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THE MEDICAL MANAGEMENT OF ERECTILE IMPOTENCE

PISA. THE CAMPANILE AND APSE OF THE CATHEDRAL.

This is to acknowledge that Jean D. Wilson has no financial interests or other relationships with commercial concerns related directly or indirectly to this presentation.

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Interests: General clinical endocrinology; androgen physiology and male reproduction; disorders of sexual differentiation with particular emphasis on disorders of androgen biosynthesis and androgen action.

INTRODUCTION

During the past decade the management of erectile impotence has shifted from a surgical to a medical problem. During most of this time reluctant and somewhat embarrassed patients confronted equally reluctant and embarrassed physicians on the subject. Suddenly, with the release of viagra the situation has changed dramatically. Now patients are demanding and physicians are prescribing the agent with abandon. The net consequence is that the purpose of my talk is not to encourage physicians to come to grips with the problem but rather to inject a note of caution.

By way of introduction, it is worth noting that in biological terms sexuality consists of those physiological, anatomical, and behavioral functions that support or elicit the union of male and female gametes and thus ensure continuation of the species, but in terms of human physiology the pleasurable aspects of the sex act are of equal importance as the reproductive aspects in promoting a sense of well being (1). At the clinical level impotence is rarely treated to improve reproductive capacity but instead is a medical problem because of considerations such as well being, mental health, marital discord, or the underlying pathology that causes the disorder. The focus of this discussion is upon one narrow aspect of sexual function, the management of erectile impotence in men.

Because of the complexity of the neurogenic and endocrine control systems involved, sexual dysfunction is exceedingly common. Occasional impotence occurs in men at all ages, and by age 65 a fourth or more of healthy men have some degree of erectile dysfunction (2). The frequency of sexual dysfunction in women is unknown but is probably equally large. There is probably no arena of medicine in which psychological factors interdigitate more closely with physiology than in sexual function, but the growing belief is that organic causes play a major role in most instances of persistent erectile dysfunction (3,4). This belief and the availability of effective medical therapies have major impacts on the workup and management of the disorder.

For a variety of reasons investigation of the physiology of sexual function lagged behind other areas of applied physiology. The advances in the field have largely been spearheaded by the studies of Tom Lu(5,6) and have been made possible by development of methods for the measurement of blood flow to the genitalia and by the application of the techniques of modern molecular pharmacology. The sexual response of the male has been studied more extensively than that of the female, but the available evidence indicates that the processes are fundamentally similar in the two sexes.

THE MALE SEXUAL RESPONSE

For didactic purposes the male sexual act can be divided into phases: sexual arousal, penile erection, emission and ejaculation, detumescence, and the refractory period:

Sexual Arousal

Two types of stimuli can elicit an erection. *Central stimuli* include auditory, visual, olfactory, gustatory, tactile, and psychogenic stimuli such as fantasy. Some of these effects are clearly conditioned, but central stimuli control nocturnal penile erections (see below), the earliest and most persistent type of erections. *Reflex stimuli* such as stroking of the genitalia can stimulate erections via spinal reflexes. Reflex erection is believed to be mediated by parasympathetic efferents whereas the neural effectors of central erections are primarily sympathetic.

The Penile Vasculature and the Mechanism of Erection

The erectile tissue of the penis is composed of two functional compartments--the *corpora cavernosa* and the *corpus spongiosum*. The corpora cavernosa consists of two cylinders with a common septum that is perforated by vessels that allow free passage of blood from one to the other and thus permits the two bodies to function in part as a single unit(5-7)(Fig. 1). The corpus spongiosum contains the urethra and enlarges distally to form the bulk of the glands penis. The erectile tissue compartments are surrounded by a dense fascial sheath, the tunica albuginea, which anteriorly anchors the penis to the symphysis pubis.

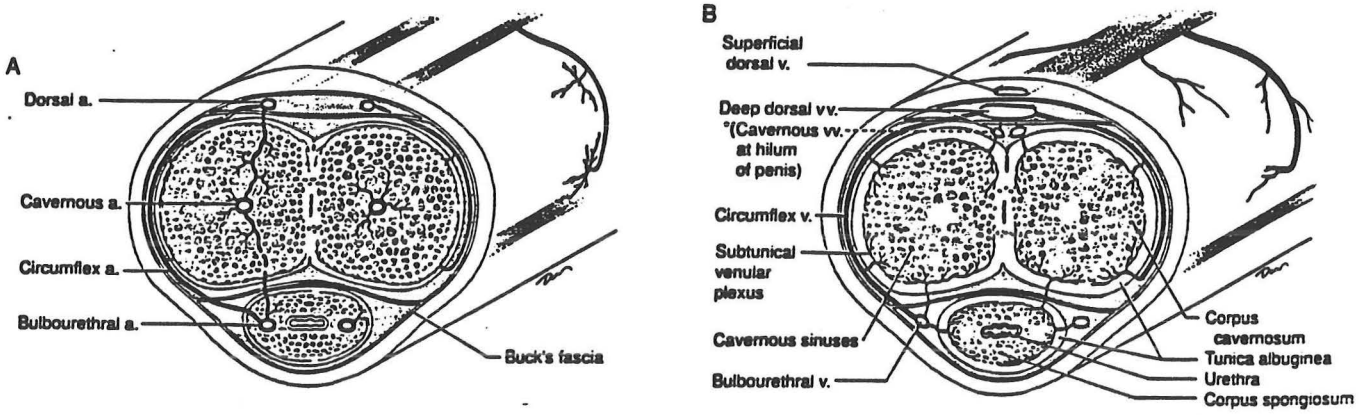


Figure 1 Arterial supply (A) and venous drainage (B) of the penis. Transverse view.

The penile artery has three branches, the dorsal artery, the bulbourethral artery, and the cavernosal artery, all of which are connected by collateral branches. The venous drainage originates in small venules from the peripheral sinusoidal spaces immediately beneath the tunica albuginea. These venules anastomose to form the

subtunical venular plexus before exiting as the emissary veins into the deep dorsal and circumflex veins.

The smooth muscles of the cavernous sinus and of the arteriolar and arterial walls are the key to erection (Fig. 2). In the flaccid state intrinsic smooth muscle tone and sympathetic discharge provide high resistance to incoming blood flow. The flaccid penis is a moderate state of smooth muscle contraction, further contracting with exposure to cold and enlarging during a hot shower. For erection to occur inflow of blood must temporarily exceed outflow.

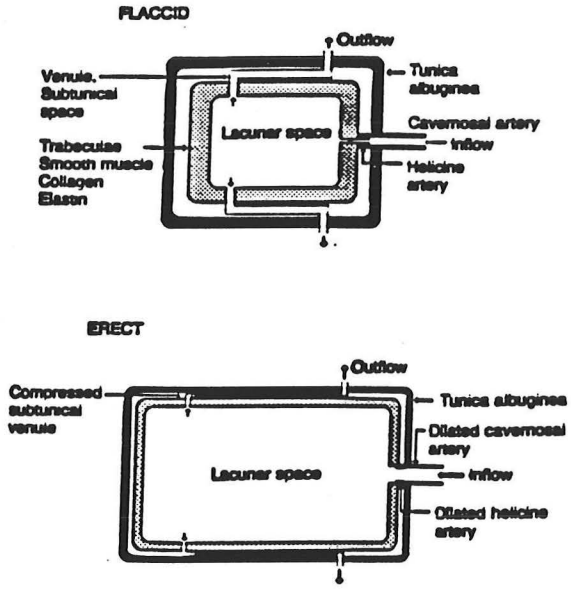


Figure 2 Schematic diagram of penile erection.

The critical event in this process is relaxation of penile smooth muscles under the control of neurotransmitters (5). This relaxation triggers: 1.increased compliance of the sinusoids and arteriolar walls, lowering the resistance to blood flow; 2. increased blood flow during both systole and diastole further dilates the arteries and arterioles; 3. the corpora cavernosa elongate and expand; 4. the subtunical venous plexuses between the tunica albuginea and the peripheral sinusoids and the emissary veins are compressed, reducing venous outflow (this compression is essential for erection which cannot be due solely to increased blood flow); 5. intracavernosal pressure increases and begins to approach the systolic blood pressure, transforming the penis from the flaccid to the erect state. Maximal erection then occurs when the bulbocavernosus reflex is triggered, causing profound contraction of penile smooth muscle and an increase in intracavernosal pressure to levels well above the systemic blood pressure. At this point ingress of blood ceases (Fig. 3). Erection thus involves sinusoidal relaxation, arterial dilation, venous compression, and smooth muscle contraction.

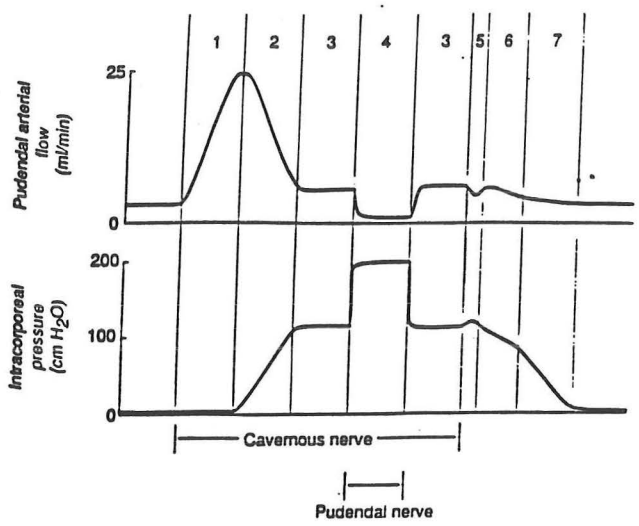


Figure 3 Blood flow and intracavernous pressure changes during the seven phases of penile erection and detumescence: 0, flaccid; 1. latent; 2. tumescence; 3. Full erection; 5. initial detumescence; 6. Slow detumescence; 7. fast detumescence.

During the erection process the volume of blood in the penis increases from about 8 ml in the flacid state to about 62 ml, and blood flow increases from an average of 2 ml/100 g/m to a maximal of about 50 ml/100 g/m and then decreases to about 12 ml/100 g/m prior to the triggering of the bulbocavernosus reflex. These changes are unaccompanied by changes in cardiac output or in blood flow to the pubic region. Maximal blood flows decrease with age, and no pharmacological therapy can be effective unless blood flow is adequate.

Nocturnal erections can first be demonstrated during the last trimester in male fetuses and occur rarely during infancy and childhood. From puberty throughout adult life, however, they occur approximately every 80-120 minutes(8) (Fig. 4).

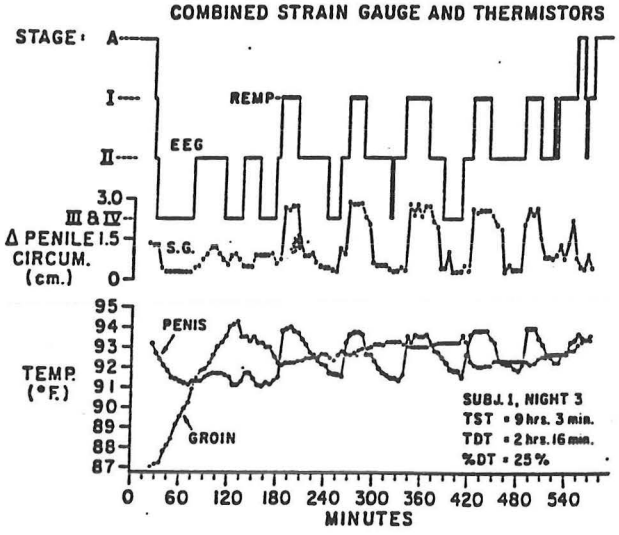


Figure 4 The pattern of nocturnal erections in a normal man.

Emission, Ejaculation, and Orgasm

Contraction of the ampulla of the ejaculatory ducts, the seminal vesicles, and the prostate causes *emission* of the semen into the posterior urethra. The process is a cord reflex and is under some cerebral control. *Ejaculation*--the expulsion of the semen from the urethra--results from the squeezing action of the bulbocavernosus

muscles at 0.8 second intervals accompanied by simultaneous contraction of the muscles of the pelvic floor and of the distal sphincter of the bladder. Ejaculation is a reflex reaction to the collection of semen in the bulbous urethra; if the bladder sphincter is incompetent, semen may regurgitate into the bladder. *Orgasm*, the pleasurable sensation associated with perception of the contraction of the pelvic musculature during ejaculation, is associated with hyperventilation and is said to be prevented if a paper sack is placed over the head to prevent a fall in pCO2. Whatever the mechanism, orgasm can on occasion be generated cerebrally without input from the genitalia, as in rare patients with temporal lobe epilepsy(9).

Detumescence

Detumescence consists of three phases: 1. a transient pressure increase as the arterioles begin to close and eventually bring arterial flow back to levels characteristic of the flaccid state; 2. a slow decline in intracavernous pressure as the venous channels slowly reopen; 3 a fast decline in pressure and size as venous outflow is fully restored (5).

Refractory Period

Detumescence is followed by a *refractory period* of variable duration during which it is not possible to achieve an erection. This process is poorly understood, but its duration increases with age and is influenced by a variety of variables including general state of health, the degree of sexual arousal, and the vigor with which it is tried.

Neurophysiology of Erection and Ejaculation

Three types of nerve fibers innervate the penis--somatic, sympathetic, and parasympathetic. Somatic innervation is derived from S2-S4 and involves almost all components of the penis, particularly the sensory innervation of the skin and the motor fibers to the bulbocavernosus and ischiocavernosus muscles. Sympathetic innervation from T11 to S2 and parasympathetic fibers from S2 to S4 intermingle and give rise to the prostatic plexus and distally to the cavernous plexus of nerves.

The predominant type of nerve ending in the penis itself is adrenergic, but the problem in analyzing the nature of the neurotransmitter control is that there are a variety of of nerve endings and hence of potential mediators including acetyl choline (both muscarinic and nicotinic fibers), vasoactive intestinal peptide, prostaglandin, calcitonin gene related peptide, neuropeptide Y, endothelin, and nitrous oxide (5). According to one formulation of erection, the control of the state of contraction of the penile smooth muscle is determined by the level of intracellular calcium. Efflux of tissue calcium (relaxation of

penile smooth muscles) can be stimulated either by an adenylate cyclase system (sensitive to CGRP, VIP, Forskolin or to alpha 1 adrenergic mediators such as prostaglandins) or by a guanylate cyc lase system sensitive to NO donors (10). Nitrous oxide, which both a neurotransmitter released in some nerve terminals of the penis and a direct vasodilator of the smooth muscle, is probably the most important physiologically, whereas the adenylate cyclase system is a major site for pharmacological intervention (Fig. 5).

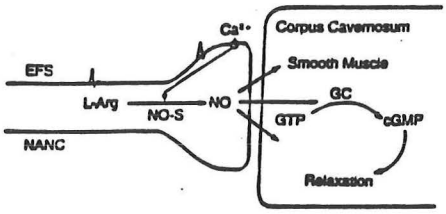


Figure 5 No generation is believed to play a central role by controlling the state of relaxation of the arteriolar smooth muscle.

There are at least three forms of nitric oxide synthase—the constitutive nitric oxide synthase of nerves (nNOS), the endothelial NOS (eNOS), and the inducible NOS (iNOS)(11). nNOS virtually disappears from the rat penile nerves after cavernous nerve neurotomy but can be made to regenerate with electrostimuilation(12,13). iNOS is present in smooth muscle itself and is induced by NO donors that increase NO levels in tissues and by androgens(13,14). Aging in male rats is associated with a decrease in the number of nNOS-containing nerve fibers(15) and by a decrease in overall penile NOS activity(16), and penile nitric oxide synthase is decreased in two types of diabetic rats (BB/WOR and BBZ/WOR) that are said to develop erectile dysfunction(17). The erectile dysfunction observed in old and very old rats can be ameliorated by the administration of iNOS inducers; even more interestingly, the injection of rat iNOS cDNA directly into the penis of very old rats is said to mitigate aging-associated erectile dysfunction(18). It would be ironic somehow if the first successful form of gene therapy were for erectile dysfunction.

The neuropharmacology of detumescence is less well understood and may involve neuropeptide Y, endothelin, and norepinephrine, all potent vasoconstrictors that can be released by the sympathetic nervous system during ejaculation.

Hormonal Control

Androgens are responsible for development of the male genitalia and for maturation of male erectile physiology and of male sexual behavior at the time of puberty(19). The role of androgens in the maintenance of male sexual behavior, once established, is less clear. Castration of male animals is followed by retention of mating capacity for a variable period of time and then by eventual failure. In the human male prepubertal castration uniformly prevents the maturation of normal male behavior, and orchidectomy

sexual activity with only occasional castrated men continuing to have intercourse over a period of years(20,21). Androgen replacement to hypogonadal men causes a rapid and reliable restoration of male sexual activity, and the principle site of this effect the human male is believed to be at the level of the CNS(22-26).

Sex Drive

No aspect of male function none is less well understood than sex drive or potentia. The permissive role of androgen in controlling male sexual desire is well established, but among healthy, sexually active young men with similar androgen levels and available sex partners there is striking variability in sex drive and in the frequency with which intercourse is initiated (illustrated schematically in Fig. 6). The cause of this variability in sex drive is obscure but may in part relate to differences in luteinizing hormone releasing hormone levels, to variable response to pheromone signals, to purely psychogenic effects, or to unidentified hormonal and/or regulatory factors. This variability is of importance when considering the causes of impotence; for example, the use of some drugs such as beta adrenergic blockers is associated with an increased frequency of impotence but does not cause such an effect in all men. Such agents may simply shift an individual's position leftward on the Gaussian distribution curve so that if one starts out on the right hand portion of the curve the likelihood of developing impotence from any cause is less than if one starts out on the left hand portion.

Sexual activity in men normally declines with age, as evidenced by reduced interest and involvement in sexual matters, difficulty achieving erections, and reduced satisfaction from sex. With age erotic stimuli must be of greater intensity to produce a response, and spontaneous erections decrease in frequency or disappear. The duration of the refractory period increases, penile filling slows, and venous occlusion and/or the bulbocavernosus reflex is less complete, resulting in less firm maximal erections, and in some men penile sensation declines substantially(27,28).

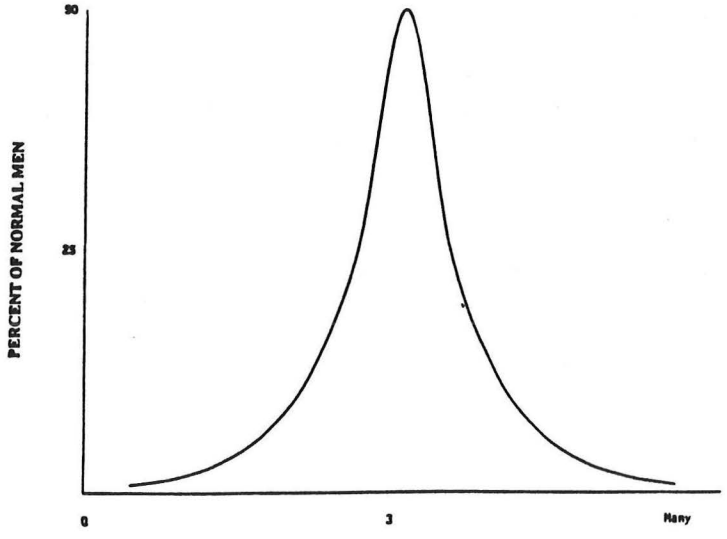


Figure 6 Hypothetical diagram of the sexual acts initiated each week by healthy young adult men who have an available partner.

IMPOTENCE

Definition

Impotence is defined by various authors as failure to achieve erection, ejaculation or both(29) or as a personally unsatisfying level of sexual performance (4). The Massachusetts Male Aging Study discerned three levels of impotence--mild, moderate, and complete, based on several criteria, including sexual activity, frequency of full erections, and frequency of erections on awakening in the morning (21). With wider recognition of the biological nature of the disorder, men now present with less severe erectile dysfunction, such as weak erections and occasional erectile failure. Furthermore, men with sexual dysfunction present with a variety of complaints, singly or in combination: loss of libido, ejaculatory failure, premature ejaculation, inability to achieve orgasm, or, most frequently, inability to initiate or maintain an erection (*erectile dysfunction*).

Loss of libido A decrease in libido or sexual desire can be due to androgen deficiency (from either pituitary or testicular disease), psychological disturbance, or to drugs. The possibility of androgen deficiency can be assessed by measurement of plasma testosterone and gonadotropins. Hypogonadism can also cause the absence of emission secondary to decreased formation of ejaculate by the prostate and seminal vesicles.

Premature ejaculation This disorder seldom has an organic cause and is usually due to anxiety in the sexual situation, unreasonable expectations about sexual performance, or emotional disorder. Behavioral therapy is usually successful in its management;.

Ejaculatory insufficiency Absence of the ejaculate can be produced by retrograde ejaculation, sympathetic nerve denervation, androgen deficiency, or drugs. Retrograde ejaculation is common after surgery on the bladder neck and in men with diabetic autonomic nervous system neuropathy. Demonstration of sperm in a postcoital urine specimen establishes the diagnosis. Following sympathectomy or after extensive retroperitoneal surgery, the innervation of the prostate and seminal vesicles may be impaired, resulting in diminution of the smooth-muscle contractions at the time of ejaculation. Androgen deficiency causes diminution in the volume of the ejaculate by decreasing the secretions of the prostate and seminal vesicle; benign prostatic hyperplasia can have the same effect. Drugs that inhibit ejaculation include guanethidine, phenoxybenzamine, phentolamine, and sertraline.

Absence of orgasm If libido, erection, and ejaculation are normal, the absence of orgasm is almost due to a psychiatric disorder.

Failure of detumescence Priapism is a persistent, painful

erection, often unrelated to sexual activity and can be secondary to clotting of blood within the sinusoidal spaces of the penis or to abnormalities of the adrenergic mechanisms that control detumescence.. The disorder can usually be distinguished from a normal erection by the absence of tumescence of the glans penis. Priapism can be idiopathic or can be associated with sickle cell anemia, chronic granulocytic leukemia, spinal cord injury, or injection of vasodilator agents (see below) into the penis. Failure to treat priapism promptly can result in fibrosis and subsequent loss of erectile function. Early, the disorder can sometimes be treated by aspiration, irrigation of the corpora cavernosa, and injection of dilute vasoconstrictors.

Erectile dysfunction In the Massachusetts Male Aging Study of men 40 to 70 years of age, 48% were potent whereas 17, 25, and 10% had minimal, moderate, or complete erectile dysfunction, respectively (30). Erectile dysfunction can be due to a variety of mechanisms (Table 1), including vascular disease, neurologic and psychiatric disorders, endocrinopathies, and local disease within the penis. Often more than one factor interacts to produce erectile insufficiency. The epidemiological features of erectile dysfunction in Massachusetts study are given in Table 1. Not surprisingly, age, cardiovascular disease, diabetes mellitus, cigarette smoking, depression, and use of medications correlated with erectile dysfunction whereas alcohol consumption and schizophrenia do not correlate. Some of the mechanisms involved deserve special comment (Table 2):

TABLE
EPIDEMIOLOGICAL CORRELATES OF ERECTILE DYSFUNCTION (ED)

Correlation with ED	No Correlation with ED	Inverse Correlation with ED
Age	Ulcer disease	Dominant personality
Heart disease, hypertension, diabetes mellitus	Arthritis	High plasma HDL cholesterol level
Associated medications	Allergies	High plasma DHEAS level
Cigarette smoking	Alcohol intake	
Depression	Schizophrenia	
Indices of Anger	Plasma cortisol or dihydrotestosterone level	

TABLE Mechanisms Contributing to Erectile Dysfunction

Type of Condition	Disorder
Vascular	
Aortoiliac arterial obstruction	Aorto-occlusive disease
Hypogastric-penile arterial obstruction	Atherosclerosis
Arterial dysplasia	Primary impotence in young men
Veno-occlusive incompetence	Age, diabetes, Peyronie disease
Neurogenic	
Central nervous system and spinal neuronal loss	Cerebrovascular accident (stroke), multiple sclerosis, epilepsy
Peripheral autonomic neuronal loss	Surgery, Shy-Drager syndrome, diabetes mellitus
Disordered signal transmission	Drugs
Psychogenic inhibition of the erotic response	Depression (psychogenic)
Endocrine	
Deficient androgen availability	
Testicular failure	Castration, radiation, chemotherapy (ketoconazole)
Hypothalamic-pituitary disease	Age, pituitary adenoma
Prolactin excess	Prolactinoma, uremia, drugs
Estrogen excess	Alcoholism, cirrhosis, drugs
Inhibition of androgen action	Spironolactone, cimetidine, ranitidine, flutamide
Secondary hyperparathyroidism	Uremia
Hypothyroidism and hyperthyroidism	
Local	
Peyronie disease	
Intersinusoidal fibrosis	Diabetes mellitus, aging
Penile trauma	
Pudendal nerve trauma	Bicycle rider's palsy
Penile carcinoma	

Vascular disease Men with vasculogenic impotence may present with total erectile impotence, decreased penile rigidity, or loss of erection during intercourse. Vascular insufficiency may be due to aortic occlusion (Leriche syndrome) or to distal atherosclerotic disease involving the hypogastric, pudendal, and cavernosa

arteries. Approximately half of 367 men with occlusive vascular disease were impotent (4), but significant disease can occur in the pudendal and cavernosal arteries in the absence of other manifestations of vascular disease. The impotence that commonly occurs after pelvic radiation is probably due to vascular causes. Obviously, impotence is most likely to occur with the most severe arterial lesions, but relief of major vessel obstruction usually does not alleviate the disorder, suggesting that distal arteries and/or intrinsic penile tissues are usually involved(36). Myocardial infarction is also associated with a high incidence of pre-existing erectile dysfunction(37). Congenital defects in the penile vasculature are a rare cause of primary impotence.

Diabetes mellitus In several series the prevalence of erectile dysfunction is about 50% in unselected men with diabetes mellitus and increases with age(38) and is almost invariably associated with defective nocturnal penile tumescence(39). The onset of impotence is inversely related to the age at the diagnosis of diabetes (Figure 9)(40). Hypogonadism does not play a role in this condition in diabetics(38,40). Neurogenic factors appear to be the predominant factor in men with insulin-dependent diabetes mellitus(41), and vascular factors predominate in noninsulin-dependent diabetes mellitus(42), as evidenced by low penile blood pressure(40) and evidence of vascular lesions by Doppler ultrasound (43).

Hypertension Although hypertension is generally thought to be associated with an increased incidence of impotence, the age specific incidence of erectile dysfunction in hypertensive men probably does not differ from that in the general population of men receiving medical care(44). However, the onset of erectile dysfunction is often associated with initiation of antihypertensive therapy of diverse types(45). None of the published studies relate the degree of blood pressure control to sexual dysfunction, but it is believed that the reduction of systemic blood pressure may accentuate the reduction in flow rate caused by obstructive lesions
so that effective control of the blood pressure might reduce maximal penile-filling capacity(46).

Neurological disease Multiple sclerosis has been thought to be associated with a high degree of sexual dysfunction, but 80% of patients in a community based survey reported no dysfunction(49). Temporal lobe epilepsy can cause erectile dysfunction, probably the consequence of impairment of arousal and worsened by antiepileptic medications(50). Cerebrovascular accidents are believed to cause erectile dysfunction as the result of impairment of the function of the erectile centers in the brain (4).

Pelvic neoplasia Among men with pelvic tumors, erectile dysfunction occurs in about 20% prior to surgery and 80% after surgery(51). Both pelvic irradiation and pelvic surgery can

impair erectile function by interrupting the autonomic fibers of the nervi erigentes that control the erectile process and/or by decreasing the penile blood supply(52,53). Walsh and colleagues(54) developed an improved technique for radical prostatectomy that results in potency rates above 75% in younger patients(55). Other treatments for neoplastic disease may also cause sexual dysfunction. For example, 24% of men who survived bone marrow transplantation had erectile dysfunction (56).

Hypogonadism As stated above androgen deficiency causes decrease in libido, erectile function, and ejaculate volume(22-26), and androgen replacement in such men is almost uniformly effective in restoring normal sexual function. The issue of whether lesser degrees of androgen deficiency could contribute to erectile dysfunction is more complicated. Plasma levels of total and bioavailable testosterone decrease with age(31), but they are no different in impotent and potent men(32). Tissue levels of androgen are also decreased with age, but tissue levels have not been compared in potent and impotent men(33). Furthermore, when testosterone levels are lowered by pharmacological means in normal men to values near the lower range of normal, there is no effect on any parameter of endocrine function(34,35). This phenomenon is almost certainly due to the fact that the androgen receptor is saturated at plasma testosterone levels below the lower limit of the normal adult male range. Empirically, the pharmacological administration of androgens to impotent men without clearcut hypogonadism is ineffective.

Elevation of serum prolactin by any cause can cause secondary decrease in luteinizing hormone and testosterone levels, but prolactin can cause impotence in the absence of secondary hypogonadism.

Uremia Approximately half of uremic men are impotent(47). Contributing elements may include elevated prolactin levels, elevated estradiol levels, and low levels of plasma testosterone, and secondary hyperparathyroidism, zinc depletion, and autonomic neuropathy may play a role. Bromocriptine, clomiphene, and androgens are of no value in treating erectile dysfunction in men on dialysis, but erythropoietin has been reported to improve sexual function(48). Erythropoietin may have multiple effects including reduction of serum prolactin levels, increasing blood volume, and increasing oxygen delivery to tissues.

Other chronic diseases Increased prevalence of erectile dysfunction has also been reported in men with chronic back pain, obstructive pulmonary disease, pulmonary fibrosis, hyperthyroidism, celiac disease, arthritis, scleroderma, and hemochromatosis (4).

Drug-related causes (Table 3) Drug therapy can cause loss of libido, erectile impotence, and ejaculatory insufficiency, but

most studies of the phenomenon are uncontrolled. The principal culprits are neurotransmitter agonists or antagonists used for the treatment of hypertension, angina, and afterload reduction and for the treatment of psychosis, anxiety, and depression. Such agents may work by a variety of mechanisms, including inhibition of the parasympathetic erectile mechanism, stimulation of alpha-adrenergic constriction, interference with central erotic responsiveness, or blockade of the dopaminergic inhibition of prolactin secretion. Agents that reduce androgen availability and/or effectiveness or act directly as estrogens include digitalis, cimetidine, ranitidine, spironolactone, ketoconazole, progestogens, LHRH agonists or antagonists, and estrogens themselves. Narcotics, cocaine, and marihuana have predominately depressive effects, although marihuana and cocaine have a reputation for lowering the threshold for erotic response.

TABLE

Drugs Associated With Impotence

Central Nervous System	α-Methyldopa, barbiturates, benzodiazepines, butyrophenones, carbamazepine, clonidine, ethanol, fluoxetine, heroin, methadone, morphine, phenothiazines, phenytoin, primidone, reserpine
Anticholinergic	Atropine, butyrophenones, disopyramide, ganglionic blocking agents, phenothiazines, tricyclic antidepressants
Antiadrenergic	Benzhexol, benztropine, bethanidine, debrisoquin, propranolol, prazosin, phenoxybenzamine, phentolamine, thioridazine
Antiandrogen	Cimetidine, cyproterone acetate, estrogens, finasteride, ketoconazole, progestins, spironolactone
Others	Amphetamines, cocaine, monamine oxidase inhibitors, thiazides

Alcohol consumption per se does not appear to affect erectile function(57), but chronic alcoholism with liver disease is associated with a high incidence of impotence(58). Sexual function returned to normal in only 25% of alcoholics after long-term rehabilitation(59). The incidence of heavy cigarette smoking is enhanced in men with erectile dysfunction(60,61), and in dogs electrically stimulated erections are inhibited by smoking or by administration of intravenous nicotine(61). The inhibitory effect of nicotine is due to inhibition of blood flow to the corpora cavernosa, suggesting that it either inhibits vasodilation of the arterioles in the penis or stimulates alpha-adrenergic vasoconstrictor activity(61). Cigarette smoking may also contribute to erectile dysfunction by accelerating development of peripheral vascular disease.

Psychogenic factors The prevalence of psychogenic factors in erectile dysfunction depends on the design of the study, but most studies suggest that organic factors can be identified in more than 90% of men above age 50(62,63). Some authors prefer a risk factor approach to the diagnosis of erectile dysfunction, because complete vascular, neurologic, and psychologic assessments are difficult to make and may be difficult to interpret if not performed in the actual erotic setting(63).

In the context of major psychiatric disease, depression but not ambulatory schizophrenia is associated with sexual dysfunction, erectile impotence, and abnormal nocturnal penile tumescence (64,65). In one study, the use of benzodiazapine drugs rather than depression per se appeared to be the cause(66). When looked at in terms of patients presenting with erectile dysfunction, significant psychopathology is unusual.

Peyronie's disease Peyronie's disease is a scarring disorder of the tunica albuginea characterized by depletion of elastic fibers(67). Characteristic plaques may be found at the periphery of the penis or in the midline where the corpora meet. Stiffening of the tunica albuginea makes it difficult to achieve venooclusion, and the plaques may also interfere with arterial inflow. In the early stages the disorder seems to be an inflammatory process whereas the latter phases are characterized by collagen deposition. Careful examination of the stretched penis may be required to detect plaques, and the disorder may first be manifested as a bent penis at the time of vasodilator-induced erection.

Diagnostic Evaluation

History and physical examination

The sexual history should record the extent of the dysfunction, its duration, its progression , and its characteristics. A self-administered form can be utilized for documenting such a record (63). Appropriate questions concern sexual activities, partner availability, the presence of spontaneous morning erections, the quality, duration , and usability of the best erections, and the ejaculatory capacity. The central issue in the evaluation of impotence is to separate those instances due to psychological factors from those due to organic causes, and the separation can often be made on the basis of history. With the exception of severe depression or occasional instances of early sensory neuropathy, men with psychogenic impotence usually have normal nocturnal and early morning erections. Consequently, if the impotent man gives a history of rigid erections under any circumstances (often upon awakening in the morning), the dysfunction is probably due to a psychogenic cause, and the workup should be limited. However, it is important to remember that impotence may be the presenting complaint in severe medical illness. The history should be probed for diabetes mellitus, manifestations of peripheral neuropathy or bladder dysfunction, symptoms referable to the vascular system such as intermittent claudication, symptoms of penile disease such as a history of priapism or penile curvature (Peyronie's disease), and any prior surgery that may have produced neurologic or vascular damage. A thorough drug history should be obtained; smoking is not only a risk for atherosclerosis but directly inhibits sinusoidal relaxation.

The sexual partner should be involved early in the discussion of sexual dysfunction and its management. Successful therapy depends to a great degree on the availability, interest, health, and psychological state of the partner. Some women, particularly older women, may not desire or be prepared for resumption of an active sexual life.

The physical examination should emphasize evidence of virilization, including testicular size and density, diminution in body hair, and presence of facial wrinkling. Penile size shape, the presence of Peyronie plaque or fibrous tissue, and the size, consistency, symmetry, and nodularity of the prostate should be assessed. Evidence of feminization such as gynecomastia should be sought. All pulses should be palpated, and the presence of bruits should be sought. The neurological examination should measure anal sphincter tone, perineal sensation, and the bulbocavernosus reflex. This reflex is elicited by squeezing the glans penis and noting the degree of anal sphincter constriction. Evaluation for peripheral neuropathy should include assessment of distal muscle function, the deep tendon reflexes, and vibratory, position, tactile, and pain sensation.

Laboratory evaluation

Laboratory evaluation should include measurement of plasma testosterone, luteinizing hormone, and prolactin. Some authors recommend the measurement of bioavailable testosterone(32) and ultrasensitive TSH (4), although the rationale for the latter is unclear.

Special diagnostic tests

With the advent of effective treatment options, invasive diagnostic evaluation is rarely indicated, particularly in older men who experience erectile dysfunction after many years of sexual function. A functional diagnostic test that is sometimes useful involves the intracorporeal injection of vasodilators such as alprostadil. This office procedure is employed to determine erectile capability directly, to determine the extent of penile distortion due to Peyronie's disease, and to demonstrate its therapeutic potential to the patient and to estimate the therapeutic dose for subsequent use as therapy(68). Initial alprostadil injections occasionally cause painful injections, priapism, hematoma, infection, local pain, or systemic hypotension(69). The quality of the erection attained provides an index of vascular insufficiency and hence provides information as to appropriate therapy. The quality of erection is evaluated on a five point scale: 5, rigid; 4, firm; 3, maximal diameter but soft and not usable; 2, partially erect; 1, some tumescence. A strong, persistent erection excludes significant vascular insufficiency as a cause of erectile dysfunction whereas a weak erection suggests

its presence. However, because this test may be negative in the office in men who subsequently use the drug successfully in more natural circumstances, there is a tendency to simply prescribe a trial of sildenafil before performing other diagnostic tests.

Nocturnal penile tumescence (NPT) is no longer commonly assessed because men with normal vasculature can have abnormal NPT because of disturbed sleep and normal NPT can be consistent with vasculogenic erectile dysfunction associated with pelvic steal syndrome(70). More than 90% of men with impotence have abnormal NPT, but both the frequency and quality of NPT episodes decrease with age in potent men (71). An alternative means of monitoring erectile capacity, visual sexual stimulation (VSS) utilizes video taped erotic material in a laboratory setting to facilitate penile erection but has not been widely applied(72).

When the presence of neuropathy is uncertain, electromyographic sacral signal tracing of the bulbocavernosus reflex or direct electrical recording of the corpora cavernosa by needle or surface electrodes may be helpful.

Pudendal arteriography provides the most accurate assessment of penile arterial patency but is expensive, invasive, and sometimes unreliable when the penis is flaccid. The penile/brachial artery blood pressure index (PBPI) is determined by dividing the penile systolic blood pressure as determined by Doppler methodology by the simultaneously determined brachial systolic pressure; the test can be utilized to diagnose the pelvic steal syndrome(73), but unfortunately it only evaluates flow through the dorsal penile artery, which is not directly involved in erection. Cavernous arteries can have significant disease not reflected in flow through the dorsal artery. Pulsed Doppler analysis and high-resolution ultrasonography after intracorporeal alprostadil can be employed to assess blood flow in the cavernosum. Alternatively, intracavernosal pressure can be measured directly to assess cavernosa blood flow. These various invasive procedures are not indicated in the usual patient with erectile dysfunction and should only be performed in centers expert in penile surgery and for erectile impotence in young men or after trauma. These various procedures are described in detail in reference(72).

Treatment

In approaching the therapy of erectile impotence it is worthwhile keeping in mind that psychological factors are nearly always present to some degree and that age per se is not a contraindication to treatment. Furthermore, in any consideration of therapy it is important to involve the partner in the decision. An attempt should be made to identify and correct any secondary factors that can contribute to impotence, such as marital tensions, cigarette smoking, use of street drugs, and excessive alcohol intake. When appropriate, medically indicated drugs, such

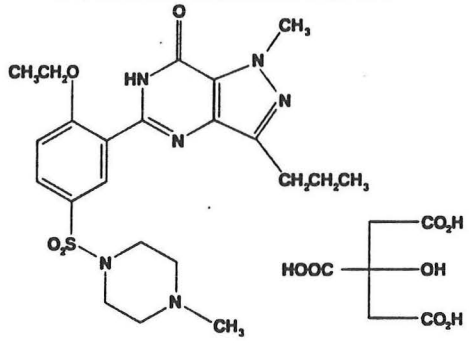
as beta adrenergic blocking agents, should be substituted with drugs not associated with impotence. Even when historical evidence suggests a relation between a specific agent and impotence, however, discontinuation of the drug may not cause a dramatic improvement in potency.

Hormone therapy Androgen replacement in hypogonadal men and correction of hyperprolactinemia in appropriate instances are usually very effective, but empiric therapy with androgens is only of placebo benefit in the absence of hypogonadism.

Drug therapy can involve oral, parenteral,or intraurethral agents:

Sildenafil (Viagra) This agent is an orally active inhibitor of type V (and type VI) phosphodiesterase, an enzyme expressed primarily in the penis and that breaks down cGMP(74-76) (Fig 7). Consequently, sildenafil acts to prolong and enhance erection only in men who synthesize a sufficient amount of cGMP. Although the agent has been released with an enormous amount of publicity and has had a major impact in terms of sales, the amount of published information about the drug, its effects and side-effects, particularly in men with coexisting diseases, is small(77).

Figure 7 **STRUCTURAL FORMULA FOR VIAGRA**



The oral bioavailability is about 40%, and in the fasting state plasma concentrations reach a peak in about one hour. A fatty meal delays the peak by about one hour and decreases the peak concentration(76). The drug is metabolized in the liver to an active metabolite, and the parent drug and the active metabolite have a half-life of about 4 hours. Clearance is slower in older men and in men with liver or renal disease. Erection usually occurs between 40 minutes and 4 hours (usually within two hours) of administration, and the mean duration of an erection is on the order of 7 to 11 minutes(76). In fixed-dose trials improvement in erections was reported by 63% of men taking 50 mg, 82% taking 100 mg, and 24% taking placebo(75). The agent does not affect libido and requires both an intact autonomic nervous system and erotic stimulation to be effective. In the stratified data presented in the package insert, it is apparent that the agent is much less effective in men with complete erectile impotence than in those with lesser degrees of dysfunction.

Figure 8

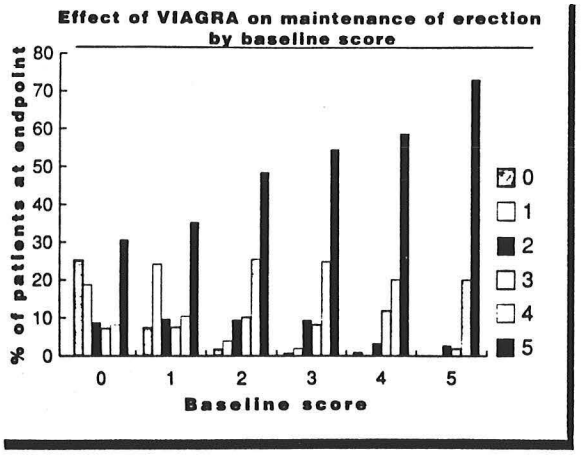


Figure 1a. Effect of VIAGRA on maintenance of erection by baseline score.

Figure 9

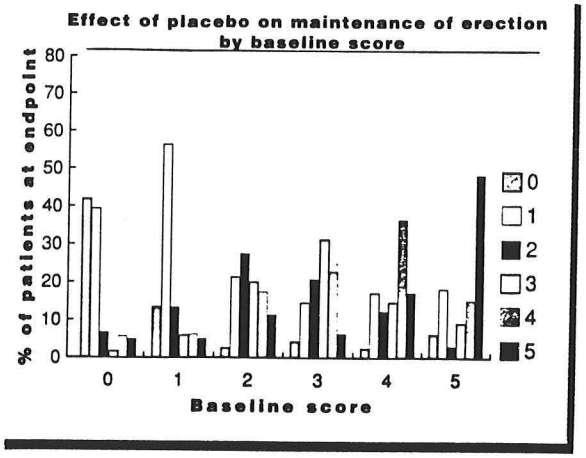


Figure 1b. Effect of placebo on maintenance of erection by baseline score.

Consequently, it is to be expected that its primary use will be in men with psychogenic impotence, in those with mild organic disorders, and as a recreational drug for men who wish to improve sexual performance that may or may not be impaired but is unsatisfactory to them(78).

Although sildenafil has not been studied extensively in men with coexisting medical disorders a variety of adverse effects and drug interactions are possible. In recommended doses, it lowers blood pressure slightly in normal subjects and substantially in patients taking nitrates in any form for angina pectoris. Consequently, concurrent use of any nitrate, short- or long-acting, could cause a potentially fatal drop in blood pressure. Priapism does not occur, and headache, flushing, and dyspepsia are the most common reported side effects(77). Abnormalities of color vision are due to effects on the type VI phosphodiesterase expressed in retina. Cimetidine, erythromycin, and ketoconazole inhibit the metabolism of dildenafil and may increase plasma concentrations; such effects are predicted for itraconazole and mibefradil.

Rare instances of ventricular tachycardia(79) and pulmonary hemorrhage(80) have been reported, but the real issue is whether the agent is associated with increased risk for acute myocardial infarction and/or sudden death. Sexual intercourse itself increases cardiac workload(81), and the risk of myocardial infarction increases by a factor of 2.5 in the two hours after sexual activity(82). However, the incidence of serious complications after sildenafil therapy appears to be small(83), with a similar incidence of myocardial infarction in men receiving sildenafil and those on placebo(84). The real question is the extent to which men with ischemic heart disease but not receiving nitrates in any form should be subjected to additional testing before the prescription of sildenafil.

In a letter to the NEJM, 15 of the spouses (women between ages 55 and 75) of 100 men given sildenafil developed acute cystitis. Presumably, this is a form of honeymoon cystitis and may be minimized by being certain that the spouses have adequate lubrication of the urogenital tract and are not estrogen

Alprostadil and other Direct Vasodilators Erectile impotence can be treated effectively by self-administration of intracorporeal vasodilators such as prostaglandin E1 (alprostadil), papaverine, or alprostadil-phentolamine-papaverine combination(86-90)(Fig. 10).

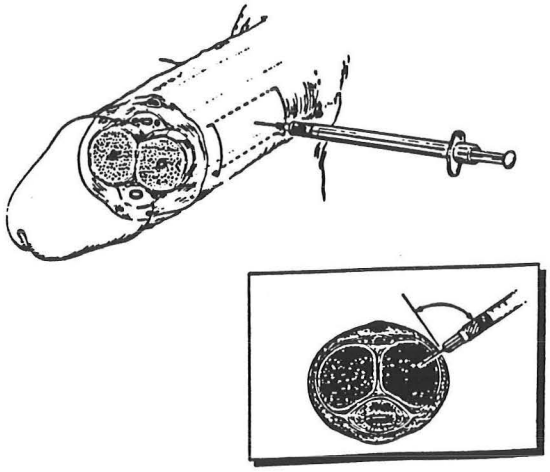


Figure 10 The objective of the dosage determination phase of the pharmacologic erection program is to define the lowest dose required for achieving an appropriate erectile response. Patients are injected initially with low doses, which are increased incrementally. An insulin syringe with a 27- to 30-gauge needle is usually employed, which minimizes pain and bleeding. Patients are also taught to compress the site of injection, typically the proximal lateral aspect of the penile shaft, for 3 minutes following therapy. Patients are told not to inject more frequently than once per day.

Alprostadil is used more frequently than papaverine-based therapies because it is effective, rapidly metabolized, causes less complications and does not affect liver function(10). It can, however, cause penile burning and discomfort in some men, impairing its acceptance, and occasionally causes priapism. The technique is shown schematically in Figure 10; because of the anastomotic connections between the two components of the corpora cavernosum and between the corpora cavernosa and the corpus spongiosum the injection of vasodilator into one side causes a complete, symmetrical erection. The complications reported in a metaanalysis of several thousand patients treated with intracorporeal injections are summarized in Table 4(10).

Table 4

METAANALYSIS OF SELF-INJECTION THERAPY (PORST)

AGENT	RESPONDERS (DROPOUT)	PRIAPISM >6h	NODULES/ FIBROSIS	PAIN
Papaverine (1,527)	61% (47%)	7.1%	5.7%	4%
Papaverine/Phentolamine (2,263)	68% (45%)	7.8%	12.4%	11.6%
Alprostadil (2,745)	72% (37%)	0.4%	0.8%	7.2%

However, it must be kept in mind that only 73% of men responded to this regimen initially and that the dropout rate was 37% of those who initially responded(10) so that at best the therapy is effective long term in only about half of patients. For those responders who persist with the therapy the regimen is usually considered very successful both by the patients themselves and by their sexual partners. A variety of new vasoactive drugs and drug combinations are now under investigation for intracorporeal administration(10). This type of therapy is ineffective in men with vascular impotence and is contraindicated in men with sickle cell anemia. It is usual to administer for therapeutic trial a 5 ug dose in the physician's office and to utilize this dose at home, provided a stage 4 or 5 erection is achieved and does not last longer than an hour; smaller or larger doses (80% of men respond to 20 ug or less) can then be tried when appropriate. Porst recommends that self administration be done no more frequently than two times a week (8); others suggest once every two weeks.

The central problem is that one has to be prepared to deal with priapism as an emergency if it does occur. If an erection lasts more than an hour the administration of 30 mg pseudoephedrine by mouth usually causes detumescence within 15 to 20 minutes. Priapism (erection longer than 6 hours) is a medical emergency and requires aspiration and irrigation.

A formulation of alprostadil (the medicated urethral system for erection [Muse] device) is now available for intraurethral administration(91) (Fig. 11).

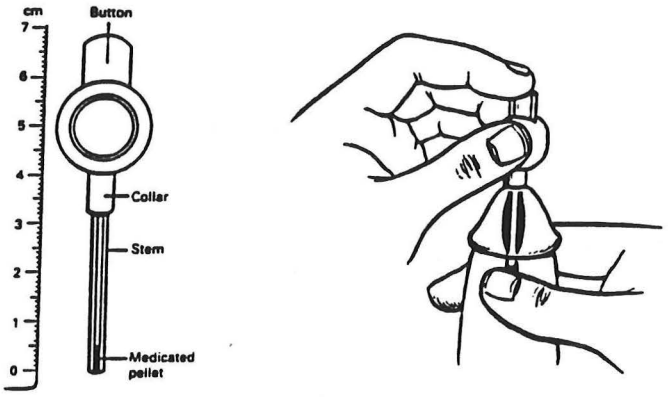


Figure 11 The Applicator for the Transurethral Administration of Alprostadil.To use the applicator, each man was asked to urinate, insert the 3.2-cm stem gently into the urethra, and then depress the button, releasing the medicated pellet.

With this modality the appropriate dosage has to be determined for each individual. Approximately half of men reach a stage 4 or 5 (out of 5) erection with the maximal dose, and more than half of the men who used home treatment reported successful intercourse; erections last for an average of 23 minutes. Priapism did not occur in 461 patients(91), but the incidence of penile pain was about the same as with the injected drug (occurring with about 10%

of administrations). Because the average dosage is larger with intraurethral administration (25-1000 ug) the systemic side effects (dizziness) are worse. In summary, this formulation avoids injection, causes less priapism, and appears to be easier to use. However, some authors have reported results that are not as favorable as initial results(92), and the formulation is not as effective as the injected form when used in maximal doses. Consequently, it remains to be seen whether the long term compliance will be better than with the injections.

External Vacuum Tumescence Devices A variety of external vacumn devices are marketed, most of which feature a large plastic cylinder enclosing the penis, a vacuum device, and an obstructing band that fits around the base of the penis (Figure 12)(93).

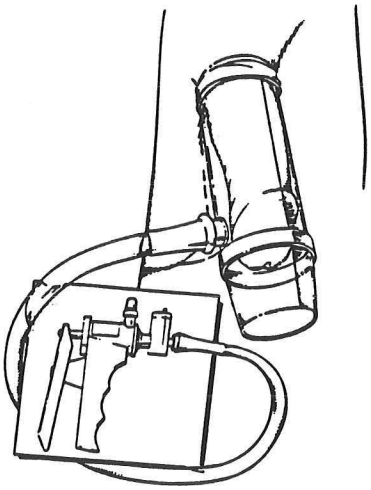


Figure 12 Although many different devices are now manufactured, the majority have three common components: a vacuum chamber, a vacuum pump that creates negative pressure within the chamber, and a constrictor or tension band that is applied to the base of the penis after erection is achieved. The patient while standing places his penis within a preformed suitably sized chamber, which is attached to a pump mechanism able to achieve negative pressure is created within the chamber, thereby drawing blood into the penis to produce an erection-like state. At the point of achieving adequate tumescence and rigidity, a constrictor band at the base of the chamber is transferred to the base of the penis, thereby "trapping" blood within the penis.

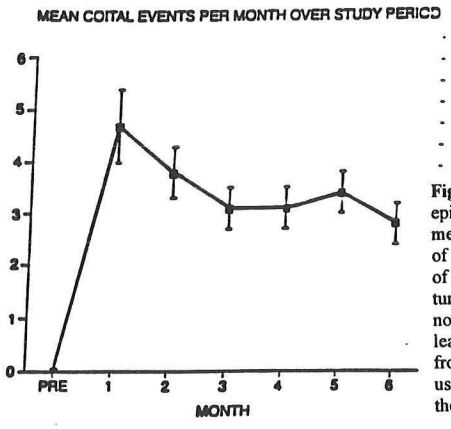


Figure 13 Monthly frequency of episodes of coitus in 19 impotent menscreened for availability of a willing partner after initiation of the use of the Erecaid vacuum tumescence device. Before treatment, no coitus had been possible for at least 3 mo. (Reprinted with permission from the American Geriatrics Society. use of a vacuum tumescence device in the management of impotence.

Application of the vacuum causes blood to pool in the penis, and when a sufficient erection is attained an obstructing band is applied to the base of the penis to retain the accumulated blood in the corpora. After the patient becomes adept in its use, the devices are usually satisfactory to both partners. A normal coital pattern is frequently restored, with 2 to 10 episodes per month. Erections last an average of 16 minutes, and the tissues are not affected adversely (although the penis appears somewhat cyanotic as long as the band is in place). The glans penis is normally distended. This technique is effective in men who do not respond to or do not adhere to pharmacotherapy (Figure 13), and the average erection lasts about 10 minutes.

The principal problems with vacuum devices are discomfort from the bands, a cold sensation in the erect penis, and either failure to ejaculate or retrograde ejaculation if the band is too tight. Interestingly, both patient and partner satisfaction with the use of this device is as high or higher than with alprostadil therapy, again with a significant dropout with time (94).

Surgical Management The surgical implantation of penile prostheses confers rigidity to the penis, either continuously with the

semirigid varieties or on demand with the inflatable prosthesess. This therapy is now considered second line treatment, and the frequency of surgical implantation has declined markedly. The principal disadvantages are that the implants are expensive and invasive, have high complication rates, produce poor quality erections, and are subject to mechanical failure. None of the devices cause swelling of the glans penis, which as a consequence is subject to trauma during intercourse. The use of implants is reviewed in reference 72.

Other surgical approaches also have a limited role to play in the management of impotence. Surgical correction of aortic obstruction on rare occasions results in improvement in erectile dysfunction, but aortic surgery paradoxically can also cause impotence if the autonomic nerve supply to the penis is damaged. Surgical revascularization procedures are effective only in occasional young men with traumatic arterial disease. The various types of vascular procedures that have been tried in this disorder are also reviewed in reference 72.

Sex therapy New insight into the pathogenesis of erectile dysfunction and the availability of effective medical therapies have led to less frequent use of sex therapy in the management of the disorder (28,95,96). Namely, in men with secondary impotence it is now common to anticipate an organic cause and treat accordingly. However, depression may interfere with sexual performance, and loss of a mate can lead to social isolation and depression. Men may lose confidence in their sexual abilities, creating anxieties that contribute to failure to establish new relationships. The physician who sees patients for impotence may have an opportunity to identify and treat depression and to refer such patients for further support (if it is available).

Sex therapy can also be useful in men with organic erectioe dysfunction. It should focus on the couple and address unrealistic expectations and any marital discord. The characteristic of a more satisfactory sex life should be defined, and behavioral changes that may improve sex life should be instituted, such as stopping smoking, arranging appropriate times and environments for intercourse, and encouraging intimacy, mutual pleasuring, experimentation, and improved communication. The effectiveness of sex therapy has never been fully evaluated, and the level of improvement is not always sufficient for coitus(97).

SUMMARY

The availability of effective means for erectile impotence has had a major impact on the work up and management of this disorder. Although better therapies, particularly safer and more effective oral agents, are needed, it is now possible to treat the majority of impotent men successfully.

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