Review of Impotence Literature

Effects of Neurotrophin for penile pain induced by intracavernous injection of prostaglandin E1

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Impotence (Journal of the Japanese Society for Impotence Research) 1996; **11**(1): 25-28.

Abstract: Intracavernous injection of prostaglandin E1 (PGE1) is widely used in the diagnosis and treatment of impotence. However, penile pain associated with the treatment is an unfavorable side effect. We examined whether or not the PGE1-induced pain could be alleviated with the concomitant intracavernous injection of Neurotrophin, a non-protein, bioactive agent extracted from rabbit skin tissue associated with inflammation that is elicited by the Vaccinia virus. The experiment was conducted by dividing 16 patients into two groups of eight. The first group was allocated 20 µg of PGE1 alone, followed by PGE1 plus 0.5 ml of Neurotrophin after 2 wks, while the second group continued on PGE1 alone after 2 wks. Eleven patients felt some degree of pain when injected with PGE1 alone and five felt no pain at all. In six of the patients who felt pain and subsequently received Neurotrophin, the pain level was lowered. Moreover, the pain was eliminated in three of them. The pain scores were also significantly lower when Neurotrophin was used. Our results indicated that Neurotrophin can alleviate pain caused by intracavernous injection of PGE1.

Editorial comment: First of all, it should be remembered that PGE1 is used as a dry powder in Japan. Secondly, it should be remembered that self injection therapy is not allowed in Japan. Neurotrophin is provided by the Nihon-Zouki pharmaceutical company. The authors used a visual-analogue scale to evaluate the pain which was significantly reduced by the use of Neurotrophin. The pain associated with PGE1 is one of the main reasons for the drop-out during PGE1 therapy. This method might be a promising method to reduce the high drop-out rate.

Y Kimoto MD

Evaluation of vibratory threshold of the penis using SMV-5 vibrator

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Impotence (Journal of the Japanese Society for Impotence Research) 1996; **11**(3): 197-201.

Abstract: As a means to neurologically examine the penis, the vibration threshold of the penis was measured using an SMV-5 vibrometer. The SMV-5 vibrometer was applied to 14 functionally impotent men and 6 neurogenically impotent men. Furthermore, the vibration threshold was measured in patients before and after undergoing intrapelvic surgery without nerve sparing (three patients underwent total cystectomy and three patients underwent radical prostatectomy). The vibration threshold (VT) was measured in the right humeroulnar head, and in the glans, dorsal side, and frenulum of the penis.

In the functional group, VT was 12.7 ± 13.7 ($\times 10^{-2}$ G, mean $\pm$ s.d.) in the humeroulnar head (ulna); 46.0 ± 24.4 in the glans of the penis (glans); 28.5 ± 13.0 in the dorsal side of the penis (dorsal side); and 44.7 ± 23.3 in the frenulum of the penis (frenulum). In the neurogenic group, VT was 9.2 ± 1.1 in the ulna; 328.5 ± 181.1 in the glans; 271.6 ± 148.4 in the dorsal side; and 280.8 ± 169.9 in the frenulum.

Even though no significant difference in VT was confirmed in the ulna between the two groups, VT was significantly higher in the neurogenic group at all locations in the penis.

The results of VT measurements, taken before and after intrapelvic surgery without nerve sparing, showed that there was no significant difference in VT before and after surgery.

It was thus concluded that the SMV-5 vibrometer is an easy-to-use and non-invasive instrument for conducting penile peripheral nerve tests on outpatients suffering from sexual dysfunction.

Editorial comment: The modalities of neurological evaluation for the penis are the measurement of bulbocavernous reflex latency time and nerve conduction velocity measurement of the dorsal nerve of the penis. However, these modalities are too expensive and complicated to be used widely. The SMV-5 vibrometer was introduced to evaluate the vibration-sensation of diabetic patients by Medience Co. Ltd, Tokyo.

This machine is inexpensive (485 000 yen or 4000 US Dollar), non-invasive and ambulatory. However since this study consists of few cases (26), to evaluate the usefulness of this machine a large study series is required.

Y Kimoto MD

Relative importance of sexuality and quality of life in patients with prostatic symptoms

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European Urology 1997; **31**: 272–280.

Editorial comment: This cross-sectional study, conducted in France and England, determined which aspects of quality of life were most affected by prostatic symptoms and which patients considered most important. Sexual function and behavior included by the patients not only between the most affected by the disease, but also between the most important aspects. Interestingly, intracultural differences were noticed, as French patients considered all sexual aspects of life more important than English patients. The study used a self-administered quality of life questionnaire, where specific questions of erectile function (for example ability to attain and maintain an erection) were not included. As erectile dysfunction is associated with numerous medical conditions, such as cardiovascular disease, renal failure and diabetes mellitus, a universally accepted Symptom Score for Erectile Function is essential, in order to determine the impact of different medical conditions on sexual function. Two Symptoms Score questionnaires for erectile dysfunction are available today. One of them has been translated into several languages and utilized in clinical trials.

A few years ago, the AUA Prostate Symptom Score was adapted as an international system to evaluate benign prostate hyperplasia associated symptomatology. The International Prostate Symptom Score questionnaire (I-PSS) has been already translated in several languages, allowing data collected from different countries to be legitimately aggregated.¹ Development or adaptation of an International Symptom Score for Erectile Function should be a priority for the International Society for Impotence Research. Such project will give the opportunity for multi-national studies, assessing not only the impact of medical conditions of sexual function, but also a more 'objective' evaluation of patients outcome in clinical trials.

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developing a methodology for multinational clinical trials. *Eur Urol* 1997; **31**: 129–140.

Dimitrios Hatzichristou MD

Does the positive intracavernous papaverine test always indicate a normal penile vascular system?

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European Urology 1997; **31**: 323–328.

Editorial comment: The diagnostic validity of a positive intracavernosal injection test has been questioned by several studies. Pescatori *et al*,¹ in a pharmacocavernosometry-based study and a highly selected group of patients with steady-state equilibrium intracavernosal pressure more than 80 mmHg, found arterial insufficiency in 19% of the cases. Cormio *et al*² using subjective criteria to define a positive erectile response (palpation), noticed peak systolic blood flow velocities < 35 cm/s in 18% of the patients tested. In the present comprehensive study, the authors observed peak systolic blood flow velocities < 35 cm/s in 46.59% of the 176 patients tested. The significantly higher percentage of arterial disease may be easily explained by the criteria used to define a positive erectile response; axial rigidity was assessed objectively by an electronic bucklometer and absence of penile deformation to an axial force ≥ 500 g was accepted as presence of rigidity adequate for sexual intercourse. Such results clearly show that a positive intracavernosal injection test reflects the hemodynamics of a functional, but not necessarily normal, erectile response. A functional erection, defined as an erection adequate to permit vaginal penetration, may coexist with some degree of erectile dysfunction, in terms of submaximal rigidity or submaximal sustaining capability. Axial rigidity therefore, represents the most critical parameter in the evaluation of the erectile response. Several factors have been proposed as determinants of penile axial rigidity, including intracavernosal pressure, penile geometry and the mechanical properties of the corpora cavernosa and the tunica albuginea. Future research demands should include hemodynamic and mechanical characterization of a functional/rigid erection.

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occlusive but not necessarily normal arterial function: a hemodynamic study. *J. Urol* 1994; **151**: 1209–1216.

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Dimitrios Hatzichristou MD

Structural alterations in the tunica albuginea of the penis: impact of Peyronie's disease, ageing and impotence

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British Journal of Urology 1997; **79**: 47–53.

Editorial comment: This histomorphometric study documented structural alterations in the tunica albuginea in patients with erectile dysfunction and Peyronie's disease. Concentration of elastic fibers was lower in impotent than in potent patients ($P=0.0365$) and in patients with Peyronie's disease. Elastic fibers concentration decreased also with age.

Tunica albuginea represents the fibrous frame of the corpora, playing a key role in the corporeal veno-occlusive mechanism. Structural alterations, such as reduction in the elastic fibers and disorganization of collagen bundles, may lead to impaired extensibility of the tunica, insufficient occlusion of the venous structures and erectile dysfunction. Such pathophysiologic mechanism has been already described in impotent patients, as well as in patients with Peyronie's disease and plaque-associated venoocclusive dysfunction. The finding that age is also associated with reduced concentration of elastic fibers should be a stimulus for future research. The authors noticed longer and more regular elastic fibers, compared with the short and fragmented elastic fibers in older patients. Should age per se be considered as a risk factor for structural alterations of the tunica albuginea or the corpora cavernosa? Epidemiological data have shown that erectile dysfunction is, at least in part, a para-aging phenomenon. Both aging and vascular disease have been reported to induce irreversible ultrastructural alterations to the corpora cavernosa and impotence. Studies on aged population, with and without vascular disease or vascular risk factors will determine precisely with impact of aging on the erectile mechanism.

Dimitrios Hatzichristou MD

Cavernosal nerve stimulation in the rat reverses castration-induced decrease in penile NOS activity

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Am J Physiol 1995; **271**: E354–E361.

Editorial comment: With the recent understanding that the nitric oxide synthase (NOS) pathway mediates erectile function, further research objectives involving this pathway have pertained to elucidating physiologic mechanisms influencing NOS function in the penis. The remarkable finding associated with this investigation is that authors demonstrate that electrical stimulation of the cavernosal nerve, which elicits penile erections, transiently restores depleted penile NOS activity levels in castrated rats to that of intact, nonstimulated animals. While they have confirmed that the NOS pathway is influenced in the penis by androgen availability, the authors moreover establish the rapid and reversible modulation of this pathway *in vivo* in this organ system. Based on these findings, the authors postulate that the cavernosal nerve stimulated increases in penile NOS activity corresponds to various sexual stimuli producing physiologic erections and thus offers a mechanism for this function. Of note, the authors curiously showed a significant reduction of penile NOS activity in normally functioning intact rats following stimulation. This notable discrepancy requires further investigation if one is to consider that momentary changes in penile NOS activity underlie normal physiologic erectile responses. In addition, this work must be reconciled with the knowledge that cavernosal nerve stimulation does not restore electrophysiologically monitored penile erections in castrated animals to fully normal levels.

AL Burnett, MD

Responses of medullary reticular formation neurons to input from the male genitalia

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J Neurophysiol 1996; **76**: 2474–2482

Editorial comment: The central organisation of neural input responsible for reflexive sexual behaviors such as erection and ejaculation has remained obscure despite the supposition that spinal and supraspinal pathways are involved. Previous neuroanatomical tracing and lesioning studies have

suggested that the medullary reticular formation (MRF) influences reproductive behaviors. The authors provide further support for this hypothesis with their detailed electrophysiological mapping studies of the MRF following mechanosensory stimulation of the male rat genitalia. They obtained MRF recordings in male rats following stimulation of neurons contained in the dorsal nerve of the penis as well as other cutaneous and visceral sites of the urogenital tract, indicating that this brain stem region significantly contributes to male reproductive tract function and sensation as a major autonomic processing center. This conclusion is in agreement with the new established role of the MRF in converging neural input associated with the control of various autonomic functions. In regards to sexual function, the MRF may then be considered to relay ascending information to rostral regions of the brain important for somatovisceral arousal and motor activity and descending information to the spinal cord that modulates segmental reflexes.

AL Burnett, MD

Afferents originating from the dorsal penile nerve excite oxytocin cells in the hypothalamic paraventricular nucleus of the rat

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Brain Res 1996; **733**: 292-296.

Editorial comment: While oxytocin secretion in the brain has been associated with several aspects of male sexual behavior, it has not been clearly understood how the oxytocin release systems are activated physiologically. This work demonstrates that oxytocin secretion from the hypothalamic paraventricular nucleus of the male rat involves afferent nerve projections from the penis. The authors have shown that both electrical stimulation of the dorsal nerve of the penis and mechanical stimulation of the glans penis, which are presumed to represent physiological tactile stimuli occurring during copulation, elicited neurohypophyseal recordings from oxytocin cells. A non-specific excitation of both oxytocin and vasopressin cells occurred in response to saphenous nerve stimulation. Since recordings were unaffected in castrated rats, specific oxytocin cell excitation did not appear to be androgen-dependent. These findings indicate that the somatosensory afferent pathway of the dorsal nerve of the penis importantly subserves a mechanism for oxytocin release in male mammals.

AL Burnett, MD

Comparative Results of goal oriented therapy for erectile dysfunction.

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J Urol 1997; **157**: 2135-2138.

Editorial comment: Recent advances in our understanding of the pathophysiology of erectile dysfunction have resulted in improved diagnostic and therapeutic alternatives for these patients. There is no consensus on the optimal approach to the diagnostic and treatment of impotence. Proponents of the pathology oriented approach support performing a thorough investigation to establish the proper diagnosis and then tailoring therapy to the specific cause of the erectile dysfunction.¹ The goal-directed approach involves minimal diagnostic evaluation and stratifies all treatment options to the patient, with the advantages of simplicity, a relatively high success rate and lower cost to the couple.² The major disadvantage being that reversible causes that may be treated specifically may be missed and that an accurate 'diagnosis' is not necessarily made. This study compared the short-term and long-term results of the first and second treatments selected using a goal-directed approach in 460 patients. Oral pharmacotherapy was the initial treatment choice for the majority of patients, despite an initial success rate of only 40%. In those whose initial therapy failed, the next treatment of choice was intracavernous therapy. Despite an initial success rate of over 70%, the dropout rate was 40% after 12 months and 73% within 43 months. The vacuum device had an initial success rate of 68%, with a > 30% dropout rate by 24 months, while insertion of penile prosthesis had a reported success rate of 83%. In total, 70% of the patients in the study were lost to follow-up or refused further therapy within 43 months. Despite high initial success rates, there is long-term couple dissatisfaction with current conservative modes of therapy and hesitancy towards more invasive, yet successful long-term therapeutic alternatives, such as inflatable penile prostheses. While the 'ideal' therapy remains to be found, the overall long-term treatment success rate may be increased through better understanding of the underlying etiology and pathophysiology of the erectile dysfunction and specific treatments aimed at correcting them. Close follow-up and counselling in cases of initial treatment failure regarding therapeutic alternatives may help to reduce the high percentage of patients who tend to refuse further therapy or become 'lost to follow-up'. Helping the couple choose the appropriate therapy, even if that treatment is a surgical option, is critical, since the long-term success rates with these devices today are as high as 95% and offer excellent couple satisfaction.³ In addition, better education of the couple

regarding all available options, including noncoital techniques, and involvement of the couple in all phases of evaluation and treatment, can only improve patient and partner satisfaction in the management of this couple's disease.

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LS Hakim, MD

The impact of aging on penile hemodynamics in normal responders to pharmacological injection: a Doppler sonographic study.

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J Urol 1997; **157**: 2129–2131

Editorial comment: Penile duplex Doppler ultrasonography in combination with pharmacological stimulation is a reliable method for assessing arterial blood flow and veno-occlusive function of the penis. It is well accepted that sexual activity changes and the incidence of erectile dysfunction increases with advancing age. In this study, the authors evaluated the effect of aging on the hemodynamics of erection. Using penile duplex Doppler studies, 64 patients, ages 17–74 were evaluated. No patient had a history of vascular risk factors, such as atherosclerosis or diabetes. Following injection of 10 µg of prostaglandin E₁, duplex ultrasound was performed and flow parameters measured. All patients had a well sustained erection for longer than one hour and cavernosal artery peak systolic velocities of more than 30 cm/s, with end-diastolic velocities of less than 3 cm/s. Patients were classified into four groups according to age (< 30, 30–39, 40–49, > 50) and flow velocities compared. These results demonstrated that cavernous arterial flow during pharmacological erection decreases with age and that the arterial response time increased with age. However, the resistive index (peak systolic velocity-end diastolic velocity/peak systolic velocity) did not vary significantly with age, suggesting that a good quality erection can be achieved and maintained over a wide range of cavernous arterial inflows, and that veno-occlusive function is of primary importance in

the aging erectile response. These findings are an important contribution to our understanding of the effect of aging on penile hemodynamics and erection.

LS Hakim, MD

Corporal veno-occlusive dysfunction: predominantly intracavernous muscular pathology.

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J Urol 1997; **157**: 1678–1680.

Editorial comment: Erection is a vascular phenomenon under neurologic control modulated by a specific hormonal environment, occurring in a particular psychological context. Relaxation of the intracavernous smooth muscle occurs during tumescence, with associated arterial dilation and lacunar space engorgement. Rigidity is accomplished by passive compression of the sub-tunical venous plexus by the lacunar spaces against the tunica albuginea. This induces resistance to flow in the emissary veins and completes the veno-occlusive mechanism. Dysfunction of this mechanism accounts for the vast majority of vasculogenic impotence. This study investigated the relationship between the flow to maintain (FTM) an erection during cavernosometry and the alteration of intracavernous structures in patients with corporal veno-occlusive dysfunction (CVID) and normal arterial flow. Computer histomorphometric analysis of smooth muscle, elastic fibers and endothelial cells was compared to the FTM following pharmacologically induced erection in 18 men with CVID. Results indicated that FTM's ranged from 15–100 ml/min. Corresponding smooth muscle cell components ranged from 19–28%, indicating a significant correlation, while there was no correlation with the elastic fiber content and/or endothelial cells over this range of flows. The investigators concluded that corporal veno-occlusive dysfunction is mainly due to smooth muscular alterations. However, the authors also suggest that other factors (alteration of the fibroelastic framework and lacunar space endothelial cells) may play some role in corporal veno-occlusive dysfunction, but to a lesser degree than abnormal smooth muscle. Further studies to determine what specific factors influence the integrity of the corporal smooth muscle remain to be performed. Factors such as vascular injury, low cavernous oxygen tensions and the association of arterial disease may all play a role in the pathophysiology of erectile dysfunction.

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