certain risk factors of ED, and the physician attitude if the patient complained about ED. Data was analyzed by the χ^2 test.

Results: The definition and main risk factors of ED were well known by most subjects (83.4%). Many agreed that ED was a common condition in aging men (85.0%),

it is an important health problem (78.7 %) and it is the local signs of certain systemic disease (89.7%). The proportion of physicians who never asked their patients about erectile function in Group A, B, and C were 7.2%, 55.3% and 60.5 %, respectively. The most common reasons for the urologists (61.4%) and non-urologists physicians (30.3%) not to initiate the inquiries about ED was "waiting for the patients to complain". If the patient complained about ED, the rate that the physicians would discuss the disease with the patients was 66.2% in group A was, 16.7% in group B and 24.4% in group C ($P < 0.01$).

Conclusion: Most non-urologist physicians and community practitioners regarded ED as an important health problem and a common condition in aging men, but they did not take an active attitude to ED in their clinical practice. Further ED education should be addressed to the physicians and practitioners.

OR8-4

Immune response modulation in the internal pudendal artery in Wistar rats with stress condition

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It has long been stated that psychogenic stressors like anxiety, depression, and stress may cause Erectile Dysfunction (ED). Many clinical studies have shown the relationship between psychogenic conditions and the development of ED (psychogenic ED). However, until recently, the exact mechanism of ED in patients with psychogenic stressors had not been understood.

To clarify the pathogenesis of psychogenic ED, an animal experimental research using psychoneuroimmunology (PNI) paradigm was conducted. The design chosen was a Randomized Control Group Posttest only Design. Forty male rats, *Rattus Nervigicus* of Wistar strain were used and at random divided into 4 groups of ten rats. Group I (control group for 5 days experiment), group II (5 days experiment group), group III (control group for 10 days experiment), group IV (10 days experiment group). The rats were 3-4 months old and had a body weight of 150-200 g. An electric footshock (EF) was used as a psychogenic stressor (as independent variable) exposed to the rats. The dependent variables observed were Immune Response Modulations (IRM) of the neurohormonal changes expressed in cortisol, catecholamines (adrenalin, noradrenalin) blood level, amount of VCAM-1 expressing endothelial cells (ECs) and amount of IL-2, IFN γ , IL-4, IL-10 producing lymphocytes in the internal pudendal artery wall, the main artery for erection. A multivariate analysis was used to evaluate the data.

The results after 5 days of EF exposure showed that cortisol, adrenalin and noradrenalin blood levels increased, amount of VCAM-1 expressing ECs increased and

amount of IL-2, IFN γ , IL-4, IL-10 producing lymphocytes decreased. After 10 days of EF exposure, cortisol, adrenalin and noradrenalin blood levels also increased, amount of VCAM-1 expressing ECs decreased and amount of IL-1, IFN γ , IL-4, IL-10 producing lymphocytes were more decreased.

To explain the mechanism, the contribution function of each variables to the development of ED is needed. Based on discriminant analysis, only 5 variables (cortisol, adrenalin, VCAM-1, IL-4, IL-10) have contribution in IRM pattern. It showed that after 5 days of EF exposure, IRM caused an increased adrenalin function, but a decreased cortisol function. VCAM-1 expressing ECs and IL-4, IL-10 producing lymphocytes functions were increased. After 10 days of EF exposure there was a prominent increased cortisol function, but a decreased adrenalin function. IL-4 and IL-10 producing lymphocytes functions were more increased whereas VCAM-1 expressing ECs function was decreased.

In conclusion: the increased adrenalin function after 5 days of EF exposure and increased VCAM-1 expressing ECs function may cause endothelial dysfunction and potentially may cause endothelial damage in the internal pudendal artery wall, and hence causes psychogenic ED. After 10 days of EF exposure cortisol function increased, which consequently caused increased IL-4 and IL-10 function. This condition, where Th2 cells are dominant may cause endothelial damage of the internal pudendal artery wall through ADCC (antibody-dependent cell-cytotoxicity) process, and hence may cause psychogenic ED.

OR8-5

Pre- and post-synaptic proerectile mechanisms of histamine in human penis

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Our previous study showed that relaxation of human corpus cavernosum (CC) muscle mediated by histamine via H₂ receptor (Adaikan & Karim, 1976) was partly dependent on nitric oxide (NO) release (LC Lau *et al*, 1997). In this study, we examined the second messenger system linked to the histamine H₂-receptor and the probability of histamine acting as a neuromodulator of penile erection. Rolipram (10 μM), a cAMP-selective phosphodiesterase, consistently enhanced the relaxant action of histamine and PGE1 in the noradrenaline-precontracted CC strips. N-Ethylmaleimide (NEM), an inhibitor of adenylate cyclase, directly increased CC muscle tone and reduced the contractile action of noradrenaline on CC muscle. NEM (100 μM) markedly inhibited the relaxant effect of histamine and PGE1 but not that of ACh. Tetraethylammonium (TEA, 1 mM), a K⁺-channel blocker,

failed to exert any influence on histamine in most strips. R-α-methylhistamine (RαMeH, 32 μM), a selective histamine-H₃ agonist, at concentration that did not cause direct relaxation of CC muscle, specifically inhibited contractile response to electrical field stimulation (70 V, 1 ms, 20 Hz) without significantly affecting contractions produced by exogenous NA. The inhibitory effect of RaMeH on sympathetic transmission was, effectively reversed by increasing the frequency of stimulation. Hence, histamine may promote human penile erection by directly eliciting relaxation of CC muscle and (possibly via H₃) reducing the release of sympathetic transmitter, which is anti-erectile. In addition to the release of NO, the relaxant action of histamine on CC muscle seems to involve adenylate cyclase-cAMP pathway.

OR8-6

Immunohistochemical identification of oestrogen receptors in corpus cavernosum

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Oestrogen receptor activation in the testis and epididymis is established in normal male fertility related to sperm production. Our earlier studies in rats have identified the pathophysiological correlation between elevated serum oestradiol level and erectile dysfunction. Since the effects of steroid hormones are mediated through specific receptors and hormone regulated genes expressed in target tissues, an attempt was made in this investigation to visualize sites of immunoexpression for oestrogen receptor subtypes α and β in the corpus cavernosum (CC). Freshly frozen CC samples from normal rabbits ($n=4$) and primates (macaque fascicularis, $n=3$) were cryosectioned (7 μm) and incubated overnight with appropriate dilution of mouse monoclonal peptide antibody (GeneTex) for oestrogen alpha or beta-receptor. Through serial processing methods, colour signals for nuclear immunostaining of ER- α and ER- β were localized within the cavernosum of these two species.

In our preliminary studies, an erectile dysfunction was precipitated in sexually mature male rats following chronic treatment with oestrogen. Thirty male Sprague Dawley rats (200-250 g) were divided into control and

two treatment groups, administered 0.01 mg and 0.1 mg of oestradiol through oral gavage daily for 12 weeks. Sexual activity in the presence of hormonally primed female rats and intracavernous pressure (ICP) response to electrical stimulation estimated the treatment-induced changes, which were correlated with serum hormone levels and penile morphology at 12 weeks. Following two-fold elevation in serum E_2 levels (and simultaneous reduction in testosterone), there was a significant impairment of mount, intromission, ejaculation latencies and decrease in frequencies. ICP response to nerve stimulation was also impaired in the two treatment groups [41.27 \pm 1.78 mmHg (0.01 mg) and 36.33 \pm 0.39 mmHg (0.1 mg) as compared to 45.28 \pm 1.20 mmHg in the normal rats]. Histologically, trichrome staining highlighted the connective tissue hyperplasia at 12 weeks.

Results of these two investigations indicate that oestradiol causes receptor-mediated pathophysiological changes in erectile function. These observations also provide a scientific basis for the possible sexual health hazards upon inadvertent exposure to environmental oestrogens.

OR8-7

Laser doppler flowmetry evaluation for traps (transpenile delivery of microvasculokinetic drugs) in erectile dysfunctions

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Microvasculokinetic drugs belonging to the Rutosides group, specifically complexed for transpenile barrier system delivery (TRAPS), are daily applied for 3 months on the penile skin of erectile dysfunction patients with (micro)-vascular impairment.

Laser Doppler Flowmetry (LDF) recordings are collected at T0, T1, T2, T3 and the Å score of the microvasculokinetic test is calculated with and without the application of the drug (tri-hydroxy-aethyl-rutoside or troxerutine Tr versus placebo P).

In the Placebo group the Å score remains unchanged at the low baseline values: PT0=6.99; PT30=7.77;

PT60=5.81; PT90=8.41. In the Tr group the Å score increases progressively: TrT0=48.76; TrT30=63.12; TrT60=74.72; TrT90=81.77. The statistical difference between P and Tr groups is highly significant ($P<0.01$ for T0, T30, T60, T90).

The Laser Doppler Flowmetry evaluation of the (micro)vasculokinetic response in parallel to the penile skin and into the corpora cavernosa represents a new objective method to analyse the efficacy of new pro-erectogenic drugs with micro-vascular activity on the penile vascular compartments for penile rehabilitation.

OR8-8

Diagnosis and treatment of functional (psychogenic) sexual disorders

Yuzuru Kameya

The treatment of organic sexual disorders can be given after identifying the physical cause. For functional (psychogenic) sexual disorders, however, analyzing complaints made by the patient does not necessarily lead to the cause. The condition of the patient's partner can often affect the disorders as well.

I always suggest that the patient's partner also see a doctor even if only the patient visits our hospital. To rule out organic disorders, I usually tell patients to see a physical doctor experienced in treating sexual disorders and to have that doctor treat them. I will simultaneously, or almost simultaneously, give both partners psychological test (CM1, SRQ-D, "ego-gram," Rorschach) and begin interviewing them (psychological diagnoses) and giving them psychological treatment. For anxiety disorders, I will motivate the couple the increased use of positive language (e.g., "Thank you," "I'm happy," etc.) in their daily lives. I will also recommend that they keep a diary.

For some cases, behavior therapy will be started as early as possible. Methods used for male patients include the non-erect method for erectile dysfunction. A male patient with an intravaginal ejaculation disorder will be instructed to practice vaginal insertion just before ejaculation after masturbation. For female patients, desensitization using the sensation detection method, masturbation training, etc., is given as a treatment.

After continual behavior therapy, counseling, and efforts to improve communication between partners, favorable results were obtained in approximately 80% of the couples treated after half a year to two or three years. Of these couples, five women succeeded in becoming pregnant under my treatment after failing to become pregnant by artificial insemination or *in vitro* fertilization recommended by the gynecologist. I would like to introduce two or three examples for your reference.

OR8-9

Vardenafil improved erectile function regardless of baseline severity, etiology and hypertensive medications in Phase II trial

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Vardenafil significantly improved erectile function in a Phase IIb study. We further evaluated whether factors like baseline severity or etiology of erectile dysfunction (ED) and concurrent use of antihypertensive medications influence the efficacy of vardenafil.

601 men with ED (>6 months duration) were randomized to placebo, 5 mg, 10 mg or 20 mg vardenafil for 12 weeks. Efficacy was assessed by IIEF-Erectile Function domains after 12 weeks.

Patients with severe erectile dysfunction (<11) at baseline improved to 18.4, 18.6 and 20.1 for 5 mg, 10 mg and 20 mg, respectively, compared to 11.5 for placebo. For those starting with mild ED (between 17 and 25), the mean values after treatment were 22.5, 26.0 and 25.6 for 5 mg, 10 mg and 20 mg, respectively, compared to 19 for placebo. Moderate severity had intermediate values.

The changes from baseline for those with organic

etiology (1.7, 7.0, 8.7 and 8.8 for placebo, 5 mg, 10 mg and 20 mg, respectively) were similar to those with psychogenic etiology (1.3, 7.2, 7.3, 8.4 for placebo, 5 mg, 10 mg and 20 mg, respectively).

Vardenafil treated patients on antihypertensives had final EF scores from 19.2 to 23.7 compared to 21.4 to 23.8 for those not taking antihypertensives. This compared to placebo final scores of 13.9 for patients on antihypertensives and 16.1 for those who were not.

Adverse events were primarily mild with headache occurring in 7% to 15%, flushing in 10% to 11%, and dyspepsia and rhinitis up to 7%, depending on dose.

We conclude that improvement of mean Erectile Function domain scores by vardenafil was similar among patients with mild, moderate or severe baseline severity, whether the etiology was organic, psychogenic or mixed and whether or not patients were taking antihypertensive medications.