
Male Sexual Function

A Guide to Clinical
Management

Edited by

John J. Mulcahy, MD, PhD



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MALE SEXUAL FUNCTION

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MALE SEXUAL FUNCTION

*A GUIDE TO CLINICAL
MANAGEMENT*

Edited by

JOHN J. MULCAHY, MD, PhD

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PREFACE

Thirty years ago there was no effective treatment of erectile dysfunction. In the late 1940s the Kinsey Report tried to define a consensus regarding male sexual function. These conclusions were based more on opinion than on any hard scientific data. In the 1960s, Masters and Johnson published a treatise on sexual response that shocked many people in that era with the techniques used to collect data.

Penile prostheses were introduced in the early 1970s. These were the first effective treatment for erectile dysfunction. A decade later intracorporal injections arrived on the scene, and in the late 1980s, vacuum erection devices were popularized. Widespread publicity in 1997 with the introduction of Muse, the intraurethral pellet for enhancing erections, resulted in astounding initial sales. This was soon followed by the introduction of Viagra, an oral medication that is effective about two-thirds of the time. This effective, simple treatment has swelled the ranks of patients seeking treatment and has overwhelmed the system, so to speak. Primary care physicians had not received much training in erectile dysfunction and are not very knowledgeable about approaching patients and discussing this topic comfortably. Symposiums, dinner talks, teleconferences, and other educational programs have been convened to educate practitioners in this area. Viagra is now a household word and its common use has softened many taboos that once prevented open discussion of sexual matters. Advances in our understanding of the anatomy and physiology of erections are progressing rapidly. The financial success of even marginally effective treatments for erectile dysfunction has encouraged vendors to develop new and improved products.

Female sexual function is now being addressed as well, as many of the products effective in men may have a similar end-organ response in women.

The need for an up-to-date, comprehensive overview of the field of male dysfunction is evident. New practitioners without extensive prior experience are entering the field and those already treating erectile dysfunction are faced with changing concepts and trends, especially in the areas of evaluation and medical therapy. *Male Sexual Function* is an aggregate of the efforts of international experts in presenting a comprehensive overview of the areas of erectile dysfunction, female sexual dysfunction, and ejaculatory disorders. It has certain information that will be helpful to all who are involved in these areas and should be especially helpful for those in primary care specialties who wish to become acquainted with the field of sexual function because increasing numbers of their patients are coming forward seeking advice and treatment.

Anatomy, physiology, and epidemiology related to erectile function and dysfunction are first addressed. A comprehensive chapter for primary care practitioners follows; this outlines ways to approach sexual function evaluation and treatment and, one hopes, will allow these practitioners to feel more comfortable when discussing this topic with their patients. Female sexual dysfunction, ejaculatory disorders, Peyronie's disease, and priapism are covered, in addition to comprehensive chapters on diagnosis and treatment. Practitioners at all levels of interest or expertise in sexual function will find practical, highly useful information in these pages.

John J. Mulcahy, MD, PhD

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1

Normal Anatomy and Physiology

Jamil Rehman, MD and Arnold Melman, MD

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INTRODUCTION

Normal sexual function in males involves libido, initiating and maintaining erection, orgasm, ejaculation, and the refractory period. The penis is a specialized vascular organ that exists in a continuum from the flaccid to the erect position. As a rigid structure, it allows vaginal penetration to ensure sufficient delivery of sperm to propagate the species. Erectile dysfunction is a condition whereby penile erection sufficient for vaginal penetration is not achievable by normal physiological means. In the last two decades, knowledge of the physiological mechanisms that regulate the erectile function of the penis has greatly expanded as a result of basic laboratory and clinical research. Anatomical studies gave the

key to our current understanding of the mechanism for restriction of blood outflow from the corporeal bodies; that is, the corporeal veno-occlusive mechanism. The availability of corporeal tissue obtained during penile prosthesis implantation and the use of animal models has allowed obtaining extensive detailed information on the physiologic mechanisms that control corporal smooth muscle tone (1–4).

Penile erection is a neurovascular event initiated by psychosomatic environment. The hemodynamic alterations associated with normal erection require precise modulation of neural pathways and the integrity of the penile vasculature (1,5–8). It involves increased arterial flow, relaxation of sinusoidal spaces, and increased venous resistance. Penile smooth-muscle relaxation is necessary for dilatation of penile arteries and penile erection proper. Conversely, penile flaccidity is due to the release of norepinephrine from sympathetic nerve terminals and contraction of corporal smooth muscle. The tone of the corporal smooth muscle, therefore, is a primary determinant in the control of penile erection. Many independent factors certainly converge on the modulation of corporal smooth muscle tone; however, majority effect via gap junction, potassium channels, and calcium channel. The discovery by Furchgott that showed that the endothelial lining of vascular tissue produces nitric oxide (NO), has shed light on the contribution of the endothelium of the lacunar spaces to the regulation of corporal smooth muscle tone, as well as the role of nitric NO in the penile erection. In a normal erection, the neural stimulation is transmitted to the penile tissues through the pelvic autonomic nerve fibers, the Nervi erigentes. These nerves release three important neurotransmitters:

1. The sympathetic fibers release norepinephrine;
2. The parasympathetic fibers release acetylcholine;
3. The nonadrenergic-noncholinergic (NANC) releases neuronal NO.

Brain cortical and hypothalamic activity influence erection. Our information on CNS how it influence of erection, is based largely on animal models and observations made on patients with spinal cord injuries Patients, that have taught us about the contribution of spinal reflexes and supra spinal influences. Superimposed on all of the above is the influence of the male sex hormone, testosterone, whose primary function in human males is to maintain the state of sexual drive or libido.

FUNCTIONAL VASCULAR AND MICROSCOPIC ANATOMY OF PENILE ERECTION

The human penis consists of three spongy cylinders: the paired corpora cavernosa and the ventral corpus spongiosum, which forms the glans penis distally Fig. 1. The cavernous bodies communicate with each other through incomplete septum, which allows them to neurophysiologically function and pharmacologically respond as a single unit. The corpora cavernosa act as a capacitor during erection. All of the corporeal bodies are surrounded by a dense fascial structure, the tunica albuginea. Buck's fascia (deep fascia) surrounds the outside of the tunica albuginea, additionally forms a thin fibrous septum between the corpora cavernosa and the corpus spongiosum. Proximally, Buck's fascia is attached to the perineal membrane; distally, it is tightly attached to the base of glans penis at the coronal sulcus, where it fuses with the end of the corpora. Buck's fascia has a dense structure and is composed of longitudinally running fibers; it is firmly attached to underlying tunica albuginea and encloses the deep dorsal vein, dorsal arteries, and dorsal nerves (neurovascular bundle).

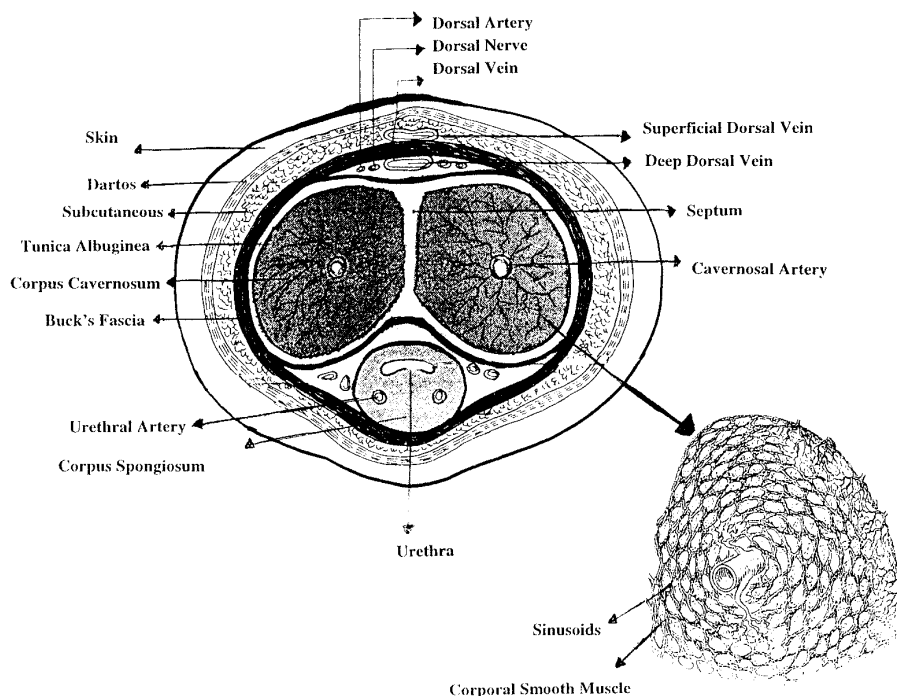


Fig. 1. Schematic representation of a cross section of the human penis. (Adapted from ref. 1a)

Surrounding the Buck's fascia is Colles' fascia (superficial fascia), which is continuous with the Scarpa's fascia of the lower abdominal wall, and dartos fascia of the scrotum (9). Surrounding this fascia is the skin. The fundiform ligament is the thickening of Colles' fascia (that continues to join the linea alba and splits to surround the body of the penis and then fuses with the septa of scrotum). Deep to Colles' fascia is the triangular suspensory ligament, which is in continuity with Buck's fascia (the attachment of that ligament to the pubic bone maintains the penile position during erection.) The proximal part of the penis is anchored to inferior pubic rami and consists of the crura of the corpora cavernosa. The bulbospongiosus muscle surrounds the penile bulb (supplied by the deep branch of perineal nerve). The ischiocavernosus muscles (supplied by the perineal branch of pudendal nerve S2-3) cover the penile crura and proximal part of the penile shaft. These skeletal muscles lie superficial to Buck's fascia and deep to Colles' fascia. The glans penis is covered with very thin and firmly adherent skin and has no fibrous sheath. The glans has a sponge like appearance due to a rich venous plexus. The loose penile skin and subcutaneous connective tissue permits considerable elongation and expansion of the cavernosa within its coverings. The covering from inside to outside can be remembered as **ABCD**: **A**—albuginea, **B**—Buck's fascia, **C**—Colles' fascia and connective tissue, **D**—dermis.

Tunica Albuginea and Fibrous Skeleton of the Penis

The tunica is composed of elastic fibers forming an irregular lattice network with collagen fibers (type I and III) (10). The detailed histologic composition of the tunia varies

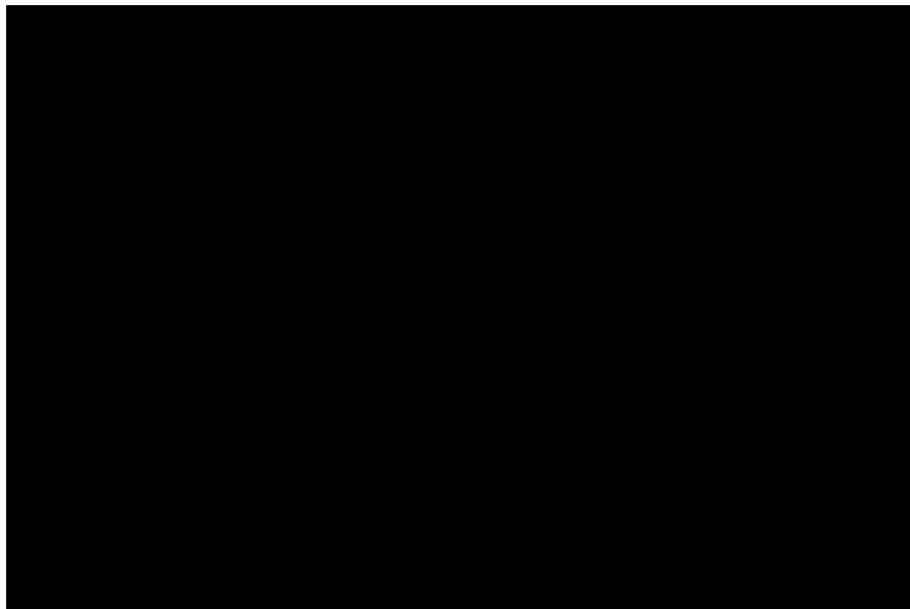


Fig. 2. Cross section of the penis that demonstrates the collagen skeleton of the penis. (Adapted from ref. 10a)

depending on its anatomical location and function. Its average thickness of 2–3 mm in the flaccid state. The tunica albuginea becomes thicker ventrally where it forms the groove to accommodate the corpus spongiosum. The tunica albuginea of the corpus spongiosum is much thinner than that of the corpora cavernosa and contains more elastic fibers. The tunica of the corpora cavernosa is a bilayered structure. The inner layer is composed of circularly oriented bundles, which support and contain the cavernous tissue. As the crura diverge proximally, the circular fibers provide the support. Radiating into the corpora from this inner layer are intracavernosal pillars (ICPs) or columns that act as struts, augmenting the septum that provides essential support to the erectile tissue. The outer layer is oriented longitudinally extending from the glans penis to the proximal crura, insert into the inferior pubic ramus. Cadaveric dissections have shown that the tunic is thinnest at the 6 o'clock position over the urethra (higher chances of perforation during implantation of prosthesis). Emissary veins run between the inner and outer layers for a short distance, often piercing the outer bundles in an oblique manner and thus can be occluded easily by the shearing action of the tunical layers during erection. The outer layer appears to play an additional role in compression of the veins during erection. Branches of the dorsal artery, however, take a more direct perpendicular route and are surrounded by a periarterial fibrous sheath that protect them from compression during erection. The tunica albuginea provides a tough uniform backing for engorged sinusoidal spaces. The cavernosal geometry design gives flexibility, rigidity, and strength (Fig. 2) (10).

Corporal Ultrastructure

Cavernosal tissue is spongelike and composed of a meshwork of interconnected cavernosal spaces, which are lined by vascular endothelium (11) and separated by trabecu-

lae, containing bundles of smooth muscle in a framework of collagen (type I and IV and lesser amount of III) (12), elastin, and fibroblasts (13). Approximately 45% of cavernosal volume is smooth muscle (14). Alterations in the relative quantities and structure of the cytoskeleton and contractile proteins may be responsible for changes in the passive and active characteristics of penile smooth muscle. Passive mechanical properties of cavernosal tissue depend on the relative proportion between muscular and nonmuscular components, particularly collagen. Ultrastructural examination of a smooth muscle cell reveals thin, thick, and intermediate filamentous structures. Thin filaments or light chain are mainly composed of actin (also called LC20 because its molecular weight is 20 KD). Thick filaments are formed of myosin. Intermediate filaments contain either desmin or vimentin. Each type of filament has a specific function.

Penile Arterial System

The internal pudendal artery (terminal branch of hypogastric artery) is mainly responsible for the blood supply to the deep structures of the penis (Fig. 3) (15). The internal pudendal artery runs in a curve in the dorsolateral pelvic wall. It enters the lesser pelvis, accompanied by the nerve, through the lesser sciatic notch. It enters the ischiorectal fossa where it courses along in Alcock's canal along the inferior insertion of the obturator internus muscle. In men the internal pudendal gives rise to scrotal and bulbar branches (via perineal branch) before continuing as the common penile artery. The latter pierces the urogenital diaphragm and continues along the medial margin of the inferior ramus of the pubis. In the anterior perineum near the bulbospongiosus, the penile artery divides into its terminal three branches (trifurcation), the bulbourethral, cavernous artery (central or deep penile), and the dorsal artery (superficial penile) of the penis (16). The glans penis can be separated completely from corpus cavernosum without compromising its supply.

1. The bulbourethral artery after giving off bulbar artery continues as urethral artery, which runs on the ventral surface of the corpus spongiosum beneath the tunical albuginea.
2. The dorsal artery of the penis is the termination of penile artery, it runs over the respective crus and then along the dorsolateral surface of the penis as far as the glans between dorsal vein medially and dorsal nerve of penis laterally (neurovascular bundle). The artery has a tortuous course configuration to accommodate for elongation during erection. On its way to glans it gives off circumflex arteries to supply the corpus spongiosum. Distally the dorsal artery runs ventrolateral position near the sulcus prior to entering the glans. The frenular artery branch of the dorsal artery curved around each side of the distal shaft to enter the frenulum and glans ventrally.
3. The cavernosal artery is responsible for flow to the corporal bodies (Intracorporal circulation). The cavernosal artery pierces the tunica, entering each corpus cavernosum at the hilum of the penis, where the two corpora come together. It gives off a short branch to the crus and then passes through out the cavernous body almost to the tip (it is eccentrically placed, medial to center towards the mid septum of the cavernous bodies except distally near the glans where it lies in the center). It gives off two types of branches (17); outer capillaries (nutritional route during penile flaccidity) that supplies smooth muscle and nerve fibers and inner terminal helicine (corkscrew shaped or helical shape allows penis to elongate and dilate without decreasing flow) arteries that open directly into the cavernous spaces without going into capillaries, which are then emptied into the post cavernous venules (supply route during erection). There are multiple layers of smooth muscle surrounding these helicine (resistance) arteries. In flaccidity, this muscle is contracted, allowing only small amounts of

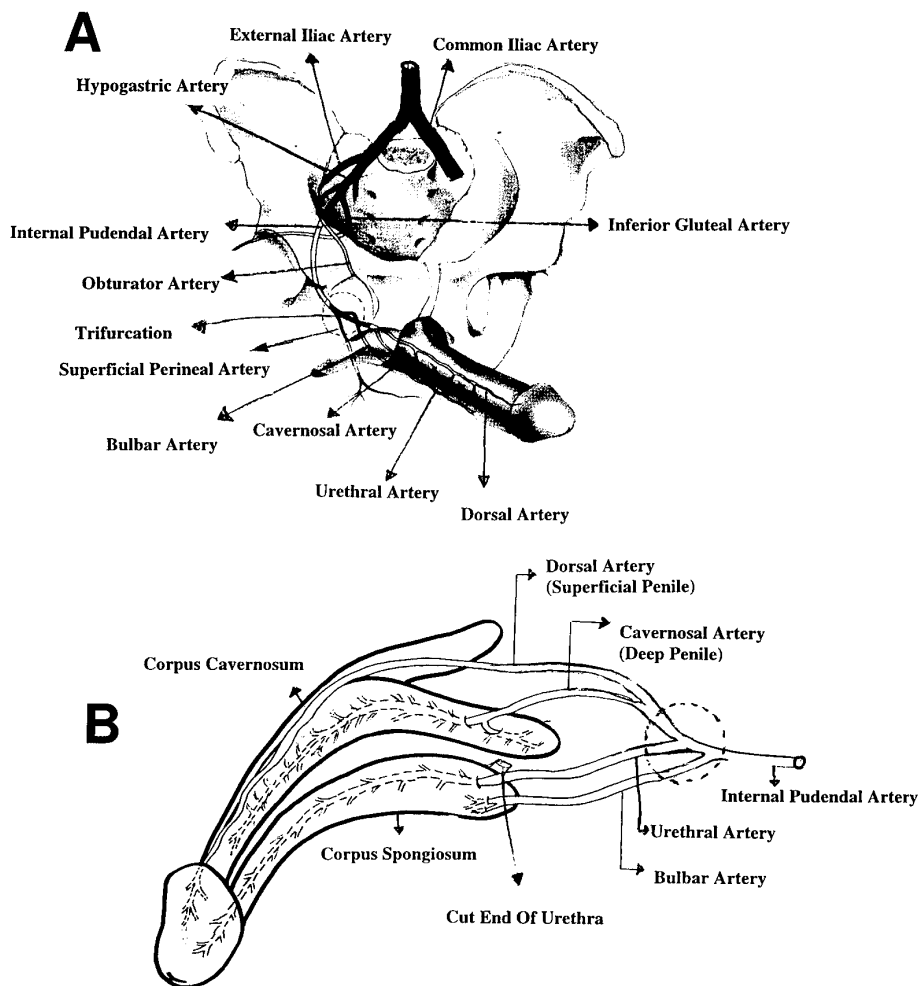


Fig. 3. Arterial supply to the penis in relationship to the bony pelvis (a) and the inner portion of the corpora (b).

blood into the lacunar spaces. After the proper stimulus, this muscle relaxes, and the arteries dilate and straighten, increasing blood flow and pressure to the lacunar spaces (18). The cavernosal arteries supply the bulk of the blood that is delivered to the corpora cavernosa. The dorsal artery passes anterior to the crus and courses distally along the dorsum of the penis under the Buck's fascia to the glans penis medial to dorsal nerve and lateral to dorsal vein). It gives off several circumflex branches (from 3 to 10) to the middorsal corpora cavernosa and, for this reason, bypass into a proximally occluded dorsal penile artery that can improve flow into the corpora cavernosa.

Anatomical variants are the rule and include both cavernous arteries originating from the same side, hypoplasia, or absence of one dorsal penile artery and accessory penile arteries arising from obturator arteries, external iliac, or others. Damage to these acces-

Table 1
Penile Arterial System

<i>Penile Inflow (Arterial)</i>
Hypogastric (Internal Iliac) artery → Internal Pudenda artery → Common penile artery → (1) bulbourethral (2) cavernous (3) Dorsal artery
Bulbourethral artery • Bulbar: enters the bulb of the penis shortly after its origin. It supplies blood to bulbourethral (Cowper's) gland and the proximal urethral bulb. • The urethral (spongiosal) artery runs longitudinally through the corpus spongiosum lateral to the urethra and also supplies glans
Cavernous or deep penile artery – enters corpus cavernosum at base and runs eccentrically to the tip. Gives off two types of branches: • Outer capillaries (nutritional) one that supplies smooth muscle and nerve fibers, and • Inner helicine (supply) arteries are multiple muscular and helical shape arteries that open directly into the cavernous spaces without going into capillaries and act like resistance arteries (helical shape allows penis to elongate and dilate without decreasing flow) (Helicine arteries → Sinusoids → Post-Cavernous Venules → Sub-albugineal Venous Plexus → Emissary Vein)
Dorsal or Superficial Penile artery: runs deep to Buck's fascia, between the centrally located deep dorsal vein and the paired dorsal nerves.

sory arteries during radical prostatectomy or cystectomy may result in vasculogenic erectile dysfunction after surgery. Collateral vessels may open up in the presence of obstruction in vessels of the penis between both cavernosal arteries or with cavernosal artery and dorsal artery (19).

The penile skin is supplied by external pudendal artery (branch of femoral artery). Each vessel divides to dorsolateral and ventrolateral branch, which supply the skin of the shaft and prepuce. At the coronal sulcus there is communication with the deep arterial system.

Penile Venous System (and Corporal Veno-Occlusive Mechanism)

There are three sets of veins draining the penis: the superficial, intermediate, and deep (Fig. 4) (20–23). The deep venous system drains both the corpora cavernosa and the corpus spongiosum. The post cavernous venules coalesce to form larger emissary veins that pierce the tunica albuginea. The emissary veins of the middle and distal penis join to form the circumflex veins, which empty into the deep dorsal vein. Both the emissary and circumflex veins have valves. The emissary veins of the proximal penis form the cavernous vein, which empties into the internal pudendal vein. The intermediate set of veins is deep to Buck's fascia. Veins from the glans penis form a retrocoronal plexus that drains into the deep dorsal vein. The deep dorsal vein courses proximally in the midline between the two corpora cavernosa and empties into the periprostatic plexus. The superficial dorsal vein drains the skin and the subcutaneous tissue superficial to Buck's fascia. It drains into the superficial external pudendal vein. Emissary veins run between the inner and outer layers for a short distance, often piercing the outer bundles in an oblique manner and thus can be occluded easily by the shearing action of the tunical layers during erection (Passive occlusion) (24).

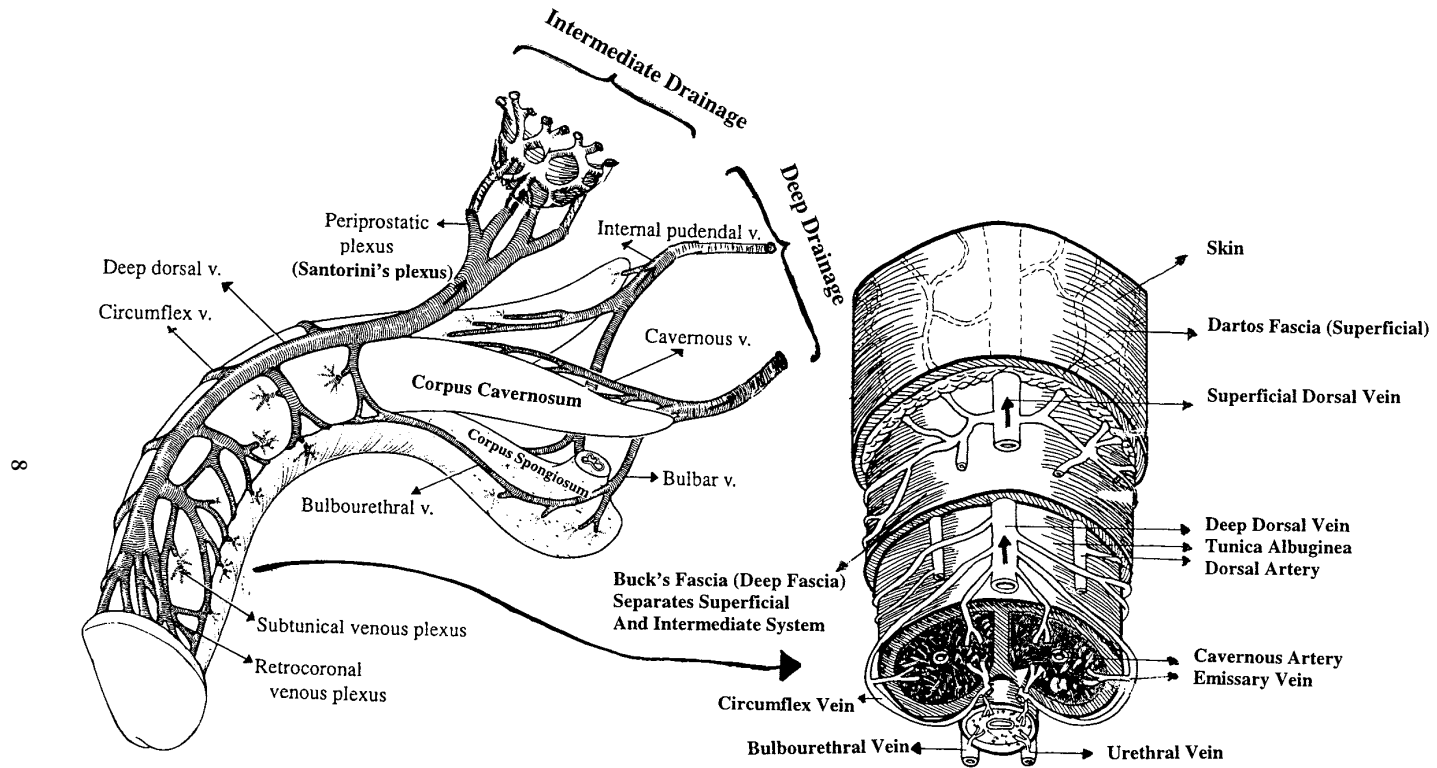


Fig. 4. Venous drainage of the penis. (Adapted from ref. 1a)

Table 2
Penile Venous System

<i>Penile Outflow (Venous)</i>		
<i>Superficial drainage outflow (Above Buck's fascia and below Colles's fascia)</i>	<i>Intermediate drainage outflow: Deep dorsal vein and circumflex system (Below Buck's fascia and above tunica)</i>	<i>Deep drainage outflow: Deep penile or cavernous system</i>
Dorsal skin and subcutaneous tissue by the superficial dorsal vein, emptying into a saphenous vein via the external pudendal vein or inferior epigastric vein.	Drains the glans and distal two-thirds corpora cavernosa corpora and spongiosum and corpus spongiosum. Small emissary veins penetrate tunica and combine into circumflex veins before draining into deep dorsal vein. Empties into Santorini's plexus (periprostatic plexus).	Drains the proximal (cavernous veins, bulbar veins and crural veins). Drains into the internal pudendal vein.

FUNCTIONAL NEUROANATOMY OF PENILE ERECTION

Parasympathetic and Nonadrenergic and Noncholinergic Outflow (Penile Erection)

Parasympathetic preganglionic input to the human penis originates in the sacral (S2–S4) spinal cord (Fig. 5) (25). In most men, S3 is the main source of erectogenic fibers, with a smaller supply coming from either S2 or S4. These preganglionic neurons are situated in the intermediolateral cell column and send dendritic projections to laminae V, VII, IX, and X of the spinal cord. These distributions for axonal processes imply that sacral preganglionic neurons receive afferent (sensory) information from both visceral and somatic structures. Dendrites also project to areas containing descending axons from supraspinal centers that integrate and coordinate the autonomic nervous system such as the hypothalamus, reticular formation, and midbrain (7). The preganglionic fibers from the sacral roots form the pelvic nerves (pelvic splanchnic nerves or *nervi erigentes*) (26) and are joined by fibers from the inferior hypogastric nerves (sympathetic) to form the pelvic plexus (aka: inferior hypogastric plexus) in the pelvic fascia on the lateral side of the rectum, seminal vesicles, prostate, and posterior bladder. These nerves also receive additional sympathetic fibers from the sacral sympathetic chain ganglia, via the gray rami. Not all axons conveyed by hypogastric or pelvic nerves synapse in the pelvic plexus. Afferent and sympathetic postganglionic neurons pass through this plexus en route to the penis. The number of distinct pelvic nerves varies from three to six between subjects. The cavernous nerve (sympathetic and parasympathetic postganglionic fibers) leaves the pelvis between the transverse perineal muscles and the membranous urethra passing beneath the arch of the pubic bone to supply each corpus cavernosum. The cavernous nerve divides into two branches; one is the lesser cavernous nerve that supplies the erectile tissue of the corpus spongiosum as well

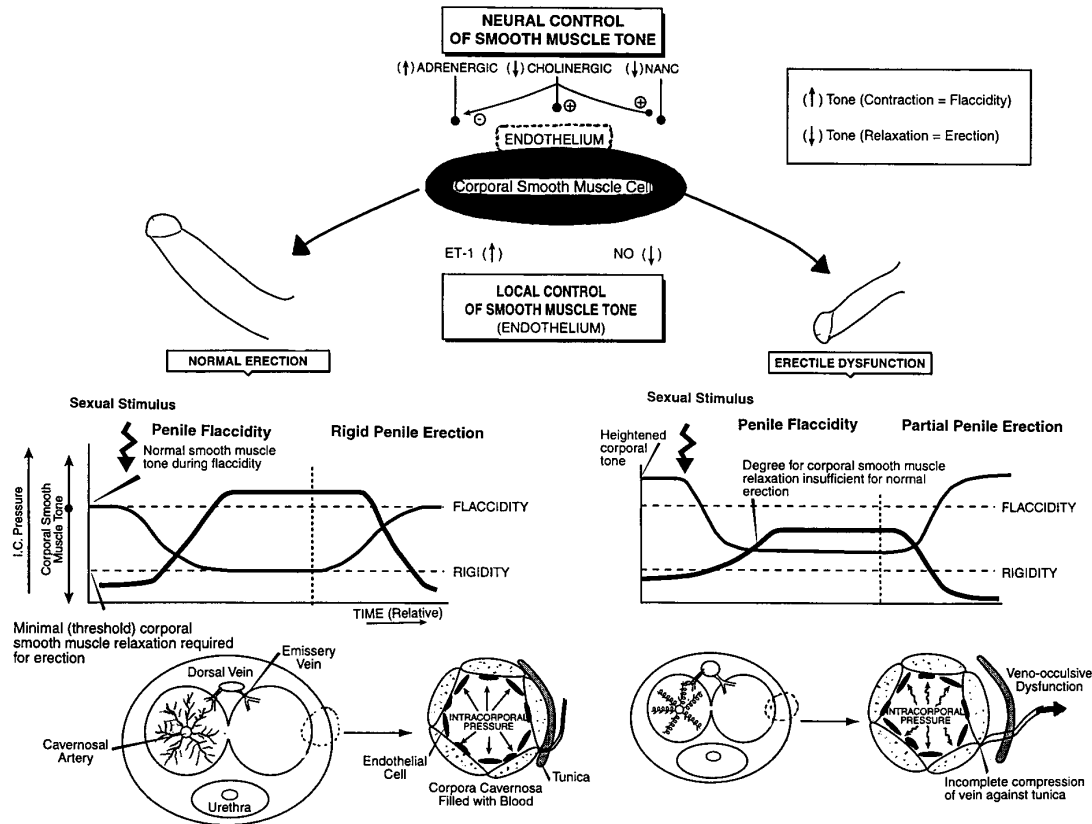


Fig. 5. Mechanism of normal penile erection. Erection is a neurovascular phenomenon initiated by psychosomatic environment. To obtain a penile erection, four physiologic events are needed: intact neuronal innervation, intact arterial supply, appropriately responsive corporal smooth muscle, and intact veno-occlusive mechanics. It involves increased arterial flow, increased venous resistance, and relaxation of sinusoidal spaces. Functional or organic pathology at different stages or individual component will lead to erectile dysfunction.

as the penile urethra. The outer branch, the greater cavernous nerve, stays beneath the prostatic venous plexus and enters the corpora cavernosa around the cavernous vessels in the hilum of the penis. The cavernous nerve runs with branches of the prostatovesical artery and veins as the so-called neurovascular bundle. After passing the tip of seminal vesicle these nerves lie with in the leaves of the lateral endopelvic fascia near its juncture with Denonvilliers fascia. It passes anterior to Denonvilliers' fascia and travel at the posterolateral border of the prostate and on the surface of rectum (lateral to prostate capsular arteries and veins). As it passes posterolaterally to the prostate, the bundle gives off fine branches to supply the prostatic capsule. At the prostatic apex the nerve passes very near to the urethral lumen at the 3 and 9 o'clock positions and enters the penile crura more anteriorly, at 1 and 11 o'clock. The cavernous nerves represent the final pathway for vasodilator and vasoconstrictor neural input to the cavernous smooth muscles (25,27).

(Parasympathetic neurons also supply innervation to the prostate, seminal vesicles vasa deferens, and bulbourethral glands. Parasympathetic efferents stimulate secretion in men from the bulbourethral and Littre's glands, as well as from the seminal vesicles and the prostate (28). The Littre's and bulbourethral glands produce mucus, which contributes to lubrication of the penile urethra. Secretions from the seminal vesicles and prostate ensure the viability and motility of the sperm and account for much of the volume of semen.)

Sympathetic Outflow (Penile Flaccidity, Seminal Emission, and Ejaculation)

The sympathetic preganglionic fibers to the penis arise from cells in the intermediolateral gray cell column and dorsal commissure (Intercalated nucleus) of the upper lumbar and lower thoracic segments of the cord (T10-L2). Dendrites from thoracolumbar preganglionic neurons project mediolaterally toward the central canal. One interpretation of the distribution of these dendritic projections is that they enable preganglionic neurons to receive input from descending supraspinal centers. Preganglionic fibers leave the cord in the ventral roots of the corresponding spinal nerve and then pass via the white rami communicantes to the paravertebral sympathetic chain. Having entered the sympathetic chain, there are two different pathways for axons to reach the penis. Some preganglionic descend to ganglia at a lower lumbar or sacral level and synapse with ganglion (paravertebral pathway) cells. The fibers then leave the chain at the sacral level, travel through pelvic nerves to the pelvic plexus and cavernous nerve or through the pudendal nerves. Others pass through the corresponding chain ganglia without making synaptic contact and travel in lumbar splanchnic nerves to synapse in the ganglia (prevertebral pathway) of the superior hypogastric plexus (aka: presacral nerve). The superior hypogastric plexus divides inferiorly into left and right hypogastric nerves, which descend to the two pelvic (inferior hypogastric aka: plexus of Frankenhäuser). The hypogastric nerves contain postganglionic sympathetic fibers (gray rami), as well as preganglionic nerves, which descend in the pelvis to synapse on cells in the pelvic plexuses (integration center). Sympathic fibers also supply smooth muscle of the ductus deferens, seminal vesicle, urethra, and prostate).

EJACULATION

Ejaculation is a two-step process. The first step is emission, whereby secretions from the periurethral glands, seminal vesicles, and prostate, as well as sperm from the vas deferens and ampulla of the vas are deposited into the posterior urethra as a result of the rhythmic contraction of smooth muscle in the walls of these organs. Accumulation of this fluid in the genitourinary tract produces the feeling of ejaculatory inevitability that

Table 3
Neuroeffector of Ejaculation

<i>Mechanism</i>	<i>Autonomic Pathway</i>	<i>Function</i>
<i>Afferent</i>		
Touch, vibration, Friction	Pudendal center (S2–S4)	Sensory
<i>Efferent</i>		
Secretion	Parasympathetic center (S2–S4)	Secretion from prostate, seminal vesicles, ampullary glands, bulbourethral gland (Cowper’s gland), Litter’s glands
Emission	Sympathetic center (T11–L2)	Contraction of: 1. Internal accessory organs: seminal vesicle, prostate smooth muscle, bulbourethral gland, 2. Closure of internal urethral sphincter, 3. Contraction of ducts: Ductuli efferentes, ductus epididymidis, vasa deferentia, ejaculatory ducts, smooth muscle of testicular capsule.
Ejaculation	Pudendal Somatic center (S2–S4)	Projectile ejaculation involves: 1. Relaxation of external sphincter, 2. Rhythmic contractions of ischiocavernosus and bulbocavernosus, 3. Contraction of pelvic musculature.

precedes ejaculation by a second or two. Emission is under sympathetic control from the presacral and hypogastric nerves that originate in the T10-L2 cord levels (28). Ejaculation proper (projectile ejaculation) itself involves closure of the bladder neck (prevent retrograde flow), which is also under sympathetic control, as well as the opening of the external urethral sphincter and contraction of the bulbourethral muscles to forcibly propel the semen out of the urethra. These are striated muscles innervated by somatic fibers carried in the pudendal nerve. Orgasm can occur with damage to the sympathetic ganglia but does not usually occur with damage to the pudendal nerve.

Somato-Sensory Innervation (Pudendal and Dorsal Nerve of Penis or DNP)

Penile sensory fibers belong to spinal segment S2, S3, and S4 and travel from the penis in dorsal nerve of the penis, which joins the pudendal nerve (29). The motor neuronal cells of the pudendal nerve form a ventrolateral group in the anterior grey column of the cord S2, S3, and S4 ‘Onuf’s nucleus’. The axons of these motor neurones supply striated muscles of the penis (bulbocavernosus and ischiocavernosus) and perineum. The pudendal nerve leaves the pelvis through the lower part of the greater sciatic foramen enters the gluteal region close to the ischial spine on the medial side of the internal pudendal artery. It then travels through the lesser sciatic foramen into the pudendal canal with the internal pudendal artery. After giving off the inferior rectal nerve, it

divides into the perineal nerve and dorsal nerve of the penis. The perineal branch innervates the ischiocavernosus and bulbocavernosus muscles, as well as the skin of genitalia, urogenital diaphragm and a branch, which supplies the corpus spongiosum. The dorsal nerve of the penis runs along ramus of the ischium and along the inferior to of the pubis with the pudendal artery on the surface of the urogenital diaphragm. It runs with the dorsal artery of the penis and ends in glans (30). The sensory innervation of the glans penis is unique compared with other cutaneous regions: 80–90% of the afferent terminals in the glans are free nerve endings. These nerves are C-fibers or A-Delta fibers (31). This somatic afferent project to spinal centers in close proximity to the dendrites from sacral preganglionic neurones. Afferent input from the penile skin, prepuce and glans conveyed by DNP initiates and maintains reflexogenic erection.

Rhythmic movements of the penis are the result of contraction of the ischiocavernosus muscles (32), which compress the crura. These periods are brief and are readily observed as small rhythmic movements of the penis. It has been suggested that intermittent supra systolic contraction occurs during pelvic thrusting when tactile stimulation and friction of the penis triggers the spinal ‘bulbocavernosus reflex’ (33).

PENILE ERECTION AND FLACCIDITY: PHYSIOLOGIC MECHANISM

Penile erection is a neurovascular event controlled by corporal smooth-muscle tone. In the flaccid state, the corporeal smooth muscle of cavernous arteries, helicine arterioles, and trabeculae are tonically contracted, limiting the inflow of blood to the corpora to a small amount of blood (5 mL/min) that enters the penis for nutritional purposes (34). To obtain a penile erection, four physiologic events are needed; intact neuronal innervation, intact arterial supply, appropriately responsive corporal smooth muscle, and intact veno-occlusive mechanics. Tactile or psychic stimuli caused by erotic activity are processed in the limbic system (median preoptic nucleus (MPOA), and the paraventricular nucleus (PVN) and coordinated in the midbrain to generate a neuronal signal, which is carried through thalamo-spinal tracts. These neural signals leave the spinal cord through nerve roots at T11–L2 for sympathetic traveling through hypogastric nerves (inhibitory), as well as via S2 to S4 for parasympathetic/NANC (stimulatory) and travel jointly through the pelvic plexus and cavernous nerve to penis. The neural signals cause release of neurotransmitter that promotes smooth-muscle relaxation, leading to dilatation of cavernosal and helicine arteries (fivefold to tenfold increase in flow). The signal that arrives in the penile tissue and spreads rapidly through the corporal tissue by gap junctions, leading to entire corporal smooth muscle relaxation and expansion of the corporal sinusoids. Corporeal smooth-muscle relaxation is presumably achieved by decreasing adrenergic tone while simultaneously increasing the release of cholinergic and/or noradrenergic/noncholinergic neurotransmitters. There are many neurotransmitter systems present in penile smooth muscle and endothelium. The increased inflow of blood temporarily exceeds the capacity of the veins to drain off the blood. The sinusoids expand and the volume of blood in the corpora increases. Compliance of the sinusoid initially prevents the rapid increase of intracavernosal pressure. When the sinusoidal system is adequately stretched, the intracavernous pressure begins to rise. Venules draining the sinusoidal spaces coalesce into a peripheral plexus below the outer fibroelastic tunica of the corporal bodies. Egress from the subtunica venular plexus is via emissary veins exiting obliquely through the bilayer tunica albuginea into deep dorsal vein in distal two-third and via the short cavernous and crural veins at the base (proximal one-third) of corporal bodies. As the corporeal sinuses, or lacunae fill with oxygenated blood,

Table 4
Mechanism of Erection

-
1. Active dilatation of arterioles and arteries increases blood flow (inflow).
 2. Expansion of sinusoids causes trapping of blood (capacitor).
 3. Subtunical venular plexuses are compressed between the tunica albuginea and peripheral sinusoids, reducing venous drainage (outflow).
 4. The tunica albuginea is stretched to its capacity and the emissary veins are compressed to maximum, further reducing venous outflow (veno-occlusive mechanism).
 5. Intracavernous pressure is increased to mean blood pressure to achieve full erection state.
 6. Contraction of ischiocavernous muscle further increases the intracavernosal pressure during contraction to several hundred mm of Hg for short duration but mainly causes rhythmic movement of the pendulous body of erect penis (throbbing).
-

expanding sinusoids dynamically compress the subtunical venules against the inner layer of tunica albuginea and structurally by differential stretching of the two primary layers of the tunica across which the emissary vein (elongation and compression of the venules) exit results in a large increase in the resistance to the passage of flow through these vessels and venous outflow is sufficiently decreased to result in turgidity of the corpora (veno-occlusive mechanism; a functional or passive mechanism).

As the erectile tissue of the penis fills with blood, the outflow is obstructed because of relaxation and elongation of the smooth muscle fibers. These fibers in turn compress the draining venules which allows the intracorporal pressure to rise to mean systolic pressure and cause penile rigidity. The unique geometry of the corpora also leads to the formation of erection. The factors that promote rigidity include the following:

1. The intrasinusoidal pressure within the corpora cavernosa distends the tunica albuginea to its maximal capability;
2. The midline septal fibers are tightly stretched between the dorsal and ventral corpora thus creating, in effect, an I-beam arrangement that accounts for the anteroposterior rigidity of the penis seen with erection; and/or
3. The relative indispensability of the paired lateral columns adds lateral stability to the penis during erection.

Vascular pulsation of the fully erect penis becomes visible when a steady state has been achieved. The pressure in the lacunar space during an erection is the result of the equilibrium between the perfusion pressure in the cavernosal artery and the resistance to blood outflow through the compressed subtunical venules. Thus, the penis, during erection, acts as a reservoir, accumulating blood under pressure. During maximal rigidity, both inflow of blood to and outflow of blood from the corpora cavernosa are practically at zero.

Although the glans penis does not have the same hemodynamic structure as the corpora cavernosa, it does experience substantial changes in blood flow during erection and detumescence. The glans penis does not possess a tunica albuginea, and the veins draining the glans penis (retrocoronal plexus) prevent a step pressure rise of the sort occurring in the shaft of the penis during erection. Blood flow through the glans and corpus spongiosum is increased over that evident in the nonerect penis. Thus, the glans maintains a steady and high arterial inflow and venous outflow (act as a large arterio-venous fistula), which enables the glans penis to share in erection but not in rigidity. The deep dorsal vein become partially compressed between three expanded corpora and Buck's fascia; thus contributes to pressure rise in the deep dorsal vein.

Detumescence can be triggered either by the cessation of sexual stimuli or by the sympathetic burst at orgasm and ejaculation. Detumescence is a reversal of the events that occur during erection: contraction of the corporeal smooth-muscle cells and helicine arteries, decrease in arterial blood flow, and resumption of normal venous out-flow. Adrenergic nerve activation and release of norepinephrine from sympathetic nerve terminals, and subsequent activation of postsynaptic (1-adrenergic receptors is the primary mediator of this event (35). Norepinephrine has generally been accepted as the principal neurotransmitter in the control of penile flaccidity. However, it has recently been demonstrated that endothelin may have an important role in the regulation of corporeal smooth-muscle tone in vivo. Therefore, as with erection, the advent of detumescence may also require the concerted efforts of several endogenous substances (cotransmission of norepinephrine and endothelin).

PENILE ERECTION AND FLACCIDITY: MOLECULAR MECHANISM OF CORPORAL SMOOTH-MUSCLE RELAXATION (ERECTION) AND CONTRACTION (FLACCIDITY)

Ultrastructural examination of a smooth-muscle cell reveals thin, thick, and intermediate filamentous structures. Thin filaments are mainly composed of actin. Thick filaments are formed of myosin. Intermediate filaments contain either desmin or vimentin. Each type of filament has a specific function. Following phosphorylation of myosin by ATP, attachments form between the globular heads of a light chain of myosin and actin. These attachments confer contractile tone on the smooth muscle (36). Maintenance of this tone is achieved at the expense of little ATP, owing to the establishment of a latch state of the cross-bridges between actin and myosin, demands a high concentration of cytoplasmic free calcium. Modulation of corporal smooth muscle tone is a complex process requiring the integration of a host of intracellular events and extracellular signals. Neurotransmitters that participate in erection and detumescence modulate corporal smooth-muscle tone, in large part through their effects on the gap junctions, calcium channels, and potassium channels (Figs 6, 7) (4,37–47). Adequate Ca^{2+} homeostasis is required for the regulation of smooth muscle tone. Three different mechanisms are involved: influx of extracellular Ca^{2+} through voltage-regulated channels; activation of membrane-bound receptors that allow extracellular Ca^{2+} to enter the cell through receptor-operated channels; and activation of specific signaling pathways relying on intracellular release of Ca^{2+} from sarcoplasmic reticulum. Furthermore, the continuous transmembrane flux of Ca^{2+} is required for the maintenance of contraction. Relaxation of smooth muscle is achieved by lowering cytosolic calcium.

Smooth-muscle Contraction is Regulated by Ca^{2+} Induced Phosphorylation of Myosin

The primary stimulus for corporal smooth-muscle contraction is certainly related to increases in intracellular calcium levels. When the cytoplasmic Ca^{2+} concentration increases to 10.5 mol/L, calmodulin-4 Ca^{2+} complex binds to the myosin light-chain kinase (myosin crossbridge four light chain, two associated with each one of the head of myosin). Initiation of contraction (penile flaccidity) is the result of phosphorylation of regulatory myosin light chains; relaxation (penile erection) is the result of the dephosphorylation of these myosin light chains. These reactions are catalyzed by (calmodulin dependent) myosin-light chain kinase (MLCK) and myosin-light chain

Table 5
Neurovascular Dynamics of Penile Erection and Flaccidity

Phases of Penile Erection and Flaccidity are Best Characterized after Intracorporal Vasoactive Agent, which Consists of the Following Stages or Phases. (Fig. 5)

<i>Erection Stage</i>	<i>Penile Blood Flow</i>	<i>Physiologic Basis</i>	<i>Intracorporal Pressure</i>
<i>Penile Flaccidity (Basal)</i>			
	Minimal inflow and outflow. (Low flow and low pressure)	Regulated by contracted corporal smooth muscles. There is dominant sympathetic influence and cavernosal, helicine arteries and cavernous sinusoid smooth muscle are contracted. (<i>Basal smooth muscle tone</i>)	5–20 mm of Hg (=Resting venous pressure)
<i>Penile Erection</i>			
<i>Initial filling (Latent)</i>	High inflow enters the corpora throughout both diastolic and systolic cycles with no increase of intracavernous pressure (6–10 times). In healthy potent man, a twofold dilatation of the cavernous artery from 0.5 mm to 1 mm (at base) and peak velocity over 30 cm of s. The corpora fill without pressure change for a period of 10 s.	Upon appropriate psychological or sexual stimulation neurogenic impulse initiate erection. Relaxation of sinusoidal and arterial smooth muscle leads to low resistance system due to inhibition of adrenergic and increased cholinergic and NANC nerve activity (<i>Active decrease in Smooth muscle tone</i>).	
<i>Partial erection (Tumescence)</i>	Penis elongates and expands, but as the rising intracorporal pressure exceeds the pressure of diastole, further inflow proceeds only during systole. Increasing intracavernous pressure with decreasing arterial flow.		50 mm of Hg

<i>Full Erection</i>	Intracavernous pressure reaches a plateau around mean arterial pressure (slightly below, i.e., 90% the systolic pressure), small inflow, and outflow. Good rigidity of the penis. The arterial pressures rather than arterial flow governs the penile rigidity under physiological conditions.	As the sinus spaces expand, the subtunical venules are collapsed beneath the tunica albuginea. The emissary veins are also further collapsed by the expanding tunica albuginea reducing venous outflow (passive venoocclusive mechanism). Maintenance of rigidity is influenced by the tactile sensory stimulation (dorsal nerve of penis) mediated by the spinal reflex system.	90–100 mm of Hg (=MAP, i.e., Erection pressure)
<i>Rigid erection</i> (Skeletal muscle or throbbing phase)	Intracavernous pressure temporarily increases to several hundred mm Hg (well above the systolic blood pressure) due to contraction of the ischiocavernosus muscles, temporary shut down of inflow and outflow. Short duration because of striated muscle fatigue.	Intermittent action <i>but it is not necessary for erection. There is no flow through the cavernous artery at this stage.</i>	100 mm of Hg (>MAP only during skeletal muscle contraction only)
<i>Decay of Penile Erection</i>			
<i>Initial rapid Detumescence</i>	Transient increase of intracavernous pressure due to smooth-muscle contraction against a closed venous system followed by rapid fall of intracavernous pressure	Reopening of the venous outflow. There is pulsatile decrease in length and girth until the penis is completely flaccid.	Pressure decay
<i>Slow detumescence</i>	Slow decrease of intracavernous pressure from slowly opening venous channels	Slowly opening venous channels	50 mm of Hg
<i>Fast Detumescence</i>	Fast decrease of intracavernous pressure to base line from completely reopened sinusoids-venous drainage	Completely reopened venous channels	5–20 mm of Hg

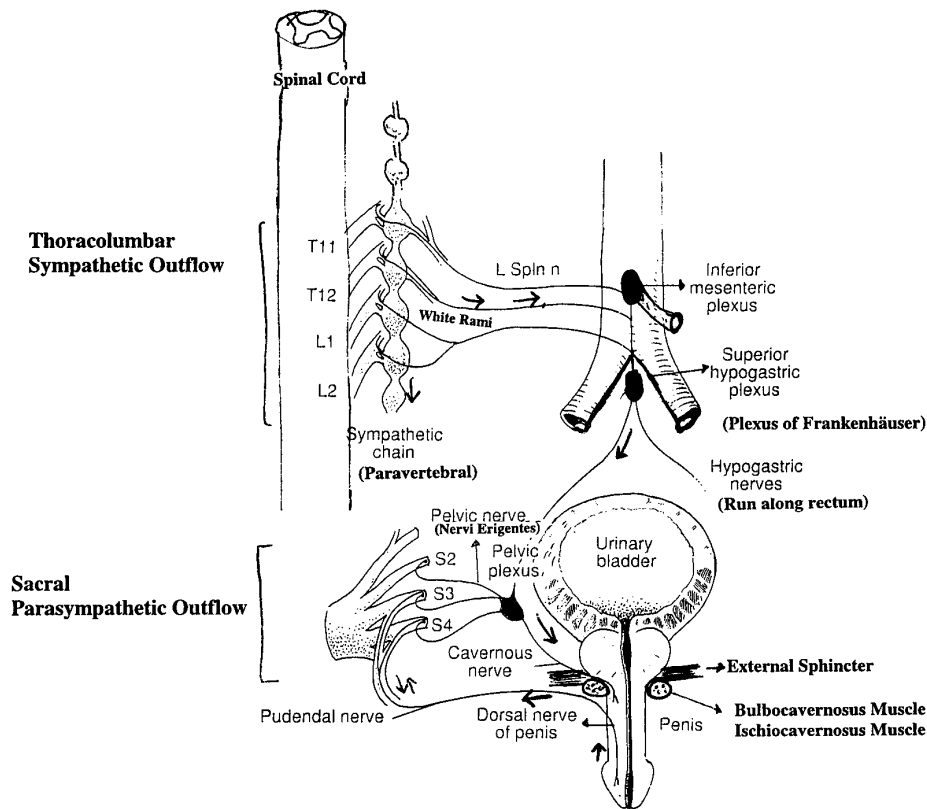


Fig. 6. Neural innervation of the pelvic structures and penile erection.

phosphatase (MLCP), respectively. Myosin-light-chain kinase is regulated by calcium in combination with calmodulin (calmodulin-4 Ca^{2+} complex as free calmodulin does not activate myosin-light-chain kinase). It has been shown at our institution, activation of both the endothelin-1 and α_1 -adrenergic receptors leads to a transient 3–10-fold increase in intracellular calcium levels in corporal smooth-muscle cells (39,48,49).

Smooth-Muscle Relaxation is Induced by Dephosphorylated Myosin

Relaxation of smooth muscle is viewed as a “resetting” of contractile machinery, by the resumption of a precontractile state accomplished by lowering cytosolic Ca^{2+} . Smooth muscle relaxes when the following events occur: cytoplasmic Ca^{2+} falls below 10.5 mol/L. The Ca^{2+} dissociates from calmodulin, which in turn dissociates from the myosin light kinase, thus inactivating it; dephosphorylated myosin light chain resumes its action of inhibiting the binding of the myosin head to actin and the ATPase activity; and the myosin head detaches from actin and relaxation occurs. There are various mechanisms whereby cytosolic Ca^{2+} can be reduced are cyclic adenosine monophosphate (cAMP) acting via PKA and cyclic guanosine monophosphate (cGMP) acting via PKG, or directly via activation of K-channels with hyperpolarization inside the cell preventing Ca entry into the cell.

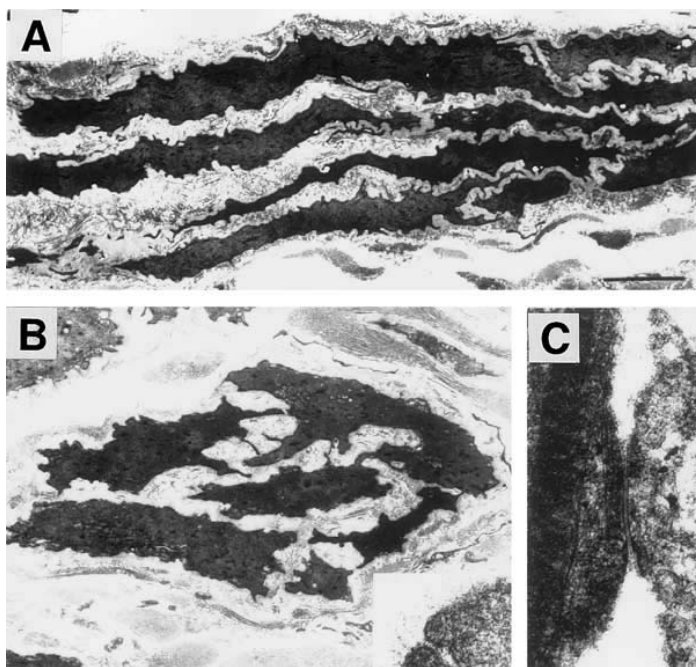


Fig. 7. Electron photomicrograph of the corpora showing the presence of gap junctions (with permission from ref. 49a).

PENILE ERECTION AND FLACCIDITY: MOLECULAR MECHANISM OF SIGNAL TRANSDUCTION IN CORPORAL SMOOTH-MUSCLE DURING ERECTION AND FLACCIDITY

Relaxation Signal and Second Messengers (cAMP and cGMP)

For corporal smooth-muscle relaxation, elevations in both intracellular cGMP and cAMP are thought to be important (4,50–54). Protein kinase G and protein kinase A activate multiple mechanisms that reduce intracellular calcium. Neurotransmitters (first messengers) bind to receptors on the smooth-muscle cell, and the neurostimulator-receptor complexes interact with Gs proteins (called G because they bind guanine nucleotides) activating adenylyl cyclase, which converts ATP to cAMP (second messenger). cAMP activates protein kinase A, which subsequently phosphorylates certain intracellular proteins, altering their activity. This pathway is activated by PGE1/VIP. 3–10-fold increases in intracellular cAMP levels have been documented in cultured human corporal smooth-muscle cells in response to activation of prostaglandin E1 (50). Cyclic nucleotide phosphodiesterase (PDEase) cleavage cAMP to AMP. Smooth-muscle relaxants, like papaverine, exert its effect through phosphodiesterase inhibition inducing the accumulation of either cAMP and/or cGMP depending on its selectivity (55). NO acts via guanylate cyclase, which produces cGMP. This pathway is activated by nitric oxide. Gi (inhibitory) inhibit adenylyl cyclase activity, e.g., epinephrine at the $\alpha 2$ receptor. In addition to the induction of cGMP formation, NO has been shown to stimulate Na pump activity. This would induce hyperpolarization, with subsequent clo-

sure of voltage-sensitive Ca^{2+} channels. Other substances accomplish muscle relaxation by way of a cAMP dependent mechanism, such as prostaglandin E, vasoactive intestinal polypeptide (VIP) and catecholamines.

Contraction Signal for Corporal Smooth-Muscle and Second Messengers (Ca^{2+} , IP_3 , and DAG) System

It is well documented that receptor- and nonreceptor-mediated increases in intracellular Ca^{2+} are a prerequisite to the initiation of corporal smooth-muscle contraction (56). Furthermore, the continuous transmembrane flux of Ca^{2+} is required for the maintenance of contraction (35,39,57,58). Neurotransmitter-receptor complex interacts with G PLC phosphophylase C, which cleaves PIP_2 in the cell membrane into {P3} and {DAG} (second messengers) (59). IP_3 causes release of Ca^{2+} from sarcoplasmic reticulum (SR). Ca^{2+} either directly complexed to calmodulin initiates contraction or altering protein activity. DAG activates protein kinase C (PKC) that phosphorylates protein, altering activity. DAG activates protein kinase C, which phosphorylates cellular protein, altering their activity. Phospholipase C and IP_3 , which increase release of Ca^{2+} from SR, mediate the contraction. Calcium enters the cell via receptor-activated calcium channels (activated by neurotransmitter); voltage-operated Ca channel (L-type) or release from SR in response to inositol triphosphate (IP_3). Christ reported that both Ca^{2+} influx via calcium channels and mobilization of intracellular calcium stores are involved during phenylephrine and endothelin-induced contraction, but only calcium channel influx is apparent during KCI-induced contraction.

The Role of Potassium Channels in Corporal Smooth Muscle

Stimulation of potassium channels causes hyperpolarization (negative charge) of corporal smooth-muscle cell. Hyperpolarization will prevent the opening of voltage-dependent calcium channels (60). As sustained contractions of corporal smooth muscle are dependent on continuous transmembrane calcium flux through voltage-dependent calcium channels, potassium channel activity will then occur. Christ (57,61) has described the diversity of potassium channels found in corporal smooth muscle, which consist of at least four distinct subtypes: the calcium-sensitive potassium channel (e.g., the Maxi-K), the metabolically regulated potassium K channel (e.g., the KATP) the delayed rectifier, and the fast transient A current {IA}. Studies to date have indicated that the Maxi-K channel mediates the most prominent potassium current on cultured corporal smooth-muscle cells, and moreover, indicated that disease-related alterations in the regulation/function of the Maxi-K channel may indeed be physiologically relevant. Recently, activation of Na^+/K^+ adenosine triphosphatase (ATPase) by NO has been shown to be involved in relaxation of corporal smooth muscle (3,62). Activation of Na^+/K^+ -ATPase will cause hyperpolarization, preventing Ca^{2+} entry via voltage-dependent Ca^{2+} channels.

PENILE ERECTION AND FLACCIDITY: MECHANISM OF SIGNAL PROPAGATION IN CORPORAL SMOOTH CELL DURING ERECTION AND FLACCIDITY

Gap Junctions (Intracellular Communication)

Smooth-muscle responses are characteristically coordinated through gap junctions. Corporal neurotransmitters and neuromodulators transmit electrical or chemical signals

Table 6
Primary Effectors of Corporal Smooth Muscle Tone

<i>Neurotransmitter</i>	<i>Source</i>	<i>Receptor</i>	<i>2nd Messenger</i>	<i>CSM Ca²⁺</i>	<i>CSM Response</i>
Norepinephrine (NE)	Adrenergic (NE)	α -Adrenergic (α_1 and α_2)	IP3/DAG/ Ca ²⁺ /PKC	Increase	Contraction
Endothelin ₁ (ET ₁)	EC, SMC?	ETA, B	IP3/DAG/ Ca ²⁺ /PKC	Increase	Contraction
ACH	CHOL neurons	M ₂ , M ₃	NO/GC/ cGMP/PKG	Decrease	Relaxation
NO	NANC (Nitredgic)	GC, K channel	GC/cGMP/PKG	Decrease	Relaxation
VIP	NANC (Vipergic)	VIP	AC/cAMP/PKA	Decrease	Relaxation
PGE ₁	EC, SMC?	EP	AC/cAMP/PKA	Decrease	Relaxation

CSM= corporal smooth muscle 2nd Messenger = second messenger EC: endothelial cells; IP3: inositol triphosphate; DAG: diacylglycerol; PKC: protein kinase C, ACH: acetylcholine; CHOL: cholinergic; M: muscarinic; NO-: nitric oxide; VIP: vasoactive intestinal polypeptide; PGE₁: prostaglandin E₁; NANC: nonadrenergic, noncholinergic; GC: guanylate cyclase; AC: adenylate cyclase; PKA: protein kinase A.

through gap junctions (Fig. 8) (38–40,46,57,63,64). Gap junctions are six homologous membrane-spanning proteins from each cell, known as connexins that join in the extracellular space to provide common cytoplasmic pathway for the flow of molecules. Electron microscopic studies have shown that gap junctions are prominent at areas of membrane apposition between adjacent corporeal smooth muscle. These gap junction channels permit the intercellular passage of current carrying ions and important second messenger molecules, such as inositol triphosphate (IP3), (DAG), (cAMP), (cGMP), and calcium ions (Ca²⁺), that diffuse between corporal smooth-muscle cells (39). Histological studies on corporeal tissue sections have revealed that the autonomic innervation of the human corpus cavernosum consists of widely distributed nerve fibers rather than intricate neuronal innervation of individual smooth-muscle cells despite the relatively sparse neuronal innervation of the corporeal parenchyma, electromyographic studies in patients with normal erectile function showed that cavernous electrical activity is synchronous throughout the entire corpus cavernosum secondary to gap junction. Gap-junction protein (connexin43 or Cx43) (37) appears to modulate α 1-adrenergic and ET-1 induced contractility as well as nitric oxide-induced relaxation responses of corporal smooth muscle. Age or disease-related alterations significant heterogeneity in Cx43 mRNA expression among tissues excised from patients with organic erectile dysfunction (65–70).

Cholinergic Mechanisms (ACH)

Acetylcholine is the preganglionic neurotransmitter of parasympathetic nerve input. For many years the parasympathetic nervous system was believed to be the sole effector of physiological erections (71). The action of postganglionic parasympathetic neurons is thought to be mediated in many tissues through the release of acetylcholine (72). However, cholinergic neurone fibers appear in limited numbers in the corpora cavernosa. In humans, intravenous or direct intracavernosal injection of the muscarinic receptor blocker atropine does not prevent penile erection. In vitro, transmural electrical

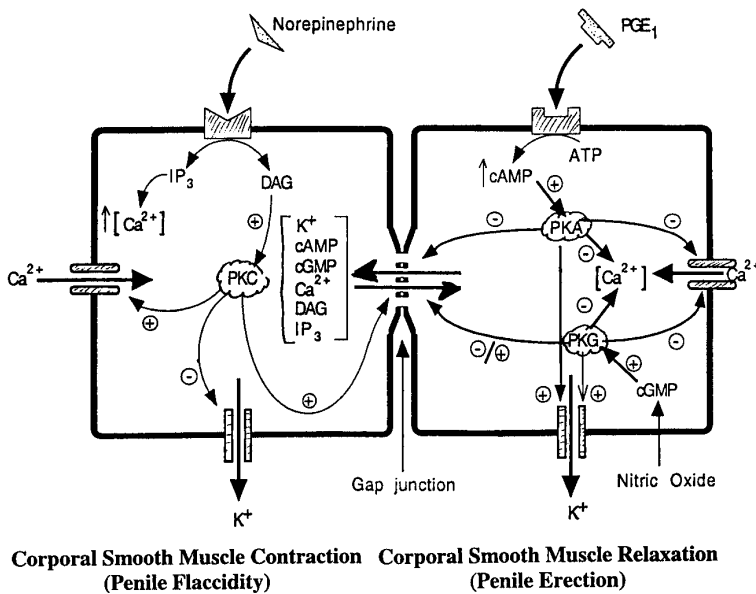


Fig. 8. Major intracellular mechanisms regulating corporal smooth-muscle tone. Shown are two corporal smooth-muscle cells A and B, interconnected by a gap junction plaque at their lateral border. Also shown is voltage-dependent Ca channels, and K channels. The left cell (A) depicts the series of intracellular events thought to be linked to corporal smooth-muscle contraction (an elevation in intracellular calcium levels). In the corpora, this might be accomplished following activation of the $\alpha 1$ -adrenergic receptor by norepinephrine, or by endothelin-1 activation of the ETA receptor. In both cases, receptor activation leads to Ca^{2+} mobilization. Specifically, activation of these receptors by norepinephrine or ET-1 leads to activation of phospholipase C, which cleaves membrane bound phosphatidyl inositol (PIP₂) into IP₃ and diacylglycerol (DAG). Conversely, the right cell (B) depicts the series of intracellular events thought to be linked to corporal smooth muscle relaxation (a diminution of transmembrane Ca^{2+} flux, sequestration of intracellular Ca^{2+} , membrane hyperpolarization and smooth-muscle relaxation). In this example, PGE-1 activates the PGE-1 receptor, to stimulate the adenylate cyclase enzyme, which then catalyzes the conversion of $\text{ATP} \rightarrow \text{cAMP}$. Increased cAMP stimulates Protein kinase A (PKA). Alternately, smooth-muscle relaxation can be achieved by nitric oxide, released from endothelial or neuronal sources. Nitric oxide diffuses into smooth-muscle cells to activate soluble guanylate cyclase, that catalyzes the conversion of $\text{GTP} \rightarrow \text{cGMP}$. Elevated cGMP levels activate protein kinase G (PKG). The effects of PKA, PKG, and PKC on gap junctions, K channels, and Ca channels are thought to be mediated via phosphorylation of specific amino acid residues on target proteins (gap junctions, K channels, and Ca channel). The result of their putative actions are illustrated as follows: {+} means a stimulatory, positive or increasing effect, and {-} means an inhibitory or negative effect. This simplified model illustrates how the interactions of these important second messenger systems might impact on gap junctions, K, and Ca channels, and thus modulate corporal smooth-muscle tone in vitro and in vivo.

stimulation of isolated corpus cavernosum strips causes frequency dependent, neurogenic relaxation that is blocked by the neurotoxin "tetrodotoxin," but it is resistant to adrenergic and cholinergic blockers (73). While cholinergic nerves do not mediate corpus cavernosum relaxation via postjunctional receptors in the corporal smooth muscle, they do act as modulators for other neuroeffector systems. In corpus cavernosum, adrenergic nerves receive inhibitory interneuronal regulation from cholinergic nerves

Table 7
Penile Erection and Flaccidity: Neurochemical Regulation

Neurogenic Control:	Cholinergic mechanism (Acetylcholine) Adrenergic mechanism (Norepinephrine) Nonadrenergic, Noncholinergic (NANC) system (Neuronal NO and VIP)
Endothelial control	Nitric Oxide (Endothelial NO) Endothelin (ET-1) Prostaglandins (PGE1, PGE2, PGI2)

(crosstalk). Cholinergic nerves may also facilitate noradrenergic, noncholinergic relaxation. There is cholinergic innervation of the endothelium, the endothelium stimulated by acetylcholine, release endothelium-derived nitric oxide, which causes relaxation of the underlying smooth muscle. However, the postganglionic dilator neurotransmitter mediating erection is now considered to be a noradrenergic noncholinergic (NANC) neurotransmitter (neuronal NO, VIP, and many others).

1. The modulator effects of acetylcholine facilitate relaxation of corporal muscle and vasodilatation. Relaxation is brought about by inhibiting the release of noradrenaline by way of prejunctional muscarinic receptors on adjacent adrenergic nerve endings (74,75).
2. Acetylcholine cause release of NO from endothelium (via postjunctional muscarinic receptors on endothelial cells), as evidenced by the fact that denuding isolated corporeal tissue strips of endothelium results in complete loss of the acetylcholine induced relaxation response.

Noradrenergic, Noncholinergic (NANC) Neuroeffector Systems (Peptidergic Including Vipergic and Nitregic)

Corporal smooth-muscle relaxation can occur in the presence of both parasympathetic and sympathetic blockers (76) and this led to the search for a NANC neurotransmitter responsible for penile erection (73,77,78). This response is significantly attenuated or blocked by substances that interfere with the synthesis or the effects of nitric oxide. This search was assisted by the discovery nitric oxide (79). Recent studies have shown with immunohistochemistry the presence of nitric oxide synthase (NOS) in autonomic nerves innervating penile blood vessels and the corporal smooth muscle (80–82). The synthesis of NO occurs as a byproduct of the conversion of L-arginine to L-citrulline by the enzyme NOS. The enzyme catalyzing this reaction is designated as NOS and exists as three different isoforms: the constitutive neuronal and endothelial NOS (nNOS or NOS 1, and eNOS or NOS 3, respectively), and the inducible NOS (iNOS or NOS 2). NO is a not stored in synaptic vesicle in nerve terminals and is synthesized on demand. In flaccid state, NOS activity is minimal. Experimentally, transmural electrical stimulation of nerves within human corpus cavernosum tissue induces NO production and relaxation (83,84), which are attenuated by the administration of NOS inhibitors. Such substances (NG-methyl-L-arginine, NG- nitro -L- arginine) also produce a decline of the erectile response to stimulation of pelvic nerves in vivo (80,85,86).

Nitric Oxide

Nitric oxide (NO) was initially released by endothelial cells. It was subsequently demonstrated that neurons could also synthesize and release NO (87–89). The neuronal and endothelial origin of NO has been demonstrated in the corpus cavernosum (53,79,83,90–94). Intracavernosal injection of NO donors elicits penile erection in man

(95–98). In vitro, many experiments have demonstrated a relaxant effect of NO on strips of corpora cavernosa and helicine arteries precontracted by norepinephrine (79,92,99,100). Furthermore, smooth-muscle relaxation is elicited by NO donors and blocked by NO scavengers or NOS inhibitors (101). However, the activity NO in response to acetylcholine or bradykinin in penile arteries is only partially reversed after administration of an inhibitor of nitric oxide synthase. Therefore, the endothelium dependent relaxing mechanisms of penile resistance arteries seem to be different from those observed in the corporal smooth muscle. Cyclic GMP is degraded intracellularly by different phosphodiesterases (PDEs), with seven PDE isoenzymes a localized to the human corpus cavernosum: PDE III (cyclic GMP-inhibited), PDE IV (cyclic adenosine monophosphate or cAMP-specific), and PDE V (cyclic GMP-specific). Spontaneous contractile activity and noradrenaline-induced contractions are opposed by different PDE inhibitors, with quazinone (PDE III inhibitor) being the most potent. Pharmacologic inhibition of NOS suppresses penile erection induced by cavernous nerve stimulation in the rat (80,102) NO from endothelial origin mediates acetylcholine and bradykinin-induced relaxation of corpus cavernosum strips (74,103). Nitrergic innervation could be the target for peripheral regulation of erection by androgens (104).

The lacunar space endothelium releases a relaxing factor (NO) when it is stimulated by physical (sheer stress) or chemical stimuli (acetylcholine, bradykinin) or cholinergic stimulation. NO derived from endothelial and neural origins subsequently diffuses into the adjacent smooth-muscle cells a (83,98,103) and activates soluble guanylate cyclase increasing intracellular cyclic guanosine monophosphate levels in the smooth-muscle cells (79,105). This cGMP synthesis in turn results in a decrease in intracellular Ca^{2+} and subsequent smooth-muscle relaxation and penile erection (4,8,106). The intensity of the histochemical detection of NADPH diaphorase in cavernosal tissue has been shown to be decreased in patients with cavernosal nerve injury (107), and corpora cavernosa from diabetic men have exhibited impaired relaxation responses to electric field stimulation (EFS) of the cavernosal nerve (100). NO increases cyclic guanine monophosphate (cGMP), which also activate Ca^{2+} - and K^{+} -sensitive channels resulting in hyperpolarization of the cell, $\text{Na}^{+}/\text{K}^{+}$ ATPase-dependent membrane pumps and eventual causing corporal smooth muscle relaxation. Relaxation of penile arteries by nitric oxide is inhibited by “charybdotoxin,” pointing to the role of calcium-activated potassium channels (84). Presently, it is known that administration of selective phosphodiesterase inhibitors facilitates penile erection, an effect that would be expected from a physiological response that depends on the nitric oxide/cGMP pathway.

VIP

VIP has been proposed by several investigators coneurotransmitter in corporal smooth-muscle cells (108,109). This was supported by the observation that VIP-immunoreactive fibers are identified in the corporal smooth muscle and that VIP elicits relaxation of corporal smooth muscle (110). VIP fibers follow the same anatomical course as cholinergic fibers and ultrastructural examination of human penile tissue shows that VIP containing vesicles are colocalized with other vesicles containing acetylcholine (111–113), suggesting cotransmission of VIP and acetylcholine (110,114). In addition, VIP relaxant effect is completely abolished by pretreatment with atropine or VIP antibody (112,115). Colocalization of VIP and NOS in human corpus cavernosum was shown not only in corporal innervation, but also in perivascular innervation (116,117). Intracorporeal injection of exogenous vasoactive intestinal peptide alone has failed to produce erections in many impotent men,

indicating that other modulators must be involved in corporal smooth-muscle relaxation (118,119). The concentration of VIP increased in man during pharmacologic or psychogenically induced erections.

Adrenergic Mechanisms (Noradrenaline)

Cavernosal and helicine arteries, as well as cavernosal smooth-muscle cells of human, receive adrenergic innervation. Adrenergic fibers outnumber cholinergic fibers in the penis. There are two types of α -adrenergic receptors in penile tissue: α_1 and α_2 . Alpha 1-receptors are the principal mediators of arterial and corporal smooth contraction with α_2 -receptors having a less significant role (13,16). Alpha-1 Adrenergic receptors can be activated not only by local nerve release of noradrenaline, but also by circulating catecholamines. Recent pharmacological and functional studies have suggested the presence of more than one α_1 -receptor subtype in human corpus cavernosum. Recent studies demonstrated that contractile response to NA is mediated by the heterogenous population of alpha receptors (α_{1d} , α_{1b} , and α_{1a}) corresponding to three different genes all expressed in human corpus cavernosum (55,120,121). The α_{1d} and α_{1a} subtypes are the ones expressed with greater density in the corporal muscle (19).

Intracavernous drug injection has demonstrated the importance of adrenergic mechanisms in erection. Injection of the α -blockers, phenoxybenzamine and phentolamine, causes erection, whereas the α -agonist, causes shrinkage of both the erect and flaccid penis (122) these findings suggest that the tone of the corporal smooth muscle in the flaccid penis is maintained by continuous α -adrenoceptor stimulation. β -adrenoreceptors that mediate smooth-muscle relaxation are present in the corpus cavernosum, but they appear to be of little physiological significance (77). Radioligand-receptor binding studies show that adrenergic receptors greatly outnumber β -adrenergic receptors (9:1) in corporal smooth-muscle cells (123). Furthermore, there is an increase in alpha-adrenergic tone with ageing and disease states (35). Therefore, alpha-adrenergic vasoconstriction may be the predominant adrenergic response over beta-adrenergic vasodilatation to sympathetic nerve stimulation. Alpha-2 receptors are present on cholinergic nerve terminals in human penile tissue. This is important in penile flaccidity, as prejunctional noradrenaline action reduces vasodilator transmitter release in addition to producing postjunctional vasoconstriction of vascular smooth muscles (124,125). Conversely, activation of muscarinic in addition to alpha-2 receptors on adrenergic terminals decreases the release of noradrenaline in human cavernous tissues (125). Thus, communication between adrenergic and cholinergic nerves (neuromodulator during penile flaccidity and erection). The α -2 adrenergic receptors distant from the adrenergic nerve terminals may be stimulated by the circulating catecholamines, which is suggested as a possible mechanism of impotence associated with high anxiety.

Other Neurotransmitters

1. Calcitonin gene-related peptide (CGRP). Immunohistochemical techniques have localized CGRP in cavernous nerves, cavernous arteries, and in cavernous smooth muscle (126). CGRP is known to be a potent vasodilator in a variety of human blood vessels. In sharp contrast to VIP, CGRP injection induces a dosage-related increase in penile inflow. CGRP acts by a direct effect on smooth muscle, which has been suggested to occur in part by release of NO. CGRP given intracavernosally induces penile erections in humans (127,128).
2. Neuropeptide Y (NPY) has been localized with NE in adrenergic postganglionic neurons (129,130). Electrical field stimulation of nerves in human cavernosal arteries and corpus

cavernous strips in vitro elicits biphasic contractile response (131). The second component of the evoked contraction can be abolished by adrenergic antagonists, but the initial contractile component is resistant. This suggests that contractile neurotransmitters other than noradrenaline are released from the nerve terminals. NPY has both direct and indirect vasoconstrictor actions.

3. Arginine vasopressin (AVP). In human cavernous tissue, AVP has been demonstrated by radioimmunoassay (RIA) in concentrations up to 10 times those circulating in plasma. It contracts human corporal strips and cavernosal artery rings in a concentration dependent manner.
4. Substance P. Substance P has an inhibitory effect on cavernosal muscle, but is found in smaller concentrations and is localized mainly in nerves around the corpuscular receptors beneath the epithelium of the glans penis (113).

Endothelin-1 (ET-1)

Endothelins are a family of three peptides: endothelin-1, endothelin-2, and endothelin-3. Endothelin-1 is a potent vasoconstrictor that also has growth factor activity, acting on fibroblasts, smooth muscle, and endothelial cells (71,98,132–135). Endothelin-1 is synthesized by human corpus cavernosum endothelium and elicits strong, sustained contractions of corpus cavernosum smooth muscle in vitro. This has led to the speculation that endothelin may contribute to the maintenance of penile flaccidity by providing sustained tone to the corporal smooth muscle. Endothelin are not stored in granules in the endothelial cells and their contractile effects are regulated by the continuous synthesis.

Prostanoids

Prostaglandins are products of arachidonic acid metabolism (52). Prostaglandins including PGE₂, PGE₁, PGF₂ α , and prostacyclin (PGI₂), as well as thromboxane, are synthesized in the corpus cavernosum endothelium. PGE is the only endogenous prostaglandin that appears to illicit relaxation of human corporal smooth muscle. During erection, there is a state of blood stasis in the corpora. The antiplatelet aggregating effects of PGI₂, together with those of NO, both released by the endothelium, may be important in preventing coagulation of blood during erection. It produces dose-dependent corporal smooth-muscle relaxation. PGE₁, in addition to relaxing cavernosal smooth muscle inhibits the α -adrenergic mechanism, which tonically contracts this muscle and maintains the flaccid nonerect state of the penis (118). Thus, it has dual erectogenic action. Clinically, the α -blocking effect may offset the sympathetic tone, in part responsible for psychogenic impotence. PGE₁ causes 3–10-fold increases in intracellular cAMP levels (4,50,136). This, in turn, stimulates proteinase A and ultimately, via the voltage-dependent calcium channels, decreases the intracellular free-calcium concentration and produces smooth-muscle relaxation (137). Recent evidence has shown that PGE₁ activates K-channel (138). Because tissue concentrations of prostaglandins depend upon the rate of degradation as well as synthesis, the activity of the corporal enzyme (prostaglandin 15-hydroxydehydrogenase system), which differentially inactivates PGE₁ reducing the possibility of prolonged erection/priapism (in vivo half-life of 15 min). Up to 90% of it is metabolized in one passage through the lungs (nearly completely within two passes) and it is excreted through kidneys and liver. It has recently been postulated that an active metabolite of PGE₁, now termed PGEO, has a longer half-life (1 h), is responsible for the majority of the clinical, as well as systemic, side effects (PGE₁) when administered intracavernosal (139,140).

Table 8
Penile Erectile Reflexes

	<i>Afferents</i>	<i>Central</i>	<i>Efferents</i>
Reflexogenic			
Tactile stimuli Friction of genitalia	Dorsal nerve of the penis, Pudendal nerve	Spinal (Spinal reflex pathway are also modulated by brain, e.g., tactile stimuli → (spinothalamic tract) → thalamic VLN+ ILN) → (Somatic sensory) → Postcentral gyrus	Pelvic and Cavernous N.
Psychogenic			
<i>Special sensory</i>	Thalamic	Supraspinal	Pelvic, Hypogastric, and Cavernous N.
Visual	(somatosensory and visual)	MPOA (medial preoptic area of hypothalamus)	
Auditory			
Olfactory	Rhinencephalon (olfactory)		
<i>Psychic</i>	Limbic (temporal and frontal lobe)	PVN (paraventricular of hypothalamus)	
Memory	for emotion and memory,		
Fantasy			
Construction	Hypothalamic		
Sleep erection	Endogenous neurotransmitters	Reticular activating system reticulospinal or Spinothalamic →	Pelvic, Hypogastric, and Cavernous N

MODES OF PENILE ERECTION

Penile erections are elicited by local sensory stimulation of the frenulum, glans penis, and penile skin (reflexogenic erections) and by central psychogenic stimuli received by or generated within the brain (psychogenic erections). Reflexogenic and psychogenic erectile mechanisms probably act synergistically in the control of penile erections. Central neural control pathways and mechanisms of erection information comes from observations made in paraplegic subjects and patients having impaired erection after neurosurgery.

Reflexogenic Erection (Spinal)

Reflexogenic erections are mediated by a spinal reflex pathway in which the afferent limb consists of sensory receptors in the penile skin and the glans, and the dorsal nerve that joins the pudendal nerve to reach the sacral spinal cord. The efferent limb arises in the sacral parasympathetic center and contributes fibers to the pelvic nerve, which enters the erectile tissue as the cavernosal nerve. Pudendal afferent pathways terminate in the dorsal commissure and medial dorsal horn. Interneurons in these regions are activated by tactile stimulation of the penis, and are presumably involved in transmitting sensations to the brain in addition to activating the sacral preganglionic neurons that ini-

tiate erection. The parasympathetic preganglionic neurons are located in the intermediolateral nucleus and send dendritic projections to the same regions that receive penile afferent input. Entirely reflex erections can be observed in men with complete spinal cord lesions above the sacral segments. In such men there is obviously no sensation and erection depends on a sacral cord mechanism in isolation from the rest of the central nervous system. The afferent pathway is in the dorsal nerve of the penis and the pudendal nerve. Afferent impulses activate spinal interneurons, which in turn activate the parasympathetic preganglionic neurones (S2 and S3 or spinal erection center).

Sleep Erections (Nocturnal)

Areas throughout the entire brain participate in the sleep–wake cycle. The waking state is maintained by the ascending reticular activating system (RAS), a diffuse collection of neurons within the medulla, pons, midbrain, and diencephalon. Electrical stimulation anywhere within this area causes the EEG pattern to change abruptly from that of the sleep state to that of the waking state, i.e., a cortical alerting (arousal) response takes place. The sleep state does not result from the passive withdrawal of arousal. Two sleep centers exist in the brain stem; one is responsible for producing slow-wave sleep, and the other produces REM sleep. The slow-wave sleep center is located in a midline area of the medulla containing the raphe nuclei: (a) the neurons within these nuclei use serotonin (5-hydroxytryptamine) as a neurotransmitter. (b) Administration of serotonin directly into the cerebral ventricles of experimental animals induces a state of slow-wave sleep, whereas lesions in this region induce a permanent state of insomnia. The REM sleep center is located in specific nuclei of the pontine reticular formation, including the locus ceruleus, which uses norepinephrine as a neurotransmitter. Lesions within this area eliminate the electrophysiologic and behavioral signs of REM sleep. In adults, non-REM and REM sleep alternate throughout the night. In view of the important role of the serotonin and noradrenaline in sleep, it is understandable that drugs may affect duration and/or content of sleep. Very little is known about the neural control of nocturnal penile erection (141). The current opinion is that reduced supraspinal inhibition of the spinal function is partly involved in the regulatory process.

Psychogenic Erection (Central)

Erection in response to sexual thoughts auditory, olfactory, imaginative, or visual stimuli only, without tactile stimulation, occurs in most normal men and is called psychogenic (7,28,142). Although this response is psychogenic in the first instance, it seems likely that once an erection is developing, receptors in the penis are stimulated by the tumescence, and the reflex mechanism is also activated. Psychogenic erections, initiated supraspinally, are believed to be mediated primarily via the sympathetic thoracolumbar path, although the sacral parasympathetic system may also participate in these erections. If the sacral cord is damaged, reflex erections disappear, but psychogenic erections still occur. Although it is generally assumed that the brain exerts both excitatory and inhibitory control on the spinal mechanisms for erection, the pathways for these mechanisms are still unknown. The inhibitory influence of the brain on spinal mechanisms of erection is evident in studies of spinally transected animals that show an increase in penile erection. Excitatory input from the brain to the spinal cord causing erection is not fully known. It is clear that psychogenic stimuli to the brain may also inhibit erections. Therefore, the brain must exert an important modulator influence over spinal reflex pathways that control penile erection.

The anatomic regions are not completely known but it appears that the thalamic nuclei, the rhinencephalon, and the limbic structures are involved in the modulation of psychogenic penile erections. Messages from diverse regions are integrated in the medial preoptic-anterior hypothalamic area. The cortico-subcortical region of the limbic system is implicated in the integration of inhibitory and facilitator signals connecting to the medial preoptic-anterior hypothalamic area. Efferent pathways from the medial preoptic-anterior area enter the medial forebrain bundle (MFB) and then pass caudally into the midbrain segmental region near the lateral part of the substantia nigra. Caudal to the midbrain the efferent pathway travels in the ventrolateral part of the pons and medulla reaching the spinal centers via the lateral funiculus of the spinal cord.

PENILE ERECTION AND FLACCIDITY: CENTRAL MECHANISMS

Cerebral Mechanisms

The cortex receives sensory information derived from the penis. Thalamic and cortical areas associated with somatomotor pathways elicit sexual feelings and genital sensations when stimulated, but do not illicit penile erection. By contrast, cortical and subcortical structures related to the limbic system elicit penile erection in response to stimulation in monkeys (5,143–145). Direct study of the human brain is restricted to observations made during neurosurgery. In contrast, stimulation of the amygdala, a limbic structure, can illicit erotic feelings identical to those experienced during intercourse. Analogous observations have been made in contrasting the experiences of epileptic patients with parietal lobe foci and those with mediobasal temporal foci. Damage to the fornix and perifornical area would include damaging the PVN outflow to the medial forebrain bundle during surgery, experiments have shown this is a descending pathway for erection in the monkey, and it might therefore be the site of the lesion responsible for impotence in these operations. The current hypothesis that the cortex plays a major role in general inhibition of neural activity is supported by the report of hypersexuality and penile erection in the Klüver-Bucy syndrome, owing to a lesion of the pyriform cortex and underlying structures. Nucleus para gigantocellularis (nPGi) has been studied for its role in coordination of erection control. The nPGi was consistently labeled transneuronally labeled studies experiment (146,147). In addition to receiving inputs from the MPOA and PVN, the nPGi receives dense projections from the midbrain central gray (148–151). The midbrain central gray has been shown to be an important component of the control of sexual function, and may be an important relay region for forebrain inputs as they descend to the spinal cord.

The Limbic System

The limbic system has been somewhat inconsistently described over the past few decades, but there is a general consensus that it includes cerebral and subcortical structures, such as the amygdala, septal nuclei, hippocampus, and fornix, which influence affect and emotional displays (6,152–158). The limbic system has inputs from centers in the cerebral cortex that connect through the limbic system to centers in the spinal cord controlling penile erection. Invasive studies in animals have revealed that penile erections may be induced by stimulation of the septal nuclei, mammillary bodies, and other elements of the hypothalamus (5,145). Anecdotal reports from human studies using implanted electrodes indicate that penile erection may occur with stimulation of the septal region or the medial forebrain bundle. Loci in the thalamus induce ejaculation when they are stimulated. In fact,

ejaculation may be induced independently of erection when these thalamic centers are stimulated (159). In neurologically intact men, ejaculation is presumed to involve afferent signals evoked by genital stimulation that reach the thalamus.

The hippocampus appears to act in concert with the PVN in erection. MacLean found electroencephalographic evidence of an interaction between the hippocampus and its projection to septum, MPOA, and anterior and midline thalamus (via fornix) during experimentally induced erection. Erection was frequently associated with afterdischarges in the hippocampus even though electrical stimulation had been applied in a medial structure, such as the hypothalamus. During this hippocampal activity, the erections became throbbing in character and reached their maximal size, often waxing and waning in size for 10 min following the afterdischarge. When certain diencephalic sites were stimulated, e.g., anterior thalamus, erection followed the termination of stimulation, rather than occurring with it. These rebound erections were concurrent with hippocampal discharges and are evidence of the intimate anatomical and functional organization of the inhibitory and excitatory mechanisms involved. Primary role for the medial preoptic area in integrating and eliciting sexual reflexes has been elucidated how this information is relayed through the brain to the spinal cord remains unknown.

The Medial Preoptic Area (MPOA)

Sexual behavior is dependent upon neural mechanisms involving the brain and spinal cord. The MPOA has been shown in numerous experiments to be a critically important component of the neural circuitry underlying the expression of male copulatory behavior in mammals (160–165). Destruction of the nerve cell bodies of the MPOA by a neurotoxin, which spares axons passing through the region seriously, disrupts the male animal's ability to copulate (166–169), whereas stimulation of MPOA induced or facilitated sexual behavior (160,162,163,170). MPOA contains a high density of receptors for testosterone (171) and is extensively interconnected with many other brain regions, including the limbic system, and lower autonomic brain stem nuclei (148,172–176). The MPOA is therefore capable of integrating sensory and hormonal signals that initiate sexual reflexes in male. Neuroanatomical tracing has demonstrated that axons leaving the MPOA pass through or terminate in many areas of the brain, including the MFB. Bilateral electrolytic lesions of various parts of the MFB abolish male sexual behavior. Electrical stimulation as well as microinjection of excitatory amino acids of MPOA induced rhythmic firing of pudendal motor neurones. Moreover, a unilateral electrolytic lesion of the MPOA combined with a lesion of the MFB on the contralateral side also abolishes male sexual behavior. The fact that this "asymmetrical" damage can disrupt male copulatory behavior to the same extent as bilateral damage at either the MPOA or the MFB is consistent with the concept that these structures are both components of the same system that functions to mediate male sexual behavior. Connections between the MPOA and the midbrain are also important for male sexual behavior (149–151,176,177).

The Paraventricular Nucleus of the Hypothalamus (PVN)

MacLean and Ploog (1964) (178), Wagner (179), and Chen (1997) (179–183) found the paraventricular nucleus (PVN) of the hypothalamus as sexual response center. Recent studies in men have found that oxytocin is released into the circulation during sexual activity (184). The hormone reaches maximum plasma levels at the time of ejaculation and then rapidly disappears from the circulation. Oxytocin in the circulation may therefore play a role in ejaculation or the refractory period, rather than erection. The oxytocinergic fibers

run the entire length of the cord supplying oxytocinergic innervation to preganglionic autonomic neurones, both sympathetic and parasympathetic. This could be another aspect of the PVN's role in integrating the neural inputs and outputs underlying the sexual response. Dopamine-receptor agonists, such as apomorphine, given systemically also induce erection in man and rats via an effect on the brain, probably by acting on the PVN, which contains dopaminergic neurones (181,185).

The Role of the Hippocampus

The hippocampus appears to act in concert with the PVN in erection. MacLean found electroencephalographic evidence of an interaction between the hippocampus and its projection to septum, MPOA, and anterior and midline thalamus (via fornix) during experimentally induced erection. Erection was frequently associated with after discharges in the hippocampus even though electrical stimulation had been applied in a medial structure, such as the hypothalamus. During this hippocampal activity the erections became throbbing in character and reached their maximal size, often waxing and waning in size for 10 min following the afterdischarge. When certain diencephalic sites were stimulated, e.g., anterior thalamus, erection followed the termination of stimulation, rather than occurring with it. These rebound erections were concurrent with hippocampal discharges and are evidence of the intimate anatomical and functional organization of the inhibitory and excitatory mechanisms involved.

SPINAL MECHANISMS AND PATHWAYS

The spinal cord is a major site for the regulation of erectile and anti-erectile outflows, and the coordination of autonomic with somatic pathways. In patients with spinal cord injuries above sacral segments, the stimulus of penile receptors triggers an erection via the sacral spinal reflex. These patients have poor-quality erections with premature detumescence because of the absence of supraspinal control (8). On the other hand, lesions of the sacral segments of the spinal cord, the sacral roots, the pelvic, or the pudendal nerves abolish reflexogenic erections. Psychogenic erections occur in men with complete lesions of the cord as high as T12, suggesting that the sympathetic pathway in these men mediate them.

In addition, bilateral anterolateral cordotomy in humans produces complete loss of erectile function and blocks the sensations associated with orgasm. As touch and two-point discrimination are not affected by this procedure, it seems likely that the erotic quality of genital stimulation depends on ascending fibers that run with the spinothalamic pathways for pain and temperature. In monkeys, electrical stimulation along the course of the anterolateral spinothalamic tract at the level of the brainstem elicits erection and ejaculation (186). The relevant fibers could be traced to the caudal thalamic intralaminar nuclei, which may be the receiving area for erotic genital sensation. Electrical stimulation of these nuclei in humans has been reported to cause erotic feelings and orgasm. Under normal conditions, it is likely that psychic and reflexogenic stimuli act synergistically in producing erections. Psychogenic erections in paraplegic men are usually short-lived, only partial, and lack the rigidity needed for coitus (187). There is evidence from animal experiments of an efferent hypothalamospinal pathway for erection running in the dorsal funiculus of the cord (188).

Penile erections remaining after sacral spinal cord lesion or lesion of the pelvic nerves are attributed to the sympathetic outflow. This suggests that penile erection

may be elicited by peripheral information integrated at a supra sacral level and activating sympathetic pathways (189,190). In confirmation of the hypothesis that the sympathetic outflow carries pro-erectile fibers is the report of erectile dysfunction caused by lesions of the paravertebral sympathetic chain in both humans (191). Furthermore, stimulation of the hypogastric nerves elicits penile erection in spinal-cord-injured patients.

PENILE ERECTION AND FLACCIDITY: CENTRAL NEUROPHYSIOLOGY

Enhancement of sexual drive is accomplished through the action of dopaminergic and adrenergic receptors and inhibited serotonergic receptors.

Dopaminergic Mechanisms

Five dopamine-receptor genes have been sequenced. D1 and D5 couple via Gs to activate adenylate cyclase whereas D2, D3, and D4 couple to Gi and inhibits adenylyl cyclase. There is evidence that dopamine agonists induce erection through their actions on dopamine D2 receptors. Selective D2 dopamine agonists cause penile erections. Such erections are accompanied by stretch yawning and sedation, all considered typical of central dopamine-autoreceptor stimuli. Dopamine released from supraspinal neurons facilitates male copulatory behavior. It has been shown that cerebrospinal fluid levels of dopamine increase during copulation. Intracerebroventricular administration of L-dopa (a precursor of dopamine) or apomorphine (a dopamine receptor agonist) increased sexual responses (192,193). However, high doses or intrathecally administered dopamine agonists inhibit penile erection neurones, belonging to the incertohypothalamic system, which seem to be involved in mediating the effects of dopamine agonists on erection. The evidence for this comes from microinjection studies in the rat. Injection of apomorphine into the PVN, which contains dopaminergic cells of the incertohypothalamic system, elicits erection, whereas injection into neighboring structures does not (185). Conversely, lesions in the substantia nigra (194) or the administration of dopamine receptor-blocking agents in doses that did not impair other motor behaviors, depressed copulatory behavior in rats (192). Apomorphine-induced erection is blocked by dopamine blockers as well as by agents that block oxytocin receptors. This suggests that apomorphine's effect depend on oxytocin release. Microinjection of oxytocin into the PVN also induces erection (180,195,196) and although this effect is also prevented by oxytocin receptor blockade, it is not prevented by dopamine blockade. Thus, it seems that dopaminergic neurones activate oxytocinergic neurones in the PVN of the hypothalamus, which act through oxytocin receptors to produce erection.

Serotonergic Mechanisms

Seven families of 5-HT receptors have been identified: 5HT 1–7. 5HT1 is further subdivided into 4 types denoted by the subscripts A-D. 5-HT3 receptors are unusual as they couple to cation channel, whereas the other families of 5-HT receptors all couple to G proteins. There are two pathways of 5-HT containing neurones in the CNS. One pathway, originating from the raphe nucleus, innervates various parts of the brain. The second pathway originates from the brain stem and sends axon to the spinal cord. Drugs that increase central serotonergic neurotransmission, on the other

hand, depress sexual activity. Peripherally serotonin agonists have also been shown to induce erection in both man and the rhesus monkey after intravenous injection. Serotonergic compounds appear more complex to study than either the adrenergic or dopaminergic ones, because they seem to have an inhibitory effect on sex drive centrally, but an erectogenic effect peripherally (197). Serotonin (5-HT) inhibits copulation behavior, but the effects of drugs that directly activate specific 5-HT-receptor subtypes are less certain. In general, activation (5-HT_{1A}-receptor inhibits, and activation of 5-HT₂) facilitates erection (198,199). The erectogenic effects of serotonin have been proposed to be mediated by the 5-HT_{1c}-receptor subtype (196,200,201). These effects may contribute to the induction of priapism in-patients treated with the antidepressant, trazodone, and the increase in erectile activity during REM sleep (202). Evidence for the involvement of 5-hydroxytryptamine (5HT, serotonin) was examined, because CNS injections of 5HT alter sexual function and neurons in the nPGi contain 5HT (198,203–205). Both facilitatory (198,206,207) and inhibitory (208–210) effects have been reported. Some of the confusion of the role of 5HT is caused by the large number of receptor subtypes and potential sites of action. Serotonergic nerves innervate the pudendal motor neurons and intermediate gray matter of the lumbar spinal cord (211–214). Tracing studies showed that 78% of the ipsilateral cells (15% contralateral) in the nPGi that project to the lumbar cord were immunoreactive for serotonin (211,213). Intrathecal application of 5HT caused complete inhibition of the UG reflex in mate rats. The inhibition was blocked by preadministration of methysergide, a general 5HT antagonist. In addition, removal of descending spinal serotonergic inputs, by intrathecal or intracerebroventricular injections of the 5HT neurotoxin 5,7-dihydroxytryptamine (5,7-DHT), allowed the UG reflex in the nonsignalized rat (215).

Noradrenergic Pathways

These pathways in the brain may exert an inhibitory influence on penile erection. In the CNS, the most distinct group of noradrenergic neurones is the locus ceruleus that is found in the pons. The neurones project, via the dorsal noradrenergic bundles, to innervate of the cortex, cerebellum and hippocampus. Other groups of noradrenergic neurones project via the ventral noradrenergic bundles to the hypothalamus, hippocampus, cerebellum, and spinal cord (216–220). Clonidine, an alpha-2 adrenergic receptor agonist and an antihypertensive, inhibits erections in rats (221). Moreover, impotence and decreased libido are common side effects of this medication. Conversely, yohimbine, an alpha-2-adrenergic receptor antagonist, reverses the effects of clonidine and increases sexual activity in rats but not primates, suggesting that sexual response is tonically inhibited by a central noradrenergic pathway, (222) at least in some species. Furthermore, yohimbine (blocks central presynaptic α -2 receptors resulting inhibition of norepinephrine release) increases sexual motivation.

Endogenous Opioid Peptides and Gamma Amino Butyric Acid (GABA)

Administration of opiate-receptor agonists to the CNS inhibits, whereas opiate-receptor antagonists facilitates, copulatory behavior in rats (221). Impotence, decreased libido, anorgasmia, as well as loss of the ability to achieve or maintain erection, are not uncommon with heroin- or methadone-addicted patients (223,224). Spontaneous erections, priapism, and ejaculation occur during narcotic withdrawal,

Table 9
Effects of Central Neurotransmitters on Penile Erection and Sexual Behavior

<i>Transmitters</i>	<i>Receptor</i>	<i>Secondary mediator</i>	<i>Pharmacological effect on sexual/erectile behavior</i>
<i>Dopamine</i> (<i>Antipsychotic block D2 receptor</i>)	D ₁ D ₂	Activate adenylate cyclase ($\uparrow$ cAMP $\rightarrow$ excitatory) Inhibit adenylate cyclase ($\downarrow$ cAMP $\rightarrow$ inhibitory)	Facilitate Facilitate <i>L-DOPA</i> (+) <i>Apomorphine</i> (+)
<i>Epinephrine</i> (<i>It is found in small neuronal cluster in brain stem especially medulla</i>)	α 1 (Postsynaptic)	($\uparrow$ Intracellular ca)	Inhibit
<i>Norepinephrine</i> (<i>Highest in locus ceruleus rich in β1 β2 receptor that activate adenylate cyclase (Excitatory)</i>)	α -2 (Pre- and postsynaptic)	Inhibit adenylate cyclase ($\downarrow$ cAMP)	Inhibit <i>Clonidine</i> (+) <i>Yohimbine</i> (-) (Activation of α -2 adrenoreceptor in the MPOA is associated with decrease in sexual behavior)
<i>Serotonin</i> (<i>Found in high concentration in raphe nuclei-certain antidepressant increases 5HT availability by reducing its uptake</i>)	5HT _{1A} 5HT _{1B} 5HT _{1C,2C}	($\downarrow$ cAMP) ($\downarrow$ cAMP) $\uparrow$ Phostidylinositol turnover (Similar to 5HT1-B)	Inhibitory (? Facilitatory) <i>8OH-DPAT</i> (+) Inhibit (? Facilitate) Facilitatory (direct stimulation of 5HT _{1C} and 2c causes erection) <i>m-CPP/Trazodone</i> (+)

Acetylcholine (Somatic and visceral nuclei) Enkephalins	5HT _{1D}	Similar to 5HTC1-C and linked phosphatidyl turnover (↑Inflow of Na and Ca)	Inhibit/Facilitate (Agonist inhibit erection but facilitate seminal emission and ejaculation)
	5HT ₂		
	5HT ₃	Act via G-protein	Facilitate/inhibit Facilitate
	ACh		
GABA	Nicotinic	Act via G-protein	Inhibit <i>Morphine</i> (+) <i>Naloxone</i> (-) (Inhibitory control on central oxytocinergic transmission)
	Muscarinic (M ₁ –M ₃)		
	mu	Open Cl channel	Inhibit <i>Muscimol</i> (+) <i>Bicuculline</i> (-)
Oxytocin Prolactin	GABA _A	↓ Release other neurotransmitter	Inhibit <i>Baclofen</i> (+)
	GABA _B		
			Facilitate
			Inhibit (Inhibition of dopaminergic activity in the MPOA)

(+) Receptor agonist and (-) receptor antagonist, L-DOPA: (A precursor of dopamine), Apomorphine (A dopamine receptor agonist) 8OH-DPAT: 8 hydroxy-2-(di-n-propylamino) tetralin, m-CPP: m-chlorophenylpiperazine, GABA: Gamma-aminobutyric acid

(224) as well as with opiate antagonists (e.g., naloxone and naltrexone) (225). It is conceivable that endogenous opiates production may contribute to impotence (226). The loss of the ability to achieve or maintain erection has been a noted side effect in heroin- or methadone-addicted patients. Spontaneous erections are reported side effects during treatment with the opiate antagonists: naloxone and naltrexone. Gamma-amino butyric acid (GABA) is present in higher concentration in MPOA of male rats (227,228). Both GABAA fibers and GABAB receptors have been demonstrated in the spinal dorsal horn, as well as in the vicinity of the sacral parasympathetic and bulbocavernosi motor nuclei (229,28). Administration of GABAA receptor agonists to the CNS inhibits, and administration of GABAA receptor antagonists facilitates, copulatory behavior in rats (8). Intrathecal baclofen (a GABAB agonist) reduces or abolishes tactile or reflexogenic erections, but is associated with preservation of nocturnal (REM) and psychogenic erections in humans. The levels of GABA in the cerebrospinal fluid increased many folds during the postejaculatory interval, at a time when the rats are completely refractory to sexual stimuli (230). GABA has a direct inhibitory effect on sacral preganglionic neurons (28,231). This suggests that GABA functions as an inhibitory modulator in the autonomic and somatic reflex pathways involved in penile erection.

Oxytocin

Microinjection of oxytocin into the lateral cerebral ventricle, the paraventricular nucleus or hippocampus induces erection (180,195,196,232). Oxytocin is localized in descending pathways from the hypothalamus to brain stem and spinal autonomic centres. Following sexual activity, serum and cerebrospinal fluid levels of oxytocin are elevated (223,233). These results suggest that oxytocin function as in excitatory transmitter in the hypothalamic regulation of erections (234). The action of oxytocin on neurones appears to be dependent on NO, because NOS inhibitors prevent oxytocin-induced penile erection in male rats (235). Interactions occur between dopaminergic and oxytocinergic mechanisms in the control of erection. PVN neurones have both dopaminergic and oxytocinergic receptors. Dopamine neurones in the PVN are located mainly in the proximity of oxytocinergic neurones (236,237). D2-agonists elicit a rise in oxytocin during penile erection in primates. Further, the facilitatory effect of apomorphine on penile erection can be blocked by either dopamine or oxytocin antagonists, where with direct microinjection of oxytocin into PVN, it is not prevented by dopamine blockade. Thus, it seems that dopaminergic neurones activate oxytocinergic neurones in the PVN of the hypothalamus, which act through oxytocin receptors to produce erection (238–240).

Prolactin

Long-term exposure to increased levels of prolactin suppresses sexual behavior and reduces potency in men. Prolactin also disrupts genital reflexes, leading to decreased frequency of erections in rats (241,242). This reduction of the number of erections is counteracted by spinal transection (243), implying that the disruption of genital reflexes is exerted at a supraspinal site. Ultimately, the mechanism through which prolactin inhibits sexual behavior may originate in alterations in brain dopamine. Independent of these observations, prolactin may also affect reduction in testosterone levels, which, in turn, effect neural mechanisms.

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Epidemiology of Erectile Dysfunction

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INTRODUCTION

Traditionally, the term impotence was used to describe the persistent inability to achieve erection with sufficient rigidity for penetrative sexual intercourse. However, following the National Institutes of Health (NIH) consensus conference in 1988, impotence was replaced by the broader term erectile dysfunction (ED) (1). Furthermore, the concept of successful vaginal penetration and ratio of failed attempts has been excluded (2). ED then, is the consistent inability to maintain a penile erection sufficient for adequate sexual relations (1). The effects of ED are profound and far-reaching, interfering with a man's self-esteem, interpersonal relationships, and overall sense of well-being (3). One study estimated that ED affects 10–20 million men (4,5). Additionally, ED accounts for more than 400,000 outpatient visits, 30,000 hospital admissions, and a total financial burden of approx 146 million dollars annually in this country (6). These figures, published in 1985, have likely increased dramatically given the recent explosion in public interest and media exposure with the FDA approval of sildenafil citrate and public testimonies of many prominent political and sporting figures. Data from the National Health and Social Life Survey (NHSLS) published in early 1999 suggests that nearly one-third (31%) of men have some form of sexual dysfunction, a broad term encompassing seven different sexual problems, of which ED is one. These data further support the fact that sexual function is highly associated with overall well-being and dysfunctions represent a problem warranting recognition as a significant public health concern (7).

Large, well-conducted epidemiologic studies on ED have been few. Early studies failed to properly address such critical elements as methods of patient selection, stratification of

patient populations by age, physiologic correlates, and even inconsistencies in the very definition of ED (8). However, the Massachusetts Male Aging Study (MMAS) provided the first robust epidemiologic data based on a large, general population. Furthermore, we now have long-term follow-up data from the MMAS to help solidify our understanding of the effects of ED (9). In this chapter, we present the current understanding of the epidemiology of ED along with the longitudinal results of the MMAS study (9).

EPIDEMIOLOGIC STUDIES

Kinsey et al. were the first to report on the prevalence of sexual dysfunction (10). Data from this study revealed an increasing rate of ED with age. Based on interviews with 12,000 men stratified for age, occupation, and education, Kinsey reported the prevalence of ED as <1% in men under 19 yr of age, 3% under age 45, 7% under 55, and 25% by age 75. Interestingly, Kinsey's data was subsequently reanalyzed by Gebhard, who found that 42% of more than 5000 men interviewed had some degree of erectile difficulty (11).

The NHSLs is the first population-based assessment of sexual dysfunction since Kinsey et al. (7). The NHSLs study was based on a national probability sample of sexual behavior in a demographically representative cohort of U.S. adults and included 1749 women and 1410 men aged 18–59 yr. The goal of the study was to quantify the risk of experiencing sexual dysfunction while describing the resultant consequences of that sexual dysfunction. Data from the NHSLs was obtained through a 90-min personal interview by a socially matched interviewer. Sexual dysfunction was detected through the use of seven “yes or no” response items representing a symptom or problem within the preceding 12 mo. Survey items included:

1. Decreased libido;
2. Erectile dysfunction in men and inadequate lubrication in women;
3. Inability to achieve orgasm;
4. Sexual performance anxiety;
5. Premature orgasm;
6. Physical pain during sex; and
7. Lack of enjoyment of sex.

The results of the NHSLs suggest that increasing age is associated with erection problems and decreased libido in men. Additionally, unmarried men have much higher rates of most types of sexual dysfunction than do married men. Higher educational level seems to decrease the risk of sexual dysfunction. The NHSLs also reports that although the variation among race and ethnic groups are modest at best among men, African-Americans are most likely to experience sexual dysfunction in general, whereas Hispanics are less likely to have problems.

Several other studies based on general populations are weakened by either sampling bias or inability to quantify the method of data collection (12). The results are widely variable and of questionable significance. Ard reported a 3% incidence of erectile difficulty among 161 couples married for more than 20 yr (13). Frank reported that 40% of men, married and sexually active with a mean age of 37 yr, had problems with either erections or ejaculation (14). Nettelbladt subsequently found that a similar number of random sexually active males with a mean age of 31 yr had some degree of ED (15). Erectile impairment in other studies range widely from 3% to 40% (12,16,17). The

Baltimore Longitudinal Study of Aging cited rates of erectile impairment ranging from 8% in men under 55 yr to 75% in men 80 yr or older (18). The Charleston Heart Study reported that sexual inactivity increases markedly with age (19). Schein reported that 27% of 212 primary care patients experienced decreased erectile function (20). Erectile problems are associated with self-reported poor health, a phenomenon that is exacerbated with increasing age (21). Morley reported that more than one-fourth of men aged 50 yr undergoing general health screening had ED (22). This concept that medical conditions are associated with a higher incidence of ED is further supported by Masters and Johnson (2) and Slag (23).

Regarding patient referral patterns, knowledge base, and expectations, Mulhall in 1994 studied 100 consecutive new patients in an ED clinic and concluded that most patients are referred by primary care physicians. Patient knowledge base was thought to be generally poor, although this may be changing in recent times owing to the increased media attention given to ED along with the ever-increasing patient access to the internet. Embarrassment still is the major deterrent to patient presentation accounting for approx two-thirds of the reasons for procrastination in presentation for evaluation (24).

The MMAS was a community-based survey of health and aging in men, conducted from 1987 to 1989 (8). Data from the MMAS was used to measure the prevalence of ED in a population of healthy aging men, while at the same time determining the effects of aging on the incidence of ED. The study also attempted to ascertain the role of certain age-related health issues as they affect ED and identify which variables affected ED aside from normal aging.

Respondents to the MMAS consisted of 1290 men aged 40–70 yr. Data was collected using a detailed questionnaire administered in patients' homes. The survey contained 23 questions, 9 of which were related to potency. The cohort studied was believed to represent the general population as closely as possible, taking care to sample random, healthy men with limited contact to the health care system. Racial minorities were appropriately represented.

The MMAS was conducted using a multidisciplinary approach, including sexual dysfunction specialists, gerontologists, social and behavioral scientists, and endocrinologists. The subjective data from the MMAS was then linked to a calibration study, which provided a direct assessment of potency status (25). Potency was then described in terms of four degrees with increasing severity: none, minimal, moderate, and complete.

According to the MMAS, the overall probability of some degree of ED was 52%. The majority of affected respondents had moderate ED (25%), followed by minimal (17%), and complete (10%). An estimated 40% of respondents experienced ED at age 40, whereas 67% had difficulties by age 75. The incidence of complete ED was 5% at 40 yr and 25% at 75 yr. Based on these data, more than 30 million men in the United States and 100 million men worldwide may have some degree of ED.

Several medical conditions were strongly associated with changes in the probability of ED after adjustment for age. These conditions included heart disease, hypertension, diabetes, arthritis, untreated ulcers, and untreated allergies. Certain medications, such as vasodilators, hypoglycemic agents, cardiac drugs, and antihypertensives, were also found to be associated with an increased probability of ED. Respondents with psychological issues including anger and/or depression had higher probabilities of moderate and complete ED. Cigarette smokers also had a markedly amplified risk of ED, with more than half of current smokers (56%) affected by erectile difficulties, whereas only 21% of nonsmokers were affected. Variables that were inversely correlated with the

probability of erectile difficulty included the presence of a dominant personality type, serum HDL levels, and serum dehydroepiandrosterone level.

Longitudinal results from the MMAS were recently published by Johannes et al. (9). This study estimated the incidence of ED in men aged 40–69 yr during a follow-up period of nearly 9 yr. The analysis sample was comprised of 847 men who completed follow-up and had no ED at the beginning of the study. ED was assessed using 13 questions from a self-administered sexual function questionnaire and one global self-rating question. Johannes et al. concluded that the risk of ED was about 26 cases per 1000 men per year. The data also suggested that risk of ED increased with age, heart disease, hypertension, and lower level of education. Extrapolation of this new data suggests that more than 600,000 new cases of ED should be expected annually in the United States.

RISK FACTORS FOR ERECTILE DYSFUNCTION

Vasculopathy

The relationship between vascular disease and ED is well established. Both arterial insufficiency and corporo-venocclusive dysfunction (venous leak) are common causes of ED (26). Patients with a history of heart attack, peripheral vascular disease, and hypertension all have a higher incidence of ED when compared to the general population. Myocardial infarction (MI) and coronary artery bypass surgery have been associated with ED in 57–64% of patients (27,28). The incidence of MI is 12% when patients are shown to have abnormal penile-brachial index (PBI), but only 1.5% in those with normal PBI (29). As many as 80% of men with peripheral vascular disease experience ED (30). One in 10 men with untreated HTN have erectile difficulties (31).

Diabetes (DM) is also associated with a higher incidence of ED at all ages when compared to the general population. With its associated microvasculopathy, between 35%–75% of all men with DM experience ED (31). In fact, 12% of newly diagnosed diabetics have erectile difficulties (32). Men with Type I diabetes have a higher incidence of ED than do those with Type II (33,34). About half of patients who develop diabetic ED do so within 5–10 yr of their initial diagnosis of DM (35,36). Patients with DM and HTN have an even higher risk of ED (37). It has been shown that the probability of ED increases with each vascular risk factor a patient possesses, including cigarette smoking, elevated cholesterol, DM, and HTN (38). This concept was further supported by the finding that vascular risk factors were more common in a group of 400 men with ED as compared to the general population (30).

Endocrinopathy

The role of androgens in the erectile response is unclear (33,39–43). Androgens are central to the growth and differentiation of the male genitalia and development of secondary sex characteristics. Although testosterone is involved in both libido and nocturnal tumescence, its role in reflex erections and/or lack thereof is not certain. Whether serum testosterone determination is a useful screening tool for ED is controversial (23,44). Furthermore, no clear consensus exists on the utility of free vs total testosterone levels in the setting of evaluating the impotent patient (45). Despite this, approx 5% of all organic ED is probably secondary to endocrinopathy (46). Examples of endocrinopathies that can lead to ED include hyperprolactinemia (with the resultant depression of LH secretion), hypogonadism, hypothyroidism (leading to secondary

Table 1
Medications Associated with Erectile Dysfunction

Antihypertensives	Beta-blockers Calcium-channel blockers Diuretics Ganglion-blockers Spironolactone
Cardiac	Antilipidemics Digoxin
Psychotropics	Butyrophenones Lithium Monoamine oxidase inhibitors Phenothiazines Selective serotonin-reuptake inhibitors
Hormones	Antiandrogens Estrogen Luteinizing hormone-releasing hormone (LHRH) agonists Progesterone 5 α -Reductase inhibitors
Anticonvulsants	
H ₂ Antagonists	
Miscellaneous	Alcohol Amphetamines Beclofen Metoclopramide Opiates

hypogonadism), hyperthyroidism (leading to elevated serum estradiol levels), DM, and adrenal disorders (involving alterations in androgen secretion).

Medications

Drug-related ED is prevalent; there are many medications that have been associated with ED (Table 1). Up to 25% of patients followed in a general medical clinic have been diagnosed with medication-induced ED (23). The most commonly implicated medications are antihypertensives (ED cited in 4–40% of patients) (47–51). These medications may act centrally or peripherally, through actions on the autonomic nervous system or merely by dropping the blood pressure below that required to maintain intracorporal pressure and penile rigidity.

Drugs with antiandrogen effects may also cause ED, including luteinizing hormone-releasing hormone (LHRH) agonists, H₂-blockers, estrogens, and spironolactone (52–54). Digoxin increases tone in corporal smooth muscle via its actions on the Na⁺-K⁺-ATPase pump, leading to ED (55). Psychotropic medications, including antidepressants and others, act centrally to potentially produce erectile difficulties (56–59). Alcohol and other recreational drugs have been linked to ED when used chronically (60–63). In the end, the diagnosis of drug-induced ED can be difficult and requires a direct temporal relationship between administration of the drug and ED in addition to improvement in erections with stopping the medication (47).

Chronic Illness

Most of the major medical conditions associated with ED have previously been discussed; however, there are several other chronic illnesses which may lead to erectile difficulties. Renal failure is commonly associated with ED. As many as 40% of men with renal failure have some degree of ED (64). Endocrinologic factors such as hypogonadism and hyperprolactinemia, diabetic neuropathy, and vasculopathy may all play a role in the erectile difficulties of renal failure patients (65). Renal transplantation may, but certainly does not always, improve erectile function (66–68).

ED has been associated with stroke (18), CNS tumors/infection, Alzheimer's disease, multiple sclerosis (MS), and temporal-lobe seizure disorders (69). One study reported 85% of men to experience ED after stroke (70), although Goldstein demonstrated that nearly three-fourths of men with MS have ED (71). AIDS-associated autonomic neuropathy may also cause neurogenic ED (72). According to Fletcher et al., chronic obstructive pulmonary disease (COPD) may be the primary causative factor of ED in a subset of men who have normal peripheral and penile pulses by Doppler (73). The mechanism by which this may occur is undetermined. The microvasculopathy caused by scleroderma may also cause ED (74), although chronic liver failure has been associated with erectile impairment in as many as 50% of patients. Interestingly, patients with alcoholic hepatic dysfunction are more likely to develop ED than those with some other etiology of liver disease (75).

Trauma

Pelvic fractures and injuries to the perineum are associated with ED. Specifically, straddle-injuries or pelvic fracture resulting in disruption of the prostatomembranous urethra are associated with ED in as many as 50% of cases (76). Goldstein reported on 35 patients with a history of trauma and ED, postulating that the mechanism is compressive injury to common penile arteries (77). Several urologic procedures are linked to ED. These include radical prostatectomy (both retropubic and perineal), regardless of nerve-sparing approach (78–82), TURP (83,84), internal urethrotomy (83,84), perineal urethroplasty (85), and pelvic extenteration (86). Recently, much attention has been focused on cycling-induced ED (87). There is little doubt that the common penile arteries traverse the ischiopubic ramus and may be compressed between a narrow, unpadded bicycle saddle and the bone. Mechanistically, nondenuding endothelial trauma may result in endothelial dysfunction or luminal stenosis. Chronic trauma may therefore lead to arterial occlusive disease. Goldstein et al. reported on the incidence of sexual dysfunction in young males in a cycling club in Boston, MA, and compared the figures to those of aged-matched members of a running club and demonstrated a three-fold higher incidence of sexual complaints including ED in the cyclists (4.2% vs 1.4%) (88). Although there is a rational scientific basis for penile artery compression-induced erectile function alteration, true cause and effect have yet to proven.

Psychological Issues

Historically, ED was thought to be from psychogenic causes in the majority of men. Recent data has shown that although most men now have an identifiable organic cause, psychological issues play a significant role in select patients. The association between depression and ED (aside from medications) has been demonstrated by several researchers (89–91). Marital relationship stress has also been shown to be a significant

factor in the presence of ED (92). Finally, as aforementioned, the MMAS has shown that various psychological factors such as depression, anger, and lack of dominance can affect erectile function (8). There is a clear association between depression and ED. Furthermore, it has been demonstrated that the successful treatment of the ED can significantly improve depression scale scores in men with ED and subsyndromal depression (93,94).

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3

How A Primary Care Clinician Approaches Erectile Dysfunction

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THE NATURE OF PRIMARY CARE

Primary care clinicians are the first point of contact with the health care system for many people. Although this care may be episodic or involve only a single visit initiated to meet a specific need, primary care clinicians usually provide continuous and comprehensive care for patients using a biopsychosocial model. This involves learning more about a patient than just their chief complaints and most superficial needs.

It sounds like primary care clinicians are expected to do everything! The health care-provider role is often expanded to that of advisor, social worker, advocate through the health care system, religious counselor, confidant, and, of course, trusted clinician. In

Table 1
Limitations Faced By Primary Care Clinicians

-
1. Time
 2. Payer demands
 3. Standards and guidelines
 4. Patient expectations
 5. Reimbursement issues
 6. Personal needs and areas of interest of the clinician
-

Table 2
Primary Care Clinician Priorities

-
1. Problems with high morbidity and mortality
 2. Disabling conditions
 3. Standards of care and guidelines
 4. Improve quality of life
 5. Patient demands
 6. Personal needs areas of interest of the clinician
-

trying to reach this lofty role, primary care clinicians are encumbered by several limitations (Table 1).

Primary care for adults is provided by a variety of clinicians including nurse practitioners, physicians' assistants, family physicians, internists, and gynecologists. The approaches may vary, and the scope of inquiry and treatment may depend on local law and care standards in various communities. The values and roles of individual clinicians are also complex because they may depend on the individual's value system and practice model (1). However, the priorities in determining what issues will be addressed during a visit or a course of care are generally similar for all primary care clinicians (Table 2). Most primary care clinicians will routinely address problems with high morbidity and mortality, disabling conditions, conditions for which there are clear standards of care, and perhaps those with well-established management guidelines. The demands of their patient and the personal interest of the clinician will also affect the choice of issues that the clinician addresses.

Issues that involve quality of life fall into a slightly lower priority category. Patients may not feel that they are important or clinicians do not recognize "improving quality of life" as being a high priority. This is especially true when the quality-of-life issue involves very personal issues and more difficult language. For example, arthritic pain, when it is not disabling, is a quality-of-life issue that clinicians readily address. The language to discuss arthritis is well known, and management guidelines are readily available. Addressing quality-of-life issues around sexual dysfunction are far more difficult; partly because there are more complex psychosocial issues involved than there are with pain. Perhaps more importantly, the language is more difficult and treatment is not well standardized. Social taboos about discussing sex or considering sex a legitimate personal need also hinder communication about sexual dysfunction.

TRENDS IN PRIMARY CARE INVOLVEMENT IN SEXUAL HEALTH

Many factors have changed the work of primary care clinicians in the recent past. Trends in population demographics, the aging of patients, managed care, and medical technology have altered demand and actual primary care activity. Results from the National Ambulatory Medical Care Survey (NAMCES) revealed that the mean age of patients visiting primary care clinicians has increased and patients have become more ethnically and racially diverse (2). The duration of visits to the doctor is decreasing with a recent study of the length of ambulatory visits to primary care clinicians having a mean of 16.3 min (3), possibly associated with the availability of nonphysician support personnel and with the prevalence of health maintenance organizations as payers. Other changes in primary care practice include an increase in single-specialty and multispecialty group practice, computerization of the office, more complex reimbursement methods, and an increasingly educated patient population. These changes, in the eyes of many, have occupied some of the energy that would better be turned toward patient care and prevention of disease.

Health care clinicians have been ambivalent about sexuality for a long time. Most early research was done by nonphysician social scientists (4). Under the influence of Sigmund Freud, psychiatrists became the sex experts. The work of Alfred Kinsey in the late 1940s, a nonphysician, also bolstered the social and behavioral sciences as the location for sexual studies. Between 1960–1970, William H. Masters, a physician, teamed with Virginia E. Johnson to research the sexual response leading to more physician interest. Even now, however, medical school instruction is limited to:

1. Some anatomy and physiology,
2. Information about AIDS and sexually transmitted diseases, and
3. Lectures on “alternative” life styles such as homosexuality.

There remains a conspicuous absence of courses on sex in general. This lack of recognition of the importance of sexual activity in a person’s life, as well as the discomfort many clinicians have in discussing sex with patients, have made office discussions difficult. Clinicians avoid discussing sexual concerns even when a problem is suspected, citing lack of knowledge and skills as a common reason (5). Clinicians may be concerned that a sexual dysfunction like erectile dysfunction (ED) will become a complex, time-consuming condition that cannot be managed properly under pressures of current reimbursement methods (6).

Recent years have seen a change in this attitude among clinicians and society in general. The motivation for primary care clinicians to help patients with sexual dysfunction should be high. General sexual dissatisfaction is very high among men, reported at a rate of 75%, noting at least one problem with dissatisfaction, avoidance, infrequency, or noncommunication (7). Specific sexual dysfunction is also prevalent, reported in approx one-third of men over age 18, with premature ejaculation is the most common sexual dysfunction reported by men followed by ED (7,8).

Experiencing a sexual dysfunction is highly associated with a number of unsatisfying personal experiences and relationships. Men with ED experience a diminished quality of life when measured as low physical satisfaction, low emotional satisfaction, and low general happiness (9). Reports of low self-esteem and relationship difficulties indicate the effect of ED on function and satisfaction with daily life activities. There are also some preliminary reports that sexual dysfunction can contribute to initiating

Table 3
Reimbursement for ED Management

ICD-9 codes for ED
607.84 – secondary to organic disease.
302.72 – related to nonorganic or unspecified causes.

clinical anxiety and depression syndromes. If “morbidity” is defined as the consequences resulting from an abnormally functioning, diseased organ or body system, then ED clearly has a recognizable morbidity. Older couples naturally want to continue to share an active sex life, less because of sexual drive but more related to the giving of comfort and security that comes as a result of intimacy.

Primary care clinicians are recognizing that (6):

1. The longitudinal and personal relationship they have is an asset in discussing and resolving sexual problems,
2. The multifactorial issues around ED are appropriately evaluable by the patient’s clinician, and
3. The long-term follow-up to be certain that a sexual dysfunction is resolved is well suited to primary care.

Most insurance carriers provide reimbursement for evaluation of ED, although patients should understand that there might be some limitations on payments for testing and treatment. Careful documentation of the need for tests will help obtain fair reimbursement. Generally, reimbursement is more likely if the sexual dysfunction occurs secondary to a comorbid organic condition such as diabetes, cardiovascular disease, or pelvic trauma. The ICD-9 codes for ED are noted in Table 3.

LEARNING TO COMMUNICATE WITH PATIENTS
ABOUT SEXUAL ACTIVITY

Discussing sexual matters with patients and helping them to resolve problems is a satisfying activity for primary care clinicians. Men have misconceptions about ED that make them less likely to come to the clinician’s office for help (Table 4). Patients are often grateful following discussions about sexual matters and show such gratitude with increased enthusiasm for better health and with increased loyalty to their clinician. They are very appreciative of the clinician’s willingness to listen and, often, a new level of patient–clinician relationship is reached in which conversation flows more easily and trust allows an enhanced co-management of other clinical problems. This “affiliative” communication style including friendliness, interest, empathy, a nonjudgmental attitude, and a social orientation is associated with significantly higher patient satisfaction (10). More overall communication, including social conversation, and more partnership building have also been related to greater patient satisfaction (11). A skilled clinician can “titrate” his/her use of control in an encounter according to the patient’s needs by understanding that less-controlling behavior can result in improved patient satisfaction and compliance (12).

The language involved in discussing sex is becoming more openly used and clinicians are learning ways to make these discussions easier in their offices. Techniques can be adopted to make the office a more comfortable place for discussion about sex (Table 5). An office in which the patient feels comfortable and welcome encourages

Table 4
Men's Misconceptions about ED (Adapted from 9a.)

-
1. Matters relating to sexual dysfunction are taboo.
 2. Loss of erection is not a common problem, and their problem is unique.
 3. Erectile dysfunction is a normal part of aging.
 4. Inability to achieve erections is primarily a psychological problem and not a physical one.
 5. Treatment options are generally lacking or are too I invasive and risky to be pursued.
-

Table 5
Making Discussions About Sex Easier in the Office

-
1. Encourage a warm, open and nonjudgmental atmosphere.
 2. Introduce the topic of sexual activity.
 3. Initiate and engage in discussion whenever appropriate.
 4. Offer help.
 5. Be optimistic about resolving sexual problems.
-

open conversation. Clinicians who engage patients in some discussion about psychosocial topics in addition to their immediate clinical problems promote openness and a feeling of caring, often improving patient satisfaction with the visit (13).

The office staff also needs to be ready to answer questions. They need to understand the importance of being sensitive in discussions and for the need for privacy during educational sessions.

SCREENING FOR ED

Screening male patients for ED is valuable to minimize the morbidity of ED. For screening to be useful it must:

1. Utilize a tool that is reliable,
2. Achieve earlier identification enhancing the likelihood of resolution, and
3. Provide a yield that is higher in value than its costs.

Because the yield of screening is related to the frequency of ED in the population, men who should be screened include: those over 40 yr of age, those with a predisposing comorbidity such as cardiovascular disease, diabetes, or depression, or anyone else who the clinician feels may be having difficulty with physical intimacy. Incorporating screening into the primary care practice becomes even easier when the clinician adopts a policy of briefly asking all patients who may be sexually active about sexual activity. This develops a habit of discussing sex in the office and helps patients understand that the topic can be raised by them at any time there is an issue.

Patients with sexual concerns report feeling most comfortable discussing these issues with their family clinician and expect to receive advice and treatment (8,14,15). Although more than 70% of adult patients in a large sample considered sexual matters to be an appropriate topic for the generalist clinician to discuss, and the rate of sexual dysfunction considered to be 35% for adult men and 42% for adult women, evidence of discussion about sexual problems is present in as few as 2% of generalist clinician's notes (1,16).

Introduction of sexual activity as a legitimate topic for conversation with patients can be done passively or actively. Examples of passive approaches to engaging the patient

Table 6
Sexual Health Inventory for Men (SHIM) (©Pfizer Inc.)

PATIENT INSTRUCTIONS

Sexual health is an important part of an individual’s overall physical and emotional well-being. Erectile dysfunction, also known as impotence, is one type of very common medical condition affecting sexual health. Fortunately, there are many different treatment options for erectile dysfunction. This questionnaire is designed to help you and your doctor identify if you may be experiencing erectile dysfunction. If you are, you may choose to discuss treatment options with your doctor.

Each question has several possible responses. Circle the number of the response that **best describes** your own situation. Please be sure that you select one and only one response for **each question**.

OVER THE PAST 6 MONTHS:

1. How do you rate your confidence that you could get and keep an erection?

Very low

Low

Moderate

High

Very high

1

2

3

4

5
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?

No sexual activity

Almost never or never

A few times (much less than half the time)

Sometimes (about half the time)

Most times (much more than half the time)

Almost always or always

0

1

2

3

4

5
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner)?

Did not attempt intercourse

Almost never or never

A few times (much less than half the time)

Sometimes (about half the time)

Most times (much more than half the time)

Almost always or always

0

1

2

3

4

5
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?

Did not attempt intercourse

Extremely difficult

Very difficult

Difficult

Slightly difficult

Not difficult

0

1

2

3

4

5
5. When you attempted sexual intercourse, how often was it satisfactory for you?

Did not attempt intercourse

Almost never or never

A few times (much less than half the time)

Sometimes (about half the time)

Most times (much more than half the time)

Almost always or always

0

1

2

3

4

5

SCORE _____

Add the numbers corresponding to questions 1–5. If your score is 21 or less, you may want to speak with your doctor.

Table 7
Indirect Ways to Engage Patients about Sexual Function

-
1. Brochures or SHIM in the waiting room
 2. Posters or displays in the examining room
 3. Ancillary staff discussions
 4. Lapel buttons
 5. Put a little informality into your office!
-

Table 8
Questions to Initiate Discussions about Sexual Activity

-
- Open-Ended Questions:
- “So how are you doing with sex lately?”
- “Are you satisfied with your sexual activity?”
- Permission-Giving Questions.
- “Many of my male patients your age have noticed some change in their sexual function. How about you?”
- “Many men with diabetes note some problems getting an erection. Are you noticing anything different?”
- Asking the partner:
- “How has sex been lately?”
- “How has (name) been functioning?”
- Asking men with chronic illnesses:
- “How has your illness affected your sex life?”
-

would include leaving pamphlets about sex-related topics or self-evaluation material (such as the Sexual Health Inventory for Men – Table 6) in the waiting room, hanging educational posters in patient care areas, or using other cues that encourage discussion of sexual activity (Table 7). Inclusion of one or more questions about sexual activity in a printed history form completed by the patient requires more active patient participation by requiring the willingness to document that a problem exists.

Clinicians initiate more of the verbal interaction and control the content, pace, and length of the interview (17). A truly active approach to initiating discussions about sexual activity is probably the most efficient discussion-initiating technique (Table 8). Clinicians should develop an ease with one of these more active approaches and incorporate it into discussions with patients (18). Questions about sexual matters are appropriate either:

1. During the initial formal history,
2. During the review of systems,
3. During a follow-up visit, or
4. During the physical examination of the inguinal area and the testicles.

Making a habit of asking these questions decreases anxiety, encourages the “routinization” of sex discussions reducing possible embarrassment, and makes screening for sexual dysfunction more efficient. Using synonyms such as “getting hard” or “coming” may help the patient better understand questions about erections. Questions about sexuality need to be sensitive to cultural, religious, and educational differences. Using terminology that is clear, simple, and respectful of the patient’s feelings can facilitate communication.

Once the patient begins to talk about a sexual problem, the clinician can facilitate the discussion using facilitation techniques well known to primary care clinicians. These include eye contact when appropriate with the patient, repeating some of the patient's major points, shaking the head up and down encouraging the patient to say more, and expressing optimism that the problem can be resolved.

Asking sexual partners about each other's sexual function is often very useful. Women ranked "partner sexual difficulties" as a common sexual concern (19). If both members of a couple are in the office, it becomes easy to introduce the topic by asking "How are you two doing together? ... How are you doing with sex?" If only one member of a couple is available, questions can still be asked both about the present patient, as well as the partner. When a sexual dysfunction is identified, talking to the partner can reveal a different picture that may substantially affect management, and can also have a therapeutic effect (20). Relationships have a profound effect on sexual health and often need to be explored to amplify the likelihood of successful resolution of the problem.

PATIENTS AND PARTNERS INITIATE DISCUSSIONS ABOUT SEX PROBLEMS

If the patient or partner initiates discussion about sex or has a specific question this will require attention equal to that of other patient complaints. If the clinician is lucky, the concern will be voiced early in the visit allowing for some exploration of the issues. More often, if the patient or partner is not asked about sexual issues, they will bring up problems at the end of the visit. Although this may seem like an afterthought, for many it may be one of the major (if not *the* major) reasons for the visit. An initial impression that their problem is being dismissed can considerably delay or prevent them from seeking further help (21). If inadequate time exists to discuss the issue at that time, recognition should be made of the patient's problem or concern and another time should be scheduled to discuss it further. Just spending time clarifying the nature of the problem can lead to more effective treatment and may, in itself, be therapeutic (21). Alternatively, the patient can be given a referral to another clinician if the primary care clinician is uncomfortable, but even a proper referral requires some further exploration.

Optimism is an essential dialog, as well as management tool, for clinicians in responding to sex issues. Patients often seek help after the problem has been around for a long time, and they need encouragement both to discuss it and to believe that it can be resolved.

BARRIERS PREVENTING MEN FROM DISCUSSING ERECTILE DYSFUNCTION

Men are often hesitant to discuss sexual problems with their clinicians because of embarrassment, ignorance or misinformation, and lack of financial means. Men consult family physicians for health-related problems less frequently than do women, thus reducing the chance of disease recognition and treatment (22). This results in men receiving less preventive care, screening, and tests. Counseling rates for sensitive topics such as sexual health and emotional well-being are especially low (22).

Research on why men do not make visits to family doctors for help revealed several key themes to explain this behavior (23). These themes included: 1) support seeking, 2) help seeking, and 3) barriers (Table 9). Potential barriers to health action also include poor relationships with doctors (24). This research on male reticence to discuss health concerns with a health professional supports the strong role played by the female part-

Table 9
Themes of Why Men Don't Seek Help [Adapted from (25)]

-
1. Support- Men get health concern support from female partners, little from male friends. Support seeking is indirect rather than straightforward.
 2. Help seeking- Men are influenced by perceived vulnerability, fear, and denial. Help is sought for specific problems rather than for general health concerns.
 3. Barriers- Sense of immunity and immortality, difficulty giving up control, belief that seeking help is unacceptable. Time and access, having to give reason for visit and lack of male care provider are also seen as barriers.
-

ner in determining health-seeking behavior. Men often come to a visit with their clinician with no complaints or just general complaints and wait for the clinician to find out why they are really there. David Sandman, co-author of the Commonwealth Study said "Physicians can be more attuned to the special health concerns of their male patients and be more proactive in initiating communication,"(25).

Men need to be offered more comprehensive care and counseling at any visit that occurs. Men often perceive their clinicians as rushed and uninterested in communication. Even though discussing ED may be embarrassing and difficult for the patient, most men are comfortable and willing to discuss their sexual function with primary care clinicians. It is unfortunate that surveys report that books, not health professionals, are the number one source of sex information reported by people age 45 and older (26).

Disabled patients are another group whose sexual difficulties are often overlooked. Either physical injury or physiologic trauma from a disabling condition can affect sexual function. These disabling conditions can be congenital or acquired. The process of approach and management of these two differing types of disability require sensitivity and care. Patients who become disabled in adulthood are much more aware of what has been lost. Loss of erectile function is the commonest sexual problem among disabled male patients (27). Discussion about sexual activity is essential in patients with any type of disability.

EVALUATING THE MAN WITH ED

A complete evaluation will often find likely etiologic factors for ED (Table 10). The evaluation of ED follows the same pattern as evaluation of any medical disorder. This includes a pertinent history, physical examination, and laboratory tests. This history, however, must include a sexual history. A well-organized brief sex history can be an effective diagnostic tool. Questions generally review the phases of male sexual response (Table 11) and focus on problems of desire, arousal/erection, orgasm/ejaculation, and sexual pain. Offering the patient several phrases that describe the same phenomenon in different ways can make the communication clearer (28).

For desire phase disorder—"Do you still feel in the mood, feel desire, have sexual thoughts or fantasies?" ED preceded by loss of desire can signal hormonal problems, relationship difficulties, medication adverse effects, and depression. It is difficult for most men to sustain an erection if they feel no desire.

For arousal/erection difficulties—"Do you have trouble getting or keeping an erection, getting or keeping hard? Or both?" An easy method of distinguishing most psychogenic ED disorders from potentially organically induced disorders is to ask if the patient ever has a spontaneous or sexually induced erection at any time? A positive

Table 10
Causes of ED and Diagnostic Clues

<i>Cause</i>	<i>History</i>	<i>Physical Examination</i>	<i>Possible laboratory findings</i>
Vascular	Coronary artery disease; hypertension; claudication; dyslipidemia; smoking	Decreased pulses; bruits; elevated blood pressure; cool extremities	Abnormal lipid profile Abnormal penile-brachial pressure index
Diabetes mellitus	Known diabetes; polyuria; polydipsia; polyphagia	Peripheral neuropathy; retinopathy; abnormal body mass index	Abnormal fasting blood glucose Elevated glycosylated hemoglobin Proteinuria Glycosuria Hypertriglyceridemia
Hypogonadism	Decreased libido; fatigue	Bilateral testicular atrophy; scant body hair; gynecomastia	Decreased morning free testosterone Increased LH Increased FSH
Hyperprolactinemia	Decreased libido; galactorrhea; visual complaints; headache	Bitemporal hemianopsia	Elevated prolactin Abnormal CT or MRI scans of pituitary gland
Hypothyroidism	Fatigue; cold intolerance	Goiter; myxedema; dry skin; coarse hair	Increased TSH Decreased free T ₄
Hyperthyroidism	Heat intolerance; weight loss; diaphoresis; palpitations	Lid lag; exophthalmos; hyperreflexia; tremor; tachycardia	Decreased TSH Increased free T ₄
Cushing's syndrome	Easy bruising; weight gain; corticosteroid use	Truncal obesity; "moon face"; "buffalo hump"; striae	Elevated overnight dexamethasone suppression test

Alcoholism	Excessive alcohol use; social, economic or occupational consequences of alcohol abuse; withdrawal symptoms	Positive CAGE screen; thin body habitus; palmar erythema; spider telangiectasias; gynecomastia; tremor	Abnormal hepatic transaminases Decreased albumin Macrocytic anemia
Neurologic	Spinal cord injury; nerve injury (prostate surgery); stroke; peripheral neuropathy; incontinence; multiple sclerosis; Parkinson's disease	Motor or sensory deficits; aphasia; gait abnormality; abnormal bulbocavernosus reflex; tremor	
Mechanical	Genital trauma or surgery; Peyronie's disease; congenital abnormalities	Fibrous penile plaques or chordae	None
Psychogenic	Nocturnal erections; sudden onset; history of depression; anhedonia; poor relationship with partner; anxiety; life crisis	Sad or withdrawn affect; tearful; psychomotor retardation	Nocturnal penile tumescence (stamp test; Snap-Gauge)
			Positive depression inventory (Beck's)
Pharmacologic	Inquire about all prescription and nonprescription drugs		

LH = luteinizing hormone; FSH = follicle-stimulating hormone; CT = computed tomographic; MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone; T₄ = thyroxine; CAGE = Have you ever felt you ought to Cut down on your drinking? Have people Annoyed you by criticizing your drinking? Have you ever felt bad or Guilty about your drinking? Have you ever had a drink first thing in the morning (Eye-opener)?—questions used to assess the presence of alcohol abuse; two 'yes' responses indicate a positive screen.

Information from references 5, 6 and 7.

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Table 11
Phases of Male Sexual Activity

-
1. Desire (libido)
 2. Excitement (erection)
 3. Orgasm (emission and ejaculation)
 4. Resolution (relaxation and refractory period)
-

Table 12
Essential Physical Examination Elements

Blood pressure and peripheral pulses
 Thyroid gland palpation
 Neurologic exam (sphincter tone, perianal sensation, bulbocavernosus reflex)
 Prostate exam
 Genital exam (testicular abnormality, penile anatomic abnormality)
 Secondary sex characteristics (gynecomastia, hair distribution)

response strongly hints at stress or anxiety as the trigger of the ED, rather than a physical cause or medication adverse effect.

Orgasm/ejaculatory phase problems can be reviewed by asking—"Do you feel you ejaculate, 'come' too quickly" (or "too slowly", or "not at all?)" ED is common in men who, for any reason, became increasingly anxious about quick ejaculations, delayed ejaculation or perceived absence of ejaculation, as can occur with retrograde emission.

To reveal Peyronie Disease or pain disorders ask about "a bend to the penis" or pain during or after sexual activity.

Questions about sexuality need to be sensitive to cultural and religious differences. Using terminology that is clear, simple, and respectful of the patient's feelings can facilitate communication. Further general questions about sex may reveal deeper misunderstandings or mishaps with sexual activity in the past. These frequently require referral to a sex therapist.

The medical history should include review of risk factors, and screening for psychologic difficulties. A medication review, including over-the-counter preparations, may reveal the source of the problem because medications have been implicated in up to 25% of cases of ED (29). Medications have adverse effects on all phases of sexual functioning making clarification of the patient's complaint a priority before ascribing symptoms to specific medication side effects (30). Brief screening for depression such as "Do you sometimes feel blue, down in the dumps?" may elicit more honest responses than "Are you depressed?" Other psychiatric conditions such as anxiety may also be responsible for ED. The social history looking for stress surrounding a relationship or substance abuse including alcohol and cigarettes is critical. Finally, a review of daily activity and review of cardiovascular status is important to determine the potential risk of enhancing ED in patients who may have a sedentary lifestyle and who may be at risk (usually minimal) for an adverse cardiac event when sexual activity potential is increased (31).

The physical examination should be comprehensive with emphasis on several areas (Table 12)(32,33). Evaluation of blood pressure and peripheral pulses may show vascular disease. A neurologic exam including pelvic sensory function and anal sphincter tone are needed to confirm both sympathetic and parasympathetic function. A prostate exam may help to determine local nerve impingement. A visual and, optimally, manual

Table 13
Goal-oriented Treatment Possibilities
(May Not Be Mutually Exclusive)

-
1. Restore sexual function
 2. Improve sexual satisfaction
 3. Improve relationships
-

exam of the penis will discover any anatomic defects and aids in identifying Peyronie's disease by the presence of possible tender plaques located in the tunica albuginea surrounding the corpus cavernosa. Immature secondary sex characteristics, including hair distribution, and penile and testicular development, may represent testosterone deficiency. The sexual exam needs to be thorough and sensitive (34). Keep in mind that it is a good practice to offer the presence of a chaperone to patients having a genital exam. Many will say that it is not necessary, but the offer will allow the more anxious patient to have the comfort of an appropriate additional person in the exam room. Some men prefer to be examined by a clinician of their own sex. Also consider any cultural differences and explore them when necessary prior to initiating the genital exam.

Laboratory tests useful in evaluating ED include:

1. A urine analysis, which may demonstrate renal disease or infection,
2. A complete blood count to note any potential hematologic disorder,
3. A chemistry profile checking glucose, hepatic and renal function, and
4. A lipid profile to rule out hyperlipidemia.

When evidence of hypogonadism is present, or the sexual dysfunction is occurring in a patient who is young or with few other identifiable etiologic factors, serum testosterone screening is appropriate. TSH and/or serum-prolactin level quantitations are added on an individual basis, as indicated by the history and physical examination.

TREATMENT OF ED

Treatment plans need to be goal oriented, ideally aimed at satisfying the needs of both the man and his partner maximizing the chance of achieving patient satisfaction (see Table 13). Based on the desired outcome, treatment can be simply pharmacologic or may require further comprehensive psychosocial and relationship counseling. In many cases, the partner can be brought in to participate in the discussion about the goal of treatment improving the chance of success.

Educational and Psychosocial Interventions

In most cases, regardless of etiology, the treatment options of the physiologic impairment of ED are the same (Table 14). Education is the first step in treatment and is personalized to the needs of the specific patient. The normal changes of aging are often misunderstood by patients and lead to problems. The easy erection begins to disappear in older men, especially those with chronic illness, such as diabetes, hypertension, or renal disease. Direct tactile stimulation of the penis may be needed to obtain and maintain an erection. The man becomes increasingly anxious causing further erectile difficulties. Information from the physician about these changes of aging can be extremely reassuring.

Partner issues vary widely. Issues around partner choice, partner participation in sexual activity, and partner physiology may impact on erectile function. When vaginal

Table 14
Treatment Options

- | |
|--|
| <ol style="list-style-type: none">1. Counseling and education2. Lifestyle changes and medication changes3. Pharmacologic interventions4. Physical interventions |
|--|

dryness, or vaginal atrophy leads to loss of lubrication and pain, women often lose interest in continued sexual activity.

Basic sex therapy can be offered by the primary care clinician. Sex therapy involves teaching improvements in sexual technique and helping the patient to concentrate on pleasure, rather than simply the achievement of an erection. This may be achieved by providing to the man or, ideally, to both partners in a relationship, information including factual information about:

1. Sexual concerns,
2. Sexual practices and sexual response individualized to the specific patient or couple,
3. By attempting to reduce performance anxiety, and
4. Encourage partners to discuss what they enjoy about sex.

More specific suggestions can be offered as the next level of sex therapy encouraging couples to renew intimacy and sensuality in the relationship and to extend foreplay for each other. The use of topical lubricants or estrogen replacement therapy for the woman may be essential, especially if increased sexual activity is anticipated. The clinician needs to have some specific knowledge about sexual performance and response to provide this level of counseling. The most detailed level of therapy often requires the assistance of a sex therapist and should be considered when the patient has been unable to understand or implement any of the more basic hints or when the counseling interventions have not worked.

When recommending new treatments, the patient's anxiety may be reduced by explaining that often treatments take time to be fully effective and that most couples need time to comfortably integrate the new treatment into their sex lives.

Lifestyle and Medication Changes

Making healthy lifestyle changes may reduce the symptoms of ED and improve general physical health. Patients need to understand that what is bad for the heart is bad for the penis. Elimination of smoking tobacco is critical, as may be elimination of all other recreational drug use. Dietary issues including reduced cholesterol and fats, eliminating hyperglycemia when present, and decreasing salt intake when salt-sensitive hypertension is noted all help to diminish vascular insufficiency progression. Exercise will increase cardiac output and improve peripheral circulation. These recommendations will help men be healthier and, hopefully, happier, although their effect on erectile functioning may not be instantly apparent.

Changing medication regimens to remove causative agents can be tried when clinically possible. Examples of this might be discontinuing a thiazide diuretic and substituting an alpha-adrenergic blocker, or weaning the patient from digoxin if the medication is not really necessary. Treatment of antidepressant-induced sexual dysfunction can sometimes be managed by reducing drug dosages, altering timing of drug dosages, taking drug holidays, adding an adjunctive drug, and switching to an alterna-

tive antidepressant (35). These substitutions and eliminations may meet with some success, but need to be individualized depending on clinical circumstances.

Direct Pharmacologic and Surgical Treatment

Specific treatment regimens for ED include oral medications, transurethral suppositories, intracavernosal injection, vacuum devices, and surgery. First-line therapies include oral medications and vacuum constriction devices (36). The newest FDA-approved oral treatment is sildenafil (Viagra). Sildenafil is effective for practically all etiologic types of ED: organic, psychogenic, and mixed (37). Sildenafil requires sexual stimulation to enhance the erectile mechanism and will not provide a spontaneous erection. Libido is not affected, although if a man feels that an erection is more likely to occur, libido may be increased as a secondary affect of using the medication.

The mechanism of action, efficacy, and adverse effects of sildenafil are described in another chapter in this volume. Initial recommended doses are a single 50-mg tablet taken approx 1 h before initiating sexual activity. Lower doses of 25 mg may be used in patients who are elderly, sedentary, have renal or hepatic insufficiency, already taking cytochrome P450 inhibitor, have spinal cord injury (more susceptible to all types of erectogenic medications), or moderate to severe cardiovascular insufficiency. A 100-mg tablet is available for those not responding to lower doses. No more than one dose is recommended daily and dosing greater than 100 mg is not recommended. The timing of taking sildenafil may need to be individualized because of the half-life of 1–4 h and the physiologic response variability in different men.

The American College of Cardiology is closely following reported blood pressure effects of sildenafil and recommends caution when using sildenafil in patients taking multiple (more than three) antihypertensive medications, having strong recent history of angina or MI, or who have severe left ventricular dysfunction (38). When used along with nitrate-containing medication, sildenafil can cause excessive vasodilation and hypotension, making concomitant use of nitrates an absolute contraindication for sildenafil administration. A frequent scenario being encountered in primary care is the man who uses sildenafil for a brief period and then, with confidence restored by improved erections, manages to continue satisfactory sexual activity without any medication aid.

Yohimbine is another oral medication that has been available for many years. Its efficacy in improving ED has never been clearly proven, especially when the strong placebo effect of any oral medication for this problem is considered (39). Results have been slightly better in men with primary psychogenic etiologies and men with primarily organic etiologies will probably not be helped. Adverse effects of hypertension and increased heart rate and its proscription with most antidepressants and in patients with cardiovascular disease make Yohimbine significantly less useful than sildenafil. The American Urologic Association does not recommend Yohimbine for ED.

The development of additional oral agents may, if approved by the Food and Drug Administration, revolutionize treatment of ED even more. Apomorphine, a dopamine agonist that causes central initiation of an erection through specific action in the brain, may offer another approach to managing ED. It is possible that pharmaceutical agents for ED will be classified into categories depending on the site of action (peripheral or central) and the level of action (initiator or conditioner) (40). This would enhance the clinician's ability to provide focused treatment based on a patient's comorbid illnesses and specific needs (40). Drug combinations using agents from each of two or more classes may become commonplace improving therapeutic results (41). The current available data

does not permit efficacy comparisons between these drugs and sildenafil (42). Other oral agents are under investigation.

Vacuum devices are a reasonable choice for many men who are in a stable relationship and their partners are willing to accept the inconvenience (43). Pumps can be hand or battery powered. The band used at the base of the penis needs to be the right size to keep the blood trapped in the penis and permit painless sexual intercourse.

Testosterone augmentation, available as patches or injection, is best reserved for patients with documented hypogonadism based on the morning free-serum testosterone level. Generally, testosterone augmentation is associated with enhanced libido. This may improve erectile status by restoring interest and perhaps through other neurohormonal mechanisms, but relying solely on testosterone to restore erectile function in the dysfunctional male is inappropriate (44). Testosterone augmentation requires thorough evaluation and monitoring for prostate cancer.

Second-line therapies for ED include injectable prostaglandin preparations (36). Alprostadil (e.g., Muse) is a prostaglandin-E preparation in a pellet form that is inserted with a plunger-like mechanism into the urethral opening (45). Ideally, the first insertion of alprostadil should be done in the doctor's office to monitor technique, change in blood pressure, and the response (although this may be blunted in the office environment). The lowest effective dosage should be used. Most men require more than 125–250-mg doses, probably the 500-mg dose will provide a response within 5 min that will last approx 30 min. Because venous drainage problems may thwart the erection being caused by alprostadil insertion by premature drainage, a ring at the base of the penis may be used to constrict venous outflow. Contraindications include usage with a pregnant partner or a partner who is likely to get pregnant, hypersensitivity to prostaglandin, and sickle cell anemia (prone to developing priapism).

Intracavernosal injection therapy with alprostadil can be considered. This injection is given directly into the corpus cavernosum through the side of the penis near the base. The success rate is high, but problems include pain, prolonged erections or priapism, and penile fibrosis and plaques (46). This therapy should be initiated in the physician's office, and caution should be exercised in patients on anticoagulation. Starting dosage is 5 to 10 μ g, although 2.5 μ g may be adequate in men with spinal cord disease.

The third-line treatment for ED in penile implant surgery. This is a successful therapy, but it should be reserved for patients who have considered or tried several other treatments. The surgery is irreversible and the normal function of the corpus cavernosa is obliterated. The surgery carries low morbidity and mortality and is relatively routine.

Some clinicians have advised that ED can be managed naturally, although no controlled trials exist. A dietary program rich in whole foods including vegetables, fruits, whole grains, and legumes has been suggested with key nutrients including zinc, essential fatty acids, vitamin A, vitamin B-6, and vitamin E being recommended. Herbal supplements such as ginseng, gota kola, and saw palmetto have also been discussed. Spices reported to increase sexual desire include nutmeg, saffron, parsley, vanilla, avocado, carrot oil, and celery.

FOLLOW-UP OF TREATMENT FOR ED

Follow-up is an essential part of managing any medical issue. Reviewing the success or lack of success of treatment, any adverse effects, and considering dose or treatment alterations is more likely to achieve the patient's goal. Patients should be seen within 1 mo after

Table 15
When to Get Help

-
1. ANYTIME
 2. Treatment failures
 3. Anatomic or hormonal issues
 4. Complex issues around sex, partnership
 5. Severe psychologic problems
-

initiation of treatment to evaluate progress. Comparison to baseline can be done by verbal exchange or by using the standardized questionnaire measuring erectly function (SHIM).

CONSULTATION

Consultation with subspecialists may be appropriate at varying intervals when managing a man with ED (*Table 15*). The major factors in determining the need for consultation are:

1. The primary care clinicians comfort in discussing and managing treatment options,
2. The depth of the psychosocial and sexual issues involved, and
3. The success or failure of initial intervention efforts.

The main obligation of the primary care clinician is to recognize ED and make the patient feel comfortable about seeking help. Initial work-up and treatment can be planned by the primary care clinician who has good communication skills about sexual activity and who is knowledgeable about first-line treatments. Urologists can be helpful in difficult or complex ED situations or when the patient presents with an anatomical problem such as Peyronie's disease. An endocrinologist may be consulted to assist in managing men with difficult-to-control diabetes, hypogonadism, or evidence of pituitary dysfunction.

Sex therapists are practitioners in the medical or mental health field who, in addition to their basic clinical education, have had additional training in sex therapy including evaluation and treatment options. Sex therapists can work collaboratively with the physician to increase the chance of therapeutic success by:

1. Resolving the sexual difficulty,
2. Teasing out important history,
3. Educating the patient and partner,
4. Suggesting sexual enhancement techniques, and
5. Helping couples resolve relationship problems.

The Association of Sex Therapists and Counselors can provide a directory of trained, certified sex therapists (phone number 319-895-8407). Most major teaching hospitals have such a trained individual on their staffs.

MANAGING SEXUAL HEALTH PROBLEMS CAN ENHANCE A PRACTICE

Patients often begin their search for a clinician by talking with friends and acquaintances to determine if they have had any experience with potential providers. When patients are impressed with care, they tell others. Initial expectations of a patient encounter most importantly include: delivery effectiveness, or will the clinician understand the patient's

Table 16
Business Values of a Relationship
[Adapted from (48)]

-
- | |
|--|
| <ol style="list-style-type: none"> 1. Understanding of each other's needs and contexts. 2. Reduces time needed to make a diagnosis. 3. Reduced likelihood of diagnostic error. 4. Reduces time needed to take protective (defensive) steps. 5. Makes working together easier, reducing "hassle" factor. 6. Provides greater comfort. |
|--|
-

needs? and will the patient receive an effective response? Another dimension of expectation is the "hassle" of getting what is needed. Hassle includes uncertainty and following procedures often more important to the provider than to the patient.

Before the development of specialization, primary care clinicians were the access point for patients to the healthcare system. With specialization, health care became more splintered and the need for coordination and responding to the needs of patients was taken on by health care organizations who see themselves as customer responsive organizations. These organizations, however, are not flexible and by virtue of contracting, become less responsive to individual needs. Primary care clinicians that adapt a customer-responsive stance can regain the ability to help patients and to actively participate in the management of health care resources to mutual benefit.

Providing a "service" means to be responsive to someone's needs in a way that the person wants and accepts. "Customer responsiveness" is a well-known marketing technique that assumes that customers (patients) want solutions to their individual needs at a reasonable cost with a minimum of hassle (47). Customer-responsive management has two dimensions:

1. Interacting with individual customers to identify their specific needs and
2. Responding to those requests with customized solutions.

This is the opposite of the usual doctor-patient visit in which the doctor offers a standardized classic medical evaluation in a homogenous manner. Customer responsiveness begins with the desired relationship and then an infrastructure that allows that relationship to evolve. Relationships are important in order to obtain maximal beneficial outcomes with minimum of effort. The motivation for a relationship is mutual benefit with benefit being a measure of how well clinical solutions solve patient needs. In the ideal relationship, both parties totally understand each other's needs, have a strong desire and ability to support each other, are totally trustworthy and predictable to each other, are accepting of each other, and communicate easily (48) (Table 16).

A major way of building a relationship is the questions and answers that occur during the initial discussion and evaluation stage of the patient visit. Because at least 30% of men and 40% of women over age 18 are estimated to be dissatisfied with sexual activity, sensitive inquiries by the clinician, as well as follow-up, discussions customized to a specific patient's problem will enhance communication and relationship between clinician and patient. These factors can increase the likelihood of patient satisfaction with medical visits and improve management of other nonsex-related medical issues. Discussing sexual matters can also add a sense of informality and, occasionally, humor into the clinical discussion helping to level the relationship between clinician and patient. These activities create patient value by solving individual patient's prob-

Table 17
Factors Affecting Patient Satisfaction^a

-
- Ease of obtaining results
 - Waiting time to see the doctor
 - Comfort of waiting area
 - Doctor's concern for your comfort
 - Availability of doctor on phone
 - Nurses' concern for your problem
 - Length of time doctor spent with you.
 - Doctor's respect for your question
 - Courtesy of nurses
-

^aFrom: Ganey Associates published in their 1995 Satisfaction Report, as reproduced in Flanagan L. Patient satisfaction surveys: How well are you treating your patients? *Fam Pract Management* January 1996; 61–75.

lems. Value is even more enhanced when the hassle of obtaining the solution is minimized for the patient as occurs with a clinician initiated discussion.

Patients with emotional distress that is recognized by the clinician report stronger relationships with their clinician than patients whose emotional distress was not diagnosed (49). So, although paying attention to patients' concerns about sexual dysfunction may divert some time and energy away from other areas of medical care, it may have the benefit of strengthening the doctor–patient relationship. This can result in more regularity with repeat visits, and referrals of friends and family.

There is demand for ED services whether or not they are covered by insurance. Even if coverage for services is not present, patients may be willing to pay for services perceived by them to be high priority. Providing care for sexual dysfunction may be a useful practice builder. When it is not reimbursed by insurance, management of ED is considered elective care with the patient determining the need for the service. If the clinician decides to provide elective care for ED it should 1) be prescribed in an individual manner for the specific patient and in a way that the clinician would prescribe for themselves or a family member, and 2) be explained honestly with the patient as to what is involved and how much it will cost (50).

External marketing of management of sexual dysfunction can be included in direct mailing or print advertising. The option exists for marketing specific services for ED, but the well-rounded primary care clinician can best accomplish this in an ethical and supportive manner by including willingness to manage a selection of “softer” issues that patients are nervous about discussing with the clinician. These could include issues such as smoking, alcohol and drug abuse, physical abuse, depression, as well as sexual dysfunction.

Patient satisfaction is an outcome that often prompts a patient to recommend a particular clinician to a friend. Being the best clinician in the world is no longer enough, more attention is being focused on the personal wants and needs of patients for courtesy, caring, and personal attention. Patients are like customers and expect customer service. The resulting benefits of patient satisfaction include the attraction and retention of patients. Patient satisfaction has been found to be related to both environmental and interpersonal events occurring in the office (Table 17). If a clinician is considering spending more time working with patients having sexual dysfunction, it might be use-

ful to survey patients about the planned change. This would allow the clinician to gage patient interest as well as to inform patients about the opportunity to discuss an area of concern that they might think is unimportant to the clinician.

Patient satisfaction results in:

1. Patients who follow instructions for care more carefully,
2. Patients with increased confidence in and loyalty to the physician, resulting in word-of-mouth endorsements and increased referrals,
3. Patients who pay their bills promptly, and
4. Patients who continue to see one physician for their health care needs (51).

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4

Psychogenic Erectile Dysfunction in the Era of Pharmacotherapy

A Theoretical Approach

John Bancroft, MD and Erick Janssen, PhD

In spite of substantial progress in understanding the peripheral mechanisms involved in erection and erectile dysfunction (ED), the key mechanisms underlying psychogenic ED have so far eluded us. Similarly, we have made little progress in identifying the psychological characteristics that relate to vulnerability to psychogenic ED. Attempts to identify personality characteristics that discriminate between psychogenic and organic types of ED have failed (1–6) or, for those few cases that apparently succeeded with small numbers, were not replicable (7–10). Some helpful attempts have been made to define the types of psychological problems that are found in psychogenic ED, e.g., (11). Levine and Althof (12) described three levels of contributory problem, performance anxiety, antecedent life changes (such as divorce, bereavement, or vocational failure) and developmental vulnerabilities. They commented that performance anxiety was an issue in most types of ED and was more of a “final common psychological pathway to erectile impairment than a specific explanation.” What has remained unaddressed is why some men with such psychological problems develop ED and others do not. A complicating factor is that, increasingly men with ED are being diagnosed as having “mixed” organic and psychogenic etiologic factors, e.g., (11) rendering the clinical usefulness of the “psychogenic” category less and less certain.

Many of us involved in sex therapy of ED have come to recognize that whereas there are certain aspects of the therapeutic process that we understand, there remain “gray areas”. The parts we understand include:

1. Improving communication and understanding between the couple;
2. Learning new methods of conflict resolution;
3. Cognitive restructuring of inappropriate “sexual meanings”.

These are all treatment objectives for which we have developed considerable skill, and which not infrequently, are sufficient to bring about the change needed. It is the direct modification of the individual’s sexual response, in particular his erections, where we are on uncertain ground. This is the interface between the relevant psychological processes and the peripheral physiological response, and about that interface we under-

stand little (13). Furthermore, with the advent of effective pharmacological methods of treatment, at least at the specific level of erectile response, we should be considering the combination of psychological and pharmacological methods. What has been lacking is a theoretical approach not only to help with the development of more successful psychological treatment methods but also to guide such combination therapy.

Until recently, the only significant attempt to understand this interface on the basis of a theoretical model was made by Barlow et al. This led to a series of interesting laboratory experiments, both by Barlow's group and by the Amsterdam group of Everaerd and Janssen [see (14) and (15) for comprehensive reviews]. Barlow (16) has focused on two particular processes:

1. "attention to sexual cues", and the negative effect on erectile response of being distracted from focussing on those cues;
2. "the amplifying effect of arousal", with negative arousal (e.g., anxiety) amplifying the negative effects of anxiety-related distractions, and positive arousal amplifying the effects of appropriate attention to sexual cues.

Janssen and Everaerd (15), after their series of studies agreed that it is necessary to consider two aspects, information processing and arousal. They proposed that men with psychogenic ED fail to respond because of a predominantly nonsexual processing of relevant stimuli, a process indeed dependent on attentional processes (i.e., distraction), but initiated at an unconscious or "automatic" cognitive level in response to psychological threats or (performance-related) worries (17).

Unfortunately, these important theoretical ideas have not been systematically applied to the development of treatment techniques, although some existing treatment formats, including Masters and Johnson's, could be described in information processing terms. As Everaerd et al. (18) noted: "People with sexual dysfunctions tend to wait and look for the occurrence of feelings, instead of feeling what occurs. Hence, the spectator role." Masters and Johnson's treatment approach can be viewed to involve a redirection of attention, through the manipulation of expectations and an increased focus on pleasant physical sensations, in an attempt to reduce the effects of interfering (distracting) thoughts or worries.

Through a cognitive window, the interface between psychological processes and genital response thus seems to depend heavily on two factors: the presence of a sexual stimulus and the absence of cognitive processes interfering with the activation of a response to a sexual stimulus.

A third component, which seems to be missing from these theoretical models, involves direct neurophysiological inhibition of erectile response. There is a variety of evidence which supports the role of such inhibition [reviewed in (19)] and we have developed a "dual control" model for male sexual response, which involves a balance between excitatory and inhibitory systems within the central nervous system (19). Our model postulates that central inhibitory mechanisms are normally adaptive, but as with the excitatory system, individuals vary in their propensity for inhibition, and whereas the majority have "normal" adaptive propensities for such inhibition, there are those with too little inhibition, who may be more likely to engage in high-risk sexual behavior (20) and those with too much inhibition, who as a consequence, will be vulnerable to sexual dysfunction.

It is noteworthy that as we have been developing our dual control model for higher levels of control, a complimentary "dual control" model of the balance between excitation and inhibition in the periphery (i.e., the erectile tissues of the penis) has been

emerging [e.g., (21)]. Clearly, if these two models have validity, then we would expect them to be linked.

Our model recognizes that there may be several mechanisms by which inhibition of genital response is achieved, and several biological functions served by this inhibition, e.g.;

1. The *refractory period*, the undoubted increase in inhibition following ejaculation that occurs across species and which presumably has biological adaptive significance;
2. The *effect of chronic stress* in inhibiting reproductive behavior across species, which is likely to be relevant to the human;
3. The *recognition of threat*, either sexual or nonsexual, where based on information processing, a threat is recognized and inhibition of sexual response is necessary to deal with that threat (19).

As a first step in exploring and testing this theoretical model in men, we needed a valid and reliable instrument or questionnaire to measure our assumed individual variability in propensity for sexual excitation and inhibition of sexual response. We predicted that we would find two factors: one related to excitation and the other to inhibition, which would be relatively independent of each other. We have developed such an instrument with good psychometric properties (22). We call this the SIS/SES questionnaire.

Interestingly, and unexpectedly, this produced *three factors*: one excitation scale and two inhibition scales. The excitation scale (SES) is based on propensity for sexual arousal in predominantly noncontact situations such as social interactions, responding to visual stimuli or fantasies, or even to nonsexual stimuli. The meaning of the questions loading on the first inhibition scale (SIS1) led us to describe this as “inhibition due to threat of performance failure”—not getting sexually aroused or losing arousal because of performance concerns, concerns about the partner’s response and distractibility. The second factor (SIS2) we called “inhibition due to the threat of performance consequences”—the inability to become aroused, or losing arousal because of risk of being caught, fear of STD or pregnancy, or concerns about moral values, or inflicting pain.

We have collected a considerable amount of data using the SIS/SES in nonclinical samples (22). In a sample of 867 men with a mean age of 31 yr, the two inhibition scales are modestly correlated with each other ($r = +0.29$, $p < 0.001$), but neither is correlated significantly with the excitation scale (SIS1, $r = +0.10$; SIS2, $r = +0.11$). With age, we find a modest negative correlation with SES ($r = -0.1$) and a positive correlation with the two inhibition scales ($r = +0.19$ and $r = +0.18$, respectively). The relationship with age becomes more pronounced after a group of young male students is excluded from this sample (SES, $r = -0.22$; SIS1, $r = +0.34$; SIS2, $r = +0.21$, $ps < 0.001$, $N = 312$, mean age = 47).

Conceptually, it looks as though the first inhibition scale, SIS1, is relevant to *sexual dysfunction* and the second, SIS2, is relevant to *sexual risk taking*. However, we believe that the second factor has psychological relevance to psychogenic ED as well. There are a number of negative consequences that might occur within sexual relationships, reflecting the problematic aspects of the relationship, which could invoke this type of inhibition.

A fundamental point is that we find a close to normal distribution of scores on each scale (see Fig. 1), i.e., we are measuring something that is continuously and “normally” variable within the general population, consistent with the idea that the middle range is the normal adaptive range. We are, therefore, starting with the normal and then looking at variations from the norm, somewhat different from the usual clinical perspective.

Starting with our nonclinical samples, we have asked about the occurrence of erectile problems in two ways (23) Subjects were asked whether 1. they had *ever* had difficulties

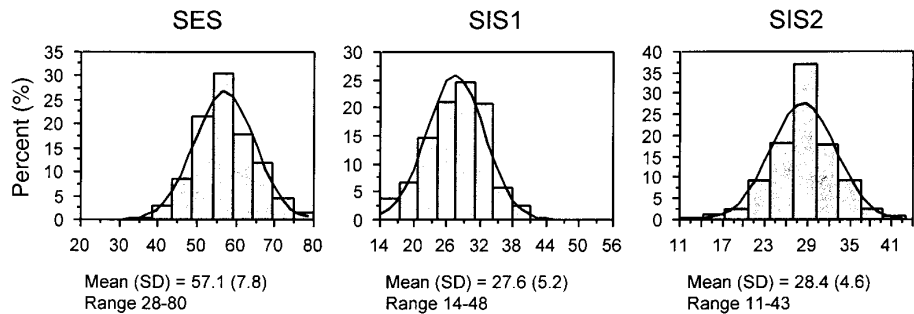


Fig. 1. Distribution of scores on the SIS/SES scales in a nonclinical sample (N = 867).

Table 1
Frequency of Erectile Problems

	Erectile Problems	
	"Ever"	"Last 3 mo"
Never	49%	75%
Occasionally	43%	18%
Less than half the time	4%	2%
Most of the time	4%	5%

in obtaining or keeping an erection and 2. whether they had such difficulties in the past 3 mo. We looked at these variables first in an older sample of 313 men with a mean age of 46.2 yr. Their responses are shown in Table 1.

We explored the relationships between our three scales and these two measures of ED by using multiple regression, with the three scales and age as the independent variables (Table 2).

In predicting answers to the “*ever had difficulties*” question, both inhibition factors and age were significant; SES did not figure in the equation. For erectile difficulties in “the past 3 mo,” SIS1 and age were both strong predictors; SES predicted weakly and negatively and SIS2 did not enter the equation.

We, therefore, find SIS1 strongly predicting erectile problems, for both time periods, whereas SIS2 was only relevant on the “*ever had difficulties*” basis.

It is noteworthy that the main difference between the two measures of erectile difficulties was in the reporting of *occasionally*, which was not surprisingly much more commonly reported “*ever*” having happened (43%) than having happened during the past 3 mo (18%). The multiple regression findings are consistent with the SIS1 measure reflecting some trait vulnerability that would persist, and as the correlation with age suggests, may be amplified by the effects of aging. In contrast, SIS2 measures a tendency to respond to threatening situations with inhibited erection, circumstances that are likely to occur occasionally, and with lower probability over a 3 mo period than for “*ever*”.

In the light of these findings, we developed our theoretical model further to account for the two inhibition scales rather than one (23). Whereas it is possible that these two scales may be reflecting different inhibitory mechanisms, we prefer an alternative explanation.

Table 2
Predictors of Erectile Problems

	Multiple Regression	
	Std. Coeff.	P-value
Erectile problems ("ever")		
SES	—	—
SIS1	0.38	.001
SIS2	0.13	.02
Age	0.15	.01
Erectile problems ("last 3 mo")		
SES	−0.12	.02
SIS1	0.36	.001
SIS2	—	—
Age	0.25	.001

^a Only significant predictors ($p < 0.05$), from multiple regression analyses with SES, SIS1, SIS2, and age as independent variables, are shown. The R^2 for the first analysis is 0.27 and 0.30 for the second analysis.

We can see SIS2 as clearly being related to the perception of external threats in specific situations, and as mentioned earlier, such threats may relate to problems in the man's sexual relationship as well as factors such as disclosure, STDs, or unwanted pregnancy.

With SIS1, we appear to be dealing with a more intrinsic threat based on learned awareness that failure of response, for that individual rather than situation, is to be expected, or in other words a "high propensity for erectile failure."

This concept, which is clearly related to the clinical concept of performance anxiety¹ implies a self-reinforcing process whereby anticipation of failure augments the preexisting propensity for failure. We postulate that this "preexisting propensity" is a manifestation of a "high inhibitory tone." In this respect, inhibitory tone refers to the level of inhibition that prevails when the subject is not actively responding to a sexual stimulus or a threat. It is thus the "inhibitory tone" that determines the size of the flaccid penis and the "inhibitory tone" that requires to be reduced as well as to be counteracted by an increase in excitation for an erection to occur. We have recently reviewed the various evidence that supports the concept of inhibitory tone (23).

We thus have two measurable traits: the first, SIS1, is clearly relevant to "psychogenic" ED and the second, SIS2, may be relevant in some circumstances. Inhibition in response to threats is not incompatible with the cognitive models discussed earlier. The cognitive processing of a threat (i.e., "perceiving a threat") could have two effects: neurophysiological inhibition and a simultaneous redirection of attention to nonsexual stimuli [i.e., "distraction" (17)]. "Inhibitory tone" is a different matter. Thus, we might expect that the "threats" reflected in SIS2 might be more amenable to psychological treatment approaches. The scope for psychological treatment of the "inhibitory tone" component, reflected in SIS1, is less certain.

So far, we are at an early stage in collecting relevant data from clinical subjects, and have some very preliminary data from a sample of 70 men seeking help for ED. In this

¹ It is noteworthy that whereas "performance anxiety" has played a central role in explanations of psychogenic (and organic) ED for many years, no systematic method of assessing this phenomenon or measuring it has been developed.

Table 3
Erectile Problems in Nonclinical and Clinical
Samples (N=1943)

	<i>N (%)</i>	<i>Age ($\pm$ <i>sd</i>)</i>
Nonclinical Sample		
Never	1256 (67.0%)	30 (12)
Occasionally	479 (25.6%)	34 (13)
Less than half the time	86 (4.6%)	35 (13)
Most of the time	52 (2.8%)	47 (16)
Clinical Sample	70 (100%)	50 (13)

group, with a mean age of 50 yr, we find a negative correlation between SIS1 and age, the opposite of what we find in nonclinical populations. This may reflect the fact that younger men presenting with ED, who do not have an obvious organic basis, are more likely to have high SIS1 scores and possibly high “inhibitory tone”; i.e., high SIS1 is particularly related to “psychogenic” ED and hence more likely to be found in cases of ED in which there are no obvious organic factors. Otherwise, the correlations between the three scales are unremarkable.

We have compared this small clinical group to our nonclinical samples, and for this purpose have added in a substantial number of men from an ongoing sexual risk taking study producing a nonclinical sample of 1873 men. Table 3 shows the proportions reporting erectile problems during the last 3 mo. Comparison of SIS/SES scores across these various subgroups, including our clinical sample is shown in Fig. 2–4. For all three scales, the “never” and “occasionally” groups are highly significantly different from the other three groups. SES scores are lower in the groups reporting erectile difficulties (see Fig. 2). With SIS1, the clinical group and the “most of the time” group are significantly higher than the <50% group (see Fig. 3), whereas with SIS2, the clinical group have significantly higher scores (see Fig. 4). Overall, we find our clinical group to be very similar to the “most of the time” nonclinical group, with the possible exception of the SIS2 scores.

We are at an early stage of exploring the clinical relevance of this model. The next step is to identify groups that are characterized by various combinations of high and low scores on the three scales, and then look for clinical characteristics, including response to treatment, that might help to interpret these group differences. There are also a number of testable predictions that can be made about the treatment of such groups.

We, therefore, predict that a man presenting with ED who has a normal or low SIS1 score, but a normal or raised SIS2 score will benefit from psychological treatment that focuses on removing the “external threat.” A man with ED who has a high SIS1 score may, however, be resistant to psychological treatment, at least if it is used on its own. In such cases, the use of pharmacological treatment in combination may be successful.

In a young man with high SIS1, an inhibition-reducing drug, such as phentolamine with its combined α 1 and α 2 blocking action, may be effective. In an older man with ED and high SIS1, the effects of age also have to be taken into account. We have already commented on the relationship between age and SES scores. Thus, the best pharmacological regime for the older man with ED may depend on the pattern of both SIS1 and SES. Such men with high SES and high SIS1 may respond to disinhibiting

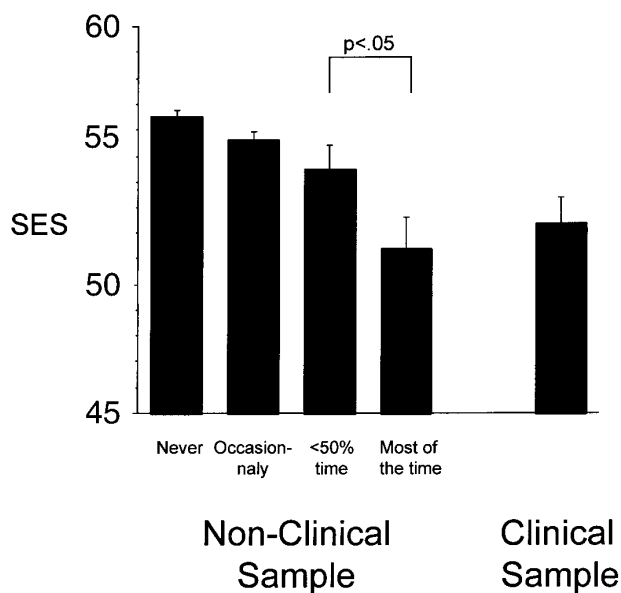


Fig. 2. SES scores in a nonclinical ($N = 1873$; by ED during the last 3 mo) and clinical ($N = 70$) sample.

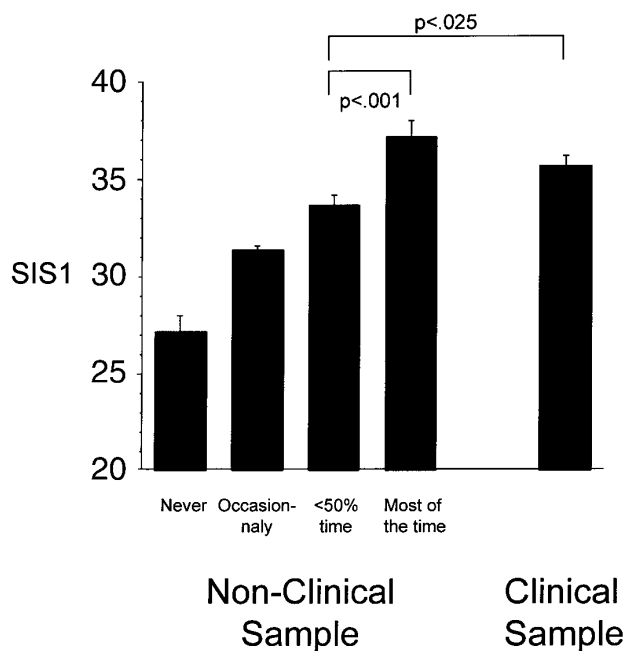


Fig. 3. SIS1 scores in a nonclinical ($N = 1873$; by ED during the last 3 mo) and clinical ($N = 70$) sample.

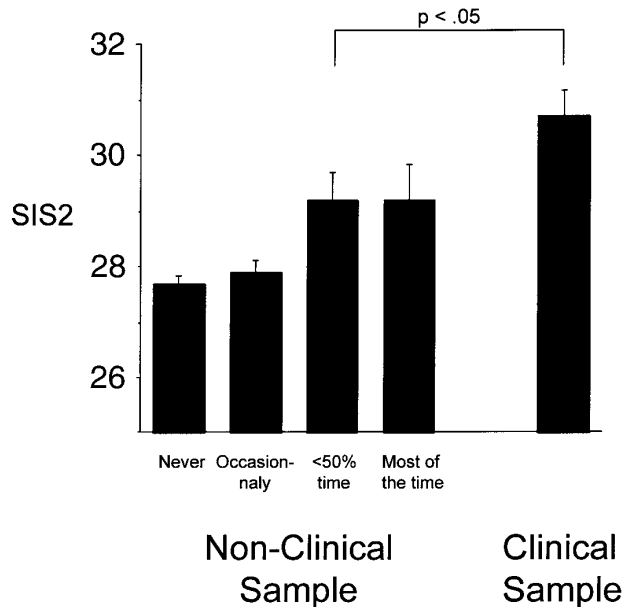


Fig. 4. SIS2 scores in a nonclinical ($N = 1873$; by ED during the last 3 mo) and clinical ($N = 70$) sample.

drugs alone, such as phentolamine. A more likely combination in the older man is high SIS1 accompanied by a low SES score, when a combination of phentolamine with an excitation facilitator such as sildenafil or apomorphine may be the best approach. When the problem exists with a low SES and a normal or low SIS1 and 2, then an excitation facilitator may be effective on its own.

If these predictions become supported by the clinical evidence, what will that tell us about the concept of “psychogenic ED”? The distinction between “psychogenic” and “organic” is already of diminishing clinical value. More often than not a “mixed” diagnosis is made. Whereas there are some cases where the presence of clear psychological problems provides an adequate explanation for the ED, we are still left with the fact that not everyone with such problems will suffer these erectile consequences. The theoretical approach taken in this chapter leads us to a different and relatively new conceptual model, in which both central and peripheral neurophysiological mechanisms have to be taken into account. Central mechanisms underlying the propensities for high inhibition or low excitation, in some cases, may be sufficient on their own to produce ED in the absence of significant external problems. More modest levels of such propensities may make an individual vulnerable to external problems that would not be sufficient to produce ED in everyone. If, on the other hand, the external problems are extreme, we may expect to find erectile problems even in those with “normal” levels of inhibition or excitation proneness.

We can draw similar conclusions about the interaction between central and peripheral mechanisms. If peripheral damage is sufficient, ED will occur in men with normal

levels of inhibition or excitation proneness. In many cases, however, the impact of a modest degree of peripheral damage will be increased by high central inhibitory tone and high propensity for inhibition and/or low propensity for excitation.

The origins of such individual variability in inhibition and excitation proneness remain as yet obscure, but are researchable. Given the close to normal distribution of scores on our measures of these traits in nonclinical populations, it is perfectly feasible to explore both genetic determinants (using behavioral as well as molecular genetic methods) and earlier experiential determinants, such as family influences, and such research is currently in progress. It will also be interesting to track the pattern of SIS/SES measures over time in individuals who go through periods of major psychological adjustment.

One aspect of central mechanisms that promises to be of considerable relevance is the impact of mood on sexual interest and response. In studies of psychological “causes” of ED, negative affect emerges as relevant in various ways, and in a large community-based study, measures of depression were significant predictors of ED, particularly in older men (24). Conventional clinical wisdom holds that, typically, negative mood is associated with impairment of both sexual interest and response. However, it is becoming increasingly apparent that the relationship between mood and sexuality is more complex than that, particularly when depression is accompanied by anxiety [e.g., (25)]. Recent studies based on our dual control model (26) have found that 15–20% of men experience an increase in sexual interest and often erectile responsiveness when they are in states of negative mood, particularly when anxiety or stress is involved. Furthermore, we have been able to predict this paradoxical pattern on the basis of SIS/SES scores; it is the man with high SES and low SIS2 scores who is most likely to report this paradoxical mood sexuality relationship. This is consistent with the concept of “excitation transfer” (27) where in the presence of low inhibition of sexual response, arousal from negative stimuli, leading to the experience of anxiety, can be recruited to augment response to sexual stimuli. This pattern provides a basis for the use of sexual response and orgasm as a “mood regulator” and is probably relevant to many examples of so called “compulsive sexual behavior.” The opposite pattern is more relevant to ED. Men with a relatively high propensity for central inhibition of sexual response are more likely to lose sexual interest and erectile responsiveness when depressed or anxious. This may not depend on cognitive processing primarily, but on the related biochemical changes in the brain that are relevant to both mood and sexual arousability. We have found this pattern to be more likely in older men (and the reverse, “paradoxical” pattern in younger men), helping to explain the findings reported by Araujo et al. (24).

Where does this conceptual analysis leave psychological treatment? Whether or not central and/or peripheral mechanisms are relevant, there may still be external factors, particularly those stemming from the man’s current sexual relationship, which tip the balance towards ED or even dominate the picture. According to this conceptualization, the sex therapist needs to evaluate three aspects of each case of ED, the likely importance of peripheral pathological mechanisms (or drug effects), the relevance of central mechanisms of inhibition and excitation, and the presence of external or interactional problems that might either invoke inhibition of response or result in insufficient stimulation of response. Where such external problems stem from the relationship, considerable benefits may result from psychological interventions. Performance anxiety stemming from anticipation of erectile failure may also be reduced. Thus, even in cases

with peripheral damage impairing erectile function, worthwhile improvement sometimes results from sex therapy.

Because of the tendency for the propensity for excitation to decline with age, the sex therapist who identifies such factors as important in a particular case may produce benefits by getting the couple to introduce new or better methods of stimulation.

Clearly, such psychological approaches can be effectively combined with pharmacological treatment, and this is likely to be important if the inhibition proneness or lack of excitation proneness are marked.

We have offered here a theoretical model, plus an instrument for measuring related traits, which could help to change our approach to the treatment of ED. Fortunately, its usefulness can be fairly readily evaluated and before too long we will know if this is a useful advance or not. If it is, it will result in a fundamental shift in how we conceptualize ED.

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5

Medications Affecting Erectile Function

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INTRODUCTION

Dramatic advances in our understanding of the physiology of an erection have taken place over the past decade. The role played by nitric oxide as an essential neurotransmitter inducing cavernous smooth-muscle relaxation has only been recognized within the past few years. The introduction of Viagra, the first effective oral agent for impotence, [now more politely designated as erectile dysfunction, (ED)] has invigorated this field of clinical investigation and basic science. Recently, the United States Food and Drug Administration held an advisory panel to review an application for approval of the first centrally acting treatment for ED, called Uprima. This new-found knowledge concerning the normal anatomy and complex physiological pathways essential for erectile activity has provided important insights into how other medical drug therapies may impact on sexual function at key central and/or peripheral levels.

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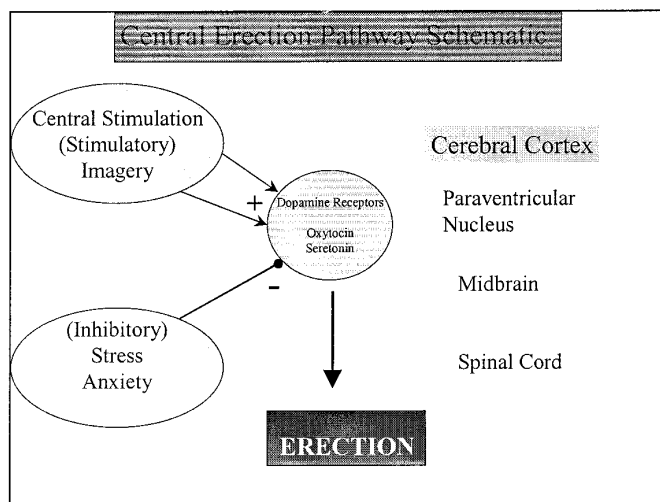


Fig. 1. Depicts the central neurological pathways that affect ED.

The actual incidence of ED remains poorly defined. In the age group of 40–70 yr, various factors are implicated in the epidemiology of ED. Within this cohort of men, pharmaco-therapy for chronic disorders such as hypertension, diabetes, and depression are very common. More than 1.5 billion prescriptions are written each year in the United States alone, amounting to more than six prescriptions per person (1). In addition to these prescriptions, other homeopathic and recreational drug use is flourishing within our culture and may have an impact on sexual functioning.

The vast majority of commonly prescribed medications has been found to impair sexual functioning (2). In one medical outpatient clinic, a 25% incidence of drug-associated impotence was noted (3). The ability to identify medical therapy as an important component of ED, a potentially reversible cause, is vital to the proper management of ED.

The complexity of the erection pathway has been described elsewhere in this volume, however, it is important to note that sexual dysfunction may be caused by a disruption anywhere along the central or peripheral pathways (Figs. 1 and 2). Drugs may impact sexual functioning in three major ways:

1. Libido and sexual drive;
2. Erectile function; and
3. Emission and ejaculation.

Penile erection requires the appropriate cerebral, neurological, vascular, and psychological environment to function adequately. Physiologic and anatomic erectile mechanisms have been well described. The corporal and lacunar smooth muscles are normally in a state of contraction mediated through postganglionic sympathetic α -adrenergic nerves. This input is believed to maintain flaccidity of the penis through increased arteriolar resistance, with reduced lacunar spaces creating an unobstructed venous outflow.

During an erection, pelvic nerve stimulation (mediated through the parasympathetic autonomic nervous system) and ultimately cavernosal nerve stimulation occur. It is at

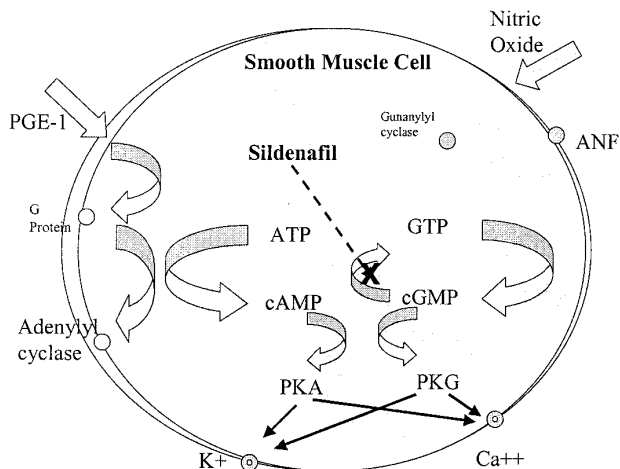


Fig. 2. Depicts the pathways and systems involved in the intracellular regulation of smooth muscle tone

this point in the pathway that nitric oxide a neuromodulator is released and activates an intracellular enzyme cascade. Nitric oxide acting via guanylate cyclase increases cyclic guanosine monophosphate (cGMP), which, in turn, decreases intracellular calcium causing a relaxation of smooth muscles culminating in erection. The relaxation of penile trabecular and vascular smooth-muscle augments the flow of blood into the lacunar spaces. This increased flow results in an increased pressure in the corpora cavernosa compressing the trabecular walls against the inelastic tunica albuginea, obstructing flow through the emissary veins, thereby enhancing penile rigidity (the veno-occlusive mechanism).

Emission is the propulsion of semen from the vas deferens, prostate, and seminal vesicles into the posterior urethra. This phenomenon, along with ejaculation, (propulsion of semen from posterior urethra and out the penile urethral meatus) requires the interaction of the thoracic and lumbar sympathetic and somatic nervous systems. The somatic efferent nerves emanate from S2-S4 and the efferent autonomic nerves originate from the T12-L2 sympathetic outflow.

Libido appears to be more dependent on male sex hormones, such as testosterone and dihydrotestosterone. Hypoandrogen states are generally related to decreased arousal and may be induced with interruption anywhere along the hypothalamic-pituitary-gonadal pathway. Drugs may also interfere with androgen production through elevated prolactin states.

This chapter focuses on common medications currently implicated in sexual dysfunction, highlighting the underlying physiologic cause. The data reviewed in this chapter are largely individual series and case reports describing drug adverse experiences. In many cases, it is difficult or impossible to separate and assign responsibility for the observed ED on the essential pharmaco-therapy or the underlying disease entity.

DIURETICS AND ED

Diuretics are frequently considered the first-line treatment for uncomplicated hypertension (4). Resulting from this extensive use, their relationship with ED has been well characterized. The most commonly used diuretics associated with impotence are: acetazolamide, amiloride, chlorthalidone, indapamide, spironolactone, and the thiazide diuretics.

The current recommendation for treatment of uncomplicated hypertension consists of diuretics and β blockers (4). Thiazide diuretics have been reported in multiple trials to be associated with ED with a reported incidence of impotence between 4–32% (5–9). Diuretic therapy is thought to induce genitalia blood flow to be rerouted away from the usually well-perfused genitalia, because of a decrease in peripheral vascular resistance (10). In one large randomized double-blind study of 625 men with essential hypertension, the reported incidence of ED was 60% among those taking antihypertensives at baseline. Those patients not taking antihypertensives had an incidence of ED of 40%. Hydrochlorothiazide (HCTZ) was added if necessary to monotherapy of propranolol, captopril, and methyldopa, to achieve blood pressure control. The addition of a thiazide to patients already taking propranolol significantly impaired libido, tumescence, and ejaculation. Patients for whom HCTZ was added to captopril monotherapy, had a significant reduction in libido (11). One thiazide diuretic with a more favorable side effect profile, not implicated in ED, is indapamide (12).

Spironolactone is a competitive aldosterone antagonist, and is also believed to inhibit dihydrotestosterone binding to androgen receptors. This results in an increased conversion of testosterone to estradiol. This effect is believed to cause significant problems with potency (13), and gynecomastia, which appears to be dose related, and resolves with discontinuation of the medication (14,15). In one study, the incidence of impotence in patients taking spironolactone was 30% (16).

Diuretic-induced ED warrants dose modification, or alternative therapy, as various antihypertensive treatment options exist. Initially, a decrease in the dosage of the medication, if medically acceptable, should be attempted (17). If this strategy is not successful, consideration should be given to switching to a different antihypertensive with a lower risk profile for sexual dysfunction. Combining diuretics with other classes of antihypertensives appears to frequently increase the severity of sexual dysfunction (18). Antihypertensives with a lower reported risk of inducing significant sexual dysfunction include the ACE inhibitors such as enalapril and captopril, and calcium channel blockers like verapamil (19,20). Additionally, selective α -1 blockers have a low reported rate of ED.

ANTIHYPERTENSIVES AND ED

Almost all antihypertensive agents have been linked to some degree of sexual dysfunction. The mechanism of such dysfunction remains to be fully elucidated. From a clinical perspective, this side effect may potentially lead to poor drug compliance. In addition to the diuretics, described previously, the β blockers, α -blockers, centrally acting sympatholytics, and vasodilators have also been found to cause variable amounts of sexual dysfunction (19,21–25).

Some of the theories behind antihypertensive-induced sexual dysfunction include:

Table 1
Antihypertensives Implicated in Sexual Dysfunction

<i>Drug/Drug Class</i>	<i>Adverse Effect</i>
Diuretics	
Thiazides	Impotence
Spironolactone	Decreased libido, and impotence
Acetazolamide	Decreased libido, and impotence
Amiloride	Decreased libido, and impotence
Chlorthalidone	Decreased libido, and impotence
β Blockers	
Propranolol, and Labetolol	Decreased libido, and impotence
α Blockers	
Selective	
Doxazosin, prazosin, and terazosin	Impotence, priapism
Nonselective	
Phenoxybenzamine	Ejaculatory dysfunction
Sympatholytics	
Methyldopa	Decreased libido, and impotence
Clonidine	Impotence, and ejaculatory dysfunction
Reserpine	Decreased libido, and ejaculatory dysfunction
Guanethidine	Ejaculatory dysfunction
Vasodilators	
Hydralazine	Impotence

1. A central adrenergic inhibition, which decreases central sympathetic outflow. This may have an effect on psychogenic erections, and may decrease the sympathetic innervation of the penis;
2. Adrenergic inhibition can cause a decrease in central neurotransmitters and may result in decreased libido (26,27);
3. Adrenergic receptor blockade may result in impaired signal transduction of the seminal vesicles, vas deferens and ejaculatory ducts. These effects may result in decreased volume of emission (10). Another potential effect of antihypertensives is;
4. Hyperprolactinemia that is often incidentally found. This may result in lowered testosterone levels, ED, and diminished libido (28,29).

β Blockers

β blockers are thought to induce ED through their action on decreasing B2 vasodilation and creating unopposed α-1 vasoconstriction that acts on the corpora cavernosa (30). β blockers have also been found to reduce serum testosterone levels (31). Some experimental work in rats has shown an effect on sexual function with short-term propranolol administration, that is believed to be mediated by the serotonin 1A receptor (32). Propranolol and labetalol are the two most commonly implicated β blockers inducing sexual dysfunction. Propranolol has been reported to result in impotence in up to 43% of patients. Most studies however, quote an incidence of ED between 10–15% (21). These effects appear to be dose related (30).

A significant reduction in the rate of impotence with β blockers has been found with the use of selective β 1 agents, such as atenolol, nadolol, and pindolol (12).

α Blockers

α -1 blockers induce resistance and capacitance vessel dilation. The most common α -1 blockers in use are doxazosin, prazosin, terazosin, and tamsulosin. These medications increase cavernosal artery inflow by impairing corporal smooth-muscle constriction (27). They have a low reported incidence of ED, mediated by inhibition of the α -1 hypothalamic receptor. In one study, which involved 934 men taking prazosin for hypertension, the incidence of ED was noted to be only 0.6% (22).

α blockers may result in priapism (19,33). This effect has been reported particularly in patients with concomitant renal insufficiency (34). To date, no studies have been published that look at tamsulosin, one of the newer α blockers, describing its effects on erectile function.

Nonselective α blockers such as phenoxybenzamine have been found to cause ejaculatory dysfunction (23,35). Some studies have shown that there may in fact be a problem with seminal emission rather than retrograde ejaculation as was initially hypothesized (36). One study evaluated post-ejaculatory voided urine in patients on nonselective α blockers, and found there to be an absence of fructose and sperm, thus implying an inhibitory process affecting the seminal vesicle contractions and eventual emission of sperm.

Sympatholytics

This class of medications includes methyl dopa (Aldomet), clonidine, reserpine, and guanethidine. These antiadrenergic agents diminish central sympathetic outflow by stimulating a central α -adrenergic pathway that diminishes vasomotor outflow. The incidence of ED in men taking methyl dopa is, on average, 20–30% (23). In this same series, an incidence of ejaculatory problems and decreased libido was approx 10%. The decreased libido is believed to be related to methyl dopa's enhancement of prolactin release (37). Methyl dopa-induced sexual dysfunction is likely on the basis of sympathetic inhibition resulting in decreased central neurotransmitter release, and inhibition of α -1 post-synaptic receptors, which are responsible for emission and ejaculation (38–40). Clonidine decreases sympathetic outflow from the brain and has a reported incidence of ED of approx 25% (24,25). Patients taking clonidine occasionally complain of decreased libido (41). On the other hand, ejaculatory failure has been a relatively rare complaint.

Sympatholytic agents such as reserpine and guanethidine act at peripheral sympathetic nerves by decreasing the amount of neurotransmitter released. Guanethidine concentrates in the sympathetic nerve endings and blocks the release of norepinephrine in response to nerve stimulation, eventually displacing the norepinephrine from its intraneuronal storage granules. This agent is occasionally used in the management of severe hypertension, but often results in orthostatic hypotension. An incidence of ejaculatory disturbances previously cited is 40% (23). Guanethidine does not inhibit parasympathetic activity and theoretically should not impair erectile capacity. However, an incidence of ED of 39% has been previously reported (42). The etiology of this impotence may be psychologically induced because of the failure of ejaculation (43). It is important to note that these reports predate the development and widespread use of validated

self-report reproducible questionnaires such as the International Index of Erectile Function, and may reflect patient confusion relative to erectile and sexual dysfunction (44). Reserpine depletes norepinephrine and thereby decreases sympathetic activity (37). With this depletion in catecholamines, emission and ejaculatory difficulties would be expected. Reserpine has also been found to increase the levels of prolactin, and this may ultimately affect libido and potency. An impotence rate upward of 40% has been described in the literature (45,46). A contributory factor in this may be that reserpine also depletes stores of serotonin and results in depression in a significant proportion of patients (47).

Vasodilators

Hydralazine acts by causing direct relaxation of vascular smooth-muscle cells. This effect on peripheral resistance is partly negated by reflex increases in sympathetic discharge (23). Because of this central effect, hydralazine is often given in conjunction with β blockers, methyldopa, or clonidine, which all block central sympathetic stimulation. Hydralazine is often used as a component of a complex multiagent antihypertensive regime. Its use with other antihypertensives makes the assessment of its independent effects on erectile function difficult to assess. However, cases have been described where ED has disappeared after the cessation of hydralazine (19,23). Another vasodilator that may be used in its place, without the same degree of sexual dysfunction, is Minodoxil (Loniten).

Antidepressants and ED

There are many putative causes of sexual dysfunction in the depressed population, including primary sexual dysfunction, sexual dysfunction associated with medical and psychiatric diseases, and sexual dysfunction associated with treatment of the depression. In one study, a group of depressed patients, prior to initiation of therapy, had an incidence of ED of 35%, and decreased libido of 31% (48). Antidepressant medication has been reported to affect libido, potency, and ejaculation. The antidepressants most commonly reported to cause sexual dysfunction include tricyclics, monoamine oxidase inhibitors (MAO inhibitors), serotonin reuptake inhibitors (SSRI's), and lithium.

Tricyclic Antidepressants

Tricyclic antidepressants are anticholinergics with sedative and antihistaminic properties. Their therapeutic impact is based on presynaptic norepinephrine reuptake blockade and to the sensitization of postsynaptic neurons to serotonin (35). Tricyclics have been associated with elevated prolactin levels and impotence (49). Decreased libido has been reported with the use of various tricyclics including amitriptyline, imipramine, doxepin, clomipramine, desipramine, and nortriptyline (50–53).

Imipramine, amitriptyline, clomipramine, desipramine, amoxapine, maprotiline, nortriptyline, and protriptyline have been reported to cause impotence (51,54–56). These effects are believed to be secondary to the anticholinergic effect (57). Ejaculatory dysfunction has also been described in patients taking tricyclic antidepressants. Painful ejaculation has been reported with clomipramine, imipramine, desipramine, and protriptyline (58–62). Inhibition of ejaculation has been proposed to be secondary to their sympatholytic effect.

MAO Inhibitors

This group of medications is most commonly used for atypical neurotic depression (63). Their mechanism of action relies on a MAO blockade, which catalyzes the oxidation of the biogenic amines tyramine, 5-HT, dopamine, and norepinephrine. The MAO inhibitors include phenelzine, isocarboxazid, tranylcypromine, clorgyline, and pargyline. Some have postulated that whereas tricyclics exert their effects on sexual functioning with an anticholinergic mechanism, MAO inhibitors have a more profound effect on sexual drive (64). In a study by Remick et al. (1989), sexual dysfunction was reported as 16–31% with patients that were taking MAO inhibitors (65). Occasional reports of ejaculatory dysfunction have been described with the various MAO inhibitors, however, these are described exclusively in case reports (66). No precise data from prospective randomized placebo-controlled trials exist to define the incidence of these side effects.

Serotonin Reuptake Inhibitors

Several possible mechanisms for impairment in sexual function have been described for patients taking SSRIs. These include potential modulating effects of dopamine, prolactin, and nitric oxide pathways. The SSRIs have most strongly been linked to ejaculatory dysfunction. These side effects are dose related, supporting careful clinical assessment to assure the lowest possible dose is used (67). One large-scale nonrandomized study looked at 596 psychiatric patients on various SSRIs. The incidence of sexual dysfunction was 20% of patients overall. The rates on various medications ranged from 16% of patients on sertraline to 38% of patients on venlafaxine. The most common effects were of delayed orgasms, absence of orgasms, and decreased desire (68).

In general, paroxetine has been found to have the greatest potential for sexual dysfunction with most reports hypothesizing that its anticholinergic activity is largely responsible for this side effect (69,70). Alternatively, it is believed that paroxetine is an inhibitor of nitric oxide synthetase (71), or has greater selectivity for serotonin reuptake relative to dopamine reuptake. Various mechanisms for avoiding the side effect profile of the SSRIs include waiting for tolerance to develop, dosage reduction, drug holidays, switching to a different antidepressant, and augmenting sexual function by adding a second medication (e.g., sildenafil) to counteract the dysfunctional effect. SSRIs may also have a positive effect on sexual functioning. The use of SSRIs in the management of premature ejaculation has been well described (72,73).

Lithium

Lithium carbonate is medication that is recommended in patients with acute bipolar disorder, depressed patients with bipolar disorder, and as long-term prophylaxis of mania in a bipolar patient. The mechanism of this effect is relatively unknown. However, it is known to increase central norepinephrine reuptake and decreases its release. Its mechanisms of action is via depression of dopaminergic activity by decreasing receptor sensitivity. The reported rate of ED in the literature is variable, however, one study of men taking lithium reported a 15% incidence of ED (74).

Several alternatives have been suggested for dealing with antidepressant-induced ED. One of the more successful strategies is to switch to a drug that has minimal effects on sexual functioning. Bupropion has been implicated as one such drug. It has mild dopamine stimulatory effects and serotonin effects and is believed to increase sexual desire and arousal (75). Other medications such as mirtazapine and nefazodone

have 5-HT₂ blocking effects postsynaptically and, in addition, are serotonin agonists, which help to maintain the ability of most patients in achieving normal orgasms (76,77). Another option for dealing with antidepressant-induced ED includes decreasing the dosage or drug holidays (78). Unfortunately, this frequently has implications on the efficacy of therapy of depression.

ANTIPSYCHOTICS AND ED

Antipsychotics have traditionally been classified into six different categories:

1. Phenothiazines;
2. Thioxanthines;
3. Dibenzoxazepines;
4. Dihydroindolones;
5. Butyrophenones; and
6. Diphenylbutylpiperidines.

The pharmacological characteristics of this drug class implicated in causing ED in patients taking antipsychotics include anticholinergic properties, α adrenergic blockade, endocrine, and sedative effects. In one retrospective chart review that compared 87 men receiving antipsychotic medication, thioridazine (a phenothiazine), an agent with significant anticholinergic, and α -blocker properties was compared to patients taking medications with less peripheral effects (chlorpromazine, trifluoperazine, thiothixene, fluphenazine, prochlorperazine, perphenazine, and haloperidol). The incidence of sexual dysfunction was 60% in patients taking thioridazine as compared to 25% in all other patients (79). The phenothiazines and butyrophenones (i.e., haloperidol) have been found to cause significant sedation, anticholinergic effects, and antidopaminergic actions localized to the hypothalamus and pituitary. Most of the reports of sexual dysfunction are described within the first 24 h of therapy, and resolve once therapy is discontinued (80).

α blockade is responsible for the decreased emission, priapism, and retrograde ejaculation found in patients taking antipsychotics. Thioridazine is probably the most commonly associated with changes in ejaculation, and in one study upward of 49% had this side effect (79). Chlorpromazine has also been found to cause ejaculatory failure, most likely a response to the α -blocking effect of the medication (81,82).

The dopamine-blocking properties of antipsychotics also have various implications on sexual functioning. Dopamine is known to stimulate the hypothalamic tuberoinfundibular system and results in an inhibition of prolactin secretion from the pituitary gland. Blocking dopamine can cause a substantial rise in serum prolactin levels (83), and may impair libido. Thioridazine has also been found to inhibit testosterone primarily (84).

The sedative effect of anticholinergics has implications for sexual functioning. The phenothiazines as a group cause the greatest amount of sedation and have subsequently been found to cause the greatest inhibition of libido of all the antipsychotics (85).

One strategy for dealing with antipsychotic induced sexual dysfunction is to attempt dose reduction. Changing medications from a phenothiazine to a nonphenothiazine antipsychotic class is another option, as there are believed to be fewer erectile function problems in the nonphenothiazine group. A third strategy would be to add an additional medication. Sildenafil has been found to be effective in cases of antipsychotic induced ED (86).

Table 2
Psychotropic Drugs Implicated in Erectile Dysfunction

<i>Drug/Drug Class</i>	<i>Adverse Effect</i>
ANTIDEPRESSANTS	
Tricyclic Antidepressants	
Imipramine, amitriptyline, doxepin, Clomipramine, desipramine	Decreased libido, impotence, painful ejaculation, inhibition of ejaculation
Monoamine Oxidase Inhibitors	
Phenelzine, isocarboxazid, Tranylcypromine, clorgyline, Pargyline	Decreased libido, ejaculatory dysfunction
Serotonin Reuptake Inhibitors	
Sertraline, paroxetine	Ejaculatory dysfunction
Lithium	Impotence
ANTIPSYCHOTICS	
Chlorpromazine	Decreased libido, impotence, anejaculation
Chlorprothixene	Inhibition of ejaculation
Fluphenazine	Decreased libido, impotence
Mesoridazine	Anejaculation, impotence
Haloperidol	Impotence, painful ejaculation
Perphenazine	Decreased ejaculation
Thioridazine	Impotence, impaired ejaculation
Thiothixene	Impotence
Trifluoperazine	Impaired ejaculation
ANTI-ANXIETY	
Benzodiazepines	
Clonazepam, diazepam	Decreased libido, impotence

ANTI-ANXIETY AGENTS AND ED

Traditionally, there was believed to be no relationship between benzodiazepines and ED. Many studies showed that these agents, including diazepam, were safe to use (87,88). Some recent studies including one from the United States Veterans, implicated clonazepam as a significant cause of ED in men being treated for post-traumatic stress disorder. Forty-three percent of men in this group had ED (89). The proposed mechanism of action is believed to be mediated through central serotonergic activity (90). In one study, the combination of lithium and benzodiazepines was found to increase sexual dysfunction in 49% of patients (91).

Some investigators have put forth a hypothesis that a low dose of benzodiazepines creates a state of disinhibition and actually improves sexual functioning (92). Diazepam however, may also decrease libido secondary to its sedative effects. The other point to keep in mind is that the sexual side effects found in the patients taking benzodiazepines may be secondary to the underlying anxiety state of the patient. Based on these reports, however, any patient who develops sexual dysfunction on an anti-anxiety agent should be switched to an alternate benzodiazepine with lower incidence of erectile dysfunction.

H2 BLOCKERS AND ED

Histamine antagonists are very frequently used in a hospital setting and have been reported to cause a depression in libido and ED. Cimetidine in particular is believed to act as an antiandrogen and is also thought to increase serum prolactin levels (93–95). Breast pain and gynecomastia are thus frequent side effects of this medication. Cimetidine is believed to inhibit testosterone from binding to androgen receptors (96), a dose-related side effect. In one study of men taking greater than 5 g of cimetidine/d, 40% of these men reported ED (97).

Ranitidine has also been found to cause an increase in prolactin levels, however, the frequency of erectile failure is less than in patients taking cimetidine. Famotidine (Pepcid) does not appear to have any antiandrogenic or hyperprolactinemic effects and has not been reported to cause any significant degree of erectile problems (19). One report has also been published looking at the incidence of ED in men taking the proton pump inhibitor omeprazole (98). The results from this report failed to demonstrate a relationship between the use of proton pump inhibitors and ED. As such, this medication has been prescribed for patients in whom significant sexual dysfunction develops while taking H2 blockers.

HORMONAL AGENTS AND ED

Antiandrogens, estrogens, LHRH agonists, corticosteroids, progestational agents and anabolic steroids have all been associated with sexual dysfunction. The antiandrogens can be classified as either steroidal or nonsteroidal. The nonsteroidal antiandrogens include flutamide, nilutamide (Anandron), and bicalutamide (Casodex). These agents are commonly used in the treatment of advanced prostate cancer. The nonsteroidal antiandrogens do not have any antigonadotropic effects; rarely an elevation in luteinizing hormone levels and serum testosterone levels is subsequently found. The nonsteroidal antiandrogens act by counteracting the effect of hormones at their target cell. Because of its mechanism of action, flutamide has less of an effect on sexual potency than steroidal antiandrogens such as cyproterone acetate. This medication has significant progestational activity, which inhibits LH release from the pituitary and produces castrate levels of testosterone for androgen receptor sites.

Other medications used for advanced prostate cancer include LHRH agonists (Luprolide acetate, buserelin, goserelin acetate), and estrogens (diethylstilbestrol). These agents have been found to suppress testosterone and dihydrotestosterone levels by acting on the hypothalamic- pituitary- gonadal axis (23,35). Chronic administration of LHRH agonists make the pituitary resistant to further stimulation by endogenous LHRH and, after approx 2 wk, the production of testicular androgens is prevented.

Anabolic steroids have also been found to cause sexual dysfunction, and is believed to result in inhibition of gonadotropin-releasing hormone release and the subsequent hypogonadism that results (99). These effects may be reversible over a period of several months (100).

The 5 α reductase inhibitor finasteride (Proscar) has been used previously for patients with benign prostatic hyperplasia, and is still currently recommended for patients with BPH, with a prostate larger than 50 g, where symptoms are unresponsive to α blockers. This medication inhibits the conversion of testosterone to its more-active metabolite dihydrotestosterone. Finasteride has been found in various studies to cause

Table 3
Miscellaneous Medications Implicated in ED

<i>Drug/Drug Class</i>	<i>Adverse Effect</i>
ANTI-HISTAMINES	
Cimetidine, ranitidine	Decreased libido, impotence
HORMONAL AGENTS	
Antiandrogens	
Flutamide, nilutamide, bicalutamide	Minimal effect on sexual functioning
Cyproterone acetate	Impotence, decreased libido
LHRH Agonist	
Luprolide acetate, buserelin, goserilin Acetate, and DES	Impotence, decreased libido
Anabolic Steroids	Impotence
5 α reductase inhibitor	
Finasteride	Impotence, decreased libido
LIPID-LOWERING AGENTS	
Fibrates	
Clofibrate, Gemfibrozil	Erectile dysfunction
HMGCoA reductase inhibitors	
Lovastatin, pravastatin, simvastatin	Erectile dysfunction
Digoxin	Decreased libido, impotence
RECREATIONAL DRUGS	
Alcohol	Decreased libido, erectile difficulty
Narcotics (codeine, meperidine, methadone, heroin)	Decreased libido, ejaculatory failure
Nicotine	Impotence
Marijuana	Impotence, decreased libido
Cocaine	Decreased libido, delayed ejaculation

ED and decreased libido. A 3–5% incidence of impotence and loss of libido has been demonstrated (101).

LIPID-LOWERING AGENTS AND ED

Lipid-lowering agents are frequently used in conjunction with other medications and in patients with cardiovascular disease, making the finding of ED in this group of men difficult to assign blame. Clofibrate was reported in one study to cause ED in 14.1% of patients who took this medication (this was significantly higher than the placebo group) (102). The lipid-lowering agents are believed to impair production of sex hormones by lowering the availability of cholesterol (103). Clofibrate is also believed to compete for protein-binding sites with androgens and thus leads to an increased clearance of androgens (104). Gemfibrozil has also been found to cause ED, however, discontinuation of therapy has been shown to reverse this effect in most patients (105).

3-hydroxy-3 methyl glutaryl coenzyme A (HMGCoA) reductase inhibitors (lovastatin, pravastatin, simvastatin) have been shown in several trials to result in ED (106–108). This effect appears to resolve once therapy has been discontinued. The mechanism of the ED has not yet been clearly elucidated.

DIGOXIN AND ED

Digoxin has a similar chemical structure to sex steroids. Because of this, digoxin has been found to cause a decrease in serum testosterone and an increase in estrogen, and subsequent sexual dysfunction has been a complaint of many digoxin users (109). Gynecomastia has also been found in many men that have been taking digoxin (110).

RECREATIONAL DRUGS AND ED

Various illicit and nonillicit recreational drugs have been implicated in sexual dysfunction. The most notable of such drugs are alcohol, narcotics, nicotine, marijuana, and cocaine. Alcohol at low doses is believed to cause a state of disinhibition, which may heighten the libido state. However, excessive use of alcohol may lead to erectile problems either acutely or chronically. Often, the sedative effects can override the disinhibiting effects. Chronic alcoholics have been reported to have erectile problems in up to 54% of the studied population (111–113). Men often report having decreased orgasmic pleasure, decreased sexual arousal, and increased ejaculatory latency (114). Some possible causes of these findings are that alcohol has been found to affect the hypothalamic-pituitary axis and may cause features of hypogonadism. Serum testosterone levels may also be decreased (115). Alcoholics may also develop a polyneuropathy, and heavy alcohol abuse may lead to liver damage with impaired ability to metabolize estrogens (116).

Narcotics such as codeine, meperidine, methadone, and heroin have been found to decrease libido and cause ejaculatory failure (117,118). Opiates have been found to decrease luteinizing hormone secretion by impairing hypothalamic secretion of gonadotropin-releasing hormone. Opiates have also been found to cause an elevation in serum prolactin levels (119). Other proposed mechanisms of opiate-induced ED is that opiates have been found to shunt blood away from the genitals into the systemic circulation. Morphine has also been found to decrease systemic vascular resistance because of its selective effects on cutaneous arteriolar circulation (120–122), and this may explain the shunting of blood away from the genitalia. The ejaculatory failure seen may be secondary to the anti- α -adrenergic effect that heroin has on the presynaptic opiate receptors that are necessary for the movement of semen into the posterior urethra (123,124).

Nicotine, perhaps one of the most commonly abused drugs, has also been found to significantly impact on sexual functioning. Smokers in one large population survey study were found to be twice as likely as age-matched nonsmoking controls to have problems with ED (125). Nicotine is believed to cause erectile problems by causing vasoconstriction locally on the internal pudendal artery (126). Smoking is also known to increase ones risk for atherosclerotic and vascular disease. Some other long-term effects may be an elevation of carbon monoxide levels and an increase in platelet aggregation, which would compound any of the previous vascular compromise seen (127).

Marijuana's active ingredient is called Δ -9-tetrahydrocannabinol (THC). Chronic use of this drug has been found to reduce erectile function (23). The mechanism by which this effect is seen is believed to be by decreasing the serum testosterone levels. Interestingly, there have also been reports of enhanced sexual function in people taking marijuana in the acute setting (113). In one survey, 68% of respondents felt that marijuana improved the quality of their orgasms, and 90% reported a global sexual improvement (128).

Cocaine also has proven to have a mixed profile regarding its effects on sexual functioning. Some have reported that cocaine reduces libido and erectile functioning when taken long-term (23). Some long-term users feel that cocaine improves their performance (129). Cocaine acts by decreasing catecholamine reuptake and this most likely causes central excitatory action, which may account for its aphrodisiac quality acutely.

SUMMARY

The current treatment of ED is evolving rapidly with new oral and topical agents expected to gain government approval over the next few years. The ability to enhance normal physiology through medications acting in the peripheral nervous system or within the central erection centers will likely become a common treatment strategy in the years to come.

At present, when ED is noted clinically, a careful assessment of the potentially reversible causes should be undertaken. Among the most easily treated aspects of this approach is a careful review of the time-course and change in any drug therapy that may be a factor inducing the ED.

In many cases, switching to an alternative medication in the same class, combining medications (such as antihypertensives and using lower doses), or altering the time of drug intake may reduce the negative effects of these agents to acceptably low levels. The clinician needs to be sensitive to the voiced concerns of the patient as drug non-compliance, secondary to drug-induced ED, is common.

Research into the physiology of erection is ongoing using novel techniques, which explore the possibility of enhancing neurotransmitter levels or alter the responsiveness of ion channels, look promising as potential future approaches dealing with medication related ED. However, until these new methods are available clinically, the best approach for the present appears to be a well-informed physician with knowledge about drug-associated ED side effects and the strategies to mitigate them.

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Management of Erectile Dysfunction Following Radical Prostatectomy

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INTRODUCTION

Prostate cancer is the most commonly diagnosed and treated solid tumor in American men. In 1999, approx 180,000 new cases of prostate cancer were diagnosed, whereas more than 37,000 men died of the disease (1). Treatment options for prostate cancer include radical prostatectomy, external beam radiation, hormonal ablation, and brachytherapy. Each of these modalities is associated to some degree with erectile dysfunction (ED) as a potential consequence of treatment. Radical prostatectomy continues to be the treatment of choice in the majority of cases of organ-confined prostate cancer. Careful extirpation of the prostate gland in these patients offers a hope for cure. Although rates of tumor eradication with this procedure are excellent, radical prostatectomy is not without morbidity. Sexual and voiding dysfunction are the most frequent complications of radical prostatectomy (2). The recently published Prostate Cancer Outcomes study reported that at 18 mo following radical prostatectomy, 8.4% of men were incontinent for urine, whereas 59.9% of men were impotent (3). These patients may also exhibit other sexual dysfunctions such as ejaculatory failure, shortening of the penis, fibrotic changes in the penis, and orgasmic dysfunction.

The overall incidence of prostate cancer increases annually as a reflection of improved screening and detection methods—namely the prostate-specific antigen test (PSA). Likewise, there has been a decrease in the mean age of diagnosis from 72 yr in 1983 to 69 yr

in 1994. As a consequence, urologists will treat an increasing number of younger men with prostate cancer. Many of these patients will weigh the prospect of losing potency against accepting the most appropriate treatment. The following is a discussion of current concepts in the pathophysiology and treatment of ED following radical prostatectomy.

ETIOLOGY AND MECHANISM OF DISEASE

Physiology

In order to understand the etiologies of ED in men undergoing radical prostatectomy, it is helpful to review the neural and vascular pathways that function during penile erection. Normal erectile function involves three synergistic and simultaneous processes:

1. Neurologically mediated increase in penile arterial inflow;
2. Relaxation of the cavernosal smooth muscle; and
3. Restriction of venous outflow from the penis.

ED in the postprostatectomy patient occurs as a result of the failure of these processes, either alone or in conjunction with each other.

The penis is composed of three bodies of tissue separated by connective tissue septae. The singular corpus spongiosum supports and protects the urethra along the ventral state surface of the penis. The paired corpora cavernosa, which lie dorsally and adjacent to each other, function as blood-filling reservoirs and provide structure to the penis in the erect state. The cavernosal bodies are composed of a network of vascular sinuses supplied by the helicine arteries (terminal branches of the cavernosal arteries). In the flaccid state, the smooth-muscle trabeculae, which support the vascular sinuses are tonically contracted and permit only a small amount of arterial inflow (4). The release of neurotransmitters from the cavernous nerve terminals and smooth-muscle endothelium in response to sexual stimulation results in cavernosal smooth-muscle relaxation. Cholinergic nerves, nonadrenergic noncholinergic nerves (NANC; nitric oxide), and other factors such as vasoactive intestinal peptide (VIP) and calcitonin gene-related peptide (CGRP) mediate cavernosal smooth-muscle relaxation. In addition, shear stress and acetylcholine receptors on the trabecular endothelium stimulate the production of nitric oxide. Nitric oxide from NANC nerves and the trabecular endothelium diffuses into the smooth-muscle cells where it directly interacts with the soluble form of guanylate cyclase to increase intracellular levels of cyclic GMP (cGMP). The increase in cGMP then influences a number of cellular processes that result in smooth-muscle relaxation, primarily through activation of the cGMP-associated protein kinase. Similar to the more familiar cyclic AMP (cAMP) pathway, cGMP activity is terminated by hydrolysis of the 3'5' bond by type-5 phosphodiesterase. VIP, CGRP, and prostaglandin-mediated pathways, which produce an increase in intracellular cAMP, may also contribute to smooth-muscle relaxation in the penis. The increased corporal arterial inflow results in an increase in intracavernosal pressure and volume. As the penis expands in length and girth, the intracavernosal pressure eventually exceeds that of the subtunical venular plexus, thereby compressing it between the tunica albuginea and the peripheral sinusoids. This process of veno-occlusion results in tumescence (5).

Neurogenic Etiology of Postprostatectomy ED

It is relatively easy to appreciate the manner in which iatrogenic disruption of the cavernosal neural innervation would cause ED in the postprostatectomy patient. The

penis receives its neural innervation from both the somatic and autonomic nervous systems. Somatic afferent fibers carry sensory signals from the phallic skin through the dorsal nerve of the penis. Somatic efferent fibers mediate contraction of the bulbocavernosal and ischiocavernosal muscles during erection. Autonomic innervation is both sympathetic and parasympathetic. Preganglionic sympathetic efferent nerves to the penis originate from the lateral horn of the spinal cord in segments T10–T12. These fibers travel through the superior hypogastric plexus to the pelvic plexus. Parasympathetic efferent nerves to the penis originate from spinal cord segments S2–S4. These fibers travel through the pelvic nerve to the pelvic plexus (6).

Within the pelvic plexus, the sympathetic and parasympathetic fibers mingle and emerge as a single source of autonomic input to the penis. These autonomic fibers penetrate the urogenital diaphragm and become the cavernosal nerves. Prior to this, however, the autonomic fibers that emerge from the pelvic plexus are located in the neurovascular bundles. The neurovascular bundles lie posterolaterally along each side of the prostate invested between two layers of the lateral pelvic fascia—the levator fascia and the prostatic fascia. The anatomic location of the neurovascular bundles makes them highly susceptible to injury during extirpation of the prostate gland.

Prior to Walsh's efforts to pioneer a "nerve-sparing" approach, the neuro-vascular bundle was routinely sacrificed during radical retropubic prostatectomy. Resulting postoperative impotence rates ranged from 90–100%. Walsh and Donker traced the autonomic innervation of the corpora cavernosa to determine the topographical relationship between the pelvic plexus and the prostate (7). Walsh hypothesized that impotence following radical prostatectomy resulted from iatrogenic disruption of pelvic plexus output. Given a more-detailed characterization of the neural innervation of the cavernosal bodies, Walsh concluded that this neural injury most likely occurred during division of the lateral pedicle or at the time of apical dissection, and developed refinements in surgical technique in the hopes of avoiding this complication while maintaining the primary goal of tumor excision (7). Walsh published potency rates of nearly 70% following implementation of his novel nerve-sparing approach. Although this degree of success was not reproduced in several other series that followed, postoperative potency rates have consistently correlated with the degree of nerve sparing (non-nerve-sparing vs unilateral nerve-sparing vs bilateral nerve sparing). Furthermore, it is clear that whereas complete neurotomy nearly guarantees impotence, preservation of the neurovascular bundle does not necessarily guarantee potency. Assuming the integrity of the neurovascular bundle, the effects of neural traction, microvascular-trauma, and tissue hypoxia must be considered when assessing the ability of cavernous nerves to function postoperatively.

Arteriogenic Etiology of Postprostatectomy ED

Likewise, it is relatively easy to appreciate the manner in which an iatrogenic disruption of arterial blood flow to the penis would cause ED in the postprostatectomy patient. The penis receives arterial inflow from the paired penile arteries, which are terminal branches of the internal pudendal arteries, beginning distal to the perineal arteries in Alcock's canal. The penile arteries divide into three branches—the bulbourethral, dorsal, and cavernous arteries. The *bulbourethral artery* is the first branch of the penile artery. Proximally, it supplies Cowper's glands and the penile bulb. As it continues its course, the bulbourethral artery supplies the corpus spongiosum, the urethra and the glans penis. The major arterial supply of the glans penis, however, is derived from the *dorsal*

artery of the penis, which lies beneath Buck's fascia. Circumflex arteries arise from the dorsal artery as it courses distally and provide accessory flow to the cavernosal bodies. The primary arterial source to the corpus cavernosum is the *cavernosal artery*. Its terminal branches are the tortuous helicine arteries, which dilate to provide increased corporal blood flow during erection (4). Because of its anatomic location, injury to the internal pudendal artery is a very rare, but potential complication, and is thus considered in this discussion of arteriogenic etiologies of postprostatectomy ED.

More significant, however, is the prevalence and role of the accessory pudendal arteries. In 1989, Breza et al. performed a detailed dissection of 10 male cadavers with the specific intent of examining the anatomy of the penile neurovascular structures. An accessory pudendal artery was identified in 7 of 10 cadavers. These accessory pudendal arteries originated from the obturator, inferior vesical and superior vesical arteries. Because these aberrant branches course along the inferior bladder and anterolateral surface of the prostate, they are much more susceptible to injury or ligation during the course of a prostatectomy. The effect of such on erections depends largely on the extent to which they contribute to penile blood flow. Breza et al. reported that the majority (75%) of accessory pudendal arteries in their cadavers fed cavernosal arteries. Patients in whom these accessory arteries are dominant, or whose primary pudendal arteries are diseased (i.e., from hypertension, smoking, diabetes mellitus, hypercholesterolemia, and so on) would likely suffer the greatest detriment to erectile function (8).

Veno-Occlusive Etiology of Postprostatectomy ED

It is relatively easy to appreciate the manner in which simple iatrogenic disruption or injury of the penile neurovascular structures causes ED in the postprostatectomy patient. What is less apparent, however, is the explanation for the development of venous leakage in these patients. During an erection, the combination of increased penile arterial blood flow and relaxation of the cavernosal smooth muscle creates an increase in cavernosal pressure. Because the cavernosal bodies are encompassed by the tunica albuginea, this increase in pressure exceeds the pressure of the subtunical venous plexus, thereby trapping venous blood within the cavernosal bodies—veno-occlusion. Failure of the cavernosal bodies to expand, secondary to structural alteration of the tissue or deficits in mediators of smooth-muscle relaxation, leads to venous leakage and ED.

Nehra et al. demonstrated a direct correlation between erectile function and the ratio of trabecular smooth muscle to total erectile tissue. Using cavernosal biopsies taken from men with ED undergoing penile prosthesis placement, Nehra demonstrated that the men with the lowest percentage of smooth-muscle composition required the highest flow to maintain erection on Doppler studies (indicating venous leakage). Histological examination of cavernosal tissue revealed a relative predominance of connective tissue in these same patients. Nehra et al. concluded that successful veno-occlusion requires a critical balance of trabecular smooth muscle and connective tissue (9).

Moreland's in vitro experiments have linked these types of structural changes to tissue hypoxia. Moreland hypothesized that differences in cavernosal oxygen tension in the flaccid and erect states regulate the expression of cytokines, autoids, and growth and vasoactive factors that play a critical role in connective tissue metabolism. Specifically, Moreland investigated the role of cavernosal oxygen tension in the expression of transforming growth factor (TGF)- β and prostaglandin E (10).

TGF- β is a cytokine that favors connective tissue synthesis by inducing the expression of collagen and other matrix components, while inhibiting the enzymes responsi-

ble for their degradation (11,12). Moreland investigated the effect of hypoxia on the expression of TGF- β mRNA in human cavernosal tissue in vitro. At oxygen tensions consistent with flaccid cavernosal tissue (30 mmHg), Moreland noted increases in TGF- β mRNA expression, twofold in 18 h and threefold in 24 h (13). Additionally, Moreland demonstrated a two- to four-fold increase in collagen synthesis by cultured human cavernosal smooth-muscle cells in the presence of TGF- β (14).

Prostaglandin E is an autocoid that acts via the cAMP pathway to relax cavernosal smooth muscle. The synthesis of PGE by cavernosal smooth muscle cells in culture is inhibited at oxygen tensions of 30 mmHg (13). Previous studies have demonstrated the reduction of collagen synthesis by cultured human lung fibroblasts treated with PGE (15). Furthermore, PGE acts via the cAMP pathway to inhibit TGF- β -induced collagen synthesis in cultured fibroblasts (16).

Moreland applied his observations from these in vitro experiments to construct the following hypothesis regarding the role of hypoxia in penile fibrosis. During the course of a normal erection, oxygen tension in the penis increases from approx 30–40 mmHg in the flaccid state to nearly 100 mmHg in the rigid state. Oxygen tensions consistent with flaccid cavernosal tissue (30 mmHg) induce TGF- β mRNA expression with concomitant prostaglandin E suppression, thereby favoring collagen deposition and tissue fibrosis. Cavernosal oxygenation influences the balance between trabecular smooth muscle and connective tissue by regulating the expression of cytokines and autocoids (such as TGF- β and prostaglandin E, respectively), which play a critical role in the synthesis and degradation of matrix components (10).

Sattar et al. demonstrated a supporting relationship between cavernosal oxygen tension and the quantity of smooth muscle fibers in vivo. Sattar et al. recorded cavernosal oxygen tension during flaccidity and 10 min after administration of intracavernosal PGE1, and performed cavernosal biopsies in order to quantify the percentage of smooth-muscle fibers. A significant correlation between the percentage of smooth-muscle fibers and the cavernosal oxygen tension in the flaccid phase was noted (17). Ciancio recently reported observing evidence of penile fibrotic changes in an unexpectedly high proportion of patients (45 of 110, 41%) referred for evaluation of ED following radical retropubic prostatectomy (18).

In addition to the aforementioned role in the development of cavernosal fibrosis and veno-occlusive ED, penile hypoxia appears to regulate the nitric oxide pathway that is critical to cavernosal smooth-muscle relaxation. Kim et al. concluded that nitric oxide synthesis in cavernosal tissue is regulated by oxygen tension. Using isolated human and rabbit cavernosal tissue strips in organ baths, Kim reported progressive inhibition of nitric oxide-mediated relaxation in response to acetylcholine and stimulation of autonomic dilatory nerves as a function of declining oxygen tension. Although the expected relaxation responses were restored with the restoration of normoxic conditions, hypoxic conditions did not impair relaxation in the presence of exogenous nitric oxide. Kim concluded that nitric oxide-mediated relaxation of cavernosal smooth muscle may be limited under conditions of reduced oxygen tension, regardless of the integrity of the nitric oxide secreting nerves and endothelium (19).

The concept of cavernosal oxygenation may be at the center of a multifactorial explanation for the development of ED in postprostatectomy patients. In the flaccid state, cavernosal oxygen tensions approach that of venous blood. The synthesis of nitric oxide may be inhibited under these conditions, thereby preventing the relaxation of trabecular smooth muscle. These conditions may likewise induce the expression of

the fibrogenic cytokine TGF- β with the concurrent suppression of the antifibrotic auto-coid prostaglandin E, thereby altering the structural composition of the corpora in favor of connective tissue synthesis. The product of these hypoxic conditions is a corporal body with neither sufficient mediators nor the appropriate histology to relax and engorge with arterial blood.

Under normal conditions, nocturnal penile tumescence and spontaneous erections in the absence of sexual stimuli may provide the corpora with transient elevations in oxygen tension sufficient to maintain a functional balance of smooth muscle and connective tissue (10). In the postprostatectomy patient, the recovery of spontaneous erectile function, even in the wake of meticulous preservation of the neurovascular bundle, routinely takes 1 yr or more to recover. During this time, the corpora may endure hypoxic conditions that can lead to the aforementioned structural changes and eventually veno-occlusive ED.

TREATMENT MODALITIES

Overall Considerations

When developing a treatment plan, it is important to recognize the following order of priorities in the surgical care of a prostate cancer patient:

1. Eradication of the tumor;
2. Maintenance of urinary continence; and
3. Preservation of sexual function.

Preoperatively, it is important to consider the patient's age and comorbid conditions. These factors may influence the patient's ability to tolerate a given procedure. In addition to age, an assessment of preoperative erectile function and the clinical grade, stage, and location of the tumor are factors that predict the likelihood of developing ED postoperatively. In keeping with tumor eradication as the highest treatment priority, these parameters may likewise dictate the type of procedure performed regarding the degree of nerve sparing attempted. Preoperative erectile function may also potentially affect procedure selection in the case of simultaneous inflatable penile prosthesis insertion. From a psychological standpoint, it is crucial to counsel the patient and his partner regarding the likelihood of developing postprostatectomy ED, and to discuss the reasonable expectations and timeline for the return of spontaneous erectile function. Access to adjuvant professional sexual counseling should be made available to all couples (20). Last, but certainly not least, we must consider and respect each patient's personal desires for postoperative potency.

Intraoperatively, the implementation of meticulous surgical technique offers the greatest hope of complete tumor eradication while maintaining urinary continence and sexual function. In general, the ability to preserve functional neurovascular bundles will improve with techniques that enhance visualization of the prostatic apex and reduce unnecessary traction injury. General measures to improve visualization include proper patient positioning, adequate lighting, and the maintenance of a clean surgical field. It has been suggested that the classical approach to radical prostatectomy involving initial division of the urethra followed by release of the neurovascular bundles may limit visualization of the prostatic apex and increase the likelihood of traction injury. Klein has reported on his experience using an approach wherein the urethra is divided

only following incision of the lateral pelvic fascia with release of the neurovascular bundles and the development of a plane between the rectum and prostate. This approach offers the advantages of improved apical visualization and reduced neurovascular bundle traction. Klein has reported a lower incidence of positive margins when employing this technique (21). Regardless of what personal modifications to classical technique are incorporated, a consistent systematic approach is likely to produce the best results.

Precise localization and visualization of the neurovascular bundle is often difficult secondary to variation in anatomic location of the cavernous nerves, lack of exposure because of body habitus, the presence of overlying tissue or blood obscuring the field, or poor lighting. Lue et al. pioneered the technique of intraoperative cavernous nerve electrostimulation as a means of increasing the precision and speed with which the neurovascular bundle may be identified. Lue noted a significant degree of tumescence in the majority (8 of 11, 73%) of prostatectomy patients who reported preoperative potency, thereby demonstrating the feasibility of this novel technique (22). More recently, Klotz and Herschorn reported on their experience using the CaverMap system (Uromed Corporation, Boston, MA) that incorporates simultaneous penile tumescence monitoring with cavernous nerve electrostimulation. Seventeen patients with preoperative erectile function demonstrated a tumescence response to cavernosal nerve electrostimulation. Sixteen of those patients (16 of 17, 94%) reported some degree of erectile function 12 mo postoperatively (11 partial erections, 5 full erections). This study suggests the utility of penile tumescence monitoring with intraoperative cavernous nerve electrostimulation in improving the surgeon's ability to preserve the neurovascular bundle, thereby improving the likelihood of postoperative erectile function. Validation of the CaverMap system's ability to objectively improve postprostatectomy erectile function is the focus of a current multi-center, blinded, randomized, prospective trial (23). The role of cavernous nerve "mapping" in prostate surgery is uncertain. However, further refinements in this relatively new technology may enhance its application in the future.

Postoperatively, early evaluation and implementation of treatment are essential. Slovick et al. recently investigated the incidence of venous leakage in post-radical prostatectomy patients with respect to the timing of the postoperative hemodynamic evaluation. The incidence of venous leakage in patients evaluated within the first 4 postoperative mo (< 4 mo) was 8%. This number climbed to 22%, however, in patients evaluated between 4 and 8 mo, and 50% in patients evaluated between 8 and 12 mo (24). Slovick et al. likewise investigated the correlation between postoperative hemodynamic diagnosis and the recovery of spontaneous erectile function within 12 postoperative mo. In men with normal vascular evaluations and presumed neurogenic impotence, 50% regained spontaneous erectile function within the first postoperative year. This number fell to 25% when Doppler studies revealed evidence of arterial insufficiency. Most significantly, however, the presence of venous leakage heralded permanent ED in all affected patients (25). These studies highlight the importance of early postoperative evaluation and treatment.

Pharmacologic Treatments

The most current approach in the management of postprostatectomy ED involves the early institution of scheduled erectogenic pharmacologic therapy. The belief that "erect-

tions are good for erections” is based on the aforementioned data supporting the role of hypoxia in the development of penile fibrosis. Two FDA approved agents are utilized in this capacity at this time—PGE1 and sildenafil citrate.

Alprostadil is a formulation of PGE1 delivered by intracavernosal injection. PGE1 binds directly to receptors on cavernosal trabecular smooth-muscle cells and induces erection by causing smooth-muscle relaxation. The pathway is mediated by an increase in cAMP. Alprostadil is the current gold standard in the pharmacologic treatment of ED in the postprostatectomy patient. The reason for this is threefold. First, the ability of PGE1 to directly relax cavernosal smooth muscle allows it to operate independently of endogenous vasoactive mediators (such as nitric oxide) that may be deficient in the postprostatectomy patient secondary to neural trauma or hypoxic conditions (26). Additionally, *in vitro* experiments have demonstrated that elevations in cAMP produced by PGE1 effectively suppress TGF- β -induced collagen deposition by cultured human cavernosal smooth-muscle cells (14). Thus, PGE1 may be beneficial in maintaining a functional ratio of trabecular smooth muscle to connective tissue. Finally, the direct acting mechanism of PGE1 may produce such a degree of smooth-muscle relaxation that patients with minimal to mild venous leakage may still occlude to the point of rigidity sufficient for intercourse (27). Linet et al. demonstrated the efficacy and safety of intracavernous alprostadil in the management of ED. Of the 683 men enrolled in a self-injection study, 50% reported penile pain at some point over the 6-mo duration of the trial, but only after 11% of actual injections. Other side effects in decreasing order of incidence included the following: hematoma or ecchymoses (8%), prolonged erections (5%), penile fibrotic complications (2%), and priapism (1%) (28).

In a prospective randomized trial, Montorsi et al. compared the recovery of spontaneous erectile function after nerve-sparing radical retropubic prostatectomy with and without early intracavernous alprostadil injections. In this study, 30 patients were randomized to two groups. Group 1 consisted of 15 patients who received thrice weekly intracavernosal injections of alprostadil for 12 wk. Group 2 consisted of 15 patients who were observed without intervention. Patients were evaluated at 6 mo postoperatively. Of the 12 patients in Group 1 who completed the treatment protocol, 8 (67%) reported the recovery of spontaneous erections sufficient for vaginal penetration, compared to only 3 patients who underwent observation (3 of 15, 20%). Furthermore, follow-up Doppler studies revealed venous leakage in only 2 patients in the treatment arm (2 of 12, 17%), compared to 8 patients in Group 2 (8 of 15, 53%). Montorsi et al. concluded that early, programmed intracavernous alprostadil injections improve the recovery rate of spontaneous erections in the postprostatectomy patient, and may inhibit the development of cavernosal fibrosis induced by tissue hypoxia (29).

Prostaglandin E is also available in a transurethral delivery system. Costabile et al. performed a retrospective analysis of the MUSE clinical trial to assess the efficacy of transurethral PGE1 in 384 patients identified with ED following prostatectomy. Whereas 70.3% of these patients demonstrated a positive response in clinic, only 57.1% actually performed sexual intercourse at home. Costabile et al. attributed this discrepancy to possible psychological factors associated with cancer and surgery. Postprostatectomy patients also reported a higher incidence of urethral pain and burning as compared to patients with other etiologies of ED (18.3% vs 10.4%). Postoperative sensitization of the corporal nerves or possible extended retention of PGE1 secondary to surgical dorsal vein ligation offer possible explanations for this difference (30). The lack of response consistency and higher incidence of urethral pain and burning make

transurethral PGE1 a second-line agent in the management of ED in the postprostatectomy patient.

Since its introduction in 1998, sildenafil citrate (Viagra) has gained wide acceptance as an effective oral medication in the treatment of ED. Sildenafil citrate is a selective inhibitor of phosphodiesterase type V (PDE5), the enzyme responsible for the hydrolysis and thus termination of cGMP. The effect of PDE5 inhibition is prolongation of cGMP activity to include the activation of the cGMP associated protein kinase responsible for cavernosal smooth-muscle relaxation (31). The initial elevation in cGMP is strictly dependent upon endogenous nitric oxide released from cavernous nerve terminals. Thus, in the postprostatectomy patient, cavernous neurotomy has a putative effect on the mechanism of sildenafil citrate. Furthermore, unlike the cAMP pathway activated by PGE1, the cGMP pathway has not been shown to influence TGF- β -induced collagen deposition. Thus, sildenafil citrate theoretically may not offer the potential additional benefit of influencing the ratio of cavernosal smooth muscle to connective tissue (26). The most frequently reported side effects of sildenafil citrate include: flushing, headache, nasal congestion, heartburn, and visual changes.

Zippe et al. investigated the efficacy of sildenafil citrate in 28 patients with ED following radical prostatectomy. Zippe et al. reported that 12 of 15 (80%) patients who underwent bilateral nerve-sparing radical retropubic prostatectomies achieved erection sufficient for vaginal penetration. In comparison, neither of the 3 patients who underwent unilateral nerve-sparing procedures, nor any of the 12 patients who underwent non-nerve-sparing procedures responded (32). A more recent and somewhat larger study by Lowentritt et al. confirmed the degree of nerve-sparing as predictive for response to sildenafil citrate. Lowentritt et al. also documented age, pathological stage, and baseline erectile function as predictive factors (33). Sildenafil citrate offers the primary advantage of oral administration. A patient's comfort with a given treatment will have a profound influence on compliance. Likewise, when considering the psychological importance of relaxation in sexual function, patient comfort may influence efficacy. More invasive therapeutic options such as intracavernosal or transurethral injections of alprostadil are associated with a significant drop-off in compliance after 1 yr (31). Thus, whereas sildenafil citrate is not the current drug of choice for early postoperative programmed erectogenic therapy, it does provide an alternative for patients with good baseline preoperative erectile function who undergo bilateral nerve-sparing procedures and are unwilling or unable to tolerate intracavernosal alprostadil injections. Currently, there are ongoing multicenter studies that compare the efficacy of oral erectogenic agents for the restoration of normal erectile function after radical prostatectomy.

Vacuum Erection Devices (VEDs)

Vacuum erection devices (VEDs) provide a safe, cost-effective, noninvasive, non-medical alternative to intracavernosal injection therapy in the postprostatectomy patient. The VED (or VCD, vacuum constriction device) consists of two components—a plastic suction chamber and a constriction band. The suction chamber is placed over the penis and manually pumped. The negative pressure in the chamber effectively opens the cavernosal sinuses thereby increasing arterial blood flow. The constriction band is then placed around the base of the penis for functional veno-occlusion.

The VED has been utilized in the management of organic ED for more than 50 yr with varying degrees of success. Patients find the noninvasive nature of the VED appealing, and those who seem to achieve the most success with it are less enchanted

with more invasive modes of treatment (i.e., surgery or intracavernosal injections). The proper use of the VED is essential to its efficacy. Learning this takes some time and practice, and thus requires a motivated patient. Patients who are not satisfied with the VED often complain that the device is cumbersome and interferes with spontaneous relations. Other frequently cited unwanted side effects of VED use include penile pain, ecchymoses and petechiae, loss of sensation, and orgasmic pain secondary to urethral compression. A lack of rigidity proximal to the constricting band creates the potential for the penis to pivot at that point.

The VED should be offered to postprostatectomy patients with ED for the initiation of programmed cavernosal oxygenation. This provides patients a less-invasive alternative to intracavernosal injection therapy. Patient satisfaction with the VED varies significantly. Cookson and Nadig reported a continuance rate of 70% with 84% patient satisfaction in a group of 115 patients with a mean 29 mo of follow-up (34). Dutta and Eid, on the other hand, reported an overall 65% attrition rate among 129 patients with a mean follow-up of 37 mo. Although most of these patients decided to discontinue VED use early, those who were satisfied (45 of 129, 35%) continued long-term use (35). This suggests that although it is clearly not for everyone, the VED is a suitable treatment modality for some patients.

Penile Prosthesis Placement

The placement of a penile prosthesis provides a potentially definitive, permanent therapy for ED. Because this alternative assumes the risks inherent to any surgical procedure requiring general or spinal anesthesia, as well as risks specific to this procedure, it is generally reserved for those who fail to respond to the less-invasive pharmacologic therapies or the VED.

Under current investigation is the role of simultaneous penile prosthesis placement with radical prostatectomy. Khoudary and colleagues published the first experience with immediate sexual rehabilitation. Using a two-team approach, this group performed non-nerve-sparing radical retropubic prostatectomies followed by penile prosthesis placement with an infrapubic approach in 50 patients. The majority of these patients (48 of 50, 96%) reported sexual intercourse within 3 mo of surgery. Surgical revision was required in 4 cases owing to curvature or mechanical failure (4 of 50, 8%). A comparison of this group to another group of 72 patients undergoing radical prostatectomy alone during the same time period revealed no significant differences in blood loss, analgesic use, or length of hospital stay. The relatively large wound, exposure to extravasated urine, and presence of indwelling pelvic drains and Foley catheter make prosthesis infection the principal concern of simultaneous prosthesis placement. The Beth Israel group reported no infections in their experience and attributed this success to the liberal use of antibiotics and strict sterile technique (36).

In patients with preoperative ED, simultaneous prosthesis placement offers the advantage of combining two indicated procedures. Only 15 of the 50 Beth Israel patients were impotent preoperatively, however. The other 35 potent men opted for the prosthesis electively after being counseled on the likelihood of postoperative ED and available therapeutic alternatives. It appears that for these men, the psychological benefits of immediate sexual rehabilitation outweigh the risks of a potentially unnecessary procedure (36). Further evaluation of this technique is necessary to validate the merit of this practice in preoperatively potent men.

EXPERIMENTAL THERAPIES

Pharmacologic

Sildenafil citrate was the first oral erectogenic agent approved by the FDA. Its overwhelming popularity has inspired further research and development in this field. Two other oral agents that are in the process of clinical investigation for ED therapy are phentolamine and apomorphine SL. Oral phentolamine is a nonspecific competitive α blocker. α -adrenergic tone helps to maintain the penis in a flaccid state. Phentolamine antagonizes α -1 and α -2 receptors in the cavernosal smooth muscle, thereby allowing endogenous vasoactive mediators such as nitric oxide and prostaglandins to operate in an unopposed fashion. Phentolamine has been utilized in the past as intracavernosal monotherapy and in a buccal formulation with only minimal to moderate success. These trials predate the validated IIEF questionnaire, however, thereby making it difficult to assess efficacy with consistency. Inclusion criteria in current trials have resulted in enrollment of men with only minimal to moderate ED. In terms of efficacy, response rates were 35% at 40 mg and 45% at 80 mg doses, compared to a 20% placebo response. Adverse effects of oral phentolamine include a low incidence of nasal congestion, dizziness, facial flushing, headaches, and tachycardia (37). Phentolamine has not met FDA approval as of 2001.

Apomorphine SL (sublingual) is a dopamine agonist. It acts primarily on D1 and D2 receptors in the paraventricular nucleus and pre-optic area of the brain. The activation of these central receptors initiates a cascade of neural events resulting in erection. In contrast to oral phentolamine, nearly 70% of men enrolled in Phase III trials for apomorphine SL reported moderate to severe erectile dysfunction by IIEF score. In terms of efficacy, 58% responded to a 4-mg dose, compared to 36% placebo response. Adverse effects of apomorphine SL include nausea, sweating, yawning, vomiting, and a low incidence of syncope. Nausea was reported by 10% of patients taking the 4-mg dose. Initiation of therapy at the lower 2-mg dose reduced the incidence of nausea (38).

The efficacies of oral phentolamine and apomorphine SL in the postprostatectomy ED group have not been specifically investigated to date.

Future testing of these agents, however, may target these patients. From a purely mechanistic perspective, both oral phentolamine and apomorphine SL are clearly dependent on endogenous vasoactive mediators such as nitric oxide and therefore may suffer from their deficiency in the postprostatectomy patient (similar to sildenafil citrate).

Sural Nerve Interposition Grafting

The application of nerve-grafting techniques in postprostatectomy patients may provide a future mode of therapy in preoperatively potent men whose tumor characteristics (i.e., grade, stage, location) necessitate bilateral sacrifice of the neurovascular bundles. The inspiration for this concept was born from experiments by Quinlan et al. demonstrating a restoration of potency following genitofemoral nerve interposition grafting in denervated rats (39). Kim et al. are the first to attempt bilateral sural nerve interposition grafting following cavernous nerve resection in humans. Their initial report documented results of only two patients with sufficient follow-up. RigiScan nocturnal penile tumescence monitoring at 4 to 6 mo revealed “erections that approached minimal criteria for normalcy” in both patients. At 14 mo, one of the patients reported an

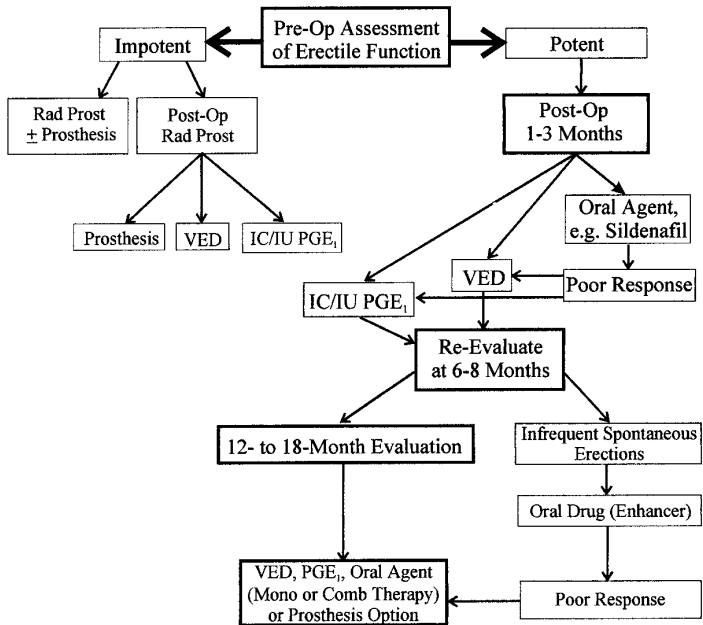


Fig. 1. Radical Prostatectomy ED Management.

erection sufficient for vaginal penetration (40). The application of sural nerve grafting following cavernous nerve resection is still in its infancy. Further refinements in this technique may be expected as more follow-up data becomes available from the initial series of patients.

MANAGEMENT ALGORITHM

The above algorithm (Fig. 1) is presented as a reasonable approach to the treatment of patients with ED following radical prostatectomy. An assessment of preoperative erectile function is helpful in planning treatment. Those patients who are impotent preoperatively may be offered the option of simultaneous sexual rehabilitation with penile prosthesis placement. Preoperatively potent patients should be evaluated no later than 3 mo into the postoperative course. The early institution of scheduled erectogenic therapy should be instituted at that time. The front line alternatives for this include intracavernosal alprostadil or the use of a VED. Patients with good preoperative erectile function who have undergone bilateral nerve-sparing prostatectomy may be considered for a trial of sildenafil citrate. Patients within this group who fail to respond should be switched to intracavernosal injections or VED. Patients should be reevaluated at 6 to 8 mo, with modifications to treatment as necessary at that time. For example, the return of some *infrequent* spontaneous erectile activity may herald the restoration of cavernous nerve function and therefore make oral sildenafil citrate a more viable and more attractive alternative in a patient who was started on a regimen of intracavernosal PGE. An outcome is deemed successful with the return of spontaneous erections sufficient

for intercourse. In the postprostatectomy patient, judgment of treatment success cannot be rendered until at least 12 mo and possibly as long as 18 mo postoperatively. At that time, patients considered treatment “failures” may explore the alternative of penile prosthesis placement. Patients considered treatment “successes” may still benefit from oral sildenafil citrate as an erection enhancer. The preceding algorithm is intended only as a guide. Each patient requires and deserves a treatment plan that is individualized for him with equal consideration for both the pathophysiology of his ailment as well as his psychological perspective. The treatment of ED in postprostatectomy patients is a common challenge for urologists to face. As our appreciation grows for the etiologic factors at play, further advances in therapy will undoubtedly surface. As we consider the feasibility, safety, and efficacy of these modalities, however, we must always remember that the ultimate end point in these patients is an improvement in their quality of life.

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Female Sexual Dysfunction: Epidemiology, Physiology, Evaluation, and Treatment

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INCIDENCE OF FEMALE SEXUAL DYSFUNCTION

Female sexual dysfunction (FSD) is a multicausal and multidimensional problem affecting between 30–50% of American women (1,2). Based on the National Health and Social Life Survey of 1749 women, 43% have complaints of sexual dysfunction. Although this study has a large sample size and minority representation, it is limited by the cross-sectional design. In addition, women over age 60 were not included, and neither menopausal nor other medical risk factors were correlated with sexual complaints. Another study, which looked at 448 women over age 60, demonstrated that two-thirds of them were sexually inactive, 12% of married women had difficulty with intercourse, and approx 14% experienced pain with intercourse. Sexual activity was strongly correlated with marital status (3). Women over age 60 were less likely to have sex if their partner was of poor health and if they had low feelings of self-worth (4). Studies of older women have failed to include specific measures of female sexual arousal, orgasm, or satisfaction.

FSD has historically been considered a problem rooted in psychology. However, although there are emotional and relational elements to sexual function, it has become

increasingly evident that female sexual dysfunction can occur secondary to medical problems and have organic roots. Ongoing epidemiological studies in women suggest that the same disease processes and risk factors that are associated with male erectile dysfunction (ED) including aging, hypertension, cigarette smoking, and hypercholesterolemia are also associated with FSD (5).

THE FEMALE SEXUAL RESPONSE CYCLE

Masters and Johnson first characterized the female sexual response in 1966 as consisting of four successive phases: excitement, plateau, orgasmic, and resolution phases (6). During sexual arousal, both the clitoris and the labia minora become engorged with blood and vaginal and clitoral length and diameter both increase. Masters and Johnson observed that the labia minora increase in diameter by two to three times during sexual excitement and consequently become everted, exposing their inner surface. In 1979, Kaplan proposed the aspect of "desire," and the three-phase model, consisting of desire, arousal, and orgasm, with desire being the factor inciting the overall response cycle (7). This three-phase model is the basis for the DSM IV definitions of FSD, as well as the recent reclassification system made by the American Foundation of Urologic Disease (AFUD) Consensus Panel in October 1998 (8). Others have recently suggested that sexual function should be considered as a circuit, with four main domains: libido, arousal, orgasm, and satisfaction. Each aspect may overlap and/or negatively or positively feed back on the next (9).

1998 AFUD Consensus Panel Classifications and Definitions of FSD

The objective of the panel was to evaluate and revise existing definitions and classifications of female sexual dysfunction. Specifically, medical risk factors and etiologies for female sexual dysfunction were incorporated with the preexisting psychologically based definitions

HYPOACTION SEXUAL DESIRE DISORDER

The persistent or recurring deficiency (or absence) of sexual fantasies/thoughts, and/or receptivity to, sexual activity, which causes personal distress.

Hypoactive Sexual Desire Disorder may result from psychological/emotional factors or be secondary to physiologic problems such as hormone deficiencies, and medical or surgical interventions. Any disruption of the female hormonal milieu caused by natural menopause, surgically or medically induced menopause, or endocrine disorders, can result in inhibited sexual desire.

SEXUAL AVERSION DISORDER

The persistent or recurring deficiency (or absence) of sexual fantasies/thoughts, and/or receptivity to sexual activity, which causes personal distress.

Sexual Aversion Disorder is generally a psychologically or emotionally based problem that can result for a variety of reasons such as physical or sexual abuse, or childhood trauma.

SEXUAL AROUSAL DISORDER

The persistent or recurring inability to attain or maintain adequate sexual excitement, which causes personal distress. It may be experienced as lack of subjective excitement or lack of genital (lubrication/swelling) or other somatic responses.

Disorders of arousal include, but are not limited to, lack of or diminished vaginal lubrication, decreased clitoral and labial sensation, decreased clitoral and labial engorgement or lack of vaginal smooth-muscle relaxation. These conditions may occur secondary to psychological factors, however, often there is a medical/physiologic basis, such as diminished vaginal/clitoral blood flow, prior pelvic trauma, pelvic surgery, or medications.

ORGASMIC DISORDER

The persistent or recurrent difficulty, delay in, or absence of attaining orgasm following sufficient sexual stimulation and arousal, which causes personal distress. This may be a primary (never achieved orgasm) or secondary condition, as a result of surgery, trauma, or hormone deficiencies. Primary anorgasmia can be secondary to emotional trauma or sexual abuse, however, medical/physical factors, as well as medications (i.e., serotonin re-uptake inhibitors) can contribute to or exacerbate the problem.

Sexual Pain Disorders

DYSpareunia

Recurrent or persistent genital pain associated with sexual intercourse. Dyspareunia can develop secondary to medical problems such as vestibulitis, vaginal atrophy, or vaginal infection. It can be either physiologically or psychologically based, or a combination of the two.

VAGINISMUS

Recurrent or persistent involuntary spasms of the musculature of the outer third of the vagina that interferes with vaginal penetration, and which causes personal distress. Vaginismus usually develops as a conditioned response to painful penetration, or secondary to psychological/emotional factors.

OTHER SEXUAL PAIN DISORDERS

Recurrent or persistent genital pain induced by noncoital sexual stimulation. This includes anatomic and inflammatory conditions including infections (i.e., HSV), vestibulitis, prior genital mutilation or trauma, and endometriosis.

The etiology of any of these disorders may be multifactorial and, often, the disorders overlap. For example, women with sexual arousal disorder often complain of diminished vaginal lubrication, pain with intercourse, decreased vaginal and clitoral sensation, as well as difficulty achieving orgasm. Ultimately, by enhancing sexual arousal (i.e., vaginal lubrication, clitoral and labial engorgement, genital sensation, and so on) orgasmic ability as well as libido may secondarily improve (10).

Female Pelvic Anatomy

Although female pelvic anatomy is comprised of a continuum of organs interrelated in both structure and function, it is helpful to group them into two categories: external and internal genitalia. The organs of the external genitalia are collectively known as the vulva, which is bound anteriorly by the symphysis pubis, posteriorly by the anal sphincter and laterally by the ischial tuberosities. The vulva consists of the labia, interlabial space, clitoris, and vestibular bulbs. The internal genitalia consist of the vagina, uterus, fallopian tubes, and ovaries.

Vagina

The vagina is a midline cylindrical organ that connects the uterus with the external genitalia, usually measuring 7 to 15 cm in length, depending on the position of the uterus. It can easily dilate and expand for intercourse and childbirth. Anteriorly, two pleats of sensitive tissue, the labia minora (inner lips) surround the opening of the vagina and are further protected by the larger folds known as the labia majora (outer lips). The labia minora enclose an area called the vestibule, which contains the clitoris, the urethral opening, and vaginal opening. The portion of the labia minora that covers the clitoris is known as the prepuce, or the clitoral hood.

The wall of the vagina consists of three layers: an inner aglandular mucous membrane epithelium, an intermediary richly supplied vascular muscularis layer, and an outer adventitial supportive mesh. Vaginal mucosa is a mucous-type stratified nonkeratinized squamous-cell epithelium that undergoes hormone-related cyclical changes during the menstrual cycle. The middle muscularis portion is known to be highly infiltrated with smooth muscle and an extensive tree of blood vessels, which engorges during sexual arousal. The surrounding outer fibrosa layer provides structural support to the vagina. The vagina has many rugae that are necessary for distensibility of the organ and are more prominent in the lower third of the vagina. Smaller ridges increase frictional tension during intercourse (11,12).

INNERVATION OF THE VAGINA

The autonomic innervation of the vagina originates from two separate plexuses; the superior hypogastric and the pelvic plexuses. Sympathetic fibers originate in the lateral gray column of T11–L2 and form the hypogastric plexuses. Parasympathetic fibers originate in the intermediolateral cell column of S2–S4 and synapse in the pelvic plexus. Sympathetic and parasympathetic fibers leave the pelvic plexus and travel within the uterosacral and cardinal ligaments, along with the vessels, to supply the proximal two-thirds of the vagina and the corporal bodies of the clitoris. Somatic motor fibers originate from the anterior horns of sacral cord levels S2–S4 and travel within the pudendal nerve to innervate the bulbocavernosus and ischiocavernosus muscles. Sensory fibers innervating the introitus and perineum travel within the perineal and posterior labial nerves to the pudendal nerve (11).

Immunohistochemical studies have revealed an abundance of nerve fibers in the distal vagina, as compared to the more proximal parts. This area of increased innervation, which plays a major role in sexual function, is important to recognize for potential damage when performing bladder suspension procedures and vaginal hysterectomies. Clearly our understanding of vaginal sensation as it pertains to sexual function, in particular arousal, is limited. Perception of pain and temperature in the vagina is mediated via sympathetic fibers, whereas proprioception (distention) of the vagina is mediated via parasympathetic fibers. To our knowledge, there is no light touch or two-point discrimination sensation in the vagina. Clinical studies are currently underway to address this paucity of knowledge.

PHYSIOLOGIC CHANGES IN THE VAGINA DURING SEXUAL AROUSAL

During sexual arousal, genital vasocongestion occurs as a result of increased blood flow. The vaginal canal is lubricated by secretions from uterine glands and from a transudate that originates from the subepithelial vascular bed, passively transported through the intraepithelial spaces, sometimes referred to as intercellular channels. Engorgement of the vaginal wall raises pressure inside the capillaries and creates an

increase in transudation of plasma through the vaginal epithelium (13). In addition to lubricating, the vagina lengthens and dilates during sexual arousal. In human and animal models, sexual stimulation results in increased vaginal blood flow and decreased vaginal luminal pressure (10,13,14).

The Clitoris

In 1974, Kaplan described the clitoris as a “small knob of tissue located below the symphysis pubis” (7). In anatomy texts, the clitoris is not accurately depicted in terms of size, and its neurovascular supply is rarely described. The bulbs are either omitted, or if described, their relationship to other cavernous tissue is not described. The female urogenital tissues are internal and relatively obscured, making investigations very difficult.

The clitoris is an erectile organ similar to the penis and arises embryologically from the same structure, the genital tubercle. It is composed of three parts: the outermost glans or head, the middle corpus or body, and the innermost crura. Studies have recently demonstrated that the glans and body of the clitoris are 2–4 cm long and that the crura are 9–11 cm (15). The clitoris consists of fused midline erectile bodies (corpora cavernosa) which gives rise to bilateral crura. The glans clitoris is visualized as it emerges from the labia minora. The labia minora bifurcate to form the upper prepuce anteriorly and the lower frenulum posteriorly. Each corpus cavernosum is ensheathed by a thick, fibrous connective tissue structure, the tunica albuginea that covers the lacunar sinusoids, which are surrounded by a trabecula of vascular smooth muscle and collagen fibers. The tunica albuginea in the clitoris is unilaminar, unlike the bilaminar structure found in the penis. Thus, no mechanism for venous trapping exists, and with sexual stimulation engorgement rather than erection occurs. The two separate crura of the clitoris, formed from the separation of the most proximal parts of the corpora in the perineum, attach bilaterally to the undersurface of the pubis along the ischiopubic rami.

PHYSIOLOGIC CHANGES IN THE CLITORIS DURING SEXUAL AROUSAL

With sexual stimulation, increased blood flow to the clitoral cavernosal arteries results in increased clitoral intracavernous pressure and tumescence and protrusion of the glans. Studies show that, unlike the penis, the clitoris lacks a subalbuginea layer between the erectile tissue and the tunica albuginea layer. In the male, this layer possesses a rich venous plexus that, during sexual excitement, expands against the tunica albuginea, reducing venous outflow and making the penis rigid. The absence of this venous plexus in the clitoris suggests that this organ achieves tumescence, but not rigidity during sexual arousal. Duplex ultrasounds of the clitoris reveal that during sexual stimulation the clitoris increases in length and diameter and blood flow almost doubles (10).

Vestibular Bulbs

The vestibular bulbs are 3-cm-long paired structures that lie along the sides of the vaginal orifice, directly beneath the skin of the labia minora. Although they are homologous to the corpus spongiosum of the penis and are composed of vascular smooth muscle, they are distinct in that they are separated from the clitoris, urethra, and vestibule of the vagina. Recent cadaver dissections reveal that in young premenopausal women, the bulbs lie on the superficial aspect of the vaginal wall and do not form the core of the labia minora. Furthermore, there are considerable age-related variations in the dimensions of the erectile tissue between young premenopausal specimens and older, postmenopausal specimens (15). The somatic sensory innervation of the labia

minora travels via the perineal and posterior labial branches of the pudendal nerve. Autonomic innervation consists of sympathetic and parasympathetic fibers that travel with the vessels to reach the vestibular bulb. In the labia minora, blood flow increases, particularly to the vestibular bulbs. This causes a two- to threefold increase in diameter and eversion of the labia with exposure of its inner surface.

Uterus

The uterine and cervical glands secrete mucous during sexual arousal to lubricate the vagina. Uterine and other pelvic surgical procedures can have significant impact on female sexual response and function. The innervation is closely proximate to the bladder and vagina, and dissection (as it is currently performed) can potentially negatively impact a woman's later sexual function, in particular, arousal and orgasm. Surgical menopause brought on by hysterectomy/oophorectomy impacts sexual function. Even hysterectomy alone, without the removal of the ovaries, can result in sexual dysfunction (16). Common postoperative sexual complaints include loss of desire, decreased frequency of sexual activity, painful intercourse, diminished sexual responsiveness, difficulty achieving orgasm, and decreased genital sensation. The anatomic/physiologic basis for sexual dysfunction posthysterectomy is still unclear and our understanding of female neurovascular anatomy vital to normal sexual arousal and function is limited. Most likely, the sexual dysfunction symptoms women experience posthysterectomy occurs as a result of nerve and/or vascular injuries, as well as loss of ovarian estrogens and androgens.

At present, we have a limited understanding of female pelvic anatomy, in particular the precise location of neurovascular structures vital to normal sexual arousal and function. Removal of the uterus and ligation of the arterial supply at the uterine pedicles can result in ovarian atrophy as well as fibrosis of vaginal wall and clitoral cavernosal smooth muscle. Disruption of the pelvic autonomic and cervical plexuses as well as the uterosacral and cardinal ligaments, which are associated with autonomic nerve fibers results in genital arousal and orgasm difficulties. Similar to the impact of radical prostatectomy on male erectile function, we believe that pelvic surgical procedures in women, as they currently are described, can also negatively impact sexual function. By preserving pelvic autonomic fibers, postoperative sexual arousal and orgasm may be consistently maintained. In circumstances involving genitourinary or gynecologic malignancies, such approaches may not be possible; however, for benign disease and well-localized tumors, "nerve-sparing" techniques may be possible. Detailed anatomic dissections and nerve tracing studies to delineate the precise location of the neurovascular bundles, as well as prospective studies on patient symptoms will key in to the definite etiology of postoperative sexual dysfunction. This is an area of current focus and research, and in the future, perhaps women will be offered nerve-sparing pelvic procedures similar to those now routinely performed in men.

PELVIC FLOOR MUSCLES

The pelvic floor is a collection of tissues that span the opening within the bony pelvis. In addition to supporting the abdominal and pelvic organs and maintaining continence of urine and stool, the pelvic floor allows for intercourse and parturition. The pelvic floor musculature, in particular the pelvic diaphragm that is formed by the levator ani muscles, the urogenital diaphragm, and the perineal membrane are important for pelvic support. The perineal membrane consisting of the ischiocavernosus, bulbocaver-

nosus, and superficial transverse perineal muscles are closely related to the vestibular bulbs and clitoris and play a role in sexual response. These muscles, when voluntarily contracted can intensify orgasm of both the female and her male partner.

The levator ani muscle has two different parts, the pubococcygeus and the iliococcygeus. These muscles can be palpated during pelvic examination as a distinct ridge just above the hymenal ring along each lateral wall of the pelvis.

The function of this group of muscles is to pull the rectum, vagina, and urethra anteriorly toward the pubic bones to compress the lumens closed. Nonvoluntary pelvic floor spasm associated with vaginal penetration or even examination with a speculum is referred to as vaginismus. This disorder prevents sexual intercourse and is associated with dyspareunia as well as other sexual pain disorders. If the opposite problem exists, consisting of laxity and hypotonia of the pelvic floor musculature due to aging, menopause, or childbirth, for instance, symptoms of vaginal hypoanesthesia, coital anorgasmia, as well as incontinence during sexual intercourse or orgasm can develop. Women with pelvic floor disorders often have coexisting urologic and sexual dysfunction complaints. Owing to this overlap, we encourage that all women who present with voiding dysfunction be questioned about their sexual function as well.

Etiologies for Dyspareunia

Leading causes and clinical examples for dyspareunia in pre- and postmenopausal women include:

1. **Hormonal:** Decreased estrogen and androgen levels resulting in vulvovaginal dystrophy and vaginal atrophy and superficial introital pain, as well as deep vaginal pain.
2. **Vaginal:** Low lubrication secondary to sexual arousal problem vestibulitis, vulvodynia, and vaginitis are all sources for dyspareunia.
3. **Iatrogenic:** Pelvic surgery including hysterotomy, vaginal prolapse repair, enterocoele and rectocele repair, medications, chemotherapy, and radiation therapy are all causes for vaginal pain.
4. **Muscular:** Levator spasm, vaginismus.
5. **Neurologic:** Pudendal neuralgia, pudendal injury, or pudendal canal syndrome.
6. **Anatomic:** Pelvic floor prolapse, vascular insufficiency, endometriosis, and pelvic vein thrombosis.

Careful diagnosis should be made in all patients recognizing the potential overlap of different medical etiologies. Efforts should be made to distinguish between superficial or introital dyspareunia vs deep dyspareunia, as the management can vary.

NEUROGENIC MEDIATORS OF THE FEMALE SEXUAL RESPONSE

Within the central nervous system, the medial preoptic, anterior hypothalamic region, and related limbic-hippocampal structures are responsible for sexual arousal. Upon activation, these centers transmit electrical signals through the parasympathetic and sympathetic nervous system. The neurogenic mechanisms modulating vaginal and clitoral smooth-muscle tone, and vaginal and clitoral vascular smooth-muscle relaxation are currently under investigation.

Nonadrenergic/Non-cholinergic Mediated Responses

Immunohistochemical studies in human vaginal tissues have shown presence of nerve fibers containing NPY, VIP, NOS, CGRP, and substance P (17). Preliminary stud-

ies suggest that vasoactive intestinal polypeptide (VIP) and nitric oxide (NO) are involved in modulating vaginal relaxation and secretory processes. In the clitoris, NO has been identified in human tissue and is hypothesized to be the primary mediator of clitoral and labial engorgement (18). Organ bath analysis of rabbit clitoral cavernosal smooth-muscle strips demonstrates enhanced relaxation in response to sodium nitroprusside and L-arginine (both NO donors) and phosphodiesterase Type V (PDE V), the enzyme responsible for degradation of cGMP, has been isolated in human clitoral, vestibular bulb, and vaginal smooth muscle culture (18). Human and rabbit vaginal smooth-muscle cells treated with the NO donor, sodium nitroprusside, in the presence of sildenafil, have enhanced intracellular cGMP synthesis and accumulation. PGE1 and forskolin also produced a marked increase in intracellular cGMP (19).

In organ bath studies, sildenafil causes dose-dependent relaxation of female rabbit clitoral and vaginal smooth-muscle strips (unpublished observation) further suggesting a role for NO as a mediator of clitoral cavernosal and vaginal wall smooth muscle relaxation. However, the exact identity of the relaxatory NANC neurotransmitter remains unclear. VIP is a nonadrenergic/noncholinergic neurotransmitter that like NO, may play a role in enhancing vaginal blood flow, lubrication, and secretions. The vagina is heavily innervated with VIP-immunoreactive nerve fibers in close relation to the epithelium and blood vessels (20).

α -1 and α -2 Mediated Responses

In males, adrenergic receptors exist in the brain centers and are associated with penile erection, libido, and ejaculation. Agents that affect these receptors have been extensively studied and used in the treatment of male ED. α -adrenergic agonists, such as norepinephrine, activate sympathetic nerve terminals resulting in contraction of penile trabecular smooth muscle and detumescence. In addition, α -2 agonists cause similar responses. Activation of α -2 receptors results in a decrease in intracellular adenosine 3'5' monophosphate concentrations, and potent contraction in blood vessels. α -adrenergic mediators also appear to play a physiologic role in female sexual arousal (21). Preliminary organ chamber experiments using rabbit vaginal tissue suggest that adrenergic mechanisms modulate smooth-muscle tone. Furthermore, there appears to be a difference in the quality of the contractile responses in upper and lower vaginal segments, which is consistent with their different innervation and embryologic origin.

Role of Estrogen in Female Sexual Function and Response

Estrogen plays a significant role in regulating female sexual function. Estradiol levels affect cells throughout the peripheral and central nervous system and influence nerve transmission. A decline in serum estrogen levels results in thinning of vaginal mucosal epithelium and atrophy of vaginal wall smooth muscle. Decreased estrogen levels also result in a less acidic environment in the vaginal canal. This can ultimately lead to vaginal infections, urinary tract infections, incontinence, as well complaints of sexual dysfunction (22).

Estrogen also plays a role in regulating vaginal and clitoral NO synthase expression, the enzyme responsible for the production of NO. Aging and surgical castration results in decreased vaginal and clitoral NO synthase expression and apoptosis of vaginal wall smooth muscle and mucosal epithelium. Estrogen replacement restores vaginal mucosal health, increases vaginal NO synthase expression, and decreases vaginal mucosal cell death (23). These findings suggest that medications such as sildenafil, that

mediate vascular and nonvascular smooth muscle via NO, may have a potential role in the treatment of FSD, in particular that associated with sexual arousal disorder.

In animal models, estradiol administration results in expanded touch receptor zones along the distribution of the pudendal nerve, suggesting that estrogen affects sensory thresholds. In postmenopausal women, estrogen replacement restores clitoral and vaginal vibration and pressure thresholds to levels close to those of premenopausal women (24). Estrogens also have vasoprotective and vasodilatory effects, which result in increased vaginal and clitoral and urethral arterial flow, thus resulting in maintenance of the female sexual response by preventing atherosclerotic compromise to pelvic arteries and arterioles (24).

Effect of Estrogen on Cardiovascular Risk Factors and Sexual Function in Postmenopausal Women

In menopause, the dramatic decline in estrogens and progestins results in a gradual rise in follicle-stimulating hormone as a result of a loss of negative feedback. With menopause, and the decline in circulating estrogen levels, a majority of women experience some degree of change in sexual function. Metabolically, menopause has a negative effect on lipid metabolism, which results in a rise in triglyceride levels and alterations in cholesterol levels; specifically, high density lipoprotein (HDL) levels decrease, although low density lipoprotein (LDL) levels increase (25). Total cholesterol levels have been found to be either maintained or slightly increased (25–27). In addition, with aging and menopause, there is a general decrease in glucose metabolism and peripheral insulin receptors, resulting in a rise in fasting serum glucose and insulin levels (25,28). Alterations in metabolic functions such as these, which occur with the onset of menopause, contribute to the high risk of cardiovascular disease in postmenopausal women.

Most epidemiologic studies of cardiovascular disease in postmenopausal women suggest a protective effect of hormone replacement therapy (HRT) (29). There appears to be a remarkably consistent reduced risk of coronary heart disease (CHD) and a somewhat less-consistent reduced risk of stroke in postmenopausal women using exogenous estrogens in the United States and Europe (26). The abundance of estrogen receptors within the cardiovascular system has been well established. Effects of HRT on sexual function, particularly sexual arousal disorder, have not been as well studied as the effects on cardiovascular disease. Nonetheless, effects of estrogen on the maintenance and function of the female genitalia have been well documented. Estrogen receptors have been shown to exist throughout the vaginal epithelium, stromal cells, and smooth-muscle fibers in the muscularis (30). Estrogen improves the integrity of vaginal tissue and has beneficial effects on vaginal sensation, vasocongestion, and secretions, which all lead to enhanced arousal (26). Furthermore, there is a direct correlation between the presence of sexual complaints and the levels of estradiol below 50 pg/cc. Symptoms are alleviated with estrogen replacement (22). To date, the only available treatments for sexual complaints associated with menopause have been hormone replacement therapy, commercial lubricants, psychotherapy and antidepressant medication.

Role of Testosterone in Female Sexual Function and Response

TESTOSTERONE

Low testosterone levels (total testosterone levels less than 20 pg/cc and free testosterone less than 0.9 pg/cc) are also associated with a decline in sexual arousal, genital sensation, libido, and orgasm. This can be accompanied by loss of pubic hair, skin thinning, and overall diminished sense of well being. Therapeutic success with testosterone for inhibited

desire in premenopausal and menopausal women has been reported in women treated with 100-mg testosterone pellet (31). Testosterone also improves sexual desire in women who are postmenopausal secondary to oophorectomy (32). At this time, there are no FDA-approved testosterone preparations for women, however, clinical studies are underway assessing the potential benefits of testosterone for the treatment of hypoactive sexual desire disorder, as well as other sexual function complaints. Therapeutic success with testosterone creams for inhibited desire, and improvement of sexual interest in menopausal women treated with combinations of estrogen and testosterone, has also been reported.

All androgens carry the risk of inducing virilization in women. Early reversible manifestations include acne, hirsutism, and menstrual irregularities. Long-term side effects such as male-pattern baldness, worsening of the hirsutism, voice changes, and hypertrophy of the clitoris are largely irreversible. There is also evidence that testosterone supplementation decreases HDL levels and increases triglyceride levels, making women with history of hypercholesterolemia and cardiac disease at significant risk. Women with history of breast cancer should not be prescribed testosterone because of the fact that it can be converted to estrogen.

Etiologies of FSD

VASCULOGENIC

High blood pressure, high cholesterol levels, smoking, and heart disease are associated with impotence in men and sexual dysfunction in women. The recently named clitoral and vaginal vascular insufficiency syndromes are, in fact, directly related to diminished genital blood flow secondary to atherosclerosis of the iliohypogastric/pudendal arterial bed (30). Although other underlying conditions, either psychological or physiological/organic, may also manifest as decreased vaginal and clitoral engorgement, arterial insufficiency is one etiology that should be considered. Diminished pelvic blood flow secondary to aortoiliac or atherosclerotic disease leads to vaginal wall and clitoral smooth-muscle fibrosis. This ultimately results in symptoms of vaginal dryness and dyspareunia. Histomorphometric evaluation of clitoral erectile tissue from atherosclerotic animals demonstrates clitoral cavernosal artery wall thickening, loss of corporal smooth muscle, and increase in collagen deposition (14). In human clitoral tissue, there is a similar loss of corporal smooth muscle with replacement by fibrous connective tissue in association with atherosclerosis of clitoral cavernosal arteries (33). Although the precise mechanism is unknown, it is possible that the atherosclerotic changes that occur in clitoral vascular and trabecular smooth muscle interfere with normal relaxation and dilation responses to sexual stimulation.

Aside from atherosclerotic disease, alterations in circulating estrogen levels associated with menopause contribute to the age-associated changes in clitoral and vaginal smooth muscle. In addition, any traumatic injury to the iliohypogastric/pudendal arterial bed from pelvic fractures, blunt trauma, surgical disruption, or trauma, can result in diminished vaginal and clitoral blood flow and complaints of sexual dysfunction.

NEUROGENIC

The same neurogenic etiologies that cause ED in men can also cause sexual dysfunction in women. These include:

1. Spinal cord injury or disease of the central or peripheral nervous system;
2. Complete upper motor neuron injuries affecting sacral spinal segments. Women with incomplete injuries retain that capacity for psychogenic arousal and vaginal lubrication

(34). With regard to orgasm, women with spinal cord injury have significantly more difficulty achieving orgasm than normal controls. The effects of specific spinal cord injuries on female sexual response as well as the role for vasoactive pharmacotherapy in this population are being investigated. A potential role for sildenafil in women with spinal cord injury has also recently been suggested.

HORMONAL/ENDOCRINE

Dysfunction of the hypothalamic/pituitary axis, surgical or medical castration, menopause and premature ovarian failure, and chronic birth control use are the most common causes of hormonally based FSD. The most common complaints associated with decreased estrogen and/or testosterone levels are decreased desire and libido, vaginal dryness, and lack of sexual arousal. Estrogen improves the integrity of vaginal mucosal tissue and has beneficial effects on vaginal sensation, vasocongestion, and secretions, which all lead to enhanced arousal. Estrogen deprivation causes a significant decrease in clitoral intracavernosal blood flow and vaginal and urethral blood flow. Histologically, diffuse clitoral fibrosis, thinned vaginal epithelial layers and decreased vaginal submucosal vasculature. Thus, a decline in circulating estrogen levels can produce significant adverse effects on structure and function of the vaginal and clitoris, ultimately affecting sexual function.

MUSCULOGENIC

The pelvic floor muscles, in particular, the levator ani and perineal membrane, participate in female sexual function and responsiveness. The perineal membrane, consisting of the bulbocavernosus and ischiocavernosus muscles, when voluntarily contracted contributes to and intensifies sexual arousal and orgasm. In addition, they are responsible for the involuntary rhythmic contractions during orgasm. The levator ani muscles also modulate motor responses during orgasm, as well as vaginal receptivity. When hypertonic, vaginismus can develop leading to or causing dyspareunia and other sexual pain disorders. When hypotonic, vaginal hypoanesthesia, coital anorgasmia, as well as urinary incontinence during sexual intercourse or orgasm can develop.

PSYCHOGENIC

In women, despite the presence or absence of organic disease, emotional and relational issues significantly affect sexual arousal. Issues such as self-esteem, body image, and the quality of the relationship with her partner can all affect her ability to respond sexually. In addition, depression and other psychological and mood disorders are associated with FSD. Furthermore, the medications commonly used to treat depressions can significantly affect the female sexual response. The most-frequently used medications for uncomplicated depression are the serotonin re-uptake inhibitors (SSRIs). Women receiving these medications often complain of decreased desire, decreased arousal, decreased genital sensation, and difficulty achieving orgasm. Several studies have recently been published documenting improvement in SSRI-induced sexual dysfunction in women with sildenafil (35).

CLINICAL EVALUATION OF THE FEMALE SEXUAL RESPONSE

Twenty years ago, complaints of male sexual dysfunction were dismissed and primarily classified as psychogenic. Today, it is generally accepted that approximately 90% of male sexual dysfunction is caused by physiologic causes, with only the remain-

der attributed to psychogenic causes. Recently, as more clinical and basic science research is being performed in the field of female sexual function and dysfunction, a similar pattern is being suggested for women. Nonetheless, even if the etiology for FSD is primarily physiologic, there are usually psychological, emotional, and relational issues that need to be addressed. For this reason, it is important that clinicians evaluating and treating women with sexual complaints take a comprehensive approach, addressing the mind, as well as the body's physical responses.

Evaluation of the patient with sexual dysfunction should contain a thorough physical examination including a pelvic examination, psychological and psychosocial assessment, hormonal studies as indicated, and physiologic monitoring of measures of arousal. In this way, both subjective and objective measures can be obtained and evaluated.

Medical/Physiologic Evaluation

Female sexual arousal results in a combination of vasocongestive and neuromuscular events, which include increased clitoral, labial, and vaginal wall engorgement, as well as increased vaginal luminal diameter and lubrication. Muscle tension, respiratory rate, heart rate, and blood pressure steadily rise during arousal, finally reaching their peak during orgasm.

In the clinical setting, female sexual responses have been difficult to quantify objectively. In contrast to the male erectile response, genital changes that occur during female sexual arousal are not only difficult to measure but are often not readily visible or recognized by the patient. Previously described techniques for evaluating physiologic changes during female sexual arousal have been performed primarily by psychotherapists and physiologists, and have focused primarily on estimating vaginal engorgement.

A comprehensive approach to evaluate physiologic changes during sexual arousal, which includes a full history and physical exam, pelvic exam, and when clinically indicated, a hormonal profile (FSH, LH, prolactin, total testosterone, free testosterone, SHBG, DHEA, and estradiol levels) is recommended. Testosterone is bound to both albumin and SHBG in the blood. Free-testosterone levels correspond with the "unbound" or bioavailable active hormone. Medical conditions that disrupt the hypothalamic-pituitary axis or hormone deficiencies secondary to menopause, chemotherapy or following bilateral salpingo-oophorectomies also influence FSD. In addition, any medication that increases SHBG levels (i.e., estrogen) can alter bioavailable testosterone levels. The etiologies of these sexual complaints are often not psychogenic in nature and are amenable to medical therapy. Medications that adversely effect sexual function should also be addressed and changed if not contraindicated (Table 1). The following comprehensive approach addresses physiological and subjective components of the female sexual response.

1. *Genital Blood Flow: Clitoral, labial (vestibular bulb), urethral, and vaginal arterial peak systolic velocity and end diastolic velocities:* Vaginal photoplethysmography is the most used and validated estimate of vaginal blood flow, or engorgement. This method, however, is subject to movement artifact and is thus not suitable for studying the patient during masturbation/stimulation. In addition, it provides arbitrary, rather than absolute units of measurement, and no anatomic formation is provided (36). Duplex Doppler ultrasonography also assesses changes in female genital hemodynamics during sexual arousal. A 12-mHz probe is used externally to measure right and left clitoral cavernosal, as well as right and left labial and urethral arterial blood flow. Urethral measurements are

Table 1
Medications that Adversely Effect Sexual Function (Desire, Arousal and Orgasm)

-
- 1) *Antihypertensive Agents* – clonidine, guanethidine, reserpine, propranolol, prazosin, spironolactone, thiazide diuretics, beta blockers, calcium channel blockers
 - 2) *Antidepressants* – imipramine, amitriptyline, clomipramine, amoxapine, MAO inhibitors, lithium carbonate
 - 3) *Serotonin Reuptake Inhibitors (SSRI's)* – fluoxetine, sertraline, paroxetine, venlafaxine.
 - 4) *Anxiolytics/Sedative-Hypnotics*-diazepam, alprazolam
 - 5) *Neuroleptics* – phenothiazines, butyrophenones, thioridazine, chlorpromazine, chlorprothixene, fluphenazine
 - 7) *Anticonvulsants* – phenobarbital, Tegretol, primidone, phenytoin
 - 8) *Antiulcer Drugs* – cimetidine
 - 9) *Anticancer Drugs* – procarbazine, busulfan, chlorambucil, cyclophosphamide, tamoxifen, raloxifene
-

recorded on the ventral surface. The largest branch on either the right or left side is recorded. Labial measurements are recorded from the posterior labial/bulbar artery. The vestibular bulb is located directly beneath the skin of the labia minora. A transvaginal probe is used to measure right and left vaginal arterial blood flow.

2. *Vaginal lubrication as reflected by pH-* vaginal pH can be measured with a digital pH meter (Sandhill, Inc.). The probe is inserted into the vagina and the mean of consecutive measurements is recorded.
3. *Vaginal compliance/elasticity: pressure-volume changes-* vaginal pressure/volume (compliance) changes can be measured with a commercially available compliance balloon (Schuster Balloon, Sandhill, Inc.). Measurements are recorded at 0 cc and then following 30-cc increments of air instillation. Maximum vaginal pressure/volume (compliance) is defined as the intravaginal pressure at maximum intravaginal volume. The maximum volume is determined when the patient experienced vaginal pressure or fullness that is uncomfortable, but not painful. A new technique using standard urodynamic equipment is being developed to measure vaginal sensation and compliance.
4. *Genital Sensation: vibration and temperature perception thresholds-* Vibratory and temperature perception thresholds are recorded from the clitoris (dorsal midline), right and left labia minora, and vagina using a Neurosensory Measuring Device (Medoc, Ltd., Israel).

To examine sexual arousal responses, physiologic measurements are recorded at baseline and following sexual stimulation using a 15-min standardized erotic video (Sinclair Institute; Femme Productions) and vibrator (Ferticare, I TLS, Inc.). Visual stimulation is maintained throughout the entire evaluation using 3-D surround sound glasses (I.O. Display Systems LLC). Studies being undertaken at our institution seek to define ranges of normal for the above parameters. Eventually, definition of these parameters prior to initiating medical therapy may become the standard of care.

Psychosocial/Psychosexual Assessment

In addition to the medical/physiologic evaluations, all patients should be evaluated for emotional and/or relational issues that may be contributing to her problem. This includes the history of the presenting problem, the impact it has had on her life and her relationship, the context in which the patient experiences her sexuality, her self-esteem and body image, and her ability to communicate her sexual needs with her partner. This

is an integral component of the female sexual function evaluation. Emotional and/or relational issues should be addressed prior to treatment, and certainly prior to determining treatment efficacy. If ongoing therapy is desired or required, it should also be provided, often in conjunction with medical intervention.

To assess subjective sexual function, in particular sexual arousal, several instruments are available. The Brief Index of Sexual Function Inventory (BISF-W), for example, is a validated 21-item self-reported inventory of sexual interest, activity, satisfaction, and preference and discriminates between depressed, sexually dysfunctional, and healthy patients. The questionnaire is easily administered and quickly scored.

A new instrument for quantifying the effects of therapy on female sexual arousal is the Female Intervention Efficacy Index (FIEI). This is a seven-question, self-report multiple-choice questionnaire that focuses on vaginal lubrication, genital sensation, ability to reach orgasm, and sexual satisfaction; and is treatment-specific (37).

Subjective sexual-response data reflects the personal experience of the patient, an important variable to evaluate because the ultimate goal is to enhance the personal sexual experience of the woman. Intervention is not considered successful unless the woman is able to subjectively experience sexual arousal, pleasure, and satisfaction. Thus, it is important to determine if physiological changes or improvement in blood flow translate into an improved sexual experience.

THERAPY

Treatment of FSD is gradually evolving as more clinical and basic science studies are dedicated to defining this problem. Thus, aside from HRT, medical management of FSD remains in the early experimental phases. Nonetheless, medical and health care professionals should realize that, not all female sexual complaints are psychological, and that there are potential therapeutic options.

Hormone Therapy

ESTROGEN THERAPY

This treatment is indicated in menopausal women (either spontaneous or surgical). Aside from relieving hot flashes, preventing osteoporosis, and lowering the risk of heart disease, estrogen replacement therapy results in improved clitoral sensitivity, increased libido, and decreased pain and burning during intercourse. Local or topical estrogen application relieves symptoms of vaginal dryness, burning, and urinary frequency and urgency. In menopausal women, or oophorectomized women, complaints of vaginal irritation, pain, or dryness are relieved with topical estrogen cream. A vaginal estradiol ring (Estring) is currently available, which delivers low-dose estrogen locally, and may benefit women who are unable to take oral or transdermal estrogen.

METHYLTESTOSTERONE

This treatment is used in combination with estrogen (Estratest) in menopausal women, for symptoms of inhibited desire, dyspareunia, or lack of vaginal lubrication, as well as for its vasoprotective effects. There are conflicting reports regarding the benefit of methyltestosterone for treatment of inhibited desire and/or vaginismus in premenopausal women. Topical vaginal testosterone is used for treatment of vaginal lichen planus. The suggested dose of methyltestosterone for pre- and postmenopausal women range from 0.25–1.25 mg/day. The dose should be adjusted according to symp-

toms, free-testosterone levels, and cholesterol, triglyceride HDL levels, and LFTs. Topical testosterone (methyltestosterone or testosterone propionate) preparations can be made in 1–3% formulations and should be applied up to three times per week. The potential side effects include weight gain, clitoral enlargement, increased facial hair, and hypercholesterolemia. Increased clitoral sensitivity, decreased vaginal dryness, and increased libido, have been reported with the use of a 2% testosterone cream. Side effects are similar to the oral preparation.

Pharmacologic Therapy

Aside from HRT, all medications listed below, although used in the treatment of male ED, are still in the experimental phases for use in women.

Currently, we have limited information regarding the exact neurotransmitters that modulate vaginal and clitoral smooth-muscle tone. Recently, NO and phosphodiesterase Type V (PDEV), the enzyme responsible for both the degradation of cGMP and NO production, have been identified in clitoral and vaginal smooth muscle (20). In addition, organ bath studies of rabbit clitoral cavernosal muscle strips demonstrate enhanced relaxation in response to the NO donors sodium nitroprusside, L-Arginine, and sildenafil.

SILDENAFIL

Sildenafil is a selective type-5 (cGMP-specific) phosphodiesterase inhibitor that decreases the catabolism of cGMP, the second messenger in NO-mediated relaxation of clitoral and vaginal smooth muscle. Phase II–IV clinical studies assessing efficacy of this medication for use in women are currently in progress. Recent studies have demonstrated that sildenafil is successful in treating FSD associated with aging and menopause and SSRI use (30,37).

L-ARGININE

This amino acid functions as a precursor to the formation of NO, which mediates the relaxation of vascular and nonvascular smooth muscle. L-arginine has not been used in clinical trials in women, however, preliminary studies in men appear promising. A combination of L-arginine and Yohimbine (an α -2 blocker) is currently under investigation in women.

YOHIMBINE

Yohimbine is an alkaloid agent that blocks presynaptic α -2 adrenergic receptors. This medication affects the peripheral autonomic nervous system, resulting in a relative decrease in adrenergic activity and an increase in parasympathetic tone. There have been mixed reports of its efficacy for inducing penile erections in men, and no formal clinical studies have been performed in women to date.

PROSTAGLANDIN E1

An intraurethral application, absorbed via mucosa (MUSE), is now available for male patients. A similar application of prostaglandin E1 delivered intravaginally is currently under investigation for use in women. Clinical studies are necessary to determine the efficacy of this medication in the treatment of FSD.

PHEHTOLAMINE

Currently available in an oral preparation, this drug functions as a nonspecific α -adrenergic blocker, and causes vascular smooth-muscle relaxation. This drug has been

studied in male patients for the treatment of ED. A pilot study in menopausal women with sexual dysfunction demonstrated enhanced vaginal blood flow and subjective arousal with the medication (38).

APOMORPHINE

This short-acting dopamine agonist facilitates erectile responses in both normal males and males with psychogenic ED, as well as males with organic impotence. Data suggests that dopamine is involved in the mediation of sexual desire and arousal. The physiologic effects of this drug are currently being tested in women with sexual dysfunction.

CONCLUSIONS

The ideal approach to FSD is a collaborative effort between therapists and physicians and should include a complete medical and psychosocial evaluation. The context in which a woman experiences her sexuality is equally, if not more, important than the physiologic outcome she experiences, and these issues need to be determined before beginning medical therapy or attempting to determine treatment efficacies. Despite the presence of organic disease, there are often psychosocial, emotional and/or relational factors that contribute to FSD. For this reason, a comprehensive approach, addressing both psychological, as well as physiologic factors is instrumental to the evaluation of female patients with sexual complaints.

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8

Hormonal Evaluation and Treatment

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CLINICAL EVALUATION OF HORMONAL STATUS

Men with low levels of testosterone (T) will commonly have alterations in their sexual functioning. The other side of this equation is not so frequently seen. Patients who have erectile dysfunction (ED) only rarely have hormonal abnormalities either contributing to or associated with their presenting complaint. However, the sexual problems of some hypogonadal men may be alleviated by directly addressing their lack of T so an understanding of this reversible cause of ED is of value.

THE EFFECTS OF TESTOSTERONE ON SEXUAL FUNCTION

It is commonly accepted that low serum testosterone (T) may result in the combination of low sexual desire and erectile difficulties. In many patients, the correlation between sexual function and serum T values follows this logical pattern. Although this is a practical concept, and one that has been examined experimentally, the reality is not always as simple or clear cut. Hypogonadal men may be capable of sexual erections, for instance only 75% of men receiving antiandrogen therapy were unable to develop erections when tested with erotic video challenge (1). Also, hormonal supplementation resulting in normal T val-

ues does not always result in restoration of libido and quality of erectile function (2). The presence of penile erections has been documented in male fetuses, by antenatal ultrasound, and *castrati* who have negligible circulating T. So, in some circumstances, there appears to be a disconnect between the biochemical picture and the clinical situation.

Hypogonadism has been shown to reduce the frequency of sexual thoughts and intercourse (3). Low T levels also decrease the frequency, volume, and quality of ejaculation (4). The effect of T on different aspects of erectile function has been studied and the current thinking is that nocturnal penile tumescence (NPT) and spontaneous erections are androgen dependent. Audiovisual erotic stimulation (AVES) predominantly cause erections through androgen-insensitive pathways, but some androgen sensitivity is likely (5). The information in this area has previously suggested compartmentalization with various functional aspects having different androgen sensitivities—that should now be regarded as unresolved. Rapid eye movement (REM) sleep has been shown to be reduced in hypogonadism and, although androgen reduction adversely affects sleep-related erections, it does not eliminate them over a 12-wk trial in healthy young adult men (6).

There are data for supra-normal levels of T from the exogenous administration of T to normal males. The pattern of sexual intercourse, masturbation, and sexual interest did not change significantly (7).

THE CLINICAL PICTURE OF HYPOGONADISM

It is without a doubt that androgens affect male sexual function in general and erectile physiology, in particular. ED and hypogonadism coexist in the same men more frequently than pure causative explanations will allow. Older men have more ED and older men have lower testosterone, but the two issues are not necessarily causally related. The age-related variation in prevalence of ED is well known from the Massachusetts Male Aging Study (MMAS) and other epidemiological studies (8). Clinical practice verifies that older men have more ED, and age is a significant variable associated with the finding of ED. Age is also a significant factor in predicting serum T and lower levels of T are found in older men (9). Yet the association between ED and low T was not found in the MMAS and, overall, the prevalence of low serum T in men with documented ED is low (10).

The prevalence of hypogonadism in the older age groups is highest—higher than initially suspected (11). There is a significant incidence of androgen deficiency in older males when measured by serum levels of bio-available T (12).

Although the MMAS was unable to show an association between ED and a decrease in the serum levels of T, a direct correlation between ED and a serum deficit in dehydroepiandrosterone (DHEA) and its sulfated form (DHEAS) was established. It is possible in a population study to link age and serum T, but the association between low DHEA and increasing age is so strong and predictable that the association between DHEA and ED is difficult to demonstrate. However, a recent study points to a true finding of lower DHEA in patients with ED compared to controls (13). A diagnosis of hypogonadism can rarely be established on the basis of history and physical examination alone (14). Sexual interest, libido, or desire is a notoriously difficult symptom group that may be depressed in men with normal T levels because of other conditions (e.g., depression) (15). Testicular size and consistency vary markedly in the adult and,

although there is a correlation with seminal parameters, there is no helpful characteristic to mark low T (16). The physical appearance of secondary sex characteristics is not sufficiently demonstrative to mark the presence of low T (17). The finding of low T depends, therefore, on the performance of a biochemical assessment. Following this, the diagnosis of clinically relevant hypogonadism depends on a comprehensive evaluation of the patient and his biochemistry.

The levels of pituitary gonadotropins, follicle stimulating hormone (FSH), and luteinizing hormone (LH) can provide an indication point to primary, secondary, or tertiary hypogonadism. However, from middle age and beyond, there is a diminution in function of the pituitary as well as a flattening in the circadian production of gonadotropins (18). Therefore, it is not uncommon to see in men with erectile problems and primary testicular failure have a low serum T with normal or only minimally elevated gonadotropins.

The other common disturbance of endocrine milieu that may be relevant to ED is hyperprolactinemia (19). Hypersecretion of prolactin may suppress gonadotropins and cause secondary hypogonadism but increased prolactin levels may also cause erectile problems, even in the presence of a normal testosterone level. Although, if the hyperprolactinemia is caused by a variant large prolactin molecule, macroprolactin, these molecules are biologically inert. Hyperprolactinemia may also be a result of medications (20). Although the common concept of hyperprolactinemia is that low desire is a reliable marker hyperprolactinemia has been found in patients not reporting major problems with a desire disorder however assessed. Clinically significant hyperprolactinemia may be reliably found with biochemical evaluation and may not be detected in patients with erectile-function domain (21) scores above 10 in assessments done using the International Index of Erectile Function (22).

In summary, although there is much to link androgens and erections, there is little that can be done from a clinical standpoint to rule out androgen abnormalities in the specific group of patients that suffer from ED. The proof that androgen status is healthy in men with ED depends on biochemical tests.

OTHER HORMONES

Further hormonal evaluation depends on the interest, expertise, and commitment of the physician and, obviously, the clinical picture. Despite overwhelming evidence, the existence of a syndrome of androgen decline in the aging male (ADAM), also known as the andropause, endocrine decline in the aging male (EDAM), or shifting hormones of the aging male (SHAME), continues to be debated. Part of the problem is that andropause is not inevitable and has a variety of clinical presentations (23). Another major reason is the fact that the signs and symptoms of andropause are shared in varying degrees with several other hormones such as insulin-related growth factor, growth hormone, melatonin, and leptins.

Measurement of other hormones (i.e., DHEA, growth hormone, melatonin, and leptin) is not indicated in the context of ED. Thyroid function may rarely have a role in sexual dysfunction and the routine assessment of thyroid function is not helpful in men with ED. Hypothyroidism may result in hyperprolactinemia, therefore, assessment of thyroid function in hyperprolactinemic patients is indicated (24). Hyperthyroidism may influence T bioavailability.

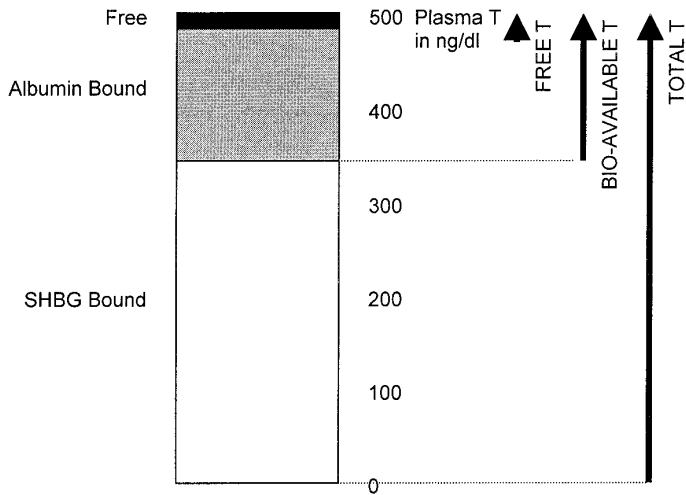


Fig. 1. Conceptual Relationship between the various common measures of testosterone along with a general guide to the range of values. The actual values reported for an individual patient should be carefully evaluated as to the exact methods of measurement used in the normal ranges to the laboratory.

THE LABORATORY DETERMINATION OF HYPOGONADISM

There are various sources of recommendations regarding suitable investigations of androgen status (25,26).

The standard approach is to measure the total serum T levels, preferably between 8 and 10 AM. In the obese and the elderly, the levels of sex-hormone binding globulin (SHBG) increase, which binds T reducing the metabolically active component (see Fig. 1). Free T levels may provide a better estimation of testicular endocrine function but is more demanding on the biochemistry laboratory. Bioavailable T (the sum of free + albumin bound T) may be the most reliable form of assessment because it determines the amount of T which is readily available to target tissues. Unfortunately the determination of bioavailable T is more costly and less available. A reasonable compromise is to determine total T and SHBG by immunoassay. (27) Regardless of the test employed, if an abnormal value for T is obtained on the initial determination, the levels should be repeated. A prolactin level may be appropriate but this depends much more on the cost-sensitivity of the medical environment.

The range of T that can be considered normal should be set in collaboration with the laboratory performing the determination. Ideally, the level may be age adjusted. A level more than two standard deviations from the norm would be considered abnormal in an elderly population. Little is known about the individual variation in T set point (particularly the longitudinal variation in individuals with age) and this may explain in part some of the difficulty in interpreting T values close to the lower limit of normal.

There is no agreement on the exact normal range of testosterone values as men age and there is no standard serum testosterone level at which a man loses his sexual function. The definition of relative hypogonadism is also uncertain. Many men have perfectly normal sexual function even with testosterone levels in the low normal range for age, although men with such values deserve a trial of testosterone if their clinical symptoms indicate.

THE TREATMENT OF HYPOGONADISM

Current treatment options include oral tablets or capsules, intramuscular preparations, both long and short acting, implantable long-acting slow-release pellets, scrotal and nonscrotal transdermal patches, and transdermal gel. Neither injectable preparations nor slow-release pellets reproduce the optimal goal of a circadian pattern of testosterone production of the testes. This may best be achieved by the use of transdermal technology, although suitable oral testosterone preparations may be made to follow a circadian pattern by suitable dosing.

Intramuscular injections of T are usually long acting, reach a maximum concentration 72 h after injection, and slowly diminish over the ensuing 10–14 d. The pharmacokinetics result in supraphysiological serum testosterone levels for the first few days (which may result, in breast tenderness or gynecomastia) and low levels before the next injection—the so-called “roller-coaster” effect well known to patients. Transdermal T therapy (TTT), uses elemental T absorbed transdermally to obtain near normal serum T levels and reproduce the diurnal physiologic variations of T observed in normal human testosterone secretion. Patches are applied at bedtime with peak T levels achieved in the early morning and a nadir prior to patch replacement. Androgen levels with these systems do not increase much beyond normal, and detrimental changes are unlikely with transdermal preparations. A recent addition to the transdermal technologies has been a fast-absorbing gel that uses the skin as the reservoir. Most oral preparations of simple testosterone undergo rapid hepatic metabolism and will fail to establish reliable or sufficient serum levels of T. With the exception of the United States, where it was not considered worth registering initially, testosterone undecanoate (TU) is widely used. TU is effective by the oral route (although some variability in absorption can be seen), is free of liver toxicity, but may result in supraphysiological levels of dihydrotestosterone. A number of other techniques for T delivery have been studied including long-acting implantable percutaneous pellets, spheres, and microcapsules.

Injectable esters of T have been available for a long time and their effects are well recognized (28). They are inexpensive and safe, but less convenient to use because of:

1. The need for periodic (every 2–3 wk) deep intramuscular injection;
2. The initial (in about 72 h) supraphysiological levels of serum T followed by a steady decline over the next 10–14 d (29);
3. The nadir immediately before the next injection. This pharmacokinetic phenomenon translates into a risk of wide mood swings and well being (the roller-coaster effect) that may be disconcerting and upsetting to both patients and their partners;
4. These pharmacokinetics also override the normal circadian patterns of serum T and the intermittent supraphysiological levels they produce may result in the development of breast tenderness and gynecomastia.

The most widely used parenteral preparations are the 17-hydroxyl esters of testosterone that include the short-acting propionate and the longer-acting enanthate and cypionate. Currently, the propionate is rarely used because its short half-life requires administration every other day. The enanthate and cypionate, on the other hand, can be administered at a dose of 200–400 mg every 10–21 d to maintain normal average testosterone levels (30). Higher doses will not maintain T levels in the normal range beyond the 3-wk limit. Appropriate treatment of hypogonadism with injectable T has been shown to improve libido, sexual function, energy levels, mood, and bone density when these problems are caused by androgen deficiency (23). Chronic supraphysio-

logic levels of serum T may suppress LH and FSH production and cause infertility (31), but have not been shown to have adverse psychosexual effects (32).

Oral preparations are clinically attractive, but there are problems with the commonly available preparations in the United States. In order to prevent inactivation in the liver, the oral agents available in the United States are the alkylated preparations (e.g., methyl testosterone). These have a potential for significant liver toxicity that includes hepatocellular adenomas, cholestatic jaundice, and hemorrhagic liver cysts (33) and may cause significant changes in lipid profile. They also provide erratic androgenic activity and should not be used. T undecanoate is a different preparation and is currently not available in the United States, but it is widely used throughout the world. It is an effective oral testosterone ester that is absorbed through the lymphatics such that, when taken with meals, it circumvents the first passage through the liver. It is free of liver toxicity and brings serum T levels within physiological range. The oral medications, when taken around the clock, do not result in a faithful reflection of the circadian level variations, but careful timing and dosing may circumvent this problem.

TTT offers the closest replication of the normal circadian cycle in serum T. Common side effects of transdermal delivery of medications are related to the need to use enhancers to facilitate absorption that may result in various degrees of skin irritation. TTT is available in both scrotal and nonscrotal patches. The former have some special inconveniences such as the problem of the patches remaining in place and the need for shaving of the scrotal skin. Patches applied at bedtime will result in peak T levels in the early morning and nadir prior to their replacement. Transdermal nonscrotal patches also produce normal levels of estradiol but, as opposed to the scrotal patches, result in normal levels of DHT (34). In addition to producing physiologically appropriate serum levels of T, the patches have been shown to lower levels of SHBG, promote virilization, and increase bone-mineral density (35). The T patches, as compared to injectable forms, appear to minimize excessive erythropoiesis and suppression of gonadotropins (36). A new transdermal gel preparation has recently been approved in the United States—the skin provides the reservoir for 24-h release (37).

Other delivery forms are not widely established, but include long-acting implantable subcutaneous (SC) pellets (38) and microcapsules (39). The SC implants are not associated with high DHT levels—desirable in the treatment of the older hypogonadal man in whom concerns regarding the prostate gland are of great importance. There are a great number of different preparations of T being readied for possible entry into the market—the common feature is that the substance delivered to the blood stream is mostly molecular testosterone and so claims for differential effect should be studied with care.

Treatment with medical grade DHEA (50 mg) has been assessed in a small number of men with ED and a positive impact on ED was reported despite no measurable change in serum T (40).

CAUTIONS IN TESTOSTERONE SUPPLEMENTATION

Testosterone replacement may be associated with possible serious adverse events:

1. Liver (mainly with methylated forms of T - yearly liver function tests).
2. Lipid profile and cardiovascular disease (relationships between androgens and cardiovascular risk factors are complex—follow-up may be advisable when supplementing androgens in patients with significant risk factors for cardiovascular disease).

3. Prostate—BPH (when hormonally deficient men are treated, prostate volume increases, but only to the size expected for eugonadal men of the same age. Most studies have shown no effect of exogenous androgens on PSA, LUTS, or prostate volume).
4. Prostate cancer (T promotes growth of an established prostatic adenocarcinoma. Whether T also promotes the *de novo* development of prostate cancer remains to be elucidated. Caution is needed here. The preponderance of evidence indicates only that over a period of a few years androgen supplementation, to eugonadal levels, does not result in serious prostatic disorders. The long-term safety of exogenous T administration is not established in regard to prostatic cancer, but to date, there is no clear evidence that prostatic biopsies are indicated prior to the initiation of androgen supplementation. It is clear that a rapid increase in PSA or the detection of abnormalities by a digital rectal examination, after androgen supplementation, would be indications for further investigation (41).
5. Sleep disorders (sleep apnea is probably not exacerbated during the administration of exogenous T).
6. Social behavior and emotional state (T administration to eugonadal or hypogonadal men resulting in normal serum T levels does not result in pathological behavior).
7. Lipid profile (abnormalities in triglycerides and high-density lipoprotein cholesterol may be corrected by restoring a physiological androgen milieu (42).
8. Cardiovascular risk factors (T normalization has complex and still incompletely understood effects).
9. Red cell mass (in younger individuals receiving androgens for sexual dysfunction the effects may be marked (43).

TESTOSTERONE FOR ED

The specific issue of whether exogenous T can be considered as a primary treatment for ED regardless of etiology is difficult. In clinical practice, there is no need to look to testosterone as first-line therapy when there are disease-specific alternatives. Although there is a recent meta-analysis (44), there are no studies that assess T vs placebo for therapy of ED of wide-spectrum etiology with good numbers and careful design comparable with modern clinical trials. T-replacement therapy for the treatment of ED should be reserved for clear or reasonable biochemical or clinical indications suggesting that androgen abnormalities are a contributing cause and that T replacement will not be harmful.

CONCLUSIONS

The use of androgen therapy in men for the treatment of ED may be summarized as follows:

1. A history of low sexual desire and a physical examination are unreliable as a basis for the diagnosis of adult hypogonadism. Biochemical determinations are, therefore, recommended to establish a firm diagnosis.
2. The most dependable tests are either a total T and SHBG or bioavailable T.
3. An abnormal T value should be confirmed by a second test.
4. Prolactin may be considered as a routine or after an abnormal T.
5. T administration must be based on a clear indication (clinical judgement and biochemical information).
6. Borderline levels of serum T are not diagnostic and a trial of androgen therapy may be considered after careful consideration of the risks and benefits.

7. In a man with coexisting hypogonadism and ED, a 3–6 mon trial of hormonal supplementation may be indicated and failure to respond should halt this test.
8. In men over age 40, a digital rectal examination (DRE) and PSA determination are mandatory. Biopsy of the prostate is reserved for those in whom an abnormality is detected.
9. The suspicion or the presence of cancer of the prostate or breast are absolute contraindications for androgen therapy.
10. The T preparation, dose, and route of administration need to be selected carefully depending on the individual needs and circumstances of the patient.
11. The clinical response is the most reliable guide to T requirements.

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9

Nocturnal Penile Tumescence and Rigidity Testing

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INTRODUCTION

Evaluation of the impotent male is a difficult task that is not likely accomplished by any single test. However, nocturnal penile tumescence and rigidity (NPTR) monitoring is considered to be a valuable tool in the assessment and management of erectile dysfunction (ED). NPTR is an objective, noninvasive measure of erectile activity and is an integral method in differentiating between organic and psychogenic causes of impotence. NPTR testing also plays an important role in the assessment of pharmacological therapies and technological advances in the analysis and treatment of impotence.

NPT was first described in infants by Halverson in 1940, and, in adult men aged 20–40 yr by Ohlmeyer in 1944 (1,2). In 1953, Aserinsky and Kleitman first described the rapid eye movement (REM) stage of sleep and later recognized that nocturnal erections seemed to occur during REM periods of normal sleep (3). It was not until 1965 when it was suggested that monitoring of nocturnal erections could aid in the assessment of ED (4–14). Fisher reported that in the normal male, three to five erections occur nightly and Karacan reported that 80% of these erections occur during REM sleep (4,8).

It was Karacan who first suggested in 1970 that NPT testing may be useful in distinguishing between organic and psychogenic causes of impotence (11). He argued that NPT would be diminished or absent in males with impotence as a result of organic

causes, such as neurological or vascular factors, because these mechanisms would be present during sleep. He further assumed that psychological factors, which inhibit sexually induced erections, would be absent during sleep. Nocturnal erections would therefore be present in these men with psychogenic causes of impotence. Some have asserted that NPT testing is the best method to make this distinction between organic and psychogenic causes of impotence, whereas others are more cautious and warn that NPT values used alone can be misleading (15,16). Despite these warnings, NPT testing remains a valuable tool in evaluating the impotent male.

In this chapter, NPT and NPT with rigidity (NPTR) testing and results from such tests in normal and impotent men are described. In addition, the limitations of NPTR testing, such as the validity of results and the difficulty in establishing normal criteria for sufficient erection, and current recommendations for the use of NPTR testing are discussed.

NPT AND NPTR TESTING

NPT testing involves the continuous measurement of penile circumference during sleep and repeated measurements of penile axial rigidity near the time of maximum tumescence. Initially, the change in penile circumference was the sole measurement used to assess the adequacy of an erection. In 1978, Karacan determined that a 20-mm increase in penile circumference represented a full erection and that a 16-mm increase (or 80% of a full erection) would be sufficient for intromission (12). However, several studies have established that in addition to changes in penile circumference, direct measurement of penile rigidity is necessary. Earls and associates have found that there is a significant delay between an adequate erection based on changes in measured circumference and the subject's perception of a sufficient erection for intromission during visual sexual stimulation (17). Also, circumference changes associated with a full erection are substantially different between patients further contributing to the need for direct rigidity monitoring.

NPT and NPTR testing is often performed in a sleep laboratory with simultaneous monitoring by electroencephalogram (EEG), electrooculogram (EOG), or electromyogram (EMG). Rigidity was initially assessed by applying an external device at the time of full erection, which measured buckling pressure. Karacan found that a buckling pressure of 100 mmHg represented a sufficient erection for vaginal penetration and that a pressure of less than 60 mmHg was inadequate for intromission (13). Several limitations and disadvantages to this method have been described. First, buckling pressure is measured as a single isolated event during which detumescence may occur. Second, measurements are subject to observer error. And finally, the use of a sleep laboratory is costly and time consuming, and the unnatural setting and procedures can cause anxiety, thereby compromising the rigidity.

These limitations in NPT and NPTR testing have led to the development of several other methods of monitoring. The use of stamps placed around the base of the penis to examine nocturnal tumescent activity was described by Barry et al. in 1980 (18). In 1982, the Snap Gauge Band device was introduced, which consisted of three preset snap release fasteners with constant release forces placed around the base of the penis (Timm Medical Technologies, Eden Prairie, MN). This method of NPT testing was modified by replacing the fasteners with plastic elements designed to break at 10, 15, and 20 ounces (19). The Snap Gauge Band devices, as well as portable strain-gage monitors, have been shown to correlate well with sleep-laboratory testing of NPT and NPTR testing (4,20–23).



Fig. 1. RigiScan ambulatory penile tumescence and rigidity monitoring device. Courtesy of Timm Medical Technologies, Eden Prairie, MN.

One drawback of these tests is that they do not provide descriptive details of erectile activity, such as frequency, duration, and degree of rigidity. This led to the development of small portable monitors, which measure rigidity continuously, while recording the number and duration of nocturnal erections. The RigiScan (Timm Medical Technologies, Eden Prairie, MN) is a home-monitoring device, which continuously records penile circumference and rigidity throughout the night (24). (Fig. 1). It consists of two loops, one placed around the base of the penis and the other at the tip of the penis proximal to the coronal sulcus, and a logging unit, which is strapped to the patient's thigh. Every 15 s, the circumference is measured and compared to the patient's baseline reading. Every 3 min, rigidity is measured by 2.8 N of radial compression applied to each loop. When the circumference increases by more than 10 mm, rigidity monitoring is increased to every 30 s. Rigidity data is expressed as a function of displacement when the loop is tightened around the penis. When no linear displacement occurs, rigidity is 100% and for each 0.5 mm of loop shortening that occurs, rigidity measurement is decreased by 2.3%. Data can be collected from the RigiScan for three monitoring sessions of 10 h in duration. During these sessions, tumescence, rigidity, and duration of each event are recorded and the data can then be downloaded and printed in graphical and numerical form. The pattern of base and tip tumescence and rigidity over time can then be compiled.

The data collected from the RigiScan are often interpreted through visual analysis of graphic printouts. In an effort to make analysis more objective, Burris et al. developed a quantitative approach using a study of 47 normal men (25). They described an integrated measure of erectile amplitude and duration using area under the curve (AUC) and found that this was a highly reproducible method to quantify tumescence and rigidity. Significant correlation was found between tumescence and rigidity ($P < 0.001$) and between tip and base measurements ($P < 0.001$).

Another simplified method to quantify tumescence and rigidity data collected from the RigiScan was described by Levine and Carroll in 1994 (26). Using an updated version of RigiScan Summary Analysis software, the number of erectile events, the cumulative duration of erectile events, the average tumescence and rigidity during each event, the integrated time-dependent measures of tumescence (TAU, tumescence activity units) and rigidity (RAU, rigidity activity units) were analyzed. An erectile event was defined as a 20% increase in base circumference lasting for at least 3 min. To calculate RAU, the minutes spent at a given rigidity level are multiplied by that rigidity level and then summed for the entire erectile event. TAU is calculated similarly with the duration of an erectile event multiplied by the increase of circumference and then divided by the estimated baseline tumescence. Both base and tip RAU and TAU measurements are collected and evaluated separately. These parameters can then be compared to the percentile distributions of a normal population. NPTR continues to be a widely used tool for evaluation of response to therapeutic interventions for ED (27,28).

NPTR MONITORING IN A NORMAL POPULATION OF MALES

The Dacomed Corporation studied more than 500 men with ED at the Uro-Center of San Diego and provided the first normal criteria for NPTR testing using the RigiScan device (29). Three to six erections per 8 h or an average of 0.375 erections h, lasting an average of 10 min was considered normal. A normal increase in tumescence for an erectile event was described as a minimum increase of 3 cm at the base and 2 cm at the tip of the penis. Greater than 70% rigidity was considered adequate for vaginal penetration, whereas less than 40% rigidity represented a flaccid penis, and measures between 40–70% correlated with various degrees of penile stiffness.

The consideration of 70% rigidity as adequate tip rigidity proposed by these findings may be an overestimate, as suggested by several studies. In a report by Bain and Guay, more than 1000 patients with ED were studied and the minimal penile rigidity necessary for vaginal penetration was defined as 60% base rigidity and 50% tip rigidity (30). Ogrinc and Linet found that by decreasing the minimal tip rigidity from 70% to 60% increased the sensitivity of RigiScan testing from 53.8 to 70.8% (31). In addition, Licht et al. compared RigiScan measurements to the assessment of adequate rigidity by a trained observer in the same evening and concluded that a base rigidity of 55% was considered normal (32). Clearly, further study is necessary to define normal rigidity.

In 1994, Levine and Carroll described the time-intensity measure of tumescence (TAU) and rigidity (RAU) in a study of 44 healthy, potent men (26). A nomogram was developed from these data, which allows a rapid comparison of NPTR findings (Fig. 2). Data was collected from the 44 men for three consecutive nights of monitoring, and although there was a high degree of uniformity in the population as a whole, individual responses were varied during the three nights (Fig. 3). Six of the 44 men had little or no tip rigidity on at least one of the three nights, suggesting that at least two nights of testing are required for adequate characterization. They also suggested that significant erectile activity during a single night, however, might be sufficient to demonstrate normal erectile function. No simple criteria for normal functioning were identified in this study. Data such as minimum number of events, duration of erections, or percentage of rigidity, as has been previously described, could not provide evidence of normal erectile activity. They did find in this patient population, however, that tumescence was highly correlated with rigidity, similar to that reported by Burris, and that these data are



Fig. 2. Cumulative distribution of penile tumescence activity (TAU) and rigidity (RAU) from 44 potent men. $N=113$ nights. Useful for comparison of NPTR results from impotent subjects. (Reproduced from ref. 26 with permission.)

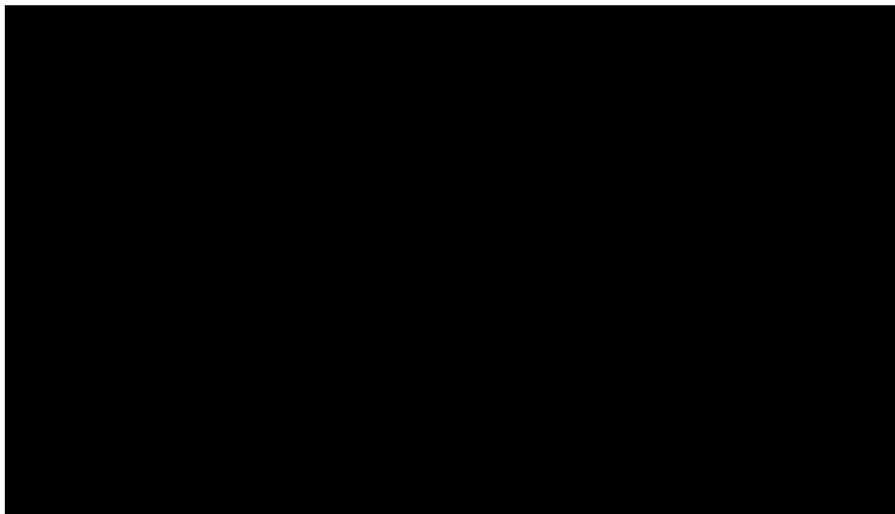


Fig. 3. Penile tip rigidity measured by RAU arranged by age in 44 potent men. Note intraindividual variation on a nightly basis but only slight downward trend of rigidity with increasing age. (Reproduced from 32a with permission.)

highly reproducible when studied in the same patient over time (25). The initial NPTR pattern was reproducible in 15 of 17 patients and that the two nonreproducible patterns could be explained by illness and alcohol ingestion.

Erectile activity in aging men has been the subject of numerous studies. Total sleep time and REM sleep has been shown to remain constant in men between the ages of 20–50 yr. In contrast, total tumescence time and the average number of erectile

episodes has been shown to decrease with age (10,13,14,33–35). Rigidity, as measured by buckling force, has been shown to remain constant, however, between men aged 30–60 yr (35). In another study, a decrease in total tumescence time was noted with advancing age, whereas a significant change in the number of erectile events or in rigidity was not found (35). In the study of normal potent males, Levine and Carroll found an increase in the number of nocturnal erectile events with increasing age; however, the duration of each event appeared to decrease with age (26). The discrepancy between these findings and others may be explained by the definition of a nocturnal erectile event. Levine and Carroll defined an erectile episode as an event lasting for a minimum of 3 min whereas other studies use 5 min to define an erectile event. A slight but significant trend toward decreasing tip rigidity with increasing age was also identified but considerable variability between individual subject responses was noted. Despite these variable findings in aging men, an overall negative trend in nocturnal erectile activity appears to occur with increasing age (Fig. 3).

NPTR MONITORING IN MEN WITH ED

It is generally agreed upon that NPTR monitoring is one of the best available methods to objectively differentiate between organic and psychogenic etiologies of ED (36–43). Based on history, physical examination, biothesiometry, plethysmography, and psychological testing, a high degree of correlation was found between NPTR results and final diagnosis in a study by Davis-Joseph et al. (44). Data analysis of RigiScan monitoring, however, may be difficult to interpret for practicing physicians. A visual review of results based on a graphic printout or an assessment of the single best erectile event over the monitoring sessions may be utilized. Several NPTR patterns, which have been associated with impotence, were identified by Kaneko and Bradley (45). These include dissociation of rigidity between the tip and base of the penis, uncoupling between rigidity and tumescence, a shortened duration of rigidity, low-amplitude rigidity, and no rigidity or tumescence. These specific patterns can be visually recognized, but are not easily compared to normal control populations. In addition, dissociation appears to be a common occurrence in the subject with ED, which makes use of base rigidity criteria for defining normal NPTR less reliable, as tip rigidity does not necessarily correlate to base rigidity in the ED population.

Several investigators have suggested that selecting the “best erection” recorded during monitoring may be another method of quantitative classification of erectile function (6,7,46,47). Sohn et al. have identified a strong correlation between NPTR and severity of ED based on the definition of the “best erection” as the erectile event with the highest rigidity and greatest tumescence (47). Another approach has been to select the best night of erectile activity, which has the highest RigiScan measures, and use the tip RAU value for that night to determine the percentile ranking based on normal values (38). Graphic printout data, the nomogram, and the highest tip and base RAU and TAU values are given below in three separate case studies.

In Case 1 (Fig. 4), a 42-yr-old man with a 1-yr history of ED and no vascular risk factors provides an example of psychogenic ED. Tip RAU data for this patient falls in the 87th percentile, consistent with normal erectile activity. Penile duplex ultrasonography demonstrated a pattern of arterial insufficiency (i.e., possibly caused by increased adrenergic tone). The mean peak systolic flow velocity was 22.5 cm/s, mean end-diastolic flow was 0, and he experienced a full, lasting erectile response to 60 mg

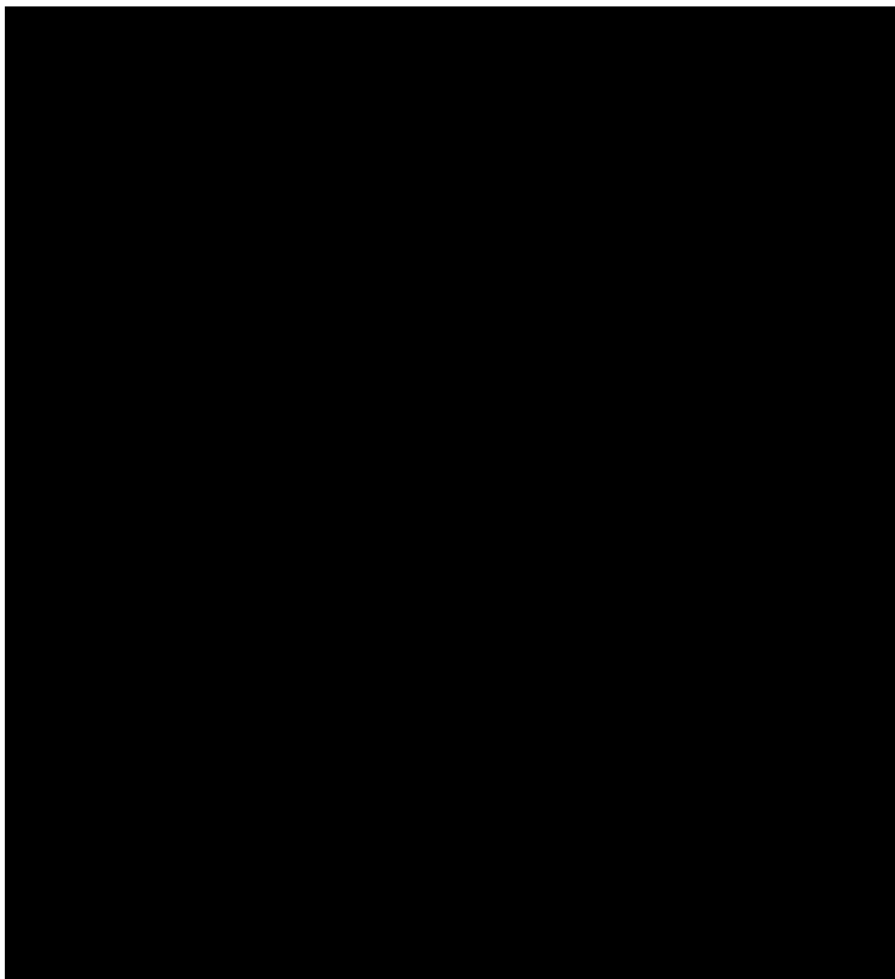


Fig. 4. Case 1. Comparison of graphic printout and cumulative distribution curve ranking using tip RAU data places this 42-yr-old man in the 87th percentile. (Reproduced from ref. 48a with permission.)

papaverine. In Case 2 (Fig. 5), a 56-yr-old man with 3 yr of progressive erectile insufficiency and a history of smoking and hypertension was studied. Several erectile events of variable duration and amplitude can be identified in the NPTR graphic display. The highest tip RAU value placed this individual in the 15th percentile, suggesting an organic cause of erectile insufficiency. Similarly, Case 3 (Fig. 6), represents a 60-yr-old man with erectile failure following radical prostatectomy. His tip RAU data falls in the 3rd percentile, clearly suggesting poor nocturnal erectile activity and an organic etiology. These three examples demonstrate that a single maximum tip RAU value allows for a simple comparison of a patient's erectile activity to that found in a normal population of men.

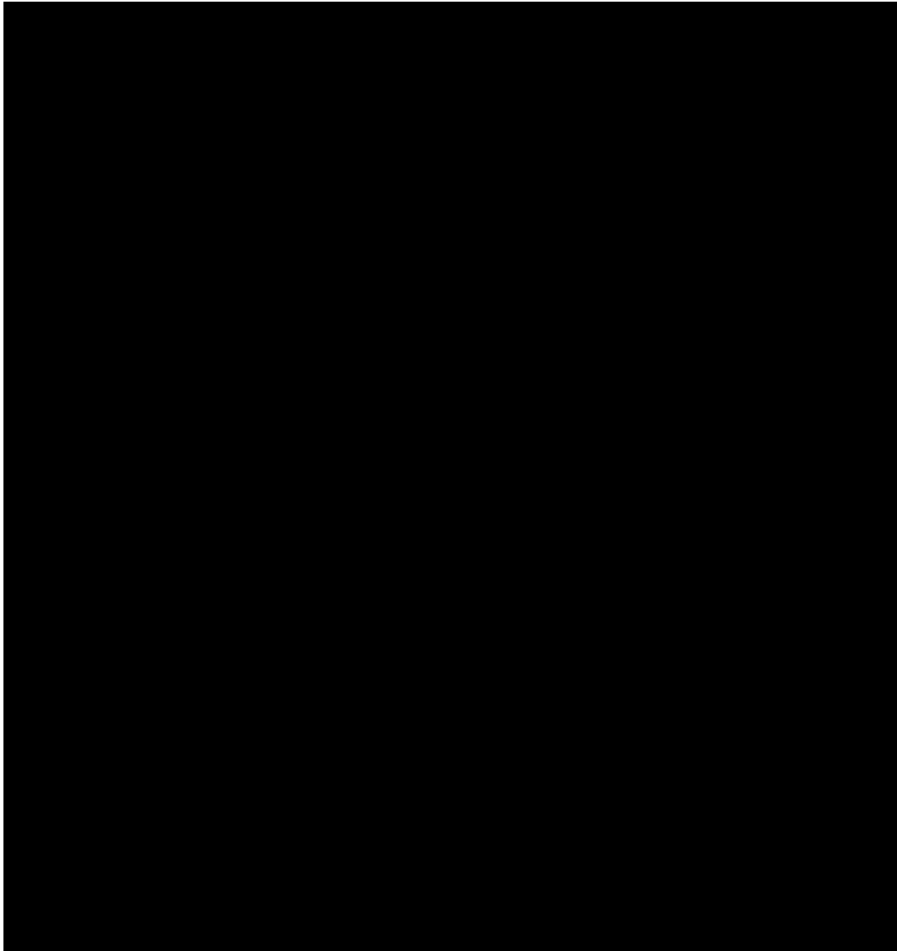


Fig. 5. Case 2. Comparison of graphic printout and cumulative distribution curve ranking using tip RAU data places this 56-yr-old male in the 15th percentile. (Reproduced from ref. 48a with permission.)

In contrast to these case studies, the etiology of impotence can be complex with combinations of psychogenic and organic causes present. In an effort to further define specific subtypes of ED, NPTR testing has been extensively studied. Shabsigh et al. compared NPT monitoring in 50 patients with ED to results obtained from penile duplex ultrasonography with intracavernous injection of vasoactive drugs (48). They found abnormal NPT results in men with vasculogenic impotence, but differentiation between arterial and venous causes was more readily detected by duplex ultrasonography with injection of vasoactive agents. In particular, this was true in patients with pelvic steal syndrome who had relatively normal NPT results. Besides utilizing RigiScan for diagnosis of erectile dysfunction, the device has been proposed to be employed



Fig. 6. Case 3. Comparison of graphic printout and cumulative distribution curve ranking using tip RAU data places this 60-yr-old male in the 3rd percentile. (Reproduced from ref. 48a with permission.)

for evaluation of autonomic nervous system in diabetic men. Bax et al. (49) found a high degree of correlation between penile tumescence at the base of less than 30 mm with abnormal autonomic cardiovascular tests, somatic tests (vibration perception threshold), and diabetic neuropathy score. The positive predictive value of this test was 79%. NPTR was considered a useful noninvasive marker in studying parasympathetic damage of the penile region.

The study by Shabsigh also found that NPT testing was more sensitive than duplex ultrasonography in the evaluation of neurogenic causes of impotence (48). In contrast, Kirkeby found that NPTR results were normal in 11 of 26 patients with known neurological disorders that affect erectile function (i.e., multiple sclerosis) (50).

Kirkeby pointed out that the absence of sufficient nocturnal erections occurs in normal men, even if performed for several sessions, and that the presence of sufficient nocturnal erections proves the capability of awake erections only in the absence of neurological disorders. When strict criteria for a nocturnal erectile event were used (rigidity greater than 80% and duration greater than 30 min), Staerman et al. found that ED in men with multiple sclerosis was not always the result of neurological impairment (51). They concluded that differentiation between psychogenic and organic causes of ED was difficult to make in this population of 16 men with multiple sclerosis.

McMahon and Touma (52) evaluated predictive value of patient history and correlated Rigiscan NPTR with results of color duplex Doppler ultrasonography and dynamic cavernosometry and cavernosography in a retrospective study of 207 patients with ED. They concluded that normal NPT correlated well with normal peak systolic velocity (PSV) (in 85%), resistive index (RI) (94%), maintenance flow rate (Q_m) (96%), but did not exclude organic impotence—16% of patients with normal NPTR were found to have organic problems. Abnormal NPTR correlated well with abnormal PSV, RI, and (Q_m) and had low (4%) false-positive rate.

Montague et al. have compared infusion pharmacocavernosometry (IPC) with NPTR monitoring in 50 patients with ED (53). They found that results from these two tests correlated poorly using standard criteria for IPC, but when modified criteria were used (logistic regression techniques) a stronger correlation was found. The conclusion of this study was that neither method alone appeared sufficient to make a specific diagnosis of ED.

Intracorporal pharmacological (ICP) erection testing has also been compared to NPT in several studies. In 37 impotent men, Allen and Brendler found that the response to ICP testing did not distinguish psychogenic from organic impotence (54). A thorough NPT evaluation provided an accurate prediction of ICP results; however, the reverse was not true. They suggested that NPT testing be performed before ICP erection testing to avoid unnecessary and inappropriate treatment of psychogenic impotence. As with ICP testing, duplex ultrasound also proved unreliable in men with a history of psychogenic illness (55). In a study of 40 men, Allen et al. compared duplex ultrasound to NPT testing and found that anxiety and increased sympathetic stimulation resulted in inaccurate responses to pharmacological stimulation and duplex ultrasound measurements. They suggested that, NPT testing should be carried out for appropriate treatment recommendations in patients suspected of having a psychogenic cause of impotence.

LIMITATIONS OF NPT AND NPTR TESTING

Several basic assumptions have been made in using NPTR testing for the evaluation of impotence. First, it is assumed that the presence of a nocturnal erection indicates the capacity to have an awake erection. Second, the physiological mechanisms responsible for a nocturnal erection are assumed to be similar to those responsible for a sexually stimulated erection. Although this assumption has been questioned, Krane has suggested that nocturnal and sexually stimulated erections occur by a similar mechanism (56). Third, psychogenic causes of impotence are assumed to not alter the ability to have a nocturnal erection. However, it has been noted that dreams containing anxiety, aggression, and other negative content are associated with abnormal NPT results (5,8).

Also, depression has been shown to reversibly decrease NPT, which can be restored upon successful treatment (57–59). Furthermore, abnormal results have been found in 15–20% of men with no identifiable organic causes of impotence (13). Because of these assumptions, several investigators have questioned the usefulness of NPT testing. Wasserman et al. have stressed that although NPT testing may be useful in differentiating organic from psychogenic causes of impotence, NPT testing has never been validated independent of the NPT measurements themselves (60). Other investigators have cautioned that erectile potential in erotic and sexual circumstances may not be adequately assessed by NPT testing (16,61).

A fourth assumption made by NPT testing is that the quality of sleep experienced and the method of testing itself does not impact nocturnal erectile activity. The concept of a first-night effect was suggested by a decrease in the number of tumescence episodes, total tumescent time, and quality of erections on the first night of sleep laboratory testing (62). Although abnormal NPT results could occur as a result of the unnatural NPT device or to interference with normal sleep, no first-night effect was found in two recent studies of normal, healthy volunteers using the RigiScan device (25,26). Sleep conditions such as sleep apnea, periodic leg movements, and nocturnal myoclonus can negatively affect NPT. In these situations, diminished NPT results would most likely not reflect abnormal erectile function (63,64). It has been suggested that disturbed sleep can inhibit the appearance of spontaneous erections (65). However, Schiavi has demonstrated that even in normal males with normal sleep patterns, full erections may not occur (66). Because NPT monitoring in a sleep laboratory is expensive and time consuming, and because home-monitoring devices cannot monitor the quality of sleep, several studies have investigated the potential of monitoring NPT during daytime naps. During a 3-h nap, it was demonstrated that healthy male subjects fell asleep rapidly, slept well, and experienced REM sleep (67). In another study, Morales et al. found that 16 of 18 men with ED experienced REM sleep during a morning nap session (68). Of these men, four did not experience tumescence during the nap session or during nocturnal sleep on two separate occasions. Of 12 patients who exhibited nocturnal erections, 9 also experienced erections during the nap session. Further investigation may reveal that NPT monitoring during a nap may be a more convenient and less costly method of evaluating NPT.

One problem with NPTR testing is the lack of accepted criteria for sufficient rigidity for vaginal penetration. Kirkeby et al. have observed that in normal potent males, nocturnal erections fluctuated in rigidity and that at least half were judged to be insufficient for vaginal penetration (29). This finding is in agreement with estimates from other studies, which have found that 23 to 48% of nocturnal erections in normal men have insufficient rigidity for intromission (69–71). One compounding factor regarding this issue is that the concept of adequate rigidity for vaginal penetration should account for the subject's particular partner and situation (i.e., vaginal size, lubrication, and partner receptivity) (72). Perhaps adequate rigidity for any given individual should be measured as a relative quantity with respect to his partner's vagina because there are no standard vaginas with respect to penetrability.

A final and important criticism of NPT monitoring is the accuracy of measuring rigidity. Early measurements of penile rigidity, such as buckling pressure, were measures of applied axial force. In contrast, devices such as the RigiScan measure rigidity as a function of applied radial pressure. Whether radial measures of rigidity are accurate when compared with axial measures of rigidity, is under intensive debate. Frohib

et al. have compared measurements of axial and radial rigidity at constant intracorporal pressures and found that they were functionally related (73). Furthermore, they demonstrated that these measures correlated with intracavernous pressure, the physiological event considered responsible for penile rigidity. On the other hand, Munoz et al. have found in a study of 17 men with ED that the RigiScan appears to underestimate rigidity at low levels (43). This underestimation could result in men with normal rigidity (psychogenic erectile dysfunction) being diagnosed with organic ED. In contrast, Allen et al. have found that the RigiScan did not correlate with axial rigidity at high levels (74). This overestimation could result in men with lower rigidity (organic ED) being characterized with a psychogenic cause of ED. However, a strong correlation between base rigidity, as measured by radial rigidity, and buckling pressure (axial rigidity), has been found by Licht et al. in a study of 28 impotent men (32). They have further found that tip rigidity correlated poorly with axial measurements. Because it has been noted that tip and base rigidity may be disassociated in impotent men, this poor correlation may merely reflect the disease state (45). Alternatively, this poor correlation may reflect the use of a trained observer measuring axial rigidity. Udelson et al. (75) further examined correlation of axial and radial rigidity. In this prospective study of 36 impotent men, axial buckling force correlated to radial rigidity measured with the RigiScan device during simultaneous pharmacocavernosometry. Penile tissue mechanical properties and penile geometry were recorded. The authors concluded that axial and radial rigidity increased with elevating of intracorporal pressures at different rates. They suggested that this could be explained by the fact that axial rigidity is a function of erectile tissue mechanical properties and penile geometry, whereas radial rigidity is a function of tunical surface wall tension. In this study, in an individual, the axial buckling measurement was not predicted by RigiScan radial deformation measurement (i.e., rigidity). It is important to understand that to date, no proposed measures of "intromission pressure" have been accepted, and measurements of axial rigidity continue to be difficult to perform. Because all of these studies attempt to correlate axial and radial rigidity in populations of men with ED, further studies are needed in normal populations to determine if these conflicting results are inherent to the RigiScan or are indicative of ED.

RECOMMENDED USE OF NPTR TESTING

The use of NPT monitoring in all men with ED is subject to debate. The authors' opinion is NPT testing is most likely not necessary in men with significant organic risk factors associated with impotence, such as diabetes mellitus, hypertension, smoking, high triglyceride or cholesterol levels, or vascular disease. On the other hand, men with no known neurovascular disease or whose history suggests a psychogenic etiology are most likely to benefit from NPTR testing. As an objective measure of erectile function, NPTR should confirm the diagnosis and aid the physician in choosing appropriate therapy. NPTR evaluation may also be useful in men with Peyronie's disease, who may complain of poor-quality erection or softening of the erection distal to the plaque. If an underlying organic cause of impotence is uncovered, and the patient does not respond to pharmacological treatment, the patient could benefit from the placement of a prosthesis to ensure penile rigidity at the time of penile reconstruction surgery and straightening of the penis (76). Because office ICP injection provides quick, inexpensive, and conclusive evidence that a patient is capable of achieving an erection, some have argued that NPTR testing should be limited (77). However, injection of a drug to

demonstrate that an erection can be induced does not address the patient's concern as to why the problem exists. Therefore, NPT monitoring is recommended to determine both the cause of ED and potentially the most appropriate treatment.

Currently, the author's approach includes a complete medical history and focused physical examination. NPTR is recommended when a clear psychogenic etiology is present or when neurovascular risk factors are absent. In general, duplex ultrasonography with pharmacological stimulation is performed first in men who present with a more complex history. The possibility of excessive adrenergic tone is suspected in men who present with the following duplex ultrasound pattern: suboptimal mean peak systolic velocity (less than 30 cm/s), normal mean end diastolic flow velocity (less than 5 cm/s), and a full erectile response to pharmacological stimulation (78,79). NPTR is also far less invasive and expensive than phalloarteriography or infusion cavernosometry. In addition, NPTR offers more objective proof to support a recommendation for psychosexual rehabilitation therapy.

In the author's opinion, the entire pattern of erectile activity, as recorded on the one or more nights of study using the RigiScan device, provides a more complete assessment of that individual's nocturnal erectile capacity as compared to the use of the "best erection" criteria. The use of TAU and RAU cumulative data allows comparison. Highest tip RAU on the best night of erectile activity as a percentile ranking of normal data provides the most useful impression of nocturnal erectile function.

Although home monitoring with the RigiScan is simple and less expensive, hospital or sleep laboratory monitoring is suggested in certain circumstances. For instance, when manual dexterity may prevent some patients from properly applying the RigiScan unit or when validity in an outpatient, unobserved setting may be a concern, particularly during medico-legal testing, or when there is a history or suspicion of sleep disturbance or malingering.

The authors agree that no single test exists that enables the physician to identify the etiology and degree of impotence. However, NPTR is a valuable resource in differentiating between psychogenic and organic causes of impotence. The ultimate goal for the practicing physician in evaluating ED is to provide useful information and to direct that patient to the most appropriate therapeutic options. For many patients, NPTR provides this information in a rather noninvasive and relatively inexpensive manner.

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Vascular Evaluation of Erectile Dysfunction

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INTRODUCTION

What is the Usefulness of Vascular Testing in the Era of Oral Agents for Erectile Dysfunction (ED)?

In the era of only two specific treatments for erectile dysfunction (ED) (penile prosthesis and vasoactive penile injection), most patients could be easily directed to therapy following a good sexual history, assessment of medical risks, and physical examination. Without diagnostic testing, efficacy, and satisfaction was a matter of chance. The next millennium

Testing for E.D.

The Present

- Primary purpose of establishing a specific diagnosis is to formulate a treatment plan.
 - Sexual history, Physical Exam, Goal Directed Rx
- Which patients should have diagnostic testing?
 - Pelvic / Perineal trauma
 - Peyronie's disease
 - Young men with 'primary ED'
 - Insurance requirement - 'authorization for treatment'
 - Oral Drug Failures!

Fig. 1. The contemporary algorithm for ED testing begins with a sexual history, physical examination, and limited laboratory blood work. Patients are then directed, typically directed toward, their preferred therapy. There are subsets of men who should receive diagnostic workups.

will see the development of multiple oral agents for the management of male sexual dysfunction. These agents with their differing mechanisms of pharmacological action will present, for the first time, the possibility for cause-specific therapy. When faced with an expanded list of treatment options for ED, the role of impotence testing will assume a twofold importance: 1. establishing an etiology-specific diagnosis and 2. formulating a treatment plan with a reasonable likelihood of success. More importantly patients failing first-line therapy by primary caregivers will seek the expertise of urologists; patients will want to know not only what is wrong with them but also why initial therapy was unsuccessful in managing their ED (Fig. 1). In order to be prepared to meet these demands, our diagnostic algorithms must incorporate new pharmacological agents. In order to tailor the particular therapy to the etiology of ED, testing should provide vascular profiles to predict which drug or combination of drugs (oral, cutaneous, urethral, or intracavernosal) will effectively restore erection. Conversely, to spare patients the potential side effects and frustration of empiric drug trials, ED testing will need to identify which patients would best be served by a mechanical solution: a vacuum device or penile prosthesis.

Do all Urologists Perform Impotence Testing?

There is little data on U.S. nationwide practice patterns in impotence testing, but a survey of urologists in six European countries was conducted in 1996 just before the introduction of oral phosphodiesterase inhibitors. As part of the study sponsored by Pharmacia-Upjohn, 3000 urologists practicing in France, Germany, Italy, Spain, Sweden, and the United Kingdom were asked how they manage ED (1).

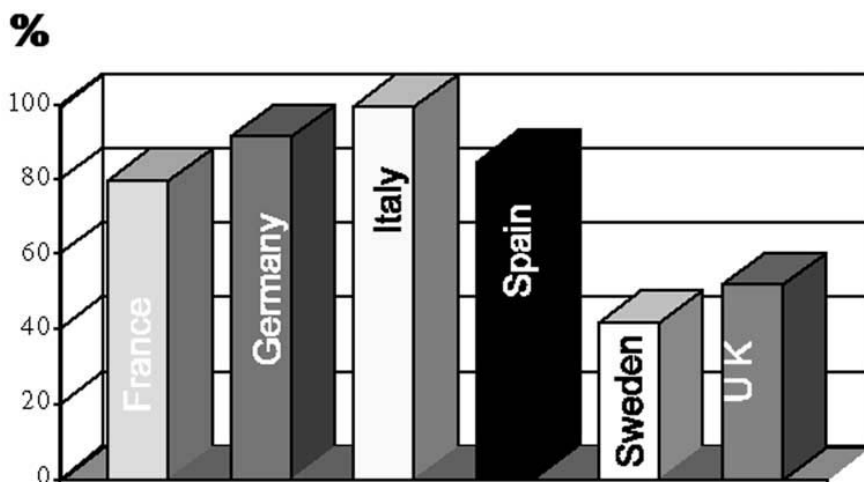


Fig. 2. Survey of 3000 European urologists, percentage by country who routinely investigate the cause of ED.

The overall response rate was 60%. The data reflect differences in diagnostic and treatment strategies, highlighting the influences of health care structure, medical economics, and cultural diversity. Perhaps most importantly, the data paints a picture revealing the state-of-the-art in ED testing and treatments before the introduction of (Sildenafil) oral phosphodiesterase-inhibitor therapy.

In Germany, Spain, Sweden, and the UK, most urologists work alone when it comes to the evaluation of ED. Urologists in both France and Italy reported high proportions of multidisciplinary teams: 72% and 78%, respectively. In Germany, most patients were self-referred (60%), whereas in the U.K. and Sweden most were referred by general practitioners (60%–73%). In each country, more than 90% of men completed a sexual questionnaire and had a physical examination during the initial visit. With the exception of Sweden (40%), urologists in European countries routinely investigated the cause of ED before initiating therapy (Fig. 2). The most commonly performed evaluation was hormonal screening (62%–68%). The second most commonly performed test was in-office intracavernous injection (ICI), (53%–81%). The preferred radiological investigation was duplex Doppler sonography combined with ICI, which was performed by 30%–65% of urologists, with the exception of the U.K. (5%). All remaining investigations were performed with less frequency: nocturnal penile tumescence and rigidity testing (12%), visual erotic stimulation (6%), cavernosometry/cavernosography (6%), electromyograms (EMG) (6%), and psychological assessments (16%) (Fig. 3). The average number of visits following the first consultation was 2.9. Surprisingly, less than 40% of physicians involved the partner during the initial visits.

HISTORICAL BACKGROUND

Numerous diagnostic tests have been employed to evaluate penile hemodynamics, including penile plethysmography, penile blood pressures, penile brachial index,

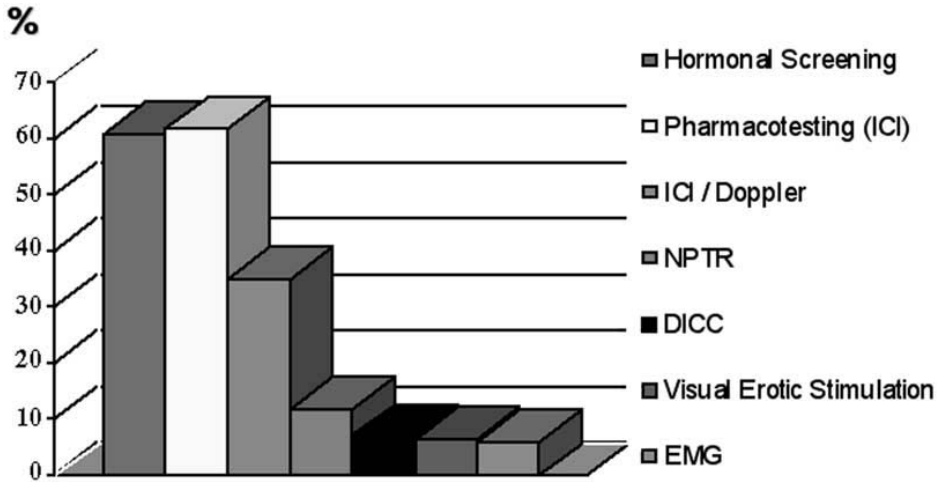


Fig. 3. Survey of 3000 European urologists frequency of diagnostic testing by preference.

duplex Doppler sonography, dynamic infusion cavernosometry/cavernosography, nuclear washout radiography, and magnetic resonance imaging (MRI). In 1971, Gaskell described a noninvasive test of penile arterial inflow using a photometer to quantify the absorption of light by the pigment oxyhemoglobin in the glans penis (2). An occlusive cuff at the base of the penis was slowly loosened, and the pressure at which oxyhemoglobin became measurable in the glans indicated the penile systolic blood pressure. Abelson used the Doppler stethoscope to measure penile blood pressure in flaccidity and compared this value to systolic brachial pressure, yielding the penile-brachial index (PBI)—maximal systolic pressure divided by systolic brachial artery pressure (3). Michal et al. and Goldstein made modifications to the PBI by adding a dynamic component of lower extremity and pelvic musculature exercises, with Doppler stethoscope auscultation before and after exercise (4,5). A decrease in the ratio of penile systolic pressures (<0.15 mmHg) was indicative of significant pelvic inflow disease. However, subsequent reviews comparing the PBI to pharmacopenile angiography found that PBI values from normal patients overlapped those from impotent patients, and pressures were inadvertently obtained from the dorsal artery not reflecting central cavernous arteries at all (6). Further misleading data was obtained when the PBI was performed with the penis in the flaccid state. In essence, the PBI could not be relied upon for accurate measurements of cavernosal artery blood flow or as an assessment of penile hemodynamics.

THE GOLD STANDARD: PENILE ARTERIOGRAPHY

Penile arteriography set the initial standards for diagnosis of vascular ED. Accurate penile angiography requires pharmacologically induced erection; the vessels of the flaccid shaft are normally contracted and tortuous. This was unappreciated in early investigations. High osmolality ionic contrast agents tended to be painful, often requiring intravenous sedative anesthesia, and they may be complicated by anaphylaxis.

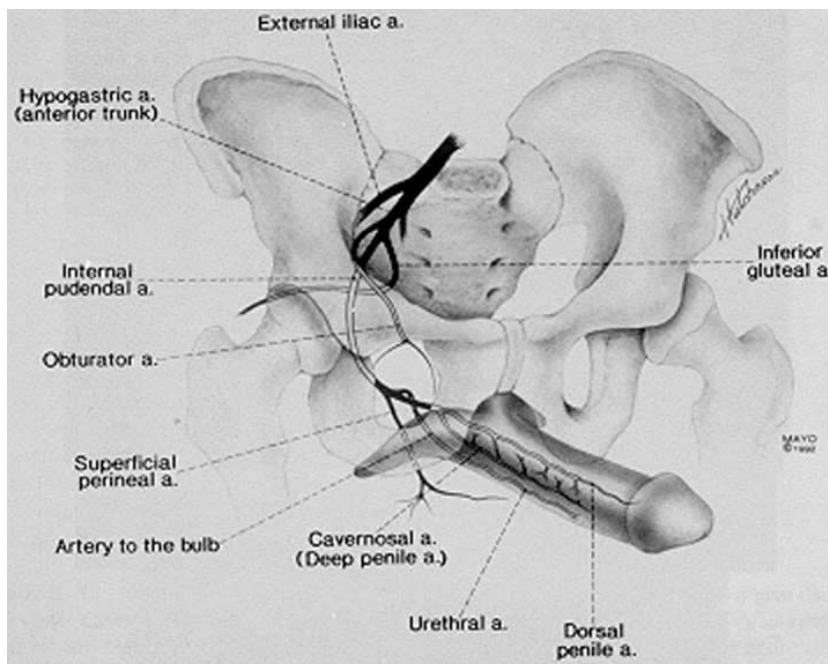


Fig. 4. Penile angiography set the initial standards for the diagnosis of vascular ED. Adequate phalloarteriography requires intracavernous and intraarterial vasodilators. Although highly invasive, it provides the best anatomic information about the origin of the common penile arteries.

Some centers used epidural or spinal anesthesia because of the additional benefit in reducing vasospasm (7). Contemporary modifications of penile arteriography include low osmolality nonionic contrast agents that reduce angiographic morbidity, but are more expensive. Simultaneously administered intraarterial and intracavernous vasodilators enhance identification of pelvic and penile vessels. Digital subtraction techniques and selective catheterization allow visualization of internal pudendal, accessory pudendal, and inferior epigastric arteries (Fig. 4). The inferior epigastrics are the vessels most commonly harvested for penile revascularization.

Indisputably, arteriography provides the best anatomic information about the origin of the common penile arteries, but these data have been difficult to correlate with patient complaints and with erection dynamics (8). The common penile artery trifurcates, giving off the bulbourethral, the cavernous, and dorsal arteries. The accessory internal pudendal artery (IPA) takes origin from the hypogastric artery, remnant of the umbilical, ischial, or obturator vessels. An accessory IPA has been variably described in 4%–70% of pelvic angiograms. Therefore, performing selective internal pudendal arteriography (SIPA), and possibly missing an accessory IPA, has an inherent false-positive rate for diagnosis of penile inflow disease (9–11). Also, confounding interpretation of penile pharmacoangiography is the anatomic fact that deviations from paired common penile arteries have been documented in 50% of normally potent volunteers: unilateral absence or hypoplasia of a dorsal artery has been shown in up to 30% of vol-

unteers (12). Anatomic variation of intrapenile arterial anatomy appears to be the rule rather than the exception (13). One group performed 35 angiographies (70 vessels) finding no relationship between visualization and nonvisualization of the IPA and the results of a variety of dynamic test: duplex Doppler, cavernous artery systolic occlusion pressure, and penile brachial index (14).

The problem for the angiographer has been twofold: how to differentiate congenital variations in penile arterial anatomy from acquired abnormalities, and how to correlate anatomic alternations in the pattern of vascular inflow with impotence. [???]Because of these issues, selective internal pudendal phalloangiography once the gold standard for diagnosing vascular ED is now reserved for those patients who are candidates for vascular reconstruction. The initial evaluation for vascular severity of ED typically begins with pharmacotesting and duplex Doppler assessment.[???]

As a screening test phalloarteriography is overly invasive and nonspecific of penile hemodynamics; it should be reserved for young men with a history of pelvic fractures and traumatic impotence. There is a significant incidence of ED following posterior urethral disruption as a consequence of pelvic fracture; these men are sometimes candidates for vascular reconstruction. Penile phalloangiography, once the gold standard of impotence testing, is now reserved for the few patients who are candidates for vascular bypass surgery.

OFFICE PENILE PHARMACOTESTING

In 1982, during the course of vascular operation Ronald Virag noted that infusion of papaverine into the hypogastric artery produced erection (15,15a). In 1983, a dramatic demonstration of the efficacy of penile self-injection was offered by Giles Brindley who injected himself in front of audience at a national meeting; he subsequently popularized the use of α -blockers (phenoxybenzamine and phentolamine) for intracorporeal injection in the management of erectile dysfunction (15b,15c). Zorngiotti and Lefleur promoted penile self-injection with the drug combination papaverine/phentolamine (16). In 1989, Ishii published the first clinical series on prostaglandin E1 (PGE1) for self-injection (17). Clinicians subsequently turned to the benefits of combination therapy: exploiting the specific pharmacorelaxing properties of different intracavernous agents, reducing the pain sometimes associated with single agent PGE1 therapy (20–33%), reducing the risk of corporal fibrosis and hepatic dysfunction (8%) associated with papaverine, and minimizing the cost and volume of penile injections (18). Bennette first described the clinical efficacy of Trimix: papaverine, phentolamine, and alprostadil (PGE1). In July 1995, Upjohn Company received Food and Drug Administration (FDA) approval to market injectable PGE1 (Caverject) specifically for the diagnosis and treatment of male ED.

The demonstration that vasoactive injections could produce penile erection without psychological or tactile stimuli revolutionized the diagnosis and treatment of erectile dysfunction by providing a direct test of end organ integrity and the first cause-specific pharmacologic therapy. Pharmacotesting consists of an intracavernous injection (ICI) and a visual rating of the subsequent erection. This test is the most common diagnostic office-based procedure for ED. It is simple, minimally invasive, and performed without monitoring equipment. A positive response (normal erectile rigidity of sustained duration) implies psychogenic impotence, presumably excluding significant venous or arterial pathology. Contemporary hemodynamic investigations suggest that a positive

injection test is indeed associated with normal veno-occlusion (low flow to maintain erection values of 0.5 to 3 mL/min and minimal contrast medium or no contrast leakage during cavernosometry and cavernosography), but not necessarily with normal arterial function (19). In as many as 19% of patients, the test may be a false negative. Despite the presence of an erection, there may be a significant disparity between the systemic and cavernous systolic arterial pressures. Recent correlation with more invasive testing confirms that a positive pharmacological erection test is indicative of normal veno-occlusion but may occur with borderline arterial function, when normal was defined as a peak systolic velocity greater than 35 cm/s and borderline as 25–35 cm/s on duplex Doppler (20). Office pharmacotesting, despite its lack of specificity, is very cost-effective and clinically helpful: at the very least a positive injection test selects patients for home injection therapy. A standard initial intracavernous test dosage has never been established. The authors use 10µg of PGE1 in the standard patient.

PENILE BLOOD FLOW STUDIES: PHARMACOTESTING AND DOPPLER PENILE SONOGRAPHY

When diagnostic testing is indicated, the penile blood flow study (PBFS), which consists of ICI and assessment by duplex Doppler ultrasound, is the most informative and least invasive means of evaluating vasculogenic ED. Color duplex Doppler (CDDU) is a further advance over gray-scale duplex sonography; it aids in visualizing vessels with the Doppler computer assigning color to flowing blood. PBFS efficiently selects patients who are candidates for more invasive testing (21–24).

The principles and techniques of PBFS with CDDU are reviewed as are the most recent criteria for distinguishing: arterial insufficiency from cavernous venous occlusive disease, high-flow from low-flow priapism, and for preoperative staging of Peyronie's disease.

DUPLEX DOPPLER AND PENILE ANATOMY

With real-time ultrasound, the corpus cavernosum (CC) and spongiosum (CS) have a homogeneous medium echogenicity, which is easily distinguished from the hyperechoic tunica albuginea and septum (Fig. 5). The tunica albuginea should have uniform thickness and echogenicity; the subcutaneous tissues and Buck's fascia are not identifiable sonographically except by the location of the dorsal vascular bundle: paired dorsal arteries (DAs) and deep dorsal vein complex (DDV). The pendulous penis is easily imaged from the dorsal, lateral, or ventral projection. The proximal third of the penis may be imaged in transverse or sagittal view by scanning the perineum below the scrotum (Fig. 6). If necessary, the urethral lumen can be imaged by retrograde filling with sterile gel or water (25,26). Proximal penile imaging below the scrotum is essential in the evaluation of straddle injuries, especially because this is the typical location of traumatic arteriovenous fistulae.

ASSESSING PENILE INFLOW

CDDU provides a detailed examination of the vascular anatomy of the penis and records the dynamics of erection. The IPA supplies the penis, but prepenile inflow vessels are not seen during sonography. Branches of the common penile artery consist of the bulbar, urethral (spongiosal), dorsal, and cavernous arteries; each of which can be identified within the penis by CDDU. The cavernous artery penetrates the tunica albug-

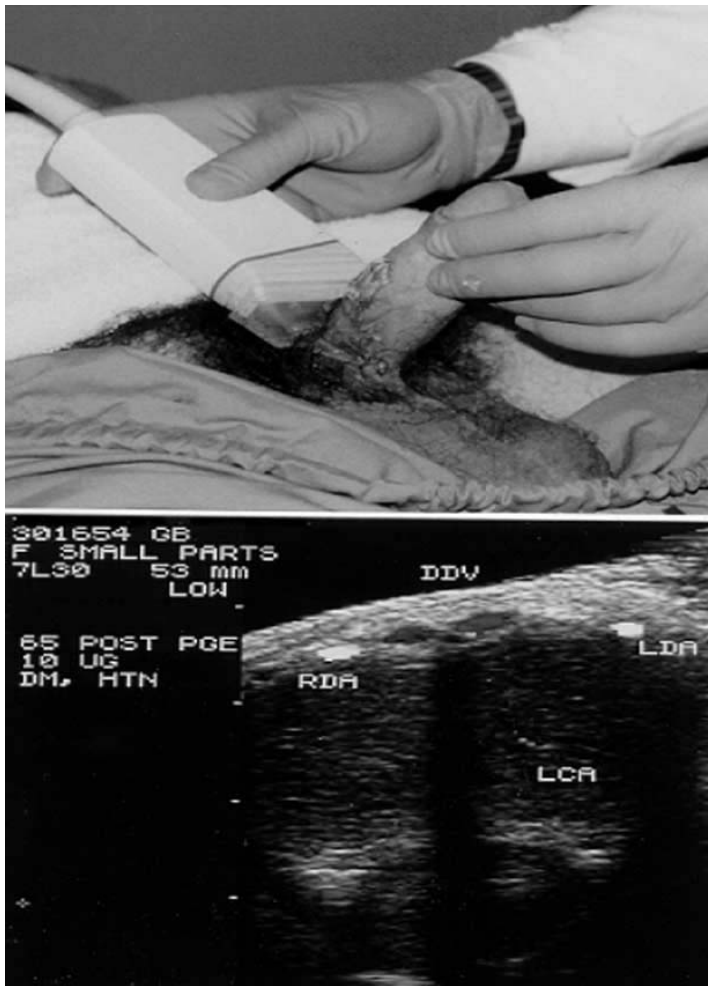


Fig. 5. The penis is held in the position of erection to straighten the cavernous vessels; imaging is begun in the transverse plane to assess anatomy. Corresponding transverse CDDU image showing right dorsal artery (RDA), deep dorsal vein complex (DDV), left dorsal artery (LDA), and left cavernous artery (LCA).

inea and enters the crura of the corpora cavernosa along with the cavernous veins and cavernous nerves. The cavernous arteries are easily identified by their echogenic walls; in the flaccid state the arteries are tortuous and ≤ 0.5 mm in diameter. With CDDU, low blood flows are visible, but detection of flow prior to injection of vasodilator depends on the patient's level of sympathetic tone (anxiety and room temperature) and is of no predictive value (21,27). Cavernosal tissue is sponge like and composed of a meshwork of interconnected cavernosal spaces, which are lined by vascular endothelium and separated by trabeculae, containing bundles of smooth muscle in a framework of collagen, elastin, and fibroblasts. The terminal helicine arteries are multiple muscular and

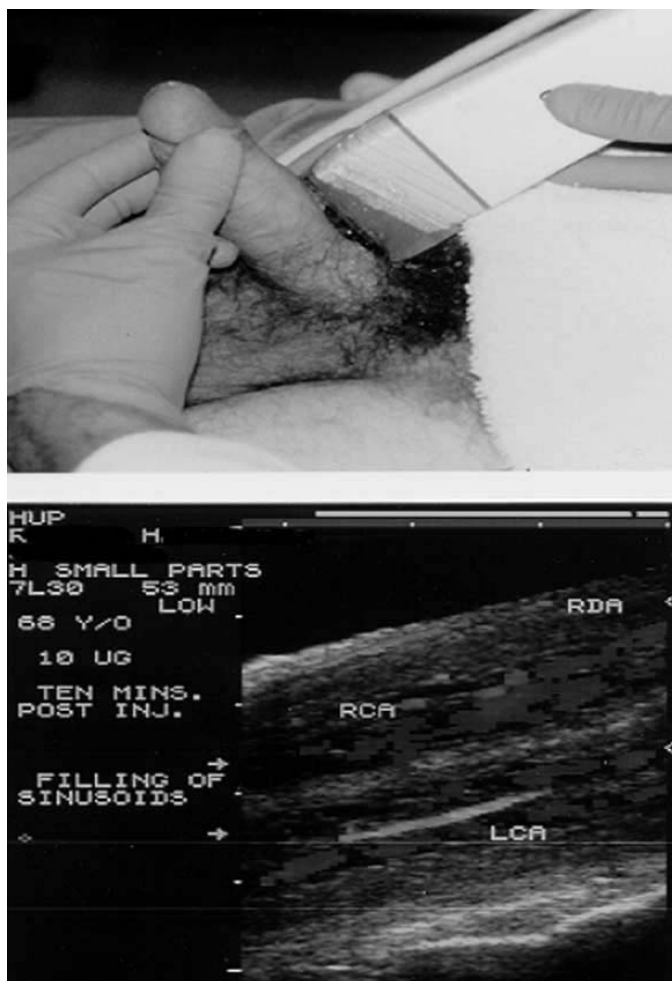


Fig. 6. The penis is held in the position of erection to straighten the cavernous vessels; imaging in the sagittal plane from the dorsum.

corkscrew-shaped arteries (150–350 μm) that open directly into the cavernous spaces and act like resistance arteries. These terminal helicine arterioles can be imaged with “power” Doppler technology. The corporal tissue becomes more hypo-echoic (darker) as the sinusoids distend with blood, making the echogenic walls of the cavernous arteries more distinct sonographically. The dorsal artery enters the penis and continues distally beneath Buck’s fascia. Between the dorsal arteries are one or more deep dorsal vein(s) and flanking each dorsal artery are the dorsal nerves. The urethral artery runs longitudinally through the corpus spongiosum lateral to the urethra. This supplies corpus spongiosum, the urethral tissue, and the glans penis. The bulbar artery enters the bulb of the penis shortly after its origin. It supplies blood to Cowper’s gland and the

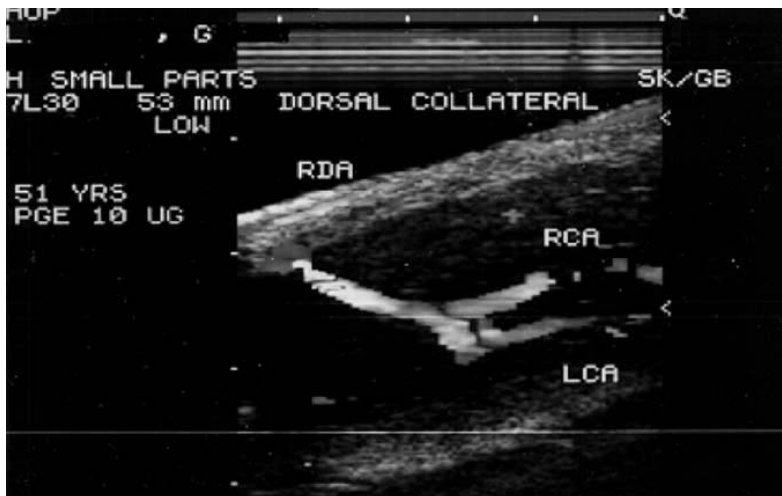


Fig. 7. Sagittal image of a 51-yr-old patient 10 min following injection of PGE1 [10 mcg]. The right dorsal artery (RDA) has a collateral branch to the right cavernous artery (RCA), which then crosses the septum to anastomose with the left cavernous artery (LCA) as well.

proximal urethral bulb. Anatomic variations of penile arterial supply include dorsal to cavernous, cavernous to cavernous and cavernous to urethral collaterals, duplication of the cavernous artery, and unilateral absence of a dorsal artery (28,21) (Fig. 7).

PENILE VENOUS OUTFLOW

Based on scanning electronic microscopy (SEM) of vascular corrosion casts, Banya et al. (29) suggested two circulatory routes in the human corpora (29). One route goes from the cavernous artery to capillary networks collected into the venular plexus just beneath the tunica albuginea. This is suggested to serve as the main circulatory pathway during the flaccid state. The other route is through anastomoses from the cavernous artery, via the helicine arteries to the cavernae (sinusoids), which are then emptied into the postcavernous venules. This ultrastructural detail cannot be visualized sonographically.

There are three sets of veins draining the penis: the superficial, intermediate, and deep. The deep venous system drains both the corpora cavernosa and the corpus spongiosum. The postcavernous venules coalesce to form larger emissary veins, which pierce the tunica albuginea. The emissary veins of the middle and distal penis join to form the circumflex veins, which empty into the deep dorsal vein. Both emissary and circumflex veins have valves. The short emissary veins of the proximal penis form the cavernous vein, which empties into the internal pudendal vein.

Veins from the glans penis form a retrocoronal plexus that drains into the deep dorsal vein. The deep dorsal vein (DDV) courses proximal in the midline and empties under the pubic arch into the periprostatic plexus. The superficial dorsal vein drains the skin and the subcutaneous tissue superficial to Buck's fascia. It drains into the superficial external pudendal vein. There may be one or several deep dorsal veins; sonograph-

ically the DDV is distinguished from the dorsal arteries by venous as opposed to arterial Doppler waveforms.

ERECTION HEMODYNAMICS

Erection is a complex event regulated by the tone of smooth muscle composing the cavernous arterioles, venules, and sinusoids. Tumescence follows a decrease in corporal smooth muscle tension: decreasing arterial, arteriolar, and sinusoidal resistance. Decreasing resistance to arterial inflow bathes the cavernous tissues in arterial blood. Venous outflow during erection is dynamically limited by distention of the sinusoids compressing the subtunical venular plexus against the inner layer of the tunica albuginea. The differential stretching of the two primary layers of the tunica albuginea during erection scissors closed the exiting emissary veins. The rigid penis is veno-occluded, in a low outflow state, with distended sinusoids and elevated intracorporeal pressure. During rigid erection arterial inflows are paradoxically very low: by Doppler estimation 1.5–5.6 mL/min, by phalloarteriography 4.7 mL/min, by radioisotope study < 5 mL/min. Dynamic cavernosometry similarly reveals that rigid erection is associated with low flow to maintain values of 0.5–3 mL/min (17,30). Detumescence and flaccidity are initiated and maintained by corporal smooth muscle contraction via sympathetic adrenergic nerves.

Lue and Wagner having studied the dynamics of erection in several species and have divided the progress from flaccidity to erection into distinct phases (31,32). In the flaccid phase, there is a dominant sympathetic influence, and the terminal arterioles and cavernous smooth muscles are contracted. In the filling phase, parasympathetic nervous activity dominates, and there is an increased blood flow through the internal pudendal and cavernous arteries. Penile resistance decreases because of dilatation of the cavernosal and helicine arteries; the penis elongates. During the tumescence phase the intracavernous pressures increases rapidly. The compliance of the sinusoidal muscle increases, causing penile engorgement. In full erection, the relaxed trabecular muscle expands and, together with the increased blood volume, compresses the plexus of subtunical venules, reducing venous outflow, increasing intracavernous pressure to 10–20 mmHg below true systolic blood pressure (minimum of 80 mmHg). In the rigid erection phase cavernous pressure may transiently increase above the systolic pressure. As a consequence of voluntary or reflexogenic contraction of the ischiocavernosus and bulbocavernosus muscles during pelvic thrusting suprasystolic pressures may be achieved. Maximal penile rigidity is compromised when bulbocavernous reflex is absent.

The separate phases of erection documented in laboratory animals do have correlates with human erectile responses during PBFS (Fig. 8). There are many variables in clinical testing which may alter the normal progression of erection phases. The threshold dosage for a single agent or multiple agents to reliably promote complete smooth muscle relaxation has not been established, and quite probably varies with levels of patient sympathetic tone (anxiety). Available data on the minimal effective dosage of PGE1 suggests [2 µg] will produce erection in 38% of men with psychogenic impotence and 20% of men with vasculogenic erectile dysfunction (33). A pattern of spectral waveform progression on CDDU has been correlated with a normal rigid response during PBFS (34). In the filling phase when sinusoidal resistance is low, 5 min following injection the waveform is characterized by high forward flow during diastole. As intrapenile pressure increases diastolic velocities decrease, with full erection the systolic waveforms will sharply peak and may be slightly less than during full tumes-

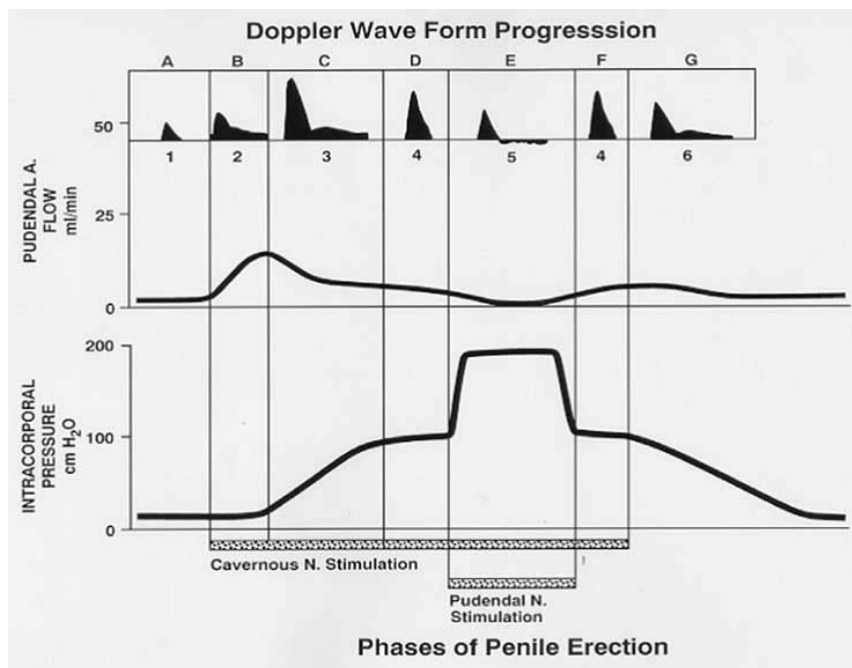


Fig. 8. Phases of the erectile response described in the animal model stimulated by the cavernous nerve, then additionally stimulated by the pudendal nerve. Pudendal arterial flow and intracavernous pressures are graphically compared to the Doppler waveform progression of a normal human erection: A) flaccid phase, B) latent phase, C) tumescence, D) full erection, E) rigid erection with reversal of diastolic flow, F) rigid erection with suppression of diastolic flow, G) detumescence.

cence; diastolic flow will be zero. In rigid erection cavernous pressure will exceed systemic diastolic blood pressure and reversal of diastolic flow occurs. Similarly in the rigid erection phase the systolic waveform may be dampened (21).

TECHNIQUE

Since its introduction by Lue (1985), duplex Doppler penile sonography has proven to be an accurate and reproducible technique for evaluating ED. With the initial gray-scale imaging of duplex sonography, study quality was highly dependent on the skill of the examiner. Vessel localization within the corporal tissue was difficult and dorsal vessel imaging all but impossible. The addition of color has facilitated consistent detection of dorsal, cavernous and urethral vessels. CDDU permits the rapid acquisition and measurement of small vessels (35–37). High frequency linear array transducers (5 to 10 MHz) provide the best images of the penis. The higher the frequency the better the near field resolution. Other have reported adequate high-resolution penile imaging with (noncolor) gray-scale 13.5 MHz probes (23).

Color flow uses the imaging principles of pulsed Doppler: a pulse of ultrasound is emitted from the transducer, is reflected back and received. When the returning echo

reflecting back off a moving object (penile blood) has a different frequency than the emitted frequency a Doppler shift has occurred. Doppler shift depends on several factors: frequency of the transducer, velocity of the moving object (penile blood), speed of sound through the medium (penile tissue) and angle between the Doppler beam and direction of blood flow. The blood flowing in a vessel that is approaching the transducer will produce echoes with a higher frequency than was emitted and blood flowing away produces a lower frequency. As blood flow velocities increase, Doppler shift increases. The Doppler shift is displayed on gray scale as spectrum (waveform) or in CDDU as two-dimensional color image. In CDDU the color display has angle dependence just like the gray-scale spectrum of the Doppler shift. If the vessel runs parallel to the skin surface, ultrasound scanning lines are perpendicular (90° Doppler angle) this will yield no Doppler shift and no color within the vessel. To correct this problem of physics, linear array transducers use phasing to steer the scan lines at a more appropriate angle or an angled standoff wedge on the end of the transducer to provide a non-perpendicular Doppler angle. Arterial flow velocity determinations depend on the ultrasound beam-vessel angle. The optimal angle is 60° . Because arterial flow velocities will be repeated several times after injecting vasodilator particular attention should be made to maintaining the same angle of insonation. For example, arterial velocities in the same vessel will be recorded at 20 cm/s, 25 cm/s, 31 cm/s, or 203 cm/s if the probe – vessel angle is altered from 30° to 45° to 55° to 85° , respectively (38,39,40,41,42).

PBFS EXAMINATION PROTOCOL

A warm, secure examination room is essential to reduce anxiety and thus sympathetic cavernous smooth-muscle tone. The patient should be assured that no one will come walking in during his testing. The patient should be supine; he need only disrobe from the waist down. His attention should be directed at the monitor with periodic explanation of images displayed. The corporal bodies should be scanned in the transverse plane from base to tip to demonstrate normal anatomy (paired cavernous and dorsal arteries); the echotexture should be homogeneous, fibrotic processes are relatively hyperechoic in comparison (Fig. 5). Peyronie's plaques will be denser than normal tunica; they may be visible as linear echogenic thickenings. If they cast an acoustic shadow like a renal stone then calcification should be suspected and plain radiographs taken following CDDU (Fig. 9). The penile vessels and flow velocities are assessed in the sagittal plane (parallel to the long axis of the penis). Vessels may be scanned from a dorsal or ventral approach (Fig. 6). Lateral scanning will demonstrate both cavernous vessels in the same image, with the hyperechoic septum in between the arteries. Cavernous to cavernous collaterals are best imaged in the sagittal projection from the lateral penis (3 or 9 o'clock). The author has noted these vessels perforating the septum in 50% of men examined. They are seen in young patients with neurogenic and psychogenic impotence suggesting congenital origin. The dynamics of collateral flow are important. High-flow collaterals may supplement acquired unilateral cavernous arterial insufficiency in the older patient. A dorsal projection is required to image the dorsal artery and ipsilateral cavernous artery simultaneously (Fig. 7). Following vasodilator injection, dorsal to cavernous collaterals have been demonstrated in 59% of men, but these were hemodynamically significant only in 15% of patients (≥ 25 cm/s) (43). The dorsal arteries are not subjected to intracorporeal pressure changes during progressive

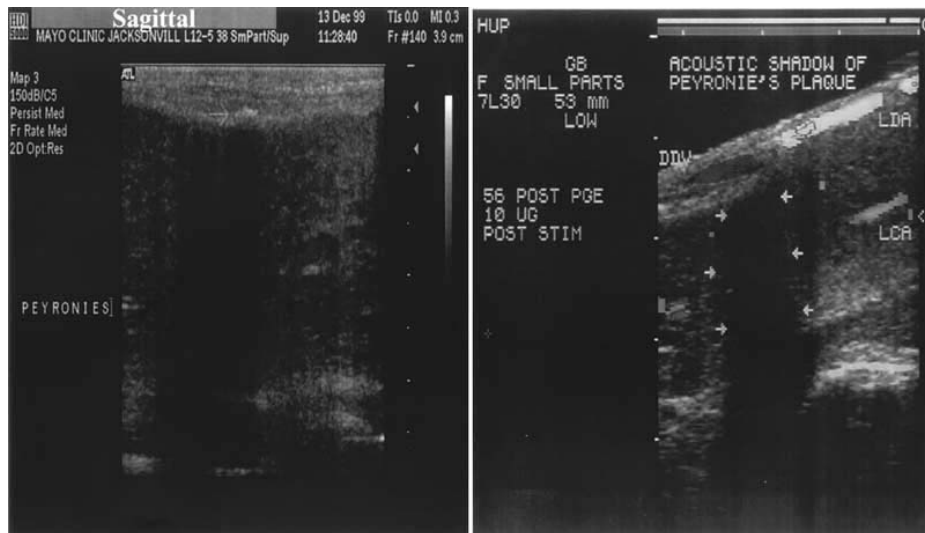


Fig. 9. On the left is a gray-scale real-time sonographic image with a discrete hyperechoic plaque casting a small, but dense acoustic shadow. On the right is a color duplex Doppler image of another Peyronie's patient with a less dense plaque which is not hyperechoic, but casts a distinct and larger acoustic shadow which prevents the doppler signal from imaging a section of the cavernous artery below.

erection phases; therefore, even in well-sustained rigidity, antegrade diastolic flow persists. During peak erection, dorsal systolic flow is maximal. Copious acoustic gel on the surface of the penis and a light touch is needed not to alter flow dynamics of dorsal vessels, by compression.

All four penile arteries should be scanned at least from the level of the peno-scrotal junction to glans. When there is asymmetry of cavernous flows (≥ 10 cm/s) or when collaterals are seen, the crura should be examined to determine if proximal inflow disease exists (pre-penile) or if intracorporal stenosis has resulted in CDDU signal assymetry (>10). Reversal of arterial flow in systole signals severe unilateral inflow disease, because blood flow should be antegrade in both cavernous arteries during systole. If the patient's legs are abducted in a frog-leg position, the perineum can be scanned, revealing the entry of the cavernous arteries into the penis. This view is especially helpful when searching for arterial sinusoidal malformations, which may develop as a result of straddle injury causing high-flow priapism (Fig. 10). Because distal flows will rapidly drop off in a normal erection, if the examiner waits too long and the erection is rigid cavernous inflows are actually suppressed by high intracorporal pressures. At peak rigidity, Doppler data will be inconsistent with observed rigidity because the waveform will be suppressed by penile pressure. Cavernous-flow velocities will be highest at the perineum and segmentally diminish, distally. Several investigators have confirmed that systolic velocities of the cavernous arteries vary significantly as a function of sampling location from proximal to distal (44,45).

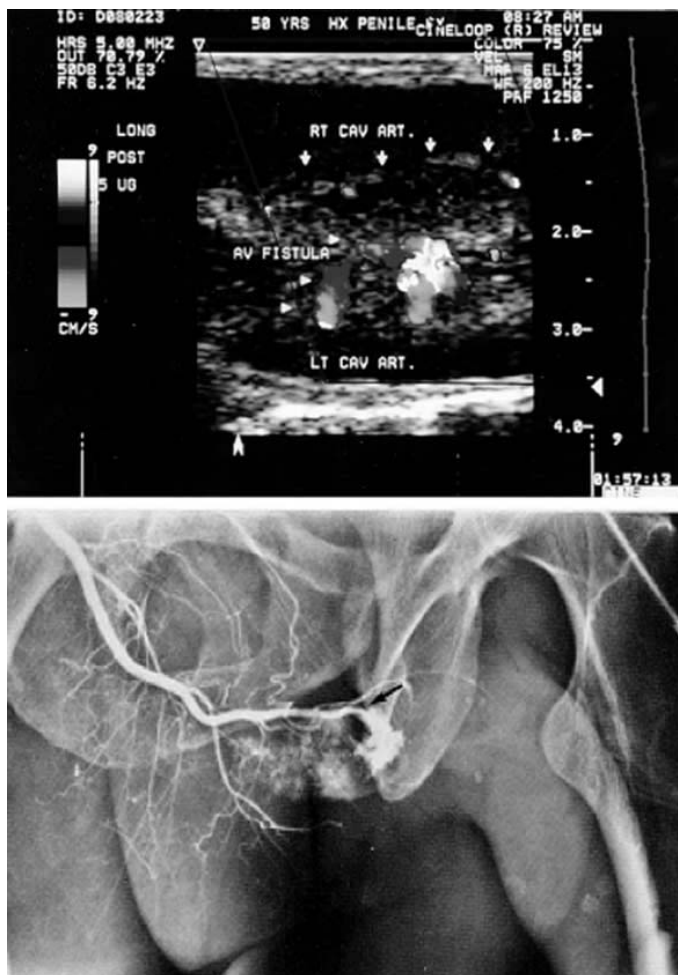


Fig. 10. High-flow priapism results from penile trauma, generally a straddle injury. Color duplex Doppler can image cavernous arterial sinuoidal fistula by scanning through the perineum (above). The fistula may also be visualized with selective internal pudendal phalloarteriography (below), but this technique is invasive and generally reserved for patients undergoing therapeutic embolization.

The principal source of error in flow-velocity determinations is incorrectly assigned Doppler angle. Holding the shaft upright stretches the normally tortuous cavernous vessels and permits consistent measurements with the probe – vessel Doppler angle remaining set. Timing is important, because arterial diameter and cavernous peak systolic velocities will maximize before rigid erection (maximal intracavernous pressure). Some investigators advocate continuous penile sampling for up to 30 min following penile injection (46). Meuleman et al. found peak velocities highest 5–10 min following vasodilator (47). Fitzgerald et al. found that 24% of patients tested did not reach maxi-

mum cavernous flow until 10–15 min after injection (48). Patel et al. noted peak systolic velocities maximized between 5–6.5 min following injection; 22% of patients had a delayed response (1–18 min) (49). If initial measurements are made at 5–10 min after injection and full or rigid erection waveforms are not seen, a period of privacy and self-stimulation will enhance the penile response in $\geq 70\%$ of patients. Alternatively, visual erotic stimulation via video monitor or headset may enhance the diagnostic yield of a penile injection. CDDU assessment is repeated immediately following self-stimulation, and notation is made of whether the response weakens or is sustained. Lue and Donatucci found that, among 90 patients performing self-stimulation after PGE1 challenge, 74% improved; among those whose responses weakened within 5 min of stimulation, 84% were noted to have moderate venous leakage on follow-up cavernosography (50). Montorsi et al. evaluated initial dosing with PGE1 10 mcg and redosing with 10 mcg vs the effects of a single dosage followed by genital plus audiovisual sexual stimulation. Erectile responses after the AVSS session was significantly greater than after re-dosing and patients more frequently achieved erections equal to or greater than those at home (51).

Again, it is very useful to rate the erectile quality during Doppler assessment: *Inadequate vs Adequate vs Unbending Rigidity sustained for 20 min*. Correlation of visual erection rating and Doppler parameters is an essential element in the diagnostic process. Although the Doppler parameters are distinctly different, tumescence without rigidity is characteristic of both severe veno-occlusive disease and arterial insufficiency. Goldstein defines the aim of penile vascular testing is to obtain hemodynamic data on the same quality of erection that the patient gets in the privacy of his own bedroom, *the best-quality erection* (23). If the patient does not think the pharmacologic erection is equal to his home erection, then the patient can be re-dosed to achieve maximal smooth-muscle relaxation (52).

The choice of intracavernous vasoactive agent for PBFS has never been standardized. The initial duplex Doppler studies were performed following injection of 60 mg of papaverine (8,53,54). Trimix has been used in efforts to achieve maximal smooth-muscle relaxation: papaverine, phentolamine, and PGE1 (18). Of the currently used agents, PGE1 is thought to have the greatest biocompatibility. PGE1 is the only FDA-approved injectable for the treatment of ED. In a dose-finding study, the median effective dosage was 5.0 μg in patients with vasculogenic dysfunction, producing a mean duration of erection of 37 min. Penile discomfort was noted in 34%, and prolonged erection (4–6 h) in 5% (33). In my experience with initial diagnostic intracavernous challenges, PGE1 is highly effective in males with vascular risk factors at dosing of 10 mcg when coupled with privacy and self-stimulation or visual erotica. With this regimen, only 4% of patients develop persistent rigidity of 2 h. Prolonged erections (1–4 h) are successfully managed with simple aspiration and or direct corporal injection of the α -adrenergic phenylephrine (100 $\mu\text{g}/\text{cc}$, using 1–3 cc).

A portable Doppler machine was recently introduced to evaluate penile blood flow in the urologist's office (MIDUS device). The pulsed Doppler unit offers the advantages of a traditional duplex Doppler ultrasound machine without the cost. Cavernosal artery blood flow is studied in a similar fashion after intracavernosal PGE1 injection and self-stimulation. Two independent groups have validated its reliability when compared to Doppler ultrasound, showing a sensitivity and specificity of 89% and 67%, respectively (55,56) (Fig. 11).

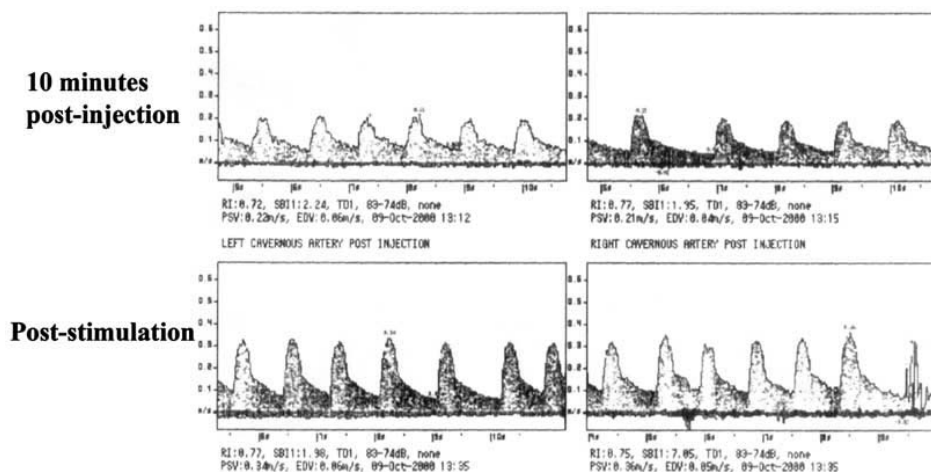


Fig. 11. Midus pulsed Doppler permits in-office-based penile blood flow study to document responses to pharmacotesting, permitting classification of ED (arterial, venous, mixed vascular).

CDDU AND PENILE INFLOW: ARTERIAL ADEQUACY

The original parameter used to infer the adequacy of penile circulation was cavernous peak systolic velocity (PSV). In efforts to further refine the diagnosis of cavernous inflow disease, Doppler parameters have been expanded: end diastolic arterial velocity (EDV), which is the flow velocity measured during diastole immediately prior to take off of the systolic waveform, systolic rise time measured in ms from the start of systolic velocity to the maximum value, and cavernous artery acceleration which is calculated by dividing peak flow velocity by systolic rise time (27,57,58). Flow velocities should be measured 5–10 min after injection; a delay in response is typical in both the hypertensive and the anxious patient. A visual rating of erectile quality should be recorded each time a set of Doppler parameters is recorded.

Penile inflow is a function of both velocity and vessel diameter. Lue originally proposed that an adequate response in the cavernous arteries should produce a > 0.7 -mm postinjection arterial diameter, and ≥ 25 cm/s PSV (Fig. 12). He found that if the cavernous arteries did not dilate by 75%, there was a high likelihood of arterial disease (59). Other investigators suggested increases of more than 100%, or could not confirm significant changes in pre- and postinjection cavernous arterial diameters (37,60,61,62). Subsequent investigations have shown that cavernous arterial diameters normally decrease from proximal to distal and that measurement of cavernous arterial lumens actually exceeds ultrasound resolution of 7–10 MHz probes. In the UCSF series normal subjects had mean PSV of 34.8 cm/s and mean arterial diameter 0.89 mm (42). In a study from Baylor University, normal volunteers had mean PSV of 40 cm/s and mean arterial diameter of 1.0 mm (63). Normal volunteers at the Harvard Medical School study had mean PSV of 47 cm/s (61). Each of these groups concurs that a peak systolic velocity < 25 cm/s suggests arterial disease. When penile angiography is compared to duplex Doppler examinations of the same patients, PSV

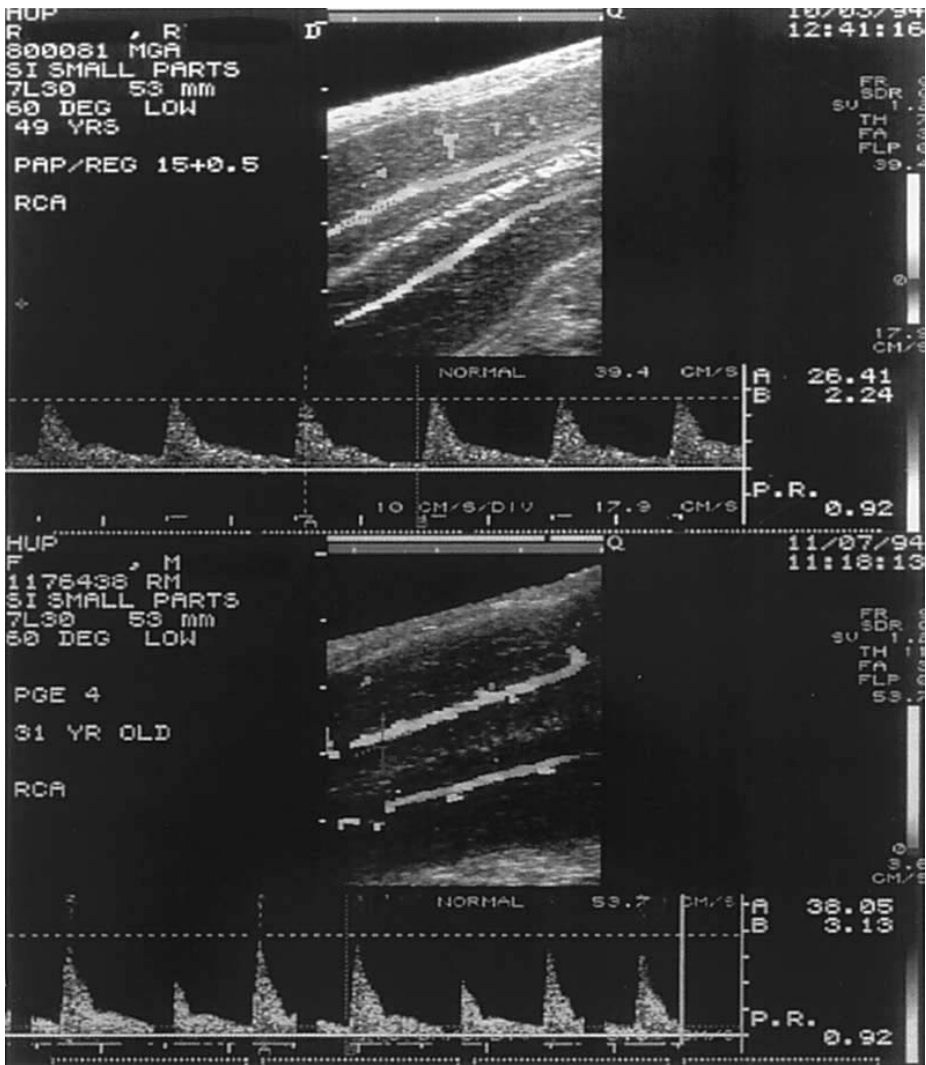


Fig. 12. Penile blood flow studies (PBFS) permit real-time imaging of penile vessels with color duplex Doppler ultrasound. Peak systolic velocity (PSV) < 25 cm/s has a 100% sensitivity and 95% specificity in selecting patients who would have abnormal penile arteriograms. PSV > 35 cm/s consistently associated with normal arteriograms.

<25 cm/s in the mid-shaft is consistently associated with severe arterial disease (Fig. 13). In the Mayo Clinic series, PSV < 25 cm/s had a sensitivity of 100% and specificity of 95% in selection patients with abnormal pudendal arteriography (64). A PSV of 35 cm/s or more is generally associated normal penile arteriogram (62). The Mayo Clinic group has recommended if a patient has a good clinical response to vasodilating injection and bilateral peak systolic velocities are > 30 cm/s with arter-

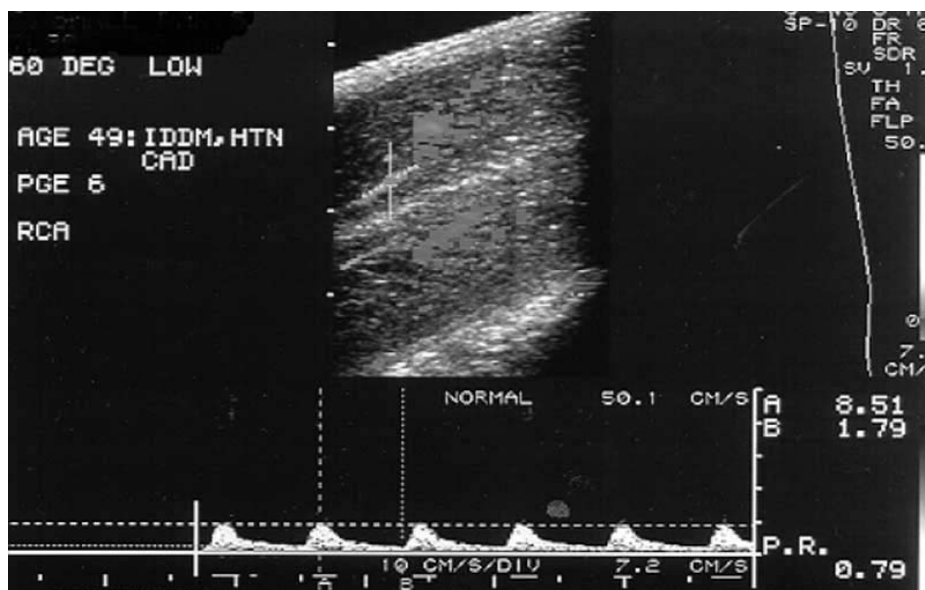


Fig. 13. PBFS of 49-yr-old patient with insulin-dependent diabetes mellitus, hypertension, and atherosclerotic coronary artery disease showing severe cavernous arterial insufficiency PSV=8.5 cm/s.

ial dilation to 0.7 mm at the mid-shaft, arteriography should not be performed. When PSV is compared to cavernous arterial systolic occlusion pressures (CASOP) generated during dynamic infusion cavernosometry (DICC), a PSV ≥ 25 cm/s predicts a normal CASOP with a sensitivity of 95% and specificity of 95% (65). If cavernous inflows are asymmetric or absent at the perineum, suspect prepenile (pudendal) arterial disease. Intrapenile arterial disease is confirmed when crural inflows are adequate and equal, but asymmetry (R vs L) of PSVs is noted in the pendulous shaft. On CDDU, severe unilateral cavernous arterial insufficiency may be associated with reversal of systolic flow proximal to the entry of a collateral.

Schwartz correlated progressive changes in Doppler spectral waveform pattern with increasing intracorporeal pressure in potent volunteers stimulated with papaverine/phentolamine. Rigid erection was associated with intracorporeal pressures ranging from 83 to 106 mmHg. During tumescence, both PSV and EDV increased, with corporal pressure in the range of 11–25 mmHg. With rigidity, EDV approached 0, and diastolic flow reversed when intracorporeal pressures reached 63–83 mmHg (66) (Fig. 14).

In 1974, Planiol and Pourcelot derived the index of vascular resistance from the Doppler spectrum. The formula for Resistive Index is $RI = PSV - EDV/PSV$. RI calculation is not directly dependent on the probe vessel angle (67). The value of RI depends on the resistance to arterial inflow, and in the context of corporal physiology, this is a function of sympathetic tone in the flaccid state and of changing intracorporeal pressure during the various phases of erection. As penile pressure equals or exceeds diastolic pressure, diastolic flow in the corpora will approach 0 and the value for RI

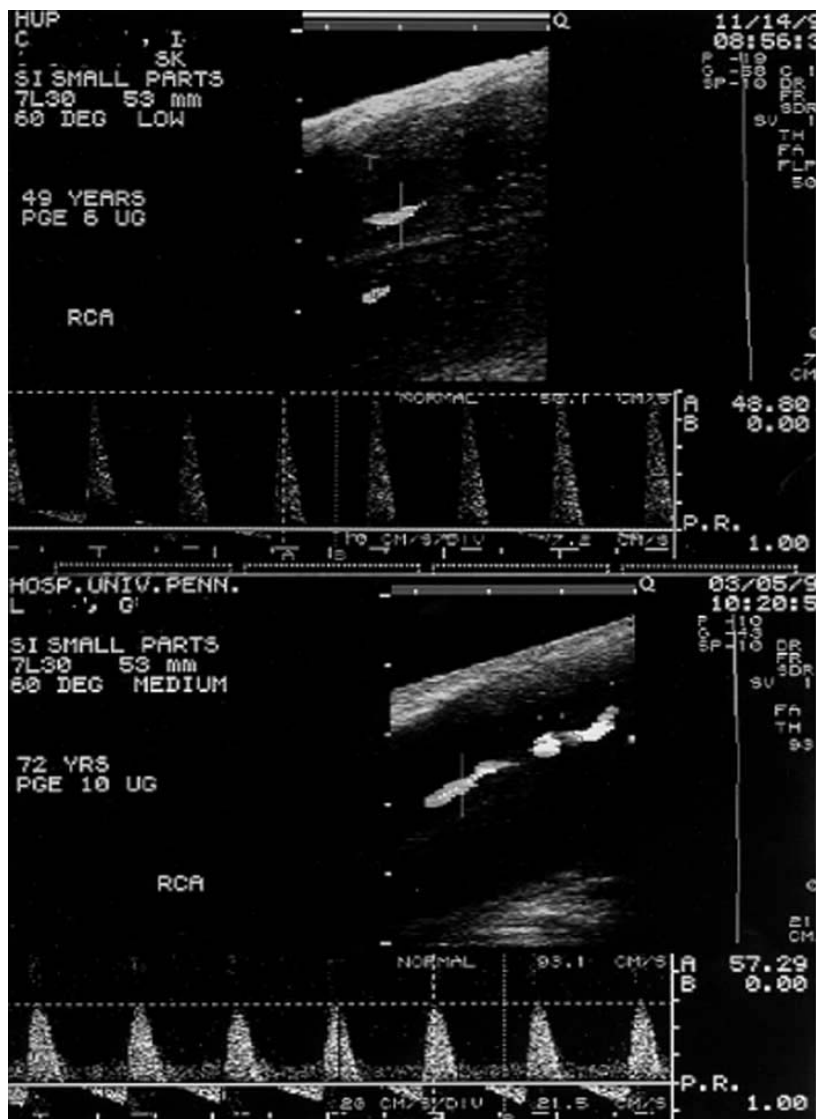


Fig. 14. Two patients with sustained unbending rigidity during pharmacotesting: above 6mcg of PGE1 resulted in peak systolic velocities of 48.8 cm/sec and suppression of diastolic flow; below 10 mcg in a 72-yr-old male resulted in normal erection associated with PSV=57 cm/s and reversal of diastolic flows.

approaches 1. During tumescence and until full rigidity, diastolic flow is antegrade and the value for RI remains < 1.0. The RI correlates very well with visual rating of erectile responses as both are descriptions of penile rigidity and pressure. Both EDV and RI are useful parameters in predicting adequacy of veno-occlusion.

EVALUATING VENO-OCCLUSIVE DYSFUNCTION

Failure of the veno-occlusive mechanism is reflected in the Doppler spectral waveform of the cavernous artery. The suspicion of venous leakage is raised when the patient has an excellent arterial response to injected vasodilator (≥ 30 cm/s PSV), with well-maintained EDV (> 3 – 5 cm/s), accompanied by transient rigidity after self-stimulation.

Quam (1989) found EDVs ranging between 0–24 cm/s after intracavernous papaverine (60 mg). Among patients with PSVs > 25 cm/s, venous leakage on cavernosometry was predicted with a sensitivity of 90% and specificity of 56% when end diastolic flow was > 5 cm/s (35,64). Fitzgerald (1991), using criteria of cavernous arterial adequacy (> 25 cm/s PSV) and venous leakage (> 5 cm/s EDV), noted that only three-fourths of patients achieved maximal responses to papaverine (60 mg) at 5 min. Data acquisition for a total of 30 min yielded a sensitivity of 95% and specificity of 83% for prediction of venous leakage (48). Merckx et al. injected patients with PGE1 [20 mcg] followed by Doppler analysis at 5-min intervals (68). Doppler parameters among 26 psychogenically impotent men were statistically identical to eight potent volunteers: at 5 min maximum PSV 49 cm/s, maximum EDV 11 cm/s, RI 0.78; at 10 min PSV was 38.8 cm/s, EDV 3.7 cm/s, RI was 0.91. The RI was the only parameter that statistically differentiated the venous incompetence. Using this 5- and 10-min scanning protocol, they noted a 93% correlation between CDDU and cavernosometry. In the Mayo Clinic series, Lewis noted an EDV of > 3 cm/s measured 15–20 min postinjection yielded a specificity of 94% and sensitivity of 69% for detection of venous leakage when compared with dynamic cavernosometry (64). McMahon found RI calculations 15 min after injection correlated well with maintenance flow rates from DICC and cavernosal decay rates (69). In a study from Japan, Naroda (1994) found RI > 0.9 was associated with normal dynamic infusion cavernosometry in 90% and RI < 0.75 was associated with venous leakage in 95% of patients (70). The conclusion reached from these investigations is that measurement of resistive index 20 min after injection and stimulation (or redosing) is a reliable, noninvasive method to diagnose cavernous venous leakage.

When the Doppler spectral waveform continues to exhibit forward diastolic flow despite peak systolic flow (> 35 cm/s), a low resistance state persists in the sinusoids and the patient may have venogenic impotence (Fig. 15). The dorsal arteries are not subjected to the intracorporeal pressure changes with each phase of erection and well-sustained rigidity is associated with antegrade diastolic flow. Deep dorsal vein flow persists during rigid erection; DDV flows are a function of dorsal arterial flow to the glans and should not be interpreted as evidence of corporal venous leakage. The primary veno-occlusive mechanism consists of passive compression of the subtunical venular plexus by the distended sinusoids. The secondary mechanism is the scissoring off of the emissary veins as they egress through the two layers of the tunica albuginea. Emissary veins unlike dorsal artery to cavernous artery collaterals are difficult to localize with CDDU presumably because of their low flow state and easy compressibility.

Cavernosometry and Cavernosography

Insufficient corporal veno-occlusion is implicated in up to 50% of patients complaining of ED who submit to vascular testing. The diagnosis and demonstration of venous leakage requires complete smooth-muscle relaxation; failure to achieve this

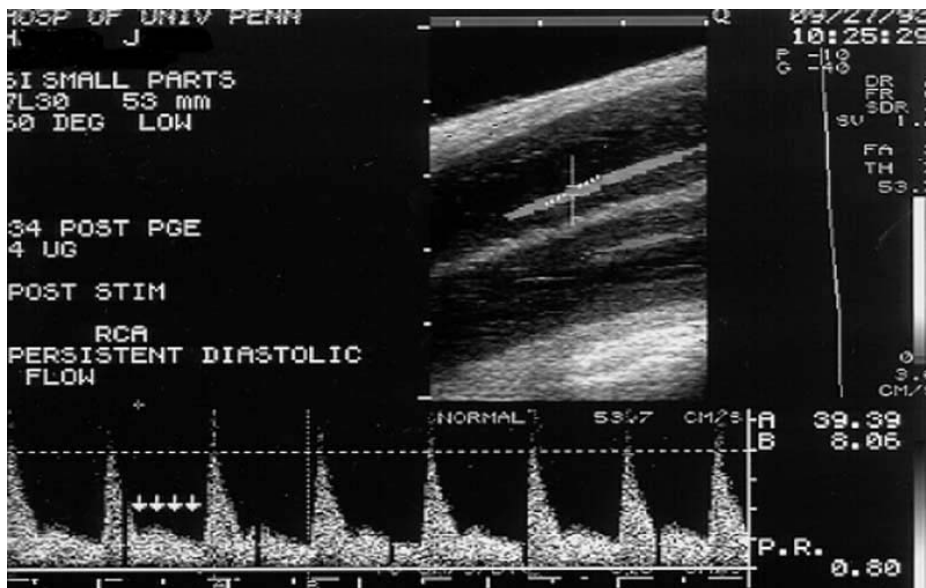


Fig. 15. Cavernous venous occlusive disease in a patient with primary ED: despite high cavernous arterial flows 39 cm/s, diastolic flows persist and patient failed to achieve rigidity despite redosing and self-stimulation.

was an inherent source of error in early reports. Dynamic infusion cavernosometry and cavernosography (DICC) is invasive, requiring two needles to remain in the penis for saline infusion and pressure recording. Therefore, it is primarily reserved for those patients considering the option of vascular reconstruction: vein ligation with or without arterial bypass (Fig. 16).

Establishing a diagnosis of isolated venous insufficiency first requires demonstration of intact arterial inflow. To achieve complete smooth-muscle relaxation, one of several intracavernous injections are given followed by determination of maintenance flow rate (MFR), pressure volume responses (PVR), cavernous artery systolic occlusion pressure (CASOP), and intracavernous pressure at which arterial pulsations reappear after suppression by saline infusion. Normal CASOP varies by less than 35 mm Hg with the brachial artery systolic pressure.

MFR is considered the most important criterion of venoocclusive dysfunction. It is the flow to maintain erection at an intracavernous pressure of 150 mmHg. This pressure, although arbitrarily selected, is clearly supraphysiologic (normal erectile rigidity is associated with intracorporeal pressure of 80–90 mm Hg) and isolates MFR from cavernous arterial inflow dependence. Unfortunately, numerous values have been suggested for normal MFR. MFR data from several studies using pharmacocavernosometry found that all normal subjects had MFRs less than 50 mL/min; 45% had MFRs less than 14 mL/min. (Wespes et al. 1986; Freidenberg et al. 1987; Vickers et al, 1992). Contemporary studies suggest that MFR following complete smooth-muscle relaxation should be 3 mL/min or

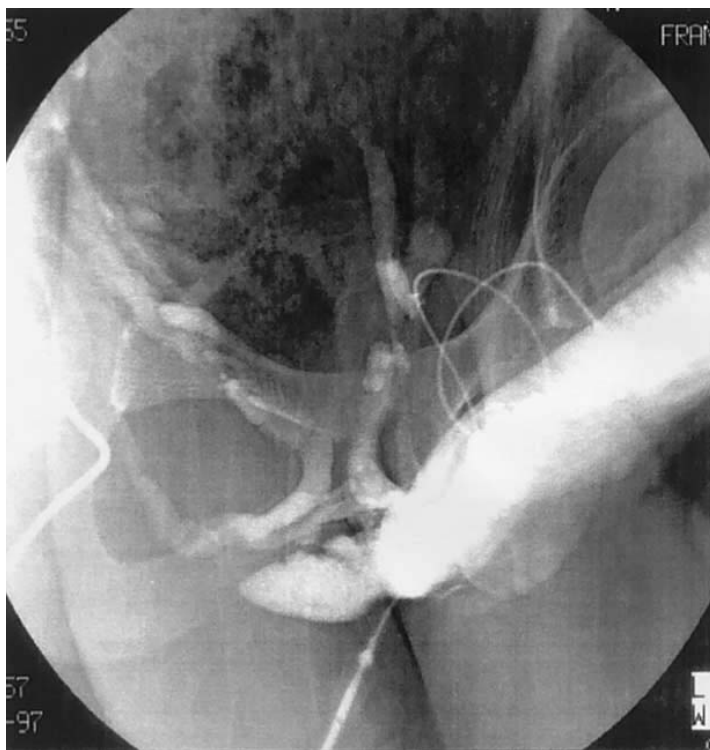


Fig. 16. DICC once commonly utilized is now reserved for select patients. The test is invasive requiring two needles be inserted into the penis one for infusion the other for measuring pressure changes.

less. Cavernosography, which is the radiographic imaging of the paired corpora is performed after cavernosometry data is obtained, at a pressure of 90 mmHg.

Power Doppler

CDDU allows precise noninvasive imaging of penile morphology and dynamics, providing direct evaluation of cavernous arteries/inflow and indirectly providing evaluation of cavernous venous outflow. The acquisition of data is facilitated by color assigned to the duplex image based on the Doppler shift. Montorsi et al. have applied a new development in sonography known as power Doppler to the study of penile 'morphodynamics' (71). With this new technology, they visualized three orders of distal branching originating from the cavernous arteries. In power Doppler imaging, the hue and brightness of the signal is a function of the number of flowing red blood cells causing the Doppler shift; the dynamic range of imaging is increased yielding higher resolution of small vessels with low flows. Further clinical investigations are merited to determine whether this additional information will expand or support the currently utilized classifications of penile vascular disease: *arterial* (PSV < 25 cm/s), *veno-occlusive* (PSV > 35 cm/s, RI < 0.9) or *mixed vascular insufficiency* (PSV > 25, < 35 cm/s, RI < 0.9) (Fig. 17).

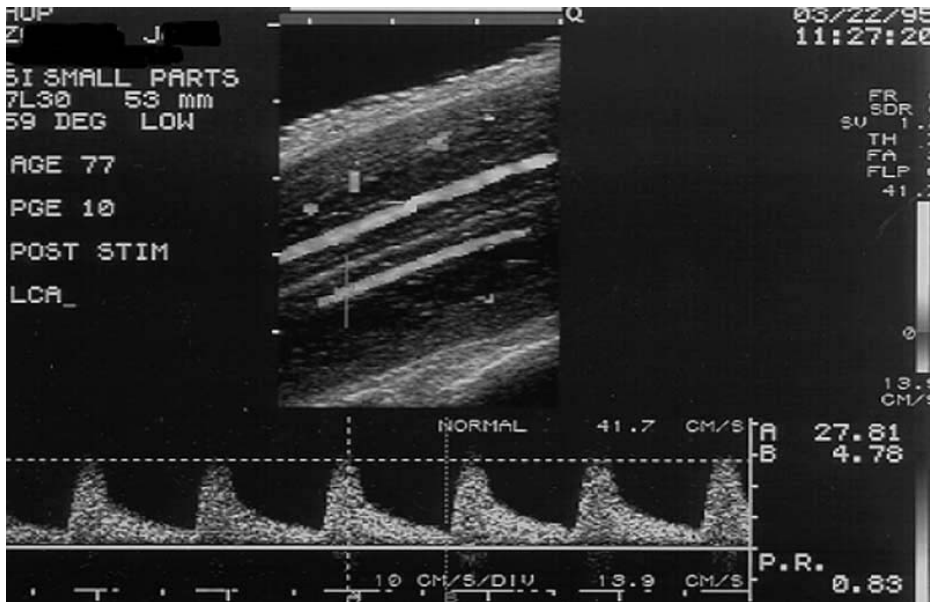


Fig. 17. Sagittal CDDU imaging shows paired cavernous arteries with left cavernous arterial flows (LCA) of 27 cm/s; end diastolic flows are elevated and resistive index low consistent with a diagnosis of mixed vascular insufficiency.

Radionuclide Phallography

Several researchers have evaluated penile response to intracavernosal vasoactive agents using radionuclide imaging. Radionuclide phallography involves using ^{99m}Tc radiolabeled autologous red blood cells to quantify changes in blood volume (plethysmography) after injection of a vasoactive substance. Radioisotope phallography provides a measure of penile blood flow, separating patients with low flow (severe arteriogenic impotence) from those with a normal arterial response (72). Glass et al. (1999) evaluated 37 men with both color duplex Doppler ultrasound and radionuclide phallography. Interestingly, there was little correlation between penile blood flow findings performed with the two different techniques (73). Unfortunately, the study did not further compare results to penile angiography. We feel that radionuclide is an investigational tool. It is costly, requires significant expertise, does not provide quantitative data on penile hemodynamics, and fails to provide the anatomical information obtained from sonography or arteriography.

MRI

Several groups have evaluated the sensitivity and specificity of pelvic MRI to evaluate internal iliac and penile arterial anatomy (Figs. 18 and 19). One group of investigators recently compared penile duplex Doppler with digital subtraction magnetic resonance angiography in patients being evaluated for possible arterial revascularization. In 7/11 patients, good correlation was seen between MR-angiography and duplex Doppler and MRA localized the disease processes from the iliac arteries down to the internal puden-

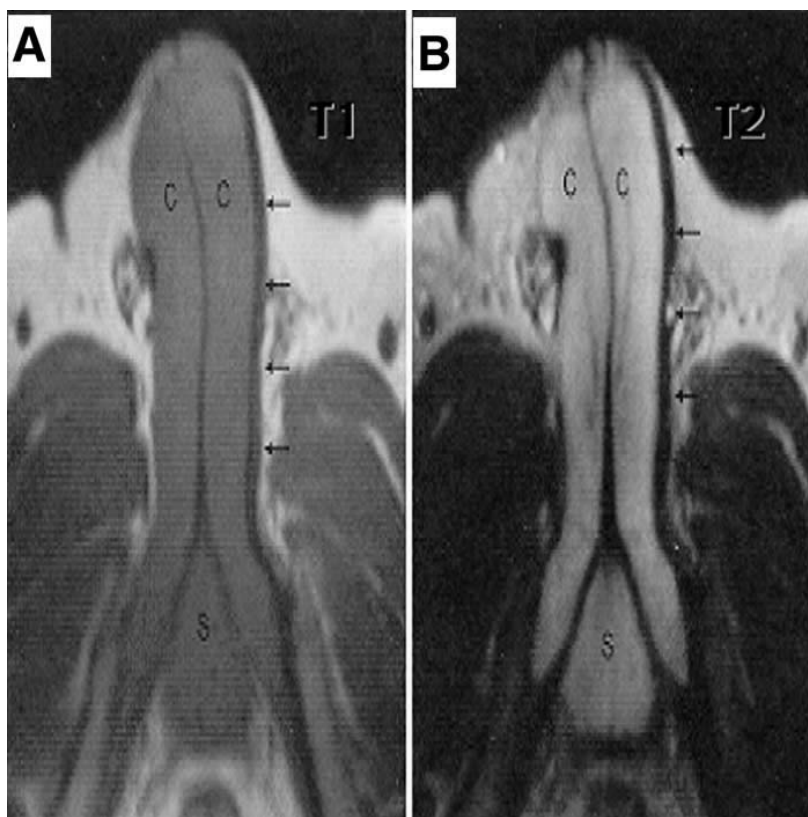


Fig. 18. Normal penile anatomy by MRI.

dal arteries (IPA). Of 22 IPAs examined, 27% had occlusions and 23% had stenoses. However, the resolution of MRA was insufficient to examine penile arteries. In a similar study by John et al. 12 patients with ED were evaluated with color Doppler ultrasound, MR-angiography and digital subtraction angiography before arterial revascularization (74). With MRI, penile vessels were visible in only 7 of 12 patients and arterial obstruction was found in 10 out of 12 patients. Indications for penile revascularization could have been based on MR-angiography alone in one patient. Nevertheless, the authors feel that there is a role for noninvasive MR-angiography in a select number of patients undergoing MRI to evaluate pelvic fracture. In these patients, MRA demonstrated an abnormality of the pelvic vessels (IPA or common penile artery) in 62% of patients (Figs. 20 and 21). The lesions were commonly unilateral in the pelvis, and subsequent color duplex Doppler localized the side consistently (Figs. 22 and 23).

Vascular Evaluation in the Patient with Peyronie's Disease

Peyronie's disease consists of induration of the penis resulting from a fibrous inelastic scar of the tunica albuginea. In the early phase of the disease process, patients experience

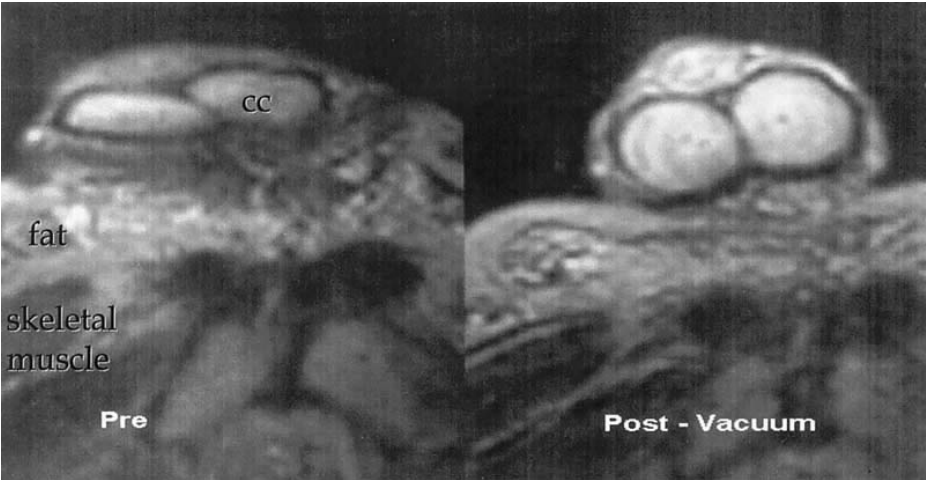


Fig. 19. Vacuum-induced erection evaluated by MRI.



Fig. 20. Gadolinium-enhanced MRAngiography in transverse and sagittal planes showing the common penile artery branching to the cavernous and dorsal arteries on the left side of the pelvis.

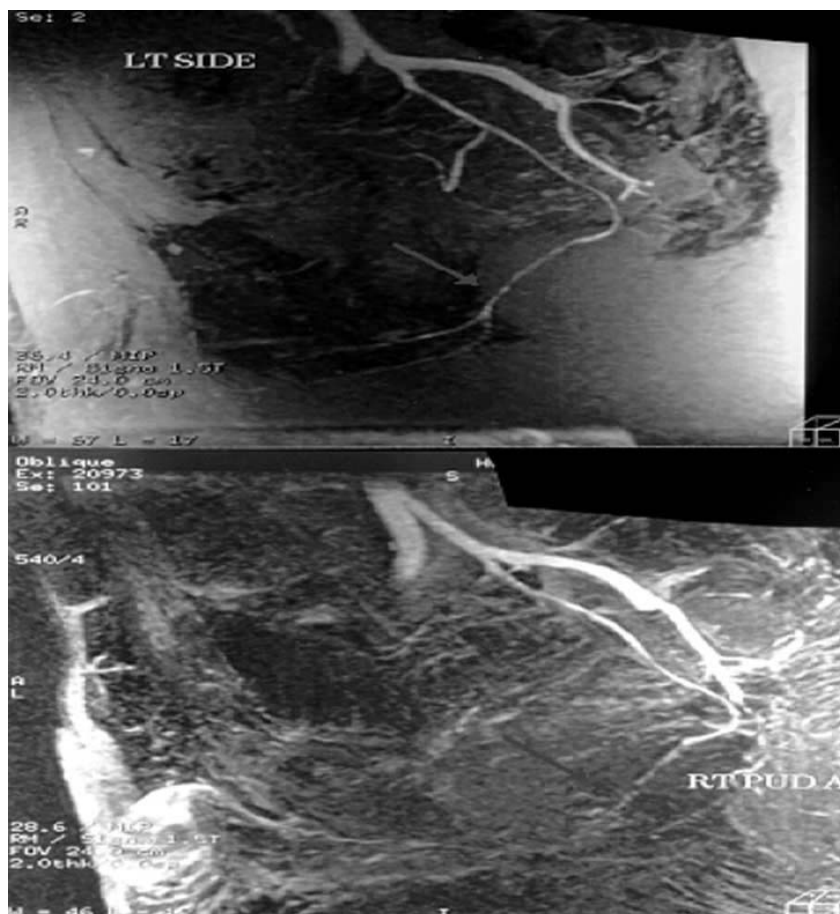


Fig. 21. MRA of normal common penile artery on the left and ablation of common penile artery on the side of pelvic fracture.

painful erections, presumably secondary to on-going inflammation. Penile deviation alone may cause significant difficulty with coital penetration. In addition, coexistent vascular ED is variably reported in 4–75% of Peyronie’s patients. Therefore, the patient’s erectile potential should be established before intervention, permitting the surgeon to appropriately counsel the patient as to the advisability of plastic surgical correction of deviation alone, correction of deviation and postoperative pharmacotherapy, or correction of deviation and simultaneous placement of penile prosthesis (Fig. 24).

In men developing a Peyronie’s plaque, there appears to be an exaggerated inflammatory response to tunical microtrauma resulting in disorganized collagen deposition, reduced elastin synthesis, and in some cases, progression to dystrophic calcification (Devine et al. 1997). ED in these patients has been variably attributed to psychogenic inhibition/avoidance, pain with increased sympathetic tone, cavernous venous occlu-



Fig. 22. MRI is expensive and of limited utility in the day-to-day evaluation of the impotent patient. One clear exception is the specialized evaluation of patients with complaints following the insertion of penile prosthesis.

sive disease, and arterial insufficiency. The unresolved question is whether a particular type of vasculogenic dysfunction correlates with the Peyronie's pathology or whether coexistent vascular ED in these men is secondary to other well-defined risk factors (atherosclerosis, hypertension, diabetes mellitus, smoking, hypercholesterolemia, and age). Earlier attempts to associate a "vasculopathy" with Peyronie's utilized dynamic infusion cavernosometry and cavernosography and suggested a preponderance of veno-occlusive dysfunction (65–75%), over arterial insufficiency (76). However, more recent reviews using much less invasive methodology of color duplex Doppler ultrasound suggest no predominance of venous over arterial insufficiency in men with Peyronie's and poorly sustained rigidity.

Because erectile quality may be altered secondary to vascular insufficiency, as well as penile deformity, we recommend that at a minimum office pharmacotesting be performed (Fig. 25). A positive response (normal erectile rigidity of sustained duration) implies psychogenic impotence, presumably excluding significant venous or arterial pathology. In



Fig. 23. Contemporary penile prosthesis have low revision rates secondary to mechanical failure; the indications for MRI include evaluation of device failure, suspicion of malposition, component infection, and persistent penile pain.

the case of Peyronie's disease, pharmacotesting permits the surgeon to confirm the presence and extent of curvature, and more importantly to determine whether the area of greatest curvature is actually localized to the area of palpable plaque.

Real-time imaging with duplex Doppler can identify penile plaques with 85–90% precision. Ultrasonographically, the tunica albuginea is normally hyperechoic compared to the corpora proper. As the corporal bodies distend with blood the cavernous sinusoids become more hypoechoic, increasing the contrast between the tunica and corpora. Penile plaques are typically hyperechoic thickenings of the tunica albuginea that underlie the dorsal vasculature. Denser plaques (calcified plaques) cast an acoustic shadow and are well visualized in either the transverse or sagittal planes. Circumferential narrowing of the corporal bodies by a plaque may be identified sonographically as a ring of thickened tunica, resulting in an hourglass-shaped erection with “hinging” at the site of the plaque.



Fig. 24. The only mandatory imaging of Peyronie's disease should be home photographs of an erection.

The most useful preoperative anatomic staging information derived from CDDU is the identification of collaterals from the dorsal vascular bundle. These are seen in a significant percentage of patients during Doppler testing. Dorsal artery collaterals diving downward through the tunica to anastomose with the ipsilateral cavernous artery are likely congenital in origin, but assume dynamic importance when primary cavernous arterial inflow diminishes with age or atherosclerosis. Operative mobilization of the neurovascular bundle in these cases would necessarily sacrifice the dorsal contribution to cavernous inflow, resulting in a technically successful repair of angulation but clinical failure from the standpoint of rigidity.

Apart from CDDU, a variety of radiographic modalities such as soft-tissue radiographs, xeroradiography, CT scanning, and MRI have been used to image penile Peyronie's. Although MRI is slightly more sensitive than CDDU in identifying Peyronie's plaques, it fails to differentiate between calcified and noncalcified plaques, a very important distinction in surgical staging (77,78). Cavernosography and dynamic infusion cavernosometry are no better at localizing plaques than plain radiographs. All the useful information from DICC regards penile dynamics. Similar information may be derived from CDDU in a minimally invasive manner without the associated pain, contrast, and X-ray exposure.

EFFECTS OF AGING ON PENILE BLOOD FLOW

Age-related decreases in erectile function have long been evident in clinical series and have now been verified in normative community groups like the Massachusetts Male Aging Study (78). Wespes has observed an age-related decrease in smooth-muscle content, using computerized morphometry of penile biopsies. Comparing young patients with penile curvature, but hemodynamically adequate erections to elderly

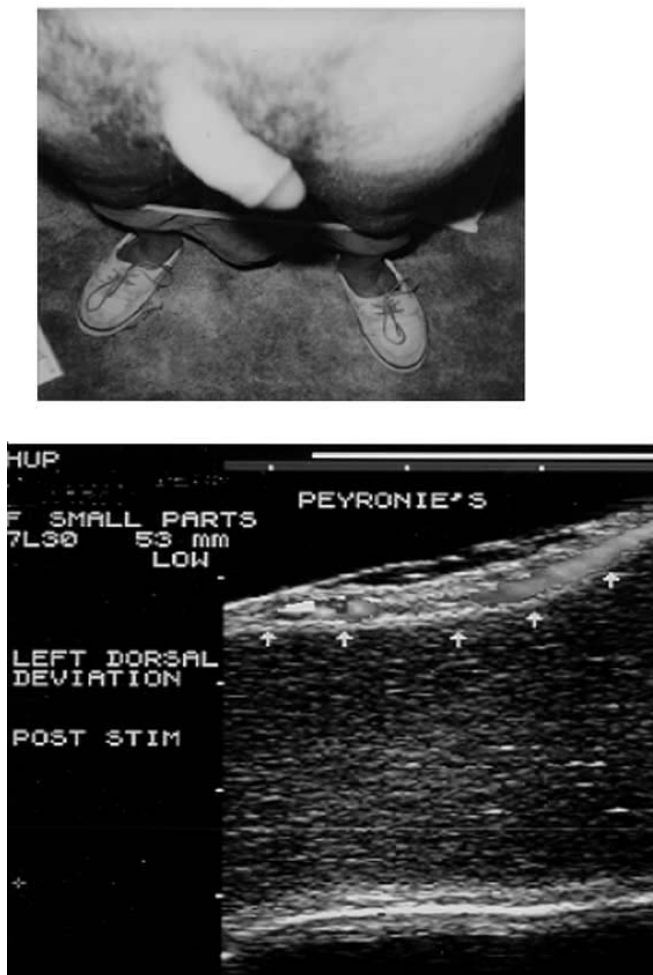


Fig. 25. Preoperative staging of Peyronie's disease includes an assessment of form and function: localizing plaque, determining presence or absence of calcification, locating dorsal to cavernous collaterals, and assessing erection dynamics.

patients with ED, he found young patients (with penile curvature) have corpora cavernosa composed of 40–52% smooth muscle; patients with corporal veno-occlusive dysfunction have 19–36% smooth muscle, and patients with arterial impotence have 10–25% smooth muscle with collagen content correspondingly increased (80).

CDDU hemodynamic parameters of a normal erection do seem to vary with age. In a retrospective review of 600 cases, there were 106 instances where intracavernous challenge with PGE1 produced excellent well-sustained rigidity of at least 20 mins and was documented in patients with a variety of ages. PBFS parameters were recorded 5–10 min following PGE1 injection and repeated following privacy and self-stimula-

Testing for E.D.

The Future

- Penile vascular profiles for:
 - Etiology specific pharmacologic Rx.
 - psychogenic vs. neurogenic vs. vascular
 - arterial vs. venous vs. mixed vascular
 - mild, moderate, severe ED
 - Combination drug regimens
 - When to counsel on prostheses

Fig. 26. The future of penile vascular testing.

tion. Mean PGE1 dosages producing excellent erections by age group were: 5 mcg, (20–49); 6 mcg, (50–59); 10 mcg, (60–79). Rigid erection following privacy and self-stimulation was associated with RI/PSV of: 0.95 / 54 (cm/s) in men 20–29-yr old; 0.93 / 45 (cm/s) in men 30–49 yr old; 0.94 / 33 (cm/s) in men 50–69-yr old; and 0.96 / 32 (cm/s) in men 70–79-yr old. The data suggests that in this group of neurogenic or psychogenic ED patients cavernous arterial flow decreases with age, but normal corporal dynamics permit penile rigidity across a wide range of PSVs. The technique of privacy and self-stimulation should permit safe and effective diagnostic dosing for the typical patient with 10 mcg. The RI parameter did not vary with age, suggesting the dynamics of veno-occlusion are the critical factor in the aging erectile response (81).

SUMMARY

Evidence-based assessments of ED have taken a secondary role in the evaluation process. The introduction of effective oral pharmacotherapy for vascular impotence has dramatically altered our approach to ED testing much like injectable vasoactive agents almost 20 yr ago. It is clinically pragmatic to begin every evaluation with a good medical history to determine the patient's relative risks for vascular ED: hypertension, atherosclerotic coronary and peripheral vascular disease, diabetes mellitus, and smoking. Sex questionnaires are a starting point of structuring the sexual history for the novice, but it is unclear whether they accurately distinguish psychogenic from vasculogenic dysfunction or whether they can qualify the severity of ED, no matter what the etiology (82). It is practical to use an oral agent in a diagnostic role and characterize the patient as having oral-agent-responsive or unresponsive ED (Fig. 26). Patients who are nonresponders, in addition to men with history of pelvic trauma, young patients with ED, and patients with Peyronie's disease have a clear indication for office pharmacotesting and specialized diagnostic evaluations testing.

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Oral Pharmacotherapy

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INTRODUCTION

The advent of the first effective oral agent in the management of erectile dysfunction (ED), sildenafil (Viagra®), has had a revolutionary impact on the management of ED. Recently, the First International Consultation on Erectile Dysfunction (Paris, 1999), sponsored in part by the World Health Organization (WHO) has indicated that the treatment selected by a patient will be influenced not only by issues such as efficacy and safety, but also by such factors as:

1. Ease of administration;
2. Invasiveness;
3. Reversibility;
4. Cost;
5. Legal regulatory approval and availability; and/or

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6. Possibly the mechanism of action. Clearly, the vast majority of ED patients worldwide opt for an oral medication. The vast majority of patients will need to consider direct treatment options for ED. The WHO recommendations are that only those pharmacological treatments that have been thoroughly tested in randomized clinical trials, with subsequent publication of results in peer-reviewed literature, should be considered for general use. Long-term follow-up of all treatment options must be performed to demonstrate durability and continued efficacy and safety, as well as patient and partner acceptability. Additionally, new treatment options that enter the arena will need to meet not only the above efficacy and safety criteria but also should be compared to available therapies for cost-effectiveness. Clearly, first-line therapies include oral erectogenic agents and sexual education and counseling. This chapter will review the current state of the art on sildenafil, the only globally approved and available oral therapy for ED, as well as therapies in advanced clinical development including sublingual apomorphine (Uprima®), selective inhibitors of phosphodiesterase type 5 including IC351 (Cialis®) and vardenafil (BAY 38-9456), as well as phentolamine mesylate (Vasomax®).

SILDENAFIL CITRATE (VIAGRA)

Sildenafil is an orally active, potent, and selective inhibitor of cGMP-specific phosphodiesterase type 5 (PDE5) (1). Although four phosphodiesterase isoforms have been identified in human penile tissue (types 2,3,4, and 5), the predominant isoform in this tissue is type 5 (1). Sildenafil thus enhances the relaxant effect of nitric oxide (NO) released in response to sexual stimulation by increasing cGMP concentrations in the corporal smooth muscle. In vitro studies showed that sildenafil has a 10- to 10,000-fold greater selectivity for PDE5 than for other phosphodiesterase isoforms (i.e., PDE1, PDE2, PDE3, PDE4, PDE6). The selectivity of sildenafil for PDE5 is approx 4000-fold greater than its selectivity for PDE3, the isoform involved in the control of cardiac contractility (1).

PDE5 is not expressed in isolated cardiac myocytes and as a result sildenafil has no direct effect on myocardium. Its effects on the coronary circulation, as will be discussed, are if anything potentially beneficial to the ischemic myocardium.

PHARMACOKINETICS AND PHARMACODYNAMICS

Sildenafil is absorbed rapidly after oral administration with an absolute bioavailability of 40%. The time to peak plasma concentrations (t_{max}) after oral dosing in the fasting state is 30 to 120 min (median 60 min) (1,2). A high-fat meal increases the time to peak plasma concentration by 60 min and reduces the peak plasma concentration by 29%. In general, an adjustment in dose is not required if a high-fat meal is consumed. Efficacy is, however, optimal if taken on an empty stomach. The terminal half-life of sildenafil is 3 to 5 hours (1,2). Clinically, efficacy may be observed for upward of 2 to 3 half-lives. Sildenafil is distributed widely in tissues. In healthy volunteers receiving single 100-mg doses, less than 0.001% of the dose was present in the ejaculate 90 min after administration (2). There is therefore no concern regarding partner or fetal exposure. In fact, it has been utilized to assist in facilitating intercourse for men whose partners are participating in hormonal programs and timed intercourse for infertility issues.

Sildenafil is metabolized by hepatic microsomal cytochrome *P*-450 isoenzymes 3A4 (major route) and 2C9 (minor route) (1,2). Potent *P*-450 3A4 inhibitors such as cimetidine, erythromycin, and ketokonazole may retard the metabolism of sildenafil. Plasma

levels of sildenafil at 24 h post-dose in healthy volunteers have been two to eight times higher than those seen in volunteers not taking these drugs. Interestingly, however, in study patients, the adverse event experience in those men combining such drugs with sildenafil has been no different from the general study population. It is recommended that patients taking protease inhibitors start at a lower dose but in general may dose upward as tolerated. Patients receiving the specific protease inhibitor, ritinovir, a compound that shares two metabolic pathways with sildenafil, however, should not administer sildenafil at doses greater than 25 mg and at a frequency of no greater than once in 48 h. The major circulating metabolite, which results from N-desmethylation of sildenafil, has a selectivity profile for PDE isoforms similar to that of the parent drug. Its *in vitro* potency is approx 50% of that of the parent drug. Plasma concentrations of the N-desmethyl metabolite are approx 40% of sildenafil concentrations. Therefore, the N-desmethyl metabolite accounts for about 20% of the pharmacologic effect of sildenafil. The N-desmethyl metabolite is further metabolized, with a terminal phase half-life of approx 4 h, similar to the parent drug. Sildenafil is excreted as metabolites in feces (80%) and urine (13%) (2). Age > 65 yr, hepatic impairment, and severe renal impairment may require dose adjustments with a starting dose of 25 mg.

Pharmacodynamically, onset of action may be seen by RigiScan® (Timm Medical Inc, Minneapolis, MN) monitoring in some individuals within 11 min and has been observed clinically within 19 min (1).

INDICATIONS

Sildenafil is indicated for the treatment of male ED. It is not at this time approved for use by women (2).

CONTRAINDICATIONS AND PRECAUTIONS

As might be expected from the impact of sildenafil on the NO-cGMP system, it potentiates the hypotensive effects of nitrates. It is therefore contraindicated in patients who are using organic nitrates or other NO donors (such as nitroprusside), either regularly and/or intermittently—including sublingual, transnasal, transdermal, and oral nitrates, as well as recreational amyl nitrate or “poppers” (3). Additionally, the use of sildenafil is contraindicated in patients with a known hypersensitivity to any component of the tablets, although the authors are unaware of any reports of such allergic reactions. The sildenafil clinical trial inclusion criteria have mimicked the clinical practice characteristics including men (18 yr or older) with a clinical diagnosis of ED of at least 6 mo duration. (4–12). Thus patients with a broad age range, underlying ED etiology, and degree of baseline ED severity were included in the clinical trials. Patients with the following were excluded:

1. Significant penile deformities;
2. Primary diagnosis of another sexual disorder (e.g., premature ejaculation);
3. Hyperprolactinemia or testosterone deficiency;
4. Stroke, myocardial infarction, or significant cardiovascular disease in the prior 6 mo;
5. Poorly controlled diabetes mellitus;
6. Major psychiatric disorder;
7. Untreated proliferative diabetic retinopathy;
8. Major hematological, renal, or hepatic disorder;

9. Active peptic ulcer disease;
10. Retinitis pigmentosa;
11. Concomitant treatment with nitrates, NO donors, androgens, or trazodone; and/or
12. History of alcohol or substance abuse (4–12). Special population studies have included patients with diabetes mellitus, spinal cord injury, multiple sclerosis, minimal depression, and more recently, the postradical prostatectomy population, as well as on-going trials that include numerous other special populations such as patients with chronic renal failure on hemodialysis, patients receiving multiple antihypertensive medications and patients with severe coronary artery disease (6–12).

In phase I clinical studies in healthy male volunteers, doses up to 800 mg sildenafil were not associated with adverse events different from those discussed below for doses ranging between 25 – 100 mg (2). A single oral 100-mg sildenafil dose in healthy male volunteers produced no clinically relevant electrocardiographic effects (2). Although sildenafil has mild systemic vasodilatory properties, no specific drug interactions with any class of antihypertensive medication has been noted (3,26). A single 100-mg dose of sildenafil administered to healthy volunteers produced a decrease in supine blood pressure with a mean maximum decrease in systolic pressure of 8.4 mmHg and diastolic pressure of 5.5 mmHg (2,3,26). In the clinical trial data base, there are more than 100 patients receiving each class of antihypertensive medication and the adverse event profile of patients taking sildenafil with and without antihypertensive medication (of any class) were identical (2,26). Additionally, although the American College of Cardiology/American Heart Association has cautioned the use of sildenafil in patients receiving multiantihypertensive regimens (29), these patients have been included in clinical trials (39 initially and 59 more recently) and, if otherwise stable with respect to hypertensive management and euvolemic, have not demonstrated a significantly different adverse event profile from the nonhypertensive study patients (2,30). Additionally, an update on product labeling by the Food and Drug Administration (FDA) has also cautioned the use of sildenafil in patient populations that were generally excluded in the clinical trials including:

1. Patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the prior 6 mo.
2. Patients with resting hypotension (BP<90/50) or hypertension (BP>170/110).
3. Patients with cardiac failure or coronary artery disease causing unstable angina.
4. Patients with retinitis pigmentosa (RP) (2). Excluding the latter, these precautions apply to the utilization of any vasoactive drug for ED in such patients. A small percentage of patients with retinitis pigmentosa have an abnormality of PDE6 and a paucity of safety data exists for the use of sildenafil in this population (although there have been anecdotal reports of exposure without any significant adverse events).

Of interest to urologists, although patients with clinically significant penile anatomical deformities (Peyronie's disease, congenital chordee, and corporal fibrosis) were excluded from clinical trials, this was caused by the potential difficulty in assessing the end point of successful sexual intercourse and not because of safety concerns (2).

DOSAGE AND ADMINISTRATION

The recommended dose of sildenafil is 25, 50, or 100 mg as needed approx 1 h before sexual activity. Although as previously noted, in some individuals onset of activity may be seen as early as 11 to 19 min (1,2). Following an initial starting dose of 50

mg, the dose may be increased or decreased based on efficacy and tolerability. The maximum recommended dose is 100 mg and the maximum recommended dosing frequency is, regardless of the dose, once daily (2). A starting dose of 25 mg may be considered for patients older than 65 yr, patients with severe hepatic cirrhosis or severe renal impairment, and patients taking drugs that inhibit cytochrome *P*-450 isoenzyme 3A4 because of the likelihood that sildenafil concentrations in plasma, efficacy, and possibly the incidence of adverse effects will be increased in these patients (2).

In the American pivotal flexible-dose study, the ultimate dose selection was 100 mg in 75% of patients, 50 mg in 23% of patients, and 25 mg in 2% of patients (4). Similarly, worldwide in flexible-dose studies, 60% of patients selected the 100-mg dose, 30% the 50-mg dose, and 10% the 25-mg dose (2).

EFFICACY

The sildenafil clinical trial designs have employed a number of efficacy measurements including the following:

1. The International Index of Erectile Function (IIEF). The IIEF is a 15-item questionnaire addressing the relevant domains of sexual function including erectile function, orgasm function, desire, intercourse satisfaction, and overall sexual satisfaction. Additionally, it is psychometrically (sensitivity, specificity, and predictive value) and validated over 20 languages. It is sensitive and specific for detecting treatment-related changes (6).
2. A global efficacy question (GEQ) with a yes or no response: "Did the treatment improve your erections?" (4,5).
3. A patient diary or log of erectile activity in which patients recorded information on the date and dose taken, presence of sexual stimulation, and whether sexual intercourse was successful. In the fixed-dose 24-wk American trial, the diary elicited data on erection rigidity employing a 4-point scale (4,5).
4. An optional two-item partner questionnaire that assessed the partners perception of the patient's ability to achieve and maintain an erection during sexual activity (5).

The sildenafil NDA submission was based on 4526 patients including 576 in phase I studies, 3003 in phase II and III studies, 769 in long-term extension studies, and 178 in Japanese studies. More than 550 patients were treated with the drug for more than 1 yr. The age range of patients in these studies was 18 to 87 yr (mean age 55 yr). The underlying etiology was felt to be primarily organic in 51.8%, primarily psychogenic in 18.0% and mixed in 25.7%. The prevalence of associated risk factors included hypertension in 24%, diabetes mellitus in 16%, cardiovascular disease in 14%, hyperlipidemia in 14%, spinal cord injury in 6%, depression in 5% and radical prostatectomy in 4% (7,19).

EFFICACY: THE INTERNATIONAL INDEX OF ERECTILE FUNCTION (IIEF)

The efficacy of various sildenafil doses, including 25 mg, 50 mg, and 100 mg, in improving erectile function was demonstrated in more than 3000 patients in 21 American and European randomized, double-blind placebo-controlled phase 3 trials lasting up to 6 mo. A variety of study designs, including fixed-dose, dose titration, parallel, and crossover designs were employed. The primary efficacy end points were question 3 (ability to achieve and erection) and 4 (ability to maintain an erection) in the IIEF (6), which reflected the NIH definition of ED [NIH Consensus Conference, Dec 1992].

Sildenafil produced significantly greater improvement in erectile function than placebo in all 21 studies. There was a significant improvement in both the ability attain an erection (question 3 IIEF-increased by 100%) and the ability to maintain an erection (question 4 IIEF-increased by 130%) as measured by the erectile function domains of the IIEF in the two pivotal American studies (4,5). In the flexible-dose study 69% (94/134) of the sildenafil group indicated that they achieved erections sufficient for vaginal penetration on most to all occasions compared to 23% (32/138) of patients treated with placebo (5). Additionally, 62% (85/132) of patients receiving sildenafil indicated that they maintained their erections after penetration on most to all occasions compared to 16% (22/138) of patients receiving placebo. Overall, 59% (81/137) of patients treated with sildenafil reported that they were able to both achieve and maintain their erections on most to all occasions compared to 15% (21/138) of placebo-treated patients (5). The results were consistent regardless of age, race, baseline severity, and etiology of dysfunction. Sildenafil has been found to be effective in patients with a history of coronary artery disease, hypertension, peripheral vascular disease, diabetes mellitus, depression, coronary artery bypass grafting, radical prostatectomy, transurethral resection of the prostate, and spinal cord injury, as well as in patients taking antidepressants, antihypertensive agents, antipsychotic agents, and diuretics (2).

There was, as expected, a secondary improvement in sildenafil group in the intercourse satisfaction, orgasm, and overall sexual satisfaction domains of the IIEF. However, the domain of desire was not increased by therapy with sildenafil, implying that it is not an aphrodisiac. It must be remembered that men who participate in clinical trials are extremely motivated and as such have a high desire level. It is not uncommon to observe diminished libido secondary to ED in clinical practice and, as such, desire may increase to normal levels in these men when successfully treated with sildenafil.

EFFICACY: GLOBAL EFFICACY QUESTION (GEQ) AND SEXUAL INTERCOURSE SUCCESS RATES (DIARY DATA)

General Population

The overall improvement in erection with treatment as evaluated by the GEQ in the American pivotal 12-wk, placebo-controlled flexible-dose study was 74% (101/136) in the sildenafil group and 16% (23/118) in the placebo group ($p < 0.0001$) (5). Overall, in all studies, improved erections were noted in patients regardless of etiology. Improved erections were noted in nearly 70% of men with predominantly organic ED, more than 75% of men with mixed ED and more than 80% of men with predominantly psychogenic ED with sildenafil therapy (2,4,5). The response to sildenafil was dose related. In randomized, double-blind placebo-controlled parallel, fixed-dose clinical trials lasting 12–24 wk ($n = 1797$), improvement in erections was reported by 63%, 74%, and 82% of patients taking sildenafil 25 mg, 50 mg, and 100 mg, respectively, compared with 24% receiving placebo (2). In the American pivotal flexible-dose study (total, $n = 329$; sildenafil, $n = 163$, placebo, $n = 166$), in the last weeks of a 12-wk double-blind placebo-controlled study, 65% of all attempts were successful in all patients (responders and nonresponders) treated with sildenafil compared to 20% of patients treated with placebo ($p < 0.001$) (2,5). If one extracts and examines the sildenafil responders in the active treatment arm, the intercourse success rate is nearly 80% and thus approximates age-matched potent men. Moreover, in the presence of similar

attempt rates, the mean number of attempts at sexual intercourse that were successful was increased fourfold for patients in the sildenafil group (5.9/mo) compared with that in the placebo group (1.5/mo) ($p < 0.0001$) (4,5). Similarly, a larger analysis of data from daily diaries kept by approx 1600 patients also revealed a higher rate of successful intercourse with sildenafil than placebo (1.3 vs 0.4 successes/wk) (2).

The pivotal American, fixed-dose double-blind randomized study (total $n = 532$; placebo = 216, 25 mg, $n = 102$, 50 mg, $n = 102$, 100 mg, $n = 107$) employed an event log that recorded the hardness of erections graded on a 4-point scale where grade 3 was an “erection hard enough for penetration but not completely hard” and grade 4 was a “fully rigid erection” (7). A dose response was demonstrated with respect to grade 3 and 4 erections—75% of patients receiving 25 mg, 80% of patients receiving 50 mg, and 85% of patients receiving 100 mg of sildenafil demonstrated a grade 3 or 4 erection in contrast to 50% of patients receiving placebo (7). However, more dramatically, 49–64% of patients in the active sildenafil arms demonstrated fully rigid (grade 4) erections in contrast to only 22% of patients in the placebo arm. Additionally, in the sildenafil-treated group, 80% of grade 3 and 94% of grade 4 erections were associated with successful sexual intercourse (7).

Interestingly, in a recent European study more than two-thirds of 176 patients with ED who were stable on intracavernosal injections of PGE₁ (≤ 20 μ g) were successfully switched to treatment with oral sildenafil (8) as measured by maintained or enhanced treatment satisfaction using the 11-item Erectile Dysfunction Index of Treatment Satisfaction (EDITS) questionnaire (9).

Diabetic Patients

An initial pilot study of 21 diabetic patients (IDDM and NIDDM) with a mean age of 50 yr and a median duration of erectile function of 3 yr examined the efficacy of sildenafil in doses up to 50 mg (10). Erectile function improvement measured by diary and questionnaire, as well as RigiScan, was noted in 48% and 52% on 25 and 50 mg of sildenafil, respectively, compared with 10% improvement in patients receiving placebo. More recently, a large study of 268 diabetic men (mean age: 57 yr, mean duration of DM: 12 yr, type 1:21%, type 2:79%) with ED (mean duration: 12 yr) who were randomized to sildenafil or placebo for 12 wk was presented (11). This was a flexible-dose study starting at 50 mg with upward (100 mg) or downward (25 mg) dose adjustments based on efficacy and adverse events. At the end of 12 wk, improved erections were noted in 56% of patients receiving sildenafil compared with 22% of men receiving placebo ($p < 0.001$). Sexual intercourse success rates with sildenafil and placebo were 48% and 12%, respectively, during the final four weeks of the study (11).

Spinal Cord-Injured and Multiple Sclerosis Patients

The efficacy of sildenafil in the spinal cord injured population has been examined in a number of studies including a single-dose double-blind two-way crossover study using RigiScan® (Timm Medical, Minneapolis, MN) evaluation in 27 patients (12). In this study 65% of sildenafil patients compared with only 8% of placebo patients had penile base rigidity greater than 60%. Additionally, no patient discontinued medication as a result of adverse events. A larger randomized, double-blind placebo-controlled crossover, flexible-dose (up to 100 mg) study of 178 patients with ED caused by spinal-cord injury employed the IIEF and partner questionnaires (13). Twenty-seven patients

had no pre-study erectile function, whereas 151 had some residual erectile function. Erectile function improved was demonstrated in 83% of patients taking sildenafil and 12% of patients taking placebo ($n = 168$). The sexual intercourse success rate in this spinal cord-injured population was over 70% with a placebo rate of 0% ($n = 145$). Clearly, the spinal cord-injured population demonstrates a very high response rate to sildenafil with a very low rate of adverse effects. In this population, significant improvements were seen for overall satisfaction in the domains of sexual life, sexual relationship with a partner, as well as concerns about erectile problems. Improvements were also reported in scores for generic quality-of-life parameters of mental health, well-being, depression, and anxiety (14). A recent double-blind placebo-controlled flexible-dose study of sildenafil in over 200 men with multiple sclerosis and ED, demonstrated improved erections in nearly 90% of the sildenafil group in contrast to a nearly 24% response rate in the placebo group [unpublished data, Pfizer].

Radical Prostatectomy and TURP Patients

In contrast to the traditional non-nerve sparing radical prostatectomy, the nerve-sparing approach has significantly improved post-operative erectile function. However, when objectively evaluated, as many as 80% of men will suffer from some degree of ED following even a bilateral nerve-sparing radical prostatectomy. In a subgroup analysis of patients, postradical prostatectomy ($n = 142$) who had participated in the pivotal American trials, 42.5% of those patients receiving sildenafil demonstrated improved erections as compared to 14.6% of patients receiving placebo (2,15). The intercourse success rates in the sildenafil group were nearly 30% as compared to less than 5% for the placebo group. However, the study population was a heterogeneous group of nerve-spared (NS) and more so non-NS patients. In our center experience, the response rate in a population of pure bilateral nerve-sparing postprostatectomy patients that were potent prior to surgery has been 81% (18/22). (unpublished data, Padma-Nathan, 2000) Zippe et al. have demonstrated an improvement in erections in 71.7% (38/50), 50% (6/12), and 15.4% (4/26) of men following a bilateral NS, unilateral NS and non-NS procedure, respectively (16). However, on closer scrutiny, the IIEF Q3/4 changes were similarly poor for the non-NS and the unilateral NS men in contrast to the excellent responses to this outcome measure seen in the bilateral NS patient (16).

In another subpopulation analysis of patients post-TURP and ED, improved erections were observed in 60.0% ($n = 171$) of patients receiving sildenafil as compared to 33.9% of men receiving placebo (2,15).

Untreated Minor Depression

ED and depression are frequent co-morbidities. A recent landmark study of 152 men with untreated depression NOS (DSM IV) (also called "minor depression") and concomitant ED examined the effect of sildenafil (17). This randomized double-blind placebo-controlled flexible-dose study examined the impact of sildenafil on ED in this population, as well as the effect of successful ED therapy on depression ratings by validated psychometric scales and the impact on quality-of-life assessment (Life Satisfaction Checklist) (17,18). Of the patients receiving sildenafil, 73% were considered responders (improved erections) in contrast to only 14% of those receiving placebo. Regardless of the treatment (sildenafil or placebo), in those patients who were deemed responders, there was a clinically significant improvement in depression parameters. This would imply that, in these patients, the depression was most likely secondary to

the ED. Additionally, this study elegantly demonstrated that successful treatment of ED can result in improvement in both sexual and nonsexual (whole life, relationship with partner, social contacts with friends and leisure situations) aspects of quality of life.

Age

Sildenafil appears to be equally effective as in elderly patients with ED as it is in younger men. In a group of patients less than 65 and greater than 65, no significant difference between responses to IIEF questions in those patients who were older and younger than 65 years. (19). Although discontinuation rates may be slightly higher in those patients over 65 yr, efficacy results are similar in both groups.

Severity of ED

A meta-analysis has been performed on a subgroup of more than 2000 men with severe ED as defined by the inability to obtain or maintain erection satisfactory for intercourse always or almost always (questions 3 and 4 on IIEF with scores 0 or 1) (20). In this severely dysfunctional group of men, 48% on 50 or 100 mg of sildenafil were able to consistently achieve functional erections (scores 4 or 5).

Other Associated Risk Factors and Drugs

In addition to the above, Sildenafil has demonstrated efficacy in other ED patient populations including those with stable coronary artery disease (21), hypertension, peripheral vascular disease, diabetes mellitus, depression, post-coronary artery bypass surgery, and in men taking antidepressants, antipsychotics, and antihypertensive medications of all classes (2,22).

Partner Data

Although partner contribution to the data was optional in most studies, partner ratings of the patient's ability to achieve and maintain erections during sexual activity were consistently significantly higher for sildenafil-treated patients than for those treated with placebo (2,5).

Long-Term Efficacy

In long-term follow-up at 1 yr ($n = 2482$), 2 yr ($n = 900$), and 3 yr ($n = 245$), more than 95% of men have maintained efficacy (improved erections) and improved ability to engage in sexual activity.

Sildenafil as a Disease-Modifying Agent

Preliminary evidence indicates that sildenafil administered nightly in patients with ED significantly increases nocturnal erectile activity. Further studies are needed to clarify the impact of this finding in clinical practice (23). This may prove to be a valuable means by which to modify the progression of ED in certain populations such as the NS-prostatectomy patient.

SAFETY

Flexible-Dose Studies

As expected from sildenafil's mild vasodilatory properties, the most common adverse events experienced in clinical trials included vasodilatory effects such as

Table 1
Sildenafil Adverse Event Experience in Worldwide
Flexible Dose Studies

Adverse Event	<i>Placebo</i>	<i>Sildenafil</i>
	(n = 734) %	(n = 725) %
Headache	16	4
Flushing	10	1
Dyspepsia	7	2
Nasal Congestion	4	2
Abnormal Vision	3	0
Diarrhea	3	1
Dizziness	2	1
UTI	3	2

headaches, flushing, and nasal congestion (as a result of hyperemia of the nasal mucosa). Additionally, dyspepsia has been observed and most probably is secondary to relaxation of the gastroesophageal sphincter. It has been demonstrated in dog models that the PDE5 may have a role to play in maintaining the integrity of this sphincter. A recent review by Morales of more than 3700 patients in 18 of the 21 clinical trials, examined the adverse events experienced over a total exposure of 1631 man-years (24). These 18 trials were of comparable design and included 18 prn, flexible-dose placebo-controlled studies and 10 associated long-term open-label studies. The most common adverse events experienced in 2% or more of patients in placebo-controlled studies are listed in Table 1 (24). Additionally, respiratory tract infection, back pain, and flu-like syndrome were noted in 2% or more of patients but occurred with equal frequency in the active drug and placebo group. Back pain, although not common or significant in prn studies, occurred in nearly 10% of patients in daily dosing and thrice-daily dosing early sildenafil studies (2). This has also been observed with other PDE5 inhibitors. The mechanism of the muscle ache is poorly understood but does not appear to be related to a vasculitis and is not associated with abnormal serum chemistries including CK (CPK) values. There were a total of 574 adverse events in the 734 sildenafil-treated patients in these studies with the majority being mild (62%) or moderate (31%) and transient in nature (24).

The overall rate of discontinuation from treatment as a result of adverse events of all causes in prn, flexible-dose placebo-controlled studies was comparable in the sildenafil (2.5%) and placebo (2.3%) treatment groups. Headaches (1.1%), flushing (0.4%), and nausea (0.4%) were the most common adverse events leading to discontinuation. Only one patient in the 2722 patients treated with up to 100 mg sildenafil discontinued treatment because of abnormal vision (24).

Fixed-Dose Studies

The American pivotal fixed-dose randomized placebo-controlled study provides further insight into the dose relationship of adverse events. (Table 2) (4,7,24). In an analysis of all prn fixed-dose placebo-controlled studies, the most common treatment-related adverse events (headaches, flushing, dyspepsia, nasal congestion, abnormal vision, and

Table 2
Sildenafil Adverse Event Experience in American Fixed-Dose Study

Adverse Event	% of Patients			
	Placebo	Sildenafil		
	(n = 216)	(n = 102) 25mg	(n = 102) 50mg	(n = 107) 100mg
Headache	6	14	21	30
Flushing	1	13	27	20
Dyspepsia	1	3	11	16
Nasal Congestion	2	1	3	11
Abnormal Vision	1	2	6	9

dizziness) were dose related (7,24). The rates of discontinuation as a result of treatment-related adverse events were comparable at 25 mg (0.6%) and 50 mg (0.4%) but slightly higher at 100 mg (1.2%). The comparable placebo-related adverse event discontinuation rate was 1.0%. Headache was the most common adverse event leading to discontinuation from treatment in the fixed-dose studies (0.6% in the 100-mg group) (7,24).

Long-Term Open-Label Studies

The most common adverse events experience by the 2199 patients in the 10 long-term open-label studies were headache (10%), flushing (9%), dyspepsia (6%), and respiratory tract infection (6%). Abnormal vision was experienced by only 2% of patients in these studies. Only 10% of patients discontinued treatment for any reason including loss to follow-up, protocol violation, lack of efficacy and adverse events. In a 1-yr analysis, adverse events and lack of efficacy accounted for 2% and 4% of withdrawals, respectively. Headache again was the most common such adverse event (24). In the entire clinical trial experience, there were no reports of priapism or prolonged erection, penile fibrosis, or Peyronie's disease (2,24).

Visual Adverse Events

Sildenafil is 10-fold more selective for PDE5 than PDE6. PDE6 plays a role in the phototransduction process, i.e., in the conversion of photon energy to a neuroelectrical impulse. Studies in dogs have demonstrated that sildenafil produces a dose-related reversible effect on hyperpolarization of retinal tissue in response to light, consistent with the aforementioned PDE6 inhibition mechanism. Long-term safety studies in mice, rats, and dogs have demonstrated no functional or morphological alteration in the retina or optic pathway (24). Acute exposure human studies have been performed employing an exhaustive battery of noninvasive visual function tests including visual acuity, visual fields, contrast sensitivity, intraocular pressure, Amsler Grid, recovery from photostress, as well as a color discrimination test. The latter was the only study that demonstrated a drug effect as demonstrated by a transient difficulty in discriminating blue-green hues (24). Clinically, this is a transient phenomena described as a blue-hue, brightness, or least commonly, a blurring of vision. In flexible-dose studies with doses up to 100-mg sildenafil, the overall incidence is 3%. It is dose related and may be seen in 9–11% of men receiving the 100-mg dose in fixed-dose studies (2,7,24). How-

ever, the incidence of this adverse event is as high as 40% at a dose of 200 mg (2). A small long-term study in a cohort of patients studied over 1 yr did not demonstrate any abnormalities of visual function (24). Sildenafil in clinical experience appears to be safe in the presence of nonproliferative diabetic retinopathy, treated glaucoma, and macular degeneration. As aforementioned, there is limited safety data regarding sildenafil in patients with retinitis pigmentosa.

Cardiovascular Effects of Sildenafil

The cardiovascular effects of sildenafil in healthy volunteers and in hypertensive patients have been aforementioned. In addition, the effects of sildenafil on cardiovascular hemodynamics was examined in a small study of eight patients who underwent Swan-Ganz cardiac catheterization and subsequent administration of intravenous sildenafil (40 mg) (25). This dosage achieved serum levels that were approx two- to five-fold greater than that achieved by a single oral administration of 100 mg sildenafil. The results demonstrated a mild decrease in mean resting systolic and diastolic pressures, as well as right atrial pressure, pulmonary artery pressure, pulmonary wedge pressure, and cardiac output. However, the normal hemodynamic response to exercise was still preserved (25). More recent studies would indicate that sildenafil has no inotropic effect and does not alter cardiac output or left ventricular function (pulmonary capillary wedge pressures (26,27).

NO donors and nitrates are known to increase subendocardial perfusion in canine coronary ischemic models (28,29). The vessels dilated are the nonmetabolic resistance vessels. These are, in fact, beneficial effects on the ischemic myocardium. Because sildenafil essentially recapitulates the effects of such drugs by its dependence on the NO-cGMP system, its effects on the ischemic myocardium are expected to be similar to that of a mild nitrate. This has been very elegantly demonstrated by Traverse et al. in a well-established canine model of coronary occlusion (26). The issues raised by Stief et al. (30) regarding increases in cyclic AMP levels in homogenized atrial appendage tissue in response to sildenafil (thus inferring a PDE3 inhibitor effect like milrinone) appear to be questionable because of:

1. The absence of a pure collection of cardiac myocytes in this study (atrial appendage tissue also contains coronary arteries).
2. The utilization of supratherapeutic doses of sildenafil.
3. The absence of any evidence that, in vivo, such "crosstalk" (that is an increase in cAMP secondary to increases in cGMP) occurs because this would require the two cyclic nucleotides to increase within the same cell (cardiac myocytes) and to date there is no evidence that sildenafil can directly affect cardiac myocytes. Thus there is no evidence that sildenafil has any affect not only on the myocardium, but also the conduction system at therapeutic or even supratherapeutic doses. Also, as was discussed, the effect of sildenafil on the coronary circulation is, in fact, a potentially beneficial one.

In the clinical trial database of the aforementioned 18 placebo-controlled studies, the incidence of any cardiovascular adverse event was 3.0% in the sildenafil group and 3.5% in the placebo group (24). Overall, 79% of all cardiovascular adverse events were mild, 16% moderate, and 6% severe for the active drug group with similar results for the placebo group. The rate of sildenafil discontinuation as a result of cardiovascular adverse events in the 18 placebo-controlled was 0.9% and comparable to placebo. The incidence of serious cardiovascular adverse events including myocardial infarction

Table 3
Incidence of MI and Death in Phase II/III Sildenafil
Studies per 100 Patient Years (31)

	<i>MI</i>	<i>Death</i>
Placebo (543 pt -yrs)	1.11	0.74
Sildenafil DB (964)	1.45	0.83
Sildenafil OL (5920)	0.69	0.35
Sildenafil total (6884)	0.80	0.42

(MI) was low and comparable between patients receiving sildenafil in placebo-controlled trials, patients receiving sildenafil in open-label trials and placebo (24). Mittleman et al. recently presented an update on the myocardial infarction and mortality experience in 53 sildenafil trials—30 double-blind (DB) and 23 open-label (OL) trials in which treatment was taken for between 6 wk and 2 yr. (31). The total exposure in the 53 trials was 6884 patient-years for sildenafil (964 DB, 5920 OL) and 543 patient-years for placebo. There were 44 nonfatal and 11 fatal MIs among sildenafil users in contrast to 5 nonfatal and 1 fatal MI for the placebo group. There were, additionally, 29 deaths from all causes among the sildenafil group and 4 among the placebo group. The incidence rates of MI and death were comparable and not statistically significantly different for patients receiving sildenafil and those receiving placebo (Table 3). As the exposure experience accumulates, this continues to be true. In fact, to date, there has been more than 11,000 man-years of sildenafil exposure and nearly 700 man-years of placebo exposure for comparison.

Sexual activity is a known risk factor for triggering the onset of a myocardial event including MI and possibly arrhythmia (28). Muller et al. have examined the relative increase in risk associated with MI “triggers” in a study of 1774 patients (1236 men) who had had a non-fatal MI. Of these men 858 were sexually active (“Onset Study”) (32). The relative risk of a MI occurring in the 2 h following sexual activity in patients previously free of cardiac disease was 2.5. In men with a prior history of a MI, this relative risk increased to 2.9. For comparative purposes, it is interesting to note that, similar to sexual activity, extreme anger may increase the relative risk of a MI by twofold. Extreme exercise increases the relative risk of a MI by greater than 10-fold. Regular exercise can reduce or eliminate this small increase in relative risk associated with sexual activity. It should be noted that sexual activity is an uncommon trigger for a MI. In the above study, only 0.9% of the MIs were felt have been triggered by sexual activity. In a recent examination of the sildenafil trial data, Mittleman found that relative risk of a MI during sexual activity assisted with sildenafil was similar to that seen in the “Onset Study” (unpublished data, Mittleman, 2000).

The American College of Cardiology and the American Heart Association published recommendations for the use of sildenafil in patients at clinical risk from cardiovascular effects (33). In addition to the nitrate contraindication issues, the ACC/AHA interim recommendation indicated caution with respect to the use of sildenafil in the following:

1. Patients with active coronary ischemia who are not on nitrates.
2. Patients with congestive heart failure and borderline low blood pressure and borderline low volume status.
3. Patients on a complicated multidrug, antihypertensive program.

4. Patients on drugs (e.g., erythromycin, cimetidine) or who have conditions (e.g., liver or renal disease) that can prolong the half-life of sildenafil. The first two recommendations are clearly logical; however, the latter two are not substantiated by data and are questionable in the light of the clinical trial data and recent cumulative field experience. The clinical trial experience to date shows patients receiving sildenafil who were receiving antihypertensive therapy had a similar incidence of dizziness, hypotension, and syncope to those patients not taking concomitant antihypertensive therapy (2,34). This was true regardless of the class of antihypertensive medication (diuretic, β -adrenergic antagonist, α -adrenergic antagonist, ACE inhibitor, or calcium-channel antagonist) or the number of antihypertensive medications—although there have been only 59 patients receiving three or more antihypertensive medications in the trials to date (2).

Patients on sildenafil therapy should not receive nitrate therapy for coronary ischemia within at least 24 h of sildenafil administration. Alternative, non-nitrate, management strategies for patients on sildenafil that experience angina include heparin, β -blockers, calcium-channel blockers, narcotics, and aspirin as appropriate (33).

The Cardiovascular Effects of Sildenafil in Patients with Severe Coronary Artery Disease

In a recent landmark publication, Herrmann et al. (27) examined the effect of oral sildenafil (100 mg) on systemic, pulmonary, and coronary hemodynamics in 14 men (mean age 61) with severe coronary artery disease at the time of cardiac catheterization and coronary angiography. Additionally, blood-flow velocity and flow reserve were assessed with a Doppler guidewire in 25 arteries including 13 severely diseased vessels (mean degree of stenosis: 78% in the target vessels) and 12 reference vessels without stenosis.

Maximal hyperemia was induced by intrarterial adenosine—an agent that increases smooth muscle levels of cyclic-AMP—before and after sildenafil. The men stopped all nitrates 24 h prior to the study. The results demonstrated that sildenafil, as expected, produced only mild decreases in systemic arterial and pulmonary arterial pressures without any significant change in systemic or pulmonary vascular resistance, heart rate, or cardiac output. There was no alteration in left ventricular function as measure by pulmonary-capillary wedge pressure. Following what should have been maximal arterial dilation by intracoronary adenosine, there was increased blood flow in response to sildenafil in both stenosed and non-stenosed vessels! This might imply a role for PDE5 in the regulation of coronary flow. The authors concluded that “oral sildenafil has no direct adverse cardiovascular effects in men with severe coronary artery disease. In addition, a small positive effect on coronary blood flow reserve was identified.” In light of this evidence, it is the opinion of the authors of this review and that of many cardiologists that the effects of sildenafil may indeed be cardioprotective. Indeed there may be a role for PDE5 inhibitors in the management of diseases that involve endothelial cell dysfunction or upregulation of PDE5 including congestive heart failure, pulmonary hypertension, and possibly angina (26,35,36).

Post-FDA Approval Field Experience

The field experience with sildenafil has revealed one adverse event that was not experienced in clinical trials—that of prolonged erections or priapisms. There were no cases of priapism (erection > 6 h duration) in any patient in the worldwide sildenafil clinical trials. However, following approval, fewer than 25 cases of prolonged erections

(> 4 h and < 6 h) and priapisms have been reported worldwide. Many of these were related to the combination of sildenafil with other pharmacologic (injection or intraurethral) therapies for ED. The safety and efficacy of such combination therapy has not yet been established.

More than 250,000 American physicians have prescribed sildenafil to now nearly 10 million men (over 100 million tablets). The most common dose has been 50 mg, administered on the average of once per week. The majority of prescriptions have been written by primary care physicians (55–60%), nonurology specialists (21–25%), particularly cardiologists and urologists (20–24%).

Management of Sexual Dysfunction Based on Graded Cardiovascular Risk

The prevalence of ED in patients with cardiovascular disease is higher than that in the general population. Conversely, the emergence of ED in a previously asymptomatic male may be a marker for occult coronary artery disease. The large numbers of patients receiving medical treatment for ED has prompted concerns and questions regarding the risk of sexual activity triggering acute significant cardiovascular events. The AHA/ACC Expert Consensus Document addressed the issue of sildenafil use in male ED patients with cardiovascular disease (33). However, cardiac risk associated with sexual activity itself, and the management of this risk, had not been adequately addressed until a recent international consensus conference on sexual activity and cardiac risk was convened at Princeton University under the auspices of the University of Medicine and Dentistry of New Jersey (37). The following recommendations were developed by this consensus panel for the treatment of sexual dysfunction in the patient with cardiovascular disease.

In general, patients can be placed into one of three major categories at the time of initial assessment based upon cardiovascular status: low risk, high risk, and intermediate or indeterminate risk. The “low risk” category includes patients in whom sexual activity is not likely to be associated with specific cardiac risk. Generally, sexual activity in these patients may be resumed or the treatment of sexual dysfunction may be initiated without need for additional cardiovascular evaluation or treatment. The “high risk” category includes those patients with cardiovascular diseases requiring specialized cardiac consultation, evaluation and priority cardiovascular management. Sexual activity and the management of sexual dysfunction in these patients should be deferred until the patient’s cardiac condition has been fully evaluated, treated, and stabilized. A third group has been identified as representing either an “intermediate or indeterminate level of risk.” These patients should not be counseled to resume sexual activity, or to undergo treatment of sexual dysfunction until a cardiac evaluation aimed at facilitating restratification of these patients into either the high- or low-risk categories has been performed. The patient profiles of the three risk categories are as follows. It should be remembered that the vast majority of patients seen by primary care physicians and urologists fall into the low-risk category. (A clinical caveat in this category is the continued contraindication of sildenafil in patients receiving nitrates.)

1. The Low-Risk Patient:

- Asymptomatic, < 3 risk factors for CAD (excluding gender).
- Controlled hypertension.
- Mild, stable angina (diagnosed by prior CV assessment).
- Post-successful coronary revascularization.

- Uncomplicated past MI (>6–8 wk).
 - Mild valvular disease
 - CHF (NYHA Class I).
2. The Intermediate- or Indeterminate-Risk Patient:
 - 3 or more risk factors for CAD (excluding gender)
 - Moderate, stable angina
 - Recent MI (> 2, < 6 wk) or CVA
 - Left ventricular dysfunction/CHF (NYHA Class II)
 - Arrhythmia of unknown cause
 3. The High-Risk Patient:
 - Unstable or refractory angina.
 - Uncontrolled hypertension.
 - CHF (NYHA Class III, IV) and cardiomyopathies.
 - Recent MI (<2 wk), CVA.
 - High risk arrhythmias.
 - Hypertrophic obstructive cardiomyopathy or IHSS and other cardiomyopathies.
 - Moderate/severe valvular disease.

New agents in development: Apomorphine (Uprima®), IC351 (Cialis®) vardenafil (BAY 38-9456), and phentolamine mesylate (Vasomax®).

The success of sildenafil has resulted in an explosive growth in the field of sexual pharmacotherapy. Currently, a number of new molecules are being examined including peripherally and centrally active drugs.

Apomorphine SL (Uprima®)

Apomorphine is structurally similar to dopamine and accordingly is classified as a dopamine-receptor agonist (38,39). Apomorphine has been documented to have activity at D1 and D2 dopamine receptor sites and has been shown to be a nonselective D1/D2 dopaminergic agonist (40) with more potent D2-like effects. Its actions are thought to be mediated postsynaptically (41). Following the pioneering work of Baraldi and Benassi-Benelli (42) in conscious male rats, peripheral injection of apomorphine has been widely used as a model of pharmacologically induced penile erection. The proerectile action of apomorphine was originally described in the freely moving rat on the basis of behavioral responses and confirmed later through recording of the intracavernous pressure (42,43). Dopamine plays a crucial role in the central control of sexual behavior in males (44,45). Increase in the activity of central dopaminergic systems correlates with sexual activity (46). Experimental results have provided neuroanatomical evidence that apomorphine, at a dose that selectively induces erections, causes specific and selective expression of *c-fos* in several brain structures that are recognized to play a crucial role in the integration of autonomic, vascular, and endocrine regulation including the paraventricular nucleus of the hypothalamus (47).

When delivered subcutaneously to humans, apomorphine produces nonsexual erections that are enhanced by erotic stimulation without significant changes in libido or desire. However, this method of delivery is associated with significant side effects, particularly nausea (48). Recently, apomorphine has been formulated for sublingual administration. This sublingual formulation has demonstrated erectogenic effects with minimal nausea (49). This novel sublingual formulation of apomorphine has a rapid onset of action (15–25 min) (50–52).

Table 4
Incidence of Adverse Events Occurring in > 5% of the Study Population

<i>Adverse Event</i>	<i>2 mg Apomorphine SL Arm</i>		<i>4 mg Apomorphine SL Arm</i>	
	<i>Placebo (n = 436)</i>	<i>Study Drug (n = 429)</i>	<i>Placebo (n = 414)</i>	<i>Study Drug (n = 426)</i>
Nausea	6 (1.4%)	11 (2.6%)	8 (1.9%)	88 (20.7%)
Sweating	0 (0.0%)	9 (2.1%)	0 (0.0%)	42 (9.9%)
Dizziness	15 (3.4%)	14 (3.3%)	9 (2.2%)	59 (13.9%)
Somnolence	9 (2.1%)	9 (2.1%)	3 (0.7%)	45 (10.6%)

In three fixed-dose cross-over studies, doses of 2, 4, 5, and 6 mg Apomorphine SL were examined for efficacy and safety (50). To be eligible for the study, patients (18–70 yr) must have been unable to achieve and maintain an erection firm enough for sexual intercourse during 50% or more of attempts made within the previous 3-mo period. In addition, patients had to have attained 55% or greater radial rigidity at the base of the penis during 1 of 2 nights of monitoring with a RigiScan® (Timm Medical, Minneapolis, MN). Patients with controlled diabetes (7%), hypertension (26.9%), benign prostatic hypertrophy (16.2%), or coronary vascular disease (14.3%) who otherwise met the above criteria were included in the study. Exclusion criteria included uncontrolled hypertension, genitourinary problems (e.g., a history of prostatectomy, implantation of a penile prosthesis, major penile deformity), or endocrine disorders (hypogonadism, hyperprolactinemia, diabetes with ketoacidosis).

Efficacy was measured by the percentage of attempts (administrations of medications with subsequent attempts at intercourse) resulting in an erection firm enough for intercourse, as well as the percentage of attempts resulting in intercourse. Patients in both the 2- and 4-mg dose groups (the doses requested for FDA approval) reported erections firm enough for intercourse significantly more often while taking the active drug than while taking placebo (45.6% in the 2-mg group, 54.4% in the 4-mg group, and 33.8% in the placebo group; $P < 0.001$). They also reported having successful intercourse significantly more often (41.5% in the 2-mg group, 50.6% in the 4-mg group, and 31.0% in the placebo group; $P < 0.001$).

Adverse effects occurring in 5% or more of patients receiving apomorphine also included nausea, sweating, dizziness, and somnolence (Table 4). The incidence of nausea, the most common adverse effect, was dose-related and tended to diminish with repeated exposure to the drug. Most episodes of nausea were mild to moderate. The most serious adverse event was syncope occurring in seven patients (0.8%): two in the 2-mg group (0.5%) and five in the 4-mg group (1.2%). Syncope was nearly always preceded by prodromal events, which included nausea, lightheadedness, sweating, and hypotension of vasovagal origin. All episodes resolved spontaneously without sequelae. No incidents of priapism were reported. Although recently submitted to the FDA, the Uprima NDA was withdrawn and studies are on-going to accumulate data from dose-optimization (dose-titration) studies as opposed to the above four fixed-dose studies. The dose-optimization data is associated with a lower incidence of adverse events, particularly nausea.

IC351 (Cialis®), Lilly ICOS, LLC

IC351 (Cialis®, Lilly ICOS, LLC) is currently under multi-center clinical investigation as a treatment for men with ED. Cialis, like its predecessor Sildenafil, is designed to be an orally active, potent, and selective inhibitor of cGMP-specific phosphodiesterase type 5. Its role in the arena of ED therapy has yet to be established, but a number of in vitro and clinical phase II studies have been published. In vitro studies have shown that Sildenafil has a 10–10,000-fold greater selectivity for PDE5 than other PDE isoforms; the IC₅₀ of Sildenafil for PDE5 is 3.5 nM. The IC₅₀ of Cialis for PDE5 is 0.94 nM; IC₅₀ is the concentration of the drug required to inhibit 50% of a given PDE (53). The isoenzyme PDE5 is found within the corpus cavernosum, platelets, skeletal muscle, vascular and visceral smooth muscle. PDE6 is found specifically in the retina; the IC₅₀ of Sildenafil for PDE6 is 34–38 nM. The IC₅₀ of Cialis for PDE6 is 730 nM. Pharmacokinetics of varying Cialis dosages up to 100 mg have been described. The time to peak plasma concentrations after single oral dosage ($t_{\max}$) of 1–10 mg ranges from 0.5–1.0 hours and for dosages 25–100 mg 1–4 hours. The terminal half-life of Cialis ($t_{1/2}$) at dosages from 1–100 mg ranges from 15–28 hours. The $t_{1/2}$ of Sildenafil is 3–5 hours (54).

The efficacy and safety of on-demand dosing of IC351 in men with a broad range of severity of erectile dysfunction was assessed in a multicenter, double-blind, placebo-controlled phase 2 study (54a). In this study, 179 men (mean age: 56 years) were randomized to receive placebo or IC351 2, 5, 10, or 25 mg, taken on demand over a 3-wk period. It should be noted that this study formulation will definitely not be the final market formulation and therefore these are not the final doses. The primary endpoints in this study were responses to questions 3 and 4 of the International Index of Erectile Function (IIEF), Sexual Encounter Profile (SEP) patient and partner diary data and a Global Assessment Question on the impact of treatment. These endpoints are similar to those for the Sildenafil clinical trials. Baseline IIEF scores characterized patients as having mild, mild-to-moderate, moderate and severe ED (8.9, 37.6, 28.7, 24.8% respectively). Mean scores on IIEF question 4 (able to maintain erection) increased significantly compared with placebo in all but the 2 mg group; IC351 significantly improved IIEF question 3 scores at all dosages compared to placebo (able to penetrate). Responses to GAQ (has treatment improved erections?) was affirmative in 51% of the 2 mg group, 59% of the 5 mg group and in 81% of the 10 and 25 mg groups in contrast to only 17% of the placebo group. The most common adverse events were headache, dyspepsia and backache. Flushing was observed in only one patient. Perhaps reflecting Cialis' selectivity for PDE5 over PDE6, there were no visual disturbances reported.

BAY 38-9456 (Vardenafil®), Bayer AG

Vardenafil is a new PDE5 inhibitor for the treatment of ED synthesized by Bayer AG. A second generation PDE5 inhibitor it is designed to have a higher in vitro potency; the IC₅₀ of Vardenafil for corporal PDE5 is 0.7 nM, and for retinal PDE6 157 nM. Pharmacokinetic data show a rapid absorption with peak plasma concentration ($t_{\max}$) of 0.7–0.9 hours for single oral dosages of: 10, 20, and 40 mg. Vardenafil plasma elimination is like Sildenafil, also rapid ($t_{1/2}$) 3.9–4.8 hours (54b). A novel conscious rabbit model has been developed by Bischoff et al 2000 for the investigation of Vardenafil and potentially other erectogenic agents (54c).

The pharmacodynamic effects of Vardenafil on penile rigidity have been reported for 10 and 20 mg dosages. In a single-center, randomized placebo-controlled, double-blind, 3-way cross-over design 21 patients were given visual sexual stimulation and monitored by RigiScan. Compared to placebo a single oral dosage of Vardenafil 10 mg increased the duration of rigidity > 60% by 24 minutes as measured at base and tip of penis. Vardenafil 20 mg increased the duration of rigidity > 60% relative to placebo by 37 minutes at the base of the penis and 28 minutes at the tip. Rigidity > 80% increased beyond placebo for both dosages, but was significant only in the 20 mg group. Pharmacokinetic data for the 10 mg patients showed a median $t_{\max}$ of 0.9 hours, and for the 20 mg dosage median $t_{\max}$ was 0.7 hours. Plasma levels declined with a mean $t_{1/2}$ of 4.2 hours for the 10 mg group and 3.9 hours for 20 mg group of patients. The most frequent adverse events reported in Phase II studies of Vardenafil have been: headache, flushing, dyspepsia and rhinitis (54d).

Phentolamine Mesylate (Vasomax®)

Phentolamine is an α -adrenergic blocking agent with both central and peripheral activity. There are currently thought to be three main mechanisms by which phentolamine acts:

1. Intracavernosal α -adrenoceptor (α_1 and α_2) blockade (55);
2. Direct intracavernosal smooth muscle relaxant effects (56,57); and
3. Central α -adrenoceptor blockade (58).

In placebo-controlled studies, phentolamine mesylate has been found to have modest efficacy in patients with mild to moderate ED (59,60). Adverse events profile include dizziness, nasal stuffiness, and tachycardia, which is generally well tolerated at the 40-mg dose (59,60). The development of oral phentolamine (Vasomax®) has been delayed because of toxicologic issues that are under reinvestigation.

CONCLUSION

Oral drug therapy is now well established as first-line therapy for ED (70). As a result of the success of Viagra, a plethora of new drugs for ED are on the horizon Uprima® Cialis® and vardenafil are in phase III development. Additionally, the combination of yohimbine and L-arginine (NitroMed) is in early phase III development. Importantly, preclinical and early clinical studies are underway of new phosphodiesterase inhibitors, cyclic AMP activators, α -adrenergic antagonists, dopamine agonists, melanocortin receptors agonists, potassium channel modulators, endothelin antagonists, and new NO donors (71,72). The future is indeed bright for this infant field of sexual pharmacotherapy.

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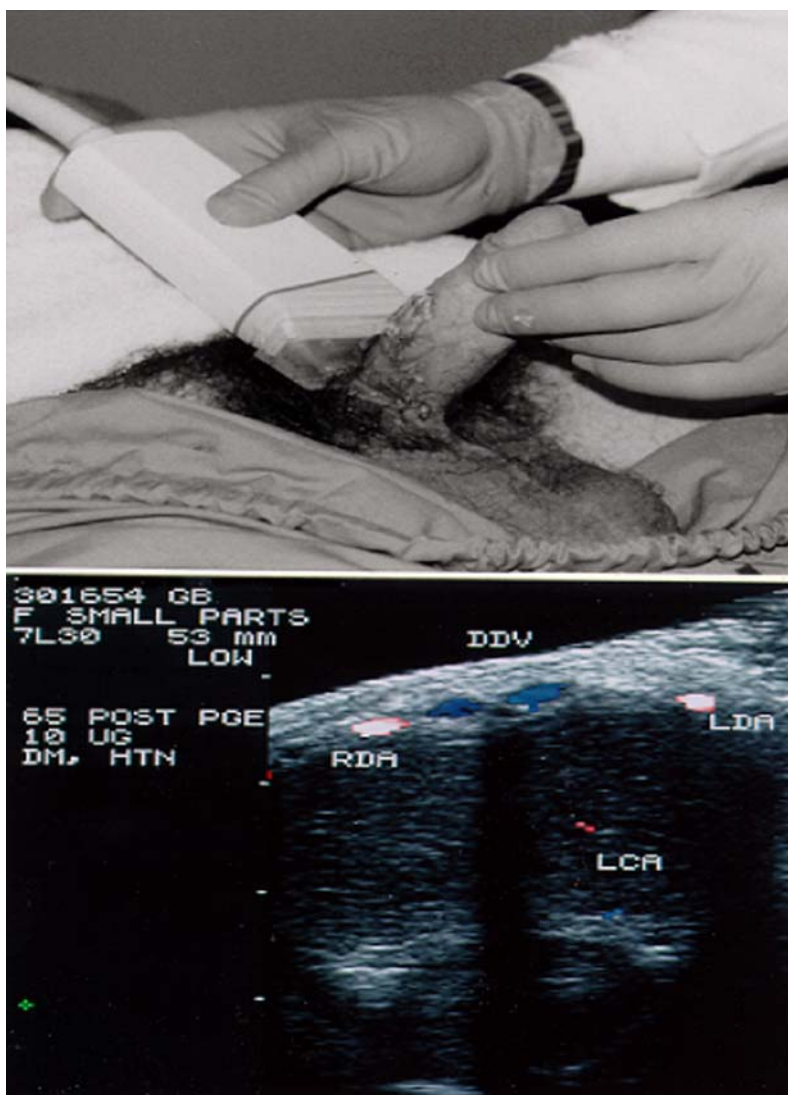


Fig. 5. The penis is held in the position of erection to straighten the cavernous vessels; imaging is begun in the transverse plane to assess anatomy. (See full caption on p. 174, Chapter 10.)

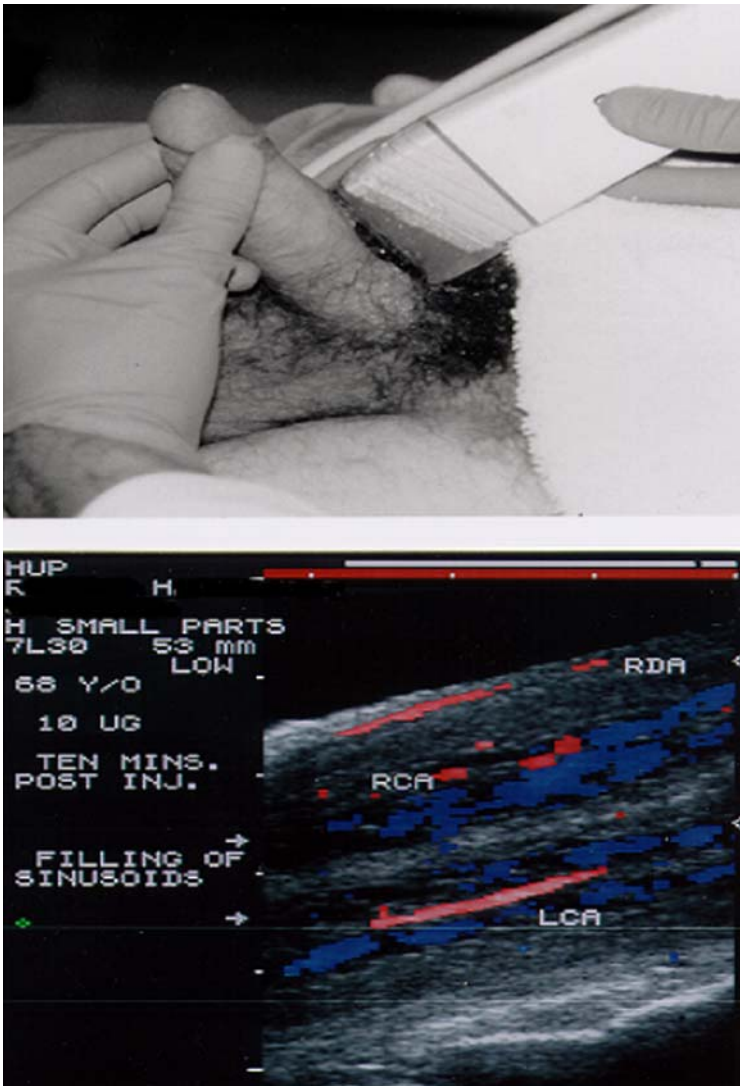


Fig. 6. The penis is held in the position of erection to straighten the cavernous vessels; imaging in the sagittal plane from the dorsum. (See full caption on p. 175, Chapter 10.)

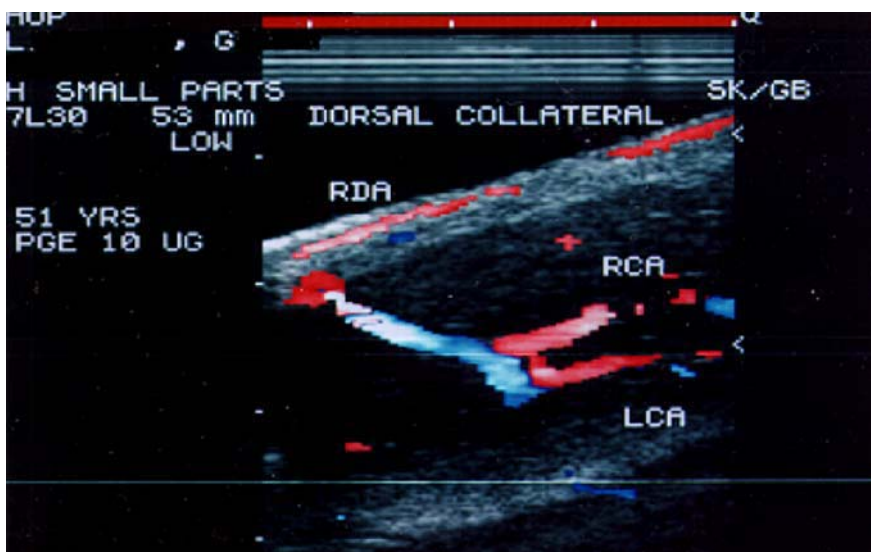


Fig. 7. Sagittal image of a 51-yr-old patient 10 min following injection of PGE1. (See full caption on p. 176, Chapter 10.)

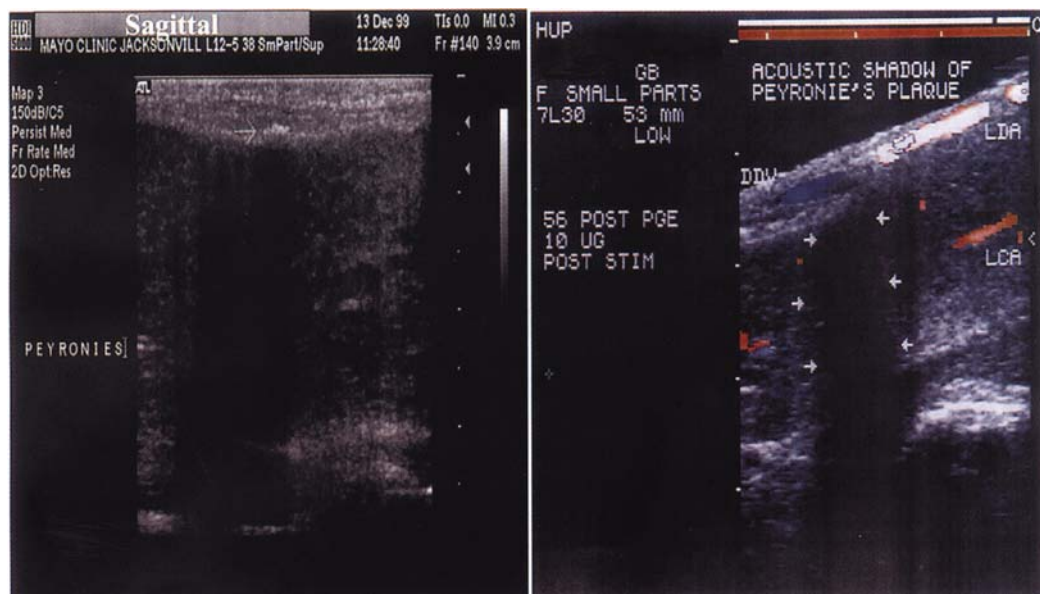


Fig. 9. On the left is a gray-scale real-time sonographic image with a discrete hyperechoic plaque casting a small, but dense acoustic shadow. (See full caption on p. 180, Chapter 10.)

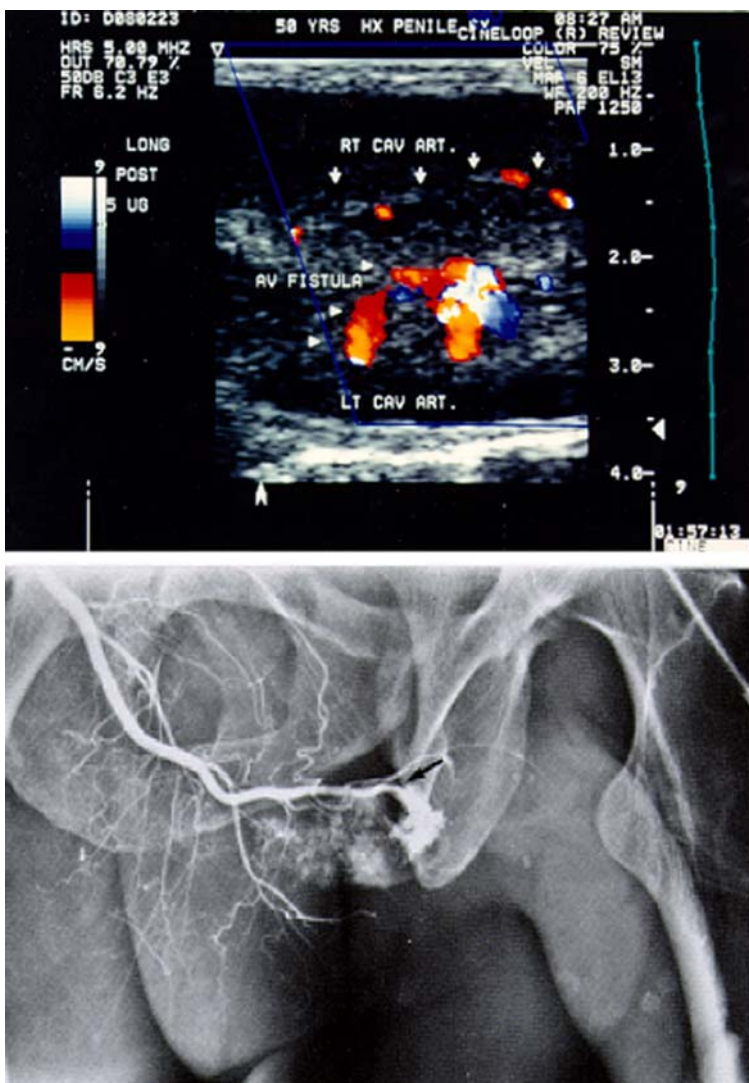


Fig. 10. High-flow priapism results from penile trauma, generally a straddle injury. (See full caption on p. 181, Chapter 10.)

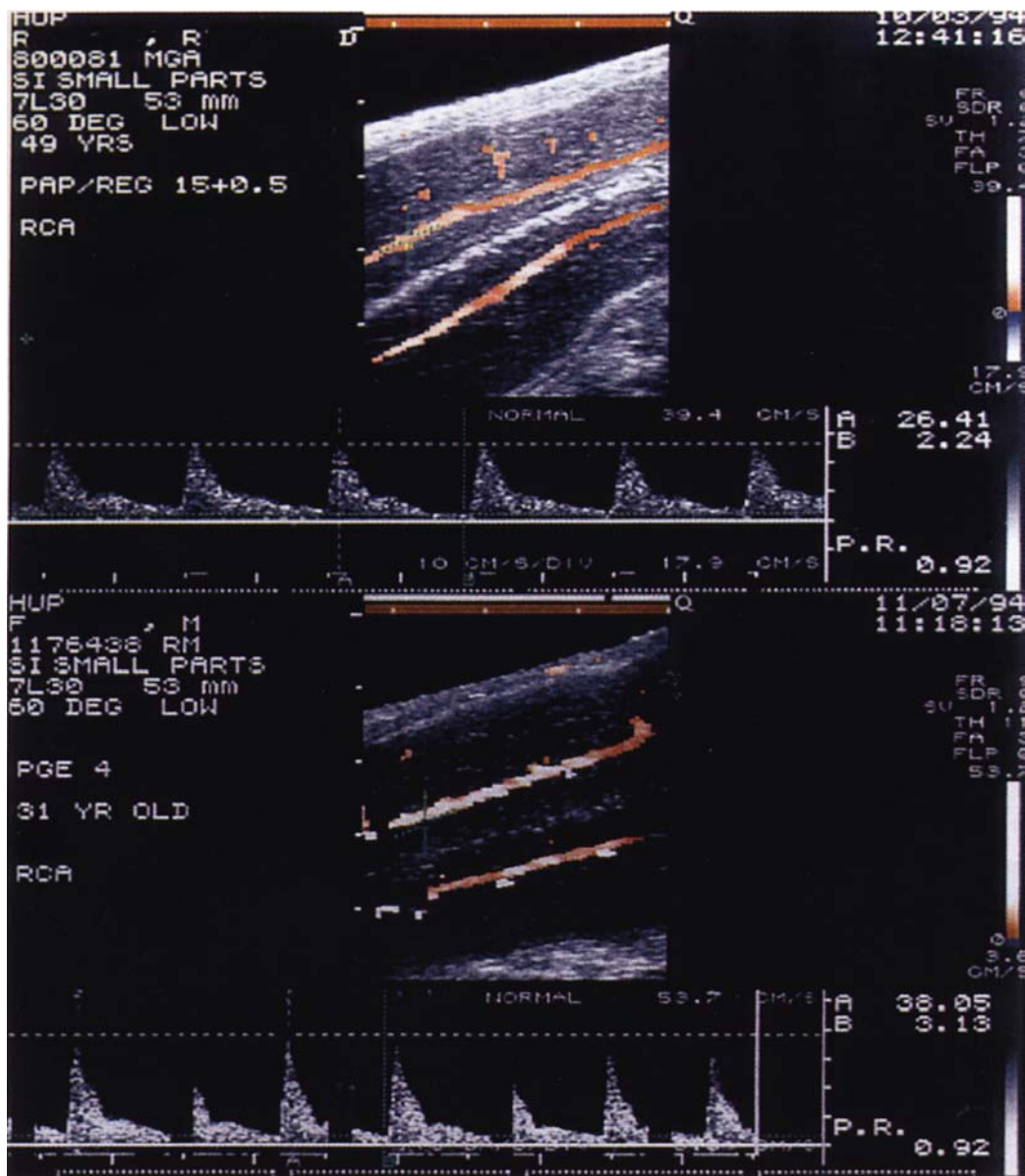


Fig. 12. Penile blood flow studies (PBFS) permit real-time imaging of penile vessels with color duplex Doppler ultrasound. (See full caption on p. 184, Chapter 10.)

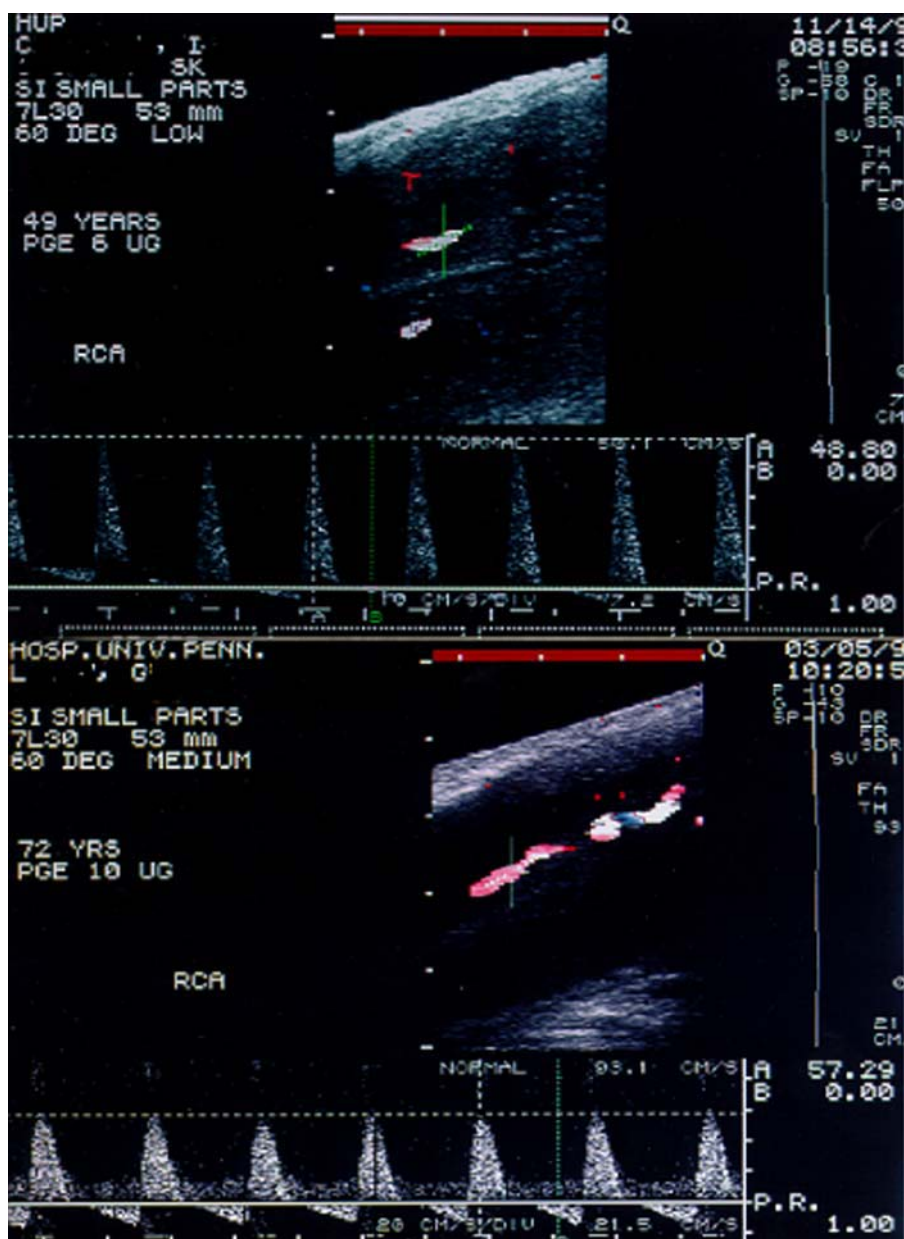


Fig. 14. Two patients with sustained unbending rigidity during pharmacotesting. (See full caption on p. 186, Chapter 10.)

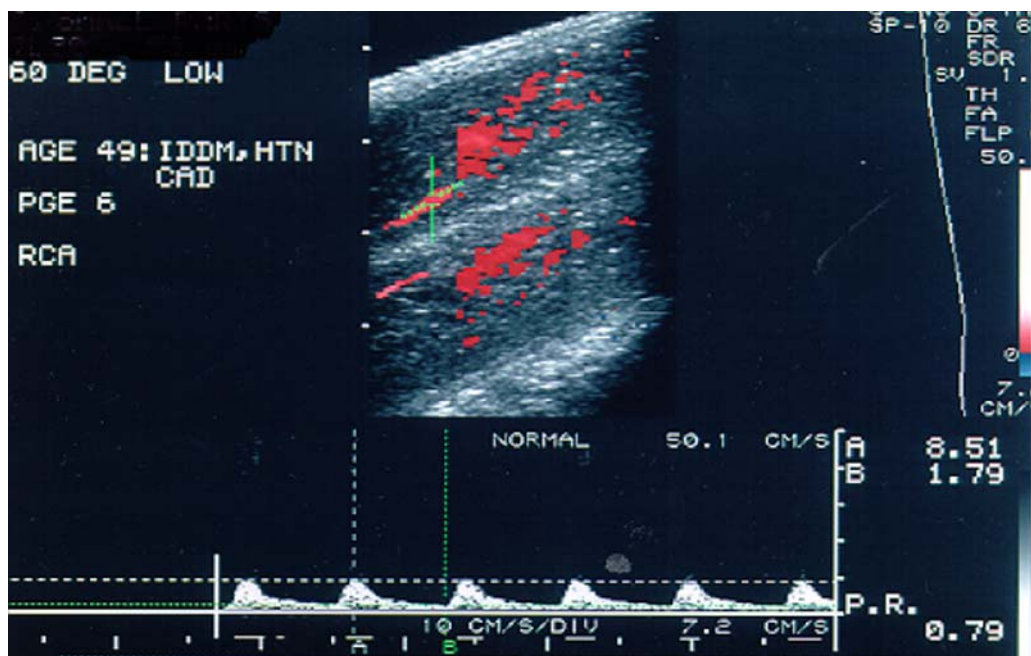


Fig. 13. PBFS of 49-yr-old patient with insulin-dependent diabetes mellitus, hypertension, and atherosclerotic coronary artery disease. (See full caption on p. 185, Chapter 10.)

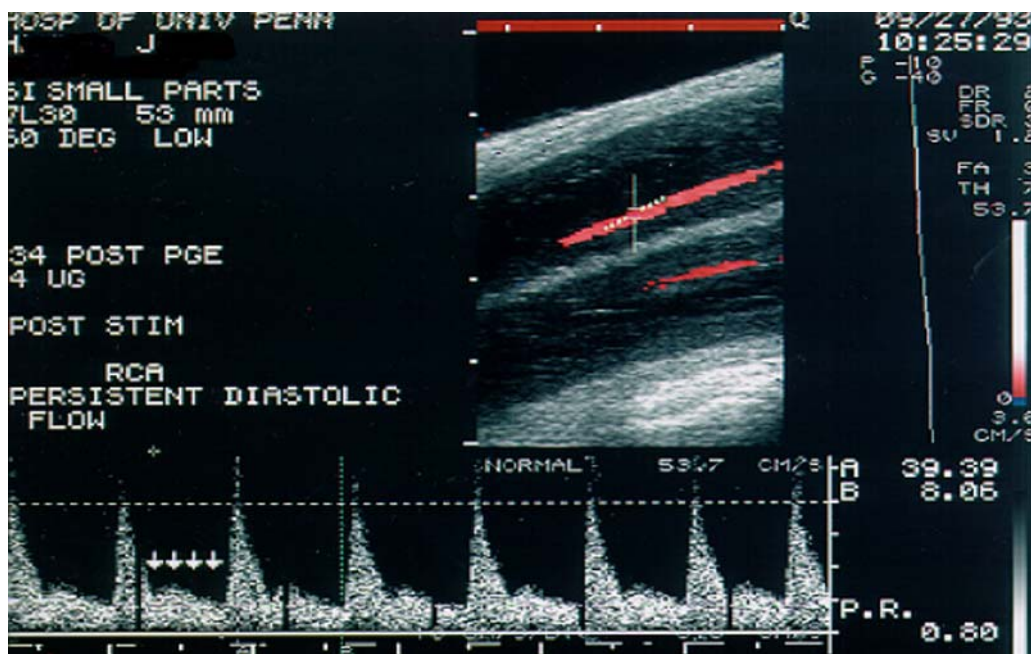


Fig. 15. Cavertous venous occlusive disease in a patient with primary ED. (See full caption on p. 188, Chapter 10.)

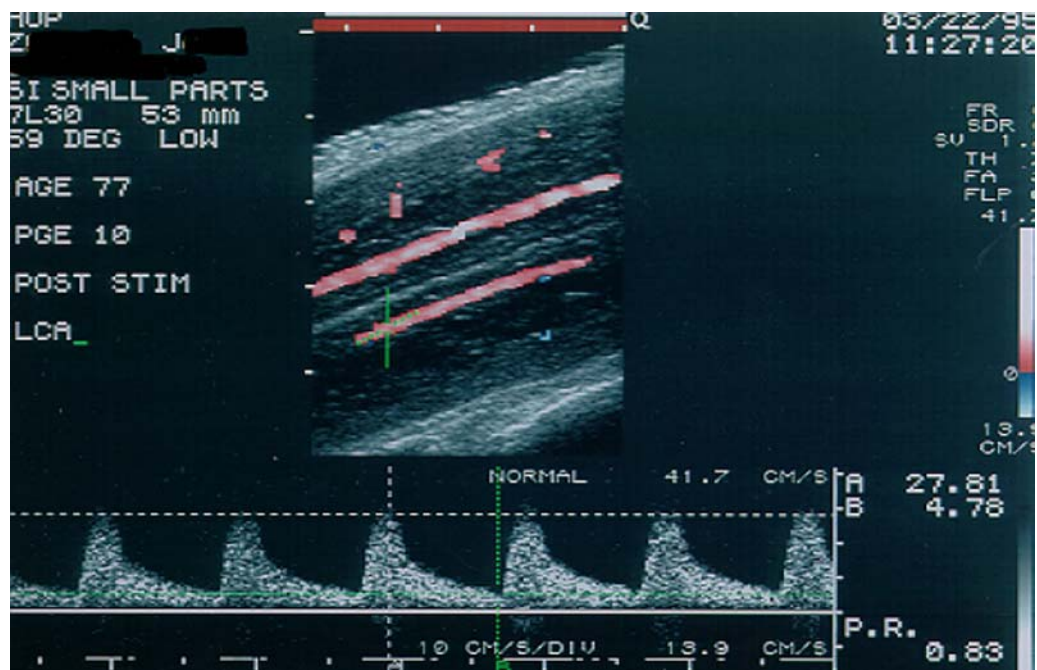


Fig. 17. Sagittal CDDU imaging shows paired cavernous arteries with left cavernous arterial flows (LCA) of 27 cm/s. (See full caption on p. 190, Chapter 10.)

12

Topical and Intraurethral Therapy

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INTRODUCTION

Until the mid 1990s (1), the only practical method of delivering vasoactive substances to the penile erectile tissues was by direct injection into the corpora cavernosa. The short-term efficacy of intracavernosal injection (ICI) therapy has ranged anywhere from 40 to 80%, and this form of therapy clearly revolutionized the nonsurgical approach to treatment of erectile dysfunction (ED). ICI has also enjoyed widespread acceptance by patients and urologists. However, despite its initial acceptance, 31–80% of men using such therapies eventually discontinue treatment for reasons relating to pain, loss of effectiveness, aversion to self-injection, and lack of interest, with dropout rates approaching 50% at one year (1–3). This *de facto* dissatisfaction with proven effective treatments is the rationale for alternative routes for the delivery of vasoactive substances.

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Intraurethral and topical therapies for the treatment of ED have been proposed as a means to circumvent some of the negative factors associated with ICI and thus have an intrinsic appeal to many patients. Intraurethral prostaglandin suppositories via the use of a commercial delivery system (MUSE) gained FDA approval in 1997 and, despite recent advances and popularity in oral therapies, remain an important part of the treating physicians' armamentarium. Currently, topical therapies for the treatment of ED remain in clinical trials and have yet to be approved for widespread use. They have the *potential* to avoid the systemic effects noted with oral therapies yet they should be considered minimally invasive in so far as they do not require needles or intraurethral instrumentation. Topical and intraurethral therapy may also provide benefit to patients unresponsive to systemic therapy or who use medications that cannot be taken along with such oral treatments (nitrate use). Questions regarding less invasive therapies for the treatment of ED using oral, topical or intraurethral methods are often raised by the patients at the time of treatment discussion. This being the case, it is important that the practitioner be aware of the issues pertaining to such alternative therapies.

INTRAURETHRAL THERAPY

General Principles of Intraurethral Agents

The concept of delivering medication via the urethra is not new. This method has been used in the treatment of urethral condyloma for years (4,5). The absorptive nature of the urethral mucosa was also demonstrated by several reports of systemic effects from urethrally instilled lidocaine, which is now commonly used as a local anesthetic for endoscopic procedures (6–8). Reports of priapism secondary to self-introduction of various substances to the urethra emphasized this as a potential route for drug therapy of ED (9,10). Despite these observations, the mechanism of translocation of vasoactive substances from the urethra into the corporal bodies has not been fully discerned. Although the urethral mucosa is not commonly used as a route of drug administration, the microenvironment theoretically seems more suitable for absorption than skin, owing to the presence of complex columnar cells rather than stratified squamous epithelium. Indeed, the absorption of intraurethral prostaglandin is rapid, with less than 20% of the medication remaining in the urethra 20 min after dosing (11). Also, the existence of submucosal venules that communicate between the corpus spongiosum, which surrounds the urethra, and the cavernosal bodies provide a possible explanation for drug transfer. Regardless of the exact transfer mechanism, intraurethral introduction of prostaglandin results in a rapid onset of hemodynamic effects in the penile vasculature similar to those seen in ICI; namely, increased corporal blood flow and increased arteriolar diameter (12).

INTRAURETHRAL THERAPY FOR ERECTILE DYSFUNCTION—BACKGROUND

The use of intraurethral delivery of a vasoactive substance as a therapeutic maneuver for ED was first published in 1993 (13). Wolfson et al. used prostaglandin E-2 vaginal suppositories to create a PGE-2 cream, then instilled this into the urethral meatus in 20 men with ED. Treatment response was determined after 20 min and graded as no penile tumescence, partial tumescence, or full tumescence. Overall, they showed a 70% response rate, with 30% of men achieving full tumescence. After this initial report, sev-

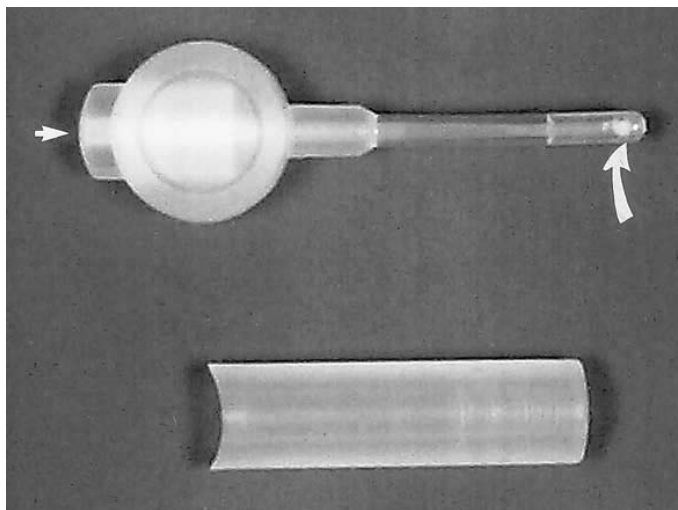


Fig. 1. Example of the MUSE device is shown here. The protective cap has been removed demonstrating the portion of the device (wick) to be inserted intraurethrally. The curved arrow points to the white-colored pellet within the tip of the wick. The arrowhead points to the button, which will deploy the pellet when depressed.

eral pilot studies using various formulations of prostaglandin E-1 showed promising results. Concurrently, a commercially available delivery system was developed using alprostadil (Medicated Urethral System for Erection or MUSE, Vivus). The system consists of a polypropylene applicator with a hollow stem 3.2 cm in length and 3.5 mm in diameter, with the tip containing a semisolid pellet of medication. The stem is inserted fully into the urethra, a button depressed to dispense the medicated pellet, and the applicator removed (*see* Fig. 1). It is important to have men urinate immediately prior to application as residual urine in the urethra helps facilitate insertion of the applicator and helps disperse the medicine. The applicators are available in 100, 250, 500, and 1000 μg dosages. Although there is emerging interest in newer intraurethral therapies using nitric oxide (NO) donors and other compounds, MUSE remains the only FDA approved intraurethral therapy at this time.

INTRAURETHRAL PGE-1

Alprostadil is a synthetic form of the naturally occurring prostaglandin E1 (PGE-1). PGE-1, and other prostaglandins in the E series, are naturally present in the seminal vesicles, the cavernous tissues of males, and in the placenta and ductus arteriosus of the fetus. Various formulations and techniques (injections, urethral suppositories, and gels) using PGE-1 have been used in the treatment of ED over the past 15 yr.

Mechanism of Action

For the treatment of impotence, alprostadil relaxes smooth muscle of the corpora cavernosa. Its effects are secondary to increasing the intracellular concentrations of cAMP. Alprostadil interacts with specific membrane bound receptors that stimulate adenylate cyclase and elevate intracellular cAMP leading to activation of protein kinase and resul-

tant smooth muscle relaxation (14). There is also recent evidence that PGE-1 may activate certain calcium-sensitive potassium channels resulting in cellular hyperpolarization (15). Alprostadil may also antagonize the vasoconstrictive actions of norepinephrine by preventing the neuronal release of norepinephrine and may enhance the actions of nonadrenergic, noncholinergic vasodilatory transmitters. In treating impotence, alprostadil induces erection by relaxing trabecular smooth muscle and dilating cavernosal arteries and their branches. Dilation of the cavernosal arteries is accompanied by increased arterial inflow velocity and increased venous flow resistance. As a result, the lacunar spaces expand and blood becomes entrapped secondary to compression of venules against the tunica albuginea. To achieve adequate tumescence and rigidity, the tunica albuginea must be sufficiently stiff to compress the penetrating venules and thus block venous outflow. This process is also referred to as the corporal veno-occlusive mechanism. Alprostadil does not directly effect ejaculation or orgasm.

Pharmacokinetics

Alprostadil has been administered by intravenous infusion, intracavernous injection, via a urethral suppository and topical administration. Intravenous administration of alprostadil requires a continuous infusion of the drug because approximately 80% of the dose is metabolized in one pass through the lungs mostly by β - and ω -oxidation. After cavernosal or intraurethral administration minimal systemic absorption occurs. Any alprostadil systemically absorbed by these routes is rapidly metabolized. In the case of veno-occlusive disease, systemic venous alprostadil levels may reach ten times baseline, but because of its rapid clearance by the lungs, this is usually of little consequence. Tolerance to the beneficial vascular effects does not appear to occur when using alprostadil in either injection or intraurethral forms. Once in the systemic circulation alprostadil is bound primarily to albumin (81%). No significant binding to erythrocytes or white blood cells occurs. Alprostadil is completely metabolized to several compounds, principally by the enzyme prostaglandin 15-hydroxydehydrogenase, and these metabolites are primarily excreted in the urine. There is no evidence of tissue retention of alprostadil or its metabolites following administration.

Response Rates

In a pilot study of the MUSE Study Group, a double-blind, placebo-controlled in-office trial looked at erectile response to either alprostadil, prazosin, a combination of the two, or placebo. All doses of alprostadil were significantly more effective than placebo and alprostadil gave better responses than prazosin alone. More than 50% of men receiving a 500- μ g dose of alprostadil achieved rigid or full erections (16).

The entire double-blind placebo-controlled trial of MUSE was published in 1997 and consisted of 1511 men with chronic organic ED from various causes (17). This was a two-tiered study that consisted of an in-office trial, followed by randomization to either drug or placebo for 3 mo at home for those who responded in office. Sixty-five percent of men had erections sufficient for intercourse after in-office testing, and of these, 96% reported the results of in home therapy. There was a statistically significant difference in the percentage of men who had intercourse successfully after alprostadil when compared with placebo (64.9% vs 18.6%). Moreover, in men with responses, seven of ten administrations were followed by intercourse. There were no differences in efficacy owing to age or cause of ED. These findings were mirrored by a later European double-blind placebo-controlled study in which 64% of men achieved in-office

erections with alprostadil and 69% of these men achieved erection sufficient for intercourse at home, as compared to 11% receiving placebo (18). It should be underscored that the reported response rates from these studies only include those patients who demonstrated erections on in-office testing, thus making the overall response rate 42–44%. Indeed, Fulgham et al. reported on their series of MUSE use in a practice setting where only 30% of patients achieved erections sufficient for intercourse and the discontinuation rate was greater than 80% (19). Other concerns about the efficacy of MUSE were reported by Werthman et al. who demonstrated full-sustained erections in only 7% of 100 consecutive patients (61). Of note, 49% of this same group responded with full-sustained erections when using ICI suggesting the superiority of the latter technique over that of MUSE. The use of MUSE as an erection “facilitator” rather than an “inducer” in such comparisons has been suggested.

Several studies have looked at responses to intraurethral alprostadil in certain clinical situations or cause-specific cases of ED. Engel and McVary reported on a subset (452 patients) of the the original MUSE study cohort who had received prior ICI therapy (20). They found that 58% of men who described ICI as “not effective” achieved an erection sufficient for intercourse after intraurethral therapy in the clinic and 47% of these men achieved intercourse at home indicating that intraurethral alprostadil may serve to “rescue” some patients who have failed prior ICI. However, this study must be interpreted cautiously because failure of ICI was retrospectively assigned. Costabile et al. performed a retrospective analysis of the MUSE trial and found that intraurethral therapy was successful in achieving erection in 70% of men in whom radical prostatectomy was the cause of their erectile dysfunction (21). However, owing to the retrospective nature of this study, they were not able to address variables such as degree of nerve sparing, tumor grade/stage, or the interval since surgery. Nevertheless, over 78% of these patients reported no residual erectile function after surgery indicating that this is a viable option in this subset of patients. Again, caution in interpretation is warranted because of the two-tiered structure of the trial and the *ad hoc* nature of the report. There is also some recent evidence supporting the efficacy of MUSE in men with a failed penile prosthesis. Benevides and Carson reported erections sufficient for intercourse in seven of eleven men with failed prostheses. They also noted improvement in glans engorgement and sensation after MUSE treatment in patients with penile prostheses. This suggests that MUSE may be used either to augment glans filling or as a bridging treatment in men awaiting repair of a malfunctioning prosthesis, although these observations need to be validated (22).

Finally, intraurethral therapy has been studied in patients with spinal cord injury (SCI) and found to be less effective. In fact, patients with indwelling catheters and those with paraplegia or quadriplegia were excluded from the original MUSE multicenter trials. Bodner et al. showed that larger doses of alprostadil (1000 µg) were needed for erection in SCI patients and although vaginal intercourse was possible, patients were less satisfied than with intracavernosal injections (23). This decreased response could relate to the altered absorption from the urethral mucosa as a result of chronic inflammation secondary to repeated catheterizations or urinary tract infections. The inability to promote erectile response by standing may also account for the lower efficacy, although neither of the above hypotheses has been substantiated.

Attempts to improve responses to intraurethral alprostadil have included the addition of a proximal penile constriction ring (Actis device) and the combination of PGE-1 and α -adrenergic antagonists. The Actis device is placed at the base of the penis prior to

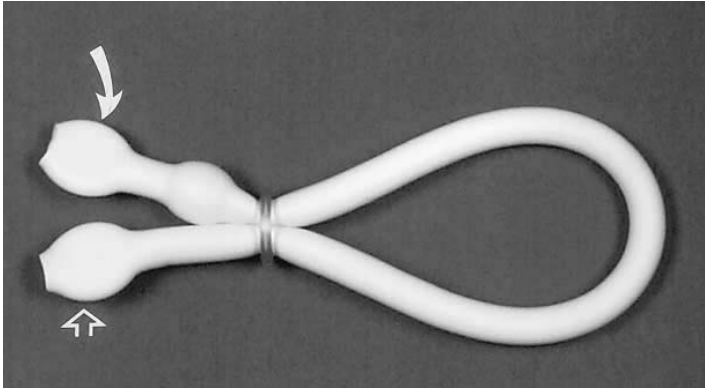


Fig. 2. Example of the ACTIS penile-banding device is shown here. The device is placed around the penis at the base. One of the ends (arrow) is pulled to constrict the band around the penis prior to insertion of the MUSE. For removal, the beaded end (curved arrow) of the device is pulled to release constriction.

administration of MUSE and acts to enhance maintenance of erectile response by decreasing venous leakage and prolonging corporal exposure to the medication (Fig. 2). It may also decrease the risk of transient hypotension due to any systemic absorption (23). In a limited evaluation of eight patients failing MUSE alone, investigators found that six were able to obtain an erection sufficient for intercourse (58). In a multicentered study of 144 patients 71% were able to achieve erections sufficient for intercourse. This was compared to a historic control of 40% suggesting a marked increase in response with the use of this device (59). Peterson et al. reported that the addition of 500 mg of prazosin to 125 and 250 μ g doses of alprostadil improved response over each of the respective doses of alprostadil alone. This benefit was negated, however, at higher doses of alprostadil (24). With the release of oral therapies for ED, there has been a renewed interest in combination therapies hoping to capitalize on the synergy derived from targeting different molecular cascades. Mydlo et al. recently reported on the combination of sildenafil and intraurethral alprostadil. In this study, the International Index for Erectile Dysfunction questionnaire was used to evaluate patients who were not satisfied with initial treatment with either medication when used as monotherapy. A significant improvement in IIEF was seen for the combination group over each of the monotherapy groups (25). This area of research holds promise for future clinical trials, but the combination of agents requires increased cost, preparation by the patient and marked motivation.

In summary, response rates from intraurethral prostaglandin are varied and range from 30 to 70%. Response appears to be independent of the etiology of ED, with the possible exception of SCI. These patients do not seem to respond as well for the aforementioned reasons.

CONTRAINDICATIONS

Alprostadil is contraindicated in patients who are prone to venous thrombosis or who have hyperviscosity syndrome and are therefore at increased risk of priapism. This includes patients with sickle cell disease, thrombocytosis, polycythemia, or multiple

myeloma. It is also contraindicated in patients with bleeding disorders or on anticoagulant therapy. In clinical trials of alprostadil urethral suppository, priapism (defined by rigid erection lasting > 6 h) and prolonged erection (rigid erection lasting 4 h, but < 6 h) were reported in 0.1% and 0.3% of patients, respectively. This compares favorably to the reported rates of prolonged erection and priapism associated with ICI (0.4% and 4%, respectively). Whether topical alprostadil has similar range of priapism has not been reported. Alprostadil in any form should be used cautiously in patients with cardiovascular disease. Symptomatic hypotension and syncope occurred in 3% and 0.4%, respectively, of patients during in clinic dosing of alprostadil urethral suppository and thus should not be used in patients at risk or with a prior history of syncope.

DRUG INTERACTIONS

There are no drug interactions reported for any of the formulations of alprostadil. Prostin VR pediatric has been a component of standard therapy for neonates with restricted pulmonary or systemic blood flow, which includes antibiotics (penicillin and gentamycin) vasopressors (i.e., dopamine, isoproterenol) cardiac glycosides and diuretics. Systemic drug interactions with MUSE (alprostadil) urethral suppository are unlikely because low or undetectable amounts of the drug are found in the peripheral venous circulation following MUSE administration. One would expect topical alprostadil to behave similarly. The potential for pharmacokinetic drug interactions with alprostadil administered via injection, topically or via urethral suppositories with other agents has not been formally studied.

ADVERSE REACTIONS

Adverse reactions of alprostadil are reported more frequently following intravenous administration, thus they may not be appropriate in a discussion of intraurethral or topical agents. Regardless, apnea has been reported in about 12% of neonates with congenital heart defects treated with alprostadil and was most seen in neonates weighing less than 2 kg at birth. Other respiratory adverse reactions occurring in less than 1% of patients include bradypnea, bronchial wheezing, hypercapnia, respiratory depression, respiratory distress, and tachypnea. Other common adverse reactions include fever 14% and seizures 4%.

As mentioned previously, hypotension, although uncommon, is a potentially serious adverse event, even with the use of intraurethral suppositories. The spinal cord patient seems to be particularly at risk, thus caution should be used when counseling these patients (23). The use of a constrictor ring at the base of the penis (Actis device) in conjunction with MUSE usage has been advocated by some to decrease the risk of systemic absorption and thus obviate some of these adverse events.

Local adverse reactions associated with alprostadil used for treating impotence are usually mild and transient. In the MUSE trial, 10.8% of treatments were associated with mild penile pain. However, as many as 7% of patients withdrew from therapy during trials because of adverse reactions. With alprostadil given intraurethrally, vaginal irritation (vaginal burning/itching) was reported by 5.8% of female partners of patients on active drug vs 0.8% of partners of patients on placebo. It is unknown if these adverse reactions in female partners were the results of medication or the result of subsequent sexual intercourse after a period of abstinence.

GENERAL PRINCIPLES OF TOPICAL AGENTS

There have been several advances in the understanding of the pharmacokinetics of locally applied therapy. The transdermal route has a well-established technology to provide durable and constant plasma levels of drugs such as hormonal replacements, narcotics, and vasodilators. When it comes to local penile therapy using direct smooth muscle relaxants, the durability and onset of action of such methods may not be useful attributes. In this regard, there are several issues worth mentioning:

1. High-systemic levels are undesirable as they may result in an unacceptable level of adverse events;
2. Agents may be largely metabolized in the first pass through the lungs or liver; and
3. The vasoactive agent(s) need to reach the corpora cavernosa in a timely fashion with the effective (highest) concentration.

With regard to these principles, topical penile therapy has a unique set of anatomic and physiologic issues that are important to consider. There are several anatomic/fascial layers between the penile skin and the corpora cavernosa. The tunica albuginea is presumed to be difficult to penetrate because of its thick layers of collagen. Therefore, topical treatment trials have emphasized exposure to the glans penis as it has direct venous communication to the corpora cavernosa (26,27). The skin itself is a relatively impermeable tissue owing to the stratum corneum. The horny cells at the stratum corneum are bonded with a very tight intercellular lipid matrix bilayer that makes the passage of drugs challenging (28). To overcome this barrier, investigators have used penetration enhancers that permeate this layer and reach the subdermis. Fortunately, the penis and scrotum are unique in that their stratum corneum is the most permeable of all anatomic locations tested. Depending on the molecular structure of the agent tested, there can be nearly 100% absorption of topical agents applied to these areas. Again, exposure to the glans affords a more easily "breached" layer. Other skin regions (e.g., back and palms) are particularly impermeable (29). An additional factor confounding efficient delivery of drug is the rich vasculature of the deep dermis which may "steal" the drugs to the systemic circulation.

With the assortment of confounding factors as mentioned above, one wonders exactly how gel applied to the penis could ever induce an erection. One attractive possibility is gel applied to the glans is rapidly absorbed through the porous skin of the glans into the venous vasculature of the corpus spongiosum. From that location, it could travel into the corpora cavernosa akin to the intraurethral delivery of drug (13,17). The known absorptive nature of the penile skin and glans make this a real possibility (29). If this were the case then delivery of drug to the shaft of the penis would seem superfluous and possibly only contribute to penile skin discomfort. Alternatively, the drug applied to the skin of the penis could theoretically be absorbed through the skin, the tunica of the corporal bodies and thus into the cavernous tissues. The large distance, multiple tissue layers and unknown permeability of the tunica makes this a formidable drug delivery challenge. A third more remote possibility involves the systemic absorption, recirculation, and delivery of drug to the penile tissues. Systemic levels have been measured with the penile skin application of papaverine and minoxidil proving that absorption does occur. However, its presence in the systemic circulation does not prove its role in the erectile response (30,31). All of the abovementioned possibilities are expected to be inefficient at transfer of active agents, thus requiring a large amount of drug to compensate the losses in the pathway.

Anticipating that topical agents were transferred through the skin and tunica to the cavernous tissues Borges tried to overcome the presumed permeation problem by performing a surgical procedure making an excision of a small area of tunica and covering the defect with a patch of deep dorsal vein (32). The intention was to apply a local medication on the skin right above the defect. This concept did not progress further, perhaps related to failure of the patch, inherent absorptive issues in the skin, or failure in the formulation of the topical agent.

Most of the delivery systems currently in use for topical therapy are intended for slow and steady release of the medications such as those used in hormonal, analgesic, or narcotic patches. This slower process is not effective as an erection initiator as the drug flux is likely to be low. Investigators are currently utilizing permeation enhancers to increased drug flux speed. In order to achieve a rapid and efficient penetration the formulation needs to have sufficient penetration enhancer to help transfer (flux) the active agent with good tolerance (no significant irritation), and release the drug at the site of action (right bondage).

Several transdermal enhancers incorporated as one of the excipients in topical formulations have been reported (26,27,33,34). The task of these enhancers is to:

1. Disrupt the stratum corneum lipid bilayer;
2. Interact with the membrane keratin;
3. Produce a weak interaction with the drug molecule; and
4. Reverse all actions in a short time.

The effectiveness of one of these agents (SEPA®) to enhance the transport of a variety of agents through human or porcine skin *in vitro* has been well established (34,35). The available evidence indicates that this agent enhances skin penetration by altering the fluidity of lipids in the stratum corneum, without any interaction with the chemical whose skin permeability is enhanced. A study by Morganti et al. examined the effect of SEPA on stratum corneum by performing FT-IR spectroscopy, differential scanning calorimetry, and scanning electron microscopy (SEM) on samples of isolated human stratum corneum (36). Changes seen suggested reversible conformational modification in stratum corneum lipids by SEPA, consistent with general lipid fluidization. When SEPA is removed *in vacuo*, the effect is reversed, suggesting that SEPAs effects are temporary, with lipid organization and barrier function being readily and spontaneously restored. During the phase of lipid fluidization, drugs can diffuse through the stratum corneum at a much higher rate than normal.

TOPICAL THERAPY FOR ERECTILE DYSFUNCTION —BACKGROUND

Organic nitrate donors were the first topical agents to be used in the treatment of ED (37). Case reports have demonstrated that blood flow to the penis and tumescence are increased after application of a nitro-based paste (38,39). The local effects on penile blood flow appear to be crucial because application of such gels elsewhere on the body does not induce erections. Topical minoxidil has also been reported in placebo controlled double masked trials (31,40). In one study, Cavallini reported 2% minoxidil as superior to 10% nitroglycerin cream in inducing improved penile hemodynamics and with fewer side effects.

TOPICAL PGE-1

Alprostadil (PGE-1) is used in a gel form for topical application. The compound is essentially the same as that previously discussed under intraurethral therapy. Although applied topically, the mechanism of action is the same as previously cited, namely, a PGE-receptor mediated increase in intracellular cAMP resulting in direct smooth muscle relaxation. The pharmacokinetics of alprostadil have been summarized previously. It is worth reiterating that the large majority of the drug is metabolized on first pass through the lungs and there are no reports of any significant systemic accumulation. Whereas there is no development of tolerance with the administration of intracavernous or intraurethral alprostadil, this has not been reported with the use of topical drug.

Response Rates

Kim and McVary in a placebo-controlled phase I/II trial of a topical PGE1 gel first reported significant increases in systolic blood flow velocity as measured by color Doppler ultrasonography (33,41). In this largely neurogenic impotent population, only two of ten patients responded with a clinical erection (no response in the placebo group). Becher reported a double-masked placebo study investigating the effect of a 0.2% and 0.4% alprostadil combined with a skin penetration enhancing gel in 52 impotent men (42). There was no statistically significant difference between active drug and placebo (66% vs 39%, respectively) in this patient population. In a noncontrolled study using a formulation of 0.4% alprostadil and an enhancer (NexMed, Inc.®) 0.5 g of the gel produced comparable cavernosal arterial changes as intracavernosal injection when measured with color Doppler. This suggested that the drug penetrates the skin and reaches the corpus cavernosum in a concentration sufficient to cause smooth muscle relaxation (26).

McVary reported a phase I/II single-blinded study with a formulation of alprostadil (0.5g, 1, and 2.5 mg) using 5% SEPA ®(Macrochem, Corp.) as a skin penetration enhancer (27). Application of the PGE1 gel correlated positively with erectile response in a majority of patients on active drug. A significant response (clinical erection) to the 0.5-, 1.0-, and 2.5-mg PGE1 doses was found in 67%, 75% and 67%, respectively (placebo 17%, $p<0.001$). This represented an advance over previous topical administration studies as significant erectile responses could be obtained with gel applications. Interestingly, the majority of patients had modest or absent responses to gel application in the initial 25 min after application. With the addition of visual or tactile stimulation this response was greatly augmented suggesting topical gels role in *facilitation* rather than *initiation* of erection. The facilitation was not seen in the placebo group. This augmentation of erectile response with tactile stimulation has been found with several oral, intraurethral, and intracorporal injection treatments (17,43,44). Importantly, Becher performed a female safety study in 18 healthy volunteers using 1 g of a gel consisting of 0.4% alprostadil (4000 µg) and applied it on the vaginal wall and introitus. Ten postmenopausal and eight premenopausal women showed good tolerance to this formulation despite one patient having minor bleeding at the cervix. All the patients showed labial and clitoral engorgement that was not referred as uncomfortable (42). The use of this medication for the treatment of female sexual complaints is in its infancy, but has shown a glimmer of promise in an early clinical trial by Becher (60).

Contraindications

As previously stated, the use of alprostadil should be avoided in any patient with a history of anticoagulant therapy, bleeding disorders, polycythemia, sickle cell disease,

thrombocytosis, or multiple myeloma. Risk of prolonged erection and whether topical alprostadil has a similar range of priapism as intraurethral administration (0.1%) has not been reported. Topical alprostadil has not been shown to have a similar risk of syncope when compared to intraurethral use (27,33). There are no drug interactions reported for any of the formulations of alprostadil. Similar to MUSE, systemic drug interactions are unlikely because the low systemic absorbance of topical prostaglandin.

Adverse Reactions

In addition to the aforementioned adverse events, topical alprostadil has unique reactions that bear mentioning. Discomfort at the application site was reported in 85% of participants after the topical application of an alprostadil/SEPA[®] gel (27). Most patients (85%) who received the SEPA[®] formulation, whether or not it contained PGE1, experienced a sensation of warmth that abated within 5–20 min after application. This time frame suggests that the SEPA formulation was the mediating substance. About 20% of the patients classified this warmth as severe burning. As this severe discomfort was not noted in the placebo group, it appears that the active drug was the responsible agent. This discomfort was localized primarily to the shaft of the penis rather than on the glans penis. One wonders if the application of the gel to the glans exclusive of the penile shaft may avoid this discomfort. It was likely to have been the function of both the carrier formulation and the active drug as it was noticed in the placebo and increased in intensity with the addition of PGE-1.

Considering the ubiquitous anatomic distribution of the large family of eicosanoids to which PGE1 belongs, it is no surprise that an alprostadil gel would influence other processes beside erection when applied to the penis. Eicosanoids exist in nearly all somatic tissues and are known mediators of a large number of physiologic processes. Pain is one known side effect of this class of compounds. Receptors for PGE-1 have been isolated in a diverse array of tissues including the nervous system (45). Prostaglandins role in the sensory afferents of pain perception is well documented although intermediates such as CGRP may be involved (46). Interestingly, in the study by McVary et al. there was no correlation between skin reaction, discomfort, side effects nor erythema with erectile response (27). This is important as the disassociation of the side effects from the positive attributes of erectile response allow for modifications in application site or drug to reduce adverse events without comprising erection.

TOPICAL MINOXIDIL

Introduction

Topical minoxidil has been used in the recent past as an investigational drug in the treatment of ED. Although little can be said about its role in that regard, there is extensive literature on its use as an antihypertensive and alopecia medication. Much of the information regarding this drug is drawn from the literature detailing its use in the former rather than latter circumstance.

Minoxidil is an antihypertensive agent whereas topical minoxidil (Rogaine) is used for alopecia. Because of its potency and adverse reactions, oral minoxidil is used mainly for patients with the severe drug resistant forms of hypertension. Tolerance to a prolonged therapy with oral minoxidil does not appear to be a problem. Subsequent to the oral dosage (approved by the FDA in 1979 for use in hypertension) topical formulations were

approved for the treatment of alopecia in 1988. Investigation of topical formulations in the treatment of ED are limited and follow on the heels of its approval for alopecia.

Mechanism of Action

Minoxidil does not have a direct vasodilatory effect on arterial smooth muscle. Instead, it is converted to minoxidil *O*-sulfate by the hepatic enzyme sulfotransferase (47). This metabolite does have a direct vasodilatory effect on arterial smooth muscle causing a reduction in peripheral resistance in blood pressure. It does not inhibit the central nervous system (CNS) or adrenergic neuronal blocking effects. Minoxidil retains its activity despite adrenergic denervation. Minoxidil-induced delay in the hydrolysis of cAMP via the inhibition of phosphodiesterase may contribute to the drug's vasodilatory action as well. All direct vasodilators produce a sympathetic response including an increase in heart rate, stroke volume, cardiac output, and a marked increase in plasma renin activity. The latter effect leads to increased sodium and water retention. The mechanism responsible for minoxidil-induced hair growth is not known. Although systemic therapy will stimulate hair growth, topical therapy does not cause hypotension. Minoxidil may either activate the hair follicle directly or stimulate the microcirculation around the follicle, increasing cutaneous blood flow. Minoxidil may also alter the metabolism of androgens in the scalp.

Regarding the treatment of ED, it is assumed that the active metabolite acts via a direct vasodilatory effect on arterial smooth muscle, causing a reduction in peripheral resistance and cavernosal muscle relaxation. Presumably, this promotes the veno-occlusive mechanism and results in erection. Such an effect from topical minoxidil is interesting when one considers that it is a prodrug that requires hepatic metabolism to become active (47). For this to be effective, the topically absorbed minoxidil would have to be metabolized through the liver, then recirculated to the penis to be active. This appears to be a substantial task. Issues regarding the site and efficacy of absorption have been addressed earlier.

Pharmacokinetics

Minoxidil can be administered topically or orally. Approximately, 90% of an oral dose is absorbed from the gastrointestinal (GI) tract, whereas topical minoxidil is poorly absorbed through the skin. The systemic absorption of topical minoxidil averages 2% (range 0.3–4.5%). The drug distributes widely throughout the body tissues and is extensively metabolized by the liver. Both the unchanged drug and its metabolites (primarily, the glucuronide conjugate of minoxidil) are excreted in the urine. Antihypertensive effects are achieved within 30 min, and although the plasma half-life of the drug is 4 h, antihypertensive effects can last 2–5 d. Despite the prolonged duration of action, no drug can be detected in the plasma after 24 h. This prolonged effect may be explained by retention of the drug in vascular smooth muscle tissues. Minoxidil is not significantly bound to plasma proteins. It is freely filtered and has no tubular secretion, thus renal clearance depends on glomerular filtration. This filtration accounts for approx 10% of total clearance. Approx 95% of a topical dose will be eliminated after 4 d.

Topical minoxidil solutions should only be applied to the skin of interest. Absorption is best when the hair and the skin are dry. If applied with finger tips, the hands should be thoroughly washed after applying. Systemic effects resulting from topically administered minoxidil are unlikely, but theoretically could occur if the drug is

overused. Skin abrasion or irritation such as excoriations, psoriasis, or sunburn can increase the systemic absorption of topical minoxidil.

Minoxidil is relatively contraindicated in patients with cardiac disease; recent myocardial infarction (MI) or cerebrovascular disease because reflex increases in heart rate and decreases in blood pressure can exacerbate these conditions. Because approx 10% of active drug is eliminated unchanged via the kidneys, minoxidil can be used safely in patients with renal impairment. Minoxidil should not be used in patients with pheochromocytoma because the hypotensive effects of the drug can stimulate catecholamine secretion.

Response rates

Reports of response rates for the treatment of ED are limited in number. Using Rigi-scans to measure penile circumference changes in response to a topical 2% minoxidil solution, Cavellini reported a significant increase when compared to topical 10% nitroglycerin or placebo ointment (40). Similarly, he reported a significant increase in penile rigidity with topical minoxidil when compared to the nitroglycerin or placebo controls. Doppler ultrasonography of cavernosal arterial flow was reported as greater with minoxidil than either control, but no quantitative information as supplied. No mention of sexual intercourse was reported. In a slightly different study design, Clark reported on the treatment of ED in diabetic males using 2% minoxidil combined with a penetration enhancer (SEPA®) (31). Response was recorded by spring tonometer (rigidity), strain gage (circumference change), and patient diary (vaginal penetration). He reported moderate, but no significant changes in erectile response to visual stimulation, penile tumescence, or penetration.

Drug Interactions

Reported drug interactions have occurred almost exclusively when minoxidil is used in its oral form. Little is known when used topically for the treatment of ED. Regardless, drug interactions of minoxidil include antihypertensive agents, nitrates, diazoxide, diuretics, estrogen, nitroprusside, nonsteroidal antiinflammatories, and sympathomimetics. Estrogens can cause fluid retention increasing blood pressure and thereby antagonizing the antihypertensive effects of minoxidil. Nonsteroidal antiinflammatories can reduce the antihypertensive effects of minoxidil by inhibiting prostaglandin synthase and/or increasing sodium and fluid retention. Sympathomimetics such as cocaine, dolbutamide, dopamine, ephedrine, epinephrine, norepinephrine, phenylephrine, or phenylpropanolamine can antagonize the antihypertensive effects of minoxidil when administered concomitantly.

Adverse Reactions

The adverse reaction profile for minoxidil depends upon on its use. Systemic adverse reactions are unlikely from topical administration. Placebo controlled trials with topical minoxidil only showed an increase in dermatologic effects from the active drug. Oral minoxidil has occasionally been associated with the appearance of a bulbous rash and Stephen's Johnson's syndrome. Topical minoxidil therapy produces local dermatologic reactions including contact dermatitis, local burning pruritus, erythema, and xerosis. Many adverse effects have been reported during the administration of topical minoxidil preparations, but none has been directly attributed to the drug.

TOPICAL PAPAVERINE

Introduction

Since the introduction by Virag in the early 1980s of injection of papaverine into the corporal bodies for the treatment of sexual dysfunction, it has become a widespread and well-accepted method (48). Its use as a topical therapy has a much shorter experience and one that has not moved beyond preliminary clinical trials.

Mechanism of Action

The most characteristic effect of papaverine is relaxation of smooth muscle, especially when it has been spasmodically contracted. Papaverine acts directly on the muscle itself by inhibition of the oxidative phosphorylation mediated inactivation of cAMP (via phosphodiesterase-PDE) and interferes with calcium mobilization during muscle contraction. This results in an increased half-life of the secondary messengers cGMP and cAMP. This relaxation is noted in the vascular system, bronchial musculature, the gastrointestinal/biliary tracts, and the urinary tract (including the corpora cavernosa). This relaxation may be prominent if spasm exists. The relaxation is a direct one and unrelated to muscle innervation, as the muscle still responds to drugs and other stimuli causing contraction. Papaverine has minimal action on the CNS, although very large doses tend to produce some sedation and sleepiness in selected patients. In certain circumstances, mild respiratory stimulation can be observed, but this is therapeutically inconsequential.

Pharmacokinetics

Serum papaverine levels after topical administration have been measured in a single study with a high performance liquid chromatography assay (30). At 60 min, mean serum levels increased 50% suggesting that absorption did occur, but not significantly over baseline values. The papaverine levels in this study indicated that topical absorption is less than 1% of a comparable intravenous dose indicating minimal systemic uptake after topical administration to the genitalia. In contrast, papaverine is present in the blood at levels from 335 to 761 ng/mL within 3 min of IC injection of 40 mg as measured by similar techniques (49). The pharmacokinetics and bioavailability of topical papaverine on animal models have been studied in which 9–12.4% of the papaverine is detected in the serum. There is a marked difference between animal models and clinical trials. This has been ascribed to differences in gel formulation (50).

Response Rates

The use of topical papaverine was reported by Kim et al. in a phase I/II single-blinded placebo controlled trial on 20 patients with organic impotence (30). The formulation included 5.5% papaverine HCl gel, and 7%, 15%, and 20% papaverine base gel along with a proprietary skin permeation enhancer. After the application of the gel at the penis, scrotum, and perineum, a dose-dependent hemodynamic effect was found during duplex ultrasonography. Only three patients achieved full erections (also when exposed to placebo). The tolerability was good both locally and systemically. Similar findings were reported using up to 20% papaverine base gel (51).

Contraindications

Intravenous injection of papaverine is contraindicated in the presence of complete atrial ventricular heart block. When contraction is depressed, the drug may provoke tran-

sient ectopic rhythms of ventricular origin, either premature beats or paroxysmal tachycardia. Papaverine does not have FDA approval for the treatment of impotence by intracorporal injection or topical application. The intracorporal injection of papaverine is known to result in persistent priapism requiring either surgical or medical intervention. Whether or not topically applied drugs would have any impact on these types of complications is a matter of conjecture at this point. Based on the bioavailability studies mentioned earlier, it is unlikely that a sufficient amount of topical drugs would be absorbed.

Adverse Reactions

Opiate derived compounds such as papaverine may cause a cholestatic hepatic dysfunction. This finding has been observed in geriatric patients taking papaverine for vascular insufficiency as well with intracavernous injection (52–54). Topical therapy has not been shown to have a similar risk in one study (30). The following side effects have been reported for papaverine when given by injection: general discomfort, nausea, abdominal discomfort, anorexia, skin rash, malaise, vertigo, headache, intensive flushing of the face, perspiration, increase of the depth of respiration, increases in heart rate, slight increases in blood pressure, and excessive sedation. Few of these have been reported when given by topical methods.

TOPICAL NITROGLYCERIN

The use of topical nitroglycerin is a standard treatment for unstable angina pectoris because predictable blood levels can be achieved. The use of nitroglycerin ointments, pastes, plasters, or patches for the treatment of ED has been tried in several studies.

Mechanism of Action

Relaxation of vascular smooth muscle is the principle pharmacologic action of nitroglycerin. Nitroglycerin produces, in a dose-dependent manner, dilation of both arterial and venous beds, dilatation of the postcapillary vessels including large veins and decreases in venous return. This results in a reduction of left ventricular diastolic pressure. Arteriolar relaxation reduces systemic vascular resistance and arterial pressure. Myocardial oxygen consumption and demand is decreased by both the arterial and venous effects of nitroglycerin results in and a more favorable supply–demand ratio. Whether topical nitroglycerin for the treatment of erectile function can have similar effects on cardiac status is not known. Contraindications to the use of topical nitroglycerin include those who have allergic reactions to organic nitrates. These are extremely rare, but they do occur.

Pharmacokinetics

Nitroglycerin transdermal delivery systems are designed to provide continuous controlled release of nitroglycerin through intact skin. The rate of release is linearly dependent upon the area of the applied system. In FDA-approved patch systems, each centimeter squared of applied system delivers approx 0.02 mg of nitroglycerin/h. In general, after approximately 12 h each system has delivered about 6% of its original content of nitroglycerin. Nitroglycerin is cleared from the body at extremely rapid rates with the resulting serum half-life of approx 3 min. The observed clearance rate greatly exceeds hepatic blood flow suggesting extensive peripheral metabolism. Known sites of extrahepatic metabolism include red blood cells and vascular walls. The first products in the metabolism of nitroglycerin are inorganic nitrate and dinitroglycerols. The

dinitrates are less effective vasodilators than nitroglycerin, but they are longer lived in the serum. The dinitrates are further metabolized to nonvasoactive mononitrates and ultimately to glycerol and carbon dioxide. In healthy volunteers', steady-state plasma concentrations of nitroglycerin are reached by about 2 h after application of a patch and are maintained for the duration of wearing that system. Whether any of these pharmacokinetic issues are pertinent to topical nitroglycerin applied to the penis is not known.

Response Rates

Owen et al. reported a double-blinded placebo controlled study using a 2% nitroglycerin paste applied at the penile shaft in 30 impotent patients (38). The evaluation included penile tumescence measurement and duplex ultrasonography. Although the patients that received nitroglycerin achieved a better response, it was not significantly different from placebo. Headache was a common side effect that developed tolerance over the applications. Heaton et al. reported a study in 174 patients that underwent duplex ultrasonography for an ED workup and received a topical application of nitroglycerin paste at the penile shaft (55). There was a significant difference in the four vessels' diameter before and after the drug application.

Clinical evaluations in a home use environment are limited. Nunez et al. reported three successful cases using 2% nitroglycerin paste (39). Sonksen reported "clinical response" in 12 of 17 spinal cord injured patients (56). However, only five achieved a "usable response" at home. Meyhoff studied ten patients with nitroglycerin patches, four patients achieved a "usable" response, and three preferred the patches to their usual I.C. papaverine treatment (57).

Adverse Reactions

The most frequent adverse reaction in patients who are administered nitroglycerin is headache, which occurs in approx 2% of patients. Other reactions occurring in less than one percent of patients are tachycardia, nausea, vomiting, apprehension, restlessness, muscle twitching, retro-sternal discomfort, palpitations, dizziness, and abdominal pain. In a smaller number of patients, additional adverse reactions such as cutaneous flushing, weakness, drug rash or exfoliative dermatitis have been reported. Allergies to the adhesives used within the nitroglycerin patches have also been reported.

CONCLUSIONS

Advances in the understanding of penile physiology, basic erectile pharmacology and alternate drug-delivery systems constitute an evolving technology that is potentially useful for the treatment of ED. Intraurethral drug delivery is now well established and appears to function as a second-level treatment depending on the patient response to oral therapy and his attitude toward ICI. With the association of modern skin penetration enhancers, it is now possible to achieve an acute transfer of drugs to the corpus spongiosum in order to take advantage of its vascular communications with the corpus cavernosum. Whether this transfer process can be exploited to address the sexual dysfunction of patients needs to be determined. Topical therapies are still experimental and may play an additional role in the future. The main advantages of local therapy for ED are its safety and good tolerability in terms of local and systemic effects. Even in the era of oral treatments, an effective, safe, and easy-to-apply topical or intraurethral agent will have its place in the physician's armamentarium to treat patients with ED.

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Intracorporal Therapy

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CONTENTS

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INTRODUCTION

With the launch of sildenafil (Viagra®) for the treatment of erectile dysfunction (ED) a new algorithm of a step care model has been established with oral medication being first line therapy. This resulted in self-injection therapy becoming the main treatment option in the second line therapy (1,2). The indications for self-injection therapy are either failure of oral medications or patients having contraindications to oral medications.

Over the past two decades, self-injection therapy has been established as an efficacious and safe treatment for ED. Following multicenter clinical trials, prostaglandin E-1 was commercialized in two forms alprostadil sterile powder (Caverject) and alprostadil-alfadex (Edex/Viridal). In addition, off-label combinations have been used by many practitioners, including papaverine + phentolamine (Bimix) or papaverine + phentolamine + prostaglandin E-1 (Trimix). Other drugs and combinations have been investigated including a combination of vasoactive intestinal polypeptide (VIP) + phentolamine in the product Invicorp, the nitric oxide (NO) donor Linsidomin (SIN-1), and Moxisylyte.

In the early 1980s, the advancement in the understanding of the physiology of erection demonstrated that injecting vasoactive agents intracorporally would produce an erection sufficient for successful intercourse. The first published report of hypogastric artery infusion of papaverine to induce erection during vascular reconstructive surgery was by Virag (3). Brindley reported results of using the α -adrenergic blocker phenoxy-

benzamine for penile self-injection in the management of ED (4). In 1985, Zorngiotti and Lefleur used a combination of the smooth-muscle relaxant, vasodilator papaverine, and the α -Adrenogic blocker phentolamine for intracorporal injection therapy (5). Several studies led also to the introduction of prostaglandin E₁ (PGE₁), a potent smooth-muscle relaxant and vasodilator, for patient use in 1986 (6).

PGE₁

PGE₁ is the best-studied injectable vasodilator and the only one approved by the FDA. PGE₁ is a potent smooth-muscle relaxant and vasodilator. It acts by increasing the synthesis of cyclic adenosine monophosphate (cAMP), causing a decrease in intracellular calcium and consequently causing cavernosal smooth-muscle relaxation, vasodilation, and erection. Erections usually occur within 5–20 min following injection, with the goal of treatment being to produce an erection that has duration of not longer than 1 h (7,8). The plasma half-life of PGE₁ is less than 1 min owing to rapid pulmonary clearance. Large prospective trials have previously documented success rates of 73–94% with intracavernosal alprostadil, either as EDEX®/VIRIDAL (Schwarz Pharma, Monheim, Germany) or Caverject® (Pharmacia & Upjohn) (9–12). Individual escalating dose titration is necessary. The most practical dose range is 5–40 mcg. The initial dose for nonspinal-cord injury patients is 10 mcg. The initial dose for young spinal-cord injury patients should be low, because of their supersensitivity to the drug and risk of priapism. In our center, we start young, otherwise healthy, men with spinal-cord injury at 2 mcg. The main side effect was pain in the penis. Some degree of pain occurs in approx 30% of patients during the titration phase and in approx 15% of patients during the long-term treatment phase. Other uncommon side effects included penile fibrosis and priapism.

A long-term open-label extension study provided valuable information (13). Included were 85 patients that had completed a previous 1-yr trial with PGE₁, (alprostadil-alfadex, Edex). Patient age ranged between 33–72 yr. The patients performed self injections at an average of 4.4–6.1 times pr mo. The average dose was 13.5 mcg. The median time to erection ranged from 8 to 12 min with a mean duration of erection of 50–70 min. During this second-year extension, all 85 patients reported satisfactory sexual intercourse. Ninety-eight percent of the injections (4741 injections) resulted in satisfactory sexual intercourse. A quality-of-life questionnaire (Case Western Reserve University Questionnaire) showed significant improvement of quality-of-life scores in both patients and partners on a scale of 0 = extremely uncomfortable to 5 = extremely comfortable. At the baseline, the mean patient score was 1.9 and the mean partner score was 2.7. At the end of the study, the mean patient score was 4.2 and the mean partner score was 4.1. The local adverse events were transient and of mild intensity. There were no systemic adverse events. This study was an attest to the excellent long-term efficacy and safety of PGE₁.

PAPAVERINE

Papaverine, an alkaloid derived from *Papaver somniferum*, is a nonspecific phosphodiesterase inhibitor (7). Papaverine increases the level of cAMP and cyclic guanosine monophosphate (cGMP). This, subsequently leads to a decrease in intracellular calcium and smooth-muscle relaxation. Papaverine causes a dose-dependent relaxation

of the corpus cavernosum (14,15). Injecting papaverine into the corpus cavernosum induces penile rigidity by increasing blood flow. In addition, smooth-muscle relaxation results in compression of the venous complexes by causing a decrease in venous out-flow (16). Monotherapy with papaverine is not considered a treatment of choice for most patients with ED because of inferior response rates and high levels of adverse events at doses sufficient to cause erections (17).

PHENTOLAMINE

Phentolamine mesylate has been used for many years as both an oral tablet and an injectable solution for the management of hypertension and pheochromocytoma. Intracavernosal injection of phentolamine with other pharmacological agents (papaverine and/or PGE₁ has been shown to cause penile erections suitable for sexual intercourse). Phentolamine is an α -1 and α -2 adrenergic receptors blocker. Because phentolamine presumably acts by blocking detumescence, it is understandable that it acts synergistically with other erectogenic agents (18,19).

BIMIX

Numerous reports have been published confirming the efficacy and safety of a mixture of papaverine and phentolamine. In one study, 144 men with ED were given injections of 15 mg papaverine and 1.25 mg phentolamine (20); 101 (68%) of the patients were satisfied with the test injections and entered the self-injection phase; 78 patients (70%) continued treatment for a mean duration of 6.5 mo (range 2–12 mo). All 78 men reported that they were able to have intercourse. In two other studies, papaverine (30 mg) plus phentolamine (0.5 or 0.83 mg) were given to treat a total of 99 patients (21,22). An erectile response occurred in 40–67%. In another study, 201 patients were treated with a combination of papaverine (22.5 mg) and phentolamine (1.25 mg) (23). The drop-out rate over the 46-mos follow-up period was 21%, even though there were relatively few adverse events: 1.5% fibrosis, 1.5% priapism, 1.5% papaverine-induced hepatic dysfunction, and 2% tachyphylaxis.

In a double-blind crossover study, 40 men were administered papaverine (20 mg) and phentolamine (0.5 mg) or papaverine (40 mg) alone (24). Of the men treated with the Bimix, 48% had an adequate erectile response in comparison with 27% treated with papaverine alone. The Bimix-treated patients also reported less pain: 17% of the patients treated with bimix, compared to 27% treated with papaverine alone. The combination of papaverine and PGE₁ had a synergistic effect when compared to papaverine and phentolamine (25). However, pain was associated with the use of PGE₁. In a randomized double-blind study of 60 patients, bimix of papaverine (30 mg) and phentolamine (0.5 mg) was compared with PGE₁ (30 μ g) (26). Fifty-four percent (54%) of the patients treated with the Bimix responded with an adequate erection, compared to 50% treated with PGE₁ alone. Prolonged erections occurred in 18% of patients treated with Bimix, and in 15% treated with PGE₁ alone. Pain was significantly higher in patients treated with PGE₁ alone (35% vs 15%). A literature review, showed that approx 7% of the 3500 patients treated with papaverine alone and 6–8% of the 5000 patients receiving the Bimix of papaverine and phentolamine reported prolonged erections (priapism longer than 6 h) (27). A summary of the 19 Bimix trials in this review showed that 71.9% (786/1093) of patients had satisfactory erection.

TRIMIX

A report on 210 patients treated with a Trimix combination of papaverine (22.5 mg), phentolamine (0.83 mg), and PGE₁ (8.3 µg) showed an adequate erectile response in 81% of the patients with a low incidence of adverse events (3.5% pain, 1.7% priapism, and 4.2% fibrotic scarring) (28). A comparative study reported on the trimix of papaverine (17.6 mg), phentolamine (0.58 mg), and PGE₁ (5.8 µg) vs PGE₁ (40 µg), in patients who had previously failed treatment with Bimix (29). An erection adequate for intercourse was observed in 50% of the Trimix-treated patients, compared to 22% of those patients treated with PGE₁ alone. Patients treated with the Trimix combination also reported a lower incidence of pain (12.5% vs 41%). In a recent study on 766 responders to a questionnaire individuals, 76.2% used PGE₁ (34.7%, <10 µg; 9.7%, 10–20 µg; 31.8%, 0–40 µg); 19.5% used Bimix of papaverine/phentolamine (15 mg/0.5 mg), and 3.7% used Trimix of PGE₁/papaverine/phentolamine (10 µg/15 mg/0.5 mg) (30). Forty percent of the patients dropped out within the first 6 mo of treatment. The reasons for drop out were inadequate penile rigidity, expense of the treatment, penile discomfort, or lack of spontaneity. Overall, 80% of the subjects were satisfied with intracorporal therapy. In this study, 74.3% (608/818) of patients treated with the Trimix combination achieved a satisfactory erection.

VIP

The literature shows evidence that the neurotransmitter vasoactive intestinal polypeptide, VIP, is involved in the regulation of penile erection in man (30,31). VIP is a highly basic, single chain, linear, 28-amino acid polypeptide occurring locally at many sites in the body, particularly at vascular beds requiring intermittent physiological vasodilatation. Reduced concentrations of VIP were found in penises of impotent men. In normal men, VIP injected intracavernosally has been reported to cause penile tumescence, but not a rigid erection unless sexual stimulation has occurred (32,33), and in most patients with erectile failure, VIP alone was not sufficient to induce erection (34).

VIP has a potent effect on the venoocclusive mechanism of erection, whereas exerting little effect on arterial inflow (35). Phentolamine, conversely, increases the arterial flow, but has little effect on the venoocclusive mechanism (36). Therefore, the combination of these two agents in one injectable solution is suitable for the treatment of ED. In an open-label study, VIP in combination with phentolamine was shown to be effective in facilitating an erection in response to sexual stimulation. More than 15,000 injections of Invicorp™ have been made without serious side effects or penile pain. A review of 9,300 injections was published recently (37).

The combination of vasoactive intestinal polypeptide and phentolamine (Invicorp™), has been under development as an injection pharmacotherapy. Invicorp™ 1 contains 25 µg VIP and 1 mg of phentolamine mesylate. Invicorp™ 2 contains 25 µg of VIP and 2 mg of phentolamine mesylate. Invicorp™ is administered using an auto-injector. The Invicorp™ auto-injector helps reduce the usual anxieties of needle use, which could interfere with the induction of erection. It is automatic, quiet, rapid, and painless in action, accurately delivering the pre-filled dose (38).

Self Injection Therapy in Nonresponder to Oral Medications

There has been a lack of information on the efficacy of self-injection therapy in patients who failed the oral medication sildenafil (Viagra). Recently, two multicenter

clinical trials investigated this issue. The first trial was an open-label, multicenter study, in which patients with ED were treated with sildenafil over a 4-wk period (39). The initial dose was 50 mg, which was increased to 100 mg if no response was achieved. Patients not responding to sildenafil treatment, measured using the IIEF (International Index of Erectile Function) questionnaire, entered an alprostadil alfadex (Edex/Viridal) in-office titration phase, to determine the optimal dose up to 40 µg. A 6-wk alprostadil alfadex at-home treatment phase followed. The results showed, in 67 patients who did not respond satisfactorily to sildenafil, the alprostadil alfadex at-home therapy resulted in improvements in questions 3 and 4 of the IIEF in 89.6% (60/67) and 85.1% (57/67) of patients, respectively. The mean improvement in IIEF score for these patients was 2.75 and 2.63 for questions 3 and 4, respectively. The most common side effect was penile pain in 29.4% (25/85) patients treated with alprostadil alfadex in-office and at home. Alprostadil alfadex therapy was found to be efficacious and safe in men who failed initial therapy with sildenafil. The second study was an open-label, multicenter study investigating the efficacy and safety of alprostadil sterile powder (Caverject) in sildenafil (Viagra) nonresponders (40). One-hundred ninety-five men refractory to sildenafil were enrolled. An effective dose of alprostadil sterile powder was established by titration. Subsequent to training in self-injection technique, men treated themselves at home. One-hundred twenty-nine (81%) men responded adequately to in-office testing and out of these 129, 105 (81%) successfully completed the home phase. Reasons for withdrawal were: 5 lack of efficacy, 5 nonserious AEs, 3 partner problems, 1 protocol violation, and 10 lost to follow-up. Considering the 105 men, 95 (90%) had successful and satisfactory intercourse. In summary, penile injection therapy with PGE-1 (either Caverject or Edex/Viridal) has been found to be highly efficacious and satisfactory in patients failing the oral medication sildenafil (Viagra).

Comparison with Intraurethral Alprostadil Therapy (MUSE)

A cross-over, randomized, open-label multi-center study in 111 patients with ED of at least 6-mo duration compared the efficacy, safety, and patient preference of intracavernosal alprostadil (EDEX®/Viridal®) with MUSE® plus optional ACTIS® (41). All patients underwent an in-office dose titration with either drug before undertaking an at-home treatment phase. The mean doses used were 26.1 µg and 922.5 µg for EDEX and MUSE, respectively. Compared with MUSE, more EDEX administrations resulted in an erection sufficient for sexual intercourse (82.5% vs 53.0%); significantly more patients using EDEX achieved at least one erection sufficient for sexual intercourse (92.6% vs 61.8%; $P < 0.0001$); and EDEX use resulted in a significantly greater percentage of patients attaining at least 75% of erections sufficient for sexual intercourse (75% vs 36.8%; $P < 0.0001$). Penile pain was the most common side effect for both medications: 20.0% vs 30.5% (in-office) and 33.8% vs 25.0% (at-home) for EDEX and MUSE, respectively. Similar numbers of adverse events were reported with either treatment during the at-home phase. Patient and partner satisfaction was greater with EDEX and more patients preferred this therapy, choosing to continue it during a patient preference period at the end of the study. Because intracavernous injection therapy was more efficacious, better tolerated and preferred by the patients and their partners, it should be offered as the first choice treatment if oral therapy fails or oral therapy is contraindicated.

SUMMARY

This review confirms that intracorporal self-injection therapy is the best second-line drug therapy after oral therapy in the new algorithm of ED treatment. Moreover, the confirmed efficacy makes it first-line therapy for those patients in whom oral therapy is contraindicated. PGE-1 is the best studied, best documented, and only FDA-approved injectable vasodilator. Off-label combinations of either papaverine and phentolamine (Bimix), or papaverine, phentolamine, and PGE-1 (Trimix) have also been used in clinical practice. A few investigational new injectables have been in clinical research including among others, a combination of VIP and phentolamine. Intracorporal self-injection therapy remains an important part of the armamentarium of the treatment of ED. Patients and partners should be educated about the efficacy and safety of this important therapy especially when patients fail oral drugs.

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Vacuum Erection Devices

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INTRODUCTION

Impotence, a crippling problem for millions of men, is the inability to achieve and/or maintain an erection of sufficient rigidity and duration to allow for satisfactory vaginal intercourse. The initiation and maintenance of an erection is a complex interplay of vascular, neural, hormonal, and psychological factors. Dysfunction involving any or all of these components can cause impotence. Impotence affects men of all ages; but its incidence increases with age. Kinsey estimated that 1.9% of all 40-yr-old men are impotent, which is greater than initially reported by Kinsey if mild, moderate, and severe erectile dysfunction (ED) are considered. Nearly 40% of men suffer from ED by age 40 and the percentage increases to > 75% by age 70.

While the incidence of impotence has remained relatively constant, therapeutic advances and greater public awareness of the problem has increased the number of men who seek treatment. During the past decade, through progress in our understanding of the basic pathophysiology of impotence, a new era in the diagnosis and treatment of impotence has dawned. Improved diagnostic procedures and effective medical and surgical therapy are now available. However, oral medications are ineffective in some men and many patients are unwilling to undergo surgery with its attendant risks for this quality-of-life disorder. The vacuum constriction device fills this void for many patients.



Fig. 1. Standard VCD with suction cylinder, pump erection, and constricting band.

DEVICES AND MECHANISMS

Many vacuum constriction devices (VCD) are now commercially available. The standard VCD consists of a suction cylinder and pump to induce erection and a constricting band placed at the base of the penis to maintain the erection-like state after the suction device is removed (Fig. 1). Newer models condense the suction cylinder and pump into one piece and incorporate a battery-driven motor to create the vacuum. Each cylinder has a pressure release valve designed to prevent penile injury from the development of excessive negative pressure. Salvatore, Sharman, and Hellstrom evaluated several commercially available VCDs and discovered that single-handed devices were more desirable to novice users (*1*). This may also be true for the elderly patient with limited manual dexterity, although this subgroup of patients was not evaluated separately. These investigators believe the single-handed, manually controlled VCD to be the system of choice for the future.

Utilizing negative pressure to distend and fill the corporal sinusoids and an external constricting ring to prevent venous return, a satisfactory erection can be produced and maintained. Current VCDs are commercially available without prescription, and satisfactory use of these devices has been reported in a large number of patients. The VCD should not be used for longer than 30 min at a time to prevent ischemia of the penis. The reported complications of VCD usage are minor and include petechiae (27%), ecchymosis (10%), initial penile pain (41%), ejaculatory difficulty usually from erec-

tile pivoting (12%), dusky discoloration of the glans, penile numbness, and trapping of the ejaculate (2,3).

PHYSIOLOGIC EFFECTS

The physiologic effect of repetitive negative-pressure expansion of the corporal tissue has been investigated in an animal model, but is incompletely understood in man. Blair et al. investigated the effect of subatmospheric pressure on the forearm-resistance blood vessels in 10 healthy volunteers (4). They demonstrated an initial increase in arterial inflow as a result of passive dilation of the vessels. Greenfield and Patterson also demonstrated a vasodilation effect on the arteries of the forearm in volunteers exposed to a subatmospheric pressure of -150 to -200 mmHg (5). Diederichs et al. investigated the effect of subatmospheric pressure on the penis in primates and demonstrated that an initial decrease in intracorporal pressure after onset of negative pressure was followed by a gradual increase in intracorporal pressure as blood flowed into the corpora cavernosa (6). Negative pressure was found to induce an expansion of the penile tissue followed by increased blood flow. Because the constricting ring was felt to make venous backflow unlikely, the authors believed the observed increase in blood flow represented arterial inflow. Additionally, they demonstrated that the tumescence thus induced would immediately be lost if venous constriction did not occur.

Broderick et al. measured the immediate effect of transient vacuum application on cavernous arterial function in humans (7). All patients studied demonstrated an increase in peak flow velocity relative to baseline values after exposure to two sequential applications of vacuum tumescence, and the cross-sectional area of the corpora doubled. They note that sexual stimulation will enhance the erection induced by use of an external vacuum by increasing the compliance of the cavernous smooth muscle before vacuum exposure. These authors documented a transient, but measurable increase in corporal inflow, and believe that practicing with the VCD without release of the band may be of therapeutic benefit. Donatucci and Lue determined the effect of chronic external vacuum device usage on cavernous arterial function in a prospective study of 26 men with vasculogenic ED (8). Mean cavernous arterial peak flow velocity in this group was 22 cm/s on the right and 18.5 cm/s on the left. Repeat duplex ultrasonography at the completion of the study revealed a mean right cavernous artery peak flow velocity of 29.7 cm/s and a left cavernous artery mean peak flow velocity of 23.6 cm/s. Chronic external vacuum device usage appeared to increase cavernous arterial flow in men with mild vasculogenic impotence.

Bosshardt et al. used different physiological parameters, (real-time and nocturnal penile tumescence monitoring), to determine the efficacy and possible beneficial effects VCD (9). Thirty men suffering from ED were selected for the trial after using the VCD for 2 wk at home. Changes in penile tumescence and rigidity before, during, and after using the VCD were assessed with the Rigiscan™ monitor. The average rigidity measured at the base and tip of the penis after application of the VCD was $>80\%$, and the duration and extent of nocturnal penile tumescence and rigidity at the start and the end of the study improved. Patients reporting spontaneous morning erections showed significant improvements in total erection time, erection phase, and plateau phase duration, effective rigidity, and tumescence increase.

CLINICAL RESULTS

Vacuum erection devices, unlike the pharmacological agents available for the ED patient, have not had to undergo rigid clinical trial to prove safety and efficacy prior to widespread availability. Therefore, the literature consists largely of single center observational series, and a collection of small prospective clinical trials. Despite the inherent limitations of such data, a wealth of clinical experience is available. There is a great deal of variability in the clinical efficacy of VCD therapy. In an evaluation of the long-term results of vacuum constriction therapy, Cookson et al. examined 216 consecutive patients using the device (10). Sixty-nine percent of patients reported regular device usage. Patient and partner satisfaction was high ranging from 82% to 89%. Of note, 79% of long-term patients reported an increase in the frequency of intercourse per month and this increase was sustained beyond the first year in 77%. Thus, an effective treatment that restored confidence in erectile ability led patients to increase the frequency of sexual activity. Vrijhof et al. reported their experience with 67 patients treated with vacuum constriction devices (11). All patients were tested in the office, and half were felt to achieve an erection sufficient for intercourse. Forty-seven patients attempted to use the device at home and adequate erections were reported by 34 of the 47 (72%).

In contrast, Derouet et al. evaluated both the medical and the psychological outcomes of external vacuum device usage in 190 patients with ED (12). Their experience with patient satisfaction using the device was less than that of Cookson and Vrijhof. The primary rejection rate for VCD therapy was 51%. Twenty percent of patients (22/110) were unwilling to use the device when it was first offered and an additional 31% (34/110) dropped out after a period of up to 16 wk. Only 42% of patients (46/110) were long-term users and most of these were patients who did not respond to intracavernosal pharmacotherapy. However, within this group 98% of patients and 85% of their partners were satisfied with the vacuum therapy. Dutta et al. attempted to evaluate, using a long-term, prospective study, the satisfaction rate, attrition rate, and follow-up treatment of patients with mild, moderate, and severe organic ED (13). One hundred twenty-nine men were assessed by follow-up questionnaire regarding satisfaction, months of use, reasons for discontinuing, and further treatment. The overall attrition rate observed was 65% and was lowest among patients with moderate ED (55%). All patients with mild dysfunction discontinued use, and a large number (70%) of patients with complete dysfunction also discontinued use. Patients who discontinued using the VCD usually did so early, (median 1 mo, mean 4 mo), and 63% who dropped out did not seek further treatment. Only 35% of patients were satisfied with the device and continued to use it long term (mean 37 mo).

The importance of proper patient selection to increase beneficial outcome of therapy is confirmed by the experience of several other authors. Meinhardt et al. followed 74 men with ED who used a vacuum device at home (14). In their report, only 20 men were satisfied with the erections achieved. However, this study was biased toward failure because the device was only offered to men who had not been helped by sexual counseling, self-injection therapy, or venous surgery. Patients with psychogenic impotence did find the VCD acceptable therapy despite the ability to achieve erections with the device and all nine declined regular use. Earle et al. also found a high dissatisfaction rate with VCD therapy in patients who failed prior therapy for ED (15). In a retrospective survey, efficacy and acceptance of VCD therapy in 60 impotent men not satisfied with intracavernosal injection therapy (ICI), 72% (43) responded to a com-

pleted questionnaire. Eighty-one percent (39) of the men abandoned the device because of a perceived lack of efficacy.

In an attempt to improve the reported efficacy and satisfaction of VCD therapy, advanced criteria for patient selection have been employed. Subpopulations of patients with specific etiologies have been identified by diagnostic evaluation and the results of VCD therapy in these groups reported. Baltaci et al. used color Doppler flow ultrasound to define the state of the penile vasculature in 61 men with ED (16). The authors evaluated erectile quality, ability to perform sexual intercourse, incidence of complications and rate of satisfaction. Eighty percent of the patients (49) used the device and were followed for 1 yr. Overall effectiveness was 67%, and the other 33% (16/49) withdrew from the trial primarily because they were unable to achieve and maintain a full erection. Arteriogenic impotence was diagnosed in 32 patients. Of these, 88% of the men (28/32) had satisfactory results and had an improvement in their capacity for spontaneous erections with the device.

Several reports examining satisfaction and effectiveness of VCD therapy in patients with corporeal veno-occlusive dysfunction (CVOD) of variable severity are available for evaluation. Using dynamic infusion cavernosometry/cavernosography (DICC), Blackard et al. evaluated 70 patients suspected of having venous leakage (17). Forty-seven of the 70 men (67%) had the clinical diagnosis of venous leakage confirmed, and a vacuum tumescence device was recommended as initial treatment for all of them. Twenty-nine patients had purchased a vacuum tumescence device, and satisfaction was expressed in 20 patients (69%) with venous leakage. Kolettis et al. evaluated 98 patients with suspected CVOD as the cause for their ED (18). Fifty patients had documented CVOD (33 by cavernosometry, 16 by ultrasound using end-diastolic flow criteria, and 1 by cavernosography). In this study, 28/50 patients (56%) reported satisfaction with VCD therapy, 13/50 patients (26%) were dissatisfied, and in 9 patients (18%), satisfaction could not be determined. The authors found no relationship between the severity of disease and the rating of erection or satisfaction with the device.

ED in diabetic men is commonly a result of the neuropathic and vasculopathic effects of this disease. The value of VCD therapy in the diabetic subpopulation of men with ED has been examined. In a small series of 12 patients with ED secondary to diabetic neuropathy, Arauz-Pacheco et al. found VCD therapy successful in 75% of the patients (19). Bodansky et al. evaluated 19 diabetic men with ED, 9 of whom had ECG evidence of autonomic neuropathy (20). Reported duration of impotence was 24 (12–168) mo and their expectation of restored sexual activity was 8 (1–28) times per mo. Rather than using questionnaires, the authors evaluated the effectiveness of VCD therapy using visual analog scales (range 1–10) at 3 and 6 mo after initiation of therapy. Eleven patients (58%) continued to use their device over 6 mo. Self-assessment values for sexual satisfaction, partner's sexual satisfaction, and self-esteem significantly increased over the 6-mo trial. In those continuing to use the device, it was considered highly effective, painless in use, and not embarrassing. Despite wearing a constriction ring to maintain their erection, ejaculation was satisfactory. Patients used the device four times per month on average.

Neurogenic factors contributing to ED may be found in up to 20% of organically impotent men. Whereas patients with neurogenic ED are very sensitive to pharmacological therapy, they are at an increased risk of prolonged erection and priapism. Complication rates after penile prosthetic surgery also are higher in the neurogenic population, particularly in patients with spinal cord injury. Thus, the low morbidity of

VCD therapy in general makes it an attractive alternative for patients with neurogenic ED. Seckin et al. studied 32 spinal cord traumatized patients who had been injured at least 1 yr previously and had a regular sexual partner (21). Most patients were satisfied and only four patients discontinued treatment because of minor complications such as ecchymoses, petechiae, and lack of motivation. The authors suggested VCD as initial treatment for the management of impotence secondary to spinal cord injury.

In the era before effective oral therapy, several direct comparisons of VCD to ICI appeared in the literature. Turner et al. examined usage rates and satisfaction in 42 patients with ED (22). Whereas patients used both therapies equally, the high initial rate of usage declined over 50% in each group by month 12. Satisfaction was expressed by 77–85% percent of patients. Interestingly, spontaneous erections also improved with both treatments. In a second direct comparison of VCD and ICI Soderdahl et al. examined 44 patients with ED in a randomized prospective clinical trial (23). Patients and partners reported a superior quality of erections with the injection method, but the variation did not reach statistical significance, and satisfaction with the sexual experience was significantly better when using injections. No difference in rate of adverse events was seen between therapies. Remarkably, at the end of the study, 80% of patients were still using the vacuum device, injections, or both; a usage rate much higher than demonstrated in previous studies. McMahon performed a direct comparison of ICI to VCD in 188 patients with ED secondary to CVOD (24). One hundred three patients used ICI, whereas 85 patients were treated by VCD. In the ICI group, satisfactory intercourse was achieved in 22 of 32 patients (69%) with mild dysfunction, 29 of 54 patients (54%) with moderate dysfunction, and in 2 of 17 patients (18%) with severe dysfunction. With a VCD, satisfactory intercourse was achieved in 23 of 30 patients (77%) with mild dysfunction, 24 of 40 patients (60%) with moderate dysfunction, and in 10 of 15 patients (66%) with severe dysfunction. Therefore, VCD therapy can be used successfully even in patients who have suffered severe loss of cavernosal smooth muscle, which has rendered them nonresponsive to high-dose ICI.

Walsh and Donatucci performed a comparative analysis of VCD vs other forms of therapy for postprostatectomy ED (25). One hundred sixty-five men were evaluated over 24 mo, ranging in age from 46 to 80 yr (average 63 yr). Time from surgery to initial evaluation ranged from 0 to 27 mo postsurgery (average 6 mo) and no patient had received prior therapy for ED. Follow-up ranged from 2 to 24 mo, averaging 12 mo. Using a goal-directed approach, all patients were informed of the nature of the therapeutic options and projected rates of efficacy. Only surgical intervention was reserved as an initial choice. The patient's initial treatment tended to be noninvasive therapy, with the VCD being most popular, (chosen by 35% of the patients initially) (Table 1). Ultimate treatment outcome is available for 118 men (2 deceased, 45 lost to follow-up). Many of the patients who had initially used the VCD had turned to ICI, whereas some had decided to forego ICI in favor of the VCD. At last contact, 8% used vacuum therapy, 29% used injections, 2% used combined vacuum/injection therapy, and 2% had undergone prosthetic implantation. The most interesting finding was that nearly 60% were not using any of these therapies. The availability of sildenafil citrate has changed the initial choice of therapy for most patients, but the results of sildenafil have been modest with post prostatectomy patients except those who have bilateral cavernous nerve preservation. Thus it appears all currently available treatments, including VCD, leave the majority of patients dissatisfied within 12 mo of initiation of therapy. To

Table 1
Post Prostatectomy Treatment Choice and Outcome

<i>Treatment Method</i>	<i>Initial Choice Frequency</i>	<i>Satisfaction With choice</i>	<i>Final Choice Frequency</i>	<i>Satisfaction With choice</i>
Oral medication	15%	0%	0%	n/a
Vacuum device	35%	28%	11%	69%
Injection	23%	46%	39%	77%
Surgery	0%	n/a	2%	100%
No Therapy	20%	n/a	46%	n/a
Injection/Oral	2%	0%	0%	n/a
Vacuum/Injection	3%	50%	2%	67%
Vacuum/Oral	1%	0%	0%	n/a

improve quality of life in postprostatectomy patients, less aversive, and more effective therapies are needed.

COMBINED AND ADJUNCTIVE VCD THERAPY

The use of an external vacuum device in combination with injection of vasoactive agents may lead to an adequate erection in patients who could not achieve one with either therapy alone. Chen et al. studied the effect of combining VCD with intracavernous injection in 10 men with ED who previously failed attempts at treatment with either method as single therapy (26). The authors measured changes in the length, circumference, and buckling pressure of the penis at baseline, after applying negative pressure (250 mmHg for 2 min), 15 min after intracavernous injection of 60 mg papaverine or 30 μ g prostaglandin E1 and after combining both modalities. With vacuum alone, the mean buckle pressure was 125.0 $\pm$ 53.6 gm, whereas after intracavernous injection, the mean buckle pressure was 117.0 $\pm$ 38.3 gm. Combination therapy increased mean buckle pressure to 565.0 $\pm$ 56.8 gm ($p < 0.0001$). After 10 mo of use, three subjects were still using the combination and were satisfied with the erectile response, and 1 no longer required therapy for ED.

Pharmacological agents delivered by intraurethral administration have also been found to enhance the effects of VCD when used in combination. John et al. attempted to improve the penile rigidity obtained with the VCD using intraurethral alprostadil in 19 men with ED (27). The amount of intraurethral alprostadil administered (20 mcg) was considerably less than the commercially available product yet significant improvement in vacuum-induced tumescence was seen. Combination therapy increased measured penile length by 33% over VCD alone (from 26 mm to 36 mm), and increased penile diameter by 75% over VCD alone (4 mm to 7 mm mean increase).

VCD has been especially helpful in patients with severe vascular disease and those with fibrosis of the erectile tissues secondary to priapism. Patients who have failed penile prosthesis insertion may also benefit from combined therapy. The use of VCD in this group markedly improves the erection obtained by intracavernous injection alone. Additionally, VCD therapy is of value in some patients with a penile prosthesis in place yet who remain dissatisfied with their erectile function. Soderdahl et al. reported the results of a retrospective analysis of 12 men using VCD therapy with a penile prosthesis in place, determining the efficacy, satisfaction, and side effects from the combina-

tion (28). Four patients had semirigid and eight had inflatable penile prostheses. After using the vacuum device to augment the erection, all reported increased rigidity and patient/partner satisfaction, and 11 of 12 described improved length and girth. Minimal complications were noted. Similarly, Korenman et al. found the VCD of value in patients who had unsatisfactory results from penile prosthetic surgery (29). Five patients had undergone removal of the prosthesis and four had the prosthesis in place. Increases were seen in mean coital frequency, mean erectile duration, and penile rigidity. Sixty-nine percent of patients and partners reported satisfaction with combination therapy. There were no significant complications.

ADVERSE EFFECTS

The VCD remains one of the safest treatment options for men with ED; observed complications are minor. In a study of VCD safety in 46 long-term users of VCD therapy (mean 27.6 mo), Derouet et al. found that 69.8% of long-term users never had problems with the device (12). Hematoma was the most commonly reported adverse event occurring in 10% of users, whereas 2% reported minor skin injury. Several authors have examined safety issues in subgroups of men with ED. Many men with vasculogenic ED are on anticoagulant therapy and concern has been voiced about the use of a negative pressure device in this patient population. Limoge et al. examined this question in a prospective randomized study of vacuum therapy and ICI during anticoagulation treatment with coumadin (30). In a 24-wk study, 33 patients were assigned to VCD therapy or ICI with crossover at 12 wk. Patients maintained diaries, and were followed with physical examinations, coagulation studies, and questionnaires. The 26 patients completing the study applied the vacuum 706 times (mean 1.9 wkly) and used ICI 605 times (mean 1.6 wkly). There were 11 acute minor complications with VCD therapy (petechiae that resolved spontaneously) and no chronic complications. Self-injection resulted in acute minor complications (3 ecchymoses and 1 prolonged erection requiring intervention) and 1 chronic complication (corporeal fibrosis with mild curvature). There was essentially no difference between VCD therapy and ICI in incidence of adverse effects, and the rate of adverse effects in patients on coumadin did not exceed the rate in the general urological population.

Concern has been raised about a possible role of VCD use in the genesis of Peyronie's disease. Kim and Carson were the first to report the development of Peyronie's disease in a patient after 4 yr of complication-free VCD use (31). Hakim et al. reported an association between the high pressure induced by use of a nonmedical, catalog-type vacuum erection without a pressure-release valve and the development of induced vasculogenic impotence and Peyronie's disease (32). The patient in this report applied the VCD after having achieved a spontaneous rigid erection. The resultant excessive overinflation of the penis was followed by dorsal curvature, diminished rigidity, and decreased erectile maintenance with a plaque on the dorsal mid shaft. The authors estimated that the pulling forces in this patient's penis were prohibitively high (approx 29 lbs) and that these intense pulling forces damaged the tunica in the midshaft. Although these case reports are cause for concern, insufficient data exist to suggest that most patients who properly use VCD therapy are at increased risk for the development of Peyronie's disease.

Rare descriptions of other isolated adverse effects after VCD use have been published. Ganem et al. reported on a series of unrelated adverse events with chronic VCD

therapy including penile skin necrosis, development of urethral varicosities with subsequent hematuria, and capture of scrotal tunica within the penile shaft (33). Discontinuation of VCD therapy promptly resolved each adverse event except the capture of the scrotal tunica. This patient developed a mass that was not present in the flaccid state and was seen only with VCD use. After a negative diagnostic evaluation, the patient was surgically explored and the penile cystic mass was found to be scrotal tunica vaginalis; a hydrocele repair was performed. Postoperatively, the patient developed testicular migration into the ipsilateral penile shaft, which necessitated orchiectomy.

CONCLUSION

The VCD, a nonpharmacological method to achieve and maintain erection, has found a role in the management of men with ED. The biomechanical and biophysical effects of vacuum therapy have been established and clinical efficacy in a variety of patients has been documented. Vacuum constriction therapy is safe, with minor adverse responses recorded even in patients using anticoagulation therapy. Although some patients may not accept VCD therapy because of the intrusive nature of the device, or to cultural impediments, the VCD will continue to be a popular, cost effective treatment for many men who are unwilling or unable to use traditional pharmacological therapy or who decline to undergo penile prosthetic surgery.

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Penile Implants

Types and Current Indications

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INTRODUCTION

Although it is estimated that nearly 20 million Americans suffer from erectile dysfunction (ED), the true prevalence of this disorder is unknown (1). Worldwide studies have demonstrated that the prevalence of ED increases with age. The overall population growth, an increase in the elderly population, the introduction of effective oral medications for ED, and the intensified public awareness and education may result in a higher rate of seeking and using treatment (2). Patients with severe end organ failure who do not respond to any nonsurgical therapy will eventually be candidates for penile prosthesis. Although the percentage of such patients compared to the total number of patients with ED may be small, penile prosthesis implantation will remain a viable option because of the large patient base. Vendors claim that sales of penile prostheses have been relatively stable in the last decade. Since the introduction of penile prosthesis implantation to treat male ED in the 1970s, the modifications and improvements of penile prostheses have remarkably improved the device's reliability, longevity, and the prosthetic surgery outcome (3). In this chapter, we review different penile prostheses available in the United States and their clinical indications.

There are two broad categories of modern penile prostheses: semirigid and inflatable. In Table 1 we summarized the currently available penile prostheses and their ven-

Table 1
Penile Prostheses

Type		Prosthesis	Vendor
Semirigid	<i>Malleable</i>	Mentor Malleable	Mentor ^a
		Accuform	Mentor
		650	AMS ^b
		600M	AMS
	<i>Mechanical</i>	Dura II	TMT ^c
Inflatable	<i>Two-piece</i>	Ambicor	AMS
		Mark II ^d	Mentor
	<i>Three-piece</i>	Alpha 1	Mentor
		Alpha 1 Narrow-Base	Mentor
		Alpha 1 with lock-out valve	Mentor
		700 CX	AMS
		700 CXM	AMS
		700 Ultrex	AMS
		700 Ultrex Plus	AMS

^a Mentor Corporation, Santa Barbara, CA.

^b American Medical Systems, Minnetonka, MN.

^c Timm Medical Technology, Eden Prairie, MN.

^d Manufacture of this device stopped in the year 2000.

dors. The detailed surgical techniques used in implantation of these devices have been reviewed elsewhere and will not be covered in this chapter.

MALLEABLE PENILE PROSTHESIS

Malleable prostheses consist of an inner twisted metal wire of silver or stainless steel and an outer silicone cover. The four currently available devices are the Mentor Malleable and AcuForm by Mentor Corporation, and 650 and 600M by American Medical System. The once-popular Bard Jonas prosthesis is no longer available on the American market. In the United States, the choice of which model of prosthesis to use is left to the discretion of the prosthetic surgeon and patient. Factors such as cost and surgeon's experience with different models influence this decision.

Malleable devices are easier for patients to use, are less difficult for surgeons to place, present less chance of failure owing to wear, and cost less. However, unnatural erection, less concealability, and inability to adjust girth have made malleable penile prostheses unfavorable to many patients. In fact the use of the malleable penile prosthesis has been markedly decreased in the last decade thanks to improved reliability and longevity of the modern inflatable prostheses. Malleable penile prostheses are still popular in some areas of the world such as Asia. In the last 10 yr, less than 5% of patients received malleable penile prostheses among all penile implant recipients at the Medical College of Georgia and VA Medical Center, Augusta. We believe this is also true nationwide. Therefore, the indications of malleable penile prostheses are limited. The most likely reason for a patient to choose a malleable implant is the cost of the device or patient's manual dexterity status. Because malleable prostheses require little

manual dexterity, patients with severe arthritis or restrictive hand problems may choose these devices if a willing partner is not available to help operate an inflatable device. Patients with little or no mental ability or with neurological deficits with impaired ability to manipulate the device may also require this type of prostheses. Some surgeons have preferentially used the malleable prostheses for ED associated with Peyronie's disease; however, patient and partner satisfaction has been less than optimal (4,5). Better results have been achieved with inflatable implants (6). The rigid cylinder is considered to be a valuable aid in holding a condom device in place. However, the Ambicor inflatable device is also a good, if not better, choice for this circumstance, because of the more rigid and pronounced glanular end of the cylinder. In fact, we do not recommend semirigid prostheses for patients with neurologic disease who use condom catheters or patients who have lost or have severely decreased penile sensation because these patients are prone to cylinder erosion with these devices. Gross et al. have reported that semirigid prostheses carried a worse outcome in paraplegic men with ED than inflatable prostheses (7).

The placement of the paired rods can be done through a variety of incisions. The most popular surgical approaches today are the penoscrotal and subcoronal because of their simplicity and low risk of injury to dorsal nerve. It is recommended that the length of rods should be about 0.5 cm less than the measured corporal length to provide improved bendability, decreased pain, and less chance of erosion (8,9).

Mentor Malleable

The Mentor malleable prosthesis was introduced into the American market in 1985. This device is composed of a single silver coil covered by a silicone elastomer. It is available in widths of 9.5 mm, 11 mm, and 13 mm. The prosthesis comes in one length, but cylinder lengths between 14–23 cm for the 9.5 mm, 16–25 cm for the 11 mm, and 18–27 cm for the 13 mm, can be created by trimming the proximal portion of the rods and by adding a 1-cm tapered tail cap to produce the desired length for the individual patient. Drawbacks of this version are springback and less optimal bendability. Mentor Corporation is not actively promoting this version because of the availability of Mentor AccuForm.

Mentor AccuForm

To improve the bendability with less springback, Mentor Corporation introduced Mentor AccuForm in 1991 (Fig 1). The only difference between the Mentor Malleable and AccuForm is the configuration of the silver wire. The Accuform rods are comprised of an outer helical wire surrounding a central wire core, which makes the device easier to bend with less springback after bending. This version provides better concealability than the Mentor Malleable does. The device does have a lifetime replacement policy.

AMS 650

In early 1996, American Medical Systems introduced AMS 650 (Fig. 2) to replace its precursor, the AMS 600, which was comprised of a central support of twisted stainless steel wire surrounded by solid silicone. The AMS 650 contains numerous thin strands with a core wire in a spiral configuration, providing easier bending with less springback. It is supplied in the 13-mm width with a trimmable outer jacket that can be removed, leaving a cylinder of 11 mm in diameter. There are three lengths of 12-, 16-,

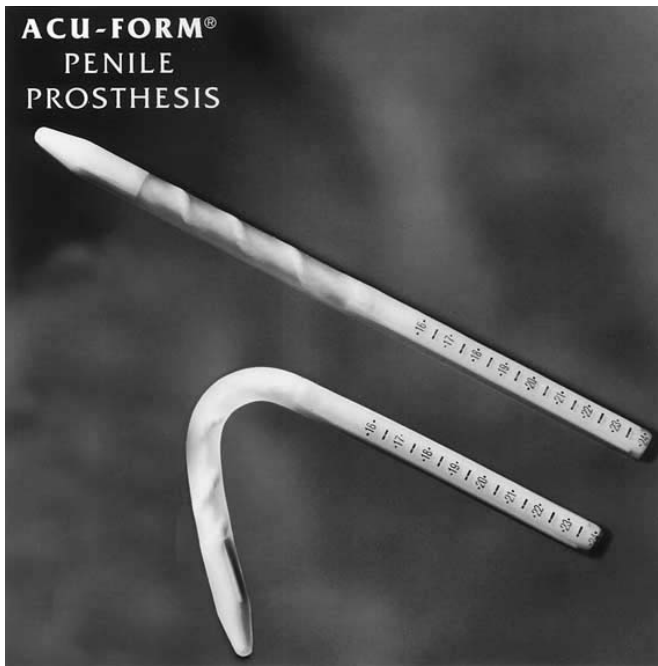


Fig. 1. Pictured is the Mentor Corporation AccuForm first introduced in 1991. Acknowledgment to Mentor Corporation, Santa Barbara, CA, for the photo.

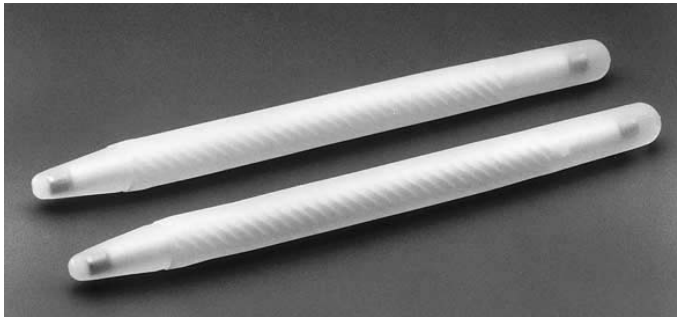


Fig. 2. Shown is the AMS 650 introduced in 1996. Acknowledgment to American Medical Systems Inc., Minnetonka, MN, for the photo.

and 20-cm rods with appropriate rear-tip extenders for accurate length sizing to within 0.5 cm. The durability of this device is very good, with few mechanical problems.

AMS 600M

AMS 600M is a narrower, but more malleable version of AMS 600. AMS is not actively promoting this device; however, some men of small stature may require this



Fig. 3. Pictured is the Dura II introduced in 1993, and currently owned and distributed by Timm Medical Technologies, Eden Prairie, Minnesota. Acknowledgment to Timm Medical Technologies, Eden Prairie, Minnesota, for providing the photograph.

downsized diameter prosthesis. This model is still available in 12-, 14-, 16-, and 18-cm lengths. The diameter of the device can be changed from 11.5 mm to 9.5 mm by stripping the pliable outer silicone sheath.

MECHANICAL PENILE PROSTHESIS

After nearly two decades of evolution, the only mechanical penile prosthesis available in the United States America today is Dura II, which is currently from Timm Medical Technology (Fig. 3). Dura II was introduced to the market in 1993. The durability of Dura II was markedly increased compared to its precursor, the Duraphase, because of the development of body segments made of high-molecular-weight polyethylene and a central cable consisting of stainless steel alloy with 7 wires and 19 strands. The body segments are covered with a polytetrafluoroethylene (Teflon) sleeve, which is then surrounded by a thin silicone membrane to prevent ingrowth of body tissues into the device. A cable fastened by a spring to a fixed post at each end passes through the center of the body segments and holds them together. There are two widths available that are 10 and 12 mm with 13-cm length. Both distal and proximal extenders are available from 1 to 9 cm.

The indications and surgical technique for placement of this device are basically the same as that of malleable penile prosthesis. Because the shortest cylinder available for this device is 15-cm long (13-cm body plus 1-cm distal and proximal extenders), it is not recommended for a patient with a very short penis, or a patient with severe penile scarring from removal of the previous prosthesis (9). Also, patients with a very broad penis may not achieve optimal axial rigidity with this device during vaginal penetration. Some authorities believe that a ventral penile incision is the favored approach to

prevent excessive angulation during insertion that may damage the device (9). However, multicenter clinical evaluation of the Dura II prosthesis revealed that subcoronal approach was used in the majority of patients (51%) without any mechanical damage of the device (10).

Dura II is very easy to manipulate with no springback after bending. There was no mechanical failure reported in a prospective, multicenter clinical evaluation of the Dura II prosthesis after 13.4 ± 8.4 mo follow-up in 196 patients with 85–91% satisfaction rates between 3 mo–2 yr postoperatively (10). This satisfaction rate may or may not change when 5-yr follow-up data is available in this ongoing prospective and multiinstitutional study. Dura II still carries the same drawbacks as the malleable penile prostheses: unnatural erection and inability to change in girth.

UNITARY INFLATABLE PROSTHESIS

Dynaflax self-contained inflatable penile prosthesis was introduced by AMS to the American market in May 1990. AMS is no longer manufacturing this device, therefore, it is discussed only for historical reasons. Like the patients with semirigid rods, patients with the Dynaflax prosthesis can have sexual intercourse with only one cylinder if the other one is not functioning. There were reports that an 88.1% satisfaction rate was obtained with this prosthesis after 50-mo follow-up (11). The Dynaflax device causes tissue expansion with deterioration in rigidity of erection (12). It is the most difficult inflatable prosthesis for patients to operate, with an initial dissatisfaction rate of more than 16% (13). Dynaflax may not provide sufficient rigidity in a large penis or sufficient flaccidity in a short penis. Adequate compression of the distal pump mechanism proves impossible in scarred and fibrotic corpora, even if the device is properly inserted. Successful operation of the inflation and deflation mechanisms of this device requires greater manual dexterity and mental ability than any of the other penile prostheses currently available (11). Therefore, some authorities consider this device to have limited value in the treatment of ED and do not recommend this prosthesis as the first-line option (8). The mechanical failure of this device was 7.5–26.2% in the follow-up of 22–50 mo (11–13).

TWO-PIECE PROSTHESIS

Two-piece prostheses were designed to improve ease of surgical implantation and to obviate the need to place a portion of the prosthesis within the subrectus space. The devices are actually composed of three pieces, two cylinders and one pump. The most common indication for two-piece prostheses is for patients in whom reservoir placement is difficult or contraindicated. These include patients with obliterated retropubic space as a result of previous surgery or radiation and patients with transplanted pelvic kidney. The main drawback of two-piece prostheses is their limited reservoir capacity, which may not provide ideal rigidity in some patients with broad or longer penises, and can be difficult to deflate in patients with small penises. Most authorities recommend a penoscrotal approach for placement of two-piece devices (8,9). We believe an infrapubic incision is superior for the implantation of this type of device. However, AMS recently decided to discontinue the larger tubing between the cylinders and the pump in the Ambicor device, marketing now only a penile-scrotal device. There were two models available in this category in the American market, the Mentor Mark II and the AMS Ambicor.

Mark II

The Mentor Mark II was introduced in 1989. It was decided by Mentor to discontinue manufacturing this device in the middle of the year 2000. This device consists of two Bioflex (a polyurethane polymer) cylinders that are preconnected to a reservoir-pump unit called a “resipump.” Unlike its precursor, Mentor GFS, the resipump of the Mark II is coated with a textured surface to eliminate the excessive periprosthetic capsule formation that may have prohibited full deflation. There is also a self-sealing penetrable port located on the inferior side of the pump for future repeated transcrotal addition of fluid. The Bioflex cylinders are tunical-dependent for limiting their expansion. The cylinder diameters of the larger prostheses are wider than the smaller ones. The cylinder length ranges from 12–22 cm in 2-cm increments with rear-tip extenders of 1–3 cm for accurate adjustment. Only about 15 mL of fluid is delivered from the resipump to cylinders for erection even though the resipump holds 25 cc.

The satisfaction rate with Mark II is very controversial. Satisfaction rate as high as more than 90% in 12–50 mo follow-up and as low as 63% in 4-yr follow-up have been reported (14). Studies showed that the mechanical complication rates were about 5% from 12–50 mo follow-up and 14.45% for a mean follow-up time of 66 mo (15). The resipump of this device is as large as a hen’s egg and may be uncomfortable for patients with a small scrotum. Therefore, this device is not recommended for slightly built men (8). It is necessary to mention that even though Bioflex is stronger than silicone, electrocautery can cause damage to Bioflex, and not to silicone. Mentor Bioflex is safe for electrocautery use with coagulation current at 35 W (16).

Ambicor

The AMS Ambicor was introduced to the American market in 1994 (Fig. 4a and b), 1 yr after this device had been used in other parts of the world. This prefilled closed hydraulic system is similar to a Dynaflex prosthesis; but there is a tiny pump preconnected to the cylinders instead of having the pump located at the end of each cylinder. The device is deflated by bending and holding the cylinders in an angle greater than 55° for 10 s or longer; the same process as deflating the Dynaflex prosthesis. The Ambicor prosthesis is available in 11-, 13-, and 15-mm diameters with even length of 14–18, 16–20, and 18–22 cm for the respective diameters. Again, like Dynaflex prosthesis, more accurate sizing is possible by using adjustable rear-tip extenders in half-centimeter increments. Levine and Morgentaler recently reported a 31.4 mo (range 8–61 mo) follow-up in 92 of 131 patients who had Ambicor prostheses (17). The overall complication rate was 7.6% and infection rate was 2.3%. Ninety-eight percent of patients reported overall satisfaction with the device.

THREE-PIECE PROSTHESIS

It is with the introduction and subsequent refinement and modification of three-piece prostheses that the revolution of the modern surgical treatment for ED occurred. Three-piece prostheses are the most successful prostheses with a high satisfaction rate because they produce the most natural-appearing erection regarding girth and length for satisfactory rigidity and excellent flaccidity for optimal concealment. All patients with ED who are candidates for penile prosthesis implantation should be offered three-piece prostheses unless obvious contraindications can be

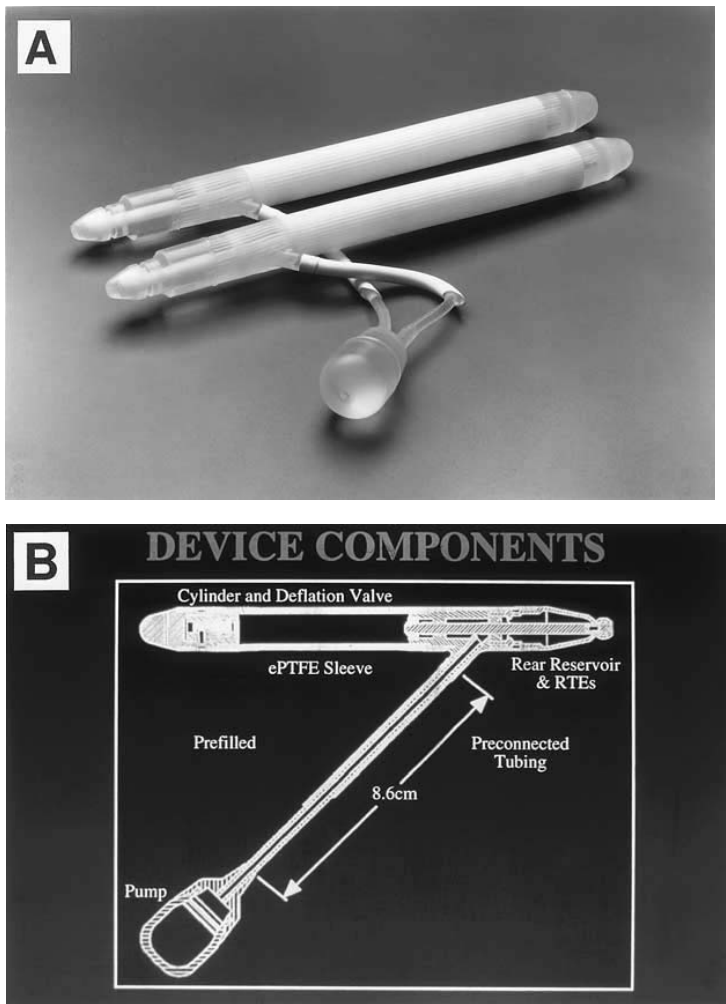


Fig. 4. (a) Pictured is the American Medical Systems Ambicor two-piece penile prosthesis introduced in to the American market in 1994. (b) Diagrammatic representation of the components of the Ambicor two-piece prosthesis. Photos courtesy of American Medical Systems, Inc., Minnetonka, MN.

established. Three-piece prostheses provide the best flaccid status while deflated. This removes the pressure from the corpora cavernosa and decreases the possibility of erosion in those highly difficult implantations. Three-piece prostheses have been recommended as the optimum choice for patients with previous extrusion, infection, severe diabetes or peripheral neuropathy, severe corpus cavernosum fibrosis or reconstruction (18). In patients with Peyronie's disease with persistent curvature after placement of a penile prosthesis, molding over the three-piece device will often eliminate the extreme curvatures (19). Even in patients with obliterated retropubic

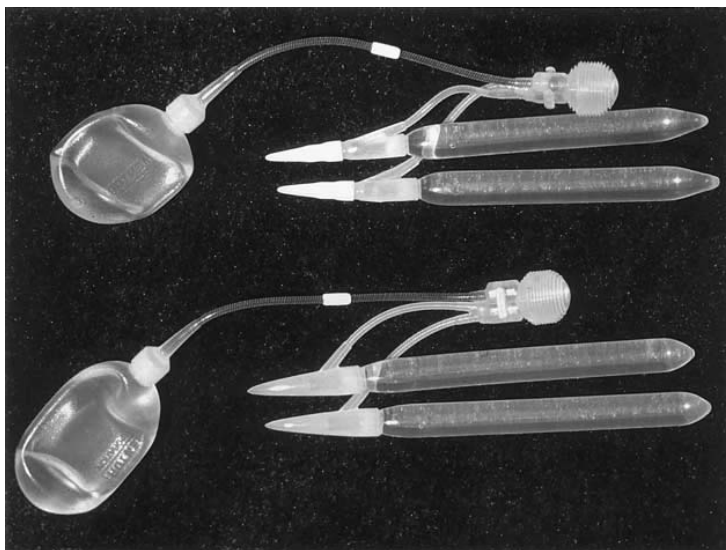


Fig. 5. Pictured are two of the three Mentor three-piece prostheses. At the top is the Mentor Alpha 1 narrow base and at the bottom of the photo is Mentor Alpha 1.

space as a result of previous surgery, the reservoir of three-piece prostheses can still be placed carefully under direct vision. Patients with impaired manual dexterity and patients with little or no mental ability or with neurological deficits with impaired ability to manipulate the device can still have three piece prostheses if a willing partner is available to assist the patient for inflation and deflation. Patients with history of external beam radiation for prostate cancer can also have three-piece prostheses for their ED without increased complications (20). Simultaneous placement of penile prostheses with three-piece devices for patients who are undergoing radical prostatectomy has been reported with encouraging results (21). There was also a case report in which a three-piece prosthesis was used to treat intractable priapism with very good results (22).

All three-piece prostheses consist of paired cylinders, a scrotal pump, and a pelvic reservoir. The system generally is filled with normal saline even though radio-opaque contrast used to be the popular filling solution. There is no silicone gel contained in penile prostheses (23). The implantation of three-piece prostheses can be done through infrapubic or penoscrotal incision. It has been reported that infection rates were not different when scrotal or infrapubic surgical approaches were used (24). The three-piece prostheses currently available from American Medical System are the AMS 700 CX, 700CXM, 700 Ultrex, and 700 Ultrex Plus; and from Mentor Corporation as Mentor Alpha 1, Alpha 1 Narrow-Base, and Alpha 1 with lock-out valve.

Alpha 1

Mentor Alpha 1 has been commercially available since 1990 (Fig. 5). The prosthetic cylinders of this device are constructed of Bioflex material (a polyurethane polymer)

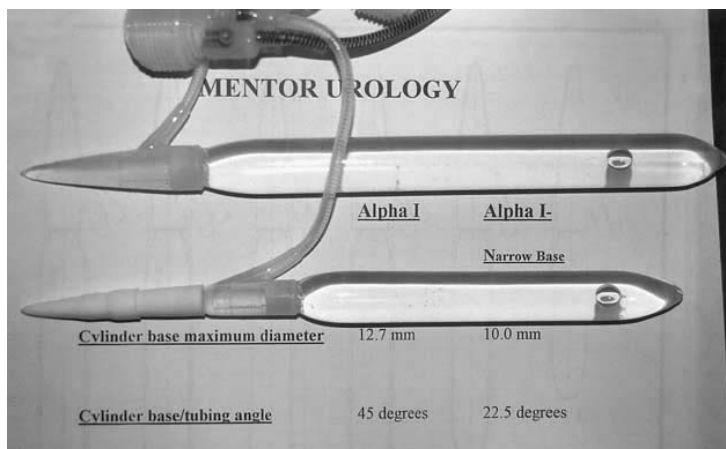


Fig. 6. The difference in the cylinder size design rear tip extenders and cylinder base tubing angle is demonstrated in this photo of the Alpha 1 and Alpha 1 narrow base Mentor three-piece penile prostheses.

which expands to 20 mm (or slightly greater) in girth without axial elongation. Bioflex cylinders have proven to be very durable, but prone to electrothermal injury, so care must be taken when using electrocautery. (See discussion of Mark II.) This device has only one connection between the pump and reservoir, whereas its precursor, Mentor inflatable penile prosthesis, had three connections. Enhancement of the Mentor Alpha 1 was made in 1992 to lengthen the tubing and to reinforce the tubing at the exit from the pump. This device is very reliable mechanically. Wilson et al. reported the 92.6% 5-yr survival rate of this enhanced model with a device failure rate of 0.8% yr for the first 3.5 yr and 3.1% yr thereafter (25). The cylinder length of Mentor Alpha 1 prosthesis is available from 12–22 cm in 2-cm increments. Accurate sizing is possible by using 1–3-cm adjustable rear-tip extenders. There are two tubing lengths with the short one for penoscrotal incision and longer one for infrapubic insertion. The capacities of the textured reservoir are 60, 75, 100, and 125 mL.

Alpha 1 Narrow Base

Mentor introduced the Alpha 1 Narrow-Base prosthesis for patients with narrow corpora in May of 1996 (Fig. 6). Compared with the standard Alpha 1 prosthesis, the narrow-base device has a 2-mm smaller cylinder with a maximum diameter of 10 mm for the cylinder base vs 12.7 mm for the standard version. The maximum diameter for the rear-tip extenders of the narrow-base device is 9 mm vs 12.7 mm for the standard version. The cylinder tubing exit angle of the narrow-base device is 25.5° vs 45° for the standard version. The anatomical tip (a frusto-conical tip shape) is designed to support the glans penis better than the radial tip. In our experience, this device has been very useful for patients with stenotic corpora secondary to corporal fibrosis.

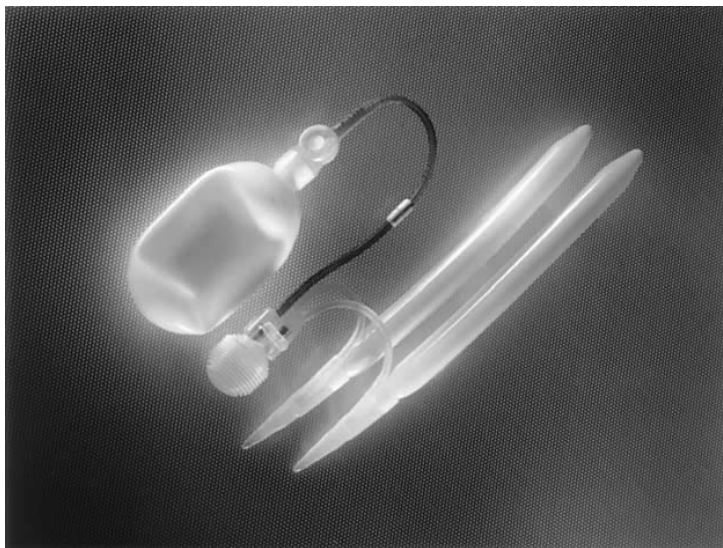


Fig. 7. Pictured is the Alpha 1 with lock-out valve recently introduced by Mentor Corporation in January 2000. Photo provided by Mentor Corporation, Santa Barbara, CA.

Alpha 1 with Lock-Out Valve

In January 2000, Mentor launched an enhanced reservoir with lock-out valve for Alpha 1 prosthesis (Fig. 7). The pressure responsive lock-out valve is designed to prevent auto inflation by inhibiting fluid transfer from the reservoir when not under demand by the pump. The lock-out valve is actually incorporated into the reservoir. Patients do not need to activate this lock-out valve because no interaction is required for the lock-out to perform its designed function. The preliminary studies have demonstrated that this new design significantly diminished the prevalence and severity of autoinflation (26,27). However, long-term follow-up studies are necessary to provide certainty.

700 CX

The AMS 700CX prosthesis was introduced to the market in 1987 (Fig. 8). The cylinders of the 700CX are three-ply construction with a sandwich-type fashion. Two silicone layers are sandwiched around a woven fabric (90% polyethylene and 10% polyurethane, Dacron mesh) that controls girth expansion from 12 mm to 18 mm. The inner silicone chamber is inflated with fluid for erection. The outer layer of silicone prevents tissue ingrowth into the fabric layer. The device comes in lengths of 12, 15, 18, and 21 cm, with 1-, 2-, and 3-cm rear-tip extenders. The 65-cc reservoir is appropriate for all lengths of cylinders. The latest model is incorporated with the prefilled pump that has been preconnected to prefilled cylinders (Fig. 9) There are two tubing lengths available, with the shorter one intended for penoscrotal implantation and the longer length for infrapubic insertion.



Fig. 8. Pictured is the AMS 700 CX prosthesis (left) along side a Mentor Alpha 1 penile prosthesis.



Fig. 9. Pictured is the new AMS 700 CX pre-connected penile prosthesis recently introduced in the year 2000. Photo courtesy of American Medical Systems, Inc., Minnetonka, MN.

The introduction of 700CX cylinders propelled AMS into the modern era of reliability. Daitch had shown that the mechanical failures of the CX and CXM model was 9.0% with significantly decreased chance of aneurysm formation after a 47.2-mo follow-up (28). This device has been considered the most versatile AMS product for use in all types of patients without contraindications for three-piece prostheses. Most importantly, the cylinders have been proven ideal for patients having had previous penile surgery and previous implants, as chances for aneurysm formation are significantly decreased (8,28,29).

700 CXM

The 700 CXM (controlled expansion, modified) was introduced in 1990 for patients with narrow corpora. This downsized model is also very useful in patients with corporal fibrosis because of priapism or previous removal of infected devices, and patients with severe Peyronie's diseases. The construction design of this device is identical to the 700 CX, except the downsized cylinders with diameter expansion from 9.5 mm to 14.5 mm. The device is available in lengths of 12, 14, 16, and 18 cm, with 1- and 2-cm rear-tip extenders. The reservoir of 50 cc is sufficient for all cylinder lengths. The pump is also smaller, which fits well into the scarred or smaller scrotum; but this also makes it difficult to grasp and has a smaller stroke volume (8,14).

700 Ultrex

AMS introduced 700 Ultrex cylinders in 1990. In this device, the middle layer of Lycra (polyurethane woven into polyethylene in two directions) provides cylinders with expansion in girth and length when stretched. The cylinder lengths can be increased up to 20% upon complete inflation with a maximum diameter of 18 mm. Like the 700 CX, the 700 Ultrex comes with the same available lengths, rear-tip extenders, and connectors. The 100-cc reservoir is needed for the 18- and 21-cm cylinders to ensure the maximum inflation.

Even though AMS does not claim that the 700 Ultrex increases the penile length, some clinicians still have the perception that this device provides better or more natural erection because of the longitudinal expansion. Holloway et al. reported 85% patients' satisfaction rate and 85% durability and reliability of the devices from their 42-mo follow-up (30). However, use of AMS 700 Ultrex with a hope of length enhancement after implantation has been disappointing (28). Increased S-shaped deformity and mechanical failure such as aneurysmal defect of the cylinder were also reported as compared to the 700 CX version (28,29).

700 Ultrex Plus

The AMS 700 Ultrex Plus was introduced in 1992 (Fig. 10). The only difference from 700 Ultrex is that 700 Ultrex Plus features a prefilled pump that has been preconnected to prefilled cylinders. Only the reservoir requires filling and only one connection is needed during the surgery. There are two tubing lengths available, with the shorter one intended for penoscrotal implantation and the longer length for infrapubic insertion. AMS collected the data from medical records of 155 patients from multiple centers and claimed that 90% of the patients remained free from revision or replacement surgery for 2 yr after implantation (8). However, to the best of our knowledge, there has been no published long-term follow-up data in the literature to evaluate its satisfactory rate, reliability, and longevity.



Fig. 10. Pictured is the AMS 700 Ultrex Plus penile prosthesis. Photo courtesy of American Medical Systems, Inc., Minnetonka, MN.

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16

Penile Implant Complications

Prevention and Management

John J. Mulcahy, MD, PhD

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INTRODUCTION

The availability of effective oral medication for the treatment of erectile dysfunction (ED) has dramatically increased awareness of this common problem and encouraged many people to seek treatment. As a result, the marketplace has ballooned many fold in the past few years. There are subgroups of patients who do not respond well to oral therapy; these include patients with severe diabetes mellitus with neuropathy, those in whom nonnerve sparing radical prostatectomy has been performed, and patients with severe venous leakage. Many have turned to alternative therapies including penile implants and according to vendors of these devices in the United States, sales are as good as ever. The mechanical reliability of implants is good with repairs rates in the range from 10 to 20% at 5 yr. There have been few changes in the construction and design of these products in the last decade, indicating that physicians and manufacturers are pleased with the current models, however, problems with these devices can occur. These may be related to mechanical breakdown of the synthetic material, to wearing through body cavities containing prosthesis parts, or to the development of infection associated with prosthetic parts. Experience with these complications has expanded and gratifying results can now be achieved with proper management.

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PREOPERATIVE DISCUSSION

Before a surgical implant of a penile prosthesis is undertaken, the patient should have a thorough understanding of alternative treatments and the purpose and limitations of the device. Whenever possible, the partner should also be included in these discussions. This would help dispel unrealistic expectations and provide information that will hopefully contribute to a more gratifying outcome. The most common reason for disappointment with the result after penile prosthesis implantation is penile size. When a cylinder is placed, a sheath of scar tissue develops as the body's reaction to healing around the cylinder. This sheath is nonexpansible and the scar tissue created will eventually contract with time. The size of the penis is usually 1–2 cm smaller than the original erection, although the change in size following surgery is unpredictable. The need for repair of the device should also be mentioned. This may be because of mechanical breakdown of the parts, disruption of body cavities with extrusion of parts, or the development of infection. It should also be mentioned that the function of the prosthesis is to provide a penis that can be inflated to good rigidity and deflated to flaccidity, or can be bent upward for erection and downward for urination and concealment. Surgery to implant the device does not usually affect sensation, libido, or the ability to ejaculate. The pain associated with prosthesis placement is usually more prolonged than the pain associated with a surgery of comparable degree, such as herniorrhaphy or appendectomy. This pain usually lasts 3–4 wk and patients may find it uncomfortable to pump the device or use the prosthesis before 6 wk. The physician should guide the patient in his choice of a particular prosthesis. The best rigidity and flaccidity are provided by the three-piece inflatable models. Patients with an especially long and broad penis would be best served by selecting one of these types. Other models may give less optimal rigidity under these circumstances. Patients with limited strength or manual dexterity or whose ability to operate the inflation–deflation mechanism is not at full capacity would be better served with a semirigid-type device. To implant an inflatable device in such patients would only lead to frustration with its operation.

SURGICAL PROCEDURE

The two standard approaches for placement of a penile prosthesis are the infrapubic and penoscrotal. The ventral penile approach, which is a modification of the penoscrotal, is very convenient for placement of semirigid rod prostheses and the devices can be readily placed under local anesthesia using this approach (1). The disadvantage of the penoscrotal approach is the blind placement of the prosthesis reservoir when a three-piece device is used. With the infrapubic approach, one must be careful of the nerves to the glans that run in the dorsal neurovascular bundle. During dilation of the corporal bodies, the dilation tools should be passed with caution with attention to the appropriate direction of the dilating instrument tips and amount of pressure exerted. Perforation can occur proximally, distally, or through the intercavernous septum, especially in cases of scarred corporal bodies. If proximal perforation occurs with a small dilator, i.e., size 9 Hegar, one should then proceed immediately to the largest dilator, i.e., size 12. If a large proximal perforation has occurred and a rod prosthesis is to be inserted, then a synthetic windsock can be fashioned around the proximal portion of the prosthesis to prevent its migration through the defect (2). If this is not done, then the rod prosthesis will migrate through the perforation site and be palpable in the buttocks. If

this perforation occurs during implantation of inflatable devices, the input tube will prevent proximal migration through this proximal opening. If distal perforation into the urethra occurs, it is impossible to close. This is usually in the area of the fossa navicularis and great disfigurement of the penis would occur in an attempt to repair this. One should implant the cylinder on the opposite nonperforated side and return in 2 mo for placement of a cylinder on the side where the perforation has occurred. If the urethra is entered at the level of the corporotomy, and if there is adequate tissue to close this opening, an attempt may be made to repair such an injury with at least two layers of tissue. However, if such a secure closure is not possible, the cylinder should be left out with return at a later date for reimplantation. Washing of the wound with antibiotic, betadine, and hydrogen peroxide solutions should also be carried out as it is not certain whether that portion of the urethra is sterile. An unusual circumstance during the operative procedure is crural crossover. This may sometimes occur in scarred cavities and is manifest most frequently as a difference in the measured size of the cylinders to be inserted, tilting of the glans to one side, or asymmetry of the penis, i.e., it looks fuller on one side. This is best handled at the time of surgery rather than being brought to the physician's attention by the patient in the postoperative period. To remedy the situation, one places a dilator into the cavity once occupied by both cylinders and then redilates the opposite side at the same time that the dilator is in place. Autoinflation of inflatable devices was the rule in the postoperative period until Mentor Corporation recently introduced a reservoir containing a lockout valve to prevent this problem. If a prosthesis without a lockout valve is employed, one can place a volume of fluid slightly less than the reservoir capacity to help minimize this problem. One should also make sure that the space containing the reservoir is adequate and that the reservoir is not compressed. In patients who have had radical prostatectomy or other pelvic surgery, the reservoir may be shaped more like a pancake rather than a sphere if the reservoir cavity is not adequate. Prior to connecting the reservoir to the system, one should also be sure that there is no back pressure or tendency to push fluid into a syringe placed on the reservoir tubing. If the pelvis is very scarred, one can place the reservoir intraperitoneally or out of the pelvis in the epigastric area where the reservoir cavity is not restrictive. Erosion of the reservoir into the bladder has been seen when it is placed in the cavity adjacent to the bladder under excessive pressure. If an intraabdominal reservoir is placed under tension against a portion of bowel, erosion into this viscus may also occur.

INFECTION

Infection associated with a penile prosthesis can be a devastating problem. The usual source of contamination is the operative wound. The skin harbors numerous organisms and care in cleansing of the skin prior to surgery is of paramount importance. The most common organism associated with a penile implant infection is staphylococcus epidermidis, a common skin inhabitant. Other organisms have been implicated and these are usually less-aggressive pathogens. However, very aggressive organisms, such as methicillin-resistant staphylococcus aureus or *Pseudomonas aeruginosa* have been associated with penile prosthesis infections. Fortunately, the incidence of implant-associated infection is low, in the range of 1–3% of cases (3). The incidence of infection with secondary or tertiary procedures is noted to be higher (4) and there have been reports of seeding of the device with infection originating in other parts of the body, i.e., during

dental procedures (5). However, this is extremely unusual. Persistent pain over parts of the implant is a common sign that infection may be starting. If this is associated with cellulitis, fever, and chills, then infection is certainly suspect. Increasing fixation of parts, especially the pump to the scrotal wall, is a sign of infection developing. Any purulent drainage from the wound, especially if it is increased upon pressing on prosthesis parts, would necessitate exploring the wound. To reduce the likelihood of an infection, one should be very careful in cleansing the skin preoperatively. Any comedones or other skin sites that may harbor pathogenic bacteria should be eradicated prior to surgery. Thorough cleansing of the skin for a number of days prior to surgery with a strong antiseptic soap is recommended. Hair at the operative site is shaved in the operating room and many urologists recommend the use of prophylactic antibiotics in the perioperative period. If antibiotics are to be used, they are usually started 1 h prior to surgery and continued for 48 h after the procedure. This allows good tissue levels at the time the wound is open and until the wound has sealed. Perhaps more important is the use of frequent irrigations during the surgical procedure. Antibiotics can be added to the irrigating solution to further reduce the chance of infection occurring. Vancomycin is very effective against staphylococcus epidermidis and other gram positive organisms. Gentamicin or another aminoglycoside is effective against gram negatives. A combination of these two can certainly be used empirically when an infection is suspect. Some physicians will use this combination prophylactically, but the chance of resistance developing against vancomycin with such an approach is remote but real, therefore others frown on its prophylactic use. A third generation cephalosporin, such as ceftriaxone would be a reasonable alternative for prophylactic antibacterial use.

If an infection is present and associated with a penile prosthesis, use of systemic antibacterials alone will not eradicate the infection. The body has created a cavity around the prosthesis composed of fibrotic tissue relatively low in blood supply. In addition, many bacteria produce a biofilm or slime that surrounds the prosthesis and prevents diffusion of nutrients and antibacterials to the area where organisms are present (6). Hence, the ability of antibacterials to penetrate the site of infection is markedly reduced. To eradicate a prosthesis infection, the entire device, including all foreign materials such as suture or synthetic grafts, must be removed. The traditional approach has been to return at a later date, perhaps in 6 mo after the infection has been cleared and the edema has subsided, to insert a new prosthesis. However, contracture of the scar that has formed has occurred with noticeable shortening of the erection in the range of 2 in. In addition, with scar tissue forming in the corpora cavernosa, it will be difficult to reinsert prosthesis cylinders in these circumstances. Returning to insert a prosthesis in a shorter time period, within 6–8 wk after prosthesis infection, will result in less penile shortening and somewhat easier cavernosal dilation. However, an alternative approach, termed a salvage or rescue procedure, involves removal of the prosthesis and all foreign material, cleansing the wound with a series of antiseptic solutions, and reinserting the prosthesis at the same sitting. A recent series of 55 patients showed that this procedure was successful in 45 of these (82%) (7). The protocol used in this series involves the removal of all prosthetic parts and foreign materials such as suture or synthetic material used for cavernosal reconstruction. The wound is then cleansed with a series of seven antiseptic solutions listed in Table 1. After the cleansing irrigations have been completed, the operative site is changed, i.e., new drapes, gowns, gloves, cautery instruments, and suction are placed around the wound, and a new prosthesis is inserted.

Table 1
Irrigating Solutions Used with Salvage Procedure

-
1) Antibiotic solution	
2) One-half strength hydrogen peroxide	
3) One-half strength Betadine	
4) Pressure washing with 1 gm Vancomycin and 80 mg Gentamicin in 5-L irrigation bag	
5) One-half strength Betadine	
6) One-half strength hydrogen peroxide	
7) Antibiotic solution	
-

The purpose of the salvage procedure is to maintain as much penile length as possible and to allow for an easier cylinder insertion. Many patients who have had an implant removed do not return for reinsertion even though they were desirous of continuing sexual activity by undergoing placement of the original implant. For those who return, the satisfaction rate with the reimplanted device is no where near what it was with the initial device, mainly because of the considerably shorter size of the penis.

Betadine is 99% bactericidal, hydrogen peroxide is effective at eradicating anaerobic organisms, and pressure washing of the wound helps to loosen and flush away the slime or biofilm that is frequently associated with these infections. In those cases where salvage has been unsuccessful, the organism has usually been more aggressive, such as methicillin-resistant staphylococcus aureus or *Pseudomonas aeruginosa*, the infection has occurred very shortly after placement of the penile prosthesis, perhaps within a week or two, and the tissue surrounding the implant is involved with considerable cellulitis. It might be prudent in such cases not to rely on salvage alone for eradicating the infection. In two such cases that were recently encountered where the infection has been associated with a virulent organism occurring shortly after implantation and associated with considerable cellulitis, success was achieved by:

1. Placing the patient in the hospital initially.
2. Draining the phlegmon.
3. Starting the patient on vancomycin and gentamicin, ascertaining in 48 h that one or both of these antibiotics were effective against eradicating the particular organism.
4. Continuing the antibiotics for another 24 h for a total of 72 h.
5. Performing a salvage procedure.

The salvage procedure itself will sterilize the cavity containing the prosthesis, but if an infection is present in the tissues, these organisms are not eradicated. Using appropriate systemic antibacterials to eradicate tissue infection, combined with salvage procedure to eradicate the cavity, has resulted in a successful outcome in both of these cases with more than 1 yr of follow-up. The patient should be advised of the alternatives of removal of the prosthesis vs a salvage procedure and make the final decision.

Salvage has not been considered in cases of tissue necrosis, ketoacidosis, and sepsis. One should also proceed cautiously with such a procedure in the immunocompromised patient. If a decision is made to remove the prosthesis and not perform a salvage procedure, and there is purulence in the corporal bodies, success has been achieved in eradicating infection by placing irrigation drains in these cavities (8). The wound is then irrigated every 8 h with vancomycin/gentamicin solution. If these antibiotics are appropriate when

culture reports are available in 48 h, the antibiotics are then continued for another day and the drains removed. This maneuver has been successful in eradicating infections in these closed cavities. The alternative, to fillet the wound and to allow granulation to occur by secondary closure, has been associated with considerable morbidity and scarring. Closing the wound over these irrigation drains has given satisfactory results.

PENILE CURVATURE

Peyronie's disease is a common indication for placement of a penile implant. When sildenafil is not successful in producing firm erections, the implant tends to straighten as well as strengthen the erection. Trauma to the penis or penile fracture also results in scar tissue deposited in the tunica albuginea of the corpora cavernosa, which results in curve upon inflation of the hydraulic implants. Whenever scar tissue is present in the penis, the distally expanding type of hydraulic implant (AMS-700 Ultrex) should not be used (9). Exaggeration of the curvature has been seen with this prosthesis. Other hydraulic implants can be used and the mere inflation of the implant will many times straighten the erection satisfactorily. If there is still curvature present despite inflation of the cylinders, the initial maneuver to straighten the penis is termed "modeling." This was popularized by Wilson et al. and consists of bending the penis in an exaggerated fashion away from the side of the curvature and holding the penis in the bent position for 90 s (10). The tubing to the cylinders should be clamped to protect the pump from damage as a result of excessive back pressure during this maneuver. This should be done after the corporotomy has been closed, and following this maneuver, the corporotomy should be checked because modeling will occasionally result in corporotomy disruption. Urethral disruption usually in the fossa navicularis has rarely been seen with this manipulation. If the initial modeling maneuver is not satisfactory, the modeling or exaggerated bending of the penis may be repeated. If modeling is not successful in satisfactorily straightening the erect penis, one may then incise the concave surface of the curve using the electrocautery down to the cylinders. Care must be taken when the bioflex material of the Mentor device is used as the cautery on settings above 35 W may injure this material (11). Multiple small incisions on the concave surface may be made or one relatively large incision may be made. If the incision is on the dorsal surface, the dorsal neurovascular bundle should be elevated to protect sensation to the glans. If it is on the ventral surface, the corpus spongiosum should be mobilized to allow access to the tunica Albuginea under this structure. Once the incision is made, the cylinders are then inflated and straightening is achieved. If the defect is small or multiple small incisions have been made, the cylinders can be left partially inflated in the postoperative period until fibrosis has occurred, bridging the gaps in the wound. If the defect is large, a graft can be inserted to bridge the gap and to assure hemostasis (Fig. 1). This is the favored maneuver and material such as Gortex or Dacron sewn in place with permanent soft sutures has worked well. Recently, natural materials such as cadaver pericardium or small intestinal submucosa have been used satisfactorily as graft material. These can be sewn in place with long-term absorbable suture and the imbibition time for these materials is somewhat prolonged, i.e., about 3 mo. This would entail that the prosthesis be kept partially inflated for this period of time with periodic deflation to prevent encapsulation of the reservoir in the collapsed state. An alternative procedure to plaque incision and graft interposition would be a variation of the Nesbit procedure (12). Using this technique, small elliptical wedges of tunica albuginea of the corpus cavernosum are removed from the convex or outer surface



Fig. 1. Goretex patch placed over penile implant cylinders and sewn to edges of the Tunica albuginea of The Corpora Cavernosa after 180° dorsal incision of the tunica albuginea to straighten a dorsal curvature. Dorsal neurovascular bundle preserved.

of the curve. The defect created is closed using long-term absorbable suture. Combinations of the graft interposition, as well as a Nesbit procedure, have been used satisfactorily. After cylinder insertion has occurred and curve correction accomplished, there may be a residual waist or indentation of the tunica upon inflation of the cylinders. With time, many of these hourglass-type deformities have resolved, i.e., the penis stretching the scar with inflation of the cylinders, the waist has disappeared. If one is concerned that this may not resolve with time, the tunica at the site of the waist can be incised longitudinally and a graft material placed to eliminate this deformity.

FIBROTIC CORPORA

Inserting an implant into scarred corporal bodies can be a challenge. In these circumstances, spongy tissue is less readily available for easy proximal and distal dilation, or the corporal body may be totally replaced with scar tissue. The situation is commonly seen with secondary insertion of an implant where the first implant has been previously removed because of infection or erosion. Following priapism, corporal abscess, or severe penile trauma, scarring of the corporal bodies may be complete. The initial maneuver is to create a cavity proximally to the ischial tuberosities and distally to the glans penis. This is more easily accomplished with a virgin corporotomy site, i.e., a corporotomy is made in an area not yet violated surgically. In this location, there is the best chance of finding spongy tissue through which the dilating scissors may be easily passed. The Metzenbaum scissors are passed carefully in a spreading and cutting motion with the scissors tips pointing away from the urethra. If a point of impassable obstruction is met when progressing distally, a second corporotomy may be made in the subcoronal area and dilation accomplished proximally. Once the cavity is made to the ischial tuberosities

and to the glans penis, the cavity can be broadened by a number of different maneuvers. Simple Hagar dilation is sometimes impossible because of the dense scar tissue present. Using narrow cylinders in these circumstances will give equally good rigidity as broad cylinders. It will also be easy to insert the narrow cylinders (AMS-700 CXM or Mentor Narrow Base). One may use the Otis urethrotome, which was originally designed to incise urethral strictures blindly. If this device is used, it is placed as far proximally or distally as possible, the cutting blade positioned away from the urethra, and the dial turned as far up as it will go. The tissue is then sharply incised. The cutting blade is then rotated about 15° and a second cut made into the scarred tunica. A third cut may be necessary, again rotating the device about 15° from the previous cut. Rotating the blade before each cut tends to thin out the scar in the tunica rather than cutting through the tunica albuginea. A Dilamesinsert may also be used, but it is sometimes difficult to insert this device into extremely tight scar tissue. The Rossello caveronotomes now come in a narrow width and can be used to shave the scarred corporal body similar to a wood rasp. The Uramix caveronotomes are also useful in these circumstances (13). They have a blunt tip and a blade that arises from the longitudinal surface of the caveronotome slightly higher than the body of the metal dilator. Using an oscillating motion, this blade can be used to shave corporal tissue. Another maneuver to broaden the caliber of scarred corporal bodies is to sharply excise scarred tissue. This, many times, necessitates an extensive corporotomy and is useful in the region where the corporotomy is placed and the scar tissue is readily seen. Whenever one is attempting to dilate scarred corporal bodies, a Foley catheter in place as a guide to the location of the urethra will be very helpful in avoiding damage to this structure or inadvertently incising into its lumen. Another option that is used less commonly is a technique originally described as cavernosal reconstruction (14). Using this technique, a long corporotomy is made and the scar tissue is incised deeply. The prosthesis cylinder is laid into the corporal cavity, and, if the edges are unable to be approximated over the prosthesis, graft material (either synthetic or natural), may be used to cover the defect. Originally, Gortex or dacron was used and a permanent suture used to secure the graft material to the edges of the tunica albuginea or associated scar. Now, synthetic material such as cadaver pericardium or small intestinal submucosa can be used successfully as well. The advantage of the latter material is that absorbable suture can be used and the presence of another synthetic foreign body is avoided. If the corporal bodies are totally obliterated proximally, a windsock can be created and placed around the input tube of an inflatable prosthesis. These can then be sewn to the periostum of the ischial pubic ramus to give moorings to the proximal portion of the prosthesis mimicking the function which the crura once provided (Fig. 2).

DISTAL PROBLEMS

Erosion of the prosthesis cylinder through the end of the corporal body is not an uncommon phenomenon. This may be caused by over-zealous dilation, aggressive use of the device, or overinflation of the AMS-700 Ultrex prosthesis, which has the ability to expand distally, as well as in girth. This may occur in two locations: into the glans where it appears that the cylinder is about to wear through the end of the penis or into the fossa navicularis, or laterally where it looks as though the cylinder tip resembles a sphere during intercourse digging into the wall of the vagina. In the former situation where urethral or distal erosion seems imminent, a hemircumcising incision is made on the side of the problem. A longitudinal corporotomy is made over the end of the

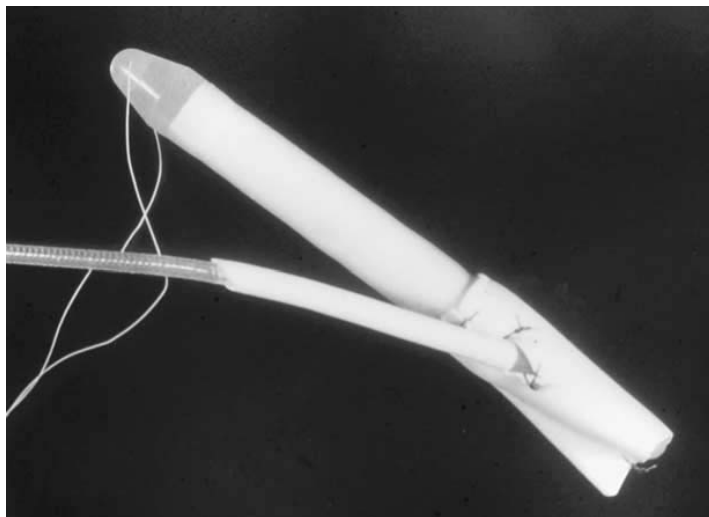


Fig. 2. Cup of Goretex fastened around the proximal end of a penile prosthesis cylinder. Tab is sewn to periosteum of the ischio pubic ramus.

prosthesis cylinder. The cylinder is removed, and if one palpates distally, one can feel a ring where the end of the corporal body once existed. A permanent soft suture is then used to close that hole in a figure-8 or purse-string fashion. The cylinder is then replaced into the corporal body and the distal portion of the corporotomy is closed. In the second circumstance, when lateral protrusion under the foreskin has occurred, one again makes a hemicircumcising incision over the end of the cylinder tip (15). A corporotomy is then made to about the midshaft over the lateral portion of the cylinder. The cylinder is then removed or retracted inferiorly. A transverse incision is made at the midshaft of the penis into the back wall of the sheath that contained the cylinder (Fig. 3). Using Metzenbaum scissors, a new plane is developed behind the sheath that contained the prosthesis cylinder. Metzenbaum scissors and Hagar dilators are used to develop this cavity. With a hydraulic prosthesis, a suture is then placed through the end of the prosthesis and using a delivery tool such as the Furlow introducer, the cylinder is then placed into this new cavity behind the back wall of the sheath that originally contained the prosthesis cylinder. The proximal portion of the corporotomy is then closed over the cylinder and the outer walls of the sheath are then closed over the inner wall thus providing a double wall of protection against recurrence of the lateral extrusion of the cylinder. If the cylinder has already eroded into the urethra, removal of the cylinder should be performed. The remainder of the device can be removed and a salvage procedure performed with reinsertion of a cylinder on the noneroded side. If the cylinder has eroded laterally to the exterior, a distal corporoplasty, as just described, can be performed in conjunction with a salvage procedure. Following either form of distal corporoplasty, a hypermobile glans may be found. This may also be seen when the glans is excessively lax on the ends of the corporal bodies. If such is the case, it may interfere with penetration during intercourse as the glans may be flexed excessively dorsally or



Fig. 3. Incision line on the back wall of the sheath, that contained the extruded prosthesis cylinder. A new cavity for the cylinder is created behind the sheath through this incision.

ventrally over the ends of the cylinders. One can remedy this situation by fixing the glans securely against the ends of the corporal bodies. A circumcising incision is made, either dorsally or ventrally, or around the entire shaft of the penis. The glans has been dissected partially off the ends of the cylinders. A nonabsorbable suture is then placed into the glans substance and into the tunica albuginea of the corpus cavernosum over the tip of the cylinder (16). This can be done dorsally, ventrally, or laterally, depending on the direction of the excessive glans mobility. If ventral glans fixation is performed, care should be taken to avoid injuring the corpus spongiosum. If dorsal fixation is to be undertaken, one should place the sutures lateral to the dorsal neurovascular bundle. One should not mistake a hypermobile glans for cylinders which are too short. This can be determined by pulling the ends of the corporal bodies away from the ends of the cylinders. If excessive redundancy of the corporal body is noted, larger cylinders or longer rear-tip extenders should be added to bridge the gap in cylinder length. This will also give additional length to the penis, a feature desired by most men.

PENILE NECROSIS

Necrosis or loss of a portion of the glans or shaft of the penis as a result of death of tissue is fortunately a very unusual condition (17). The situation results from a diminished blood flow to the corpus spongiosum or portions of the corpora cavernosa. There is no way to predict who will develop this problem but patients with poor peripheral vascularity to begin with are certainly more prone. To help avoid this problem, attention should be made during the operative procedure to using maneuvers which would tend to promote good distal vascularity. Longitudinal incisions on the shaft of the penis are preferable to circumferential. Use of a catheter for an extended period of time should be avoided. Compression dressings on the shaft of the penis to reduce edema or exces-

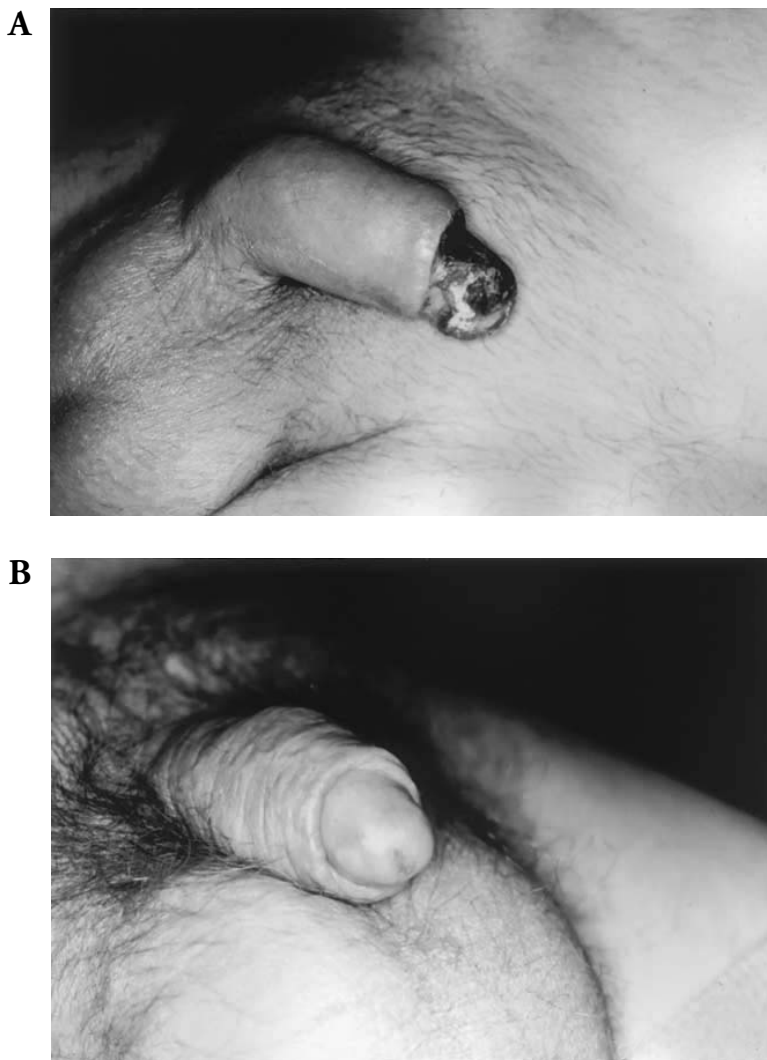


Fig. 4. A. Necrosis of the glans penis 3 wk after placement of a penile prosthesis. **B.** Healing of glans at 3 mo after prompt removal of the implant and superficial slough and debridement of necrotic tissue.

sive hemorrhage can contribute to this problem as blood to the end of the penis comes only from the proximal end. Proper sizing of cylinders is of paramount importance and one should err on the side of being slightly too short rather than slightly too long. Inflating the cylinders to maximum for prolonged periods of time should also be avoided.

When necrosis is obvious, the implant should be removed. Any associated infection should be treated aggressively and necrotic tissue should be debrided carefully (Fig. 4). The end of the penis should not automatically be amputated and an attempt should be

made to salvage any viable tissue that is present. Even irregular portions of tissue may be used for future reconstructive purposes. A suprapubic catheter should be placed to avoid any pressure of an indwelling urethral catheter while the process is in evolution. Hyperbaric oxygen has been recommended under these circumstances, but it provides only transient improvement in tissue oxygenation. Because the problem is poor distal blood flow, reduced oxygenation will return once the hyperbaric oxygen has been stopped. Heat and peripheral vasodilators may be helpful in improving the distal perfusion of the penis.

CONCLUSION

As physicians gain experience in the implantation of prostheses and management of problems that may arise, they develop more confidence in managing these adverse situations. The ultimate goal is to restore the patient to a satisfactory erectile state. Once a penile prosthesis has been placed, the only satisfactory method of maintaining the patient's erections is with a penile prosthesis. Every attempt should be made to remedy an unfavorable situation to give the patient a functioning implant. The patient chose an implant in the first place because this was the desired method of managing his problem or alternative methods were not effective. The highest satisfaction rate among all treatments for ED with both patients and partners has been the penile implant (18). More than 80% of patients and partners are gratified with the results of this product. Employing the techniques and approaches as aforementioned can help avoid some of the problems that may develop and hopefully return the patient and his partner to a state where they can enjoy the benefits the implant has to offer.

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Vascular Surgery for Erectile Dysfunction

Jonathan P. Jarow, MD

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INTRODUCTION

Erectile dysfunction (ED) is a common disorder that affects almost 1 in 10 men throughout their lifetime. The Massachusetts Male Aging Study demonstrates that although the prevalence of ED increases with age, men of all age groups are affected (1). In addition, when all degrees of ED are included, almost 70% of elderly men complain of this disorder. There are many effective medical therapies currently available for the treatment of ED. Hence, the management of ED has evolved into a goal-oriented process whereby after a minimal evaluation, men choose their therapy among a menu of options (2). In this setting, the underlying etiology of their ED is rarely determined and often has little impact upon management (3). However, the vast majority of these treatments could be considered palliative rather than curative because the underlying disorder causing the ED is never corrected. Examples of this include penile implants, vacuum erection devices, and pharmacologic erection therapy. It is the exceptional patient in whom we can cure his ED and restore normal sexual function without any further therapy.

The underlying etiologies of ED can be classified as psychogenic, endocrinologic, neurogenic, and vasculogenic. Unfortunately, neurogenic etiologies cannot be cured, but all of the other etiologies are potentially curable. Performance anxiety can be cured

with sexual therapy. Also, endocrine disorders such as prolactin-secreting pituitary adenomas can be cured with either dopamine agonists or pituitary surgery. Despite the inference from the AUA ED guidelines pane (4) that vascular surgery is experimental, most clinicians now believe that vascular surgery can be curative in a very small, highly select group of patients. This chapter describes how to identify this select patient population and how to properly perform vascular surgery. To accomplish these two objectives one must first have a thorough understanding of erectile physiology.

ERECTILE PHYSIOLOGY

Our understanding of erectile physiology has increased considerably since the advent of intracorporeal pharmacologic stimulation of an erection in the early 1980s. Intracorporeal administration of vasodilators has played a critical role in the study of erectile physiology in animal models, diagnostic testing of patients, and as a form of therapy. It is now known that the creation and maintenance of an erection in man is based upon a delicate hemodynamic balance between arterial blood flow into the corpora and restriction of venous outflow (5). This process is critically dependent upon normal compliance of the corporeal sinusoidal tissues and tunica albuginea.

Erectile physiology was already described in detail in Chapter 1, but the points worth repeating as they apply to vascular surgery are described herein. The primary event in the production of a human erection appears to be nonadrenergic, noncholinergic (NANC) stimulation of vascular endothelium synthesis of nitric oxide (NO), which causes smooth-muscle relaxation of the sinusoidal tissue within the corpora and penile arteries. Blood flow into the corpora increases dramatically and the sinusoids expand as they fill with blood. During the flaccid state and the early-filling stage of an erection, the venous drainage of the corpora is unimpeded. However, as the sinusoids expand, the emissary veins are compressed on the underside of the tunica albuginea and passively occluded (6). During the latter portion of the filling phase, the penis becomes engorged and eventually becomes rigid as intracorporeal pressure reaches mean arterial blood pressure. Patients with impaired arterial blood flow, but a normal veno-occlusive mechanism may take longer to fill but can frequently still achieve adequate rigidity. During a full erection, the arterial blood flow is reduced, but still higher than during the flaccid state. Intracorporeal pressures are transiently higher than arterial blood pressure due to skeletal muscle (bulbocavernosus and ischiocavernosus muscles) contraction around the corpora. Orgasm and ejaculation are associated with immediate detumescence because of release of adrenergic neurotransmitters (7). That is why α -adrenergic agents such as phenylephrine are so effective at reversing the effects of pharmacologically stimulated erections. In addition, endogenous catecholamines released by the adrenals in response to anxiety can interfere with a patient's response to pharmacologically stimulated erection and produce artifactual results to testing in the clinic (8).

Thus, an imbalance between arterial inflow and venous occlusion will interfere with the development of and/or maintenance of adequate penile rigidity for sexual relations. Vascular etiologies are the most common causes of ED in men over age 45 and vascular risk factors are extremely common in men with organic ED (9). However, it is not clear when it is caused by arterial occlusive disease, veno-occlusive dysfunction, or a combination of both. Patients with inadequate arterial occlusive disease could theoretically be treated with arterial reconstructive surgery to enhance arterial inflow. Conversely, patients with veno-occlusive dysfunction could theoretically be treated with venous ligation pro-

cedures. The end result of chronic vascular disease of the penis and age is an alteration of the connective tissues of the corpora that interferes with normal compliance and produces a clinical picture that is indistinguishable from that of veno-occlusive dysfunction (10,11). Neither arterial revascularization nor venous ligation procedures will be successful in a patient that lacks normal compliance of the sinusoidal tissues. The clinical application of this information is that patients with either chronic vascular disease or diffuse pathology are not good candidates for vascular surgery.

VASCULAR EVALUATION

Arterial blood flow is one of many critical components necessary for the production of a human erection. Without an os penis, the human penis is dependent upon adequate arterial inflow and a normal veno-occlusive mechanism in order to achieve intracorporal pressures sufficient to provide adequate rigidity for sexual intercourse. Absolute normal values for arterial blood flow and venous occlusion do not exist. It is more important that arterial inflow significantly surpasses venous outflow in a relative sense during the filling phase of an erection than the actual absolute value. Therefore, adequate levels of arterial inflow for one individual may not be sufficient for others, depending upon factors such as penile volume, autonomic tone, and degree of venous occlusion. Arterial inflow that is considered normal or adequate for one patient may, in fact, be inadequate for a patient with veno-occlusive dysfunction. But this same patient may be able to achieve an erection with greater than “normal” arterial inflow. Conversely, patients with inadequate arterial blood flow who fail to fill the sinusoids will have veno-occlusive dysfunction because the sinusoids never expanded enough to passively compress the venous outflow. These factors should be kept in mind during the vascular evaluation. Please see Chapter 12 for a more complete discussion of the vascular evaluation.

There are very few indications for a complete vascular evaluation and most patients can be treated without obtaining a definitive diagnosis. The principal indication for a complete arterial evaluation is to determine whether a patient is a candidate for vascular surgery. Therefore, the majority of patients undergoing this evaluation are younger (less than 50 yr old), do not smoke, and have risk factors suggestive of a correctable vascular etiology such as trauma or primary ED.

The traditional “gold standard” diagnostic test of the penile arterial blood supply is angiography. However, this is an invasive test with both false-positive and negative results depending upon the level of experience of the radiologists. The first tests used to noninvasively screen patients for arterial occlusive disease were the penile Doppler and plethysmography. These tests are not very accurate and have been largely abandoned. The penile Doppler measured blood pressure in the dorsal artery of the flaccid penis. The result was expressed as an index compared to the brachial blood pressure, with less than 0.7 being abnormal. Interestingly, an abnormal penile brachial index (PBI) was found to be a better predictor of a future major vascular event than cardiac stress testing (12). The results of both PBI and plethysmography tend to be accurate when positive, but have a high false-negative rate. The main reasons for this is that the blood pressure is measured in an artery that does not normally contribute to an erection and at a time when the demand for penile blood flow is significantly less than during an erection. A more modern technique to utilize penile Doppler blood pressure is when it is combined with dynamic infusion cavernosometry (13). The occlusion pressure of the cavernosal arteries is determined after pharmacologic stimulation of an erection

and the intracorporeal pressure is raised by intracorporeal infusion of saline until the artery is occluded and the Doppler signal disappears. Recent studies suggest that this method of arterial blood flow assessment is as accurate as duplex ultrasonography (13). However, cavernosometry is a much more invasive test and is not necessary in most patients.

A reasonable approach to screening patients for arterial occlusive disease is to begin with a pharmacologic erection test in the office. In order to minimize the clinic effect, a high dose of vasodilator (10–20 mcg of PGE₁ as a single agent or 0.3–0.5 mL of Trimix) should be employed. However, it is important to keep the patient in the office until the penis has become flaccid if they achieve a full erection in response to the drug in order to avoid priapism. The high-dose vasodilator can be combined with self-stimulation to maximize the effect (14). Patients with a full response to vasodilator may have mild arterial occlusive disease but do not have either severe arterial occlusive disease or veno-occlusive dysfunction (15). Conversely, a patient who does not respond to high-dose vasodilator may have either arterial occlusive disease or veno-occlusive dysfunction. Unfortunately, anxious patients with psychogenic ED may not respond normally either. Repeated testing in the office and repeated testing at home can help exclude most, but not all, patients with psychogenic ED. The next step in the management of patients who do not respond to vasodilators is to perform a duplex Doppler ultrasound evaluation of the penile arteries (16,17).

Duplex ultrasonography allows a real-time assessment of the cavernosal arteries to measure peak blood flow velocity. The blood flow cannot be measured. Duplex ultrasonography also supplies anatomic information about the penile vasculature. Unfortunately, penile ultrasonography does not provide any information regarding the origin of the penile arteries. One of the key indicators of normal arterial blood flow is the presence of arterial pulsations on real-time ultrasonography after administration of a vasodilator. The results of penile duplex ultrasonography are operator dependent. In addition, the presence of anatomic variations of the penile arterial anatomy can influence the interpretation of this study. Anatomic variations are extremely common and have been documented in up to 80% of men being evaluated for ED (18,19). The most common vascular anomaly producing a false result is a distal perforator from the dorsal artery. In addition to their effect upon the interpretation of the duplex ultrasound study, anatomic anomalies of the penile blood supply have a significant impact upon arterial reconstructive surgery. Knowledge of these possible anatomic variations and assessment of total blood flow velocity, rather than assessing each side individually, helps avoid misinterpretation of a duplex ultrasound study.

A penile duplex ultrasound study has also been utilized to screen for veno-occlusive dysfunction by measuring end-diastolic velocity (20). The end-diastolic velocity is also a surrogate parameter for the quality of erection. In other words, the rigidity is a reflection of intracavernosal pressure and the end-diastolic velocity decreases as the intracavernosal pressure rises (21). As with the pharmacologic erection test, a full response to vasoactive agent is a reliable predictor of the absence of veno-occlusive dysfunction. Thus, it is not clear whether measurement of end-diastolic velocity provides any independent information regarding the presence or absence of veno-occlusive dysfunction.

A pudendal arteriogram is the next step in the preoperative evaluation of a patient with an abnormal duplex ultrasound study. The purpose of the arteriogram is twofold; to document the presence of an arterial lesion and to obtain a road map for reconstruction. Bilateral flush oblique aortogram studies are performed to assess the inferior epi-

gastric arteries and rule out an anomalous derivation of the pudendal arteries. A selective study is then performed as distally as possible following intracorporeal administration of vasodilator. Intravascular administration of vasodilator is not adequate to visualize the intrapenile arteries. The intrapenile arterial anatomy and presence of distal run off determines whether vascular reconstruction is feasible and which procedure should be employed.

The diagnosis of veno-occlusive dysfunction is suspected in the patient who does not respond fully to a maximal dose of vasodilator and does not have evidence of arterial occlusive disease by duplex ultrasonography. However, patients with psychogenic ED can have the same clinical picture. The next step in the evaluation is dynamic infusion cavernosometry and cavernosography (DICC) to quantify the amount of veno-occlusive dysfunction and to identify the site of the leak. Cavernosometry is performed to quantify the amount of venous leakage. Maximal smooth muscle relaxation is achieved by administration of vasodilator on a repetitive basis if necessary (22,23). Unfortunately, many studies have shown that DICC has a very high false-positive rate. In other words, many normal men have an abnormal study (24–26). This is particularly true for the cavernosography portion of the examination (27). The diagnosis of veno-occlusive dysfunction is based upon the results of cavernosometry and not cavernosography. The sole purpose of cavernosography is to provide anatomic information. Therefore, it is imperative to obtain formal nocturnal tumescence studies to rule out psychogenic ED before considering surgical therapy in patients with a presumptive diagnosis of veno-occlusive dysfunction.

ARTERIAL RECONSTRUCTIVE SURGERY

Healthy young patients with segmental arterial occlusive disease, preferably of traumatic origin, and adequate distal run off are good candidates for arterial reconstructive surgery. The type of procedure performed is determined by the surgeon's preference and the arterial anatomy. Most surgeons prefer to use the inferior epigastric artery as the donor vessel and the dorsal artery of the penis as the recipient vessel. However, anatomic anomalies or prior surgeries may interfere with that routine. When the inferior epigastric artery is not available, the author prefers to use a reversed saphenous vein graft between the superficial femoral artery and the penis. An arterial-to-arterial anastomosis is most likely the best reconstructive procedure for arterial occlusions. However, arterialization of the dorsal vein has been proposed as an alternative when anatomical considerations prevent this.

Arterial Bypass

The most common procedure performed is an anastomosis between the inferior epigastric and the proximal dorsal artery. An alternative to the dorsal artery is the cavernous artery (28). However, there are several potential disadvantages to this approach. The location of the cavernosal artery within the corpora makes it a more difficult artery to approach, leads to more bleeding that interferes with microsurgery, and the tunica of the corpora has to be closed in such a way as to provide hemostasis, but not occlude the graft. Preoperative arteriography is mandatory to establish the presence of a good donor vessel and to choose an appropriate recipient artery. Variant penile arterial anatomy is present in up to 80% of impotent men (19,29). Common variants include both dorsal arteries originating from the same penile artery and distal cavernosal perforators from the dorsal

artery. The goal of the vascular surgery is to direct as much blood flow as possible into the corpora. Therefore, patients with classic penile arterial anatomy are best served by an end-to-end anastomosis to the proximal dorsal artery on the side of the lesion in order to maximize blood flow into the corpora. The presence of distal cavernosal perforators may require an end-to-side anastomosis to an intact dorsal artery or an end-to-end anastomosis to the distal portion of the dorsal artery in order to maximize blood flow into the corpora. An intraoperative arteriogram may be necessary if the preoperative arteriogram does not adequately visualize the intrapenile arterial anatomy (30).

The procedure is performed with the patient in the supine position. A transverse or paramedian abdominal incision is performed in order to harvest the inferior epigastric artery. Alternatively, a laparoscopic approach may be utilized to harvest this artery (31). It is important to handle the donor vessel gently and avoid cautery close to the main trunk. Small arteriole side branches are frequent and should be managed with bipolar cautery. One or two vena comitantes run with the artery with numerous cross-ing branches that may be controlled with bipolar cautery. The artery is harvested to or just beyond the umbilicus from the underside of the rectus abdominis muscle. The inferior epigastric artery is usually still larger in diameter than the dorsal penile artery at this level. Systemic heparin (5000 U) is administered just prior to ligating the artery superiorly. A topical vasodilator such as Marcaine is applied using a warm sponge and attention is then turned to the penile vasculature. A separate incision at the base of the penis is used to expose the dorsal penile arteries. A short pubic tunnel is created beneath the fascia of the anterior rectus sheath between the two incisions. The inferior epigastric vessels are passed through the tunnel with care not to twist or kink the artery. A segment of the dorsal artery is carefully dissected and prepared for anastomosis by stripping away loose tissue attached to the adventitia. The operative microscope is then utilized to prepare the arteriotomies and perform the anastomosis. Because of the large relative size of the inferior epigastric artery compared to the dorsal penile artery, and end-to-end anastomosis is technically easier. However, an end-to-side anastomosis may be necessary depending upon the pattern of penile arterial blood flow. The anastomosis is performed using interrupted 10.0 nylon suture on a tapered needle, being careful to exclude adventitia from the lumen and to avoid tension on the anastomosis. Low-molecular-weight dextran (40%) is administered intravenously in a 100-mL bolus immediately upon completion of the arterial anastomosis and then maintained at 20 mL/h for 5 d. A drain may be placed for each incision site. The patient should avoid cigarette smoke and any foods containing vasoconstrictors. The patient is also treated with one aspirin daily. Sexual activity should not be performed for 6 wk.

Arterialization of the Dorsal Vein

Arterialization of the deep dorsal vein to correct vasculogenic impotence was first described by Virag (32). He has subsequently modified his procedure several times and other investigators have also suggested modifications (33). The procedure has been employed with limited success in patients with isolated veno-occlusive dysfunction, pure arteriogenic impotence, and patients with combined etiologies. This procedure theoretically impedes venous outflow through the deep dorsal vein at the same time as increasing intracorporeal arterial blood flow. Thus, the balance between arterial inflow and venous outflow is significantly shifted to enhance penile engorgement. The patient is prepared in a similar manner to the arterial bypass operation. The inferior epigastric artery is harvested through a separate abdominal incision as aforementioned. The deep dorsal vein is

isolated at the base of the penis through a separate incision at the base of the penis. An isolated segment of the deep dorsal vein with its emissary veins intact should be prepared by ligating the deep dorsal vein both proximally near the hilum of the penis and distally prior to its trifurcation near the glans penis. The inferior epigastric artery is brought down through a tunnel beneath the fascia of the anterior rectus sheath. Again, it is important to not twist or kink this vessel. A venotomy is then created in the side of the deep dorsal vein. The deep dorsal vein has intact venous valves preventing retrograde flow into the corpora except in patients with massive veno-occlusive dysfunction. These venous valves must be ablated in order for this procedure to have any significant benefit over simple ligation of the deep dorsal vein. A leather valvulotome or Fogarty balloon catheter may be used to mechanically disrupt these valves. Alternatively, the valves can be excised through a venotomy using microsurgical techniques. All of these methods have the risk of damaging the vessel wall intima of the veins and resulting in eventual clotting of the blood vessel. In addition, disruption of the valves within the deep dorsal vein does not guarantee that blood flow will extend all the way into the corporeal sinuses. Therefore, valves of the emissary veins must be ablated as well. The anastomosis between the inferior epigastric artery and the deep dorsal vein is performed in an end-to-end or end-to-side fashion using interrupted 10.0 nylon sutures.

The overall success rate of this procedure has been disappointing. Modifications of this procedure have been developed to improve the success rate. Virag has described a modification where a window is created in the corpora by excising an ellipse of tunica albuginea (32). The arterialized segment of the dorsal vein is then anastomosed to the corpora in a side-to-side fashion in an effort to increase the blood flow directed into the corpora. Alternatively, Hauri has described a technique whereby the dorsal artery is anastomosed side-to-side to the arterialized dorsal vein segment in an effort to increase blood flow and maintain patency of the anastomosis (33).

Postoperative management includes placement of a drain and systemic anticoagulation as described for the arterial bypass procedure. The patient should avoid cigarette smoke and foods containing vasoconstrictors postoperatively. Sexual activity should be delayed for at least 6 wk to avoid disruption of the anastomosis. A major complication of this procedure is hypervascularity of the glans penis (34). This is because of excessive blood flow reaching the glans penis through arterialized collateral veins. Hypervascularity of the glans penis usually presents in the early postoperative period, but may present late. The treatment consists of ligation of the collateral veins located between the arterialized segment of the deep dorsal and the glans penis (35). The intraoperative Doppler is helpful in identifying these arterialized collateral veins. The dorsal arteries should be spared to prevent ischemic damage to the glans penis. Alternatively, the inferior epigastric artery can be ligated proximal to the anastomosis if the original procedure was not effective in restoring potency.

VENOUS LIGATION SURGERY

Venous ligation surgery is based upon the premise that the pathology in men with veno-occlusive dysfunction is in the veins themselves. If this were true, then ligation of abnormal veins would prevent venous leakage during an erection and restore potency. However, veno-occlusive dysfunction may be caused by a variety of factors that are not amenable to surgical correction. These factors include terminal nerve dysfunction, smooth-muscle atrophy, intracorporeal fibrosis, and alterations of tunica albuginea

structure (36–40). Patients with veno-occlusive dysfunction secondary to any of these disorders will not benefit from dorsal penile vein ligation. There may be a subset of young healthy patients with either primary ED or focal veno-occlusive dysfunction secondary to trauma that may benefit from surgical correction. However, it is important to remember that because of overlapping clinical features, veno-occlusive dysfunction is often mistakenly diagnosed in patients who actually have psychogenic ED (25). Therefore, it is imperative to rule out psychogenic ED as best as possible through formal testing of nocturnal erections before proceeding to surgical therapy.

Penile Vein Ligation

Penile vein ligation is performed upon patients with veno-occlusive dysfunction and without evidence of either arterial or psychogenic ED. Preoperative cavernosometry demonstrates the severity of venous leakage, whereas cavernosography determines the site of leakage. The normal venous drainage of the penis includes the superficial and deep dorsal veins, cavernosal and crural veins, and occasionally the corpus spongiosum. All of these venous systems can be approached through a single inguinoscrotal incision located at the base of the penis or through a combination of that and a circumcission incision (41). Placing the patient in lithotomy position enhances exposure for the proximal dissection beneath the pubic symphysis. The penis may then be degloved through this incision to expose both the dorsal veins and any circumflex veins communicating to the corpus spongiosum. The deep dorsal vein or veins (frequently there are multiple) are completely resected from its trifurcation located 2–3 cm proximal to the glans penis all the way to underneath the symphysis pubis. All circumflex and emissary veins are ligated as well. The cavernosal veins can be identified at the hilum of the penis after detaching the suspensory ligaments. Optical magnification with loupes and the intraoperative Doppler assist in the hilar dissection in order to avoid inadvertent ligation of the arteries. Crural veins visualized on preoperative cavernosography may be ligated following further dissection along the lateral aspect of each corpus. It is critical to re-approximate the suspensory ligament in multiple layers upon completion of the venous dissection in order to prevent significant postoperative penile shortening (42). This procedure may be performed on an outpatient basis under general or regional anesthesia. Sexual activity should be delayed for several weeks. Potential complications include penile paresthesia, penile shortening, and hematoma formation. Some patients who are not “cured” by the procedure may have improved to the point that either oral medical or self-injection therapy may now be effective.

Modifications of the aforementioned procedure may be performed depending upon the anatomic site of leakage on cavernosography. For instance, if the leakage appears confined to the crura, then a perineal approach may be employed to ligate these veins alone (43,44). Alternatively, patients with diffuse leakage including the corpus spongiosum may require even more extensive dissection than aforementioned including spongiolysis (45). An alternative approach to open surgical penile vein ligation is percutaneous ablation of the penile veins (46,47). Access to the penile veins for sclerotherapy may be obtained through the femoral vein, a deep dorsal vein cutdown, or a combination of the two.

RESULTS

The techniques for vascular surgery have evolved as our understanding of erectile physiology and penile vascular anatomy has improved. For instance, an early approach

Table 1
Selected Series Depicting the Results of Arterial Reconstructive Surgery

	<i>N</i>	<i>Mean Age</i>	<i>Follow-Up (mo)</i>	<i>% Success</i>	<i>Procedure</i>
McDougal and Jeffrey ('83)(50)	8	55	>12	75	Dorsal artery
Hauri ('86)(33)	50	—	—	78	Hauri procedure
Crespo ('87)(51)	257	—	60	77	Dorsal artery
Pearl and McGhee ('87)(52)	10	—	60	60	Dorsal artery
Wagenknecht ('88)(53)	15	57	26	67	Dorsal vein
Konnak and Ohl ('89)(28)	9	—	31	22	Cavernosal artery
Sohn ('92)(54)	74	44	15	55	Hauri procedure or dorsal vein
Löbelenz ('92)(55)	19	48	13	58	Hauri procedure or dorsal vein
Schramek ('92)(56)	35	42	27	77	Hauri procedure
Cookson ('93)(57)	12	38	24	67	Dorsal artery
Melman ('93)(58)	18	50	15	33	Dorsal artery
Janssen ('94)(59)	21	47	22	62	Dorsal artery or vein
Jarow and DeFranzo ('96)(60)	11	42	50	64	Dorsal artery or vein
Depalma ('97)(61)	12	—	33	27	Dorsal artery
Sarramon ('97)(62)	114	—	17	48	Dorsal artery and vein
Manning ('98)(63)	62	48	41	34	Hauri procedure

to penile revascularization was a direct arterial anastomosis to the cavernosal body, which, when it remained patent, resulted in a high rate of priapism. The most current approach to penile revascularization takes into account the high vascular resistance within the corporal bodies when the penis is flaccid. These modifications have had a significant impact on success rates for vascular surgery that is not apparent in the literature because of a tendency to only report positive results. Another area of evolution that has had a significant impact upon the results of penile vascular surgery is the role of vasoactive agents in the understanding of penile hemodynamics, both for research and diagnostic testing. Misdiagnosis is potentially the most common cause of failure for penile vascular surgery and this is particularly true for patients being treated for veno-occlusive dysfunction. First, it is common for patients with psychogenic ED to have clinical findings consistent with veno-occlusive dysfunction as aforementioned. Second, patients thought to have isolated arterial occlusive disease may have concomitant veno-occlusive dysfunction secondary to decreased sinusoidal compliance. Finally, many patients with diffuse atherosclerotic vascular disease undergo penile revascularization with little chance of success. The application of intrapenile injection of vasoactive agents allows us to evaluate the distal penile arteries preoperatively and better select patients for surgical therapy.

The reported results of penile arterial vascular surgery very significantly (Table 1) with a success rate ranging from a low of 22% to a high of 78%. A large part of this variation is owing to patient selection. Other factors include surgical technique, method of evaluation, duration of follow-up, and definition of success. Moreover, almost all of these studies lack objective follow-up data utilizing either nocturnal tumescence monitoring to quantify erectile function or vascular studies to quantify blood flow postoperatively. Follow-up

Table 2
Selected Series Depicting the Results of Venous Ligation Surgery

	<i>Procedure</i>	<i>N</i>	<i>Follow-Up (mo)</i>	<i>% Success</i>
Lewis ('88)(64)	Dorsal vein ligation	50	15	24
Lue ('89)(42)	Dorsal vein ligation	64	12	82
Glina ('90)(65)	Crural plication	23	19	48
Schwartz ('92)(46)	Embolization	22	12	25
Knoll ('92)(66)	Dorsal vein ligation	41	28	46
Weidner ('92)(67)	Dorsal vein ligation	37	32	49
Freedman ('93)(68)	Dorsal vein ligation	46	15	24
Montague ('93)(69)	Dorsal vein ligation	18	24	61
Kim and McVary ('95)(70)	Dorsal vein ligation	15	29	60
Vale ('95)(71)	Dorsal vein ligation	27	12	64
Berardinucci ('96)(72)	Dorsal vein ligation	100	45	31
Schultheiss ('97)(73)	Dorsal vein ligation	126	33	11
Sasso ('99)(74)	Dorsal vein ligation	23	17	52

ranged from just over 1 yr to as long as 5 yr. The most popular technique reported is an anastomosis to the dorsal artery with a success rate of approx 66% in most series. An alternative approach that is utilized when it is not possible to connect to an artery or there is concomitant veno-occlusive dysfunction is arterialization of the dorsal vein. Surprisingly, the success rate for this technique is similar to that of the dorsal artery approach. Finally, a procedure described by Hauri includes simultaneous anastomosis to the dorsal artery and dorsal vein, which theoretically has the advantage of providing continuous blood flow through the anastomosis when the penis is flaccid to help prevent clotting of the anastomosis (33). The success rate for the Hauri procedure is similar to that of the others in experienced hands and appropriately selected patients.

Venous ligation surgery suffers from the same possible problems as arterial surgery stated above. Although the success rates reported in the literature (Table 2) appear only slightly lower than arterial surgery, the general consensus today is that venous ligation surgery is usually ineffective. Potential morbidity from penile ligation surgery is significant. Many patients complain of penile shortening and transient numbness. In addition, there is a significant risk of damaging the cavernosal artery at the hilum of the penis. However, the two main problems with penile ligation surgery are: difficulty in patient selection owing to lack of good objective diagnostic tests and the fact that pathology is often a result of a lack of sinusoidal compliance, rather than venous anomalies.

SUMMARY

The introduction of surgical procedures to cure vasculogenic impotence was greeted with a great deal of initial enthusiasm because of limitations in other therapies. Unfortunately, the published long-term results of these procedures fall far short of our initial expectations. Numerous surgical techniques have been developed and modified and none appear to significantly improve outcome. The reported success rate for arterial surgery ranges from as low as 50% to as high as 90%, depending upon the population treated, method employed, and length of follow-up (48). Despite early reports of 65% success rates, long-term results of venous ligation surgery have been extremely disap-

pointing, approx 30%. The current sentiment is that many or all of these procedures should be abandoned. The gaps in our understanding of erectile physiology and the flaws in our diagnostic evaluation may lead to a misdiagnosis and inappropriate application of these surgical therapies. We have learned which patients will not benefit from these procedures. This includes any patient with end-organ disease of the penis including the elderly, diabetics, and patients with severe ischemic vascular disease. Many patients who are thought to have veno-occlusive dysfunction potentially suffer from psychogenic impotence. DICC is our least-standardized test and the lack of a gold-standard method for the diagnosis of veno-occlusive dysfunction is a major handicap. The best candidates for vascular surgery are young healthy patients with an identifiable segmental vascular pathology such as patients with traumatic injuries or those with congenital abnormalities. However, these patients are rare and represent only a small fraction of the patients seen in standard practice. Patients undergoing penile vascular surgery should be made aware of the potential risks, alternative therapies, and the investigational nature of these procedures.

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18

Peyronie's Disease

History and Medical Therapy

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INTRODUCTION

Although Fallopius described a condition that caused curvature of the penis as early as 1561, Francois de LaPeyronie (1678–1747), founder of the Royal Society of Sciences in France, is credited with the disease. In 1743, he described a series of patients with “rosary beads of scar tissue extending the full length of the dorsum of the penis,” in a paper entitled “Some Obstacles Preventing Normal Ejaculation of Semen.” Peyronie, who was First Surgeon to King Louis XV, suggested the condition was caused by “irritation” and should resolve with *spa specific* (Bareges) mineral water (1,2).

The true incidence of Peyronie's disease, also called plastic induration of the penis or penile fibromatosis, is unknown, but it is estimated to affect 1% of Caucasian men, often between the ages of 40–60. In 1991, Lindsay reported the incidence of Peyronie's disease in Rochester, MN as 26:100,000 and the prevalence as 389:100,000 (3). More recent epidemiologic data collected from Germany estimates the prevalence of Peyronie's disease to be 3.2% (4).

In a series of 21 patients, Williams (5) described the natural course of Peyronie's disease. The main presenting complaints were pain and curvature with erections, painful intercourse, impotency, and a notable lump. Over an average period of 4 yr, greater than 50% of the patients had gradual resolution or improvement in their symptoms. Pain seemed to resolve first, followed by plaque softening, and disappearance.

Peyronie's disease is reported to be associated with Dupuytren's contractures, Paget's disease of the bone, Lederhose's disease, and tympanosclerosis (6,7).

ETIOLOGY

Trauma

After more than 200 yr, the exact pathophysiology of the Peyronie's disease remains a mystery. Devine et al. (8) proposed a detailed model of trauma as a cause for Peyronie's lesion. The fibers of the midline septum fan out and join with fibers of the inner circular layer of the tunica albuginea at right angles. Devine compared this anatomy to a steel I beam. During intercourse, the septum provides the penis with vertical rigidity. A downward vector force applied to the erect penis is felt greatest at the junction between the septum and tunica. Young men have the ability to generate high intracavernosal pressures to resist these forces and also have compliant tissues that can resist the tearing forces should a bend occur. As men get older, they lose tissue resilience and fail to generate high intracavernosal pressures because of decreased arterial inflow and venous leakage. This scenario provides the perfect setup for a tear in the tunica albuginea during intercourse (9).

Devine proposed that in older men, deforming forces to the erect penis cause tear or delamination injury within the layers of the tunica albuginea. Following this injury, blood vessels are disrupted, and fibrin clot is deposited where the septum and tunica join. With repetitive trauma and tissue fatigue, delamination injury occurs more readily. The combination of repeated injury and a decreased ability to clear fibrin deposits results in an inflammatory cascade that leads to scar formation within the tunica. The majority of the lesions occurs dorsally where the septum and tunica join, but plaque may form ventrally and laterally. Penile curvature is caused by inelastic scar, elevated in type III collagen, that shortens the involved side of erect tunica albuginea of the corpora cavernosa. Others have reported trauma from vacuum erection devices and intracorporal injections as the initiating factor for tunical injury (10–12).

Immunogenetics

Family studies indicate that Peyronie's disease has a genetic component. Ziegelbaum et al. (13) reported on identical twins with Peyronie's disease and the human leukocyte antigen (HLA) B27. Nyberg et al. (14) reported on several multigeneration families with Peyronie's disease. B7 cross-reactive antigens occurred in all three families; however, inheritance of Peyronie's disease was independent of this HLA gene complex.

Some inflammatory disorders are autoimmune in nature and have associations with the HLAs. Peyronie's disease has been proposed to have an autoimmune component that is triggered by some environmental stimulus. Several investigators have studied the potential role of the immune system in Peyronie's disease. Leffell (15) noted that the histopathology of Peyronie's plaque was similar to that of localized fibrotic lesions that occur in some B27 spondyloarthropathies. Stewart et al. (16) reported an increase in antielastin antibodies in patients with Peyronie's disease. Schiavino et al. (17) found that many patients with Peyronie's disease expressed abnormal immunologic tests; however, no data clearly associates Peyronie's disease with any autoimmune process.

Several bacterial and venereal infections have been linked to reactive arthritides. It is thought that the mechanism of action is molecular mimicry, where the immune system identifies bacterial antigens that are similar to self-expressed epitopes. Up to 90% of

patients with reactive arthritis following venereal or enteric infection is HLA B27 positive (18). Infection by *Klebsiella pneumoniae* has been linked to ankylosing spondylitis and HLA B27 (19), whereas rheumatoid arthritis has been identified with *Proteus mirabilis* and HLA DR4 (20). Other organisms that are reported to cross react with HLA B27 are *Shigella*, *Salmonella*, *Yersinia*, *N. gonorrhea*, and *Campylobacter*. Thus, certain HLA serotypes may be associated with abnormal healing and collagen deposition when the appropriate environmental stimuli are present.

Rompel et al. (21) reported on the association of certain HLA haplotypes and Peyronie's disease. In their study they found an association with the class II antigens, DR3 and DQ2, and a small increase in the frequency of the class I alleles, A1 and B8. Both Leffell and Rompel reported on the B7 cross-reactive group frequencies in patients with Peyronie's disease. In both studies the individual frequencies approximated those of the normal population, and no definite HLA association was identified with Peyronie's disease.

Bottazo et al. (22) found a significant association with HLA B27 antigen and Peyronie's disease. They reported a relative risk of three for developing Peyronie's disease for those who have the HLA B27 antigen. They did not find an association with the remaining antigens in the B7 cross-reactive group or any association with HLA A1, DR3, or DQ2. No enteric organisms were cultured from feces of these patients, and all urethral cultures were negative for venereal organisms. In addition, the antibody titers for *E. coli*, *Proteus*, and *Klebsiella* were not elevated. Although staggering evidence for an immunogenetic basis for Peyronie's disease is lacking, there is some data to suggest that certain individuals may be predisposed to developing this disease. There may be an environmental trigger to be identified in the future that predisposes an individual with a certain genotype to develop Peyronie's disease.

PATHOLOGY

Histology

Understanding Peyronie's disease begins with the anatomy of the tunica albuginea. Lue et al. (23) have described the anatomy as a bilayered structure of connective tissue with an inner circular layer and an outer longitudinal layer. The inner layer gives rise to a midline septum that separates the two corporal bodies. This layer also provides intracavernous pillars that project into the erectile tissue, inserting on periarterial sheaths and cavernous sinusoids to provide the penis with additional strength. The dorsal and lateral thickenings combined with the lateral bundles anchor the penis to the pubic rami.

Under the microscope, the tunica is seen as a delicate lattice of elastin fibers that serve as a background for undulating collagen bundles. Collagen provides the tunica with strength, whereas the elastic network provides it with resilience so that it can resume its relaxed state following an erection.

In Peyronie's disease, the delicate lattice structure of elastin fibers and collagen bundles is lost in the area of the plaque. Smith (24) was the first to describe the histologic findings of 26 cases from the files of the Armed Forces Institute of Pathology. He believed Peyronie's disease began as an inflammatory process with "lymphocytic and plasmacytic infiltrate in the areolar connective tissue sleeve between the corpus cavernosum and tunica albuginea" that gradually progressed to fibrosis.

Davis (25) summarized the microscopic pathology seen in Peyronie's disease. In early disease, perivascular lymphocytic infiltrates with increased number of fibroblasts

are seen within the tunica albuginea and immediately between the tunica and Buck's fascia. As the disease progresses, the normal undulating pattern of collagen bundles is lost; the collagen bundles are arranged haphazardly with random orientations and sometimes extend into the erectile tissue. Elastin fibers are sparse and fragmented. Using a fibroblast-populated, collagen lattice to study the organization of collagen fibers, Ehrlich demonstrated that the plaque of Peyronie's disease was not caused by scar contracture (26).

Somers et al. (27) made an interesting comparison between the histologies of plaque tissue, nodular tissue from Dupuytren's contracture, and penile scar from the tunica, but not Peyronie's plaque. Aberrant collagen staining was seen in 97% of Peyronie's plaques and 88% of Dupuytren's scars. Disrupted elastin fibers were seen in 94% of plaques and 63% of Dupuytren's lesions. Fibrin deposition was demonstrated in 95% and 88% of plaques and Dupuytren's scars, respectively. Normal tunica and penile scar tissue had none of these histologic abnormalities.

Transforming Growth Factor- β

Inflammation follows all injuries and is vital to normal tissue repair. However, when the inflammatory cascade continues unabated, the results can be devastating. In Peyronie's disease, an abnormal inflammatory response lies in the heart of the problem. As proposed by Devine (8), following a delamination injury to the tunica albuginea, fibrin clot is deposited within the bilayered structure. Fibrin deposition continues for several days under the influence of Vascular Permeability Factor (28). The fibrin network serves as a spider web to trap inflammatory cells and platelets in the wound. Lymphocytes bind to receptors on endothelial cells and trapped erythrocytes to begin the cytokine cascade. By 48 hs, the predominant cell in the wound is the macrophage, which releases transforming growth factor-beta (TGF- β), and platelet derived growth factor (PDGF), a chemoattractant for fibroblasts (29,30). In the presence of these lymphokines, the fibroblast starts to deposit collagen. With repetitive injury and inflammatory stimulation, this cascade of events can become pathologic, resulting in excess scar tissue and penile deformity.

Lue et al. (31) studied the effects of surgical trauma on rat tunica. Eight weeks following surgical incision, these investigators found disorganized collagen bundles within the tunica, but interestingly, the elastic fiber network remained intact. Immunoblot assays for TGF- β , a cytokine known to be increased in several fibrotic conditions including Peyronie's disease, demonstrated a modest upregulation of TGF- β after 1 d that returned to normal shortly thereafter. This study suggested that the scar of Peyronie's disease is inherently different from the scars generated by normal healing processes.

TGF- β is a cytokine with a plethora of functions that has received much attention in the study of Peyronie's disease and other inflammatory disorders. It stimulates the production of extracellular matrix and also attracts inflammatory cells to the wound. By promoting the synthesis of cell membrane receptors, it also increases the adhesion of monocytes to laminin, type IV collagen, and fibronectin, which adds to the inflammatory brigade (32). The overproduction of TGF- β has been implicated in several fibrotic conditions. It has been shown to cause pulmonary and hepatic fibrosis in rats (33,34) and may also contribute to fibrotic liver disease in humans (35). By interfering with the function of TGF- β , chronic hepatitis and proliferative glomerulonephritis can be prevented (36,37). Excessive production of TGF- β is also seen in cardiac fibrosis after

infarction (38). TGF- β has been shown to induce fibrosis of rabbit corpus cavernosum and may play a role in erectile dysfunction (ED) (39).

Lue et al. (40) studied the expression of TGF- β protein in the tunica albuginea of patients with Peyronie's disease. Eighty-six percent of the Peyronie's patients had expression of TGF- β 1, compared to only 1 out of 6 controls. There was no increase in the production TGF- β 2 or TGF- β 3. These investigators have proposed an animal model for Peyronie's disease (41). Rats were injected with cytomodulin, a synthetic heptapeptide with TGF- β -like activity. After 6 wk, the tunica albuginea was examined under light and electron microscopy. Elastic fibers were fragmented and disorganized. Condensation and clumping of collagen bundles were also seen, as well as an increased perivascular collagen deposition. These histologic changes were very similar to those seen in the plaques of Peyronie's disease.

Oxygen-Free Radicals

Some investigators have explored the role of oxidative cell damage in the pathogenesis of Peyronie's disease. Based on microvascular and tissue injury seen in Peyronie's disease, Schellenberg et al. (42) proposed that oxygen-free radicals were involved in the fibrotic process. Ahuja et al. (43) examined the in vitro response of human cavernosal cells in culture when exposed to glyceraldehyde, a promoter of oxygen-free radical formation. Fibroblasts obtained from patients with Peyronie's disease showed elevated production of type III collagen when compared to patients without the disorder. The addition of α -tocopherol, a free-radical scavenger, resulted in lower levels of collagen synthesis. Gamma interferon was also found to reduce collagen production in vitro when given before or after the addition of glyceraldehyde.

MEDICAL THERAPY

Patients with Peyronie's disease seek medical advice for a variety of reasons: penile deformity or curvature, painful intercourse, plaque or induration, or inadequate erections. Although it is not a life-threatening disease, the distressed patients are anxious to correct their problems. Surgery is not recommended at the early stages of disease before the plaque is mature and well defined, for fear of recurrent curvature. This leaves the clinician with conservative medical management until the curvature or plaque disappears or stabilizes.

Because de LaPeyronie recommended the mineral waters of southern France, many other empiric therapies have come and gone: mercury, arsenic, copper, sulfur, and bromides (2). Virtually all the published early studies on medical therapy are empiric and based on anecdotal findings. Some forms of therapy are over a long duration, and the successful results are difficult to decipher from the natural resolution of disease. Although all authors claim success, by reason of low numbers, limited follow-up, and lack of placebo-control, the reported results are unreliable and have not been consistently reproduced in subsequent studies. Table 1 lists the medical therapies of Peyronie's disease. The following medical therapies, some antiquated, others still in use, are described by route of delivery: topical, oral, infusion, and injection.

Topical Therapy

Dimethyl sulfoxide (DMSO), an industrial solvent known to relieve various inflammatory states, was first proposed to treat Peyronie's disease in 1967. Persky (44)

Table 1
Medical Therapy for Peyronie's Disease

<i>Therapy</i>	<i>Date</i>	<i>Author</i>
Mercury + mineral water	1743	de LaPeyronie
Radiation	1911	Lavenant
Radium	1922	Kumer
Vitamin E	1949	Scardino and Scott
Cortisone injections	1954	Teasley
Potassium para-aminobenzoate	1959	Zarafonetis and Horrax
Histamine iontophoresis	1960	Whalen
Prednisolone	1963	Chesney
Ultrasound	1967	Heslop et al.
Dimethyl sulphoxide	1967	Persky and Stewart
Steroid iontophoresis	1967	Rothfeld and Murray
Procabazine	1970	Aboulker and Benassayag
β -Aminopropionitrile	1983	Gelbard et al.
Collagenase injection	1985	Gelbard et al.
Prostacyclin	1988	Strachan and Pryor
Lithotripsy	1989	Bellorofonte et al.
Interferon α 2b	1991	Benson et al.
Tamoxifen	1992	Ralph et al.
Verapamil	1994	Levine et al.
Colchicine	1994	Akkus et al.

Adapted from Ralph and Pryor (88).

reported a series of 13 patients treated with topical DMSO twice daily for 8–12 wk. Six patients had significant improvement in penile angulation, one with complete resolution and three with some evidence of decreased fibrosis. Restricted to topical application only, it was quickly absorbed and found to produce a garlic-like odor on patient's breath shortly after application. Persky concluded that when conventional therapies fail, DMSO is an alternative option. In addition to a local rash over applied areas, it has been noted to cause cataract formation in animal models (45).

Another topical therapy that has been proven ineffective is β -aminopropionitrile. A potent collagen cross-link inhibitor, it irreversibly inhibits lysyl oxidase and prevents normal collagen formation. The response of β -aminopropionitrile applied topically to nine patients was poor (46). The slow turnover of collagen in established, resting Peyronie's plaque leaves little new collagen cross-linking to be inhibited.

Over the century, various modes of energy transfers have been used to treat Peyronie's plaque. Past treatments include electricity, UV light, radiation, radium, diathermy, iontophoresis, and ultrasound. In spite of the extinction of radium therapy, much literature exists on the subjective effectiveness for Peyronie's disease. The discovery of radium by Marie Curie in 1895 led to its application for many diseases, including Peyronie's disease. Reported to cure 50 cases of keloids, a form of hypertrophied scar, Fricke (47) applied radium to 112 Peyronie's plaque over a 6-yr period. No improvement was noted in 50 (44.6%) cases. However, in combination with tocopherol therapy, Burford (48) found 84% improvement or cure of Peyronie's disease, compared to 77% improvement or cure with radium therapy alone. The dangers of radium are well documented, and radium is no longer employed (49).

Literature on radiation therapy has been mixed. In 1972, Helvie (50) published a paper reviewing 40 cases of radiation therapy, total dose 900 to 1000 rads, for Peyronie's disease. Questionnaire results revealed 72% overall improvement (72% relief of pain, 29% decreased angulation, 35% decrease plaque size). Twenty-three percent noted no change and 5% had progression in the average follow-up of 2.2 yr. He concluded that radiation is an effective therapy for Peyronie's disease. In the same year, Bystrom (51) published a less-successful series of 19 patients who received a mean dose of 1200 rads. Seven of the twelve were also treated with vitamin E. Four patients (three in combination with vitamin E) noted improvement, whereas 15 remained unchanged. A long-term study, spanning 37 yr, was reported by Martin (52). One hundred forty-two patients were treated with radiation, but only 77 were alive and contacted via telephone or mail. He reported a 33.8% cure rate. In the failure group of 51 patients, improved curvature was noted in 62.7%, improved pain in 84%, and improved induration in 76.4%. A 1985 publication by Carson (53) summed up the general consensus of radiation therapy for Peyronie's disease. He noted little improvement in curvature or plaque in 40 patients, followed for an average 23 mo. However, 78% of the patients had resolution of pain fairly quickly. He concluded that external beam radiation therapy had only a limited application for pain with Peyronie's plaque. Rodrigues (54) confirmed this conclusion with a reported 76% decrease in pain for 38 patients. One potential caveat reported is corporeal fibrosis from penile irradiation (55).

Heslop (56) first reported ultrasound as possible therapy for Peyronie's disease in 1967. Used favorably in treating scars and contractures, the mechanism of ultrasonography was thought to be selective heating between the intersurfaces of different physical properties (57). Like diathermy, generated local heat supposedly increased blood flow and decreased fibroblast binding (58). Heslop reported 9 patients who underwent 10-min applications for 6–42 treatments. Pain was relieved in all patients; 4 had disappearance of plaque; and 6 were able to resume intercourse. In 1971, Frank (57) reported a subjective improvement in 92% of his patients followed for 2 mo–11 yr. Others have used hydrocortisone with ultrasound therapy to try and improve results (58). Again, results are difficult to evaluate by virtue of the natural history of disease and lack of placebo control.

Glucocorticoid ionophoresis (59) or histamine ionophoresis (60) have been reported as promising therapy, but no definitive studies have been reported.

Extracorporeal shockwave lithotripsy (ESWL) is the most recently published mode of energy transfer suggested to treat Peyronie's disease. Modest improvements in 24 patients treated with ESWL are reported by Abdel-Salam (61). Four (17%) had improved or complete resolution of penile curvature; six (25%) had improved pain, but 10 (41%) failed therapy and continued to surgical correction. No other controlled or well-followed studies are available to evaluate ESWL and Peyronie's disease.

Oral Therapy

The search for the magic pill to cure Peyronie's disease still continues, and agents such as mercury, iodines, orgotein, or procabazine have proven ineffective in this search. Procabazine (Natulan) was reported to resolve Dupuytren's contractures in individuals undergoing treatment for Hodgkin's disease. This led to its trial therapy for Peyronie's disease. In 1978, Morgan (62) reported a series of 34 men treated with a 12-wk course of Procabazine and tocopheryl acetate (Ephynal). Of the 22 men who completed the study, 90.9% remained stable or worsened. In fact, he noted better results in the vitamin E only

group with improvement in 39%. Oosterlinck (63) confirmed the disappointing results of procarbazine in his series of 10 patients. Reported GI distress, skin eruptions, leucopenia, alcohol intolerance, infertility, testicular atrophy, and possible carcinogenic activity for a nonmalignant condition quickly halted further studies (2,62,63).

Tocopherols act as antioxidants, preventing lipid peroxidation to lipid peroxides (64). In 1946, Steinburg claimed vitamin E was effective for treating Dupuytren's contracture. This led to its application for treating Peyronie's disease. In 1949, Scardino and Scott (65) reported the results of a 2-yr follow-up study for 23 patients treated with mixed tocopherols. An additional 10 cases were reviewed for an overall 81% improvement in curvature, plaque, and pain. Devine and Horton (66) reported a 60% improvement in 30 patients treated with vitamin E, and Morgan (62) reported a 39% improvement. On the other hand, Bystrom reported 17 patients who received vitamin E for 3–12 mo. Only one patient noted slight improvement and the rest were unchanged (51). As a result of its low side-effect profile and cost, vitamin E remains one of the more common agents used today for Peyronie's disease.

Potassium para-aminobenzoate (POTABA) is another common oral agent used for Peyronie's disease. It is reported to be effective for diseases of excess fibrosis, like scleroderma, by softening and reversing the cutaneous changes. Others have postulated that it increases oxygen utilization at the tissue level and enhances activity of oxygen-dependent monoamine oxidase (67). It was first applied to Peyronie's disease by Zarafonitis (67) in 1959. All 21 patients treated with 12 gm of POTABA for 3 mo–2 yr had resolution of pain. Three patients had resolution of deformity, improvement in 11, and no change in 3. Two patients had disappearance of plaque, decrease in 14, and unchanged in 5. A more recent study reported a mean, subjective improvement in 60% of the 2752 cases reviewed (68). Other published studies (69) suggest a place for POTABA in the medical armamentarium for Peyronie's disease, but significant GI side effects and its expense contribute to its poor compliance and unpopularity.

Colchicine has been used as an antiinflammatory agent for many years and has been shown to block the transcellular movement of procollagen, thereby reducing collagen formation, and fostering its destruction by increasing collagenase formation. The drug interferes with cell mitosis and binds microtubular proteins, inhibiting mobility and adhesion of leukocytes. Colchicine is also known to block the lipoxygenase pathway of arachidic acid, reducing chemotaxis and inflammation (70). Domingues-Malagon (71) demonstrated that the main cellular changes were collapse of the rough endoplasmic reticulum cisternae, reduction of myofilaments, and disappearance of intracellular widely spaced collagen. El-Sakka et al. (72) have used their animal model for Peyronie's disease to study the effects of colchicine on the fibrosis of tunica albuginea. Tunical fibrosis was induced in 36 male rats with TGF- β injections. They were divided into three groups of different oral therapy: Group 1 colchicine, Group 2 ibuprofen, and Group 3 water. After 6 wk, tunical tissue was collected and examined in Group 1 and 3. Group 2 received delayed colchicine treatment and was euthanized 6 wk later. Rats treated early with colchicine had less collagen deposition and elastic fiber fragmentation than the other two groups. Western blot analysis demonstrated a significant down-regulation of TGF- β 1 in the early colchicine-treated animals. The beneficial effects of colchicine were seen only in animals treated early with the drug. Akkus (70) performed a pilot study of 24 patients receiving escalating doses of colchicine, maximum dose 1.2 mg BID, for 3–5 mo. Pain resolved in 7 (78%), markedly improved curvature in 5 (26%), and decreased plaque in 10. Severe GI distress (abdominal pain, diarrhea, nau-

sea, vomiting) was noted in 33%, leading to early termination in 4 (17%). Other potential side effects were agranulocytosis, aplastic anemia, myopathy, and angioneurotic edema (70, 45).

Tamoxifen is shown to increase secretion of TGF- β in vitro and is assumed to inhibit inflammatory responses in vivo. In high concentrations, TGF- β causes macrophage deactivation and T-lymphocyte suppression, thus decreasing the inflammatory response and fibrinogenesis. Ralph (73) reported results of 36 patients treated with tamoxifen 20 mg BID for 3 mo. Penile pain improved in 16 of 20, deformity in 11 of 31, and plaque shrinkage in 12 of 35. Patients with less than 4 mo duration of Peyronie's disease responded better than those with longer duration. Overall response rate was 55%. Minor side effects included reduced libido, facial flushing, and reduced ejaculate volume. Further studies are needed to evaluate tamoxifen as another oral agent for Peyronie's disease.

Infusion Therapy

Infusion therapy does not foster outpatient treatment for Peyronie's disease; hence, not many are reported. Prostacyclin, known to dilate vessels and inhibit platelet aggregation, is used to treat Raynaud's and peripheral vascular disease (64). Because the mechanism of action of tocopherol therapy for Peyronie's disease is believed to be a prostacyclin-like effect, Strachan (64) studied prostacyclin infusion in five patients with painful Peyronie's plaque. Three of the five had improvement in pain, but it was only maintained in one patient. Four of five patients suffered severe side effects of nausea, flushing, and bradycardia. One required cardiovascular resuscitation for bradycardia and hypotension. Obviously, the results did not justify the risks of complications.

Intralesional Plaque Injection Therapy

The advantage of intralesional injection therapy is the delivery of the active agent directly into the plaque. Fibrolysin and trypsin injections were practiced in the early 1900s, followed by various other agents: steroid, parathyroid hormone, collagenase, interferon, and Verapamil.

The concept of intralesional steroid injections for Peyronie's disease was introduced by Teasley in 1952 (74). In the 24 patients treated with intralesional Cortone, no complete failures or complete resolutions were found. The rationale of local steroid injection is based on the antiinflammatory influence of glucocorticoids on connective tissues. Chesney (7) reported the results of steroid injections in combination with vitamin E therapy in 30 patients. Some with extensive plaques were given 18–20 injections, but most received 12. Overall improvement was not more than 60–70% in men under the age of 45 and 30–40% in older men. Best results were seen in diseases of short duration and plaque in the intracavernosal septum. Desantis (75) also advocated combination therapy with steroid injections and oral vitamin E. In a series of 28 patients (14 steroid alone, 6 steroid + vitamin E, 11 other), overall benefit was noted in 81% of the patients. All patients treated with both steroid + vitamin E showed moderate to marked improvement in their symptoms compared to 85% improvement in the steroid only group. It is interesting to note that they disregarded new plaque formation in tabulating success rate because of the progressive nature of Peyronie's disease. Hence, the results are questionable. Intralesional steroid injections are not without complications. Bystrom (51) reported local complications of pain, ulceration of the skin at the injection site in one patient, and circumscribed areas of gangrene around the

meatus in two. Secondary infections have been reported as well (49). Many injections were done under local anesthesia because of the pain and difficulty of injections from the high pressures generated. Because of difficulty in delivering the medication into the plaque, Winter (76) introduced the dermo-jet, a needleless injector to infiltrate the plaque with steroids. Eighty-six percent of the 21 patients treated for 6 mo reported pain relief and improved sexual performance. Seventy-six percent report improvement or resolution of plaque and/or chordee. It is difficult to evaluate treatment outcomes secondary to the natural course of disease, but 71% of the patients had prior treatment failures with other modalities.

Collagenase is one of the better-studied agents for intralesional injection therapy for Peyronie's plaque. Gelbard (77) performed the first phase-I clinical trial of intralesional collagenase injections in 1985. Thirty-one men were treated with purified clostridial collagenase with adjuvant β -aminopropionitrile to blunt fibrosis. Within 4 wk, 20 had objective improvement by plaque measurements and tracings of the erect penis. Thirteen of fourteen had resolution of pain, and three of four regained sexual function. During the follow-up of 4–15 mo, one recurrent curvature was noted. Side effects were minor and included 21 patients with ecchymosis at the injection site, and two with pain. Concern for humeral immune responses and type-I hypersensitivity reactions from circulating clostridial collagenase were cited from its scheduled use in the clinical trials. Hamilton (78) studied the human IgG and IgE antibody response in 150 controls and 44 patients receiving intralesional collagenase. Untreated, initial serum samples from 34% of the controls and 58% of the Peyronie's disease patients contained low detectable levels of IgG antibody. At 1–2 mo following injection of Nucleolysin in the Peyronie's group, IgG antibody levels increased to greater than two times pretreatment levels in over 50% of patients. No change was noted in the control group. Of the 186 individuals tested, only one (0.5%) had detectable collagenase-specific IgE antibody. No induction of collagenase-specific IgE was found in response to high dose injections of clostridial collagenase, but it should be warned that very low IgE levels could be associated with severe allergic reactions. In the first prospective, randomized placebo-controlled double-blind study in 1993, Gelbard et al. (79) set out to clarify drug effect versus hydraulic effect of the injections. He was the first to stratify patients and collagen dosage based on the Kelami system (80). Symptom survey from 49 men were performed at 1 mo and 3 mo follow-up. Overall, a statistically significant difference was seen between treatment and placebo group, but the largest response was from Group 2 (angular deformity between 30–60° and/or plaque dimension between 2–4 cm).

The rationale for the use of calcium channel blockers for the treatment of Peyronie's disease is based on *in vitro* and *in vivo* studies that show inhibition of synthesis and secretion of extracellular matrix macromolecules: collagen, glycosaminoglycans, and fibronectin. The exocytosis of extracellular matrix macromolecules is a calcium-dependent process. Verapamil, the only injectable calcium channel blocker, is postulated to stimulate remodeling and degradation of Peyronie's plaque. Because of high concentrations required to inhibit the extracellular matrix collagen synthesis, Verapamil needs to be delivered directly into the plaque to avoid systemic toxicity. In 1994, Levine (81) performed a nonrandomized, dose-escalating study of 14 men receiving biweekly injections of Verapamil for 6 mo. In the 10-mo follow-up, 91% had rapid resolution of pain within 2–3 injections, maximum single dose of 10 mg. Curvature improved in 5 of 12 patients (42%). Perceived improvement in sexual performance was reported in 7

of 12 subjects (58%). Four patients failed therapy and went on to surgical treatment. No toxicity or recurrent symptoms were recorded for intralesional Verapamil. In 1997, Teloken et al. (82) reported no advantage to Verapamil over placebo in a controlled trial of 36 patients. Levine et al. (83) believed Teloken's poor results were a result of injections made around the plaque, instead of into the plaque. In the same year, Levine et al. (83) reported a nonrandomized, prospective study of 46 men followed for an average 22 mo. Pain resolved in 97% of the patients; 76% had subjective decrease in curvature; and 72% had improved sexual function. Levine concluded that the ideal candidates are those that do not want surgery, and complain of pain, curvature less than 90° and plaque less than 5 cc without calcification (83). Further studies by Rehman (45) and Lasser (84) confirm the benefits of intralesional Verapamil injections. The most recent data presented at the AUA 2000 by Levine (85), updates the 143 men treated with intralesional Verapamil therapy for Peyronie's plaque. Pain relief was achieved in 84%, improved sexual function in 91%, subjective reduction in deformity in 63%, and objective reduction in deformity in 61%.

Benson (86) introduced interferon, α -2b in 1991. It is a potent antifibrotic agent capable of reducing collagen and glycosaminoglycan production and increasing collagenase formation. Ten patients with Peyronie's plaque were treated with interferon injections and followed for 8–12 mo. All experienced disappearance of pain; 8 of 10 noted softening and diminishing plaque size; and 5 of 10 noted diminished penile curvature with PGE₁ therapy. In 1999, Ahuja (87) reported promising results of a 6-mo biweekly interferon injection study. Twenty men completed the study with 90% resolution of pain, 65% improvement in curvature, and 85% decrease in plaque size. Results were most pronounced in early disease, but further studies are warranted for this exciting new therapy.

CONCLUSION

Peyronie's disease is a crippling condition to the sexual function of healthy middle-aged to older men. Unfortunately, even after 200 yr, the comprehension of this disease is not imminent as reflected by the multiple treatment options currently available. It is known that the majority of those afflicted will have improvement or resolution of their disease, but for the unfortunate individuals plagued with this disease long-term, the search for cure will continue. Medical treatment is a reasonable, initial option for management of pain, curvature, impotency, and palpable plaque, whereas the course of Peyronie's disease is to be determined. Candidates for medical therapy also include those who are not psychologically ready or interested in surgical treatment. The evaluation of every medical treatment is beyond the scope of this chapter, but a summary of the more popular regimens has been reviewed. The ultimate treatment strategy will be in the hands of the physician and patient based on their preferences, treatment side effects, and costs. For those who fail adequate medical management, surgical options are available.

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Surgical Treatment of Peyronie's Disease

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INTRODUCTION

Although described more than 250 yr ago, Peyronie's disease still remains a dilemma. The disease is characterized by focal or generalized alterations in the collagen and elastic fibers of the tunica albuginea resulting in narrowing or curvature of the penis during erection (1). Regarding its natural history, spontaneous resolution of the disease is uncommon and gradual progression or no change is the main outcome after the acute inflammatory phase (2). Many nonsurgical treatments are currently used, with varying degree of success [oral (3), intralesional injection (4), radiotherapy (5), ultrasound (6), laser (7) and extracorporeal shock-wave therapy (8)].

Peyronie's disease, if progressive, can result in dense fibrous plaques within the tunica albuginea, causing different degrees of angulations, indentation, or narrowing that may preclude or impair sexual intercourse, and in some cases, lead to partner dyspareunia. Although pain almost always subsides after several months, it may persist for years especially during vaginal penetration. The majority of patients retain the ability to obtain and maintain erection, but erectile dysfunction (ED) may occur in about 20% of these patients (9). The exact underlying cause of this high incidence is not completely clear. Vascular insufficiency, either arterial or veno-occlusive has been reported in 62.5% of patients with Peyronie's disease (10). About 59% of impotent men with Peyronie's disease had abnormal veno-occlusive function and 36% had evidence of

impaired arterial blood flow (11). Some believe that structural alterations in the trabecula of the corpus cavernosum result in failure to compress the subtunical venules causing veno-occlusive dysfunction (1).

Surgical treatment has evolved over the years. The goal of the procedures is to straighten the curved penis to allow resumption of sexual intercourse. In the patient in whom impotence is present, this factor must also be addressed. Unlike in the past when all patients, potent or impotent, were offered a penile prosthesis implantation, today we are much more conservative. The advent of less invasive treatments for ED (oral sildenafil, intracavernous injections, intraurethral therapy, and vacuum constriction devices) has changed the management of these patients. If the patient is satisfied with nonprosthetic therapy for his ED, we prefer to offer reconstructive surgery for penile deformity as long as the patient realizes the need to continue ED therapy after surgery.

INDICATIONS AND THERAPEUTIC STRATEGY

There is considerable variation in the deformity that makes sexual intercourse difficult. Usually, it causes more psychological distress than physical disability in young men and sometimes even little deformities need to be corrected in this group. In contrast, a man who has a stable relationship is able to cope with much more severe deformity. In general, ventral curvatures cause much more difficulty than dorsal or lateral ones.

We usually discuss the following therapeutic strategy with patients with Peyronie's disease. No treatment is recommended in men with minimal deformity that does not interfere with sexual function. Nonsurgical treatment is offered to patients with pain, plaque, or deformity of less than one year's duration. Surgical treatment should be delayed until the acute inflammatory phase has resolved and the disease process has stabilized (12). Surgery is indicated in the patient with severe deformity of more than one year's duration, whose condition has been stable for more than 3 mo and for patients who have penile shortening, narrowing, or indentation, or a combination of the above that preclude normal sexual intercourse. If the patient is also impotent and fails to respond to nonsurgical ED treatment, we recommend a penile prosthesis insertion (13).

Patients with unrealistic expectations will not be satisfied with surgical outcome and are not good candidates for corrective procedures. In addition, any patient who is not psychologically ready or interested in surgery, regardless of the duration or severity of disease, should not be considered for surgery (14). Patients with persistent painful erections for more than 1 yr should be advised that the pain might not subside after surgery.

PREOPERATIVE EVALUATION

History

A detailed medical and psychosexual history should be obtained, including mode of onset (sudden or gradual), progression of symptoms, history of trauma or penile surgery, drug abuse, medication, and family history. It is also important to note the ability to have intercourse, penile rigidity, shortening, indurations, hourglass constriction, pain with or without erection, and psychological impact.

Physical Examination

The penis can be examined while gentle stretching is applied to identify plaque's size, number, and location. We routinely measure and note the penile length in both

the flaccid (stretched length) and erect (short and long side) state. Penile erection can be induced by intracavernous drug injection (alprostadil or papaverine), masturbation, or applying a vacuum device. A photograph or drawing of the erect penis to document penile deformity is highly recommended. The circumcision status should also be evaluated (9).

Other Investigations

ULTRASONOGRAPHY

High-resolution sonography allows for detailed objective assessment of the plaque and help defining multiple areas of involvement. However, except in cases in which early calcification can be identified, information obtained from sonography is often not superior to that obtained through a careful physical examination (15).

COLOR DUPLEX SONOGRAPHY

This exam performed before and after intracavernous injection of a vasodilator allows for a thorough assessment of the structure of the corpus cavernosum, tunica albuginea, and penile vascular function. Moreover, it is an excellent tool to detect collateral arterial connections between dorsal and cavernous, as well as the cavernous and spongiosal arteries (9). Surgical damage to these collateral vessels during neurovascular bundle dissection may lead to impotence (16). Therefore, color duplex sonography is highly recommended in patients who complain of impaired erection or are contemplating plaque surgery (9,15–17).

DYNAMIC INFUSION CAVERNOMETRY CAVERSONOGRAPHY

This is a more invasive test used only in impotent patients with strong suspicion of corporeal veno-occlusive dysfunction. If localized venous leak is found, patients are given the option to undergo a venous surgery at the same time of the surgical correction of penile deformity or a penile prosthesis (15).

MRI

Magnetic resonance imaging is applied only in the rare cases of extensive Peyronie's disease for a detailed anatomy visualization prior to a surgical intervention (18).

SURGICAL TECHNIQUES

Over the years, urologists have developed different techniques and modified existing surgical approaches in an attempt to correct the penile deformity associated with Peyronie's disease (19). Currently, the surgical procedures usually used to treat patients with this disease can be classified into three different groups:

1. Reconstructive surgery performed on the convex side opposite the curvature (shortening procedure);
2. Reconstructive surgery on the concave side, which means plaque excision or incision and grafting (lengthening procedure);
3. Penile prosthesis placement with or without excision or incision of the plaque (15).

The combination of techniques is frequently described, as well as modifications of a standard procedure, what makes the judgment of the results sometimes confused in the literature. Because no single technique is feasible to all patients, the surgical procedures

indicated are highly dependent on the type, degree of deformity and penile vascular status of the patient (20). Good patient selection, attention to surgical details, and personal experience of the surgeon with each technique are factors that may influence the final results, no matter the technique applied.

Tunica-Shortening Procedures

NESBIT PROCEDURE

This is one of the most popular and frequently used techniques to correct Peyronie's deformity. Described initially by Nesbit for the treatment of erectile deformities because of congenital abnormalities (21), it was first applied to Peyronie's patients by Pryor et al. with good initial results (22). The largest series on this surgery, with 359 patients submitted to this procedure, mentioned 82% of overall success (ability to have coitus with a full erection and a residual deformity of less than 10 degrees). Owing to better patient selection, their success rates increased to 90% in recent years (23). Others authors reported it as a relatively simple, safe, and effective procedure. Goldstein et al. (24) reported on 19 patients, all of them had successful results and Poulsen and Kirkeby (25) described good (85%) and acceptable (6%) results in 48 patients.

The surgery is performed through a circumcision incision. The penile skin is retracted and an artificial erection is induced by injection of saline into one of the corpora cavernosa via a 21-gage scalp vein needle, while the crura are compressed. Although a tourniquet might be used, some authors refer that it can sometimes lead to inaccurate assessment of the bend (16). The site of maximum convexity is marked with a surgical pen or a stay suture, usually contralateral to the plaque. Some surgeons prefer to apply two Allis forceps to the tunica albuginea while the penis is flaccid and then repeat the erection in order to be sure about the amount of tissue to be excised. The Buck's fascia is incised and dissected medially. If necessary, the dorsal neurovascular bundle or the corpus spongiosum is carefully dissected and retracted from the tunica albuginea. A 5–10 mm transverse ellipse of the tunica albuginea is excised at the point previously marked. It is estimated that the ellipse should be 1 mm wide for every 10 degrees of curvature (26). The tunica albuginea defect is closed with absorbable sutures (0 PDS), making sure to bury the knots. An artificial erection is repeated to check the immediate result. The Buck's fascia and the skin are closed with 4.0 chromic sutures and the penis is wrapped with a light dressing. Patients are advised to avoid intercourse for 6 wk. Variants of this technique have been reported, with good results as well (27,28).

Despite the good results in terms of straightening the penis, this technique presents a high incidence of penile shortening (13–37%) (19,26). This complication, however, does not preclude the great majority of men from having sexual intercourse. Nevertheless, patients should be warned about the shortening during the preoperative evaluation (26). Other complications reported are ED, hematoma, urethral injury, suture granuloma, glans numbness, and phimosis (26). Besides, penile herniation due to dehiscence of the tunica has been reported (9). The candidates for this procedure are potent patients with adequate penile length, curvatures of less than 60° or impotent patients who are satisfied with oral, intracavernous drugs, or vacuum device for erections.

MODIFIED NESBIT PROCEDURE

A modification of the Nesbit procedure was described by Lemberger (29) and further refined by Yachia (30). Basically, the approach is similar to the Nesbit procedure:

after degloving the penis, Allis clamps are used to grasp and gather the tunica albuginea opposite to the point of maximum penile curvature, during an artificial erection. A long longitudinal (1–2 cm) or multiple smaller incisions are made between indentations left by the jaws of the Allis clamps. The incisions are then closed horizontally using permanent or absorbable suture with knots buried at both ends. Buck's fascia is closed over the corporotomy with absorbable sutures. The postoperative management is similar to the Nesbit procedure.

Many authors reported a high percentage of good results. Lemberger et al. (29) reported successful correction of the curvature in 95% of patients, at a mean follow up of 10 mo. Sassine et al. (31) described satisfactory outcome in 95% of patients with congenital and Peyronie's disease in a 10-yr period. In a recent series of 30 cases, Licht and Lewis reported better results in terms of correction of curvature (93%) when compared to standard Nesbit procedure (79%). None of their patients was impotent postoperatively and 83% were satisfied with the procedure (19). Excellent rates of penile straightening (89%), satisfaction (79%), and preservation of erectile function (95%) was also reported by Daitch et al. recently (32). The procedure is relatively easy to perform, prevents removal of any tissue, requires minimum postoperative care, and presents low complication rates. However, penile shortening remains the major drawback of this corporoplasty procedure, affecting as many as 67% of the patients (19). The same indications for the Nesbit procedure are applied to this technique.

PPLICATION PROCEDURES

This procedure aims to have the same straightening effect to the penis as the others surgeries previously described, but not necessarily making any incision or excision in the tunica albuginea. Some authors recommend this as an option for cases with minor curvature (less than 60°), no hourglass deformity or hinge effect in potent patients, or impotent men that are willing to undergo intracavernous injection after surgery (16). Others consider this procedure for most cases of deformity because of Peyronie's disease (27,33,34). Plication takes approximately 30 min and can be performed on an outpatient basis, depending on the experience of the surgeon. We usually perform this surgery under local anesthesia. After the genitalia are prepared in a sterile fashion, a local penile block is achieved with 0.25% bupivacaine at the base. An artificial erection is induced by intracavernous injection of papaverine (30–60 mg) or alprostadil (10 µg). In cases of dorsal curvature, a longitudinal ventral incision is made to identify the corpus spongiosum. Deep parallel nonabsorbable sutures (2-0 Ticron® or Tevdex® are placed in the paraurethral ridges, about 3 mm from the spongiosum (Fig. 1A). For ventral curvature, a circumcision incision is made; the skin and subcutaneous tissue are dissected and reflected to the base of the penis. Deep plicate sutures are placed onto the tunica marked with a marking pen between the deep dorsal vein and the arteries (Fig. 1B). The 2-0 Ticron sutures are tied gradually until the penis is straight to avoid over- or undercorrection. Two to three pairs of sutures on each side are usually required. No dissection of the neurovascular bundle or corpus spongiosum is necessary. For lateral curvature, lateral sutures are placed. If the penis remains erect at the conclusion of the plication, a 21-gage scalp-vein needle is inserted, 10 mL of corporeal blood are aspirated and diluted phenylephrine hydrochloride solution (500 µg) is injected every 3 to 5 min until detumescence is achieved. The skin is reapproximated with 4-0 chromic sutures and the penis is wrapped with a lightly compressive dressing, which is changed the following morning. The patient is advised to abstain from sexual intercourse for

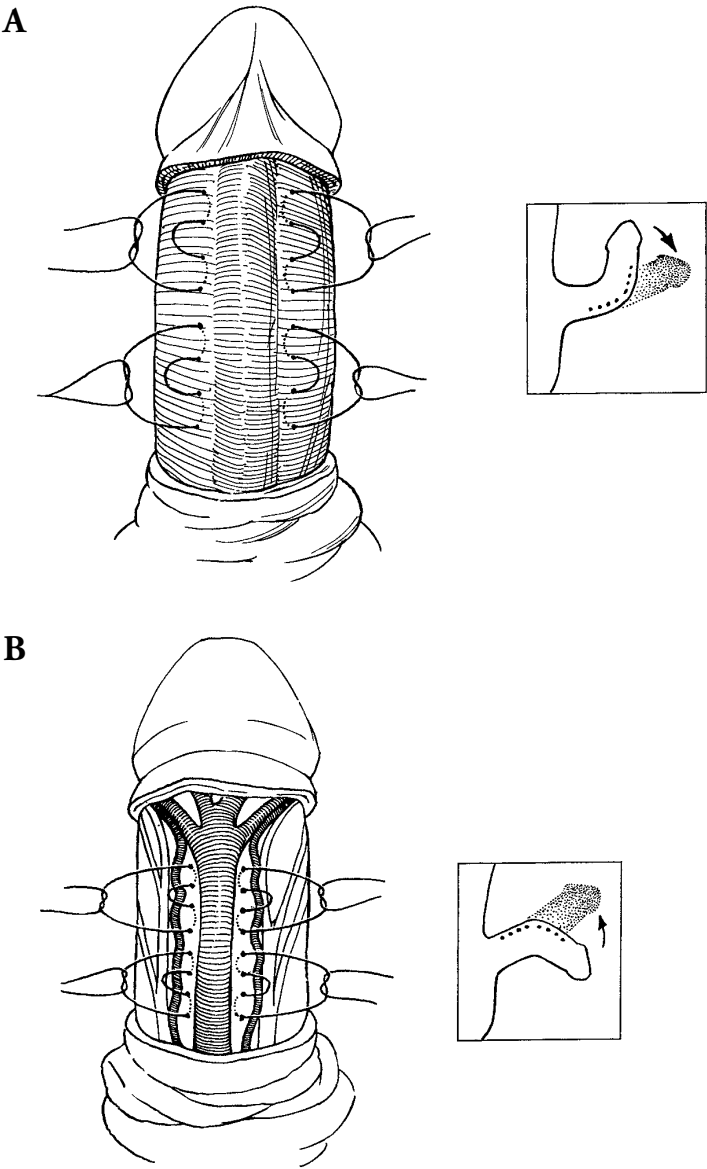


Fig. 1. Plication procedures performed on a papaverine-induced erect penis. Dissection of neurovascular bundles is not necessary. The location of paired non-absorbable plication sutures is shown: **A**, perispongiosal for dorsal curvature. **B**, between dorsal vein and dorsal arteries for ventral curvature. The suture entry sites are marked with a marking pen before suture placement.

4–6 wk. Because the procedure is performed on an erect penis and the sutures are tied until the penis is straight, this is the least invasive and most successful technique in the authors' experience.

The results of plication vary significantly between series. Klevmark et al. (35) reported 100% of success, whereas Poulsen and Kirkeby reported good results in only 38% of the patients after primary plication (25). Levine and Lenting (16) reported 91% of complete straightening and potency after mean follow up of 19.5 mo. Recently, Thiounn et al. (33) reported 81% of satisfactory cosmetic and 62% of satisfactory functional results. Evaluating nocturnal penile tumescence (NPT) in a group of potent and impotent Peyronie's patients before and after this procedure, Claes and Baert (34) found that corporeal plication significantly enhanced the quality of erectile episodes, by increasing penile rigidity, during rapid eye movement sleep.

The complication rates reported are lower, mainly erectile insufficiency (9%) and narrowing of the shaft (16). We have also seen encapsulated hematoma, prolonged painful erection, and complaint of discomfort from granulomas caused by the nonabsorbable sutures. Some authors described high recurrence rates and poor results with long follow up (25,27,36,37). In our recent survey of 84 patients with congenital and acquired penile curvatures the recurrence of curvature, shortening and pain was 14%, 51%, and 8%, respectively. The overall patient satisfaction with the procedure was 98%, reflecting an adequate preoperative counseling (38).

Tunica-Lengthening Procedures

Lengthening of the tunica with graft replacement is indicated in patients with severe curvature resulting in a shortened and deformed penis or presence of narrowing or hourglass deformities. It can also be applied to patients that present recurrent curvature after other surgical procedures. Several reconstructive surgical techniques using different kinds of autologous tissues or synthetic materials [dermis (39), tunica vaginalis (40), dura mater (41), temporal fascia (42), dorsal or saphenous vein (43), polytetrafluoroethylene (44), and Dacron (28)] have been reported. Most of these surgeries applied the concept of Devine and Horton of plaque excision and patch of the tunical defect with a dermal patch (39). They reported years later a high rate of reduction of curvature and pain (85%) and patient satisfaction (70%) using this kind of patch (45). Hicks et al. (46) applied the same technique in 15 patients, and described return to normal sexual function without residual chordee or pain in 75% of the patients. However, others authors could not reproduce the good results. Melman and Holland (47) reported a series of seven patients treated with the dermal graft, with failure in all patients. Palomar et al. (48) reported disappointing results in seven of ten patients undergoing the dermal grafting procedure. Venogenic impotence following the surgery has also been reported (49). Because of the high incidence of ED (9) contracture of the graft, late recurrence and unpredictable long-term results, excision of plaque, and grafting with dermis is less performed nowadays.

In 1991, Gelbard and Hayden (42) introduced the concept of incision of plaque and grafting, decreasing some of the complications of excising the tunica albuginea. These authors stated that, because of the diffuse nature of the disease process, excision and patching a focal plaque was not justified. The less the tunica and its underlying erectile tissue are altered, the better the postoperative erectile rigidity. They applied a temporalis fascia free graft as patch in 12 patients with disabling penile deformities. According to these authors, this tissue presents high tensile strength, low

metabolic requirement, and minimal contracture when applied as free graft. Good results were obtained in 11 patients, and long-term follow up (22 mo) showed no recurrences. Some years later, Gelbard (50) reported his last 30 cases using the temporalis fascia, with good results (straight penis) in 80%. He also concluded that lateral curvatures were much more difficult to correct using the incision technique and patch graft.

Rigaud and Berger (51) introduced the concept of multiple plaque incision to lengthen the penis in 22 patients with Peyronie's disease. Five men underwent incision of the plaque and dermal patch, but in two of them, further penile shortening occurred and a prosthesis implantation was carried out. Eight patients underwent incisions in the tunica and penile prosthesis implantation, without patches. All patients were able to have sexual intercourse postoperatively, but penile paresthesia was reported in two patients. Five men with severe shortening underwent surgical reconstruction by circumferential incision of the tunica, dilation of the corpora, and implantation of prosthesis. The corporotomies allowed the distal shaft to be telescoped forward and the defects were covered with polytetrafluoroethylene. An average of 1.5 in in penile length was gained with this maneuver. The overall patient satisfaction rate was great, but also the complications (50% in both groups). Placement of dermal patch after incision of the tunica is also recommended by others authors. Levine and Lenting reported 94% of complete straightening in cases of complex or bidimensional curvatures, with 75% of full erectile capacity (16).

So far, there is no graft material that is perfect for replacing the diseased tunica albuginea. The synthetic materials are inelastic and have some risks of foreign body reaction and infection. Dura and fascia may provide a strong covering for the tunica, but they do not stretch like a normal tunica, and recurrence of the curvature may occur. The free dermal graft usually contracts after several months and the good results applying a penile dermal flap are based on a single experience (52). An ideal patch material should combine some features: flexibility, availability, rapidity of healing, low cost, little tissue reaction, strong enough to sustain the intracorporeal pressure during erection, and technical ease (53). In our opinion, the venous patch graft has many of these characteristics. Animal studies showed that the venous patch attained the thickness of the normal tunica albuginea after several months and remained pliable and supple (53,54). Theoretically, venous patch can regain blood supply within minutes, thus preventing graft contracture (9). Recently, Lue et al. (55) reported a lengthening procedure using circumferential tunical incision and circular venous graft, followed by daily stretching with a vacuum device in four patients. Two of the four patients gained two inches at 12-mo follow up and regained partial penile rigidity similar to preoperative erections. All patients were satisfied with the surgery.

PLAQUE INCISION AND VENOUS PATCH GRAFTING (FIGURE 2)

A circumcision incision is made and the skin and subcutaneous tissue are reflected to the base of the penis. For dorsal curvature the deep dorsal vein is identified, ligated, resected. The paired dorsal neurovascular bundles are carefully dissected off the tunica albuginea. Surgical loupes are used to dissect the bundle free from any fibrous extensions from the plaque, restoring its length. If an arterial communication between the dorsal and cavernous arteries is identified on preoperative duplex ultrasonography, great effort should be made to preserve it. For ventral curvature, the corpus spongiosum is dissected off the corpora cavernosa. To assess the curvature, an artificial erection is induced with

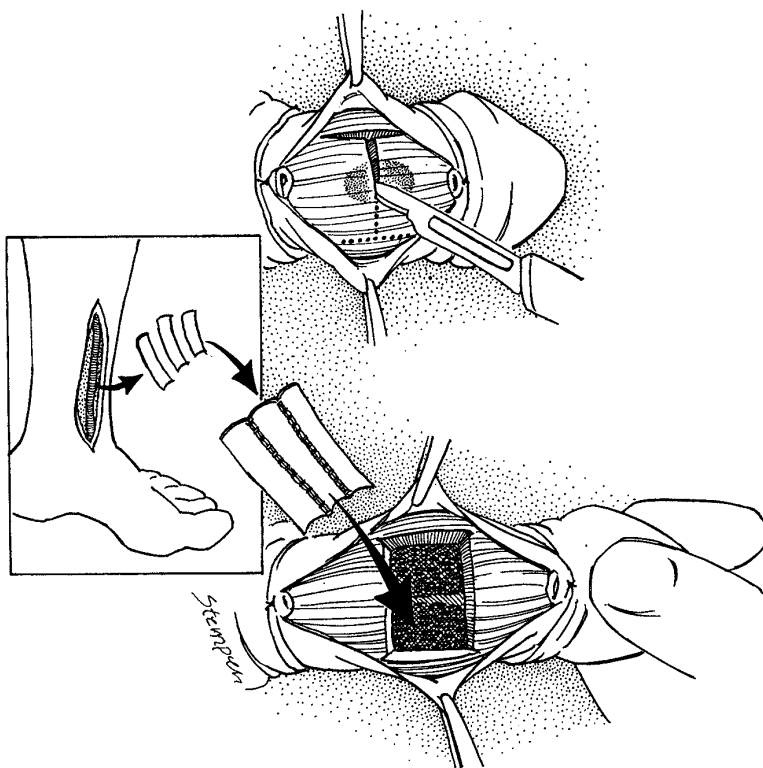


Fig. 2. H-incision and saphenous vein grafting. H-shaped transverse relaxing incision in the center of plaque for correction of penile curvature. Dissection of neurovascular bundles (medial to lateral) with tenotomy scissors was previously performed under $\times 3$ or $\times 5$ magnification loupes. The tunical defect is measured by stretching the penis longitudinally and transversely. A segment of saphenous vein is resected, opened, cut into several pieces and stapled together with vascular clips. The vein graft is sutured to the tunical defect with the endothelial surface facing the inside of the corpus cavernosum.

saline solution injected into the corpus cavernosum via a 21-gage scalp-vein needle while the crura are compressed. The site of the relaxation incision is marked with a surgical pen (usually in the center of the curvature). An H-shaped relaxation incision is made; transverse for curved penis, longitudinal for hourglass deformity. The penis is stretched longitudinally and transversely and the defect is measured to determine the appropriate size of the graft. Occasionally, more than one incision may be necessary to correct a longer or complex deformity, but the H-shaped incision suits most deformities. The saphenous vein is isolated near the ankle or in the thigh and harvested. The vein is divided into several segments and assembled with vascular clips applied to the adventitial surface. The patch graft is then sutured to the defect, endothelial side down, with continuous 4-0 polyglycolic acid sutures. Another artificial erection is induced to assess the deformity. If necessary, another patch graft may be applied. If minor correction is still needed, a 2-0 Ticon plication suture is placed to compensate for under or over correction, or to correct a lateral curvature. The penile wound is closed with 4-0 chromic sutures and wrapped with

light dressing, which is changed daily for 10 d. The patient is advised to abstain from sexual intercourse for 6 wk (56).

A large series of 112 patients treated with this technique was reported recently (10). In approx 96% of patients, the penis became straight, with no narrowing or indentation, and in 83%, the postoperative length was the same or longer. A subjective evaluation of surgical results showed that 92% of the patients were satisfied and improved their psychological state and partner relationship. Postoperative complications included penile edema for more than 3 mo (3 patients); leg-wound infection (3 patients); prolonged lymphatic leakage after femoral incision (2 patients), and lymphocele (1 patient). Less-rigid erections postoperatively was observed in 13% of the potent patients, and 46% of the impotent men who complained of decreased penile rigidity before surgery. Possible causes are further deterioration of the erectile tissue after grafting, unrealistic patient expectations, or worsening of vascular insufficiency. Kadioglu et al. (57) reported straightening in 75% of patients treated with the same technique, but 20% presented residual curvature. The potency was preserved in all patients (20), except one, and shortening was not seen in their patients. Moriel et al. (58) reported approx 80% of straightening with the venous graft, but plication sutures were also necessary in 100% of the cases. Arena et al. (59) reported their results using dorsal vein in 24 patients with severe curvature (60°–90°). After a median follow up of 24 mo, 19 patients were able to perform sexual intercourse, but 50% reported some degree of penile shortening Kim et al. (37) in a long-term follow-up (31 mo) after plaque incision with carbon dioxide laser and venous patch graft, showed good results in 67% of the patients, but high rate of shortening as well. Based on the existing reports, we agree with others authors (60) that, in select patients, plaque incision with grafting represents an excellent option for surgical management of Peyronie's disease.

New graft materials, such as cadaveric human pericardium (61) and porcine small intestinal submucosal (62), has recently been used to fill the defect after plaque incision or excision. Longer-term studies on larger cohort of patients are needed before recommendation can be made.

Penile Prosthesis Implantation

This is the treatment of choice for patients with both Peyronie's disease and ED and who are dissatisfied with nonprosthetic ED therapies. In the past, many potent patients with penile deformity were treated with a prosthesis. However, this indication has been modified since the less-invasive treatments replaced penile prosthesis as the initial treatment for ED. Many urologists will now offer reconstructive procedures to the patient if he responds well to any of the nonprosthetic treatments for impotence (9). The patients who fail straightening procedures with postoperative erectile inadequacy requiring medical or surgical support for coitus are also candidates for penile prosthesis implantation. This is a single procedure that has excellent success, low morbidity, and corrects both penile deformity and ED (63).

Regarding the type of prosthesis, it appears that the inflatable type is best tolerated and produces better results than the malleable ones. Carson reported a series of 30 patients treated with the AMS 700 CX inflatable prosthesis, with 93% of straightening, no postoperative infection, mechanical malfunction, or urethral erosion (63). Montorsi et al. (64) in a study using the same prosthesis described 70% of complete penile straightening at 6-wk follow-up and 75% of satisfaction on long-term follow up. How-

ever, the shortening of the penis due to advanced Peyronie's disease was not corrected by the operation, and was the main cause of postoperative patient dissatisfaction. As attested by others authors, this is an important issue that should be explained to the patients in the preoperative interview. As a result of the pathological changes induced by the disease in the corpora cavernosa and tunica albuginea, there is a limited potential for postoperative penile elongation in penile prosthetic surgery (64). The malleable penile implants may also be used. Whereas some investigators have described good results with this kind of implant (65), Montorsi et al. (66) reported that on a long-term basis, placement of a semirigid penile prosthesis for Peyronie's disease is associated with a significant patient-partner dissatisfaction rate (52 and 60%, respectively). With the high level of reliability of the modern inflatable prosthesis, mechanical failure is no longer an important issue. However, if an inflatable penile prosthesis is used, it is recommended not to use the distally expanding prosthesis, such as AMS 700 Ultrex, because when the device lengthens it also tends to bend the penis (9). Buckling during sexual intercourse was also reported with this prosthesis (67).

For most patients, placement of a penile prosthesis will adequately straighten the penis. However, if significant deformity remains after the prosthesis is inflated, an additional procedure will be needed to straighten the penis. Options include modified Nesbit corporoplasty, plaque incision with or without grafting, penile modeling, and multiple relaxing incisions (63). Wilson and Delk (68) described the procedure of bending the penis forcefully over the inflated cylinders at the area of maximum curvature. For this procedure, high-pressure cylinders such as AMS 700CX or Menthor Alpha-1 appear to be best suited. Though high success rate with minimal complication is reported (63,68), caution should be exercised during the maneuver because complete anesthesia of the penis has been reported (9). If adequate penile straightening is not achieved with this maneuver, plaque incision may be carried out. After inflation of the prosthesis, the area of maximum curvature is incised. Careful dissection of the neurovascular bundle and the urethra is required for this procedure. The remaining defect must be grafted if the defect is very large, or there is risk of bulging or protrusion of the cylinder when the prosthesis is inflated. Autologous or synthetic materials can be used as a graft. Satisfactory results have been reported with multiple plaque incisions without patch (51). For severe curvatures, a series of small incisions may be used rather than a large relaxing incision, expanding the scarred tunica maximally and preventing possible bulging effect of the prosthesis (50).

No matter what approach is used, the patient should be well advised about possible complications of a penile prosthesis implantation (infection, mechanical failure, distal penile hyperesthesia or hyposthesia, scrotal and penile pain, persistent curvature, flaccid glans) and no guarantees or promises should be given in terms of additional length (69). Extra caution should be exercised with the diabetic patients, as the infection rates are higher in this group. In order to prevent dissatisfaction with the surgical results, all unrealistic expectations should be addressed with the patient and the partner during preoperative consultations.

CONCLUSION

Peyronie's disease remains a poorly defined disease because of inadequate understanding of its pathophysiology and pathogenesis. Most of the researchers agree that surgical management of Peyronie's disease should only be attempted after the disease

is stable, as one of the characteristics of the disease is the progressive pattern in the first months. The tunical alterations are unpredictable, leading to different degrees of curvature and other related symptoms. Assessment of the erection status is essential to better management of the condition.

Proper patient selection and attention to surgical detail are essential to good results when treating Peyronie's disease, and the approach over the past several years has been more conservative. In our view, if penile length is not a concern, it is better to perform plication procedure or Nesbit technique or one of its variations. Grafting the incised tunica with vein patch is an excellent alternative, but requires more surgical skills and experience. Penile prosthesis implantation is a good choice for patients with both erectile dysfunction and penile deformity.

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INTRODUCTION

Priapism, described as “intense erection, which lasted through the night with but little mitigation” by Tripe (1) in *The London Lancet* in 1845, has an ancient origin derived from Greek mythology. Priapus, a fertility god, is generally depicted as bearing a huge and erect phallus (2). Priapism, a prolonged, usually painful erection, is now recognized as a spectrum of diseases with multiple etiologies that require different diagnostic and therapeutic strategies to avoid erectile dysfunction (ED). Recent research has further defined the pathophysiology of ischemic corporal tissue responses, high-risk populations, and optimal treatment algorithms. This chapter will review the clinical management of both low-flow (ischemic) and high-flow (arterial) priapism.

PATHOPHYSIOLOGY

Penile flaccidity results from the balance of vasoconstrictive and vasorelaxant influences in the corpus cavernosum. Basal arterial inflow is low, and the contracted state of the trabecular smooth muscle allows immediate venous drainage. Perturbation of either aspect of this balance will lead to tumescence and eventual rigidity. Neural regulation of the penile vasculature is not limited to the cavernosal arteries, but extends to the tra-

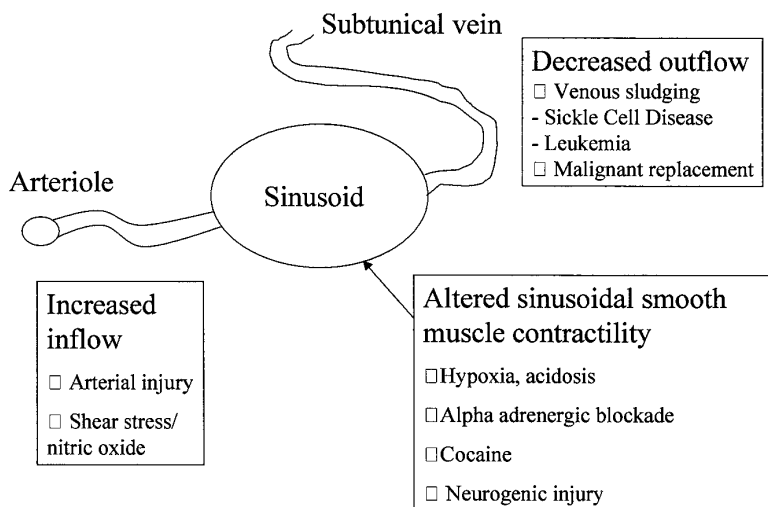


Fig. 1. Points of regulation of sinusoidal filling in the corpus cavernosum.

becular smooth muscle and endothelium of the intracorporal sinusoids (3). Corporal arterial inflow is determined by the diameter of the cavernous artery, which, in turn, is controlled by the parasympathetic and sympathetic innervation of the arterial smooth muscle, as well as potent dilators and constrictors from the endothelium. Venous outflow control is a more complex phenomenon, and can be influenced by numerous anatomical, neurological, pharmacological, and hematological conditions that effect the sinusoids, surrounding smooth muscle and subtunical veins (see Fig. 1).

Priapism is defined as a prolonged penile erection, often causing pain (4). Recognizing that some patients have no pain, a classification based on intracorporal oxygenation status and the pathophysiology of prolonged erection has been adopted. Both subtypes represent an imbalance between the arterial inflow and venous outflow of the corpora cavernosa. Low-flow priapism results from an abnormal venoocclusive state leading to intracorporal hypoxia, acidosis, and painful erection. Traumatic injury to the arterial inflow of the penis leads to a high-flow state with normal venous outflow and a different time-course, treatment, and long-term outcome.

High-Flow Priapism

High-flow priapism results primarily from traumatic injuries to the cavernous arterial system. The condition was first described by Burt et al. (5), but Hauri et al. (6) first used the term high-flow priapism in 1983. Since then, many cases have been reported. Erection results from the loss of regulation of arterial inflow, without activation of venoocclusive mechanisms (7). Batsuba et al. (8) noted that arterial priapism occurs in the absence of neurogenic-mediated relaxation, and may be sustained by high-oxygen tension and shear stress associated with laceration of the cavernous artery. Blunt trauma to the penis or perineum is the most common cause, with a variable delay in the onset of painless erection: erection has developed as quickly as 1 d after injury,

but the development of an arterial-sinusoidal fistula may take several days to develop and a delayed presentation is not unusual. Because the corpora are not ischemic, patients have presented with several-year-histories of painless partial erection.

Blunt trauma is the typical initiating event in high flow priapism, but other mechanisms of injury have been reported. These include penile revascularization, intracavernous injection therapy, prior treatment of low flow priapism, sickle cell disease, and idiopathic (9–11). The common pathophysiology is deregulation of arterial inflow to the penis, which overloads venous outflow. Several centers have postulated that high-flow priapism may occur as a result of *treatment* of ischemic low-flow priapism (11,12). Whether this represents an anatomical injury to the cavernous arterial system or a more global defect in smooth-muscle constriction after ischemic injury remains unknown.

Veno-occlusive Priapism

Veno-occlusive priapism rapidly leads to conditions that further impede smooth-muscle contraction, thus making resolution less likely with time. Although the events initiating the ischemic state are varied, progressive hypoxia and acidosis are common to all causes of low-flow priapism. Broderick and Harkaway showed that there is a clear trend toward deoxygenation, acidosis, and hypercarbia with prolonged erection after intracavernous injection (13). In vitro studies confirm that corporal smooth-muscle contractile responses are highly pH dependent (14). The time-course of these events progresses over a 3–6-h period, with acidosis preceding severe hypoxia. Acidosis alteration in smooth-muscle responsiveness does not alter the contractile properties of norepinephrine, and emphasizes the role of early intracorporal pharmacological intervention in the treatment of priapism.

ETIOLOGY/EPIDEMIOLOGY OF LOW-FLOW PRIAPISM

Low-flow priapism comprises the great majority of cases of prolonged erection reported in the literature. Common causes include psychotropic medications, hematological abnormalities, and intracavernous injection. Despite the reduced use of intracavernous injection therapy in the sildenafil era, urologists will continue to see new populations of patients as a result of new central nervous system agents and increasing illegal drug use.

Idiopathic

Priapism without a known cause should be a diagnosis of exclusion. Numerous patients will present without any risk factors, but careful evaluation is critical to exclude any correctable or life-threatening causes. As many as 30–50% of cases of low-flow priapism are considered idiopathic (15).

Sickle Cell Disease

African Americans are affected by sickle cell disease (SCD) as homozygotes (0.2%) and heterozygotes (8%). Priapism as a result of sickle cell anemia remains one of the least-investigated complications of this disease, although it affects a significant percentage of males with SCD (16). The pathophysiology of hemoglobinopathy-related priapism is not completely understood, but the proposed mechanism is one of sickling of red blood cells and sludging of blood within the corporal sinusoids, without thrombus formation (17). Other factors include the mild acidosis accompanying hypoventila-

tion during sleep, and abnormal endothelial adherence (18). Sludging leads to hypoxia, acidosis, and thus impairment of smooth-muscle function, which may amplify the ischemic environment within the cavernosa.

Tarry et al. in 1987 suggested that approx 10% of patients with SCD experience priapism (17). Two categories of priapism were noted: recurrent short episodes referred to as stuttering priapism, and single prolonged episodes (19). More recent clinical studies suggest a markedly higher incidence of priapism. Fowler et al. found that 38% of men with sickle cell anemia reported past priapism attacks, although many of these episodes were self-limited and very few developed ED (20).

In a 1999 study of 98 patients with homozygous sickle cell anemia (Hb SS) and sickle cell beta (0)-thalassemia (Hb S-beta (0)) between 5–20 yr of age, Mantadakis et al. (21) determined that the actuarial probability of experiencing priapism by 20 yr of age was 89%. The mean age at the initial episode was 12 yr, the mean number of episodes per patient was 15.7, and the mean duration of an episode was 125 min. Seventy-five percent of the patients surveyed had at least one episode starting during sleep or upon awakening, and the episodes most commonly started at 4:00 AM. These investigators concluded that the high probability of priapism in males with SCD warrants much greater vigilance on the part of parents and physicians.

Thus, SCD can cause a variety of presentations, ranging from single episodes of self-limited prolonged erection to intractable low-flow priapism requiring shunting and leading to severe corporal fibrosis (22). Hematological parameters do not seem to predict severity of erectile response (20), and even the sickle cell trait (heterozygotes) may be a risk factor for acute priapism associated with the use of proerectile agents such as sildenafil (23). As outlined below, interventions for cases of SCD-related-priapism must be tailored to the severity of the presentation, and a more-aggressive approach to this potentially devastating complication has recently been proposed (24).

Other Hematological Disorders

Diseases other than SCD that affect hemoglobin and red blood cell function have been implicated in priapism. Erythropoietin therapy in a patient on chronic hemodialysis led to priapism; the effect of erythropoietin on the coagulation cascade may explain this unusual complication (25). Hb Olmsted (beta 141 *Leu*→*Arg*), a rare hemoglobin variant, necessitated splenectomy in a boy who developed priapism 8 yr after splenectomy, during a hemolytic febrile episode (26).

Leukemia, most commonly chronic granulocytic but also acute variants, may lead to priapism in children and adults. The presumed mechanism is sludging of white blood cells within the corpora (27,28). The association between heparin and priapism has been recognized: abnormal platelet aggregation has been implicated in the pathogenesis of this side effect, and for this reason, irrigation of the corpora with heparinized saline is no longer recommended (29).

Total parenteral nutrition has been linked to priapism, and is most likely related to lipid infusions. High concentrations of parenteral lipids may increase blood coagulability, distort erythrocytes, and increase red blood cell aggregation (30). Reduction of the lipid concentration from 20 to 10% may reduce the likelihood of further episodes of priapism.

Intracavernous and Intraurethral Therapy

Ironically, the most common cause of priapism in many emergency rooms is the appropriate or inappropriate use of intracavernous injection therapy. All intracaver-

nosal therapy can induce prolonged erections, although different agents have different risk profiles (31). Alprostadil was reported to have a priapism rate of 1% in clinical trials reported by Linet et al. (32). Patients at highest risk for priapism include those with neurogenic or psychogenic ED (33). The intraurethral administration of alprostadil has a much lower incidence of priapism (34); no episodes were reported in clinical trials, but cases have been reported (35).

Prescription Drugs

Numerous pharmacological agents have been reported to cause priapism. The most common agents include psychotropic drugs and antihypertensives. In a large series of patients with priapism, 28% were related to phenothiazines and trazadone after excluding ICI (36). Of psychotropic drugs, antipsychotic agents, both typical and atypical, cause a significant number of priapic events; the alpha-adrenergic antagonist properties of these drugs relates to the frequency of prolonged erections (37). Antidepressants, especially trazadone, but also the selective serotonin reuptake inhibitors, also cause ischemic priapism (38,39). The mechanism of trazadone-induced priapism is well elucidated and relates to its alpha adrenoreceptor blocking properties (40). Antihypertensive agents most commonly implicated in priapism include hydralazine, guanethidine, and alpha-adrenergic antagonists (41).

Drug therapy for sexual dysfunction may also induce priapism. Sildenafil citrate caused ischemic priapism in a young male with mild ED (42), and androgen-replacement therapy with high-dose testosterone and androstendione has also been complicated by priapism (43,44).

Numerous other drugs have been reported to cause priapism including the antirejection agent FK 506 (45), and combinations of the aforementioned drugs with illegal drug use can also increase the risk for priapism.

Illegal Drugs

Cocaine has been implicated in an increasing number of cases of priapism. Both nasal cocaine and crack have led to ischemic prolonged erections (46,47). The pathophysiology is unclear, but may represent the impaired ability to achieve detumescence, which could be the result of a depletion of presynaptic norepinephrine, preventing sinusoidal contraction and the efflux of penile blood (48). Fiorelli et al. postulated that the cocaine-induced erection might be a result of the accumulation of serotonin with consequent peripheral vasodilatation and sinusoidal pooling (47). Priapism following trazadone overdose with cocaine use has also been reported (49). Marijuana has been associated with priapism in only one peer-reviewed publication in *MEDLINE* between 1966 and the present (50).

Malignancy

In addition to the hematological malignancies, priapism can be the initial clinical manifestation of metastatic carcinoma with invasion of both corpora cavernosum and spongiosum (51). Cancers that may result in priapism include bladder, prostate, renal, and rectal cancer, presumably as a result of malignant obstruction of venous outflow or replacement of the sinusoids with malignant tissue (52). Needle biopsy can make the diagnosis (53).

Neuropathic Injury

Spinal cord injury can be a rare cause of priapism, usually occurring within several hours of suprasacral cord injury. The loss of blood flow regulation below the cord

lesion is the proposed mechanism, and relates to the completeness of the injury (54). Most cases of priapism related to acute spinal shock resolve spontaneously and do not require intervention.

Lumbar stenosis can lead to ischemic priapism (55), and a case of priapism has been reported in a chronic spinal-cord-injury patient in association with terazosin (56). Most cases of neurogenic erections occur during spinal or general anesthesia and do not require treatment unless it interferes with the proposed surgery (57). In these cases intracorporal injection of phenylephrine is indicated (58).

EVALUATION

The key first step in the evaluation and appropriate treatment of priapism is to differentiate between low-flow and high-flow states. A careful history and physical examination will usually lead to the correct diagnosis. Confirmation of the clinical suspicion with corporal blood gas analysis should be carried out in all cases except those clearly related to intracavernous injection therapy.

The case history should accurately define the onset and nature of symptoms and identify any risk factors for priapism. The rapidity of onset, relationship to sexual activity, trauma, duration of erection, and prior history of prolonged erection should be elicited. A recent history of needle injury, penile, or perineal trauma should raise the index of suspicion for high-flow priapism, as should the absence of pain. The past history should focus on predisposing medical conditions, medication use, recreational drug use, and history of malignancy. In cases of ICI-related priapism, the exact dose and formulation of the drug may help predict likelihood of response to therapy.

Physical examination should include vascular and lymph node assessment in addition to a detailed abdominal and genital examination. The classic presentation of low flow priapism is complete rigidity of the corpora cavernosa without engorgement of the corpus spongiosum or glans penis. The penis is usually tender. In contrast, patients with high flow priapism often present with partial erections (60–100% rigidity) (4). Ecchymosis or penile swelling are rarely present, but can help confirm the diagnosis of blunt trauma. Rectal examination is necessary to evaluate for potential malignancy.

Laboratory testing can be of diagnostic use in priapism. A complete blood count should be performed in all cases of suspected low-flow etiology to detect unrecognized leukemia or other hematological causes. In cases of suspected sickle cell disease, hemoglobin electrophoresis or sickle preparation is indicated.

Aspiration of the corpus cavernosum for blood gas analysis allows a rapid distinction between low- and high-flow states. Although the time-course to ischemia varies, in most cases of low-flow priapism, blood gas results are unequivocal. The blood is characteristically dark, and corporal pH < 7.25, PO₂ < 30, and PCO₂ > 60 is considered pathognomonic for ischemic priapism (18). A nonischemic picture, with bright red blood, without acidosis or hypercarbia distinguishes high-flow priapism. The evaluation and initial management of priapism is summarized in Fig. 2.

INITIAL MANAGEMENT

The optimal management of prolonged priapism depends on the etiology and duration of erection. For most cases of low-flow priapism, *regardless of etiology*, aspiration of the corpora and injection of alpha-adrenergic agonists is the standard initial intervention. The treatment of sickle cell priapism remains controversial, but new evidence suggests that

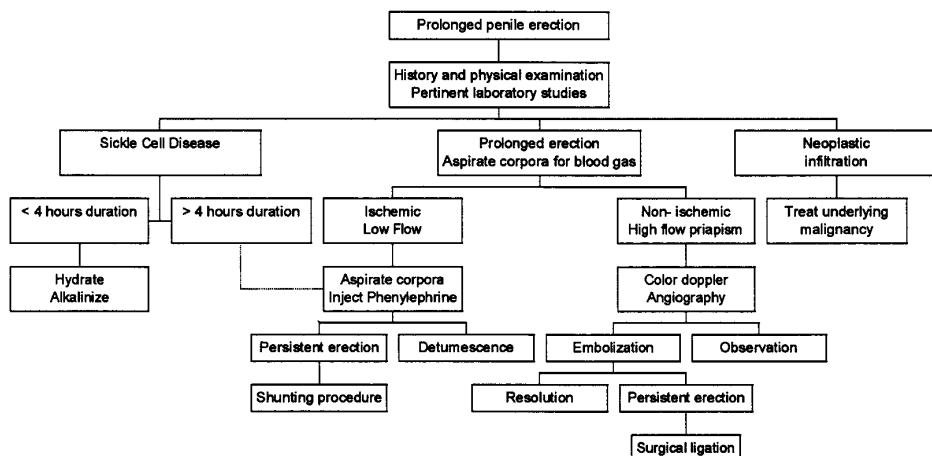


Fig. 2. Algorithm for the management of priapism.

early outpatient aspiration and irrigation is very successful (24). Malignant infiltration of the penis requires rapid induction chemotherapy or other appropriate intervention.

Low-Flow Priapism

In suspected cases of low-flow priapism, infiltration of the skin with 1% plain lidocaine allows insertion of a large bore butterfly needle to obtain blood gas samples, aspirate blood, and irrigate with saline or vasoconstrictors. This avoids repeated needle sticks and lessens the likelihood of ecchymosis. Once the diagnosis of ischemia has been confirmed, initial aspiration of blood is followed by irrigation with vasoconstrictors. A mixture of 500- μ g phenylephrine per mL is used in our institution. The advantage of this selective α -1 adrenergic agonist is the lack of tachycardia. Reflex bradycardia is possible, as is hypertension, and thus automated blood pressure monitoring is recommended, especially in older patients with cardiovascular disease. Repeated dosing of 100–200 μ g every few minutes can be repeated until detumescence occurs. Recent in vitro findings that high doses of phenylephrine can elicit full contraction of corporal smooth muscle, even under acidotic conditions, has led Goldstein and associates to experiment with very high doses of phenylephrine (personal communication).

The duration of priapism may predict response to therapy and need for more aggressive interventions (59). Priapism of short duration (4–6 h) related to intracavernous injection almost invariably responds to outpatient instillation of phenylephrine. In these cases, penile blood gases are generally not necessary. Kulmala and Tamella (59) found that most priapism of < 36 h duration can be successfully managed with aspiration and α -adrenergic irrigation. Conversely, with greater than 48 h of ischemic priapism, few patients could be treated with irrigation alone and shunts were needed in all such patients. An attempt at pharmacological detumescence is usually indicated, however, prior to shunting.

One reported case in the literature documented the use of intracorporal fibrinolysis for low-flow priapism (60). Although complete detumescence was achieved after intra-

corporal perfusion with streptokinase, the prior instillation of metaraminol, an agent that has been associated with death (18), and prior irrigation with heparin-saline solution make this report unorthodox.

The variability in presentation of priapism in patients with SCD is highlighted in the different responses to treatment. A prospective study in young patients with SCD evaluated aggressive initial therapy for priapism (24). All evaluable patients whose priapism resolved after aspiration and irrigation self-reported normal erectile function at a median of 40 mo. The authors concluded that aspiration of the corpora cavernosa followed by irrigation with dilute epinephrine should be the initial therapy employed for patients with SCD and prolonged priapism.

Rarely, in cases of difficult stuttering priapism refractory to standard management, prophylactic or on-demand therapy has been instituted. Costabile (61) reported the use of oral androgen blockade, whereas Levine et al. used gonadotropin releasing-hormone analogs (62). Others have reported success in small series of patients using a number of agents including epinephrine, oral hydroxyurea, and combined oral/injectable etilefrine (63–65).

Alternatives to irrigation and aspiration have been sought, especially for men with priapism related to ICI. Terbutaline, a β -2 adrenergic agonist, induces smooth-muscle relaxation in bronchial tissue; the rationale in the treatment of priapism is unclear, but is postulated to involve improved venous drainage (66). The evidence supporting the use of oral pseudoephedrine and terbutaline comes from case reports and case series (67,68). In a randomized prospective study, Lowe and Jarow found that terbutaline was more efficacious than pseudoephedrine or placebo, but only 38% of patients responded to the former drug (69). In another randomized study, terbutaline showed no increased efficacy vs placebo (70). The induction of anesthesia has anecdotally been associated with resolution of priapism, but no controlled study has demonstrated the benefit of this approach (68,71).

As our understanding of the mechanisms involved in the control of smooth muscle tone increases, new targeted oral therapies may emerge to enhance smooth-muscle contractility and avoid the devastating complications of priapism. However, no current oral therapy has been shown to be efficacious for the treatment of low-flow priapism.

High-Flow Priapism

Initial management in high-flow priapism involves establishing the diagnosis and then instituting one of several treatment options. The diagnosis can be made either by penile blood gas or by color duplex ultrasonography. Even in cases of clear perineal trauma, ultrasonography is useful to confirm the diagnosis, lateralize the site of injury, and guide subsequent angiographic intervention. It may also provide useful information about the viability of the contralateral cavernous vessel (4). High-flow priapism can take on several sonographic appearances. Typical is a cystic area of extremely high blood flow within the corpus cavernosum (Fig. 3). A clear arteriovenous fistula may only rarely be evident. Finally, pseudocapsule formation may be visible. Once the location has been confirmed, treatment can be selected.

Men can tolerate long periods of partial rigidity and nonischemic priapism without significant complications. Although potency can be retained without treatment, most will desire therapy (72). Direct perineal compression has rarely been effective in causing a fistula to close, alone or in conjunction with duplex guidance (73). Ice packs have not been shown to be useful. In most cases, angiography is the treatment of choice. The



Fig. 3. Duplex ultrasonographic appearance of a right-sided cavernosal-sinusoidal fistula in a patient with high-flow priapism: transverse view.

injection of methylene blue, an inhibitor of nitric oxide (NO) synthase, has been reported for the treatment of high-flow priapism (74). However, a subsequent report of penile necrosis and abscess have dampened enthusiasm for this therapy (41,75). Angiographic embolization has also been associated with abscess formation, and not enough evidence exists to make a clear recommendation regarding the risks and benefits of methylene blue (76).

INTERVENTIONAL RADIOLOGICAL MANAGEMENT FOR HIGH-FLOW PRIAPISM

Radiological intervention has become the treatment most commonly performed for high-flow priapism. Prior to angiography for suspected arterial priapism, a duplex

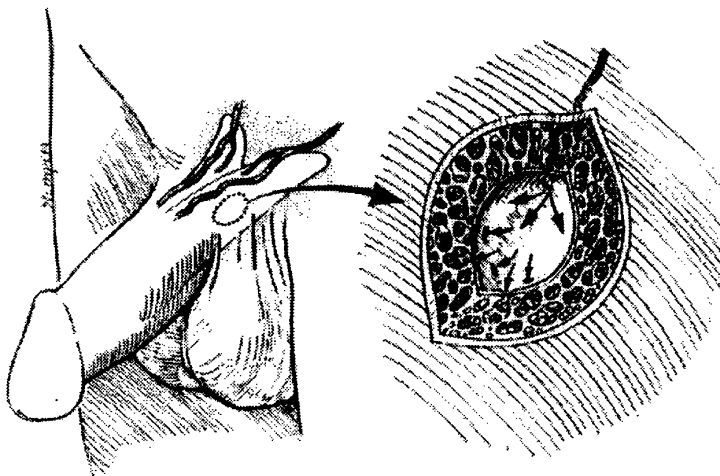


Fig. 4. Drawing of sinus and arterial inflow in high-flow priapism (Taken with permission from ref. 4).

Doppler scan may be useful not only to identify the arterial lesion, but also to obtain a baseline study for subsequent comparison (72).

Arterial embolization for high-flow priapism was first described in 1977 (77), and many techniques have been proposed. The use of autologous clot has been advocated as a potentially reversible obstruction of the cavernous artery with less risk of long-term ED (78). Other methods include superselective embolization (79,80), coils (81), and cyanoacrylate (82).

The risk of ED is considered low following embolization. Of the evaluable patients in several series (4,8,72), none reported permanent ED. Ligation of the cavernosal artery at the site of the fistula has been used in several cases in which embolization was not successful, and in theory may spare devascularization of larger portions of the corpus cavernosum (4,83). A pseudocapsule may serve as a landmark; conversely, intraoperative identification of the abnormal vascular formation with ultrasonography can guide surgical approach. Direct entry into the corpus cavernosum and surgical suture ligation of the injured arterial branch within the sinus cavity is recommended (Fig. 4) (4).

SURGICAL SHUNTING FOR LOW-FLOW PRIAPISM

Surgical shunting of the corpus cavernosum is indicated in cases of low-flow priapism, which do not respond to intracorporal irrigation. Patients must be counseled regarding the risk of potential ED related to the shunt (84), although clearly the risk of ED from untreated low-flow priapism is dramatically higher.

All shunts share the common goal of establishing an alternative venous egress from the ischemic, damaged venoocclusive mechanism. Because the corpus spongiosum and glans are spared from priapism, these structures form the basis of most shunts. Venous shunts to the dorsal vein or saphenous vein have been described (85,86), but in our experience, are technically more difficult and more prone to premature clotting. Thus, we use the glans as first-line surgical therapy and the spongiosum for shunting when glanular shunts fail.

Cavernoglanular Shunts

A shunt from the distal corpora to the glans penis is the most expeditious and simple shunt. Although no comparative study has determined the optimal cavernoglanular shunt, the Winter shunt is most commonly attempted (50). A fistula is created by excising cores of the tunica albuginea from both distal corpora cavernosa using a Tru cut needle. A minute stab wound is made to allow easier entry into the glans. All old blood should be milked out of the penis and bright red blood should be visible coming out of the wounds. Once detumescence has been achieved, the skin is closed with chromic sutures to allow shunting of blood.

Alternatives to the Winter shunt include Lue's modification in which 1-cm incisions are made through the glans into each corpus cavernosum (personal communication). Deep stellate cuts are made with the 11 blade, through the tunica albuginea, to allow detumescence. A butterfly needle is placed into the corpus cavernosum to monitor intracorporal pressure (ICP), and if necessary, to irrigate distal corpora with saline. The ICP line is attached to the CVP monitor and measured before and after closure of the skin incisions. If the ICP remains less than 40 cm H₂O, the procedure is terminated. If ICP fails to remain within the normal range, a more aggressive shunt should be considered.

The Al Gorab shunt involves a larger transverse glanular incision distal to the coronal sulcus (87). Sharp dissection identifies the distal corpora and a portion of the tunica is excised. The skin incision is closed with an absorbable suture.

Cavernospongiosal Shunts

These shunts are a reliable second line shunt when distal shunting fails. The Quackel's shunt establishes flow between the proximal corpus cavernosum and the corpus spongiosum. Advantages include the ability to create a large shunt and also allow blood egress without traversing the entire length of the ischemic corporal tissue. We prefer a perineal incision, so that the anastomosis between cavernosum and spongiosum is performed in the bulb, where a thicker spongiosum reduces the risk of urethral injury and fistula. The patient should be placed in lithotomy position to allow a midline incision. The spongiosum can be partially mobilized to allow easy tension free side to side anastomosis. Parallel longitudinal 3 cm incisions are made through the tunica of both the spongiosum and cavernosum.

The ischemic blood is evacuated and a single layer running vascular anastomosis is made with an absorbable monofilament such as PDS or Maxon. First, the back wall is approximated and then the front wall (Fig. 5).

POTENCY ISSUES AND PRIAPISM

Early aspiration and irrigation can prevent the devastating long-term complications of low-flow priapism including corporal fibrosis and permanent ED. In cases of prolonged erections, the outlook is considerably worse, with estimates in the past of 50% loss of potency (88). Kulmala et al. reported that men with < 24 h of priapism have a 92% return of potency, vs 22% for those with more than 7 d of erection. Young men have a greater likelihood of maintaining erectile function, and aggressive use of small distal shunts also was more likely to preserve function (89). Others have confirmed that in sickle cell disease, shunts performed within 48 h, especially in postpubertal children, seemed more likely to preserve potency (90). Thus, some authors advocate aggressive

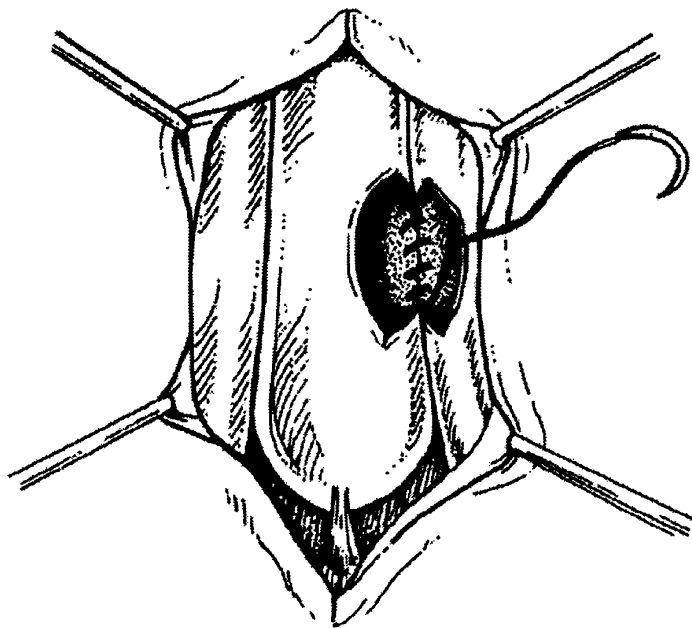


Fig. 5. Technique of Quackel's cavernospongiosal shunt (Taken with permission from ref. 41).

shunting in cases when priapism has lasted longer than 36 h, skipping attempts to aspirate and irrigate the corpus cavernosum (59).

A more radical approach to prolonged ischemic priapism in the sickle cell population is implantation of a penile prosthesis. Because of the difficulties with insertion of a penile prosthesis into the fibrotic corpus cavernosum, several authors have advocated early implantation before waiting for recovery of potency (22,91,92). However, because some men will regain potency, especially young men treated aggressively with shunts, we do not subscribe to this approach. Education of patients and parents of males with SCD, earlier and more aggressive attempts at aspiration and irrigation, and shunting before 24 h may be the most appropriate means to prevent ED.

CONCLUSION

The pathophysiology of priapism has been considerably elucidated and distinction of low- and high-flow states allows appropriate intervention. Sickle cell disease remains a major cause of priapism, and new evidence suggests that the incidence is very high. Many pharmaceutical agents and illegal drugs have been implicated as well. Low-flow priapism represents a significant risk to erectile function, and early aspiration and irrigation, with shunting as indicated, is necessary to preserve potency. In contrast, the treatments of high-flow priapism, such as angiographic embolization, may pose more of a risk to the patient than the problem itself.

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Ejaculatory Disorders

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INTRODUCTION

Intravaginal ejaculation is necessary for perpetuation and preservation of most mammalian species. In the human, the ejaculate is derived from the testes (10%), prostate (15–30%), and seminal vesicles (50–80%). Pre-ejaculate secretions are derived from the bulbourethral glands. The first part of the ejaculate is the richest in spermatozoa, followed by a portion enriched in prostatic fluid, and a final portion derived from seminal vesicular secretions. The majority of ejaculations in the human are not associated with procreation, but are an important part of sexual intimacy. Ejaculatory dysfunctions can lead to personal distress and interpersonal difficulties (1). The prevalence of ejaculatory disorders far exceeds any other sexual dysfunction in the American male, approaching 40% (2). The purpose of this chapter is to review the central and peripheral physiology of ejaculation, ejaculatory dysfunctions, and their cause and current treatments of the problem.

NEUROLOGIC CONTROL

Central

Central ejaculatory control originates from hypothalamic nuclei that network extensively with a phylogenetically primitive portion of the brain, the limbic system. In view of the importance of the ejaculatory function for reproduction, this is not surprising. Much of the work on ejaculatory control has been carried out in the rat with selective pharmacological or radio-frequency ablative control. The hypothalamic paraventricular nucleus (PVN), parvocellular neurons, medial preoptic areas, bed nucleus of the stria terminalis, and dopamine secreting neurons from the nucleus accumbens control both “psychogenic” and copulatory erections and behavior. The magnocellular PVN neurons mediate normal ejaculation. Lesions in the oxytocinergic neurons of the PVN of the rat hypothalamus are associated with a significant decrease in seminal emission at the time of ejaculation, but mount frequency, intromissions, and ejaculatory latencies are unaffected (3–5). In the rhesus monkey, bilateral ablation of the medial preoptic-anterior hypothalamic (MP-AH) area reduced or completely eliminated intromissions and ejaculations without interfering with masturbation, an expression of sex drive. The results regarding primate copulatory behavior were consistent with the effects of MP-AH lesions in rats, cats, and dogs (6). The inhibitory role of the paraventricular (PGi) reticular nucleus on ejaculation was demonstrated in sexually experienced male rats that were allowed to mate to sexual exhaustion. Males with PGi lesions showed an increased time to sexual exhaustion and an increased number of ejaculations prior to exhaustion. It is felt that the oxytocinergic neurons have a salutatory effect on seminal emission (7).

Peripheral control

Ejaculation or orgasm is the last phase of the human sexual response cycle as described by Masters and Johnson (8). The ejaculatory process can be broken into three phases, each possibly occurring independent of each other: emission, ejection, and orgasm. Emission is the movement of the semen along the genital tract to the posterior urethra, ejection is the antegrade propulsion of semen out of the urethra, and orgasm is the pleasurable sensation associated with ejaculation (9), see Table 1. In a neurologically intact individual, cortical facilitation is necessary for ejaculation to occur.

EMISSION

Emission is controlled by the sympathetic spinal cord reflex (T10-L2). Efferent fibers emerge bilaterally from the spinal column to form the lumbar sympathetic ganglia chain, which lies lateral and adjacent to the aorta. Just below the bifurcation of the aorta, the preganglionic nerves combine in the midline to form the hypogastric plexus, then passing into the pelvic plexus to terminate in the postganglionic fibers of the bladder neck, prostate, seminal vesicles, vasa deferentia, and epididymes. It is not clear whether the preganglionic fibers travel exclusively to their ipsilateral end organs.

Sympathetic stimulation results in closure of the bladder neck, contraction of the epididymes, vasa, seminal vesicles, and prostate. The ejaculate is then deposited in the posterior urethra with a feeling of ejaculatory inevitability from distension of the posterior urethra (10). Damage to the sympathetic ganglia during retroperitoneal surgery for testis cancer or aortic replacement can result in failure of emission.

Table 1
The Three Mechanisms of Normal Antegrade Ejaculation

<i>Emission</i>
Sympathetic spinal cord reflex (T10-L2)
Genital and/or cerebral erotic stimuli with considerable voluntary control
Peristaltic contraction of epididymis and vas deferens
Contraction of seminal vesicles and prostate
Expulsion of spermatozoa and seminal/prostatic fluid into posterior urethra
Ejaculatory inevitability sensation resulting from distension of posterior urethra
<i>Election</i>
Sympathetic spinal cord reflex (S2-S4)
Limited voluntary control
Rhythmic contractions of bulbocavernosus/pelvic floor muscles
Bladder neck closure
Relaxation of external urinary sphincter
<i>Orgasm</i>
Build-up and release of pressure in posterior urethra
Smooth muscle contraction of accessory sexual organs and urethral bulb
Sensation as a result of cerebral processing of pudendal nerve sensory stimuli

EJECTION

Ejection is controlled by the S2 to S4 sympathetic efferents. Sensory input from the glans penis and urethra send sensory afferent input via the dorsal penile nerve, to the pudendal nerve, then to a large area of the cerebral cortex (11,12). Cortical efferents then travel down to the S2–S4 somatic efferents, which exit the spinal cord in the motor branches of the pudendal nerve. The motor efferents then innervate the bulbospongiosus, ischiocavernosus, and pelvic floor musculature resulting in rhythmic contraction of the muscles and antegrade expulsion of the semen.

ORGASM

Orgasm is the least understood phase of ejaculation, but appears to be controlled centrally. Though commonly believed to be associated with ejaculation, it can occur independently of emission, ejaculation, and erection. Impotent and potent men after radical prostatectomy will experience orgasms despite the absence of a prostate, and seminal vesicles. The lack of semen deposition in the posterior urethra does not prevent the orgasm. Though altered, many men, after radical prostatectomy, describe the orgasm as comparably pleasurable to before surgery. Peripheral sensation of the penis is also not necessary. Men who have had spinal cord transection or penectomies can still experience orgasms without cortical awareness of penile sensation. Repeat orgasms rarely occur without an interim recovery period. This recovery period is termed the refractory period. The physiologic reason for the refractory period in the male is unclear as is not seen in women, who can experience multiple successive orgasms. It is possible for the man to regain his erection during the refractory period. The refractory period lengthens with advancing age and repeated orgasms. In the rat, the absolute refractory period increases with increasing ejaculatory frequency (13). The effect of multiple ejaculations is also

Table 2
Ejaculatory Disorders

I. Premature ejaculation
a. Primary
b. Secondary
II. Delayed or absent ejaculation
1. Anejaculation
a. Primary
i. with Orgasm
ii. without Orgasm
b. Secondary
2. Retrograde ejaculation
3. Failure of emission
4. Aspermia

evident in the adult macaques. During a 3-h heterosexual pairing test, the males achieved 11–19 ejaculations during a single test. Progressive increases in the refractory period for the initial 2–4 ejaculations of the series was followed by either a plateau or a transient decrease in the interval (14). Many men with PE will try the technique of solitary masturbation before sexual intercourse as a way to increase their ejaculatory latency with intercourse.

Neurochemical Control of Ejaculation

The role of serotonin (5-HT) in the control of sexual behavior was proposed when rats that were administered p-chlorophylamine, a serotonin depletor, demonstrated compulsive hypersexual behavior (15,16). The serotonergic neurons are located on the dorsal raphe nucleus (17). Lorraine suggested a role for serotonin in the ejaculatory refractory period (18). More than 16 different 5-HT receptors have been characterized, with both excitatory and inhibitory influence on sexual function. The same receptor at different locations can act in different ways (19). Other putative facillatory neurotransmitters include dopamine and oxytocin (7,20,21). Oxytocin was found to reverse the serotonin induced inhibition of ejaculation in rats (22).

EJACULATORY DISORDERS

Ejaculatory disorders range from premature ejaculation (PE) to inability to ejaculate. They can be lifelong problems or acquired see Table 2. In a recently published survey of American men aged 18–59 yr, 7–9% were unable to achieve orgasm, whereas 30% described PE. The incidence of anejaculation or PE were not affected by age. PE was associated with poor to fair health, emotional problems or stress, liberal attitudes about sex, partners having abortions, same sex activity, and having been touched sexually before puberty (2) see Tables 3–5. Other studies corroborate the high prevalence of PE in the United States and abroad (23–25).

PREMATURE EJACULATION (PE)

Whereas the vaginal deposition of sperm is crucial for procreation, the length of time that it takes from excitation to ejaculation varies from species to species. In the

Table 3
From Lauman et al. JAMA 1999; 281: 6. Prevalence of Dysfunction Items by Demographic Characteristics (Men)*

<i>Predictors</i>	<i>Lacked Interest in Sex</i>		<i>Unable to Achieve Orgasm</i>		<i>Climax Too Early</i>	
	<i>No.(%)</i>	<i>Adjusted OR (95% CI)</i>	<i>No. (%)</i>	<i>Adjusted OR (95% CI)</i>	<i>No. (%)</i>	<i>Adjusted OR (95% CI)</i>
Total	1249		1246		1243	
Age, y						
18–29	56 (14)	Referent	28 (7)	Referent	121 (30)	Referent
30–39	52 (13)	1.52 (0.95–2.42)‡	28 (7)	1.31 (0.71–2.40)	122 (32)	1.01 (0.72–1.42)
40–49	45 (15)	2.11 (1.23–3.64)†	26 (9)	1.79 (0.90–3.55)‡	83 (28)	0.88 (0.60–1.30)
50–59	30 (17)	2.95 (1.60–5.44)†	15 (9)	1.74 (0.79–3.83)	55 (31)	0.95 (0.61–1.49)
Marital status						
Currently married	77 (11)	Referent	49 (7)	Referent	214 (30)	Referent
Never married	71 (19)	2.75 (1.74–4.36)†	31 (8)	1.55 (0.86–2.79)	111 (29)	0.95 (0.68–1.33)
Divorced, separated, or widowed	31 (18)	1.69 (1.05–2.73)†	15 (9)	1.29 (0.69–2.39)	54 (32)	1.12 (0.77–1.62)
Education						
Less than high school	30 (19)	Referent	18 (11)	Referent	61 (38)	Referent
High school graduate	42 (12)	0.61 (0.35–1.05)‡	25 (7)	0.62 (0.31–1.21)	125 (35)	0.91 (0.61–1.35)
Some college	65 (16)	0.88 (0.53–1.47)	32 (8)	0.68 (0.35–1.30)	106 (26)	0.58 (0.39–0.87)†
College graduate	44 (14)	0.71 (0.40–1.24)	22 (7)	0.55 (0.27–1.12)‡	87 (27)	0.65 (0.42–1.00)†
Race or ethnicity						
White	134 (14)	Referent	68 (7)	Referent	290 (29)	Referent
Black	27 (19)	1.13 (0.67–1.90)	13 (9)	1.14 (0.57–2.26)	49 (34)	1.14 (0.75–1.72)
Hispanic	12 (13)	0.94 (0.47–1.86)	8 (9)	1.24 (0.54–2.83)	25 (27)	0.78 (0.46–1.31)
Other	10 (24)	2.02 (0.94–4.32)‡	8 (19)	2.83 (1.24–6.50)†	17 (40)	1.63 (0.86–3.09)

* Data are from National Health and Social Life Survey. Estimated ratio of odds of reporting a given symptom for members of the specified group to odds for reference group. Derived from logistic regression models performed on respondents with at least 1 partner during the 12-month period prior to the survey. The model includes all predictor variables as well as controls for religious affiliation and residence in rural, suburban, or urban areas. Percentages are derived from respondents in each category, and the total number represents those who responded to the questions. OR indicates odds ratio; CI confidence interval.

† $p \leq .05$

‡ $p \leq .10$

Table 4
Latent Classes of Sexual Dysfunction by Risk Factors (Men)^{a*}

Predictors	Adjusted OR (95% CI)		
	Premature Ejaculation	Erectile Dysfunction	Low Desire
Health and lifestyle (n = 1202)			
Daily alcohol consumption	0.79 (0.36–1.69)	1.63 (0.61–4.34)	2.24 (0.89–5.54)‡
STD ever	1.10 (0.70–1.73)	1.29 (0.64–2.59)	1.05 (0.51–2.15)
Urinary tract symptom	1.67 (0.95–2.93)‡	3.13 (1.46–6.63)†	1.68 (0.71–3.97)
Poor to fair health	2.35 (1.40–3.95)†	2.82 (1.25–8.33)†	3.07 (1.36–6.81)†
Circumcised	0.87 (0.58–1.31)	1.30 (0.63–2.70)	1.64 (0.75–3.58)
Emotional problems or stress	2.25 (1.68–3.20)†	3.56 (2.00–6.34)†	3.20 (1.81–5.67)†
Social status (n = 1232)			
Household income (1988–1991), % change			
1–20 increase	Referent	Referent	Referent
0–20 decrease	1.09 (0.74–1.61)	1.49 (0.79–2.82)	1.23 (0.65–2.34)
>20 decrease	1.41 (0.87–2.29)	2.11 (1.01–4.38)†	1.38 (0.62–3.07)
Liberal attitudes about sex	1.72 (1.17–2.53)†	1.33 (0.72–2.46)	1.07 (0.57–2.00)
Sexual experience (n = 1039)			
≥5 Lifetime partners	0.96 (0.64–1.45)	1.02 (0.50–2.05)	1.25 (0.61–2.60)
Sex frequency no more than once monthly	0.94 (0.58–1.52)	1.20 (0.55–2.63)	1.57 (0.79–3.12)
Thinks about sex less than once weekly	0.99 (0.49–2.02)	0.77 (0.25–2.42)	3.63 (1.57–8.40)†
Masturbation at least once monthly	1.09 (0.73–1.64)	0.66 (0.33–1.33)	1.72 (0.86–3.42)
Any same sex activity ever	2.11 (1.15–3.86)†	0.72 (0.23–2.33)	2.51 (1.10–5.74)†
Partner had an abortion ever	1.83 (1.15–2.90)†	0.63 (0.24–1.61)	1.98 (0.92–4.23)‡
Sexually forced a woman ever	1.74 (0.70–4.30)	3.52 (1.03–11.98)†	0.49 (0.05–4.08)
Sexually harassed ever	1.43 (0.97–2.11)‡	1.27 (0.66–2.47)	1.31 (0.69–2.48)
Sexually touched before puberty	1.80 (1.12–2.90)†	3.13 (1.49–6.59)†	2.23 (1.10–4.56)†

* From Laman et al. JAMA 19; 281: 6.

* Data are from National Health and Social Life Survey. Estimated ratio of odds of membership in a given latent class for members of the specified group to odds for reference group in the default latent class of having no problems. Derived from multinomial logistic regression models performed on respondents with at least 1 partner during the 12-month period prior to the survey. Three models were run separately for each sex health and lifestyle, social status, and sexual experience). Predictor variables, in addition to those listed for health, lifestyle, and sexual history, included age, marital status, education, race and ethnicity, religion, and place of residence. OR indicates odds ratio; CI, confidence interval, and STD, sexually transmitted disease.

† $p \leq .05$

‡ $p \leq .10$

lion, the dominant male will impregnate multiple estrous females, ejaculation takes a matter of seconds with a very short refractory period. In this way he can maximize the dissemination of his gene pool. In the dolphin, intercourse occurs by necessity underwater and ejaculation occurs within seconds of intromission. In most animal species, the copulatory act results in a period of vulnerability for both the male and

Table 5
Quality-of-Life Concomitants by Latent Classes of Sexual Dysfunction^{a*}

<i>Latent Class</i>	<i>Satisfaction With Primary Partner and Happiness</i>		
	<i>Low Physical Satisfaction</i>	<i>Low Emotional Satisfaction</i>	<i>Low General Happiness</i>
Women	(n = 1441)	(n = 1442)	(n = 1462)
No problems	Referent	Referent	Referent
Low desire	4.31 (3.04–6.11) [†]	3.52 (2.59–4.78) [†]	2.61 (1.76–3.88) [†]
Arousal disorder	7.04 (4.71–10.53) [†]	4.28 (2.96–6.20) [†]	5.17 (3.36–7.95) [†]
Sexual pain	2.39 (1.21–4.74) [†]	1.96 (1.08–3.57) [†]	2.62 (1.31–5.23) [†]
Men	(n = 1218)	(n = 1219)	(n = 1238)
No problems	Referent	Referent	Referent
Premature ejaculation	0.79 (0.47–1.32)	0.97 (0.63–1.48)	1.28 (0.75–2.18)
Erectile dysfunction	4.38 (2.46–7.82) [†]	2.40 (1.33–4.33) [†]	2.48 (1.22–5.05) [†]
Low desire	3.14 (1.74–5.69) [†]	1.57 (0.85–2.90)	2.61 (1.28–5.31) [†]

* From Lauman et al. JAMA 1999; 281:6.

^a Data are from National Health and Social Life Survey.¹⁷ Data are presented as adjusted odds ratio (95% confidence interval). Estimated ratio of odds of respondents of each latent class having negative concomitant outcomes. Derived from logistic regression models performed on respondents with at least 1 partner during the 12-month period prior to the survey. The dependent variables are the concomitant outcomes and the predictor variables, modeled simultaneously, include latent classes as well as controls for age, marital status, education, race and ethnicity, religion, and place of residence.

[†] $p \leq .05$

the female. By having a short ejaculatory period, the period is kept to a minimum. Yet in the cactus mouse, prolonged copulation appeared to facilitate pregnancy (26). In the human, a rapid ejaculation can be detrimental to sexual intimacy. Despite a perception that men should be able to control their ejaculation until the female is ready for orgasm, the average ejaculatory latency is 3 min and only 30% of women will reach orgasm with vaginal intercourse regardless of their partner's ejaculatory control (27).

There is no standard definition of PE. Whereas precoital ejaculation is clearly premature, PE is not defined by a specific ejaculatory latency time. Nonetheless, the reported incidence of PE is 30% in the American male population (2). The Diagnostic and Statistical Manual of Mental Disorders define PE as the “persistent or recurrent ejaculation with minimal sexual stimulation before, on or shortly after minimal sexual stimulation before, on or after penetration and before the person wishes it...” which is associated with “marked or interpersonal difficulty...” (28). Lack of standardization of the definition leads to confusion in the literature as to what constitutes a problem and efficacy endpoints of treatment methods (29).

CAUSES

Hormonal

There is no evidence that the etiology of PE is hormonal. In several studies, serum plasma testosterone levels in men with PE, erectile dysfunction (ED), and normals were not statistically different at 620 ng/dL (30,31).

Psychological

It is important to distinguish between primary premature ejaculators (PPE) vs secondary premature ejaculators (SPE). Although Minnesota Multiphasic Personality Inventory (MMPI) testing was normal in a group of premature ejaculators (32), PPEs and SPEs differed on a number of clinical and psychometric variables in another study. Clinically SPEs were significantly more likely to manifest a coexisting erectile disorder, reduction in sex drive, and a decrease in arousal during sexual stimulation than SPEs. They were significantly less likely to report high levels of anxiety during coitus. On the Derogatis Sexual Functioning Inventory, PPEs were significantly more "impaired" than the SPEs as reflected by scores on the symptoms and satisfaction scales. They were significantly less impaired on measures of sex drive (e.g., drive and fantasy). On the Hamilton Anxiety Rating Scale (HRAS), the PPEs scored as significantly more anxious than the SPEs (33). Other psychological traits associated with PE include fear of the vagina, hostility toward women, misogynistic attitudes, anxiety disorders, interpersonal conflicts, passivity and masochism in marriage, obsessive-compulsive character, female arousal disorder, or conditioned patterns of rapid ejaculation (34–38). Treatment of the performance anxiety with propranolol does not appear to be effective (39).

Neurophysiological

Evoked sacral potentials were used to study the bulbo-cavernous reflex in 85 patients with PE. Results suggest a reflex hyperexcitability, or an impaired "modulation" of the motor neurons of the pudendal nucleus by the regulating upper centers in the PE patients (40). Penile biothesiometry was performed in 120 patients with PPE without ED and neurological deficit, and in 66 normal potent male volunteers. Vibratory thresholds on the glans penis and penile shaft show the values in patients with PE were significantly less than those in normal potent men ($p < 0.001$). In normal potent men, an age dependency of biothesiometric parameters was noted. There was a significant increase in vibratory threshold at the glans penis and penile shaft in older patients. However, in patients with PE there were consistently decreased values without age dependency at the glans penis and penile shaft ($p > 0.05$) (41,42). Cortical somato-sensory evoked potentials (SEPs) from pudendal stimulation were determined in 23 patients with PE and in 25 normal subjects as a control group. SEPs give a cortical representation of the sensory stimuli arising from the genital area. Results show a greater cortical representation of the sensory stimuli from the genital area and suggest an organic basis for PE (43). Other studies show no increase in penile sensitivity (44). In a study of PE after spinal cord injury: 6 men had sudden onset of severe premature emission after spinal cord injury. Sexual therapy using squeeze and stop/start techniques was unsuccessful in all cases. Patients were started on phenoxybenzamine, terazosin, or prazosin and reported slight improvement. The injury in the conus area of the spinal cord was believed to disinhibit the ejaculatory mechanism and allow for premature emission (45). There appears to be an increasing body of evidence to suggest that there may be an organic reason for PE in some patients.

TREATMENT

The long-term successful cure remains elusive. Sex therapy, behavior modification, desensitization techniques, and most recently, medication are all part of the armamentarium. Recidivism is common despite successful initial treatment. At the beginning of

Table 6
Medications Used to Treat Premature Ejaculation

<i>Medication</i>	<i>Class</i>	<i>Dosage</i>	<i>Peak Plasma Level</i>	<i>T_{1/2}</i>	<i>Mechanism</i>	<i>Side Effects</i>
Chlomi-pramine	Tricyclic Antidepressant	25–50 mg	2–6 h	32 h	Non selective 5HT reuptake inhibitor	Drowsiness, Tremor, Dizziness, Insomnia
Fluoxetine	Antidepressant, Anti-OCD	20–40 mg	6–8 h	36 h	Selective 5HT reuptake inhibitor	Drowsiness, Tremor, Nausea, Asthenia
Paroxetine	Phenylpiperidine Antidepressant	20–40 mg	5 h	21 h	Selective 5HT reuptake inhibitor	Drowsiness, Nausea, Asthenia, Dizziness, Insomnia
Sertraline	Antidepressant	50–200 mg	4–8 h	26 h	Selective 5HT reuptake inhibitor	Drowsiness, Nausea, Asthenia, Dizziness, Insomnia

the century, common forms of treatment included alternating warm and cold enemas and urethral irrigations, urethral instillations of silver nitrate, and oral strychnine preparations (46).

Behavioral Therapy

Addressing underlying neuroses and anxieties can be helpful as the PE may be a somatic symptom of underlying psychological conflicts. Many men with PE will experience initial favorable results with individual and/or couples sex therapy and exercises such as behavior modification (47), pelvic floor exercises (48), and the pause squeeze technique (29,49). In the squeeze technique, the partner is instructed to stimulate the man to the point of inevitability, at which time he/she squeezes his penis in a way to cause the urge to ejaculate to disappear. As the man is able to delay his ejaculation in time, intercourse is gradually introduced. Although the number of published studies is limited, the results with sex therapy are remarkably consistent. By use of a variety of techniques, the prognosis for a successful initial treatment of PPE in men approaches 65%, the highest of any of the sexual disorders (50). The treatment of secondary or situational orgasmic dysfunction is more difficult and results in much lower success rates. Short term and 3-yr follow-up of couples being treated with group therapy for PE showed short-term gains that were not sustained at 3 yr (51). Successful behavioral therapy requires a motivated patient and, optimally, his partner. Poor insurance reimbursement, and excessive time commitment are frequently given by patients as reasons for not seeking treatment, but many are unwilling to face the underlying psychological imbalance that is manifested as PE.

PHARMACOTHERAPY

Selective Serotonin Reuptake Inhibitors

The serotonin reuptake inhibitors (SSRI), see Table 7, frequently cause sexual dysfunction. Unlike the 14% sexual dysfunction with self-reporting, recent investigators suggest that the incidence of sexual dysfunction approaches 58% when patients on SSRIs are queried by their physicians. Orgasms appear to be most affected (52). The effects of SSRIs on male and female sexual functioning seem strongly dose-related and may vary among the group according to serotonin and dopamine reuptake mechanisms induction of prolactin release, anticholinergic effects, inhibition of nitric oxide synthetase, and propensity for accumulation over time. Sexual side effects of SSRIs should not be viewed as entirely negative; studies have shown improved control of PE in men (53). Male patients who suffered from PE before treatment, experienced delayed ejaculation and their sexual satisfaction, and that of their partners, clearly improved (54). The mechanism of action of the SSRIs on ejaculation is different from that causing the psychotherapeutic effects. Whereas the antidepressant effects typically require treatment periods of several weeks at much higher doses, the effect on PE can be seen with single and lower "as needed," prn, doses.

Clomipramine (Anafranil)

The first description of the clinical use on clomipramine for PE appeared in the 1977 after anecdotal reports of anejaculation had appeared in patients treated with this tricyclic antidepressant (55). The central mechanism of action appears to be central inhibition of 5-HT reuptake (56). Clomipramine causes dose-dependent decreases in nocturnal penile tumescence (57) and increases in penile sensory thresholds (58). In a double-blind placebo-controlled crossover study of up to 40 mgs of clomipramine followed by a 3-mo open label period, there was no difference between drug and placebo. Nonetheless, during the follow-up open label period, 56% of the patients were found to have derived benefit from open label daily treatment (59). Other placebo-controlled studies have showed efficacy in doses from 25 to 50 mg with increases in ejaculatory latency of up to 6.4 and 8 min, respectively, (60–62). The dosage for treatment of PE is much less than that used for depression, which can be more than 100 mg/d. The risk of anejaculation is dose dependent. The administration of clomipramine can either be daily or on demand (4–6 h before) sexual activity (63). Regardless of the method of administration, the beneficial therapeutic effect does not appear to continue after the medication is discontinued. In a comparison between clomipramine and SSRIs, clomipramine was the most effective medication, but had significantly more side effects that interfered with its therapeutic efficacy.

Paroxetine (Paxil)

In several placebo-controlled comparisons, patients attained better ejaculatory control than with placebo. Although both on-demand and daily dosing were effective, daily dosing was superior. Paroxetine is an inhibitor of the P450 2D6 enzyme, which is responsible for its first pass metabolism. Prolonged administration results in a disproportionately increasing concentration with every dose (9). With daily dosing, up to 17% of patients had side effects including anejaculation, anorexia, gastrointestinal upset, and reduced libido (64–66). Improvement in ejaculatory latency disappeared in 90% after cessation of drug (67). In a review of the side effects of SSRIs, paroxetine

Table 7
Drugs Causing Ejaculation Disorders

Antihypertensives	Others
Phenoxybenzamine hydrochloride	Alcohol
Phentolamine	Baclofen
Prazosin	Chlordiazepoxide
Terazosin	Epsilon-Aminocaproic Acid
Thiazides	Methadone
Reserpine	Naproxen
Guanethidine	Antiandrogens
Antipsychotics	Antidepressants
Chlorpromazine	Fluoxetine
Chorprothixene	Fluvoxamine
Haloperidol	Sertraline
Perphenazine	Citalopram
Thioridazine	Paroxetine
Trifluoperazine Hydrochloride	Chloripramine
Pargyline	Amitriptyline
Phenelzine sulfate	

provoked more delay of orgasm or ejaculation and more impotence than fluvoxamine, fluoxetine, and sertraline. Paroxetine may be the most effective SSRI (54).

Sertraline (Zoloft)

Sertraline was studied in a placebo-controlled study of 50–200 mg/d until clinical response, followed by maintenance for 8 wk. The maximum dose as an antidepressant is 200 mg. Efficacy was established at all doses over placebo (68). In another study of daily 50 mg of sertraline, ejaculatory latency was improved after 4 wk of treatment and no subjects discontinued therapy for adverse events (69). Sertraline had the fewest side effects in a double-blind placebo-controlled comparison study of fluoxetine, sertraline, and clomipramine in patients with PE (70). When compared to fluoxetine, the beneficial effect on ejaculatory latency was comparable (71). In studies to assess efficacy and to see if the beneficial effect could be maintained after drug cessation, 67% of responders on 50-mg daily dose were able to maintain increased ejaculatory latency after discontinuation of the medication (27,72). Prn dosing of 50 mg or 100 mg at 5 PM on the day of sexual intercourse was successful when the patients were first “loaded” with daily sertraline for 2 wk (73). Sertraline caused a greater increase in ejaculatory latency than fluoxetine with fewer side effects than clomipramine (70). Sertraline, like paroxetine and fluvoxamine, but unlike fluoxetine, possess shorter elimination half-lives of approx 1 d and are metabolized to clinically inactive compounds. Because of their favorable pharmacokinetic profiles, paroxetine, sertraline, and fluvoxamine are less likely than fluoxetine to interact with other drugs (74).

Fluoxetine (Prozac)

Double-blind placebo-controlled and open-label studies of 5–40 mgs of daily treatment have demonstrated the efficacy of fluoxetine (75–77). Forty-eight PE patients were evaluated in a double-blind placebo-controlled study before and after treatment for

intravaginal latency, penile sensory threshold values, of sacral evoked response and cortical somatosensory evoked potential tests. Findings suggested that fluoxetine was effective treatment for PE probably as a result of its effect of increasing the penile sensory threshold, without changing the amplitudes and latencies of sacral evoked response and cortical somatosensory evoked potential (78). Side effects from fluoxetine included drowsiness, insomnia, nausea, and impaired sexual desire. Anejaculation was a dose-dependent adverse event and took a long time to resolve because of the slow elimination of fluoxetine and its comparably active first metabolite. Priapism has been reported once (79).

Fluoxamine and Citalopram (Luvox and Celexa)

Like the other SSRIs, these also affect ejaculatory latencies. Their therapeutic use for PE had not been investigated.

Summary of SSRIs

In summary, the SSRIs can effectively treat PE in either daily administration or on an “as-needed” basis. The mechanism is separate from the antidepressant mechanism. The antiejaculatory effect is dose dependent, as are the side effects. Pharmacokinetics require dosing 2–6 h before intercourse. The development of a more-specific and faster-acting SSRI for PE is needed.

OTHER MEDICATIONS

Propanolol

The use of propanolol to treat the “performance anxiety” component of PE has not been effective despite adequate β blockade. Patients were not segregated as PPE or SPE (39).

α -Adrenergic Blockade

Phenylbenzamine is a nonspecific α -adrenergic receptor antagonist. It has been used in the treatment of bladder outlet obstruction and at therapeutic doses results in incompetence of the bladder neck with retrograde ejaculations. Several trials, including one placebo-controlled trial, demonstrated subjective improvement in patients with PE (80–83). Alphuzosin and terazosin have been in a double-blind controlled cross-over trial. Alphuzosin and terazosin proved effective in approx 50% of the case (84). The uroselective α -blocker tamsulosin, which causes retrograde ejaculation in 15% of patients, has not been investigated. The mechanism responsible for the α -blocker effectiveness in PE has not been explained.

Injection Therapy

A potential treatment for PE is to create an erection that will last beyond the ejaculation. To this end, injection therapy is ideal. In a study of eight patients using intracavernous vasoactive drugs, all patients responded successfully to this treatment. Three patients stated they were cured and stopped the treatment. The other five patients continued using the medication after 14 mo. The drug-induced erection lasted between 2–4 h despite ejaculation (85). The risk of priapism and penile fibrosis must be carefully weighed in PPEs with normal erectile function. It would be ill advised to embark in injection therapy in PPEs without concurrent psychosexual counseling.

Phytotherapy

Phytotherapeutic medications are part of a blossoming industry without rigorous investigations, standardization, or regulations. In a rat model, the effect of an ethanolic extract of *Salvia haematodes* roots was studied on the sexual behavior of male rats. The results show that the extract (500 mg/kg, orally) produced a significant increase in episodes of penile erection, enhanced the orientation of males towards the females and increased the period to ejaculation (86). Further similar studies, as well as placebo-controlled human studies, are needed to add credibility to industry advertising claims.

Topical Therapy

The use of a topical agent to decrease the sensitivity of the penis has long been used. Many of the remedies for PE sold in popular magazines are variations of topical anesthetics. An open unblinded study examined lidocaine-prilocaine cream in 11 men with PE. The patients were instructed to apply 2.5 gm of the cream 30 min before sexual contact and to cover the penis with a condom. Nine of eleven showed improvement in PE. No adverse effects were noted (87). Korean investigators studied SS-cream. SS-cream is a topical agent derived from the extracts of nine natural products included Ginseng Redix Alba, applied to the glans penis 1 h before intercourse then washed off just before intercourse. Normally, the latency and amplitude of somatic-evoked potentials stimulated at the glans penis are significantly longer and greater than those stimulated at the penile shaft. The glans penis latency increased and the amplitude decreased after application of SS-cream, nearing levels of normal potent men. No significant differences in the latency stimulated at the penile shaft before and after the application of SS-cream were detected (88,89). The ejaculatory latency, measured by stopwatch, improved from 1.37 min to over 10 min with SS-topical cream with placebo improvement of 2.45 min (18.49%). Adverse events included a sense of mild local burning and mild pain in 18.5% of subjects. No adverse effect on sexual function of the partner and no systemic side effects were observed (90).

ABSENT OR DELAYED EJACULATION

Anejaculation

Primary anejaculation is rare. When it is associated with lack of orgasm, in an otherwise neurologically normal individual who is on no medication, the cause is usually psychogenic. The usual reason for consultation is infertility as the patient is too embarrassed or does not realize his pathology, because he has never experienced either ejaculation or orgasm. A careful psychosexual history will frequently reveal a sexually repressive upbringing or anxieties/neuroses about sexual intimacy. The treatment clearly falls within the realm of the mental health professional with experience in sexual dysfunction. Psychopharmacologic intervention is frequently necessary to treat underlying anxiety and panic disorders. Primary anejaculation with intact orgasmic ability is usually caused by underlying neurological problems, congenital abnormalities such as Mullerian duct cysts, Wolfian duct abnormalities, bladder neck incompetence or profound hypogonadism (91). Secondary anejaculation is most often caused by medication, neurological disease, surgery, congenital disease, or psychogenic problems, see Tables 7 and 8. Identification of the underlying etiology is important in treating possible reversible causes.

Table 8
Causes of Ejaculation Disorders

Neurogenic Factors	Anatomic Abnormalities
Central Nervous System Spinal Cord Injury Transverse Myelitis Multiple Sclerosis Myelomeningocele	Congenital Ureterocele Extrophy/Epispadias Posterior Urethral Valves Hypogonadism
Peripheral Nerve Injury or Dysfunction Retroperitoneal Lymph Node Dissection (Testis Cancer, Lymphoma) Diabetes Mellitus Abdominopelvic Colorectal Surgery Abdominal Vascular Surgery Radical Prostate/Bladder Surgery Sympathectomy Drugs	Acquired Transurethral Resection Prostate Transurethral Incision of the Prostate Open Prostatectomy Y-V Plasty Urethral Stricture Disease Bladder Neck Incision Radical Prostate/Bladder Surgery Surgery Complication Psychogenic Primary Secondary Idiopathic

SSRI Induced

The incidence of antidepressant-induced sexual dysfunction is difficult to estimate because of the potentially confounding effects of the illness itself, social and interpersonal comorbidities, medication effects, and design and assessment problems in most studies. Estimates of sexual dysfunction vary from a small percentage to more than 80%. The popularity of this drug class, as well as the high incidence of associated sexual dysfunction, make it the drug class most commonly linked with ejaculatory dysfunction. Among the sexual side effects most commonly associated with SSRIs, are delayed ejaculation and absent or delayed orgasm, and sexual desire (libido) and arousal difficulties. The specific association of these disorders to SSRI use has not been consistently shown. The effects of SSRIs on sexual functioning seem strongly dose-related and may vary among the group according to serotonin and dopamine reuptake mechanisms, induction of prolactin release, anticholinergic effects, inhibition of nitric oxide synthase, and propensity for accumulation over time. A variety of strategies have been reported in the management of SSRI-induced sexual dysfunction, including waiting for tolerance to develop, dosage reduction, drug holidays, substitution of another antidepressant drug, and various augmentation strategies with 5-hydroxytryptamine-2 (5-HT₂), 5-HT₃, and α -2 adrenergic receptor antagonists, 5-HT_{1A} and dopamine receptor agonists, and phosphodiesterase (PDE5) enzyme inhibitors, see Table 9. In only 5.8% of patients, the dysfunction disappeared completely within 6 mo, with 81.4% showing no improvement at all by the end of this period (54).

Retrograde Ejaculation

Closure of the bladder neck is necessary for antegrade ejaculation. Orgasm is not affected by retrograde ejaculation. Examination of the postorgasmic urine will always

Table 9
Medications to Alleviate SSRI-Induced Sexual Dysfunction

	<i>Mechanism</i>	<i>Dose</i>	<i>Timing</i>
Cyproheptadine (97–99)	5HT-2 antagonist	4–12 mg	1–2 h before intercourse
Yohimbine (100,101)	Central α 2-adrenoceptor blocker	5.4 mg	TID or prn
Amantadine (102)	Dopaminergic	100 mg	5–6 h before intercourse
Methlyphenidate (103–106)	Central CNS stimulant Sympathomimetic	10–40 mg	Daily
Buspirone (107,108)	Dopaminergic	20–60 mg	Daily
Buproprione (109)	Dopaminergic	75–150 mg	prn or daily
Sildenafil (110–112)	PDE-5 inhibitor	50–100 mg	1–2 h before intercourse

yield sperm as long as there is no concurrent genital duct obstruction. Any surgery that disrupts the functional integrity of the bladder neck will cause retrograde ejaculation. The incidence of retrograde ejaculation in a transurethral or open prostatectomy approaches 90%. The incidence is considerably lower in the transurethral incision of the bladder neck (92). Though currently rarely performed, Y-V plasty of the bladder neck will cause retrograde ejaculation (93). α -blockers, such as phenoxybenzamine and tamsulosin, used to treat bladder outlet obstruction may result in retrograde ejaculation. Discontinuation of the α -blockers will result in return of antegrade ejaculation. Spinal cord injury through trauma, birth defect, neoplasm, or surgery may result in dys-synchrony of the bladder neck during ejaculation with resulting retrograde flow of semen. Most men having had prostate surgery have an established family unit and are only inconvenienced by the ejaculatory dysfunction, as orgasmic function is unimpaired. Infertility caused by irreversible retrograde ejaculation can be treated successfully with current methods of assisted reproductive technology (ART) such as in vitro fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI). As sperm are able to be directly harvested from the testis and injected into a waiting ovum, the limiting factors for fertility are financial and female fertility.

FAILURE OF EMISSION

Emission is a sympathetically controlled reflex. Any trauma, surgery, medication, or disease process that interferes with the sympathetic outflow to the pelvic plexus may affect emission. Nonnerve-sparing retroperitoneal lymphadenectomies, abdominal vascular surgery, abdominal pelvic or colorectal surgery, sympathectomies, neurologic diseases, and diabetes can all cause failure of emission, see Table 8. The fluids of ejaculation are never propelled into the posterior urethra, thus creating a functional partial or total obstruction. Orgasm, being a centrally mediated event, is not affected. A postorgasmic urine with sperm will not exclude emission failure, as some sperm may “leak” into the urethra and be washed out with urination. Men with pure emission failure seek urologic consult for infertility instead of sexual dysfunction because orgasmic function is unaffected. Unlike retrograde ejaculation, which usually occurs in men after family units have been formed, emission disorders frequently occur more often in younger men, i.e., juvenile onset diabetics and testis cancer patients. When the sympathetic injury is

partial, patients may respond to α -sympathomimetic medication or imipramine (94–96). Modern ART has resolved many of the infertility issues caused by emission failure.

ASPERMIA

Aspermia, or total lack of ejaculate, is uncommon and is rarely associated with reversible causes. The treatment of prostate cancer is the most common cause. Radical prostatectomy with removal of the prostate, seminal vesicles, and partial vasectomy will eliminate all ejaculate. Men will nonetheless experience orgasms and can still father children through modern ART. Radiation therapy causes fibrosis of the prostate and seminal vesicles with resulting possible loss of ejaculate. Finally, total androgen ablation may result in involution of all accessory sex glands with resulting “dry ejaculate.” When the androgen ablation is removed, as in “pulse hormonal therapy” for advanced disease, the ejaculate returns. Libido and orgasm are also drastically negatively impacted during total androgen ablation.

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Gene Therapy for Erectile Dysfunction

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INTRODUCTION

Despite the safety issues with human gene therapy clinical trials (1), this approach to the treatment of specific disease states continues to hold enormous promise. This is based on the recently reported remarkable scientific achievement of deciphering most of the human genome (2), and the potential impact of utilizing the novel gene expression microarrays both at the RNA and protein levels (3,4). Considerable published evidence shows that the transfer of genes to humans is feasible, with expression varying from a few days to several months and years (5,6). Cystic fibrosis, adenosine deaminase deficiency, and familial hypercholesterolemia are some diseases where a partial correction of the abnormality via gene therapy has already been obtained. Although the ultimate goal of a stable, tissue-specific, and efficient production of the recombinant protein is currently difficult to achieve, prospects are promising.

In comparative terms, gene therapy of the diseases of the urogenital system has not obtained the same attention that has been directed toward other nonurogenital conditions. However, in the case of prostate cancer, several clinical trials are currently under-

way including suicide genes, immunomodulatory genes, autologous vaccines, tumor-suppressor genes, antisense strategies, and antioncogenes (7,8). The same strategies are being tested with bladder cancer (9). Also, in the case of bladder reconstructive surgery and incontinence, the possibility of combining tissue engineering based on autologous cells with *ex vivo* gene transfer opens other avenues where gene therapy may be applicable (10). Similar approaches are being applied to renal transplantation, certain kidney diseases, and renal hypertension (11–13).

Within this background of considerable clinical and scientific interest with substantial promise for the treatment of life-threatening diseases, male erectile dysfunction (ED) appears at first sight as an unlikely candidate for gene therapy in men. The main reason is that impotence is a condition that seriously hampers the quality of life, but does not involve physical pain or endangers life, and therefore the perceived risks of gene therapy may not justify yet this approach. In this chapter, we will provide evidence showing that far from this being the case, gene therapy for the treatment of ED is a logical and well thought-out concept, where specific molecular targets and pathways for safe biological modulation are available, and where the easy accessibility of the penis to external manipulation provides a good approach for cDNA delivery.

GENERAL STRATEGIES OF GENE THERAPY

Most of the gene therapy trials are focused on the treatment of inborn errors of metabolism and cancer (5,6,14,15), with several hundred on-going clinical studies and a large number of preclinical trials in animal models. The main objective is to identify a biochemical pathway that is crucial for the desired physiological or pharmacological response, and then a gene encoding a protein that controls the overall output of the selected pathway. The recombinant cDNA must be transfected or infected into the selected tissue, organ, or the body in general, and the expression of the active recombinant mRNA and protein must occur as preferentially as possible in the target tissue or organ, for as long as it is necessary.

In some cases, the desired effect is to correct an inactivating mutation, in which case the cDNA has to be transfected to replace the silent gene by homologous recombination. In other cases, the protein is active but it is expressed at low levels or its biological activity is downregulated, so that the recombinant cDNA aims to hyperexpress the normal protein. Finally, in many conditions, it is fundamental to block the expression of a noxious protein either because of its direct pharmacological effects or because it controls complex processes such as cell replication, death, and so on. In this case, it is necessary to apply the antisense cDNA that blocks its mRNA translation, or the ribozyme that cleaves specifically this mRNA. Alternatively, antisense oligonucleotides representing a fraction of the coding sequence, rather than whole cDNAs, may be used to achieve the same inhibition.

The success of gene therapy depends essentially on six main factors:

1. Efficient delivery of the cDNA construct or oligonucleotide.
2. Preferential tissue or organ targeting of the cDNA construct or oligonucleotide.
3. Selective tissue or organ expression.
4. Persistent hyperexpression or inhibition of the desired active protein.
5. Absence of immune responses against the proteins encoded by the recombinant vector or cDNA.
6. Conditional activation of protein expression to permit selective time frames of biological effects.

The overall objective is to satisfy as many of these requirements as possible, so that eventually an efficient sustained expression of the desired gene product, triggered by a pharmacological intervention, occurs exclusively in the selected tissue and organ within a certain period.

The first aspect to consider in designing a gene therapy approach is to aim the expression of the autologous species selected protein in order to minimize the possibilities of either to fail in the recognition of cellular receptors or other specific biochemical targets, or to induce antigenic rejection. This is a caveat of many animal preclinical trials where results may be distorted by expressing heterologous recombinant proteins with low biological activity, or by short-term rejection of the foreign protein. Once the suitable cDNA is identified, cloned, and sequenced, it must be subcloned into the adequate vector for delivery to and expression in the target tissue. There are essentially two types of vectors: plasmid and viral.

Plasmid Vector

The plasmid vector is a circular episomal DNA able to replicate and sustain efficient expression of the cloned cDNA in mammalian tissues. The induction of the expression is the result of the presence of either a nonregulable strong eukaryotic promoter, such as CMV or HSV, that is fully active in most mammalian cells, or a regulable promoter that responds to external manipulation for turning mRNA expression on or off. The introduction of the cDNA construct into cultured cells or tissues is called transfection, and in the body this can be done by systemic or local injection of either an aqueous solution ("naked DNA") or as a homogeneous lipophylic emulsion, usually in cationic liposomes. The latter allows for an easier penetration of the plasmid through the cell membrane.

The plasmid construct is first tested *in vitro* in appropriate cell cultures that should express the cDNA and distinguish it from endogenous expression. The transfection efficiency is determined by using in parallel cultures the same plasmid vector but containing a cDNA that expresses a reporter protein such as green fluorescent protein (GFP), β -galactosidase (β -Gal), or luciferase (Luc), that can be detected and/or measured by fluorescence emission, luminometry determination, histochemistry, or immunohistochemistry. Then, the presence of the foreign plasmid containing the selected cDNA is determined by polymerase chain reaction (PCR) using primers pairing in vector and cDNA sequences, and the cDNA expression is demonstrated at the mRNA level (RT/PCR, Northern blot, and so on.) or protein level (Western blot, immunocytochemistry, ELISA, enzyme reactions, and so on.). The desired functional effects in terms of modifying a biochemical pathway or getting a physiological response are then assessed, but this is usually not possible in cell cultures that may not necessarily resemble the situation in the tissue or whole body. Finally, the plasmid construct must be tested in animals, usually by injection, but also given by continuous infusion, transdermally, orally, and other routes. The determination of efficiency of delivery, expression, and physiological effects, is performed as *in vitro*, with the additional possibility of following-up the tissue distribution with the reporter gene constructs and evaluating safety by standard tests.

Although plasmid constructs were the first to be used both *in vitro* or *in vivo*, they suffer from several disadvantages, namely poor efficiency of cell uptake, nonintegration of the recombinant DNA into the host genome, and relatively short period of expression at pharmacological levels (usually days or weeks). The "naked" DNA

approach is used in only a small fraction of animal or clinical trials, and the usefulness of plasmids in gene therapy depends on the development of more efficient liposomal preparations, or alternative procedures. If the efficiency of plasmid transfection and the stability of its episomal expression succeeds, plasmid DNA may offer safety advantages over viral constructs.

Viral Vector

The utilization of viral constructs is designed to increase the efficiency of transfection since the virus carrying the recombinant cDNA will infect in theory 100% of the cells it hits, based on binding to cell receptors specific for each type of viral particles. The efficacy of delivery and distribution becomes a limiting step. The packaged viruses used for gene therapy are replication-defective, which means that they can only replicate in the presence of helper virus or in cells engineered to express a missing crucial protein. Therefore, each virus hits a cell only once and this infection is not productive in the sense of generating more virus. This virtually eliminates any risk of generating pathogenic viruses. Finally, the original viral vectors are usually modified to express a minimum of viral proteins (or none), in order to reduce antigenicity ("gutless or second (as above) generation vectors").

The more-widely employed viral vectors belong to either adenovirus (AdV) and adenoassociated viruses (AAV) for nondividing cells *in vivo*, or retrovirus (RV) for *ex vivo* modification of tissues or cells to be reinjected into the patient. In the case of AdV, the recombinant cDNA remains in general notintegrated in the genome. The development of helper-dependent AdV, where all sequences coding for viral proteins have been removed except for the packaging signals (16–18), should help to reduce immunogenicity and increase the duration and intensity of the recombinant protein expression. This will probably remove some of the objections raised against the use of AdV, which so far have achieved mixed results in animal and clinical trials (14,15). The third or subsequent generation AdV may completely eliminate the risk of unforeseen immunoreactions. New purification procedures will avoid any contamination with helper virus or factors that may allow replication of the recombinant virus. In general, the same considerations described for plasmid constructs apply for AdV, because the latter carry in the viral cassettes similar promoter, regulatory, and expression signals and reporter genes, and are, therefore, evaluated in cultured cells and in animals in the same way. The main difference is the considerably higher efficiency of gene transfer in the case of AdV vectors, and a longer expression in the range of months for the newer generation vectors.

In turn, the AAV is a novel vehicle for delivery of cDNA, which has a series of potential advantages (19–22), such as:

1. No immunogenicity.
2. Nonpathogenicity.
3. Long-term expression of the recombinant gene, specifically in neural tissue and skeletal muscle.
4. relative independence of host chromosome replication and cell cycling.

However, its cloning capacity is smaller than AdV, and it is more difficult to produce in large amounts. A series of vectors containing the AAV terminal repeat (TR) at both extremes and *gfp* reporter gene driven by the CMV promoter, have been developed (22,23). These vectors allow the detection of expression by direct fluorescence, carry a

selective trait for transfection (*neo* or others), and in addition, the CMV promoter can be replaced by cell type-specific promoters (23–25). Their ability to sustain long-term expression in at least skeletal muscle and neural tissue is indicated by experiments in immunocompetent mice with an AAV carrying a *lacZ* reporter where the recombinant protein was detectable for over 1.5 yr (20). The same occurred with an AAV construct of insulin-like growth factor 1 (IGF-1), given directly to the skeletal muscle of adult mouse muscle, which, over 6 mo, was effective in preventing the aging-associated sarcopenia (26). This allows an interesting strategy that is also feasible with AdV, where a given organ, such as the skeletal muscle, is converted into a “factory” of recombinant protein secreted to the circulation (21,22,27). Clinical trials with AAV are still rare, because of the technical difficulties in their production. A phase-I study of rAAV carrying the cystic fibrosis transmembrane conductance regulator (CFTR) is currently under way (28).

On the other hand, retroviral vectors are mainly restricted to anticancer approaches because they require actively dividing cells, or to ex vivo therapies, where cells or tissues are transfected efficiently in culture, and then implanted into the live animal or patient. This is a promising approach, because the extraordinary advancements in tissue engineering will facilitate a gene-transfer approach to modify the biochemical makeup of the tissue prior to implant (10). Clinical trials with retrovirus are ongoing in ADA deficiency, familial cholesterolemia, different immune responses to tumors, and so on. (5,6).

The *Journal of Gene Medicine Clinical Trial* site (<http://www.wiley.co.uk/wileychi/genmed>) provides a comprehensive information on gene-therapy trials, and allows us to search the database by vector, gene, disease, investigator, country, and other features. According to a recent search, more than 350 trials are listed, of which 299 in the United States. The vast majority are in cancer, followed by monogenic diseases, infectious diseases, and gene marking. Vascular disease is represented by 11 trials, using two growth-factor genes: vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF).

GENE THERAPY WITH NOS cDNA CONSTRUCTS FOR CONDITIONS OTHER THAN ED

Nitric oxide (NO) is the main mediator of penile erection, and, therefore, one of the obvious targets for gene therapy of ED is to increase NO production in the penile corpora cavernosa by gene transfer to this tissue of cDNA constructs encoding nitric oxide synthase (NOS) (29–31). This enzyme is responsible for NO synthesis in the reaction that converts L-arginine into citrulline. In the corpora cavernosa and vascular system, NO modulates the tone of the smooth muscle by activating guanylyl cyclase and increasing the levels of cGMP. This causes a reduction of cytosolic Ca^{2+} and the subsequent smooth muscle relaxation. Three NOS isoforms have so far been identified (32–35):

1. The neuronal NOS (nNOS, or NOS I) found in the brain, nerves, and epithelial cells.
2. The endothelial NOS (eNOS, or NOS III) present in the endothelium and certain neurons.
3. The macrophage or inducible isoform (iNOS, or NOS II) found in a wide variety of cells upon induction, mainly macrophages, smooth muscle cells, chondrocytes, hepatocytes, and so on.

Until recently, nNOS and eNOS were considered to be constitutive because their tissue concentrations were relatively constant and no transcriptional inducers had been identified. Therefore they were assumed to be controlled exclusively at the level of

enzyme activity. In contrast, because no basal expression of iNOS had been detected in the absence of induction by cytokines and bacterial products, this isoform was proposed to be exclusively inducible and named as such. In addition, iNOS was assumed to be refractory to enzyme activity modulation. Most, if not all, of these concepts have now been revised in the light of current findings, showing on one side that the expression of both nNOS and eNOS is subject to transcriptional regulation under physiological and developmental conditions, and that iNOS may be spontaneously expressed during aging in the absence of exogenous inducers (34–39).

In addition to its specific role in penile erection, NO in the whole organism is a pleiotropic effector that exerts multiple functions, mainly the induction of smooth-muscle relaxation in the control of the tone of the peripheral vascular bed, and in retrograde neurotransmission all along the central and peripheral nervous system. NO controls smooth-muscle cell proliferation, inhibits blood clotting, intervenes in wound healing, and, when produced in large amounts, induces inflammation and cytotoxicity as a defense mechanism against cancer, infections, and heterologous cells. The manipulation of NOS expression has therefore been an objective of early and current gene-therapy approaches aimed to correct vascular conditions, transplant rejection, cancer, and wound healing, in animal models. Although no clinical trials with NOS constructs have yet been reported, the experimental studies are promising and very relevant to the approaches intended to overexpress NOS within the penis for the treatment of ED. In addition, these studies are important to understand the different effects that NOS gene transfer to the penis may elicit on other organs if the expression is not mainly confined to the target organ. Therefore, a brief synopsis of NOS gene therapy of conditions other than ED is presented.

Historically, the first successful attempt to employ NOS gene therapy was based on a construct of a bovine eNOS cDNA applied in a liposome/HJV virus vehicle into the rat carotid artery submitted to balloon injury of the endothelium in which the neointimal vascular lesion was inhibited (40). The general purpose of this study and the subsequent ones was to devise an antiproliferative strategy to avoid smooth-muscle proliferation and intimal hyperplasia in restenosis after angioplasty (41,42). This aim then extended to the treatment of vascular bypass graft occlusion and transplant coronary vasculopathy for which no known therapy exists (43).

Because of the need to transform multiple cells irrespective of their rate of proliferation, adenoviral vectors are by far the preferred delivery vehicles. Using this approach, it was shown that human saphenous veins can be transduced *in vitro*, resulting in functional transgene expression with increased NO release and relaxation of the tissue rings (44). A similar result was obtained with porcine coronary arteries (45). In addition, the usefulness of eNOS gene therapy of cerebral vasospasm after subarachnoid hemorrhage was shown by improving the impaired NO-mediated relaxations of rings of basilar arteries from dogs exposed to this condition (46). A related possible therapeutic application was also evident from the efficacy of eNOS *in vitro* transfer to inhibit the contractions of radial artery conduits, thus suggesting that this strategy could prevent vasospasms in the implantation of arterial grafts (47). An interesting approach was the *in vitro* transduction of rat heart preparations with AdVeNOS that were then implanted heterotopically into the abdomen of syngeneic recipient rats to try to determine whether this production of NO can attenuate the complications of heart transplantation (48).

The protection exerted by eNOS in avoiding the development of allograft arteriosclerosis was shown in a recent study performed in a murine chronic rejection

model, but in this case it was iNOS gene therapy what prevented this condition in eNOS knockouts. This confirmed the role of iNOS in suppressing neointimal smooth-muscle cell accumulation and inhibiting adhesion of platelets and leukocytes to the endothelium (49). The iNOS gene transfer has been intensively studied for gene therapy for the last 4 yr. Billiar's group showed that because tetrahydro-biopterin (BH4) is an essential factor for iNOS that is not synthesized in unstimulated vascular smooth-muscle cells, this may be an obstacle to successful vascular iNOS gene therapy. This group also showed (50) that cotransfection with a construct of guanosine triphosphate (GTP) cyclohydrolase I (GTPCH), the rate-limiting enzyme for BH4 biosynthesis, is able to reconstitute iNOS activity in BH4-deficient tissues.

An AdV construct of iNOS given to rats receiving aortic allografts with strong genetic disparity suppressed completely the development of allograft atherosclerosis in both untreated recipients and recipients treated with cyclosporin (51). The same group showed that the AdV iNOS was able to completely reverse delayed wound healing in iNOS-deficient mice, thus establishing the key role of iNOS in wound closure and the possible application of iNOS gene therapy in iNOS-deficient states such as diabetes, and steroid treatment (52). Retrovirus constructs of iNOS have also been used to infect *in vitro* highly metastatic human renal carcinoma cells and induce autotoxicity, suppression of tumorigenicity, and abrogation of the metastatic lesions (53). Also, plasmid iNOS in sponges placed subcutaneously in male rats with cutaneous incisions succeeded in enhancing collagen synthesis during normal wound healing (54). A very efficient inhibition of intimal hyperplasia in injured rat carotid arteries and in porcine iliac arteries, a model more relevant to human vascular healing, was achieved by AdViNOS (55).

On the other hand, the *ex vivo* transfer of AdViNOS to organ isografts has been tested in the case of the liver (56) and vein grafts (57). Cold-preserved liver grafts can be infused *in vitro* into the microcirculation, with iNOS expression virtually restricted to hepatocytes. In the case of vein grafts, as with eNOS, the objective is to prevent intima hyperplasia and avoid vein graft failure. It was shown that AdiNOS can efficiently transduce vein segments *ex vivo*, and when this is done by co-transfection with GTPCH, the iNOS enzymatic activity is optimized. This suggests that this cotransfer technique may be used to engineer vein grafts before coronary artery bypass (58,59). The nonviral delivery of iNOS cDNA in cationic liposomes for cardiovascular disease has also therapeutic relevance, as demonstrated by experiments where rabbit SMC were successfully transfected with high efficiency both *in vitro* and *in vivo* without inducing necrosis nor apoptosis (60). At least one biotechnology company (61) is actively involved in preclinical studies with iNOS cDNA constructs for the prevention and treatment of restenosis.

In contrast with the other two NOS isoforms, nNOS gene therapy has not virtually been tested yet, except for the potential use for renal disease (62,63). This probably is owing to the fact that nNOS is located predominantly in neuronal and epithelial cells, and, therefore, unless neuronal-specific promoters are used in the constructs to be delivered, the possibility of a selective expression in these restricted target tissues is very limited. These problems are addressed later.

GENE THERAPY OF ED WITH NOS cDNA CONSTRUCTS

Within this context, it is obvious that the goal for gene therapy of organic impotence is to induce the ability to sustain physiologically elicited erections without resorting to

pharmacological treatment immediately prior to the sexual act, be it derived from injections or oral administration. This implies a stable biological correction of some facets of the impaired erectile mechanism; what could be defined as a medium or long-term cure, rather than a palliative intervention to ameliorate the underlying symptoms. Therefore, even if the cDNA construct may be given by injection to the penis, the treatment is sporadic because it is expected that the effects will last for weeks, months, or even years, according to the vector, promoter, and delivery procedure used.

In the specific case of NO, it is assumed that ED results from a reduction in the synthesis of this mediator in the penile nerve terminals, and/or an impaired mechanical compliance of the target cavernosal smooth muscle to the relaxation induced by NO (8,64), possibly combined with a putative increase in the response to, or the levels of, contractile factors. Therefore, the modulation of endogenous penile NO synthesis through gene therapy of the corpora cavernosa with NOS cDNA, may achieve a more stable and biologically controlled effect than that caused by vasoactive drugs injected into the corpora cavernosa, provided the enhanced NOS levels are activated only upon physiological stimulation in the penis. This is a likely scenario based on what is known on the neural control of penile erection and the mechanism of NOS activation, and the neural dependence for eliciting the response would resemble the effects of oral phosphodiesterase inhibitors like Viagra (65,66), except that the correction would be long-term or even permanent, and not necessarily dependent on any type of drug prior to intercourse.

Because a penile variant of nNOS having a 34 amino-acid insert (PnNOS) is considered to be responsible for the synthesis of NO in the nerve terminals of the penis (67,68), and even in the hypothalamic regions involved in the central control of penile erection (69), PnNOS is a reasonable candidate for gene therapy of ED. In addition, although the penile-specific activation would occur by a neural signal triggered by sexual stimulus, the expression of a recombinant PnNOS protein may provide a further control site for enzyme activation in the nerves and hence NO synthesis. This would be caused by the assumption that the catalytic activity of this nNOS variant is regulated by factors acting on the 34 amino-acid sequence absent in the brain type counterpart. Similarly, although the role of eNOS in cavernosal relaxation is not clear and probably only ancillary, the fact that eNOS appears to be located within the corpora cavernosa in the vascular endothelium and in the lining of the cisternae, suggests that this isoform is also a potential target for biological modulation, as in the therapy of cardiovascular disease.

The first demonstration that gene therapy of ED is feasible and that the modulation of NOS expression is a valid target was published in 1997 (70). Paradoxically, it was not the cDNA for eNOS or nNOS the one selected, but rather the cDNA for iNOS, the NOS isoform, which is not normally expressed in the body unless induced during inflammation or immune response [however, see (36–39)]. The rationale was based on the availability of the recombinant variant cloned from the rat penile smooth-muscle cells induced with cytokines, and the fact that the iNOS enzyme catalytic activity would be independent from factors controlling PnNOS and eNOS enzymes, such as Ca^{2+} or phosphorylation. The expression of recombinant iNOS would then allow for a potentiation of the nitroergic signal triggered by PnNOS in the cavernosal nerve terminals during sexual stimulation, through the generation of a higher basal output of NO within the cavernosal smooth muscle itself.

This study reported that treatment of rats with a small amount (5 μg) of a construct containing the rat penile iNOS coding region in a plasmid under the control of the CMV promoter in a lipofectamine preparation, injected directly into the corpora caver-

nosa, improved aging-related ED. At 10 d after injection, the (MIP) maximal intracavernosal pressure elicited by electrical field stimulation (EFS) of the cavernosal nerve in 20-mo-old rats treated with the iNOS recombinant DNA was significantly increased (46%) over the control animals without iNOS injection. The MIP in the “old” rats even surpassed the 5-mo-old controls, without NO-induced side effects. No changes in mean arterial pressure (MAP) occurred. The plasmid iNOS cDNA was detected in the penile DNA preparation by PCR, and iNOS overexpression was shown by RT/PCR and Western blot. The recombinant iNOS protein appears to be activated only when the cavernosal relaxation is initiated by a physiological stimulus in the penile nerve terminals, because no priapism or hypotension was observed in the rats. This justifies the hypothesis that the therapeutic increase of penile NOS levels may ameliorate a deficient or insufficient NO synthesis responsible for ED. An important point to consider is that the syncytial nature of the corpora cavernosal smooth muscle, derived from the cell-to-cell communication through gap junctions, may compensate for the restricted site of delivery of iNOS cDNA (or any other gene) into the tissue (70,71).

Very recently, eNOS has been shown to improve ED in the aged rat, by administering into the corpora cavernosa an AdVeNOS construct where the expression of the recombinant protein was driven as above by the CMV promoter (72). As expected, eNOS gene transfer increased the expression of eNOS and the Ca^{2+} dependent NOS activity in penile tissue, and the concentration of cGMP in both penile tissue and the plasma. The stimulation of cavernosal pressure after EFS of the cavernosal nerve was comparable to that seen in the earlier study with iNOS, but measurements were restricted to a much shorter period (1 d after injection). The relaxation responses of the corpora cavernosa in the animal receiving acetylcholine or the phosphodiesterase inhibitor zaprinast were also stimulated, suggesting an enhanced endothelial-mediated NO release. In a subsequent study (73), the same group changed the AdV vector to prolong the time of expression. By using a β -gal construct with the same vector, it was shown that reporter gene expression peaked at 5 d after injection and was sustained up to 30 d. In the rats injected with the AdVeNOS, there was an increase in the EFS, acetylcholine, and sildenafil-induced erectile response, but these measurements were limited again to a short period (5 d) after transfection.

A recent abstract (74) reported the *in vitro* transformation of skeletal muscle myoblasts with adenoviral constructs of iNOS and their subsequent implant into the corpora cavernosa of adult rats. The authors claimed that their procedure was more efficient than direct plasmid or adenoviral injection into the penis in inducing a transient increase (1 wk) in the erectile response to EFS. However, in contrast to the previous results there was a high basal erection in the absence of EFS. This was probably caused by uncontrolled iNOS activity in the transfected cells (skeletal muscle), that are not naturally programmed to control high levels of iNOS induction or to be harbored in the corpora cavernosal environment. A similar approach applied to penile smooth-muscle cells *in vitro* may be more successful in this respect, and it may actually turn to be a logical paradigm in view of the current interest in tissue and organ reconstruction (10).

nNOS is certainly a strong candidate for gene therapy of ED because of the location of variants of this isoform both in the nerve terminals of the penis and in the hypothalamic regions controlling erection. A recent communication (74a) claims a successful stimulation for at least 4 mo of the erectile response of adult rats by injecting very large amounts of a naked plasmid construct of the human brain-type nNOS into the corpora cavernosa. However, the naked DNA approach is inefficient and may eventually cause

an immunogenic reaction against the excess DNA itself, in addition to the caveat in this study posed by the expression of a heterologous protein for such a long period that may trigger related immune responses against the recombinant protein.

The recent cloning of the penile specific nNOS variant (PnNOS) (67,68) allows for a strategy that is particularly attractive because of the putative tissue-specific control of enzyme activity that may be conferred by its 34 amino-acid insert. The region where this sequence is inserted harbors autoinhibitory elements (75), and speculatively the 34 amino-acid insert may modulate the function of the autoinhibitory sequence and may provide some type of tissue specificity to NOS activation during erectile response, through a differential response of PnNOS as compared to the brain-type nNOS. Adenoviral and plasmid constructs of the cDNA for the full length PnNOS protein (α form) are currently being tested (Gonzalez-Cadavid, Rajfer, et al.) in the aging rat model, and the preliminary results (75a) are encouraging. The PnNOS β form lacks the ability to bind physiological modulators of nNOS catalytic activity [PIN, CAPON, and possibly the NMDA receptor, see (29,68,76,77)] and therefore it may be insensitive to endogenous inhibition. If this hypothesis is correct, this variant PnNOS cDNA would be an even more efficient tool for gene therapy than the α form.

GENE THERAPY OF ED WITH cDNA CONSTRUCTS FOR OTHER GENES

Although NOS is an obvious candidate for potential manipulation by gene therapy, many other genes expressed in the penis control critical processes in the complex process of erection, and therefore are amenable to this approach. One good example is the hSlo cDNA, which encodes for the α -subunit of the human smooth-muscle maxi-K⁺ channel (71,72,78). The study demonstrated first that expression of reporter β -Gal triggered by a plasmid under a CMV promoter persisted for up to 75 d in the corpora cavernosa, when it was transfected into the rat penis as naked DNA. Intracorporeal injection of a naked similar vector encoding for the hSlo cDNA (100 μ g) increased intracavernosal pressure response to EFS in aged rats over their respective controls for at least 2 mo. Although the equivalent amount in men would be rather excessive (close to 3 mg plasmid DNA), this study shows that a overexpression of the maxi-K⁺ channel in the cavernosal smooth muscle may be an effective way to modulate intracellular Ca²⁺ levels and transmembrane Ca²⁺ flux in this tissue, and therefore improve ED.

Interestingly, a single intracorporeal injection of the same naked plasmid construct as aforementioned improved the erectile response in 9-mo-old rats 1 wk after the injection, not only to EFS of the cavernosal nerve, but also to electrical stimulation of the medial preoptic area (MPOA) in the hypothalamus (79). This shows that the gene therapy-induced amelioration of the erectile response occurs even under conditions evoking the central stimulus conveyed from the hypothalamus. A similar improvement in the erectile response to cavernosal EFS was seen in severely streptozotocin-induced diabetic animals 1–2 mo after injection of the hSlo cDNA (80).

Another approach (81) has been based on the possibility of increasing by gene transfer the expression in the penis of growth factors that may be essential for correcting tissue damage involved in neurogenic and vasculogenic ED, namely in nerve regeneration and angiogenesis, respectively. In both cases, the selected cDNAs were cloned in AAV vectors, a strategy that may end up to be superior to at least the early generation AdV vectors because it reduces immunogenicity and prolongs expression. In addition, AAV are neu-

rotrophic, and this may be particularly useful for nerve regeneration interventions. In one of the studies (82), it was shown histochemically that intracavernous injection of the construct for brain-derived neurotrophic factor (AAV-BDNF) can prevent in rats, after bilateral cavernous nerve freezing, the degeneration of nNOS containing neurons in the pelvic ganglion and stimulate nerve regeneration. As a consequence, the erectile response to EFS in the animals with neurogenic impotence, which were treated with AAV-BDNF was notably increased after 4 wk, and particularly 8 wk. This is promising for the recovery of erectile function after bilateral cavernous injury.

Using a rat model of penile venous leak induced by castration, the intracavernosal administration of an AAV construct of vasoendothelial growth factor (VEGF) cDNA induced at 9 wk a considerable stimulation of the intracavernosal pressure after papaverine, and of the maintenance rate after saline (83). This was below the one achieved by VEGF protein itself or by testosterone, but still suggested that VEGF gene therapy may be partially effective in preventing venous leak.

FUTURE DIRECTIONS

The experimental efforts in making gene therapy of ED a viable therapeutic alternative are likely to continue intensively in a series of directions, some specific to the nature of the selected gene to be manipulated or the physiology of the corpora cavernosa itself and other ones extrapolatable from the advancement of gene therapy in general.

In the first category, in the case of NOS gene therapy, it may be envisaged that the selection of the NOS isoform cDNA will initially be based on studies in the rat similar to the ones presented above using strong promoters like CMV without tissue specificity, and comparing the efficiency of the later generation AdV or AAV cassettes, with special liposome formulations or other methods of delivery of plasmid constructs. Different dosages, and possible reinoculations, or methods of continuous infusion into the corpora cavernosa should be tested.

The isoform selected will, in turn, dictate the choice of the most-adequate gene promoter to favor expression of the protein in the respective target tissue. For PnNOS, specific promoters for neural tissue like the neuronal specific enolase (NSE) (24,25) should restrict expression to nerves and ganglions. Even if the levels of PnNOS protein are elevated throughout the central and peripheral nervous system, the actual stimulation of catalytic activity is the only factor determining the increase in NO synthesis, and this should only occur in the penis upon appropriate sexual, pharmacological, or electrical stimulation, according to the animal models. For iNOS to be expressed in the smooth muscle, a promoter such as the α -smooth-muscle actin (84) may provide the tissue specificity that is needed. In addition, the knowledge of several endogenous factors that control PnNOS activity, such as PIN or CAPON, may spur the design of gene-transfer approaches based on inhibiting the expression of these proteins with ribozyme or antisense approaches (85–87), or competing with their binding to PnNOS. The same considerations can be applied to the other genes aforementioned, regarding selection of promoters, vectors, or cofactors.

The comparison of these variables in several rat models (aging, venous leak, diabetic, bilateral cavernous nerve injury) may need to be followed by further studies in larger laboratory animals, such as rabbits (high-cholesterol diet) and tests of safety in nonhuman primates by direct intracavernosal injection. Any delivery procedure that can enhance the efficacy of plasmid vectors or decrease the required viral load will

simplify the regulatory procedures. In this sense, the possibility of turning on and off the expression of the transfected gene at will may facilitate approval of protocols, because the treatment can be interrupted at the desired stage in order to avoid reaching a potentially excessive level of the recombinant protein. Novel vectors and transgenic mice are available where the recombinant cDNA is placed under a promoter regulable by very low nonhazardous doses of a drug, such as doxocyclin, ecdysone, or RU486 (88–91), and active only in a given tissue.

If a regulatable promoter is combined with a vector assuring long-term expression, the production of the recombinant protein may remain silent everywhere in the organism after the actual transfection or infection, and be activated only in a specific tissue when the drug is given. Suspension of the drug stops further expression, and the cycle may be repeated. If two recombinant genes (e.g., *NOS* and *VEGF*) are placed under control of a different regulable promoter it would be possible to activate their expression separately or together according to the drug used. It is hypothetically possible to combine temporal expression with oral treatments with cofactors or regulators of the respective enzyme activity, so that the basal frame of the gene product is enhanced at will, and then the protein is activated in a more conventional way by direct modulation of a temporarily hyperexpressed product.

It is foreseeable that the application of the novel gene microarray (3,91,92) and proteomic (4) technologies will allow the discovery of genes, other than the ones already identified, whose expression is severely affected in the impotent corpora cavernosa. Functional laboratory studies will determine whether these genes are crucial for the regulation of erectile function in animals and in this way they may constitute new targets for gene transfer approaches. Although at first sight, gene therapy of ED in men may appear rather remote at this moment, the advances in recombinant DNA technology and delivery procedures in the last few years may drastically change this perception in a near future.

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Male Sexual Function

A Guide to Clinical Management

Edited by

John J. Mulcahy, MD, PhD

Indiana University Medical Center, Indianapolis, IN

With the introduction of Viagra in 1999, primary care physicians, many of whom had received little training in erectile dysfunction and were not very comfortable about discussing this topic with patients, suddenly found themselves overwhelmed by patients seeking treatment. In *Male Sexual Function: A Guide to Clinical Management*, leading clinicians and basic scientists comprehensively survey the background, diagnostic tools, associated conditions, causes, and treatments of erectile dysfunction. Here the busy practitioner will find concise and useful information on the anatomy and physiology of erectile function and dysfunction, ejaculatory disorders, Peyronie's disease, and priapism—as well as a chapter on female sexual dysfunction—in addition to thorough chapters on diagnosis and treatment.

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