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Pharmacological Effects on Nocturnal Penile Tumescence (NPT)

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Introduction

The phenomenon of cyclically-occurring penile erections during sleep was first recognized by German investigators in the mid-1940's (1,2). The temporal association of nocturnal erections with rapid eye movement (REM) sleep was subsequently noted by Aserinsky and Kleitman (3), and demonstrated experimentally in the 1960's by Fisher, Gross and Zuch (4), and Karacan (5) using modern sleep laboratory (polysomnographic) procedures. Penile tumescence was measured in these studies by means of the mercury-in-rubber strain gauge technique (6,7). Subsequent studies have shown that sleep-related erections are present throughout the life cycle in healthy males, although a significant reduction in the frequency, amplitude and duration of nocturnal erections occurs with aging (8). Nocturnal erections are relatively unaffected by pre-sleep sexual or non-sexual activity, dream content or imagery, or the presence of a full bladder (9). Little is known at present about the occurrence of sleep-related erections in other species (10,11).

Based upon evidence of diminished nocturnal erections in diabetic men, Karacan (12) proposed that laboratory assessment of nocturnal penile tumescence (NPT) be used clinically in the differential diagnosis of organic erectile dysfunction. Testing is typically performed over several nights in a sleep laboratory, with concurrent measurements of EEG sleep and penile tumescence. Penile rigidity measures are usually obtained. The underlying assumption is that nocturnal erectile activity reflects the waking capacity for adequate erection, independent of the role of psychogenic or interpersonal factors. Despite mixed empirical support for this hypothesis (13-17), NPT testing became widely adopted in the 1980's as the "gold standard" for clinical assessment of male erectile disorder (18-19). In recent years, several ambulatory or home-based recording systems have been developed, ranging from simple "snap-gauge" or "stamp-ring" devices, to the technically-sophisticated Rigiscan system (20-21). Notwithstanding the obvious advantage in cost-effectiveness of these devices, significant problems have been noted in regard to the overall sensitivity and reliability of ambulatory recording devices (22).

Relatively few studies have addressed the neurophysiological mechanisms involved in NPT. Although there is a strong temporal association between REM sleep and nocturnal tumescence in normal males, Schiavi (23) has argued that the two processes are controlled by separate mechanisms, and that disassociation is possible under certain conditions. In contrast, Bancroft (24) has recently speculated that NPT is partially mediated by a "switching off" of noradrenergic neurons in the locus coeruleus during REM sleep, which is associated with a reduction in peripheral sympathetic tone and removal of the normal inhibitory effects of noradrenergic tone in the erectile tissue of the penis. It has also been shown that EEG hemispheric

asymmetry, which occurs as a correlate of sexual arousal in the waking state, also occurs in association with NPT (25-26). Finally, nocturnal erections have been shown to be highly androgen-dependent, in contrast to erections induced by visual or erotic stimulation (27-28). In hypogonadal men, for example, the relative absence of nocturnal erections prior to treatment is rapidly reversed following adrogen replacement therapy, whereas responses to visual stimulation are minimally affected (28).

In the present article, the role of NPT studies in the evaluation of drug effects on male sexual response is considered. Studies of this topic are relevant to our understanding of basic mechanisms in sexual arousal, in addition to the clinical management of common sexual disorders. Although a broad range of prescription and non-prescription drugs have been investigated to date, major emphasis is placed on the effects of cardiovascular and antidepressant drugs. These are among the most widely prescribed drugs in industrialized societies and sexual side effects are frequently reported (29-30). Effects of androgenic and anti-androgenic drugs are also considered, as well as the recent category of "pro-sexual" or aphrodisiacal drugs (31). Conceptual and methodological issues are considered, and specific recommendations are made for future research on this topic.

Androgenic and Anti-androgenic Drugs and NPT

Studies of NPT in hypogonadal males have been used to investigate sexual dysfunction in these individuals, in addition to assessing the effects of androgen replacement therapy on sexual libido and arousal. Prior to treatment, hypogonadal men typically have low levels of sexual desire and arousal, as well as markedly diminished frequency and amplitude of NPT (32). Following androgen replacement, NPT responses typically normalize within 3-4 weeks and are highly correlated with increased levels of libido and spontaneous daytime erections (27-28). Additionally, it has been shown that improved nocturnal erections following androgen replacement therapy are not secondary to changes in REM sleep or total sleep time (28).

In the first double-blind study of androgen replacement, Davidson, Camargo and Smith (29) evaluated the effects of testosterone enanthate (im) or placebo in six adult males with primary or secondary hypogonadism. Two doses of testosterone (100 mg and 400 mg) were administered over a five-month period. Among the various measures of sexual response and erectile capacity in this study, self-report of nocturnal erections was found to be the most sensitive index of hormone replacement. In a subsequent study (27), these investigators compared the effects of high and low testosterone doses (200 mg, 400 mg) and placebo during consecutive one-month treatment periods in five hypogonadal men and one castrate. Nocturnal tumescence was assessed by means of a portable monitor (Event Systems, Inc), and compared with responses to visual stimulation (i.e., erotic videotapes) and sexual fantasy. Again, NPT measures were highly correlated with changes in circulating testosterone levels, while responses to film and fantasy stimuli were relatively unaffected by drug treatment. Similar findings were reported by O'Carroll, Shapiro and Bancroft (28), who administered four doses of oral testosterone undecanoate in a double-blind, placebo-controlled design with eight hypogonadal men. In this study, measures of frequency, duration, and amplitude of NPT were obtained under controlled sleep laboratory

conditions. Again, NPT measures were highly correlated with changes in sexual interest and libido, which were related to circulating testosterone levels as in the previous two studies (27,29).

Most recently, these findings have been replicated in a long-term study of hormone replacement therapy in hypogonadal men (33). In this study, gradual improvements in both NPT and libido were observed during the course of a six-month treatment period. Similarly, significant improvements in NPT and subjective measures of sexual arousal were noted in a recent double-blind study of androgen replacement therapy in nine patients with gonadotropin-deficient hypopituitary syndrome (34).

Anti-androgenic drug effects on NPT have been evaluated in several studies with paraphilic or sexually hyperactive individuals. For example, Wincze, Bansal and Malamud (35) studied the effects of medroxyprogesterone acetate (MPA) in three chronic pedophiles, using a placebo-controlled, within-subject, crossover design. Results indicated a significant negative effect of MPA administration on both the amplitude and duration of NPT, which was highly correlated with subjective measures of sexual desire and libido. As in the previous studies, penile responses to visual stimulation were relatively unaffected by drug treatment. Similar results were obtained in a subsequent study of cyproterone acetate (CPA), a potent anti-androgenic agent, which was administered for a two-month period to five chronic pedophiles (36). Although slight changes were observed in the waking measures of sexual arousal and orgasm, the effects of treatment were most clearly evident in the suppression of both NPT and circulating testosterone levels following treatment.

Overall, the pattern of results in these studies is strikingly consistent. In hypogonadal males, NPT assessment has been shown to be a sensitive and reliable index of response to treatment, which is also highly correlated with changes in sexual desire or libido. This is in marked contrast to the lack of treatment effects on stimulus-dependent measures of erection, such as responses to visual stimulation. Similar findings have been obtained in studies of anti-androgenic agents (MPA, CPA) in the treatment of paraphilic patients, in which NPT measures were again shown to be highly responsive to the effects of hormonal therapy. Taken together, these findings lend strong support to the two-process model of male erection, including androgen-dependent (i.e. spontaneous) versus androgen-independent (i.e. elicited) erections (23).

Cardiovascular Drugs and NPT

Cardiovascular drugs, such as antihypertensive and anticholesterolemic agents, are among the most widely prescribed medications in most western societies. Concerns about potential sexual side effects of these drugs have increased markedly in recent years (37), as reports from large-scale, clinical trials have shown that many patients on these drugs experience sexual desire or arousal difficulties (38-39). Recently, nocturnal erection studies have been used to document drug-related impairment of arousal in male patients and to investigate specific pathophysiological mechanisms involved. In interpreting these results, it should be noted that chronic hypertension per se has been associated with significant impairment of erection in middle-aged males (40).

Beta-adrenoceptor blocking agents (beta-blockers) are widely used in the treatment of hypertension, cardiac arrhythmias, and other cardiovascular disorders. Several studies in our laboratory have investigated the effects of specific beta-blockers on NPT and other measures of male sexual function (41-42). In our first study, 30 healthy male subjects were randomly assigned to a double-blind, placebo-controlled evaluation of the effects of four common beta-blockers, including propranolol, a nonselective lipophilic beta-blocker, metoprolol, a selective lipophilic beta-blocker, atenolol, a selective hydrophilic beta-blocker, and pindolol, a nonselective beta-blocker with intrinsic sympathomimetic activity. Each drug was administered for a 1-week treatment period, following which measures of NPT, testosterone, and subjective arousal were obtained. Results indicated a significant decrease in plasma and free testosterone levels with all four study drugs, particularly propranolol. A similar trend was observed in the frequency, amplitude and duration of NPT, which was independent of changes observed in REM sleep or total sleep time. Only one study drug, pindolol, was associated with a significant decrease in REM time. Within each drug condition, testosterone levels were significantly correlated with the frequency of intercourse and subjective ratings of desire for sex. These findings are consistent with reports of decreased plasma testosterone levels in patients receiving chronic beta-blocker administration (43).

More recently, we evaluated the effects of clonidine, a central alpha-adrenergic agonist, and propranolol, in a placebo-controlled, double-blind, crossover study of 47 male hypertensive patients (44). Each study drug was administered for a 3-month period, and was followed by a 1-month drug-free washout period. As in the previous study, polysomnographic measures of sleep were obtained prior to and following each treatment phase, in addition to frequency, amplitude and duration of NPT. As shown in Figure 1 below, the average duration of NPT was markedly reduced in younger patients on both clonidine and propranolol, whereas NPT amplitude was significantly decreased in older patients taking propranolol. Clonidine was not administered to elderly hypertensives in this study, due to increased risk of orthostatic hypotension.

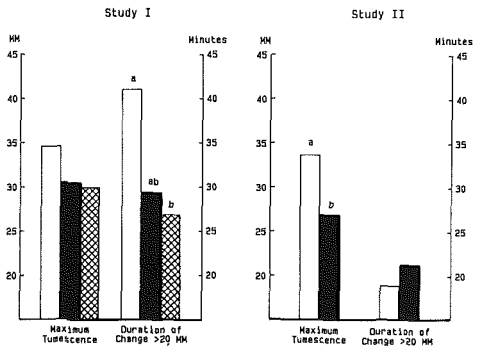

Fig. 1. Effects of antihypertensive drugs on NPT measures in younger (Study I) and older hypertensive patients (Study II). Means with the same letter are not significantly different at $p<0.05$. Solid bars = propranolol; hatched bars = clonidine; open bars = placebo. (From Kostis et al., Psychopharmacol 1990; 102 : 163-170. Reprinted with permission)

It has been proposed that changes in sexual function associated with antihypertensive drugs may be directly due to the blood pressure-lowering effects of these drugs (45). To investigate this hypothesis, we compared the effects of propranolol (80-160 mg/d) and placebo with a 3-month nondrug treatment intervention, consisting of weight loss, isometric exercise, and

relaxation training (46). As in the previous study, propranolol administration was associated with a significant decrease in the frequency and duration of NPT, compared to both nondrug therapy and placebo. Specifically, the frequency of full erections declined by approximately 50% in the drug condition, compared to a modest increase in both the placebo and nondrug therapy. In contrast, patients receiving nondrug therapy reported significant improvement in self-ratings of erection, orgasm and satisfaction following treatment. These findings provide strong evidence of the pharmacological effects of the drug (propranolol) on NPT and sexual function, independent of the blood-pressure lowering or expectancy effects associated with drug administration.

Another hypothesis to be tested is that patients with a prior history of sexual dysfunction are at greater risk for sexual sequelae of antihypertensive drugs. To investigate this issue, we conducted a placebo-controlled, double-blind crossover study in 13 middle-aged, hypertensive males with a history of erectile difficulties and/or low sexual desire (47). Treatment drugs for the study were alpha-methyldopa (500 mg bid), propranolol (80 mg bid), atenolol (100 mg qd) and hydrochlorthiazide/triamterene (50/25 mg bid). Each study drug was administered for a one-month treatment period, followed by a two-week washout period, according to a counterbalanced, Latin square design. Although a trend was observed towards diminished amplitude and duration of NPT with each of the drugs, these effects were less noticeable than in our previous study with non-dysfunctional patients. It is possible that drug effects were partially obscured by a "floor effect", in that markedly lower baseline levels were noted prior to the initiation of treatment.

Few studies to date have evaluated NPT or sleep changes associated with cholesterol-lowering drugs, such as the HMG CoA reductase inhibitors (e.g., pravastatin, lovastatin). Accordingly, we conducted a placebo-controlled, double-blind study of pravastatin (40 mg/d) and lovastatin (40 mg/d) in middle-aged males with chronic hypercholesterolemia (48). Patients received each study drug in counterbalanced order for a 6-week treatment period, separated by one-month washout periods. Analysis of NPT data in this study revealed that both study drugs were associated with a significant increase in the duration of maximum tumescence at two weeks of treatment (See Figure 2 below). A similar trend was observed for measures of maximum tumescence adjusted for total sleep time, peak tumescence, and duration of partial tumescence. Although the trend was maintained, these differences were not significant after six weeks of treatment. Results are interpreted as possibly due to improved endothelial function and enhanced endothelium-dependent relaxation of corporal smooth muscle in the penis (49).

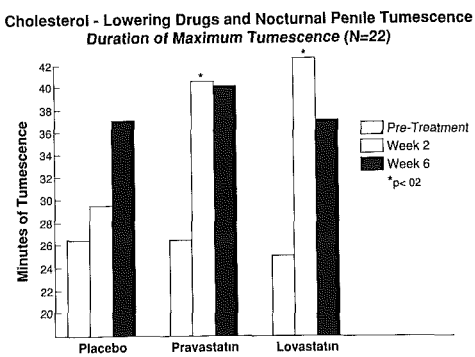

Fig. 2. Effects of cholesterol-lowering drugs (pravastatin, lovastatin) on NPT duration in hypercholesterolemic patients. Adapted from Kostis, Rosen & Wilson, Clinical Pharmacol (In Press).

Taken together, these studies suggest that nocturnal erections are affected by a wide variety of cardiovascular drugs, and that these effects are associated with changes in hormonal and subjective measures of sexual function. Suppression of NPT has been associated with the effects of adrenergic-inhibiting antihypertensive agents in both normal males and hypertensive patients, independent of the effects of these drugs on sleep architecture or continuity. Moreover, NPT changes are not directly attributable to the blood-pressure lowering effects of the drugs. Results need to be cautiously interpreted, however, considering the possible influence of cardiovascular disease per se on sexual function, as well as the potentially confounding effects of obesity, sleep apnea, depression, and other comorbid conditions. Finally, it should be noted that cardiovascular drugs may be associated with positive as well as negative effects on NPT, as illustrated in our recent study of HMG-CoA reductase inhibitors.

Antidepressant Drug Effects

Despite widespread use of antidepressant drugs in the treatment of psychiatric disorders, there are relatively few systematic studies of the effects of these drugs on sexual desire or arousal. Frequent case reports have documented sexual side effects of tricyclic antidepressants (TCA's), monoamine oxidase inhibitors (MAOI's), and most recently, the selective serotonin-reuptake inhibitors (SSRI's). Male and female patients on these drugs report frequent difficulties with sexual arousal or orgasm, in addition to diminished desire or libido (50). It should be noted, however, that depressed individuals often show a marked reduction in sexual desire or arousal associated with the disorder itself (51-52). Significant impairment in the amplitude and duration of NPT has been observed in male patients with clinical depression, which appears unrelated to changes in sleep architecture and daytime sexual activity (53). In one study, normalization of nocturnal erections occurred following successful treatment of depression in 10 male patients (54).

Tricyclic antidepressants have been associated with marked suppression of NPT in normal males (55). Drugs administered in this study were amitryptiline, a tricyclic antidepressant, and mianserin, a tetracyclic alpha-2 receptor blocker. Each of the study drugs was administered in a double-blind, crossover design for 2 weeks, following which overnight polysomnography and NPT was recorded in all subjects. Results indicated a significant decrease in both the amplitude and duration of nocturnal tumescence with both study drugs, compared to placebo. Duration of full erection was reduced from 114.6 min. per night on placebo, to 47.2 min. on amitryptiline and 42.8 min. on mianserin. This effect was attributed to the inhibition of central alpha-adrenergic activity involved in the control of erection. Results need to be cautiously interpreted, however, due to the small number of subjects in this study (N=6), and lack of control for the sleep-altering effects of the drugs. Specifically, REM time was significantly reduced in both drug conditions.

More recent studies by Ware and associates (56-57) have investigated NPT effects of several antidepressant drugs with central and peripheral neurotransmitter actions. In the first study (56), the effects of trazodone, a triazolopyridene derivative with both serotonergic and alpha adrenergic effects, was compared to trimipramine, a sedating tricyclic antidepressant with relatively potent alpha adrenergic effects. Each of the study drugs was administered to six healthy

young males in a placebo-controlled, crossover design involving polysomnographic measures of sleep and NPT. As shown in Figure 3 below, a significant increase in total erectile activity was observed in the trazodone condition, compared to both trimipramine and placebo. In contrast, trimipramine was associated with a non-significant decrease in NPT activity. Of particular note, trazodone administration was associated with a significant reduction in skin conductance activity during sleep, compared to both placebo and trimipramine (See Figure 3B below). This latter finding suggests that the prolongation of nocturnal tumescence observed in the trazodone condition is related to the sympathetic-blocking effects of the drug. In turn, this finding can be viewed as supporting Bancroft's (24) hypothesis concerning the noradrenergic blocking effects of REM sleep in the facilitation of nocturnal erections.

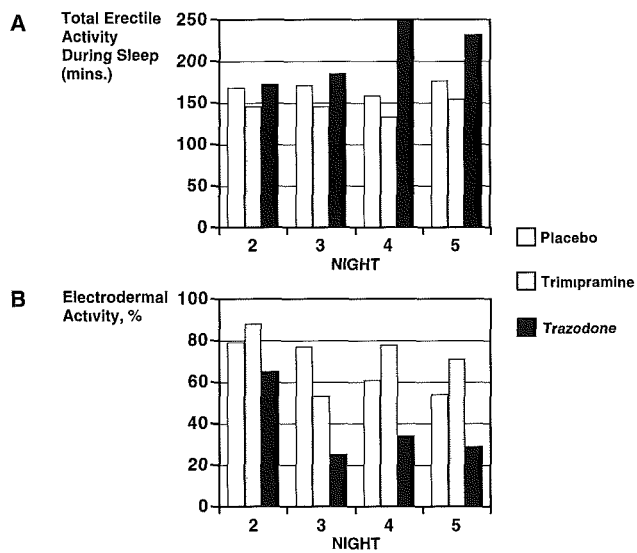

Fig. 3. Antidepressant drug effects on measures of NPT and electrodermal activity in normal males (N=6) Total duration of NPT is shown above (A), and the mean frequency of electrodermal activity is shown below (B). Adapted from Saenz de Tejada et al., J. Urol 1991; 145.60-64

In a subsequent study (57), the effects of trazodone were compared with nefazodone, a potent 5-HT_2 antagonist and 5-HT reuptake inhibitor, and buspirone, a mixed anxiolytic and antidepressant agent, with partial 5-HT_{1A} activity. Each of the study drugs was again administered in a placebo-controlled, double-blind, crossover design to healthy young male volunteers. Polysomnographic measures indicated that sleep architecture was significantly altered by nefazodone, as latency to REM onset was decreased and total duration of REM sleep was significantly increased with this drug. A slight decrease in REM time was noted with the other two study drugs (trazodone, buspirone), although only trazodone was associated with a significant increase in NPT, despite the marked increase in REM time observed with nafazodone. This finding is interpreted as consistent with the weaker alpha-adrenergic effects of nefazodone, compared to trazodone. Buspirone was associated with no discernible effects on either sleep or NPT in this study.

Several conclusions can be drawn from the above studies: (i) Antidepressant drugs are associated with both positive and negative effects on NPT, depending upon the degree of alpha

adrenergic activity and sympathetic inhibition associated with each drug. (ii) Changes in NPT are independent of alterations in sleep architecture or continuity. Whereas most antidepressant drugs reduce REM sleep time and increase REM latency, at least one drug (nefazodone) significantly increased the amount of REM sleep. (iii) None of the studies to date have investigated antidepressant drug effects on NPT in clinical patients, nor have laboratory studies been performed on the effects of serotonin-reuptake inhibitors. Studies in each of these areas are strongly indicated.

Pro-sexual Drug Effects on NPT

In the past decade, several pharmacological agents have been identified as having potential pro-sexual effects. Included in this category are dopamine agonists, alpha-2 adrenergic and serotonin antagonists, cholinergic agonists, smooth muscle relaxants, and miscellaneous substrates (58). Some of these agents have been evaluated for their potential role in the treatment of sexual dysfunction, while others have been used to investigate basic neurophysiological mechanisms in sexual response. Despite the rapid growth of research and clinical activity in this area, few studies have investigated pro-sexual drug effects on NPT.

Yohimbine is an indole alkaloid found in the bark of the yohembe plant. Among its pharmacological properties, yohimbine is a preferential presynaptic alpha-2 antagonist, which also effects serotonin and dopamine transmission. It has the capacity to increase libido and erectile capacity, according to several recent studies in animals and humans (59-61). In one recent study (62), yohimbine (21.6 mg/d) was administered in a double-blind, placebo-controlled design to 40 male patients with chronic erectile dysfunction of mixed etiology. Nocturnal tumescence was assessed by means of the "snap-gauge", a simple home-based device for detecting presence or absence of nocturnal erections. Based upon this measure, significant improvement in the frequency of nocturnal erections was observed in 40% of patients diagnosed with organic impotence. In contrast, none of the patients on placebo showed improved nocturnal erections. Most patients with changes in erectile response also reported increased sexual desire, and 4 of 11 patients reported improved orgasm on yohimbine. Current studies in our laboratory are investigating the effects of yohimbine on NPT, hormonal, and visual stimulation measures in males with psychogenic erectile dysfunction and hypoactive sexual desire.

Other central alpha antagonist drugs have been investigated. Most recently, Bancroft and associates (63) assessed sleep and NPT effects of RS 15385, a new alpha-2 adrenoceptor antagonist. The effects of two dosage levels of the drug were compared in normal volunteers (N=12) and patients with chronic erectile dysfunction (N=24). A significant increase in the duration of tumescence was observed at the lower dosage level in the controls, which contrasted with reduced erections at the higher dosage level in the same group. Although no overall drug effects on NPT were observed in the dysfunctional group, a modest increase in non-REM erections was reported in the younger dysfunctional patients. Specifically, percentage of non-REM time with nocturnal erections increased in younger patients from 11% on placebo to 18% at the higher dosage level of the drug. These findings should be cautiously interpreted, however, since drug administration was associated with significant changes in sleep architecture and

continuity, especially at the higher dosage level in the normal controls, and at both dosage levels in the dysfunctional patients.

At present, pro-sexual drug effects on nocturnal erections have not been clearly established. Relatively few controlled studies have been conducted to date, and additional replication is clearly needed. Moreover, the relationship between pro-sexual drug effects on NPT and other measures of sleep and sexual function remains uncertain. Given the growing interest in this area among both researchers and clinicians, further studies of pro-sexual drugs and NPT will undoubtedly be available in the near future.

Conclusion

This article has reviewed pharmacological effects on NPT in four major areas: (i) androgenic and anti-androgenic drugs; (ii) cardiovascular drugs; (iii) antidepressant drugs; and (iv) pro-sexual drug effects. In each of these areas, NPT assessment has provided an objective and reliable measure of androgen-dependent or spontaneous erectile capacity. Despite widespread use of NPT assessment in research and clinical settings, basic issues need to be considered concerning the neurophysiological mechanisms involved, and relationship to other measures of sexual function. Furthermore, interpretation of drug effects on NPT is potentially confounded by the effects of the underlying disease process (e.g., hypertension, depression), in addition to pharmacologically-induced changes in REM or total sleep time. Finally, studies are lacking in several key areas, such as the effects of SSRI's and the newer pro-sexual drugs on NPT, sleep, and sexual responsivity.

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Discussion - PHARMACOLOGICAL EFFECTS ON NOCTURNAL PENILE TUMESCENCE (NPT)

J. Herbert

Could I ask you about the effect of testosterone on NPT? What do you think testosterone is acting on? Is this an effect on spinal neurons?

R.C. Rosen

That is a good question. My guess is that it is more spinal than central but, partly because the effects seem to cut across so many different drugs and so many different preparations, it is hard for me to believe that there is a central mechanism that all of these drugs are effecting directly.

P. Gutiérrez

I noticed that you did not measure rigidity in your study, you measured only tumescence, and I would like to know your opinion about that. When you refer to total time of tumescence to what measure do you refer?, over 15 or 30 or 50 mm increase over the base line?

R.C. Rosen

In most of our studies we did not measure rigidity directly and that is for a few reasons: I am very dissatisfied with the state of our rigidity measurements. It is one thing, clinically, to have a male who may have reasonable tumescence response, but is lacking rigidity for some reason and you want an independent assessment of rigidity that may have clinical implications. In this case we may be willing to put up with some artifact problems and crudity of measurement. But it is another thing when you are trying to do very fine-grained analysis of pharmacological effects in these placebo controlled designs. There, that kind of measurement error becomes more troubling, and so I am uncomfortable in that sense. The second issue concerns the Rigiscan. This device is relatively new and has only been in use for about three years now, while some of these studies began five or six years ago. Up to the point of introduction of the Rigiscan, there was no measure of rigidity that did not substantially interfere with sleep.

And in all of our studies we have been as concerned and interested in sleep as we have been in NPT. I do not like the old buckling pressure measure which does substantially influence and disrupt sleep in those patients. So, in many of these studies we have not included rigidity measures. More recently, for instance in the yohimbine study which we have underway now, we are including Rigiscan as well as conventional sleep measures.

With regard to total tumescence time, we have calculated that measure in different ways, and I agree with John Bancroft's comment this morning that it is relatively arbitrary whether you pick up increases in circumference above 20 mm or above 30 mm. We always reanalyse our data looking at time, that is, time above 20 mm or time above 30 mm, and I must say that we generally end up with similar results. Depending on the drug and dosage, you may see a more robust effect on one or another of those measures. In our study presentations we like to present all of them, usually in a table. I do not think it makes a big difference which one of those variables you look at. I agree with John, that the duration measure overall is a better measure. You are more likely to see drug effects on duration that on maximum amplitude, whichever duration measure you chose.

J. Bancroft

We also analysed the measures using 'area under the curve' and one comes up with very similar results. The reason why we tend not to present 'area under the curve' data is because they are incomprehensible as figures, but it is reassuring to know that you get basically the same result.

B.D. Sachs

I want to comment on the androgen receptors in the spinal cord and their relation to erection. To my knowledge, these receptors have been identified in the motor neurons of the striatal penile muscles but have not been isolated in the motor neurons to the smooth muscles of the penis. In fact, if I understand right, in the penile tissues androgen receptors are down-regulated after puberty and may be absent in the cavernous tissue, while they are up-regulated after castration. So I think that the role of androgen in the spinal cord and peripheral to the spinal cord in mediating erection

remains largely unknown.

M. Mas

Testosterone and castration can modify tyrosine hydroxylase activity and other functional indices in peripheral neurons,such as those in the sympathetic ganglia, including the hypogastric nerves. We also have some data showing that castration and testosterone treatments influence the levels of amines in the spinal cord.

B.D. Sachs

I would think that those changes in spinal concentrations of monoamines are the consequence of brain effects of testosterone and not actions of testosterone at this spinal level. Some effects have been demonstrated on the major pelvic plexus, the major pelvic ganglia and I think those may be relevant to erection. I would doubt that any effects in the hypogastric plexus are relevant because those are probably largely detumescence fibres coming from the hypogastric nerve rather than tumescence fibres.

M. Baum

But I think that there are some recent data (Mills et al. Biol. Reprod. 51: 234, 1994) suggesting that with erection induced by stimulation of the cavernous nerve you also get enhancement with testosterone in castrated animals in a rather short time. This suggests that effects distal to the site of stimulation are augmenting the response. That stimulus is rather androgen dependent.

B.D. Sachs

But what we have there is systemic testosterone acting on cavernous stimulation. I think they even cut the proximal portion of the cavernous nerve but where the testosterone is acting in those cases to promote erection remains to be determined. All I am saying is that the mechanism for testosterone within the cord or distal to the cord remains at least poorly known, if not unknown

J. Bancroft

Are there testosterone receptors within the spinal cord or DHT receptors? Where

would they be?

B.D. Sachs

Certainly there are both testosterone and DHT receptors in the spinal cord. They are in the motor neurons of the striate penile muscle, that is unquestioned. What I am stressing is that since the striatal penile muscles are not necessary for erection in humans, what those testosterone receptors contribute to normal erection, particularly to the cavernous relaxation, remains unknown.

J. Bancroft

So do the neurons involved in the tactile production of erection, say touching the genitalia, the reflex circle in the spinal cord, have testosterone receptors?

B.D. Sachs

The striatal penile muscles are involved in those erections but they are not necessary for them.

M. Murphy

The testosterone receptors are on the motor neurons supplying striate muscle. The striatal muscle, although is not necessary for a full erection, is necessary for maximal rigidity. So is their a role in enhancing the rigidity of an erection, particularly, through the glandipudendal reflex (bulbocavernosus reflex), and would not that also account for what we have heard about reduced rigidity in NPT studies in androgen-deficient men?

J. Bancroft

I think the answer to that is no. I believe Wagner has data that rather contradicts that.

G. Wagner

Only in part. It is easy to understand, from a teleological point of view, that there should be androgen-sensitive neurons because it has to do with ejaculation and in such

an important point of reproductive pattern therefore there should be such an androgen-sensitive system.

J. Bancroft

Yes, but you say that the striatal muscle contraction is needed in order to produce ejaculation of the semen rather than to produce rigidity in erection.

K.E. Andersson

I think that there is evidence that the autonomic nerves to the penile erectile tissue can be influenced by testosterone, because testosterone can restore the number of nitric oxide synthase containing nerves in castrated animals, and also I think that castration per se leads to the disappearance of these neurons.

C. Carani

I studied NPT in many prepubertal boys and there are no differences between prepubertal boys and adult hypogonadal men. Particularly, I examined six prepubertal boys with thalassaemia and also prepubertal males with late puberty and the number of NPT episodes were the same as in adult hypogonadal men.

B.D. Sachs

As I understand the NPT data, the number of episodes are similar in hypogonadal men and eugonadal men but the duration and intensity are different. There is a low intensity and a low duration, is that what you are saying in the case of prepubertal boys?

C. Carani

Yes, low duration was evident.

D. Vanderschueren

Does anyone know if alpha reductase inhibitors affect NPT?

In rats they reduce reflexive erections (Bradshaw et al. Endocrinol. 109: 1047, 1991).