

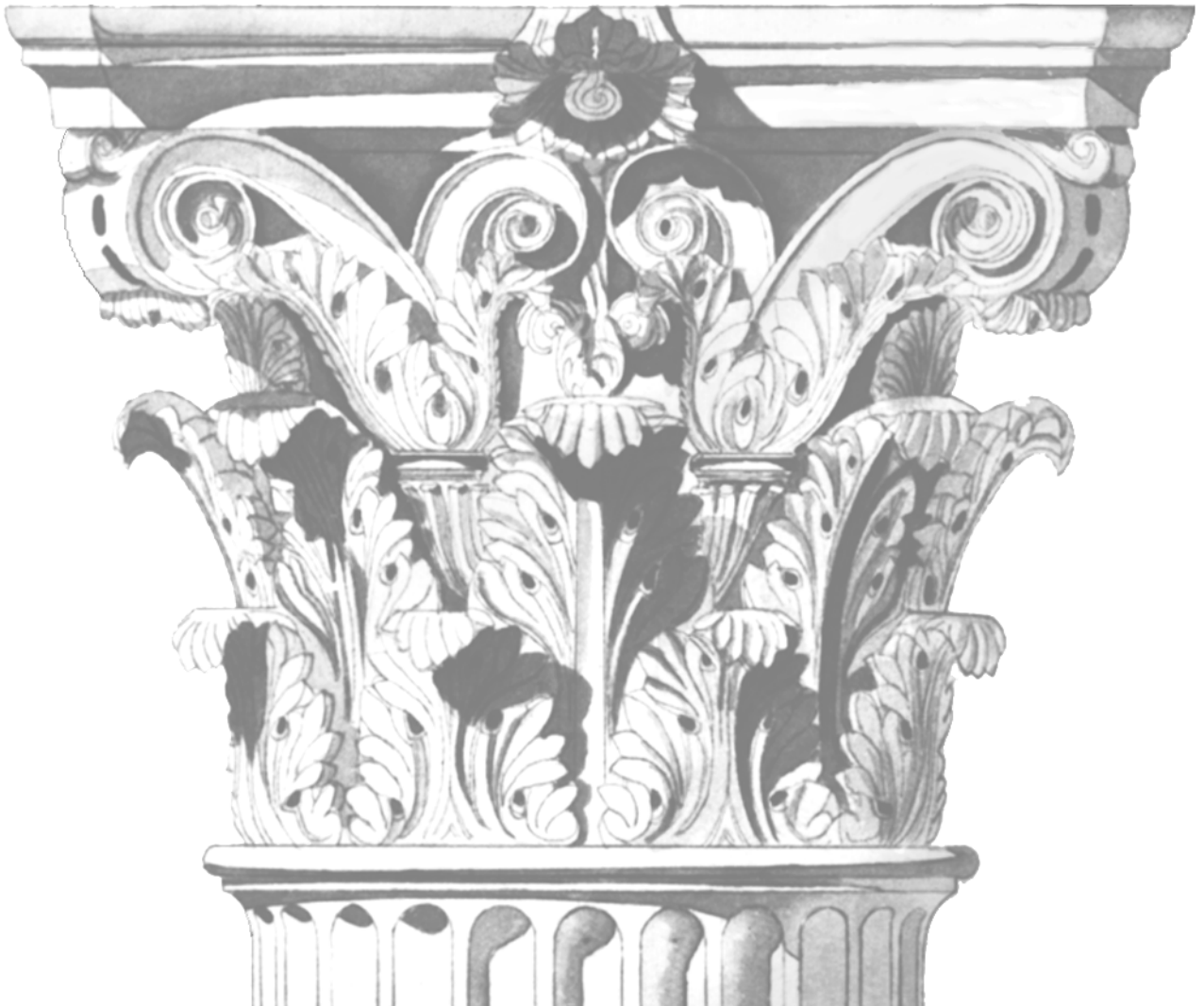
# SEXUAL DYSFUNCTION

The roles of yohimbine hydrochloride and intracavernosal vasoactive drugs in the treatment of erectile dysfunction, the effect of transurethral resection of prostate on sexual functions and the impact of dihydrotestosterone on andropausal symptoms

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OULU 1999



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Academic Dissertation to be presented with the assent of the Faculty of Medicine, University of Oulu, for public discussion in Auditorium I of the University Hospital of Oulu, on November 26th, 1999, at 12 noon.

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Manuscript received 20 September 1999  
Accepted 06 October 1999

Communicated by  
Docent Martti Ala-Opas  
Docent Martti Talja

ISBN 951-42-5386-8  
(URL: <http://herkules.oulu.fi/isbn9514253868/>)

ALSO AVAILABLE IN PRINTED FORMAT

ISBN 951-42-5385-X  
ISSN 0355-3221 (URL: <http://herkules.oulu.fi/issn03553221/>)

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*Dedicated to my family*

**Kunelius, Pekka, Sexual dysfunction: the roles of yohimbine hydrochloride and intracavernosal vasoactive drugs in the treatment of erectile dysfunction, the effect of transurethral resection of prostate on sexual functions and the impact of dihydrotestosterone on andropausal symptoms**

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1999

Oulu, Finland

(Manuscript received 20 September 1999)

***Abstract***

The aim of this study was to clarify the effects of yohimbine hydrochloride and three intracavernosal vasoactive agents in patients with erectile dysfunction and the effect of dihydrotestosterone gel in men with andropausal symptoms. The effect of transurethral resection of prostate (TURP) on sexual functions was also examined.

Altogether 406 patients were included in five studies, and all patients were examined and controlled in the Oulu University Hospital during the years 1991-1998.

Twenty-nine patients with mixed-type erectile dysfunction (ED) were recruited into a randomized, controlled, double-blind crossover comparison of placebo and high-dose yohimbine hydrochloride (36 mg per day orally). Positive clinical responses were obtained in 44% of the patients during yohimbine treatment and in 48% during placebo treatment.

Thirty patients with ED underwent an intracavernosal injection test (ICI) using three different active agents (prostaglandin E1 (PGE1), papaverine hydrochloride (PV), moxisylyte (MS)) and physiological saline. PGE1 produced significantly better rigidity than either PV or MS.

Sixty-nine patients with ED who had started ICI therapy with PGE1 at least three years previously were invited to a control examination to find out the long-term outcome of this treatment and to evaluate the patients' overall satisfaction with their sexual life. 46.4% of the patients had discontinued PGE1 therapy, the mean time of using PGE1 having been 23.3 months (range 0-48 months). 34.8% of the patients reported that their own spontaneous erections had improved during the PGE1 therapy.

The sexual functions of 155 patients with benign prostatic hyperplasia (BPH) were evaluated before TURP and 6 and 12 months afterwards with questionnaires. Only 26% of the patients had completely satisfactory erections before TURP, while 22% had satisfactory erections 6 months later and 24% 12 months later. The majority of patients (about 70%) were satisfied with their sexual life both before and after the procedure.

123 men with symptoms of andropause participated in a randomized, placebo-controlled study to assess the effects of dihydrotestosterone (DHT) gel in men with andropausal symptoms. The drug was administered transdermally once a day during six months. Early morning erections improved significantly ( $p < 0.003$ ) in the DHT group by the three-month control, the ability to maintain erections was better, and there was also a positive effect on libido. In the patients with a elevated ( $\geq 12$ ) international index of the prostatic symptoms score (I-PSS) before DHT treatment, I-PSS decreased from 17.7 to 12.3 points.

As a conclusion yohimbine hydrochloride is no better than placebo in the treatment of patients with mixed-type ED. PGE1, PV and MS are well tolerated, and PGE1 was shown to be the most effective drug of the three. ICI therapy with PGE1 in long-term use is safe and effective. Sexual functions in men did not change after TURP, and this group of aging men were fairly satisfied with their sexual life despite of the fact that they had some ED and one third of the patients had not had intercourse during the previous year. Transdermal administration of DHT in aging men improves sexual function.

**Keywords:** sexual dysfunction, intracavernous injection (ICI) test, andropause, prostaglandin E1



## Acknowledgements

This study was carried out at the Department of Surgery, Oulu University Hospital during the years 1991-1998. I thank Professor Matti Kairaluoma, M.D., Ph.D., Head of the Department of Surgery in those years, for giving me opportunity to do the study.

I owe my warm thanks to professor Matti Kontturi, former head of Division of Urology, who first suggested this kind of study to be done in our clinic.

I am deeply grateful to my supervisor, professor Olavi Lukkarinen, for introducing me into the interesting field of scientific research and specially into male erectile dysfunction, and also Jukka Häkkinen, M.D., with whom we had and shall have many exciting projects around this study.

I wish to express my sincere gratitude to professor Olof Alfthan, who provided great support and encouragement during this work.

I express my truly special thanks to Docent Pekka Hellström, M.D., Ph.D. for support and guidance during this study and providing constructive comments and criticism.

I'm grateful to Docent Martti Ala-Opas, M.D., Ph.D., and Docent Martti Talja, M.D., Ph.D., for reviewing the present manuscript.

My sincere thanks are due to my co-workers: Docent Juha Tapanainen M.D., Ph.D. for the professional attitude to create a scientific article and all the nurses at the Outpatient Department of Urology, specially Mrs. Anita Tikkala and Mrs. Pirta Körkkö, and Mrs. Sirkka-Liisa Leinonen for revising the English language of this thesis.

I wish to express my gratitude to all the surgeons and personnel of the Department of Surgery for their support.

During all these years the support of my friends has been extremely irreplaceable. I give my thousands of thanks to members of the rhythm and blues band Cool Operator and WB-brothers, which are Mr. Koskenkari M.D., Mr. Wiik M.D., Mr. Rautio M.D., Mr. Välimäki M.D., Ph.D., Mr. Kurtti M.D., Mr. Fors M.D., Mr. Veijola M.D. and Mr. Ryhänen M.D., Ph.D..

Finally, my warmest thanks belong to my wife Anne, and our children Hanna, Heidi and Anniina for their patience and love. This study was supported by Urological Association of Finland.

Oulu, October 1999

Pekka Kunelius



## Abbreviations

AVSST	audiovisual sexual stimulation test
BCRL	bulbocavernous reflex
BMI	body mass index
BPH	benign prostatic hyperplasia
cc-EMG	corpus cavernosum electromyography
CVD	cardiovascular disease
DD	duplex-Doppler color sonography
DHEA	dehydroepiandrosterone
DHT	dihydrotestosterone
ED	erectile dysfunction
E2	estradiol
FSD	female sexual dysfunction
FSH	follicle stimulating hormone
GTP	guanosine-5``-triphosphate
HDL	high-density lipoprotein
ICI	intracavernosal injection
IIEF	international index of erectile function
LH	luteinizing hormone
MS	moxisylyte
NO	nitric oxide
NPT	nocturnal penile tumescence
NPTR	nocturnal penile tumescence and rigidity
PGE1	prostaglandin E1
PSA	prostate-specific antigen
PV	papaverine hydrochloride
REM	rapid eye movement
SHBG	sex-hormone binding globulin
T	testosterone
TRUS	transrectal ultrasound
TURP	transurethral resection of prostate
VAS	visual analogue scale
VCD	vacuum/constriction device



## **List of original publications**

This thesis is based on the following articles, which are referred to in the text by their Roman numerals:

- I Kunelius P, Häkkinen J & Lukkarinen O (1997) Is high-dose yohimbin hydrochloride effective in treatment of mixed-type impotence? A prospective randomized, controlled double-blind crossover study. *Urology*: 49:441-444.
- II Kunelius P & Lukkarinen O (1998) Intracavernous injection test in the evaluation of patients with erectile dysfunction: a blind, cross-over placebo-controlled study between three different vasoactive agents in 30 impotent patients. *Sexual Dysfunction* 1:35-38.
- III Kunelius P & Lukkarinen O (1999) Intracavernous self-injection therapy of prostaglandin E1 in the treatment of erectile dysfunction. *Int J Impot Res* 11:21-24.
- IV Kunelius P, Häkkinen J & Lukkarinen O (1998) Sexual functions in patients with benign prostatic hyperplasia before and after transurethral resection of the prostate. *Urol Res* 26:7-9.
- V Kunelius P, Lukkarinen O & Tapanainen J (1999) The effects of transdermal dihydrotestosterone on andropause symptoms: a prospective, randomized, double-blind study. Submitted for publication.



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# 1. Introduction

The inability of a male to attain and maintain an erection sufficient to allow sexual intercourse is called erectile dysfunction (ED). It is a part of the general male sexual dysfunction called impotence, which also includes libidinal, orgasmic and ejaculatory dysfunction. Until the 1990's, "impotence" was the term used in clinical work to refer to erectile dysfunction.

The most usual sexual dysfunction of man is weakness of erections. Erectile dysfunction affects millions of men, and although it may not mean a total loss of sexual satisfaction, it often creates a mental stress that affects the man's quality of life. Erectile dysfunction goes hand in hand with aging. The prevalence of complete ED is estimated to be approximately 5% among 40-year-olds, 10% among men in their 60s, 15% in men in their 70s, and 30-40% in men in their 80s (Feldman *et al.* 1994).

Erectile dysfunction is a common problem. In the 1970s it was believed that most of the problems causing erectile dysfunction were psychological. Nowadays, about 50-85% of ED patients can be shown to have a somatic cause by modern methods of examination (Mulligan & Katz 1989). One must, however, recognise that there are always some psychological factors at the background. Erectile dysfunction may also occur as a result of a specific illness or medical treatment. Various operations may similarly cause erectile dysfunction (Quinlan *et al.* 1991).

Knowledge of erectile dysfunction has increased remarkably over the past decade: the most striking finding was the possibility to use intracavernosal (papaverine hydrochloride) treatment, which was reported by Dr. Virag in the early 1980s (Virag 1982). Since that time, many other injectable vasoactive medicines have been introduced (Buvat J *et al.* 1989, Lue 1990, Chao & Clowers 1994). The other important finding was sildenafil, which enables the use of effective oral medication for ED (Goldstein *et al.* 1998).

The mechanism of erection is also better understood now when the new drugs have been investigated (Hedlund & Andersson 1985, Goldstein *et al.* 1998). The clinical investigations of erectile dysfunction have become more sophisticated: color duplex Doppler (DD) sonography, audiovisual sexual stimulation tests (AVSST), and computer-aided programs are available for the analysis of erections and nocturnal penile tumescence (NPT) (Rigiscan device). It is also possible to examine the etiology of erectile dysfunction with intracavernosal injection tests (ICI) (Stackl *et al.* 1990).

Nowadays the most important contemporary treatments of ED are peroral sildenafil and intracavernosal pharmacotherapy using vasoactive medicines. 70%-90% of all patients with ED are able to restore their erections with these treatments (Benard *et al.* 1990, Virag *et al.* 1991, Goldstein *et al.* 1998). However, these drugs are not suitable to every patient. More noninvasive methods to treat erectile dysfunction, such as oral medication or locally applicable preparations are needed.

## **2. Review of the literature**

### **2.1. Prevalence and epidemiology of erectile dysfunction**

Until the 1970s, sex was a private matter and publications about sexual behaviour were rare. Erectile dysfunction was a non-threatening disorder, and only a minority of the patients suffering from it consulted a doctor.

The first thorough epidemiologic study in the United States was published by Kinsey and associates in 1948. According to Kinsey's survey, which covered 4108 adult males, less than 1% of the population were affected before the age of 30 years, while 6.7 % of men were affected between 45 and 55 years, 25% at the age of 65 years, and up to 75% of men at the age of 80 years. One should notice, however that only a minority of these patients, namely 306, were aged above 55; it is therefore difficult to draw very definite conclusions concerning elderly men's prevalence of erectile dysfunction on the basis of Kinsey's report. Spector and Carey (1990) reviewed 23 studies on sexual dysfunction in males and females carried out between 1948 and 1988 in different settings, among the general population and in different clinical settings, reporting that the prevalence of ED was 4% to 9%. The most recent epidemiologic study is the the Massachusetts Male Aging Study (MMAS) reported by Feldman and colleagues (1994), where 1290 males aged 40-70 years filled in a sexual questionnaire with 9 items between the years 1987 and 1989. This study reports a combined 52 % prevalence of minimal, moderate and complete impotence. Age was the variable most strongly associated with impotence. The authors concluded that erectile dysfunction increases with age, and the probability of complete impotence tripled from 5 to 15 % between the ages of 40 and 70 years. Prior studies have shown similar relationships between impotence and aging (Kinsey *et al.* 1948, Pearlman & Kopashi 1972, Frank *et al.* 1978, Mulligan *et al.* 1988). The MMAS study could conclude, based on these figures, that impotence is a major health concern in view of its high prevalence. It has been noticed in various investigations that 80-90% of men over 60 years of age continue their sexual activity (Brecher 1984).

Erectile dysfunction is often multifactorial in etiology. When the patient is diagnosed as having organic ED, it means that organic factors are the main contributors to his ED. For didactic purposes, ED has been divided into organic and psychogenic types. Atherosclerotic vascular disease accounts for nearly half of all ED in men more than 50 years of

age (Mulligan & Katz 1989). Heart disease and two associated risk factors, hypertension and low serum high-density lipoprotein, significantly correlated with impotence in the MMAS sample (Feldman *et al.* 1994). Several studies on impotent men have shown that the number of abnormal penile vascular findings significantly increases when the patient history includes myocardial infarction or vascular risk factors, such as hypertension and cigarette smoking (Shabsigh *et al.* 1991).

Diabetes is known to be associated with impotence. The prevalence of ED in the diabetic population ranges from 15% to 55%, depending on the age and extent of the disease (Smith 1981). In the MMAS sample, the age-adjusted probability of complete impotence was 3-fold in subjects reporting treated diabetes compared to those without diabetes (Feldman *et al.* 1994).

Of the many other diseases causing ED, chronic renal failure induces ED in up to 40% of the men affected (Abrams *et al.* 1975). Several neurological diseases have also been associated with ED. Multiple sclerosis is associated with a high incidence of ED (Lilius *et al.* 1976). Loss of erection was reported in 53% of 55 male Alzheimer's disease patients (Zeiss *et al.* 1990).

Endocrine disorders are commonly associated with ED, and hypopituitarism, non-functioning pituitary tumors, prolactin-secreting pituitary tumors and hyperthyroidism may cause ED (Braunstein 1983). The effect of androgens on libido and sexual behavior is well established, but their contribution to the erectile mechanism remains unclear (Korenman 1990). In the MMAS survey, of the 17 hormones measured, only dehydroepiandrosterone was strongly associated with impotence (Feldman *et al.* 1994).

Psychogenic ED is more prevalent in young men, but its prevalence in older men cannot be ignored, especially not the widower's syndrome (Morley 1985).

Men suffering from depression may have organic ED due to the decreased testosterone levels caused by elevated levels of corticotropin-releasing factor (CRF) (Ono *et al.* 1984). Several chronic infectious diseases are associated with ED. The outcome of prolonged priapism is usually ED, while many conditions are associated with priapism and are often drug-induced and are caused by or sickle cell disease, trauma, neoplasia, leukemia, intracavernosal injections and total parenteral alimentation.

Cigarette smoking has been shown to be an independent risk factor for vasculogenic impotence (Rosen *et al.* 1991). The roles of excessive alcohol consumption, obesity and physical inactivity are unclear (Fried *et al.* 1986, Friedman *et al.* 1986, Kosch *et al.* 1988).

Trauma to the pelvic structures may cause ED in a significant number of men affected, and urologic surgery is also closely associated with ED. Radical prostatectomy using the retropubic approach and a nerve-sparing procedure causes ED in 15% to 30% (Quinlan *et al.* 1991). Transurethral resection of prostate (TURP) has resulted in a high incidence of ED in many studies, but the incidence varies from none to 40% (Holtgrave & Valk 1964, Finkle & Prian 1966, Hargreave & Stephensen 1977, Bolt *et al.* 1987, Libman & Fichten 1987, Mebust *et al.* 1989).

Drug-induced erectile dysfunction is common. The data available on this topic are based on empirical observations, case reports and pre- or post-marketing drug surveys. Most of the studies have been uncontrolled. Slag and colleagues (1983) found a 25% prevalence of drug-associated impotence in a medical outpatient population. Most of the drugs causing male erectile dysfunction have been associated with the available antihyperten-

sive agents, including sympatholytics,  $\beta$ -adrenoceptor blocking agents, vasodilators and diuretics (Wein *et al.* 1988). Many drugs that produce central nervous system sedation or depression, such as opiates, are also associated with ED by causing elevation of plasma prolactin levels (von Graffenreid *et al.* 1978), as are also drugs that lower plasma testosterone levels, such as estrogen, ketokonazole and digoxin (Pont *et al.* 1982, Przybilla & Schill 1985). There are numerous drugs and many different mechanisms that could also cause ED (Table 1). More and more drugs are being identified as causing ED, but consideration should also be given to the natural occurrence of ED.

*Table 1. Drugs that may produce erectile dysfunction (from Benet & Melman 1995).*

Drug type	Drugs
Diuretics	Thiazides Spironolactone
Antihypertensives	Methyldopa Clonidine Reserpine $\beta$ -Blockers Guanethidine Verapamil
Cardiac	Clofibrate Gemfibrozil Digoxin
Tranquilizers	Phenothiazines Butyrophenones
Antidepressants	Tricyclic antidepressants Monoamine oxidase inhibitors Lithium Prozac
H <sub>2</sub> antagonists	Cimetidine Ranitidine
Hormones	Estrogens Progesterone Corticosteroids Cyproterone acetate Eulexin Proscar Gonadotropin-releasing hormone agonists
Cytotoxic agents	Cyclophosphamide Methotrexate Roferon-A
Anticholinergics	Disopyramide Anticonvulsants
Miscellaneous	Metoclopramide Baclofen Carbonic anhydrase inhibitors Nonsteroidal anti-inflammatory Tobacco Alcohol Amphetamines Opiates

## 2.2. Physiology of penile erection

The central sensory psychogenic stimuli or penile stimulation or both increase parasympathetic activity, resulting in relaxation of the penile smooth muscle (Saenz de Tejada & Moncada 1996). This phenomenon is mediated by activation of the NO/cGMP pathway and by additional activation of the cAMP pathway, which result in increased blood flow through the penile arteries.

NO exerts a significant impact on the penis, operating as the principal mediator of ED (Burnett 1997). NO is a free radical and therefore a highly reactive and chemically unstable molecule. NO crosses the plasma membrane of cells targeting on the guanylate cyclase enzyme, producing a conformational change in the molecule that increases its activity. Activated guanylate cyclase catalyzes the conversion of guanosine-5'-triphosphate (GTP) to 3',5'-cyclic guanosine monophosphate (cGMP). The accumulation of cGMP sets in motion a cascade of events at the intracellular level which induce a loss of contractile tone of penile smooth muscle and increase of blood flow in cavernous body (Saenz de Tejada & Moncada 1996, Figure 1).

The other pathway for inducing relaxation and erection is mediated by vasoactive intestinal peptide (VIP) (Ehmke *et al.* 1995). The VIP receptors in the cavernous body are coupled to specific proteins that stimulate the catalytic activity of adenylate cyclase with the formation of cAMP (Fig.1). Endogenous prostanoids participate in the regulation of penile smooth muscle contractility. The receptor that mediates relaxation to PGE is designated "EP receptor" (prostaglandin E receptor, Fig. 1). The stimulation of beta-adrenergic receptors by catecholamines causes relaxation of the arterial and trabecular smooth muscle. The beta-2 subtype is probably the most important receptor mediating these effects (Dhabuwala *et al.* 1985). Adrenaline has high affinity for this receptor, whose stimulation partly counteracts the constrictor effects of this catecholamine, which are mediated by alpha-adrenergic receptors.

One of the mechanisms by which cyclic nucleotides induce the relaxation of smooth muscle is through the opening of potassium channels, which hyperpolarize the cell. The activation of potassium channels by PGE1 action, an effect mediated by AMPc, has been demonstrated (Christ *et al.* 1996).

The termination of erection takes place via increased adrenergic activity, and it has two components: a direct constrictor effect on the smooth muscle mediated by the alpha1- and alpha2-receptors and an indirect effect, whereby the vasodilator effect of noncholinergic neurotransmitter nerves is inhibited by a prejunctional, alpha2-adrenergic-mediated mechanism (Saenz de Tejada & Moncada 1996).

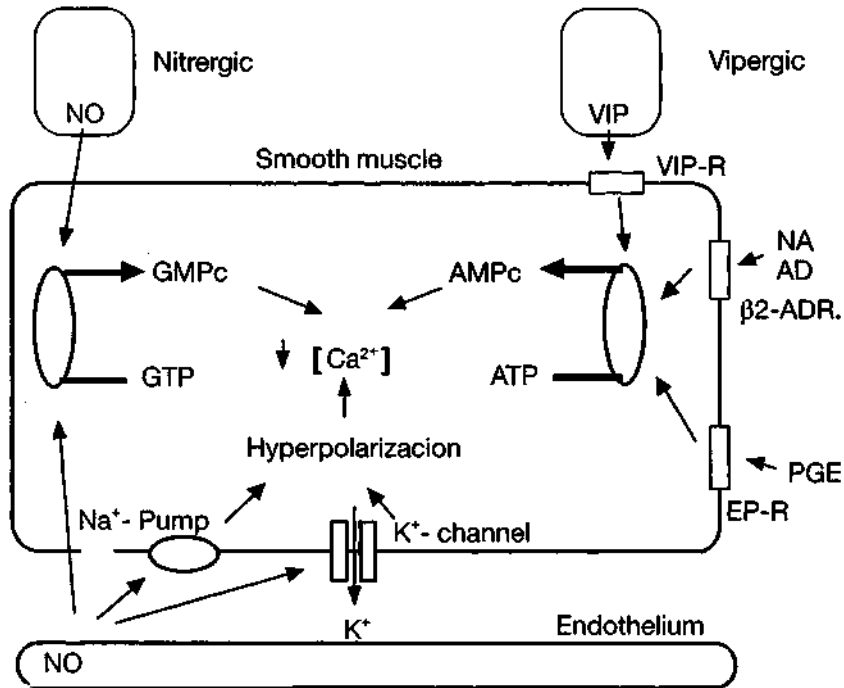


Fig. 1. The three pathways that regulate penile smooth muscle relaxation: cGMP, cAMP and hyperpolarization. (NA=noradrenaline, AD= adrenaline,  $\beta$ -ADR=  $\beta$ 2-adrenergic receptor, EP-R=prostaglandin E receptor, VIP-R= vasoactive intestinal peptide receptor, Na<sup>+</sup>-pump= Na<sup>+</sup>-K<sup>+</sup>-ATPase, NO nitric oxide) (From Saenz de Tejada & Moncada 1996).

## 2.3. Evaluation of erectile dysfunction

### 2.3.1. Patient history and use of questionnaires

The evaluation of ED begins with a comprehensive patient history and physical examination. A careful sexual history and knowledge of current illnesses and medications are essential. In the study by Davis-Joseph and colleagues (1995), history and physical examination had 95 % sensitivity, but only 50% specificity in diagnosing organic ED. The accuracy rates of history and physical examination in diagnosing ED were 80% and 60%, respectively.

The history of sexual function is best obtained through self-reporting by the patient. In an effort to improve the way in which men communicate about their sexual function, O'Leary and colleagues (1995) developed and validated a self-administered questionnaire, which they found useful in practice and research. The goal of the analysis was to identify the minimum number of questions that would reliably and validly describe the

four main domains of male sexuality: sexual drive or libido, erection, ejaculation and overall satisfaction. The resulting 11-item index captures the key areas of male sexuality as clearly and concisely as possible.

Visual analogue scale analysis has seldom used for assessment of ED, mainly it is used in evaluating pain in clinical studies (Gillam *et al.* 1997, Yalcin *et al.* 1998) also concerning pain after intracavernosal injections (Kim *et al.* 1997, Sato *et al.* 1998).

Recently, several international questionnaires have been developed. The International Index of Erectile Function (IIEF) has been used widely, and it has been validated in several languages (Rosen *et al.* 1997, Goldstein *et al.* 1998). According to Goldstein and colleagues (1998), the efficacy of sildenafil was assessed on the basis of the scores for the five separate response domains concerning male sexual function on IIEF: erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction.

### ***2.3.2. Laboratory tests***

The laboratory tests of an impotent patient aim to identify treatable conditions or previously undetected medical illnesses that may contribute to ED (Carroll *et al.* 1992). The value of routine endocrinologic testing in the evaluation of impotent men is controversial, as the overall incidence of endocrinopathy in impotent patients varies from 1.7% to 35%, with most large series reporting incidences closer to 1.7% (Johnson & Jarow 1992). The effectiveness of hormonal replacement in the treatment of hypogonadal impotence has also been rather disappointing. Morales and associates (1994) reported a total response rate of only 9% among patients treated with oral androgen replacement. Up to 20% of elderly men who undergo estrogen therapy or surgical castration for prostate cancer are able to maintain erections adequate for intercourse despite the castrate levels of testosterone (Ellis & Grayhack 1963). Therefore, some investigators have suggested that an evaluation of endocrinopathy is only necessary in men who demonstrate clinical evidence of hypogonadism (bilateral testicular atrophy) or report decreased libido (Johnson & Jarow 1992, Friedman *et al.* 1986). If hormonal evaluation is done, it is enough to assess serum testosterone. The National Institutes of Health (NIH) suggested the use of an a.m. serum testosterone value (NIH Consensus Conference 1993). Serum testosterone levels, however, vary widely in normal men and are related to the episodic secretion of LH (Spratt *et al.* 1988).

### ***2.3.3. Functional studies of ED***

Evaluation of nocturnal penile tumescence (NPT) was one of the earliest tests devised to study erectile dysfunction. The association between sleep and erections was documented as early as 1940 by Halverson. Aserinsky and Kleitman (1953) first described rapid eye movement (REM) sleep and later recognized that nocturnal erections seemed to correspond to the REM periods during normal sleep. Fischer (1965) found the association between REM sleep and erections. In 1970, Karacan suggested that NPT could be used to evaluate ED. NPT testing might be a useful method for differentiating between organic

and psychogenic impotence: the mechanism of NPT is presumed to rely on neurovascular response mechanisms similar to those seen in erotically induced erections. The basic assumption is that the relevant psychologic factors which may inhibit sexually induced erection while awake would be inoperative during sleep. The truth of this assumption has not been proven. Some investigators have reported that NPT studies correlate poorly with patient-reported sexual performance (Condra *et al.* 1986). At least two consecutive nights of recording NPT are necessary to evaluate nocturnal penile tumescence and rigidity; in addition, sexual intercourse seems to decrease nocturnal penile tumescence and rigidity, although not statistically significantly (Hatzichristou *et al.* 1998).

The validity and usefulness of NPT studies in the evaluation of ED have been questioned, and the normative values and the standardized technique available for determining such parameters as the number of episodes, the degree of tumescence and rigidity, have not been well established. Nor has it been determined what constitutes a normal NPT study (Wein *et al.* 1981, Sohn *et al.* 1993).

In 1985, Bradley and Timm described the Rigiscan monitoring device (Dacomed Corporation, Minneapolis, MN) used by patients at home to provide continuous recording of penile tumescence and rigidity (NPTR)(Figure2). It has been used widely in NPT studies (Karadeniz *et al.* 1997) and also for monitoring during audiovisual sexual stimulation (AVSS) (Martins & Reis 1997).

AVSS tests have been used for the initial screening of psychogenic erectile dysfunction: a positive response to visual erotic stimulation is strongly indicative of a predominantly psychogenic cause of erectile dysfunction (Martins & Reis 1997). The use of vibrotactile stimulation and visual sexual stimulation together may assist in determining the potential sexual potency of men experiencing erection problems during the process of differential diagnosis (Rowland *et al.* 1994).



**Fig. 2. Rigiscan ambulatory penile tumescence and rigidity monitoring device.**

### 2.3.4. *Pharmacotest*

Intracorporeal injection of vasoactive agents, which was first introduced by Virag and associates, was found to be useful as a diagnostic tool in patients with suspected vasculogenic impotence (Virag *et al.* 1984, Abber *et al.* 1986). Theoretically, vasoactive substances substitute for the neurotransmitter to activate arterial and sinusoidal mechanisms. Initially, a positive erectile response, defined as rigid erection, has been presumed to signify normal vascular status. If only short-lived, partial or no response resulted from the injection, vascular ED was presumed (Lue & Tanagho 1987). In 1994, Pescatori and co-workers demonstrated that a positive erectile response implies normal veno-occlusive function, but not necessarily normal arterial function. A negative erectile response may be due to excessive adrenergic constrictor tone as a result of anxiety (Buvat *et al.* 1986). It has also been noticed that the level of norepinephrine in penile blood during a pharmacotest is higher in patients with psychogenic ED than in healthy controls or patients with vascular ED (Kim & Oh 1992).

There are many vasoactive agents that can be used for pharmacotesting and administered as therapy for ED (Junemann & Alken 1989, Stackl *et al.* 1990). In a multicenter study comparing papaverine, papaverine-phenolamine and PGE1, PGE1 emerged as the most reliable diagnostic drug with an overall erection rate of 74% and a prolonged erection rate of only 0.1% (Porst 1990). Nisen & Cormio (1993) concluded in their study that pharmacotesting with a high dose of prostaglandin is a useful screening test for vasculogenic impotence. There have been several methods to enhance the diagnostic accuracy of pharmacotesting: it has been used with initial high doses or re-dosing or combined with genital self-stimulation or vibratory stimulation (Donatucci & Lue 1992, Janssen *et al.* 1994, Incrocci *et al.* 1996). Visual erotic stimulation (VES) or AVSS have also been used with pharmacotesting to improve its accuracy (Katlowitz *et al.* 1993, Janssen *et al.* 1994, Vrugink *et al.* 1995). Montorsi and associates (1996) showed that a combination of injection and genital plus audiovisual sexual stimulation caused a significantly greater erectile response than re-dosing.

The most feared complication of pharmacotesting is prolonged erection (Fouda *et al.* 1989). Younger patients with nonvascular ED are most prone to prolonged erection (Lomas & Jarow 1994). Therefore, the dose used for testing should be adapted to the history of the patient and reduced in the presence of suspected neurogenic or psychological ED (Witjes *et al.* 1992).

### 2.3.5. *Vascular evaluation of ED*

Color duplex Doppler ultrasound is a minimally invasive method for studying the arterial blood supply to the penis (Lue *et al.* 1985, Gall *et al.* 1989, Lewis & Mauda 1994). It assesses the integrity of the arterial supply to the penis and provides some useful information on the veno-occlusive mechanism (Nisen *et al.* 1993). Because the arterial diameter and the flow rate change during the different phases of erection, duplex Doppler ultrasound is performed after pharmacostimulation and, if necessary, after self-stimulation (Lue 1990). Montorsi and associates (1996) suggested that color Doppler sonography

should be performed after an injection plus genital and audiovisual sexual stimulation: when the erectile response does not equal the maximal physiological erection reported by the patient, a second injection with stimulation should be given. Ultrasonic and pulsed Doppler scanning after pharmacostimulation can only be done on the area distal to the pubic bone. When the study suggests an arterial disease and medical treatment is unsuccessful, further visualization with internal pudendal arteriography may be indicated (Lue & Tanagho 1987). It is recommended that all pudendal angiographies should be done after an intracavernosal injection, which gives good visualization of the penile arterial tree (Lue & Tanagho 1987).

A more precise assessment of this mechanism requires a specialised invasive test: the alternatives for diagnosing veno-occlusive dysfunction are cavernosography and pharmacologic cavernosometry (Wagner 1981, Wespes *et al.* 1986, Shabsigh *et al.* 1991). These tests should be done if patient history supports congenital venous leakage or arterial supply of cavernous body has been shown to be normal and intracavernosal injection test is negative.

Although many impotent men who underwent cavernosography were found to have a venous leak, the initial enthusiasm for venous ligation procedures has waned due to the poor long-term outcome seen in many patients (Kim & McVary 1995). The finding of venous leakage is often related to other abnormalities in the erectile mechanism, such as intrinsic sinusoidal disease (Aboseif *et al.* 1992).

Over the past few years, attention has been focused on structural investigation of cavernous tissue obtained by needle biopsy as a tool in the diagnosis of diseases of the cavernous body (Wespes *et al.* 1992).

### ***2.3.6. Neurogenic evaluation of ED***

The diagnosis of neurogenic ED is problematic, as there is no test available to examine the autonomic nervous system (Weiske 1997). The measurement of the latency of the bulbocavernous reflex (BCRL) is probably the most widely used neurophysiologic test. It can reveal only lesions of the somatic penile innervation (pudendal nerve), but not of the autonomic innervation (parasympathetic and sympathetic nerves). Wagner and Gerstenberg (1988) reported measurement of electric potentials in the cavernous body. Unfortunately, corpus cavernosum EMG (cc-EMG) does not meet the demand to detect reliably autonomic neuropathy of the cavernous body and smooth muscle dysfunction as a result of degeneration because of artifacts; there is, however, some hope that intelligent software will be capable of identifying and eliminating these artifacts in the future (Stief *et al.* 1994).

## 2.4. Conservative treatment options

### 2.4.1. Psychosexual therapy

Psychosexual therapy for ED problems was introduced in the early part of this century with Freudian-style psychoanalysis. In 1970, a treatment programme involving a combination of behavioral and psychotherapeutic elements was described, and a 70% success rate after 5 years of follow-up was reported (Barnes 1991). Nowadays, these methods have mostly been replaced by more behaviorally oriented therapy, which aims to reduce performance anxiety via programmed relearning of sexual behavior. Hartman (1998) concluded that psychosexual therapy is a feasible treatment option, with significant improvements in 50 to 80% of cases, but its long-term outcome is less favorable.

Surridge and co-workers (1998) concluded that men with ED want to have a rigid penis, while they and their partners are less interested in having help with relationship issues, general sexual issues and life style issues.

### 2.4.2. Vacuum devices

The vacuum constriction device (VCD) works by a combination of the twin principles of vacuum and tension: the negative pressure (vacuum) device increases corporeal blood flow, thereby inducing an erection, which is maintained by a constriction ring (tension) around the base of the penis that decreases corporeal venous drainage. VCD was developed over 100 years ago. Dr. John King introduced the first device in 1874, and the first patent was issued for the device to Dr. Otto Lederer in 1917. It took over 100 years before the device was approved as a legal treatment option; Osbon's device (ErecAid™) was granted FDA permission in 1982 (Osbon 1983).

It has been reported that erections have succeeded in 84-95% of cases (Nadig *et al.* 1986, Cookson & Nadig 1993, Baltaci *et al.* 1995) and overall satisfaction with the device has been slightly lower, 72-94% (Turner *et al.* 1991, Price *et al.* 1991, Vrijhof *et al.* 1994).

Complications are generally of minor nature: pain, either during the suction (20-40%) or caused by the ring (45%), is the commonest complaint, which is most frequently presented at the beginning of treatment (Turner *et al.* 1990). Pain on ejaculation has been reported by 3-16% of users, and an inability to ejaculate by 12-30% (Witherington 1989, Turner *et al.* 1991, Cookson & Nadig 1993). Petechiae on the penis have been reported by 25-39%, concurrent bruising by 6-20% (Cookson & Nadig 1993, Baltaci *et al.* 1995), and numbness as a major problem during erection by 5% (Cookson & Nadig 1993). Few serious complications have been reported, usually due to misuse of the device, such as skin necrosis (Meinhardt *et al.* 1990), Peyronie's disease (Kim & Carson 1993) and Fournier's gangrene (Theiss *et al.* 1995). Many find the main disadvantage of the VCD to be the lack of spontaneity in the production of effective erection and some men complain that the rings act as a reminder of their inadequacy (Turner *et al.* 1992).

In patients who fail to respond both subjectively and objectively to either intracavernosal injection or VCD, a combination of these options should be tested (Chen *et al.* 1995).

### 2.4.3. Hormonal treatment

Testicular function of both the exo- and endocrine compartments decreases at old age, causing a series of clinical symptoms that are analogous to, although less pronounced than, the menopausal syndrome: these symptoms are considered to represent the male climacterium or andropause (Vermeulen 1993, Swerdloff & Wang 1993). With age, an increase of sex hormone-binding globulin (SHBG) occurs in plasma and a corresponding decrease is seen in non-SHBG-bound testosterone, which is believed to be the only effectively bioavailable agent for target tissues (Nahoy & Roger 1990, Gray *et al.* 1991). The circadian rhythmicity in blood testosterone decreases in healthy aging men compared to healthy young men (Bremner *et al.* 1983). Long-term androgen deficiency in aging men may lead to asthenia, a decrease of muscle mass, osteoporosis, decreased sexual activity and, in some cases, changes in mood and cognitive functions (Swerdloff & Wang 1993).

Androgen substitution may improve ED in some patients with diagnosed hypogonadism (Krane *et al.* 1989). Improvements in mood and sexual function can be elicited in hypogonadic men by increasing the plasma concentrations of either testosterone (T) or dihydrotestosterone (DHT) (Kuhn *et al.* 1986). However, it has been demonstrated that, in hypogonadal men with impotence, the administration of testosterone alone results in improvement of erection in only approximately 60% of patients (Morales *et al.* 1997). Androgens facilitate erection, and their absence does not necessarily preclude good erectile function. Furthermore, there are some hypogonadal men in whom ED is more dependent on vascular risk factors than low testosterone levels (Morales *et al.* 1997). In elderly men, short-term studies on a small number of patients have been performed and have shown favorable effects on sexuality, well-being and muscular strength (Morley *et al.* 1993, Tenover 1992). However, it is well known that a great majority of prostatic carcinomas are androgen-dependent, and it is reasonable to believe, until proved otherwise, that androgen substitution might accelerate the growth and evolution of prostatic carcinoma, which is why androgen substitution should only be performed under strictly controlled conditions (Vermeulen 1993). Kirby (1994) proposed that testosterone should not be used in eugonadal men with ED because it may enhance prostatic hyperplasia or promote the growth of prostate cancer.

Which hormonal changes could be implied in the pathophysiology of prostatic anomalies in men aged over 50 years remains to be debated: testosterone (T) and dihydrotestosterone (DHT) are two potent androgens with opposite effects regarding aromatase activity, which presents in prostatic stroma and is suspected to have a pathogenic influence through local estradiol synthesis. Testosterone is the main substrate for aromatase and estradiol synthesis, while dihydrotestosterone is not aromatizable and, at a sufficient concentration, lowers the testosterone and estradiol levels (de Lignieres 1993). In a 1.8-year survey of 37 men aged 55-70 years, daily percutaneous DHT treatment (>8.5 nmol/l) effectively induced clinical benefits while slightly but significantly reducing prostatic size. DHT may therefore be considered an attractive alternative for long-term treatment of andropause (de Lignieres 1993).

Because of the poor bioavailability of the drug, oral therapy with testosterone is less effective than parenteral testosterone in achieving normal serum testosterone levels and has a higher incidence of hepatotoxicity and adverse serum lipid effects (Krane *et al.*

1989, Morley & Kaiser 1989). New transdermal formulations of testosterone and dihydrotestosterone as well as oral formulations without associated liver toxicity have been developed (Wagner & Tejada 1998).

Bromocriptine has been used successfully in men with hyperprolactinaemia-associated hypogonadism, with subsequent improvements in erectile dysfunction (Leonard *et al.* 1989).

#### **2.4.4. Oral drug therapy**

*Yohimbine* is an indole alkaloid derived from the bark of the Central African *Pausinystalia yohimbe* tree. It has been classified as an aphrodisiac for over a century, but it was only recently investigated in controlled trials. Yohimbine is a centrally and peripherally acting alpha-2-adrenoceptor antagonist (Grunhaus *et al.* 1989); it produces a rise in sympathetic drive by increasing noradrenaline release and the firing rate of cells located in noradrenergic nuclei of the central nervous system. It is 50 to 100 times more active at presynaptic compared to postsynaptic receptors (Brown *et al.* 1980). Many studies have failed to demonstrate any statistically significant benefit of yohimbine over placebo in the treatment of erectile failure (Morales *et al.* 1982, Susset *et al.* 1989). Otherwise, several placebo-controlled, non-randomized trials have suggested the efficacy of yohimbine (Miller 1968, Sobotka 1969, Sonda *et al.* 1990). A promising effect of yohimbine on psychogenic impotence was reported by Reid and associates (1987): a 62% response rate versus a 16% rate for placebo. Many studies have supported the original assessment of yohimbine as an erectogenic agent, although the optimal dose remains undetermined (Susset *et al.* 1989). Yohimbine has no effect on erectility when given intracavernosally (Brindley 1986). The adverse effects of yohimbine hydrochloride include anxiety, nausea, palpitations, fine tremor and elevation of diastolic blood pressure (Morales *et al.* 1995), but serious adverse reactions are infrequent and reversible (Ernst & Pittler 1998).

In association with testosterone and strychnine, yohimbine contributed to a 80 % improvement or cure rate in a series of 10,000 impotent men reported by Margolis and associates (1971). Clark and co-workers (1985) concluded that testosterone is not required for the enhancement of sexual motivation by yohimbine and supported the suggestion that alpha-2-adrenoceptors are involved in the modulation of sexual arousal. Recent studies have attributed a synergistic effect to a combination of yohimbine and trazodone (Montorsi *et al.* 1994).

*Trazodone* is an antidepressant that has been used empirically for the treatment of erectile dysfunction. In addition to its serotonergic activity, trazodone has also been demonstrated to have alpha-blocking properties. Its activity was initially found incidentally through anecdotal observations of improved libido and the development of priapism in men (Saenz de Tejada *et al.* 1991) and a woman taking trazodone for its antidepressant properties (Pescatori *et al.* 1993). The mechanism of trazodone has not been elucidated, but it is recognized that the drug acts centrally by increasing serotonin at the 5-HT<sub>1c</sub> receptor through reuptake inhibition (Abber *et al.* 1987). Some studies have reported that trazodone used as a single agent is effective in about 60% of patients (Abber *et al.* 1987). Meinhardt and co-workers (1997) concluded recently that in a group of patients

not selected on the basis of the etiology of ED, the efficacy of trazodone could not been demonstrated over placebo. When injected intracavernosally to patients with impotence, trazodone causes tumescence, but not full erection (Azadzo *et al.* 1990).

*Phentolamine*, which is an alpha1/alpha-2-receptor antagonist, was suggested to be effective in an initial study by Gwinup (1988). Zorigniotti reported a 42% positive response in men with psychogenic or mild vascular impotence in 1993. In an trial by Becker and associates (1998), the drug was found to be free of major systemic side effects. Phentolamine mesylate is now being examined in large multicenter studies in men with ED, and it will also be examined in women with female sexual dysfunction (FSD) (Goldstein *et al.* 1998).

*Apomorphine* is a dopaminergic agonist with direct central D2 receptor agonist activity. It has long been known to induce bouts of yawning and penile erections in animals and humans when administered by subcutaneous injection (Morales *et al.* 1995). Morales and co-workers (1995) developed a buccal tablet of apomorphine that appears to be effective in many patients with minimal vascular impotence; 67% of patients with psychogenic impotence experienced durable erections with apomorphine. The adverse effects of apomorphine include persistent yawning, nausea, vomiting and hypotension, but recent formulations (a sublingual, sustained-release tablet) minimise these side effects (Heaton *et al.* 1995).

*L-Arginine* is a precursor of nitric oxide. The only study reported in the literature is a placebo-controlled trial in which large oral doses of L-arginine (2800 mg) were given daily for a short period (2 weeks). 40% of the patients experienced improvement in their erections (Zorigniotti & Lizza 1994).

*Sildenafil* is a competitive and selective inhibitor of cGMP type V phosphodiesterase, the predominant isozyme metabolizing cyclic GMP in the corpus cavernosum (Boolell *et al.* 1996). Normal penile erection depends on the relaxation of smooth muscles in the corpora cavernosa. In response to sexual stimuli, cavernous nerves and endothelial cells release nitric oxide, which stimulates the formation of cyclic guanosine monophosphate (GMP) by guanylate cyclase (Burnett 1995). In a large study of patients with erectile dysfunction of organic, psychogenic or mixed causes, it was found that 69 percent of all attempts at sexual intercourse were successful among men receiving sildenafil as compared to 22 percent of those receiving placebo (Goldstein *et al.* 1998). Headache, flushing and dyspepsia were the most common adverse effects of sildenafil, occurring in 6 to 18 % of the men (Goldstein *et al.* 1998).

#### **2.4.5. Topical drug therapy**

*Nitroglycerin (glyceryl trinitrate)*, a nitric oxide donor, applied topically to the penis or the perineum has been shown to induce some degree of penile erection (Claes & Baert 1989). Side effects include hypotension and severe headache, which may also be experienced by the partner; this can be avoided by applying the pasta to the perineum.

*Papaverine* gel applied topically to the penis has been shown to increase penile blood flow (Kim *et al.* 1995): it appears to augment reflex erections in patients with spinal cord injuries and may be of benefit in this population.

*Minoxidil* is a vasodilator widely known for its capacity to reverse alopecia androgenetica, and it has also been investigated in the management of erectile dysfunction. In a direct comparison with nitroglycerin, minoxidil was shown to be more effective in producing erectile rigidity (Cavallini 1991). It has further been shown that the addition of capsaicin may increase the efficacy of minoxidil (Cavallini 1994).

Topical *prostaglandin E1* has also been investigated in the treatment of ED. Kim and McVary (1995) concluded, in a phase I placebo-controlled, non-blinded investigation, that topical prostaglandin E1 appears to be safe and well tolerated after application to the genitals and significantly increases blood flow to the penis.

#### ***2.4.6. Transurethral drug therapy***

Padma-Nathan and co-workers (1994) reported that intraurethral administration of alprostadil 500 µg elicits marked cavernosal smooth muscle relaxation. Alprostadil pellets measuring 1 x 1 mm are placed 2 to 3cm into the distal urethra after voiding followed by massaging of the distal shaft. Approximately 20% of the medication absorbs into the corpus cavernosum via intercommunicating veins. The remaining 80% of the drug is absorbed into the systemic circulation, although 99% of it is metabolized on the first pass through the lungs (Padma-Nathan *et al.* 1994).

In 1997, Padma-Nathan and associates reported a double-blind, placebo-controlled multicenter phase II study including 1511 men with chronic erectile dysfunction due to various organic causes. The men were first tested in the clinic with up to four doses of the drug (125, 250, 500 and 1000 µg), and those with sufficient responses were randomly assigned to treatment with either an effective dose of alprostadil or placebo for three months at home. 64.9% of the patients showed responses sufficient to enter the "at home phase" of the study. 62% of the patients who used this system at home had, on at least one occasion, an erection sufficient for intercourse. The most common side effect was mild penile pain, which occurred after 10.8% of alprostadil treatments. Hypotension occurred in the clinic in 3.3% of men receiving alprostadil. None of them had priapism or penile fibrosis. Porst (1996) concluded in his study that, due to the superior efficacy and fewer side-effects, intracavernosal self-injection therapy with alprostadil remains the gold standard in the management of male impotence.

#### ***2.4.7. Intracavernosal therapy***

In 1982, Virag reported incidental findings of penile erection induced by an intracavernous injection of papaverine. One year later, Brindley reported the induction of erection with phenoxybenzamine (Brindley 1983a). 1984 Virag and co-workers suggested that intracavernous injection of papaverine could be used diagnostically to differentiate between vasculogenic and nonvasculogenic impotence. Since then, a number of agents have been utilised for diagnostic and treatment purposes, most commonly papaverine and phentola-

mine and later alprostadil (PGE1). Zorgniotti and Lefleur (1985) began teaching patients autoinjection of a mixture of papaverin and phentolamine in home use. These drugs have been administered alone or in a variety of combinations with good results.

#### 2.4.7.1. *Papaverine hydrochloride*

Papaverine is an opium derivative that increases intracellular cAMP via nonselective inhibition of phosphodiesterases. In this way, papaverine alters the membrane calcium channel function and increases the efflux from cells, resulting in a decline of intracellular calcium levels and subsequent smooth muscle cell relaxation (Wang & Large 1991). Papaverine relaxes all components of the penile erectile system, i.e. the penile arteries, the cavernous sinusoids and the penile veins (Kirkeby *et al.* 1990). Papaverine is acidic in solution (pH 3 to 4) and may precipitate at pH higher than 5. Papaverine has relatively short plasma life (1-2 h), and it is extensively metabolized in the liver. High concentrations are obtained following intracavernosal injection, and the drug is relatively slow to clear from the corpora (Hakenberg *et al.* 1990).

Various doses of papaverine have been used in the diagnosis and treatment of ED. At the University of Iowa, from 1986 to 1989, papaverine alone was used for test injections, and 55% of 232 patients achieved satisfactory erectile response at initial doses of 5 to 60 mg (Fallon 1995). Only 35% of 356 patients combined from five studies using papaverine alone achieved full erection (Juneman & Alken 1989). In Virag and associates' follow-up study in 1980-1988, the average doses were  $20 \pm 12$  mg of papaverine for the psychogenic type and  $40 \pm 25$  mg of papaverine for the organic type of erectile dysfunction (Virag *et al.* 1991).

Because corporal clearance of papaverine is relatively slow, papaverine tends to predispose to priapism (Fouda *et al.* 1989, Hwang *et al.* 1991). According to a literature review of agents, papaverine alone produced priapism in 9.5% of 2,134 patients, papaverine-phentolamine in 5.3% of 2,914 patients, and PGE1 in 2.4% of 1,284 patients (Juneman & Alken 1989). A lethal complication of papaverine-induced priapism has also been reported: when papaverine and phentolamine failed to produce adequate erection, the patient injected a second dose, which resulted in priapism and death from massive pulmonary embolism (Hashmat *et al.* 1991).

Fibrotic nodules were reported in 5.4% of 1,573 patients collected from different series using papaverine monotherapy and papaverine-phentolamine combinations (Juneman & Alken 1989). In a prospective study, Levine and coworkers (1989) reported that the percentage of men with painless nodules almost consistently doubled from one follow-up examination to the next, being 8% at 1 month, 17% at 3 months, 32% at 6 months, and 57% at 12 months. Aboseif and coworkers (1989) studied monkeys which were given 75 intracavernous injections of papaverine over a nine-month period and found significant histologic changes with a loss of normal architecture in both light and electron microscopy.

The solution of papaverine hydrochloride is acidic (pH 3 to 4), and the importance of this for the production of intracavernous fibrosis has been discussed (Seidmon & Samaha 1989). It was suggested that an intracavernosal injection buffered by blood will lead to

precipitation of the drug, which may cause primary intracorporeal scarring. After all, rabbit studies have shown that intracorporeal scarring is related to the drug itself rather than the pH or osmolarity of the solution (Stackl *et al.* 1989). Papaverine is extensively metabolized in the liver and some elevation of liver transaminases may therefore take place, but the hepatotoxicity of papaverine is less well known (Andersson *et al.* 1991). Prolonged pain after intracavernous papaverine monotherapy or papaverine in combination with phentolamine is rare (Levine *et al.* 1989).

#### 2.4.7.2. Prostaglandin E1 (alprostadil)

PGE1 is a natural constituent of many mammalian tissues (Piper 1973), and human cavernous tissue generates prostaglandins (Roy *et al.* 1984). PGE1 is known to have a variety of pharmacological effects: it produces systemic vasodilatation, prevents platelet aggregation and stimulates intestinal activity. Administered systemically, the drug has been used clinically to a limited extent. It has been given to keep the ductus arteriosus patent in congenital heart disorders and also as a treatment of peripheral vascular disease. It is of interest that it has a short duration of action and is extensively metabolized; as much as 80% may be metabolized upon one pass through the lungs, which may partly explain why PGE1 seldom causes circulatory side-effects when injected intracavernosally (Stackl *et al.* 1988, Andersson *et al.* 1991).

PGE1 relaxes the isolated penile smooth muscle contracted by noradrenaline and PGF 2-alpha (Hedlund & Andersson 1985). It exerts its effect by activating adenylate cyclase via G-protein cleavage. When administered intracavernosally, PGE1 has a half-life of 5 to 10 minutes (Stackl *et al.* 1988) and is almost completely metabolized in the corporal tissue.

The published reports on intracavernosal use of PGE1 since 1986 (Ischii *et al.* 1986, Virag & Adaikan 1987) consist primarily of data derived from uncontrolled retrospective studies with different formulations. PGE1 has been used as monotherapy for erectile dysfunction in doses typically ranging from 1 to 40 µg. Earle and associates (1990) reported that patients with spinal cord injury are very sensitive and may respond to as little 1 or 2 µg. Hwang and co-workers (1989) treated 80 impotent men with a single 20 µg injection of prostaglandin E1, and their overall positive response rate was 79%, while in patients with psychogenic and neurogenic impotence the response rate was 100%. The assumption that intracavernous injections of vasoactive drugs, including PGE1, are most successful in patients with neurogenic, psychogenic and mild arteriogenic impotence was supported by Gerber and Levine's findings in 1991. Men with psychogenic and neurogenic impotence and those with ED following a radical pelvic operation required significantly lower doses of prostaglandin E1 to achieve tumescence. PGE1 was increasingly effective as the doses increased from 2.5 to 20 µg (Schramek & Waldhauser 1989). A dose-response relation was also found in another trial of alprostadil by von Heyden and colleagues (1993). Fallon (1995) has concluded several studies of PGE1 with an overall response rate of 71%, but the erectile dysfunction in these studies has been of mixed origin. The most frequently used initial dose was 20 µg. Typically, a latency of about 10 minutes was noted before the onset of erection, and the duration of erection ranged from 30 minutes to 6 hours with an

average of about 2 hours. Several studies have confirmed the efficacy of PGE1 to induce erections sufficient for intercourse, and in one meta-analysis PGE1 proved to be the most efficient monotherapeutic intracavernosal drug with an overall success rate of 75% (Juneman & Alken 1989).

Prolonged erection or priapism is seldom seen in PGE1 users. In a literature review of different agents, PGE1 produced priapism in 2.4% of 1,284 patients (Juneman & Alken 1989). Linet and Ogrinc (1996) reported, in their three separate multi-institutional prospective studies, prolonged erection (4 to 6 h) in 5% of men and priapism (> 6 h) in 1%. Many large studies have reported no priapism at all (Stackl *et al.* 1988, Ishii *et al.* 1989, Sarosdy *et al.* 1989, Gerber & Levine 1991). Gerber and Levine (1991) conclude that, while prolonged erections may still occur with prostaglandin E1, their likelihood is extremely small once the proper PGE1 dose has been determined.

PGE1 monotherapy seems to result in a very low incidence of fibrosis (Ravnik-Oblak *et al.* 1990, Gerber & Levine 1991, Linet & Ogrinc 1996, Porst 1996). Chen and associates (1996) compared PGE1 users with or without penile scarring and did not find any significant differences between the groups with regard to the duration of follow-up, the injection frequency, the PGE1 dose per injection, the total number of injections or the total PGE1 dose: penile scarring and fibrosis are sporadic and unpredictable. Support for the lack of side-effects in cavernous tissue associated with PGE1 has also been derived from animal studies (Aboseif *et al.* 1989, Stack *et al.* 1989, Hwang *et al.* 1991): Aboseif and colleagues (1989) found that monkeys injected with 20 µg of prostaglandin E1 twice weekly until a total of 75 injections was reached showed few pathological changes in cavernous tissue. The changes were similar to those caused with intracavernosally injected saline alone.

Prolonged pain, which is variously described by patients as occurring through the shaft of the penis, in the perineum or both (Fallon 1995) or an aching sensation along the ventral surface of the penis lasting for 30 minutes to 3 hours (Gerber & Levine 1991) after the injection is quite common with PGE1 alone. The incidence of penile pain after the injection of PGE1 has varied in different series from 0 to 91% (Stackl *et al.* 1988, Hwang *et al.* 1989, Ishii *et al.* 1989, Lee *et al.* 1989, Earle *et al.* 1990, Schramek *et al.* 1990, Linet & Ogrinc 1996, Kim *et al.* 1997). In most cases, however, the pain is mild. Gerber and Levine (1991) did not find any difference in pain incidence based upon the etiology. The etiology of pain has not been fully elucidated. The pain is probably induced by alprostadil itself, because PGE1 can sensitize the peripheral terminals of primary afferent nociceptors and, consequently, produce hyperalgesia (Ferreira 1983, Capetola 1983). Alkalinization of the injected solution from pH 4.17 to 7.05 by the addition of sodium bicarbonate was found to produce significant alleviation of penile pain in a randomized study of patients injected with a mixture containing 10 µg of PGE (Moriel & Rajfer 1993). The addition of procaine has also been experimentally used as a method of reducing PGE1-associated pain (Schramek *et al.* 1994): a combination of 20 µg of PGE1 with 20 mg of procaine decreased the incidence of local pain significantly. Multidrug combinations including PGE1 have resulted in a lower incidence of pain (Govier *et al.* 1993, Montorsi *et al.* 1993).

### 2.4.7.3. *Phentolamine*

Phentolamine is a competitive alpha-adrenoceptor antagonist with similar affinity for alpha1- and alpha2-adrenoceptors (Andersson *et al.* 1991). In addition, the drug may have a direct non-specific, relaxant effect on vessels (Taylor *et al.* 1965). Its plasma half-life is 30 minutes. Since a single intravenous phentolamine injection does not result in a satisfactory erectile response in most cases, the drug has been used in combination with other agents, primarily papaverine (Zorgniotti & Lefleur 1985, Juneman & Alken 1989).

### 2.4.7.4. *Phenoxybenzamine*

Phenoxybenzamine is a potent alpha1- and alpha2-blocker. It also blocks the receptors for acetylcholine, histamine, and 5-HT. The adrenergic blockade is prolonged and the serum half-life is 24 hours, and prolonged effects of phenoxybenzamine may be demonstrable for 3-4 days (Andersson *et al.* 1991). Systemic side effects are common, including postural hypotension, which may be associated with reflex tachycardia and cardiac arrhythmias. Local pain at the injection site, prolonged erections and cavernous fibrosis may occur, and the agent has also been demonstrated to have carcinogenic effects in rodents (Flind 1984).

### 2.4.7.5. *Vasoactive intestinal peptide (VIP)*

VIP is a potent vasodilator that inhibits contractile activity in many types of smooth muscle and stimulates cardiac contractility and many exocrine secretions (Fahrenkrug 1989). Gu and associates (1984) suggested that VIP not only was the principal neurotransmitter involved in penile erection, but that the depletion of peptide may also play a key role in the development of impotence. In animals works, VIP was later shown to be the most important noncholinergic transmitter involved in penile erection (Juenemann *et al.* 1987, Aoki *et al.* 1990). Later, however, the weak intracavernosal erectile response suggested that it cannot be the only noncholinergic mediator for the relaxation of penile erectile tissues (Roy *et al.* 1990). Combination with phentolamine has resulted in a better erectile response (McMahon 1996).

### 2.4.7.6. *Moxisylyte (thymoxamine)*

Thymoxamine has a competitive and relatively selective blocking action on alpha1-adrenoceptors and may also have antihistaminic actions (Andersson 1991). Brindley (1986) showed that moxisylyte produces erection when injected intracavernosally. It has been shown that moxisylyte is less active than papaverine, but its main advantage is its safety (Buvat *et al.* 1989). Navratil and co-workers (1995) concluded that there was no instances of priapism and no pain was experienced on injection. Moxisylyte is able to

induce an erectile response at a minimum dose of 10 mg. Costa and co-workers (1993) found out in their double-blind study that, compared to placebo, intracavernous injection of 10, 20 and 30 mg of moxisylyte is efficient at inducing pharmacological penile erection without any side effects: a majority of the patients had predominantly psychogenic ED (Costa *et al.* 1993). Buvat and associates (1991) also found out that there is a reduced rate of fibrotic nodules in the cavernous bodies following intracavernous injections of moxisylyte compared to papaverine.

#### 2.4.7.7. *Multidrug combinations*

The first combination used was papaverine combined with phentolamine, which has been extensively used since 1985 (Zorgniotti & Lefleur 1985). This combination has been more effective, especially for older men, than papaverine alone (Richter *et al.* 1990). A combination of three drugs, papaverine-phentolamine-PGE1 (Trimix), was introduced in 1991 by Bennet and associates. They concluded that the synergism of agents reduces the amounts of individual drugs needed while improving erectile quality and reducing side effects. A randomized crossover study of 228 patients comparing the efficacy of Trimix with that of PGE1 alone and with a mixture of papaverine and phentolamine also revealed the superiority of Trimix (McMahon 1991). A long-term follow-up also showed a low incidence of priapism (1.7%), pain (3.5%) and scarring (4.2%) (Govier *et al.* 1993). It has further been shown that the total dose and volume of the injected drugs is reduced when several vasoactive drugs are combined (Bennet *et al.* 1991, McMahon 1991, Govier *et al.* 1993, Montorsi *et al.* 1993, Fallon 1995). Montorsi and co-workers used (1993) a four-drug vasoactive mixture (papaverine hydrochloride, PGE1, phentolamine mesylate, atropine sulphate) for intracavernous injection therapy in 94 patients with vasculogenic impotence with good results, the total response rate being over 90%. A mixture of six vasoactive substances has been described, which is called Ceritine (contains papaverine hydrochloride, ifenprodil tartrate, atropine sulphate, yohimbine, dipyrindamole, piribedil), which is equally effective as a three-drug combination (Virag *et al.* 1991).

#### 2.4.7.8. *Miscellaneous agents*

Linsidomine, a nitric oxide donor (SIN-1), has been used to treat ED, but it has not been shown to be of significant benefit (Wegner *et al.* 1994). Calcitonin Gene-Related Peptide (CGRP) is a potent vasodilator, as it has been shown in bladder and penis smooth muscle: a combination of CGRP to alprostadil allowed the use of subthreshold dosage of the latter (Stief *et al.* 1990).

#### 2.4.7.9. Long-term results and acceptance of intracavernosal therapy

Many reports do not mention the initial acceptance rates, but after a trial injection at the office, some of the responders normally refuse injection treatment because of pain, inconvenience, lack of regular partner, etc. (Cooper 1991). Long-term follow-up has shown that the proportion of drop-outs varies from 11% to over 50 % (Virag *et al.* 1991, Gerber & Levine 1991, Montorsi *et al.* 1993, Govier *et al.* 1993, Valdevenito & Melman 1994): most reports do not have cover periods beyond 2 or 3 years, but those which have longer-term information show the retention rate of patients to be high (Virag *et al.* 1991). Many reasons for dropping out in the long term have been described: recovery of spontaneous erections, loss of interest, complications, disacceptance of the injection technique, etc. (Fallon 1995). There have been several reports in the literature of transient, partial or complete restoration of spontaneous coital or nocturnal erections in patients using self-injection (Virag *et al.* 1984, Aravena & Bustamente 1986, Buvat *et al.* 1987, McMahon 1991). In conclusion, intracavernous injection therapy is often associated with the restoration of spontaneous erections in patients with psychogenic impotence, but is rarely seen in patients with organic impotence.

### **3. Outlines of present research**

Erectile dysfunction, i.e. a persistent inability to achieve and maintain an erection sufficient for satisfactory sexual activity, is known to be a common condition, which increases with age. This study had the following aims: First, we wanted to use the modern investigation modalities (AVSST, questionnaires, VAS, Rigiscan) in the evaluation of ED. Second, we wanted to learn more about erectile dysfunction and sexuality in men (I-V), especially aging men (IV, V), and third, we wanted to obtain more knowledge about specific questions related to the modern conservative treatment options.

The purposes of the present research were:

1. to determine the effectiveness and safety of high-dose yohimbine for the treatment of mixed-type impotence (I).
2. to test the effectiveness and safety of prostaglandin E1 (PGE1), papaverine hydrochloride (PV) and moxisylyte (MS) and to evaluate the suitability of these three agents for intracavernosal injection tests (ICI test) (II).
3. to assess the long-term outcome of PGE1 treatment and the patients' overall satisfaction with their sexual life (III).
4. to evaluate the sexual functions of aging men with benign prostatic hyperplasia (BPH) before and after transurethral resection of the prostate (TURP) (IV).
5. to study the effect and tolerance of transdermal dihydrotestosterone (DHT) in men with andropausal symptoms (V).

## **4. Patients and methods**

The present work was carried out at the Department of Surgery, Urological Unit, Oulu University Hospital during the years 1991-1998. More detailed descriptions of the materials and methods have been given in the original papers (I-V).

### **4.1. High-dose yohimbine hydrochloride in the treatment of mixed-type impotence (I)**

The series of patients consisted of 29 men with mixed-type erectile dysfunction. Two patients did not complete the whole treatment schedule. Purely psychogenic or organic causes were excluded including patients having a definite arterial or venous cause for impotence. The mean age of the patients was 51 years, the youngest subject being 25 years old and the oldest 69.

The patients underwent the following tests and examinations before the beginning of the treatment: filling in an anamnestic form, physical examination, blood pressure, pulse rate, weight, laboratory tests (hemoglobin, white and red blood cells, platelets, creatinine, testosterone, prolactin, thyroxine, thyroid-stimulating hormone, prostate-specific antigen, urine analysis), assessment of the sensory pain threshold of the dorsal nerve of the penis, bulbocavernous reflex, prostaglandin E1 injection test, AVSST, visual analogue scale (VAS, a 0- to 100-point scale), assessments of libido, rigidity of the penis, failure of erection, duration of erection, and sensation of orgasm. Duplex Doppler ultrasonography was performed on all patients.

The treatment consisted of two 25-day therapy with a 14-day washout period between courses. Patients therapy was started randomly with yohimbine hydrochloride (36 mg per day orally) or placebo and switched over to other test medication.

The patients came for a control visit three times: the first took place at the end of the first part of the trial (25 days), the second at the end of the washout period (39 days) and the third at the end of the second part (64 days). The following examinations were made

on each occasion: blood pressure, pulse rate and weight, testosterone, assessment of side effects, VAS scales, and AVSST. Penile tumescence and rigidity were tested with a portable monitor (Rigiscan) during the AVSST.

The Mann-Whitney test was used to compare the data of the groups.

#### **4.2. Intracavernous injection test in the evaluation of patients with erectile dysfunction (II)**

The study population consisted of 30 consecutive patients with ED at a mean age of 55 years (range 22-71 years). The patients had been referred to our outpatient clinic in the university hospital by primary care physicians. All patients were suspected to have organic erectile dysfunction. Each patient filled in our own questionnaire on sexual disorders. Apart from a clinical examination and hormonal laboratory tests (total testosterone and prolactin), the patient underwent an ICI test with each of the agents: (papaverine hydrochloride (PV), prostaglandin E1(PGE1), moxisylyte (MS) and saline solution (NaCl)) during different visits. Each patient made five visits. Altogether 120 ICI tests were administered.

The order of the ICI test agents was randomized for each patient. A Rigiscan device was used to measure the tumescence and rigidity of cavernous tissue for 15 minutes after each injection. Pulse rate and blood pressure were recorded before the injection and at 5 and 15 minutes afterwards. The degree of erection was estimated clinically (grades 0-5) by the doctor. Grade 0 was no response after the injection, grade 1 was minimal tumescence and no rigidity, grade 2 was moderate tumescence and no rigidity, grade 3 was full tumescence and no rigidity, grade 4 was moderate rigidity, but the penis could be bent, and grade 5 was full rigidity. The grades 4 and 5 are sufficient for penetration. In addition, after each ICI test, the patient evaluated his own satisfaction with the erection and the amount of pain on a visual analogue scale (VAS a 0- to 100-point scale). If the erection persisted for more than two hours, it was released by giving the patient an intracavernous dose of 5 mg of etilephrine before discharge. The ICI tests doses for different test agents were physiological saline 1 ml, papaverine hydrochloride 40 mg (1ml), prostaglandin E1 20 µg (1ml) and moxisylyte 20 mg (1ml). The amounts of PV, PGE1 and MS administered are commonly used in the treatment of impotence.

A statistical comparison of the treatment and control groups in terms of the response to treatment was carried out using the Mann-Whitney U-test.

#### **4.3. Intracavernous self-injection of prostaglandin E1 in the treatment of erectile dysfunction (III)**

The primary study population consisted of 95 patients with ED who had been started on intracavernosal PGE1 medication in the Oulu University Hospital at least three years previously. The patients were invited to a control visit after three years. 26 patients did not come, and the final study population hence consisted of 69 patients. The mean age of the

patients was 60.5 years (range 44 - 83 years). All patients had erectile dysfunction: 30 had mainly a vasculogenic etiology, 31 had mainly a psychogenic etiology, and 8 had mainly a neurogenic etiology. The primary examinations consisted of a thorough sexual history with a questionnaire, physical examination, laboratory tests (hemoglobin, white cells, serum creatinine, serum glucose, serum cholesterol, serum total testosterone). Each patient underwent an intracavernous injection test (ICI) with PGE1 (20 µg) and duplex Doppler ultrasonography of the penile vessels.

Before the control visit, all patients filled in a follow-up questionnaire at home, and the responses were checked when the patient came for the control visit. The questionnaire included several items pertaining to various aspects of sexual function at home and possible problems with PGE1 self-injection. Each patient also evaluated his own satisfaction with erection with or without intracavernosal injection as well as his ejaculation, orgasm and libido on a Visual analogue scale (VAS a 0- to 100-point scale). A clinical examination was made, and the penile shaft was examined by ultrasonography (5MHz, Bruel & Kjaer). Apart from the clinical examination, the patients underwent an ICI test with their home dose of PGE1. The tumescence and rigidity of erection were determined with a portable monitor (Rigiscan). The degree of erection was also estimated clinically (grades 0-5) in the same way as in study II. The erection induced in the examination room was compared to the erection attained at home by the patient.

#### **4.4. Effect of transurethral resection of the prostate on sexual functions (IV)**

The primary study population consisted of 212 consecutive patients with BPH referred for elective electroresection of the prostate. 57 patients were not included in the analysis because of a lack of data. The mean age of the patients was 69 years (range 49-86). The mean prostatic volume determined by transrectal sonography (Bruel & Kjaer) before TURP was 50.4 cm<sup>3</sup> (range 14.0 - 107.0 cm<sup>3</sup>). The mean weight of the prostate chips resected in TURP was 27.4 g (range 3 - 96 g). Incidental malignancies were diagnosed from the chips in only three of the 155 patients (2%).

On the day before TURP, each patient filled in a questionnaire related to this study in our hospital. The questionnaire consisted of 22 items pertaining to various aspects of sexual function, including the patients' life styles and general health, libido, satisfaction with their current sex life, occurrence of early morning erections, coital frequency, sexual potency, satisfaction with erection and ejaculation, percentage of successful intercourses, and the possible detrimental effect of the procedure on potency. When necessary, the staff helped the patient to fill in the questionnaire. The patients completed the same questionnaire 6 and 12 months after TURP.

The Prat test was used to compare the different sexual functions before and after TURP.

#### **4.5. Effects of transdermal dihydrotestosterone on andropausal symptoms (V)**

A total of 123 males aged 50 to 70 years (mean age 58) participated in this mono-center, double-blind, randomized, placebo-controlled, parallel group study. The subjects were randomized into a DHT (61) and a placebo (62) group.

The patients included were to have had rarefaction of nocturnal penile tumescence ( $\leq 1$  time/week) and at least one of the following symptoms of andropause: asthenia, depressive mood, erectile dysfunction, decreased libido and urinary disorders. In addition, the subjects were to have total serum testosterone  $\leq 15\text{nmol/l}$  and/or SHBG over  $30\text{nmol/l}$ .

The patients were excluded from the study if they had neurogenic impotence, major depression, significant psychiatric pathology, suspected prostatic pathology (PSA over  $10\text{ng/ml}$ ), prostatectomy, known diabetes, other known endocrinological pathology, polyglobulia (Hb over  $170\text{g/l}$  and/or hematocrit over  $50\%$ ), clinically significant hepatic dysfunction, renal dysfunction, lipid profile out of the normal age-adjusted range, coronary heart disease, uncompensated heart failure, unstable hypertension, thromboembolic disease, alcohol or narcotics abuse. Other reasons for exclusion were androgenic or other hormonal therapy or therapy with inhibitors of 5-alpha-reductase, anticoagulants or platelet antiaggregants. Significant obesity ( $\text{BMI}>30$ ) was also an exclusion criteria.

The patients were treated for 6 months with DHT or placebo, and the drug was applied transdermally to the shoulders once a day. The doses of DHT varied within  $125 - 250\text{mg}$  daily; for all patients with a DHT level  $<5.8\text{nmol/l}$  the daily dose was  $250\text{mg}$  of gel, for patients with a DHT level between  $5.8$  and  $11.6\text{nmol/l}$  the daily dose was  $187.5\text{mg}$  of gel, and for patients with a DHT level  $\geq 11.6\text{nmol/l}$  the daily dose of  $125\text{mg}$  was maintained. The gel was applied to both forearms, arms and shoulders.

The study findings were evaluated with the Quality of Life questionnaire, which also includes sexual questions, with the International Prostate Symptoms Score (I-PSS), with transrectal ultrasonography (TRUS) and with laboratory tests (PSA, total testosterone, SHBG, FSH, LH, hemoglobin, hematocrit, platelets, liver function tests, creatinine, cholesterol, triglycerides). The patients came for a control visit at one, three and six months after the randomization.

All the parameters were analyzed using the ANOVA test for the main efficacy criteria analysis and Student's t-test for the analysis of quantitative variables.

## 5. Results

A summary of the results is presented here. More detailed results have been given in the appropriate papers (I-V).

### 5.1. High-dose yohimbine hydrochloride in the treatment of mixed-type impotence (I)

The average weight, pulse rate, and systolic and diastolic blood pressure of the patients during each treatment did not differ statistically significantly between the two groups. The patients' subjective assessments of libido, rigidity of the penis, duration of erection, and sensation of orgasm on the VAS scale (0 to 100) are shown in Table 2.

*Table 2. The patients' subjective visual analogue scale (0-100) assessments of libido, rigidity of the penis, duration of erection, and sensation of orgasm before and during placebo and yohimbine treatments<sup>a</sup>*

Period	Libido	Rigidity of penis	Duration of erection	Orgasm
Before treatments	74 (0-100)	49 (0-100)	60 (0-100)	79 (0-100)
During placebo treatment	72 (14-100)	58 (0-99)	40 (0-91)	79 (0-99)
During yohimbine treatment	75 (27-98)	59 (0-96)	47 (2-100)	82 (17-100)

<sup>a</sup> The results are given as arithmetic means and ranges.

Orgasm was achieved slightly more frequently in the yohimbine group, but the difference was not significant. The results of the audiovisual sexual stimulation test with Rigiscan device measurements of rigidity and tumescence showed that rigidity at the base of the penis was slightly, but not significantly, better in the yohimbine group. On the whole, none of the parameters revealed a statistical significance between the control group and the yohimbine group. Only 3 of the 27 (11%) patients on yohimbine hydrochloride and 2 of the 27 (7%) on placebo reported having received adequate help for their

impotence. 33% of the patients in the yohimbine group and 41% in the placebo group reported some help, while 56% in the yohimbine group and 52% of those on placebo felt no effect at all.

High-dose yohimbine hydrochloride (36 mg/day) was tolerated moderately well, but there were two serious side effects, one hypertensive crisis and one severe palpitation. Both patients discontinued the trial after the episode.

## 5.2. Intracavernous injection test in the evaluation of patients with erectile dysfunction (II)

There was no difference in the amount of tumescence between the three vasoactive agents. Measured with the Rigiscan device, PGE1 produced significantly ( $p < 0.05-0.01$ ) better rigidity both at the base and at the tip of the penis than papaverine hydrochloride or moxisylyte. 15 minutes after the ICI, the physician estimated the grade of erection. The results are presented in table 3. As it can be seen, PGE1 produced much better erections even when estimated clinically.

*Table 3. Grade 3-5 erection and the duration of erection (grades 4-5) achieved with physiological saline (NaCl), papaverine hydrochloride (PV), prostaglandin E1 (PGE1) and moxisylyte (MS) at 15 minutes after the injection. The results are expressed as arithmetic means.*

Injected agent	Patients with grade 3-5 erection (no.)	Duration of erection (min)
NaCl	0%	0
PV	37% (11)	13.4
PGE1	77% (23)	40.2
MS	27% (8)	6.5

The patients' satisfaction with the erection in the ICI test was measured with VAS: overall, it was quite low, being mean 33% (range 0-86 %) in the PGE1 group and 18% (0-98%) in the PV, 12% (0-96%) in the MS and 3% (0-15%) in the NaCl groups, respectively. VAS was also used to identify the amount of pain just after the injection and when the erection began. The pain score was 22% (0-76%) for PGE1, 22% (0-100%) for PV, 13% (0-50%) for MS and 5% (0-38%) for NaCl. There were no statistically significant changes in the pulse rate and blood pressure values 5 and 15 minutes after the injection in correlation to preinjection values. The erection lasted for two hours in three patients given PGE1, two patients given PV and one patient given MS, and all of those was given etilephrine (5 mg) which ceased the erections effectively.

After the ICI tests with every study medicine, the patients were presented the treatment options. Nine patients (30%) started intracavernosal treatment: seven patients selected PGE1, one PV and one MS according to their preference in blind testing. In addition, nine patients (30%) wished primarily to try oral medication before the use of intracavernosal injection. Twelve patients (40%) underwent further investigations.

### 5.3. Intracavernous self-injection of prostaglandin E1 in the treatment of erectile dysfunction (III)

The mean home dose of PGE1 was 17.5 µg (4-40 µg). The most common dose of PGE1 was between 10-15 µg (33%). 25% of the patients used 15-20 µg, 20% 5-10 µg, 16% 20-30 µg, 3% under 5 µg and 3% over 30 µg. 13% of the patients had changed the home dose of PGE1 after they had first been prescribed it three years ago. Nearly half (46.4%) of the patients had discontinued PGE1 therapy. Most of the patients (84.1%) had found it easy to learn the injection technique, and the rest (15.9%) had only had difficulties in the beginning. The mean time of using PGE1 was 23.3 months (0-48). The mean coital frequency with ICI therapy was 2.8 times per month (0-8). Erection began after the injection within 9.4 minutes (2-20), and the duration of erection at home was 58.7 minutes (0-240). The injections failed to produce a sufficient erection in 2% of the patients after at least ten attempts. 34.8% of the patients reported that their own erections improved after the introduction of ICI therapy: most of the patients who reported improvement of their own erections had a psychogenic etiology (54.2%), while 37.5% had a vasculogenic dysfunction and 8.3% a neurogenic etiology.

Table 4 shows the reasons for the discontinuation of therapy, loss of efficacy and spontaneous erections being prominent. The dropout rate was highest among the patients with vasculogenic dysfunction (56.3%) compared to the other etiologies.

*Table 4. Reasons for dropping out among 69 patients who began intracavernosal home therapy with PGE1.*

Reasons for dropping out	Number
Loss of efficacy	9 (13%)
ICI therapy too expensive	2 (2.9%)
Illness of wife	2 (2.9%)
Wife disapproved of treatment	2 (2.9%)
Spontaneous erections	8 (11.6%)
Did not get a new prescription	2 (2.9%)
Fibrosis in the penile shaft	3 (4.3%)
Pain after injection	4 (5.8%)
Total	32 (46.4%)

All the complications within the use of PGE1 were slight, and the most common problem was hematomas, which occurred in 10.1% of the patients, but were small and did not cause discontinuation of the therapy. Three instances of priapism (4.3%) occurred at the beginning of the therapy, but after an adjustment of the amount of PGE1, there were no further problems. 7.2% of the patients reported some kind of pain immediately after the injection, which did not, however, cause discontinuation of therapy. Four patients (5.8%) had fibrosis in the penile shaft at the control visit, which was also detected by ultrasound, the mean size being 1.75 cm (1-2cm).

The mean value of libido estimated on a VAS scale at the time of the control checkup was 65.3% (5-97). The patients' satisfaction with their erections at home without injections was only 23.5%, but PGE1 therapy increased it up to 67.3%.

The ICI test was done with the home dose of PGE1, and erection was determined with the Rigiscan device. The mean maximal rigidity at the tip and the base of the penis was 56.6% and 53.3%. The degree of erection was estimated as in study II by the doctor, and there was grade 3-5 erection in 85.9% of the cases. About half of the patients estimated their erection at the control visit worsen than in a "real situation" at home, while 40.4% said their erection was the same as at home. Only 7% considered their erection better at the office than at home.

#### 5.4. Effect of transurethral resection of the prostate on sexual functions (IV)

In this study population, only 7% of the 155 patients had been treated by pharmacotherapy for impotence before TURP. 60% of the patients reported good libido before TURP, while 59% did so at 6 months and 54% at 12 months. Before TURP, 56% of the patients reported failure of intercourse on half or more than half of occasions, while after the procedure the corresponding percentages were 51% at 6 months and 43% at 12 months. The patients estimated their erections, and 26% of the patients had completely satisfactory erections before TURP, while 11% had no erections at all before the procedure. After the operation, 22% of the patients had completely satisfactory erections at 6 months and 24% at 12 months. No erection was reported by 13% of the patients at 6 months and 16% at 12 months. Orgasm was experienced during intercourse on half or more than half of the occasions by 76% of the patients before the procedure, and by 70% at 6 months and 74% at 12 months. 12% of the patients did not have ejaculation before TURP, and 84% of the patients did not have it after the operation. Early morning erections were reported by 53% of the patients before the procedure, and 83% at 6 months and 72% at 12 months, the difference before and after TURP was significant ( $p < 0.01$ ).

A majority of the patients, i.e. 68%, were satisfied with their sex life before TURP despite of the fact they had some ED. Satisfaction did not change notably after the procedure, being 67% after 12 months. There were no differences in coital frequency before and after the procedure, and 32% of the patients reported not having had intercourse during the previous year (Fig. 3.)

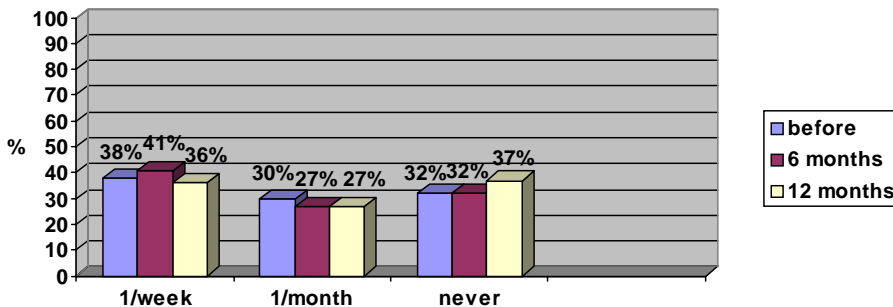
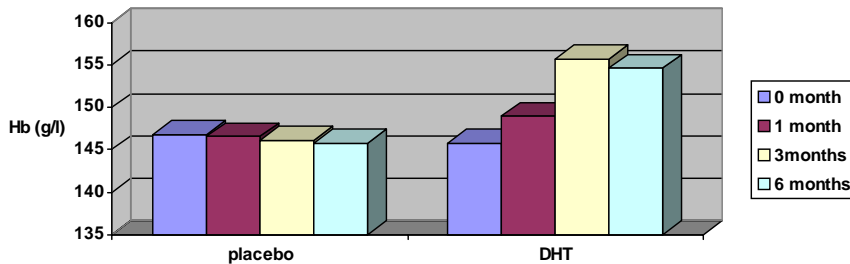


Fig. 3. Coital frequency in the study group before and after TURP.

### 5.5. Effects of transdermal dihydrotestosterone on andropausal symptoms (V)

The most common amount of DHT gel used was 187.5mg (44.3% of patients), followed by 250 mg (31.1%) and 125mg (24.6%). Early morning erections improved significantly in DHT group at three months ( $p < 0.05$ ) and correspondingly the ability to maintain erections improved significantly at six months ( $p < 0.05$ ). DHT also had a positive effect on libido, which improved in 26.5% of the subjects receiving DHT compared to 8.5% in the placebo group ( $p < 0.02$ ). There were no differences in positive well-being or vitality in either treatment group.

Among the patients who had high I-PSS-scores initially (over 12 points), the I-PSS score decreased from 17.7 to 12.3 points. Prostatic volume did not change in the DHT group. PSA did not change in either group. There were no major adverse events; three patients (5.6%) had mild headache during the DHT treatment. As regards adverse events, one subject with acute pyelonephritis in the DHT group, and two subjects suffering from worsened angina pectoris plus one subject with skin cancer in the placebo group dropped out: these adverse events were not considered to be related to the treatment. The active medication group showed a significant reduction in serum estradiol, serum testosterone and S-SHBG ( $p < 0.005$ ). There were no changes in the serum cholesterol and HDL values, but triglycerides were higher in both groups at the end of the study. Hemoglobin (Fig. 4) and hematocrit increased significantly in the DHT group. Liver function tests did not change in either group.



**Fig. 4. Effect of DHT on the hemoglobin level during the treatment.**

## 6. Discussion

### 6.1. General

For the evaluation of erectile dysfunction, there are several modalities available, but all of them suffer from certain weaknesses: the results of objective measurements (ICI test, Rigiscan device, duplex Doppler –ultrasound, etc.) vary from time to time, and the investigator must know that a natural relaxing atmosphere gives the most appropriate values (Buvat *et al.* 1986). You can get "the right values" only in a real situation with your partner at home. In large series of patients evaluating the efficacy of ED therapy, the most practical method to have answers is a questionnaire, which allows the patients to make their own estimations about their sexual functions (Andersen & Broffitt 1988). Multidimensional scales have been said to be better in the evaluation of treatment efficacy than monodimensional scales (Stewart & Ware 1992). We used both multidimensional questionnaires and VAS scales. When internationally standardized questionnaires are used, the investigators can compare the results of different studies.

When treating aging men, we should first take a careful sexual history, for which purpose questionnaires are helpful, and also notice symptoms other than ED and try to conclude which is the main problem and which symptom is the target for treatment; men older than 50 may also have other symptoms of andropause than ED, e.g. decrease of libido and well-being or depressive mood (IV,V).

The first-line treatment of ED always includes testing of the medicine at home, and before the treatment the patient should have all the available information about the medicine, including how it should be taken and how it works. Before the ICI –program, precise determination of the home dose of PGE1 and counselling concerning the technique are important (I,II,III). At the beginning of androgen therapy, it is necessary to inform the patient that androgens affect mainly libido and well-being (V). Furthermore, it is useful to arrange follow-up to assess the effectiveness of the treatment and, when necessary, change the medication or give more advice concerning the administration of the medicine. Especially when having androgen treatment, one should consider the efficacy of the treatment, because unnecessary treatment should be avoided (V,Vermeulen 1993).

Before surgical procedures, which may have negative consequences on sexual functions, e.g. TURP, the patient must have appropriate information about it: unnecessary fear about a total loss of erection may lead to ED (IV). At the time of the first postoperative control checkup, it would therefore be wise to ask about the patient's sexual functions and give him a possibility for treatment.

During treatment for ED, we should always bear in mind the possibility of side-effects, as there is no totally safe treatment option available (I,II,III,V). Especially in old men with severe heart disease and other concurrent problems, it is not feasible to introduce new treatment modalities for ED and predispose the patient to extreme physical distress.

## **6.2. High-dose yohimbine hydrochloride in the treatment of mixed-type impotence(I)**

Yohimbine has been known for over 100 years: it increases parasympathomimetic or cholinergic activity and reduces sympathetic or adrenergic activity (Murburg *et al.* 1991). Yohimbine hydrochloride produces a rise in sympathetic drive by increasing noradrenaline release and, theoretically, by blocking the alpha-2-adrenergic receptors and increasing the blood supply to cavernous body tissues (Grunhaus *et al.* 1989, Murburg *et al.* 1991). Because erection is dependent on cholinergic activity, yohimbine has long been used to treat impotence. The response rates have varied a lot from no effect to a statistically significant benefit compared to placebo (Reid *et al.* 1987, Susset *et al.* 1989, Sonda *et al.* 1990, Morales *et al.* 1995). Studies have shown yohimbine to be an erectogenic agent, but the optimal dose remains undetermined (Susset *et al.* 1989). In cases of impotence, there has not been good assessment of high-dose yohimbine in a complete crossover design using modern treatment modalities with placebo.

Our study showed high-dose yohimbine hydrochloride to have no effect on mixed-type impotence contrary to many other studies (Reid *et al.* 1987, Susset *et al.* 1989, Deamer & Thompson 1991, Nessel 1994). Montorsi and co-workers (1994) have noticed in their study that combination treatment with trazodone is clearly better than placebo alone for the treatment of psychogenic impotence (Montorsi *et al.* 1994).

Reported side-effects have been minimal (Morales *et al.* 1995). However, two patients in this study had serious side-effects that necessitated an interruption of the trial, one had a hypertensive crisis and the other severe palpitation. Yohimbine may elevate blood pressure and pulse rate by increasing serum noradrenalin (Murburg *et al.* 1991). High dose treatment with yohimbine hydrochloride should be accepted critically.

Over half of the patients had no effect on sexual function either with placebo or with active medication. Positive clinical results (complete and partial responses) were obtained in 12 cases (44%) at the end of yohimbine phase and 13 (48%) after placebo period. In our study concerning ED, the response rates in the placebo group were high compared to many other studies (Reis *et al.* 1987, Goldstein *et al.* 1998).

In this study, yohimbine appeared to be no better than placebo as a first-line treatment for mixed-type impotence.

### **6.3. Intracavernous injection test in the evaluation of patients with erectile dysfunction (II)**

After the finding that penile erection can be induced by intracavernous injection of papaverine in 1982, examinations of various intracavernosal medications were started. Since then, a number of agents have been utilized for both diagnostic and treatment purposes. One year later, Brindley reported the induction of erection with phenoxybenzamine and phentolamine (Brindley 1983a, Brindley 1983b).

In the course of developing treatments for erectile impotence and priapism in 1986, Brindley made, using himself as an object, observations on the actions of a number of other drugs given intracavernosally, including imipramine, verpamil, naftidrofuryl, salbutamol, hydralazine, lignocaine, bupivacaine, neostigmine, atropine propranolol and idazoxan. He ended up suggesting the use of thymoxamine, phentolamine, verpamil and guanethidine (Brindley 1986). Later in 1988, especially in France, a thymoxamine called moxisylyte was introduced into clinical use. In the same year, the first reports about prostaglandin E1 in intracavernosal use were published (Ischii *et al.* 1986).

The most widely used agents for ED injected alone are papaverine hydrochloride (PV), prostaglandin E1 (PGE1) and moxisylyte (MS). PGE1 has been claimed to cause occasionally painful erections (Stack *et al.* 1990), while papaverine has been found to cause prolonged erection, priapism and fibrosis (Levine *et al.* 1989, Lakin *et al.* 1989), and moxisylyte has been criticized for its poor effectiveness (Buvat *et al.* 1989).

We noticed in our study that PGE1 was the most effective of these three vasoactive agents both objectively (Rigiscan measurement) and subjectively (VAS questionnaire). Induced tumescence was about the same in all the three groups. Pain was evaluated to be more intense by the PGE1 and PV users (22 % on a VAS scale in both groups). There were no serious side-effects in the tests, and the pulse rates and blood pressure values were low. The present findings strongly suggest that PGE1 is the most effective drug in the ICI test.

### **6.4. Intracavernous self-injection of prostaglandin E1 in the treatment of erectile dysfunction (III)**

One of the most significant improvements in the treatment of erectile dysfunction took place in 1982, when intracavernosal injection therapy was introduced (Andersson *et al.* 1991). Most of the impotent patients (70-90%) can be treated by intracavernosal agents (Stackl *et al.* 1988, Schramek *et al.* 1989, Ravnik-Oblak *et al.* 1990). The most common vasoactive agent nowadays is PGE1 (Gerber 1991). Its effectiveness and safety have been proved in several studies (Stackl *et al.* 1988, Ravnik-Oblak *et al.* 1990, Hwang *et al.* 1991). Prolonged pain immediately after the injection has been described with PGE1 (Ravnik-Oblak *et al.* 1990). There are very few local complications, such as indurations and fibrosis, during long-term use.

The patients were followed up for three years after starting the ICI program. The mean coital frequency with ICI therapy was quite low, 2.8 times per month. Most of the patients did not have problems with giving injection themselves even in the beginning (84.1%).

The mean dose of PGE1 used at home was 17.5 micrograms. The most frequently used dose of PGE1 is 20 µg (Stackl *et al.* 1988, Hwang *et al.* 1989, Ravnik-Oblak *et al.* 1990). Erection began within a normal time (9.4 minutes), and its duration was about one hour, which is less than reported previously (Stackl *et al.* 1988, Ravnik-Oblak *et al.* 1990, Hwang *et al.* 1991).

Almost all attempts at intercourse succeeded with PGE1 at home. When measured with Rigiscan at the office, the home dose of PGE1 showed the erection to be fairly good (mean maximal rigidity 53.3% at the base and 56.6% at the tip of the penis). When the patients themselves evaluated the rigidity of the penis in the ICI test situation compared to that at home, the majority did not have equally good erection at the office (52.6%) as at home. This can be explained by sympathoconia or adrenergic constrictor tone due to anxiety (Buvat *et al.* 1986).

There were no systemic side-effects with PGE1. 7.2% of patients had prolonged pain after the injection, leading to discontinuation by 5.8% of the patients. This is less than in most of other studies where PGE1 has been used alone. When PGE1 is used in combination with other drugs, the incidence of pain could be less (Stackl *et al.* 1988, Gerber & Levine 1991, Schramek *et al.* 1994). Priapism occurred in only 3 cases at the beginning of the treatment, but after finding the right dose, no more problems occurred. Priapism used to be a relatively common complication in papaverine users, but after the introduction of PGE1 treatment it has become rare (Fouda *et al.* 1989, Hasmat *et al.* 1991).

Fibrosis was seen in 5.8% of the patients using PGE1 for three years. It led to discontinuation of the drug in 4.3% of the cases. The fibrosis or nodules were small, their mean size being less than 2 cm. In the literature, papaverine users have been reported to have penile scarring and fibrosis more often than PGE1 users (Chen *et al.* 1994, Hwang *et al.* 1991).

Many studies have reported improvement of spontaneous erections in men using intracavernous injections (Gerber & Levine 1991, Virag *et al.* 1991, McMahon 1992, Sharlip 1997). In our study, 34.8% of the patients reported improvement of their own erections after PGE1 therapy. 11.6% of the patients discontinued the ICI therapy for this reason and majority of those patients had a psychogenic etiology. High amount of psychogenic etiology may be one reason for the high dropout percentage up to 49% in some studies (Sister 1990, Gerber & Levine 1991, Govier *et al.* 1993, Fallon 1995).

The main reasons why many patients do not continue their PGE1 therapy in the long run include the fact that their own erections improve or that there are changes in their life situation. At the baseline, precise determination of the home dose of PGE1 and instruction with the technique are important for treatment acceptance.

## **6.5. Effect of transurethral resection of prostate on sexual functions (IV)**

Transurethral resection of the prostate (TURP) continues to be the commonest and most effective method of treating benign prostatic hyperplasia (BPH) despite the new treatments available. It may, however, have some adverse effects, most commonly disturbances of sexual function, which have been reported to occur in 4 - 40% of the patients under-

going this procedure (Bolt *et al.* 1986, Libman & Fichten 1987, Mebust *et al.* 1989). Our interest was to examine prospectively the effect of TURP on sexual functions. At the same time, we would have a good sample of aging men with BPH to ask about their life-styles, libido, satisfaction with their current sex life, erection and coital frequency.

Erection is a complex phenomenon that involves neurological, hormonal, arterial, venous and muscular components and is further influenced by psychogenic, cognitive and environmental factors (Lue & Tanagho 1987, Bush *et al.* 1992). TURP can have an effect on these components, causing erectile dysfunction: ED can be brought about via several different routes, including the psychogenic effect of an invasive procedure in the genital region, injury of the nerve tracts supplying the corpus cavernosum as a result of electro-coagulation, thrombosis of the arteria cavernosa, venous leakage, and injury of nerve tracts resulting from urethral dilatation and uretrotomy before TURP (Walsh & Donker 1982, Handbury & Sethia 1995, Padma-Nathan & Goldstein 1998).

Our patients were rather old, with a mean age of 69 years, and the resected tissue in TURP was quite extensive: TURP did not cause overall changes in the patients' libido, erection, orgasm and sex life in our study. Early morning erections even improved after the operation. No such result has been reported previously. Also the amount of reported failures of intercourse reduced after TURP. This may be explained by that fact that the patients already had some ED before the operation, and they were fairly satisfied with their sex life as a whole both before and after the operation, although one third of them had not had coitus for a year. On the other hand, this may be explained by the fact that after TURP voiding problems diminished and overall condition was better. These results could also be explained by the fact that detailed information was given to the patient on the nature of TURP as well as on the possible risks related to it and their probability, and the study was prospective and the patients' memories did not hence influence the results.

## **6.6. Effects of transdermal dihydrotestosterone on andropausal symptoms (V)**

Serum testosterone is said to decline in aging men, but this process is slow and the clinical picture is therefore difficult to recognize (Gray *et al.* 1991). This situation has been called "andropause", "male climacterium", "male menopause", "mid-age crisis" or "androgen decline in the aging male (ADAM)".

Androgens stimulate the production of erythropoietin in the kidneys, increasing hemoglobin concentrations (Bagatell *et al.* 1994) and hematocrit (Tenover 1992). Because older men tend to have slightly lower hematocrits than young adult men, the hematopoietic effects of androgens may only rarely lead to problems with polycythemia (Tenover 1992). In our study, both hemoglobin and hematocrit increased significantly during DHT treatment, however staying in normal value range in all patients. Despite this, in patients using DHT, Hb should be controlled after 3-6 months of treatment.

The administration of androgens decreases plasma HDL cholesterol in adolescent boys with delayed puberty and in men with hypogonadism (Sorva *et al.* 1988). Treatment with parenteral administration of normal doses of either T or DHT to healthy aged men induce limited changes in circulating lipids with tendency to lower total levels of The significance

of this finding is that low HDL and high LDL-to-HDL ratios are associated with increased risk for coronary heart disease (Swerdlhoff & Wang 1993). On the other hand, some authors have reported a favourable effect on HDL cholesterol after moderate doses of natural testosterone (Marin *et al.* 1992). It has also been concluded that low circulating testosterone levels might be associated with hypercoagulability and could therefore contribute to an increased risk of ischemic heart disease (Bonithon-Kopp *et al.* 1988). In our study, there were no changes in cholesterol and HDL values in either group, but, for some unknown reason, both the DHT and the placebo groups had an increase in the triglyceride values.

Huge doses of parenteral administration of testosterone may reduce insulin sensitivity (Cohen & Hickman 1987), but normal doses improve insulin sensitivity in middle-aged abdominally obese men (Marin *et al.* 1992). In our study, there was no changes in plasma glucose level during the medication.

Percutaneous testosterone and DHT have been shown to be equally effective in the treatment of hypogonadal men (Kuhn *et al.* 1986). Testosterone increases plasma estradiol levels, which DHT does not do, though it has been shown to reduce the estradiol levels (Fiet *et al.* 1982). In our study, there was a significant reduction in the estradiol and also in serum testosterone and S-SHBG levels.

There were no changes in the liver function tests in either group in this study. Alkylated androgens administered at high doses in long-term use may cause liver dysfunction (Gurakal *et al.* 1994).

It has been earlier noticed that testosterone administered to elderly men involves the risk of stimulating the growth of subclinical prostatic carcinoma (Vermeulen 1993). Furthermore, it has been recognized in some studies that physiological testosterone enanthate supplementation results in sustained stimulation of PSA (Tenover 1992, Hajjar *et al.* 1997). Holmång and associates (1993) reported that testosterone increased the mean prostatic volume in a study where 160 mg/day testosterone undecanoate was used for 8 months. Many other studies have failed to reveal any change in prostatic volume during the treatment (Cooper *et al.* 1998). It has therefore been recommended that aging should be screened carefully and followed periodically throughout testosterone therapy (Tenover 1992).

It has been noticed that the administration of estradiol both stimulates prostatic growth (Suzuki *et al.* 1994) and increases the incidence of prostatic carcinoma in rats (Shirai *et al.* 1994). Rats treated with DHT plus estradiol did not develop tumors (Shirai *et al.* 1994). In a 1.8-year open survey of 37 men aged 55-70 years treated with daily percutaneous DHT treatment, high plasma levels of DHT (>8.5 nmol/l) effectively induced clinical benefits in andropausal symptoms, while slightly but significantly reducing prostatic size (de Lignieres 1993). It has been concluded in many studies that estrogens play an important role in the pathogenesis of BPH. Estradiol but not DHT acts in concert with SHBG to produce an 8-fold increase in intracellular cAMP in human BPH tissue, causing growth of the prostate, while DHT, which blocks the binding of estradiol to SHBG, completely negates the effect of estradiol (Nakhla *et al.* 1994). In our study, the size of the prostate remained the same and serum PSA did not increase, and there was also some relief in the obstructive symptoms in BPH patients with high symptom scores (I-PSS) before the study.

Androgens are expected to have some positive effects on the central nervous system and a stimulating effect on sexual function in men (Burriss *et al.* 1992, Bagatell *et al.* 1994). There was no clear positive effect on well-being and vitality, which may be because the patients mostly expected the drug to have an effect on their sexual function.

In our study, morning erections improved and libido was better in the DHT group, and the maintenance of erections during the intercourse was also better in the actively medicated group. We found DHT to be a safe option for long-term treatment of andropausal symptoms, it may also have a positive effect on urinating problems.

## 7. Conclusions

1. This study could not show any benefit from high-dose yohimbine hydrochloride in correlation with placebo in the treatment of mixed type ED. The medication was moderately well tolerated, but two serious side-effects were reported (a hypertensive crisis and a severe palpitation) leading to discontinuation of medication.
2. PGE1 was shown to be the most effective of the three agents (papaverine hydrochloride(PV), prostaglandin E1 (PGE1) and moxisylyte (MS)), both subjectively and objectively. There were no differences in the amount of tumescence produced by these drugs. PGE1 and PV caused more pain than MS, but not significantly. All the vasoactive drugs were well tolerated. When using pharmacotest to evaluate ED, the most effective vasoactive drug is strongly suggested to be the drug of choice, which was PGE1.
3. In long-term use PGE1 is well tolerated and has only minor problems. The patients' satisfaction with their erection at home was good. The high dropout percentage in long term use of PGE1 may be due partly to the fact that spontaneous erections did improve, especially with patients with a psychogenic etiology. Precise determination of home dose of PGE1 and teaching of the technique are important at the beginning of this treatment modality.
4. TURP does not affect the sexual function of patients with BPH, with exception of retrograde ejaculation. Early morning erections even improved after the operation. The majority of patients were satisfied with their sexual life both before and after procedure, although one third of them had not had coitus for a year.
5. Transdermal administration of dihydrotestosterone (DHT) improves sexual function and libido and offers a useful and safe alternative in the treatment of andropause. If oestrogens play a role in prostate growth, as has been suggested, the use of non-aromatize androgens may be beneficial compared with aromatizable androgens. Controlled follow-up trials of androgen replacement therapy in general are needed to clarify the possible long-term benefits and risks.

## 8. References

- Abber JC, Lue TF, Luo J, Juenemann K & Tanagho EA (1987) Priapism induced by chlorpromazine and trazodone: Mechanism of action. *J Urol* 137: 1039-1042.
- Abber JC, Lue TF, Orvis BR, McClure RD & Williams RD (1986) Diagnostic tests for impotence: A comparison of papaverine injection with penile-brachial index and nocturnal penile tumescence monitoring. *J Urol* 135: 923-925.
- Aboseif SR, Baskin LS, Yen TS, Benedict Y & Lue TF (1992) Congenital defect in sinusoidal smooth muscles: A cause of organic impotence. *J Urol* 148: 58-60.
- Aboseif SR, Breza J, Bosch R, Benard F, Stief CG, Stackl W, Lue TF & Tanagho EA (1989) Local and systemic effects of chronic intracavernous injection of papaverine, prostaglandin E1 and saline in primates. *J Urol* 142: 403-408.
- Abrams HS, Hester LR, Sheridan WF & Epstein GM (1975) Sexual functioning in patients with chronic renal failure. *J Nerv Ment Dis* 160: 220-226.
- Andersen BL & Broffitt (1988) Is there a reliable and valid self-report measure of sexual behavior? *Arch Sex Behav*. 17: 509-525.
- Andersson KE, Holmquist F & Wagner G (1991) Pharmacology of drugs used for treatment of erectile dysfunction and priapism. *Int J Impot Res* 3: 155-172.
- Aoki H, Matsuzaka J, Yeh KH, Banya Y, Fuzioka T, Kubo T & Yasuda N (1990) Studies on the role of VIP (vasoactive intestinal polypeptide) in penile erectile dysfunction. *Int J Impot Res* 2(Suppl 2): 28-29.
- Aravena EP & Bustamente E (1986) Treatment of psychogenic erectile incompetence with intracavernous injection of papaverine In: *Proceedings of the fifth Conference on Vasculogenic Impotence and Corpus Cavernosal Revascularisation. Second World Meeting on Impotence. Prague: International Society for Impotence Research (ISIR)* 11: 18.
- Aserinsky E & Kleitman N (1953) Regularly occurring periods of eye motility and concomitant phenomena during sleep. *Science* 118: 273-274.
- Azadzi KM, Payton T, Krane RJ & Goldstein I (1990) Effects of intracavernosal trazodone hydrochloride: animal and human studies. *J Urol* 144: 1277-1282.
- Bagatell CJ, Heiman JR, Rivier JE & Bremner WJ (1994) Effects of endogenous testosterone and estradiol on sexual behavior in normal young men. *J Clin Endocrinol Metab*: 711-716.
- Baltaci S, Aydos K, Kosar A & Anafarta K (1995) Treating erectile dysfunction with a vacuum tumescence device: a retrospective analysis of acceptance and satisfaction. *Br J Urol* 74: 102-105.
- Barnes P (1991) Role of sex therapy in the management of erectile dysfunction. In: Kirby RS, Carson C, Webster GD, eds. *Impotence: diagnosis and management. Oxford, Butterworth-Heinemann*: 133-142.

- Becker AJ, Stief CG, Machtens S, Schultheiss D, Hartmann U, Truss MC & Jonas U (1998) Oral phentolamine as treatment for erectile dysfunction. *J Urol* 159 (4): 1214-1216
- Benard F & Lue TF (1990) Self-Administration in the Pharmacological Treatment of Impotence. *Drugs* 39: 394-398.
- Benet AE & Melman A (1995) The epidemiology of erectile dysfunction. *Urol.Clin.NA* 22(4): 701.
- Bennet AH, Carpenter AJ & Barada JH (1991) An improved vasoactive drug combination for pharmacological erection program. *J Urol* 146: 1564-1565.
- Bolt JW, Evans C & Marshall VR (1987) Sexual dysfunction after prostatectomy. *Br J Urol* 58: 319-322.
- Bonithon-Kopp C, Scarabin PY, Bara L, Castanier M, Jacqueson A & Roger M (1988) Relationship between sex hormones and haemostatic factors in healthy middle-aged men. *Atherosclerosis* 71: 71-76.
- Boolell M, Allen MJ, Ballard SA et al (1996) Sildenafil: an orally active type 5 cyclic GMP-specific phosphodiesterase inhibitor for the treatment of penile erectile dysfunction. *Int J Impot Res* 8: 47-52.
- Bradley WE, Timm GW, Gallagher JM & Johnson BK (1985) New method for continuous measurement of nocturnal penile tumescence and rigidity. *Urology* 26: 4-9.
- Braunstein GD (1983) Endocrine causes of impotence. Optimistic outlook for restoration of potency. *Postgrad Med* 74: 207-217.
- Brecher EM (1984) *Love, Sex and Aging*. Boston: Little, Brown & Co.
- Bremner WJ, Vitiello MV & Prinz PN (1983) Loss of circadian rhythmicity in blood testosterone levels with aging in normal men. *J Clin Endocrinol Metab* 56: 1278-1281.
- Brindley GS (1983a) Cavernosal alpha-blockade and human penile erection. *J Physiol* 342, 24P.
- Brindley GS (1983b) Cavernosal alpha-blockage: a new technique for investigating and treating erectile impotence. *Br J Psychiatry* 143: 332-337.
- Brindley GS (1986) Pilot experiments on the action of drugs injected into the human corpus cavernosum penis. *Brit J Pharmacol* 87: 495-500.
- Brown J, Doxey JC & Handley S (1980) Effects of alfa-adrenoceptor agonists and antagonists and of antidepressant drugs on pre- and postsynaptic alfa-adrenoceptors. *Eur J Pharmacol* 67: 33-40.
- Burnett AL (1995) The role of nitric oxide in the physiology of erection. *Biol Reprod* 52: 485-589.
- Burnett AL (1997) Nitric oxid in the penis: physiology and pathology. *J Urol* 157: 320-324.
- Burriss AS, Banks SM, Carter CS, Davidson JM & Sherins RJ (1992) a long term, prospective study of physiologic and behavioral effects of hormone replacement in untreated hypogonadal men. *J Androl* 13: 297-304.
- Bush PA, Aronson WJ, Buga GM, Rajfer J & Igrarro LJ (1992) Nitric oxide is a potent relaxant of human and rabbit corpus cavernosum. *J Urol* 147: 1650-1655.
- Buvat J, Buvat HM, Dehaene JL & Lemaire A (1986) Is intracavernous injection of papaverine a reliable screening test for vascular impotence? *J Urol* 135: 476-478.
- Buvat J, Buvat-Herbaut M, Lemaire A & Marcolin G (1991) Reduced rate of fibrotic nodules in the cavernous bodies following auto-intracavernous injections of moxisylyte compared to papaverine. *Int J Impot Res* 3: 123-128.
- Buvat J, Lemaire A, Buvat-Herbaut M & Marcolin G (1989) Safety of intracavernous injections using an alpha-blocking agent. *J Urol* 141: 1364-1367.
- Buvat J, Lemaire A, Marcolin G, Dehaene JL & Buvat-Herbut M (1987) Intracavernous injection of papaverine (ICIP). Assessment of its diagnostic and therapeutic value in 100 impotent patients. *World J Urol* 5: 150-155.
- Capetola RJ, Rosenthale ME, Dubinsky B & McGuire JL (1983) Peripheral antialgesics: a review. *J Clin Pharmacol* 23: 545-556.
- Carroll JL, Ellis D & Bagley DH (1992) Impotence in the elderly: Evaluation of erectile failure in men older than seventy years of age. Jefferson Sexual Function Center. *Urology* 39: 226-230.

- Cavallini G (1994) Minoxidil and capsacin: an association of transcutaneous active drugs for erection facilitation. *Int J Impot Res* 6 suppl. 1: D70.
- Cavallini G (1991) Minoxidil versus nitroglycerin: a prospective double-blind controlled trial in transcutaneous erection facilitation for organic impotence. *J Urol* 146: 50-53.
- Chao R & Clowers DE (1994) Experience with intracavernosal tri-mixture for the management of neurogenic erectile dysfunction. *Arch Phys Med Rehabil* 75: 276-278.
- Chen J, Godschalk MF, Katz PG & Mulligan T (1995) Combining intracavernous injection and external vacuum device as treatment for erectile dysfunction. *J Urol* 153: 1476-1477.
- Chen RN, Lakin MM, Montaque DK & Ausmundson (1996) Penile scarring with intracavernous injection therapy using prostaglandin E1: a risk factor analysis. *J Urol* 155: 138-140.
- Christ GJ, Brink PR, Brook S & Ney P (1996) PGE1-induced alterations in maxi-K+-channel activity in cultured human corporal smooth muscle cells. *J Urol* 155: 678A.
- Claes H & Baert L (1989) Transcutaneous nitroglycerine therapy in the treatment of impotence. *Int Urol* 44: 309-312.
- Clark JT, Smith ER & Davidson JM (1985) Testosterone is not required for the enhancement of sexual motivation by yohimbine. *Physiology and behavior* 35: 517-521.
- Cohen JC & Hickman R (1987) Insulin resistance and diminished glucose tolerance in powerlifters ingesting anabolic steroids. *J Clin Endocrinol Metab* (64): 960-963.
- Condra M, Morales A, Surridge DH, Owen JA, Marshall P & Fenemore J (1986) The unreliability of nocturnal penile tumescence recording as an outcome measurement in the treatment of organic impotence. *J Urol* 135: 280-282.
- Cookson MS & Nadig PW (1993) Long term results with vacuum constriction device. *J Urol* 149: 290-294.
- Cooper AJ (1991) Evaluation of I-C papaverine patients with psychogenic and organic impotence. *Can J Psychiatry* 36: 574-577.
- Cooper CS, Perry PJ, Sparks AE, MacIndoe JH, Yates WR & Williams RD (1998) Effect of exogenous testosterone on prostate volume, serum and semen prostate specific antigen levels in healthy young men. *J Urol* 159(2): 441-443.
- Costa P, Sarrazin B, Bressolle F, Colson MH, Bondil P & Saudurbray F (1993) Efficiency and side effects of intracavernous injections of moxisylyte in impotent patients: a dose-finding study versus placebo. *J Urol* 149: 301-305.
- Davis-Joseph B, Tiefer L & Melman A (1995) Accuracy of the initial history and physical examination to establish the etiology of erectile dysfunction. *Urology* 45(3): 498-502.
- de Lignieres B (1993) Transdermal dihydrotestosterone treatment of andropause. *Ann Med* 25: 235-241.
- Deamer RL & Thompson JF (1991) The role of medications in geriatric sexual function *Clin Geriatr Med* 7: 95-111.
- Dhabuwala CB, Ramakrishna VR & Anderson GF (1985) Beta-adrenergic receptors in human cavernous tissue. *J Urol* 133: 721-723.
- Donatucci CF & Lue TF (1992) The combined intracavernous injection and stimulation test: Diagnostic accuracy. *J Urol* 148: 61-62.
- Earle CM, Keogh EJ, Ker J, Cherry DJ, Glatthaar C, Tulloch AGS, Lord DJ & Wisniewski ZS (1990) Intracavernosal injection therapy for impotence due to spinal cord injury. *Int J Impot Res*: 2: 297-298.
- Earle CM, Keogh EJ, Wisniewski ZS, Tulloch AgsS, Lord DJ, Watters GR & Glatthaar C (1990) Prostaglandin E1 therapy for impotence, comparison with papaverine. *J Urol* 143: 57-59.
- Ehmke H, Junemann K-P, Mayer B & Kummer W (1995) Nitric oxide synthase and vasoactive intestinal polypeptide colocalization in neurons innervating the penile circulation. *Int J Impotence Res* 7: 147-156.

- Ellis WJ & Grayhack JT (1963) Sexual function in aging males after orchiectomy and estrogen therapy. *J Urol* 89: 895-899.
- Ernst E & Pittler MH (1998) Yohimbine for erectile dysfunction: a systematic review and meta-analysis of randomized clinical trials. *J Urol* 159: 433-436.
- Fahrenkrug J (1989) VIP and autonomic neurotransmission. *Pharmacol Ther* 41: 515-534.
- Fallon B (1995) Intracavernous injection therapy for male erectile dysfunction. *Urol Clin North Am* 22: 833-845.
- Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ & McKinlay JB (1994) Impotence and its medical and psychological correlates: Results of the Massachusetts male aging study. *J Urol* 151: 54-61.
- Ferreira SH (1983) Prostaglandins: peripheral and central analgesia. In: *Advances in Pain Research and Therapy*. Edited by J.J. Bonica, U. Lindholm, A Iggo. New York, Raven Press, 5: 627-629.
- Fiet J, Morville R, Chemama D, Villette JM, Gourmel B, Brerault JL & Dreux C (1982) Plasma androgen and gonadotrophin levels in normal adult men after percutaneous administration of 5- $\alpha$ -dihydrotestosterone. *Int J Androl* 5: 586-594.
- Finkle AL & Prian DV (1966) Sexual potency in elderly men before and after prostatectomy. *JAMA* 196 (2): 139-143.
- Fischer C (1965) Cycle of penile erection synchronous with dreaming sleep. *Arch Gen Psychiatry* 12: 29-45.
- Flind AC (1984) Cavernosal alpha-blockade: a warning. *Br J Psychiatr* 144: 329-330.
- Fouda A, Hassouna M, Beddoe E, Kalogeropoulos D, Binik YM & Elhiali MM (1989) Priapism: an avoidable complication of pharmacologically induced erection. *J Urol* 142: 995-997.
- Frank E, Anderson C & Rubinstein D (1978) Frequency of sexual dysfunction in "normal" couples. *New Engl J Med* 299: 111-115.
- Fried LP, Moore RD & Person TA (1986) Long-term results of cigarette smoking and moderate alcohol consumption on coronary artery diameter. Mechanism of coronary artery disease independent of arteriosclerosis or thrombosis? *Amer J Med* 80: 37-44.
- Friedman DE, Clare AW, Rees LH & Grossman A (1986) Should impotent males who have no clinical evidence of hypogonadism have routine endocrine screening? *Lancet* 1: 1041, Letter.
- Gall H, Baehren W, Scherb W, Stief C & Thon W (1989) Diagnostic accuracy of Doppler ultrasound technique of the penile arteries in correlation to selective arteriography. *Cardiovasc Intervent Radiol* 11: 225-231.
- Gerber GS & Levine LA (1991) Pharmacological erection program using prostaglandin E1. *J Urol* 146: 786-789.
- Gillam DG, Bulman JS & Newman HN (1997) A pilot assessment of alternative methods of quantifying dental pain with particular reference to dentine hypersensitivity. *Community Dent Health* 14(2): 92-96.
- Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD & Wicker PA (1998) oral sildenafil in the treatment of erectile dysfunction. *N Engl J Med* 338: 1397-1404.
- Goldstein I & the Vasomax Study Group (1998) Efficacy and safety of oral phentolamine (Vasomax) for the treatment of minimal erectile dysfunction *J Urol* 159: 240.
- Govier FE, McClure RD, Weissman RM, Gibbons RP, Pritchett TR & Kramer-Levien D (1993) Experience with triple-drug therapy in a pharmacological erection program. 150: 1822-1824.
- Gray A, Feldman HA, McKinlay JB & Longcope C (1991) Age, disease, and changing sex hormone levels in middle-aged men: results of the Massachusetts male aging study. *J Clin Endocrinol Metab* 73: 1016-1025.
- Grunhaus L, Tiogco D & Zelnik T (1989) Intravenous yohimbine: selective enhancer of norepinephrine and cortisol secretion and systolic blood pressure in humans. *Clin Neuropharmacol* 12: 106-111.

- Gu J, Polak JM, Lazarides M, Pryor JP, Blank MA, Polak JM, Morgan R, Marangos PJ & Bloom SR (1984) Decrease of vasoactive intestinal polypeptide (VIP) in the penises from impotent men. *Lancet* ii: 315-318.
- Gwinup G (1988) Oral phentolamine in non-specific erectile insufficiency. *Ann Int Med* 109: 162-163.
- Hajjar RR, Kaiser FE & Morley JE (1997) Outcomes on long-term testosterone replacement in older hypogonadal males: a retrospective analysis. *J Clin Endocrinol Metab* (82): 3793-3796.
- Hakenberg O, Wetterauer U, Koppermann U & Luhman R (1990) Systemic pharmacokinetics of papaverine and phentolamine: comparison of intravenous and intracavernous application. *Int J Impot Res* 2: 247-248.
- Halverson HM (1940) Genital and sphincter behavior of the male infant. *J Gen Psychol* 56: 95-99.
- Handbury DC & Sethia KK (1995) Erectile function following transurethral prostatectomy. *Br J Urol* 75: 12-13.
- Hargreave TB, Stephenson TP (1977) Potency and prostatectomy. *Br J Urol* 49: 683-688.
- Hartmann U (1998) The efficacy of psychosexual therapy for erectile dysfunctions: a critical review of outcome studies and suggestions for future treatment strategies. *J Impot Res* 10: S23.
- Hashmat AI, Abrahams J, Fani K & Nostrand I (1991) A lethal complication of papaverine-induced priapism. *J Urol* 145: 146-147.
- Hatzichristou DG, Hatzhimouratidis K, Ioannides E, Yannakoyorgos K, Dimitriadis G & Kalinderis A (1998) Nocturnal penile tumescence and rigidity monitoring in young patient volunteers: reproducibility, evaluation criteria and the effect of sexual intercourse. *J Urol* 159(6): 1921-1926.
- Heaton JPW, Morales A, Adams MA & Johnston B (1995) Recovery of erectile function by oral administration of apomorphine. *Urology* 45: 200-206.
- Hedlund H & Andersson K-E (1985) Contraction and relaxation induced by some prostanoids in isolated human penile erectile tissue and cavernous artery. *J Urol* 134: 1245-1250.
- Holmäng S, Marin P, Lindstedt G & Hedelin H (1993) Effect of long-term oral testosterone undecanoate treatment on prostate volume and serum prostate-specific antigen concentration in eugonadal middle-aged men. *Prostate* 23: 99-106.
- Holtgrewe HL, Valk WL (1964) Late results of transurethral prostatectomy. *J Urol* 92: 51-55.
- Hwang T, Yang I-S, Wang C-R, Chang S-J, Tzai T-S, Chang C-H & Wu H-C (1989) Impotence evaluated by the use of prostaglandin E1. *J Urol* 141: 1357-1359.
- Hwang TI, Yang C & Ho WL (1991) Histopathological changes of corpora cavernosa after long-term intracavernous injection. *Eur Urol* 20: 301-306.
- Incrocci L, Hop WC & Slob AK (1996) Visual erotic and vibrotactile stimulation and intracavernous injection in screening men with erectile dysfunction: a 3 year experience with 406 cases. *Int J Impot Res* 8(4): 227-232.
- Ischii N, Watanabe H, Irisawa C, Kikuchi Y, Kubota Y, Kawamura S, Suzuki K, Chiba R, Tokiwa M & Shirai M (1989) Intracavernous injection of prostaglandin E1 for the treatment of erectile impotence. *J Urol* 141: 323-325.
- Ischii N, Watanabe H, Irisawa C & Kikuchi Y (1986) Studies on male sexual impotence. Report 18. Therapeutic trial with prostaglandin E1 for organic impotence. *Nippon Hinyokika Gakkai Zasshi* 77: 954-962. (In Japanese.)
- Janssen E, Everaerd W, Van Lunsen RH & Oerlemans S (1994) Visual stimulation facilitates penile responses to vibration in men with and without erectile disorder. *J Consult Clin Psychol* 62: 1222-1228.
- Johnson AR & Jarow JP (1992) Is routine endocrine testing of impotent men necessary? *J Urol* 147: 1542-1544.
- Juenemann KP, Lue TF, Huo JA, Jadallah SI, Nunes LL & Tanagho EA (1987) The role of vasoactive intestinal polypeptide as a neuro-transmitter in a canine penile erection: a combined in vivo and immunohistochemical study. *J Urol* 138: 871-877.

- Juneman KP & Alken P (1989) Pharmacotherapy of erectile dysfunction: a review. *Int J Impot Res* 1: 71-93.
- Karacan I (1970) Clinical value of nocturnal penile erection in the prognosis and diagnosis of impotence. *Med Aspects Hum Sexual* 4: 27, 31, 32, 34.
- Karadenitz T, Topsakal M, Aydogmus A & Beksan M (1997) Role of Rigiscan in the etiologic differential diagnosis of erectile dysfunction. *Urol Int* 59(1): 41-45.
- Katlowitz NM, Albano GJ, Morales P & Golimbu M (1993) Potentiation of drug-induced erection with audiovisual sexual stimulation. *Urology* 41(5): 431-434.
- Kim ED, el Rashidy R & McVary KT (1995) Papaverine topical gel for treatment of erectile dysfunction. *J Urol* 153: 361-365.
- Kim ED & McVary KT (1995) Long-term results with penile vein ligation for venogenic impotence. *J Urol* 153: 655-658.
- Kim ED & McVary KT (1995) Topical prostaglandin-E1 for the treatment of erectile dysfunction. *Urology* 45(6): 1828-1830.
- Kim JH & Carson CC III (1993) Development of Peyronie's disease with use of vacuum constriction device. *J Urol* 149: 1314-1355.
- Kim SC, Lee SW & Seo KK (1997) Characteristics of pain following intracavernous injection of prostaglandin E1. *J Korean Med* 12(4): 327-331.
- Kim SC & Oh MM (1992) Norepinephrine involvement in response to intracorporeal injection of papaverine in psychogenic impotence. *J Urol* 147: 1530-1532.
- King J (1874) *The american physician-domestic guide to health*. Indianapolis: Streight and Douglass 384.
- Kinsley AC, Pomeroy WB & Martin CE (1948) *Sexual behavior in the human male*. Philadelphia, WB Saunders, pp236-237.
- Kirby RS (1994) Impotence: diagnosis and management of male erectile dysfunction. *BMJ* 308: 957-961.
- Kirkeby H-J, Forman A & Andersson K-E (1990) Comparison of the papaverine effects on isolated human penile circumflex vein and corpus cavernosum. *Int J Impot Res* 2: 49-54.
- Korenman SG, Morley JE, Mooradian AD, Davis SS, Kaiser FE, Selver AJ, Viosca SP & Garza D (1990) Secondary hypogonadism in older men: its relation to impotence. *J Clin Endocr Metab* 71: 963-969.
- Kosch SG, Curry RW, Jr & Kuritzky L (1988) Evaluation and treatment of impotence: a pragmatic approach addressing organic and psychogenic components. *Fam. Prac Res J* 7(3): 162-173.
- Krane RJ, Goldstein I & Tejada S (1989) Impotence. *N Engl J Med* 321: 1648-1649.
- Kuhn JM, Laudat MH, Lignieres B de, Bricaire H & Luton JP (1986) Traitement androgenique percutane des hypogonadismes masculins. Efficacite comparee de la testosterone et de la dihydrotestosterone: etude de 40 observations. *Contrasept Fert Sex* 14: 1031-1036.
- Lakin MM, Montaque DK, Medendorp SV & Tesar L Schover LR (1989) Intracavernous injection therapy: analysis of results and complications *J Urol* 143: 1138-1141.
- Lederer O (1913) Specification of letter patent. United States Patent Office # 1,225,341. Application filed Nov 29; serial No, 1917, 803,853 Granted May 8.
- Lee LM, Stevenson RWD & Szasz G (1989) Prostaglandin E1 versus phentolamine/papaverine for the treatment of erectile impotence. *J Urol* 141: 549-550.
- Leonard M Nickel, JC & Morales A (1989) Hyperprolactinemia and impotence: why, when and how to investigate. *J Urol* 142: 992-995.
- Levine SB, Althof SE, Turner LA, Risen CB, Bodner DR, Kursh ED & Resnick MI (1989) Side effects of self-administration of intracavernous papaverine and phentolamine for the treatment of impotence. *J Urol* 141: 54-57.
- Lewis RW & Mayda J II (1994) Diagnosis and treatment of vasculogenic impotence. *Acta Chir Hung* 34: 231-241.

- Libman E & Fichten CS (1987) Prostatectomy and sexual functions. *Urology* 29: 467-478.
- Lilius HG, Valtonen EJ & Wikstrom J (1976) Sexual problems in patients suffering from multiple sclerosis. *J Chron Dis* 29: 643-647.
- Linnet OI & Ogrinc FG (1996) Efficacy and safety of intracavernosal alprostadil in men with erectile dysfunction. *Urology* 334: 873-877.
- Lomas GM & Jarow JP (1994) Risk factors for papaverine-induced priapism. *J Urol* 147: 1280-1281.
- Lue TF (1990) Impotence: a patient's goal-directed approach to treatment. *World J Urol* 8: 67-74.
- Lue TF (1990) Intracavernous Drug Administration: Its Role in Diagnosis and Treatment of Impotence. *Seminars in Urology Vol VIII, No 2*: 100-106.
- Lue TF, Hricak H, Marich KW & Tanagho EA (1985) Vasculogenic impotence evaluated by high resolution ultrasonography and pulsed Doppler spectrum analysis. *Radiology* 155: 777-781.
- Lue TF & Tanagho EA (1987) Physiology of erection and pharmacological management of impotence. *J Urol* 137: 829-836.
- Margolis R, Prieto P, Stein L & Chinn S (1971) Statistical summary of 10,000 male cases using Afrodex in treatment of impotence. *Curr Ther Res* 13: 616-622.
- Marin P, Hollmang S, Jonsson L, Sjostrom L, Kvist H, Holm G, Lindstedt G & Bjornthorp P (1992) The effects of testosterone treatment on body composition and metabolism in middle age obese men. *Int J Obesity* 16: 992-997.
- Martins FE & Reis JP (1997) Visual erotic stimulation test for initial screening of psychogenic erectile dysfunction: a reliable noninvasive alternative? *J Urol* 157(1): 134-139.
- McMahon CG (1991) A comparison of the response to the intracavernosal injection of a combination of papaverine and phentolamine, prostaglandin PGE1 and a combination of all three agents in the management of impotence. *Int J Impot Res* 3: 113-121.
- McMahon CG (1996) A pilot study of the role of intracavernous injection of vasoactive intestinal peptide (VIP) and phentolamine mesylate in the treatment of erectile dysfunction. *Int J Impot Res* 8: 233-236.
- McMahon CG (1996) The return of spontaneous erections after self-injection of prostaglandin E1. *Int J Impot Res* 4: 179-186.
- Mebust WK, Holtgrewe HL, Cockett ATK, Peters PC & Writing Committee (1989) Transurethral prostatectomy: immediate and postoperative complications. A cooperative study of 13 participating institutions evaluating 3885 patients. *J Urol* 141: 243-247.
- Meinhardt W, Kropman RF, Lycklama a Nijeholt AAB & Zwartendijk J (1990) Skin necrosis caused by use of negative pressure device for erectile impotence. *J Urol* 144:983.
- Meinhardt W, Schmitz PI, Kropman RF, de la Fuente RB, Lycklama a Nijeholt AA & Zwartendijk J (1997) Trazodone, a double blind trial for treatment of erectile dysfunction. *Int J Impot Res* 9(3): 163-165.
- Miller WW (1968) Afrodex in the treatment of impotence. A double-blind cross-over study. *Curr Ther Res* 10: 354-359.
- Montorsi F, Guazzoni G, Barbieri L, Rigatti P, Pizzini G & Miani A (1996) The effect of intracorporeal injection plus genital and audiovisual sexual stimulation versus second injection on penile color Doppler sonography parameters. *J Urol* 155 (2): 536-540.
- Montorsi F, Guazzoni G, Bergamaschi F, Dodedini A, Rigatti P, Pizzini G & Miani A (1993) Effectiveness and safety of multidrug intracavernous therapy for vasculogenic impotence. *Urology* 42(5): 554-558.
- Montorsi F, Strambi LF, Guazzoni G, Galli L, Barbieri L, Rigatti P, Pizini G & Miani A (1994) Effect of yohimbine-trazodone on psychogenic impotence: a randomized, double-blind, placebo-controlled study. *Urology* 44: 732-736.
- Morales A, Heaton JP, Johnston B & Adams M (1995) Oral and topical treatment of erectile dysfunction: present and future. *Urol Clin NA* 22: 879-886.

- Morales A, Johnston B, Heaton JP & Lundie M (1997) Testosterone supplementation for hypogonadal impotence: assessment of biochemical measures and therapeutic outcomes. *J Urol* 157: 849-854.
- Morales A, Johnston B, Heaton JW & Clark A (1994) Oral androgens in the treatment of hypogonadal impotent men ( see comments). *J Urol* 152: 1115-1118.
- Morales A, Surridge DH, Marshall PG & Fenemore J (1982) Nonhormonal pharmacological treatment of organic impotence. *J Urol* 128(1): 45-47.
- Moriel EZ & Rajfer J (1993) Sodium bicarbonate alleviates penile pain induced by intracavernous injections for erectile dysfunction. *J Urol* 149: 1299-1300.
- Morley JE (1985) Impotence. *Am J Med* 80: 897-905.
- Morley JE & Kaiser FE (1989) Sexual function with advancing age. *Med Clin North Am* 73: 1483-1495.
- Morley JE, Perry M, Kaiser FE, Kraenzle D, Jensen J, Houston K, Mattammal M & Perry HM (1993) Effects of testosterone replacement therapy in old hypogonadal males: a preliminary study. *J Am Geriatr Soc* 41: 149-152.
- Mulligan T & Katz PG (1989) Why aged men become impotent. *Arch Intern Med* 149: 1365-1366.
- Mulligan T, Retchin SM, Chinchilli VM & Bettinger CB (1988) The role of aging and chronic disease in sexual dysfunction. *J Amer Geriatr Soc* 36: 520-524.
- Murburg MM, Villacres EC, Ko GN & Veith RC (1991) Effects of yohimbine on human sympathetic nervous system function. *J Clin Endocrinol Metab* 73: 861-865.
- Nadig PW, Ware JC & Blumoff R (1986) Non invasive device to produce and maintain an erection-like state. *Urology* 27: 126-131.
- Nahoul K & Roger M (1990) Age-related decline of plasma bioavailable testosterone in adult men. *J Steroid Biochem* 35: 293-299.
- Nakhla AM, Khan MS, Romas NP & Rosner W (1994) Estradiol causes the rapid accumulation of cAMP in human prostate tissue. *Proc Natl Acad Sci* 91: 5402-5405.
- Navratil H, Costa P, Louis JF, Andro MC & Saur P (1995) Efficacy and safety of intracavernous injection in patients with erectile dysfunction: dose/effect relationship versus placebo. *Progres en Urologie* 5: 690-696.
- Nessel MA (1994) Yohimbine and pentoxifylline in the treatment of erectile dysfunction . *Am J Psychiatry* 151: 453.
- NIH Consensus Conference (1993) Impotence. NIH Consensus Development Panel on Impotence. *JAMA* 270: 83-90.
- Nisen H & Cormio L (1993) Pharmacotesting with high dose prostaglandin E1 in impotence. *Ann Chir et Gyn* 82: 63-68.
- Nisen HO, Saarinen O, Ruutu ML & Edgren J (1993) Duplex doppler scanning with prostaglandin E1 in the diagnosis of cavernous leakage. *Acta Radiologica* 34: 335-338.
- O'Leary MP, Fowler FJ, Lenderking WR, Barber B, Sagnier PP, Guess HA & Barry MJ (1995) A brief male sexual function inventory for urology. *Urology* 46: 697-706.
- Ono N, Lumpkin MD, Samson WK, McDonald JK & McCann SM (1984) Intrahypothalamic action of corticotropin-releasing factor (CRF) to inhibit growth hormone and LH release in the rat. *Life Sci* 35: 1117-1123.
- Osbon GD (1983) Erection aid device. US patent, 4, 378,008, Mar 29.
- Padma-Nathan H & Goldstein I (1998) The pathogenesis of post-TURP impotence. *J Urol* 139: 275A.
- Padma-Nathan H, Hellstrom WJG, Kaiser FE, Labasky RF, Lue TF, Nolten WE, Norwood PC, Peterson CA, Shabsigh R, Tam PY, Place VA & Gesundheit N (1997) Treatment of men with erectile dysfunction with transurethral alprostadil. *N Engl J Med* 336: 1-7.
- Padma-Nathan H, Keller T & Proppiti R (1994) Hemodynamics effect of intraurethral alprostadil: the medicated urethral system for erection (MUSE). *Int J Impot Res* 6: A42.
- Pearlman CK & Kobashi LI (1972) Frequency of intercourse in men. *J Urol* 107: 298-301.

- Pescatori ES, Engelman JC, Davis G & Goldstein I (1993) Priapism of the clitoris: a case report following trazodone use. *J Urol* 149: 1557-1559.
- Pescatori ES, Hatzichristou DG, Namburi S & Goldstein I (1994) A positive intracavernous injection test implies normal veno-occlusive but not necessarily normal arterial function: A hemodynamic study (see comments). *J Urol* 151: 1209-1216.
- Piper PJ (1973) Distribution and metabolism. In Cuthbert MF (ed): *Prostaglandins: Pharmacological and therapeutical advances*. Philadelphia, Lippincott: 125-150.
- Pont A, Williams PL, Azhar S, Reitz RE, Bochra C, Smith ER & Stevens DA (1982) Ketoconazole blocks testosterone synthesis. *Arch Intern Med* 142: 2137-2140.
- Porst H (1990) Diagnostic use and side-effects of vaso-active drugs: A report on over 2100 patients with erectile failure. *Int J Impot Res* 2(suppl 2): 222-223.
- Porst H (1996) The rationale for prostaglandin E1 in erectile failure: a survey of worldwide experience. *J Urol* 155: 802-815.
- Price DE, Cooksey G, Jehu D, Bentley S, Hearnshaw JR & Osborn DE (1991) The management of impotence in diabetic men by vacuum tumescence therapy. *Diabetic Med* 8: 964-967.
- Przybilla B & Schill WB (1985) Side-effects of drugs on male sexual function (Ger). *Z Hautkreis* 60: 1105-1114.
- Quinlan DM, Epstein JI, Carter BS & Walsh PC (1991) Sexual function following radical prostatectomy: influence of preservation of neurovascular bundles. *J Urol* 145: 998-1002.
- Ravnik-Oblak M, Oblak C, Vodusek DB, Kristl V & Zihel S (1990) Intracavernous injection of prostaglandin E1 in impotent diabetic men. *Int J Impot Res* 2: 143-150.
- Reid K, Surridge DH, Morales A, Condra M, Harris C, Owen J & Fenemore J (1987) Double-blind trial of yohimbine in the treatment of psychogenic impotence. *Lancet* II: 421-423.
- Richter S, Gross R & Nissenkorn I (1990) Cavernous injection therapy for the treatment of erectile dysfunction in elderly men. *Int J Impot Res* 2: 43-47.
- Rosen MP, Greenfield AJ, Walker TG, Grant P, Dubrow J, Bettman MA, Fried LE & Goldstein I (1991) Cigarette smoking: an independent risk factor for atherosclerosis in hypogastric-cavernous arterial bed of men with arteriogenic impotence. *J Urol* 145: 759-763.
- Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J & Mishra A (1997) The International Index of Erectile Function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology* 49: 822-830.
- Rowland DL, den Ouden AH & Slob AK (1994) The use of vibrotactile stimulation for determining sexual potency in the laboratory in men with erectile problems: methodological considerations. *Int J Impot Res* 6(3): 153-161.
- Roy AC, Tan SM, Kottegoda SR & Ratnam SS (1984) Ability of human corpora cavernosa muscle to generate prostaglandins and thromboxanes in vitro *IRCS Med Sci* 12: 608-609.
- Roy JB, Petrone RL & Said SI (1990) A clinical trial of intracavernous vasoactive intestinal peptide to induce penile erection. *J Urol* 143: 392-397.
- Saenz de Tejada I, Ware JC, Blanco R, Pittard JT, Nadig PW, Azadzo KM, Krane RJ & Goldstein I (1991) Pathophysiology of prolonged penile erection associated with trazodone use. *J Urol* 145: 60-64.
- Saenz de Tejada & Moncada I (1996) Pharmacology of penile smooth muscle. In book Porst H (Ed): *Penile disorders. Proceedings of the International Symposium on Penile Disorders*. p 125-143.
- Sarosdy MF, Hudnall H, Erickson DR, Hardin TC & Novicki E (1989) A prospective double-blind trial of intracorporeal papaverine versus prostaglandin E1 in the treatment of impotence. *J Urol* 141: 551-553.
- Sato Y, Suzuki N, Adachi H, Hisasue S, Horita H & Tsukamoto T (1998) Evaluation of alleviative action of neurotrophin for penile pain associated with intracavernous injection of prostaglandin E1 assessed using the visual analogue scale. *Int J Impot Res* 10(1): 1-3.

- Schramek P, Dorninger R, Waldhauser M, Konecny P & Porpaczy P (1990) Prostaglandin E1 in erectile dysfunction. Efficiency and incidence of priapism. *Brit J Urol* 65: 68-71.
- Schramek P, Plas EG, Hubner WA & Pfluger (1994) Intracavernous injection of prostaglandin E1 plus procaine in the treatment of erectile dysfunction. *J Urol* 152: 1108-1110.
- Schramek P & Waldhauser M (1989) Dose-dependent effect and side-effect of prostaglandin E1 in erectile dysfunction. *Br J Clin Pharmacol* 28: 567-571.
- Seidmon EJ & Samaha AM JR (1989) The pH analysis of papaverine-phenolamine and prostaglandin E1 for pharmacological erection. *J Urol* 146: 1458-1459.
- Shabsigh R, Fishman IJ, Toombs BD & Skolkin M (1991) Venous leaks: anatomical and physiological observations. *J Urol* 146: 1260-1265.
- Shabsigh R, Fishman IJ, Schum C & Dunn JK (1991) Cigarette smoking and other vascular risk factors in vasculogenic impotence. *Urology* 38: 227-231.
- Shirai T, Imaida K, Masui T, Iwasaki S, Mori T, Kato T & Ito N (1994) Effects of testosterone, dihydrotestosterone and estrogen on 3,2' dimethyl-4-aminobiphenyl-induced rat prostate carcinogenesis. *Int J Cancer* 57: 224-228.
- Sister MP (1990) Prostaglandin E1 in erectile dysfunction: 20 months of experience with 483 patients in self-injection program. *Int J Impot Res* 2: 287-288.
- Slag MF, Morley JE, Elson MK, Trencle DL, Nelson CJ, Nelson AE, Kinlaw WB, Beyer HS, Nuttall FQ, Shafer RB (1983) Impotence in medical clinic outpatients. *J.A.M.A.* 249: 1736-1740.
- Smith AD (1981) Causes and classification of impotence. *Urol Clin N Amer* 8: 79-89.
- Sobotka JJ (1969) An evaluation of afrodex in the management of male impotency. *Curr Ther Res* 11: 87-97.
- Sohn MH, Seeger U, Sikora R & Jakse G (1993) Criteria for examiner-independent nocturnal penile tumescence and rigidity monitoring (NPTR): Correlations to invasive diagnostic methods. *Int J Impot Res* 5: 59-68.
- Sonda P, Mazo R & Chancellor MB (1990) The role of yohimbine for the treatment of erectile impotence. *J Sex Marital Ther* 16: 15-21.
- Sorva R, Kuusi T, Taskinen M-R, Perheentupa J & Nikkilä EA (1988) Testosterone substitution increases the activity of lipoprotein lipase and hepatic lipase in hypogonadal males. *Atherosclerosis* 69: 191-197.
- Spector IP & Carey MP (1990) Incidence and prevalence of the sexual dysfunctions: A critical review of the empirical literature. *Arch Sex Behav* 19: 389-408.
- Spratt DI, O'Dea LS, Schoenfeld D, Butler J, Rao PN & Crowley WF Jr (1988) Neuroendocrine-gonadal axis in men: Frequent sampling of LH, FSH and testosterone. *Am J Physiol* 254: E658-E666.
- Stackl W, Hasun R & Marberger M (1988) Intracavernous injection of prostaglandin E1 in impotent men. *J Urol* 140: 66-68.
- Stackl W, Hasun R & Marberger M (1990) The use of prostaglandin E1 for diagnosis and treatment of erectile dysfunction. *World J Urol* 8: 84-86.
- Stackl W, Stief CG, Benard F, Aboseif SR, Bosch RJ, Loupal G, Lue TF & Tanagho EA (1989) Intracavernous injection of solutions with different osmolarity and pH in the rabbit. *Int J Impot Res* 1: 197-200.
- Stewart AL & Ware JE (eds) 1992 *Measuring Function and Well-Being: The Medical Outcomes Study Approach*. Durham and London: Duke University Press.
- Stief CG, Benard F, Bosch JLHR, Aboseif SR, Lue TF & Tanagho EA (1990) A possible role for calcitonin-gene-related peptide in the regulation of the smooth muscle tone of the bladder and penis. *J Urol* 143: 392-397.
- Stief CG, Junemann KP, Kellner B, Gerstenberg T, Merckx L & Wagner G (1994) Consensus and progress in corpus cavernosum-EMG (CC-EMG). *Int J Impot Res* 6: 177-182.

- Surridge DHC, Lee JC, Morales A & Heaton PW (1998) Penile rigidity may supersede partner and counseling issues. *J Urol* 159: 5 supplement 114.
- Susset JG, Tesier CD & Winze J (1989) Effect of yohimbine hydrochlorid on erectile impotence: a double-blind study. *J Urol* 141: 1360-1363.
- Suzuki K, Takezawa Y, Suzuki T, Honma S & Yamaka H (1994) Synergistic effects of estrogen with androgen on the prostate-effects of estrogen on the prostate of androgen-administered rats and 5- $\alpha$ -reductase activity. *Prostate* 25: 169-176.
- Swerdloff RS & Wang C (1993) Androgens and aging in men. *Experimental Gerontology* 28: 435-446.
- Taylor S, Sutherland GR, Mackenzie GJ, Staunton HP & Donald HW (1965) The circulatory effect of intravenous phentolamine. *Circulation* 31: 741-754.
- Tenover JS (1992) Effects of testosterone supplementation in the aging male. *J Clin Endocrinol Metab* 75: 1092-1098.
- Theiss M, Hormockel G & Frohmuller HG (1995) Fournier's gangrene in a patient with erectile dysfunction following use of mechanical erection aid device. *J Urol* 153: 1921-1922.
- Turner LA, Althof SE, Levine SB, Tobias TR, Kursh ED, Bodner D & Resnick MI (1990) Treating erectile dysfunction with external vacuum devices: impact upon sexual, psychological and marital functioning. *J Urol* 144: 79-82.
- Turner LA, Althof SE, Levine SB, Bodner DR, Kursh ED & Resnick MI (1991) External vacuum devices in the treatment of erectile dysfunction: a one-year study of sexual and psychosocial impact. *J Sex Marital Ther* 17: 81-93.
- Turner LA, Althof SE, Levine SB, Bodner DR, Kursh ED & Resnick MI (1992) Twelve-month comparison of two treatments for erectile dysfunction: self-injection versus external vacuum devices. *Urology* 39: 139-144.
- Wagner G (1981) Methods of differential diagnosis of psychogenic and organic erectile failure. In Wagner G, Green R (eds): *Impotence*. New York, Plenum, p 89-129.
- Wagner G, Gerstenberg T (1988) Human in vivo studies of electrical activity of corpus cavernosum. *J Urol* 139: 327A.
- Wagner G, Tejada IS (1998) Update on male erectile dysfunction. *BMJ* 316: 678-682.
- Valdevenito R & Melman A (1994) Intracavernous self-injection pharmacotherapy program: Analysis of results and complications. *Int J Impot Res* 6: 81-91.
- Walsh PC & Donker PJ (1982) Impotence following radical prostatectomy. *J Urol* 128: 492-497.
- Wang Q & Large WA (1991) Modulation of noradrenaline-induced membrane currents by papaverine in rabbit vascular smooth muscle cells. *J Physiol (Lond)* 439: 501-512.
- Wegner HEH, Knispel HH, Klän R, Meier T & Miller K (1994) Prostaglandin E1 versus Linsidomine Chlorhydrate in erectile dysfunction. *Urol Int* 53: 214-216.
- Wein AJ, Fishkin R, Carpiniello VL & Malloy TR (1981) Expansion without significant rigidity during nocturnal penile tumescence testing: A potential source of misinterpretation. *J Urol* 126: 343-344.
- Wein AJ & Van Arsdalen KN (1988) Drug-induced male sexual dysfunction. *Urol Clin N Amer* 15: 23.
- Weiske EH (1996) Epidemiology and diagnostics of erectile dysfunction. In book Porst H (ed): *penile disorders; proceedings of the international symposium on penile disorders*. Hamburg, Germany, January 26-27. Springer, p 120-121.
- Vermeulen A (1993) The male climacterium: *Ann Med* 25: 531-534.
- Wespes E, Delcour C, Struyven J & Schulman CC (1986) Pharmacocavernometry-cavernography in impotence. *Br J Urol* 58: 429-433.
- Wespes E, Moreira de Goes P & Schulman C (1992) vascular impotence:focal or diffuse penile disease. *J Urol* 148: 1435-1436.

- Virag R & Adaikan PG (1987) Effects of prostaglandin E1 on penile erection and and erectile failure. *J Urol* 137: 1010 (letter).
- Virag R, Frydman D, Legman M & Virag H (1984) Intracavernous injection of papaverine as a diagnostic and therapeutic method in erectile failure. *Angiology* 35: 79-87.
- Virag R, Shoukry K, Floresco J, Nollet F & Greco E (1991) Intracavernous self-injection of vasoactive drugs in the treatment of impotence: 8-year experience with 615 cases. *J Urol* 145: 287-293.
- Virag R (1982) Intracavernous injection of papaverine for erectile failure (letter). *Lancet* II: 938.
- Witherington R (1989) Vacuum constriction device for management of erectile dysfunction. *J Urol* 141: 320-322.
- Witjes WP, Meuleman EJ, Lycklama N, Van Driel MF, Leliefeld HH, Kropman RF & Doesburg WH (1992) the efficiency and acceptance of intracavernous autoinjection therapy with the combination of papaverine/ phentolamine. A prospective multicenter trial. *Int J Impot Res* 4: 65-71.
- Von Graffenreid B, del Pozo E, Roubicek J, Roubicek J, Krebs E, Pödingner W, Burmeister P & Kerp L (1978) Effects of synthetic enkephalin analogue FK 33-824 in man. *Nature* 272: 729-730.
- Von Heyden B, Donatucci CF, Marshall GA, Brock GB & Lue TF (1993) A prostaglandin E1 dose-response study in man. *J Urol* 150: 1825-1828.
- Vrijhof HJ & Delaere KP (1994) Vacuum constriction devices in erectile dysfunction vacuum tumescence device: a retrospective analysis of acceptance and satisfaction. *Br J Urol* 74: 102-105.
- Vruggink PA, Diemont WL, Debruyne FM & Meuleman EJ (1995) Enhanced pharmacological testing in patients with erectile dysfunction. *J Androl* 16(2): 163-168
- Yalcin S, Altundag K, Asil M & Tekuzman G (1998) Sublingual piroxicam for cancer pain. *Med Oncol* 15 (2): 137-139.
- Zeiss AM, Davies HD, Wood M & Tinklenberg JR (1990) The incidence and correlates of erectile problems in patients with Alzheimer`s disease. *Arch Sex Behav* 19: 325-331.
- Zorgniotti AW (1992) 'On demand' oral drug for erection in impotent men. *J Urol* 147: 308A.
- Zorgniotti AW & Lefleur RS (1985) Auto-injection of corpus cavernosum with vasoactive drug combination of vasculogenic impotence. *J Urol* 133: 39-41.
- Zorgniotti AW & Lizza AF (1994) Effect of large doses of the nitric oxide precursor, L-arginine, on erectile dysfunction. *Int J Impot Res* 6: 33-35.